



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colon Cancer

Version 1.2022 — February 25, 2022

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***Al B. Benson, III, MD/Chair †**
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

***Alan P. Venook, MD/Vice-Chair † ‡**
UCSF Helen Diller Family
Comprehensive Cancer Center

Mahmoud M. Al-Hawary, MD ☐
University of Michigan Rogel Cancer Center

Nilofer Azad, MD †
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

***Yi-Jen Chen, MD, PhD §**
City of Hope National Medical Center

Kristen K. Ciombor, MD †
Vanderbilt-Ingram Cancer Center

Stacey Cohen, MD †
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Harry S. Cooper, MD ≠
Fox Chase Cancer Center

Dustin Deming, MD †
University of Wisconsin Carbone Cancer Center

Linda Farkas, MD ¶
UT Southwestern Simmons
Comprehensive Cancer Center

Ignacio Garrido-Laguna, MD, PhD †
Huntsman Cancer Institute
at the University of Utah

Jean L. Grem, MD †
Fred & Pamela Buffett Cancer Center

Andrew Gunn, MD ☐
O'Neal Comprehensive Cancer Center at UAB

J. Randolph Hecht, MD †
UCLA Jonsson Comprehensive Cancer Center

Sarah Hoffe, MD §
Moffitt Cancer Center

Joleen Hubbard, MD † ‡
Mayo Clinic Cancer Center

Steven Hunt, MD ¶
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

William Jeck, MD ≠
Duke Cancer Institute

Kimberly L. Johung, MD, PhD §
Yale Cancer Center/Smilow Cancer Hospital

Natalie Kirilcuk, MD ¶
Stanford Cancer Institute

Smitha Krishnamurthi, MD † ☐
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center
and Cleveland Clinic Taussig Cancer Institute

Wells A. Messersmith, MD †
University of Colorado Cancer Center

***Jeffrey Meyerhardt, MD, MPH †**
Dana-Farber Brigham and Women's
Cancer Center

***Eric D. Miller, MD, PhD §**
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Mary F. Mulcahy, MD ‡ †
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Steven Nurkin, MD, MS ¶
Roswell Park Comprehensive Cancer Center

Michael J. Overman, MD † ‡
The University of Texas
MD Anderson Cancer Center

Aparna Parikh, MD †
Massachusetts General Hospital Cancer Center

Hitendra Patel, MD †
UC San Diego Moores Cancer Center

Katrina Pedersen, MD, MS †
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Elizabeth Raskin, MD ¶
UC Davis Comprehensive Cancer Center

***Leonard Saltz, MD † ‡ ☐**
Memorial Sloan Kettering Cancer Center

Charles Schneider, MD †
Abramson Cancer Center
at the University of Pennsylvania

David Shibata, MD ¶
The University of Tennessee
Health Science Center

John M. Skibber, MD ¶
The University of Texas
MD Anderson Cancer Center

***Constantinos T. Sofocleous, MD, PhD ☐**
Memorial Sloan Kettering Cancer Center

Elena M. Stoffel, MD, MPH ≠
University of Michigan Rogel Cancer Center

Eden Stotsky-Himelfarb, BSN, RN † ¶ ≠
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

***Christopher G. Willett, MD §**
Duke Cancer Institute

NCCN
Kristina Gregory, RN, MSN
Lisa Gurski, PhD

☐ Diagnostic/Interventional radiology	≠ Pathology
≠ Gastroenterology	≠ Patient advocacy
‡ Hematology/Hematology oncology	§ Radiotherapy/Radiation oncology
☐ Internal medicine	¶ Surgery/Surgical oncology
† Medical oncology	* Discussion Section Writing Committee

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- [Sessile Polyp \(Adenoma\) with Invasive Cancer \(COL-1\)](#)
- [Colon Cancer Appropriate for Resection \(COL-2\)](#)
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[Principles of Adjuvant Therapy \(COL-G\)](#)

[Principles of Survivorship \(COL-H\)](#)

[Staging \(ST-1\)](#)

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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<https://www.nccn.org/home/member-institutions>.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2022.



Updates in Version 1.2022 of the NCCN Guidelines for Colon Cancer from Version 3.2021 include:

General -- FOLFOXIRI replaced with FOLFIRINOX

[COL-2](#)

• Clinical T4b

- ▶ The following option added: ([Nivolumab ± ipilimumab] or pembrolizumab) (dMMR/MSI-H only)

[COL-4](#)

• Workup

- ▶ Bullet 5 modified: NGS Panel clarified as tissue- or blood-based (also applies to footnote w) (also added to footnote kk on COL-9)

[COL-5](#)

• Treatment

- ▶ Resection noted as preferred and local therapy added as an additional or alternate option to resection.

[COL-6](#)

• Re-evaluate for conversion to resectable

▶ Converted to resectable

- ◊ Resection noted as preferred and local therapy added as an additional or alternate option to resection. (also applies to COL-11)
- ◊ Footnote z added: Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (COL-C and COL-E). (also applies to COL-11)

▶ Remains unresectable

- ◊ Systemic therapy *and consider local therapy for select patients* (also applies to COL-11)
- ◊ Footnote y added: Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

- Footnote ee modified: *Cetuximab or panitumumab should only be used for left-sided tumors.* The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab in first-line therapy for metastatic disease. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking. (also applies to footnote g on COL-D 7 of 13; footnote added to COL-11)

[COL-8](#)

- Timing of Chest/abdominal/pelvic CT clarified with addition of “from date of surgery”

[Principles of Imaging](#)

[COL-A 2 of 2](#)

• Stage IV disease

- ▶ Sub-bullet 2 modified: PET/CT can be considered for assessment of response and liver recurrence after image-guided liver-directed therapies (ie, ablation, radioembolization) *or serial CEA elevation during follow-up*

[Principles of Pathologic and Molecular Review](#)

[COL-B 4 of 8](#)

• Methods for Testing added

- ▶ Bullet moved from under *KRAS, NRAS, BRAF* Mutation Testing: The testing can be performed on formalin-fixed paraffin-embedded tissue (preferred) *or blood-based assay.*

[COL-B 5 of 8](#)

• *NTRK* Fusions

- ▶ Bullet 1 modified: ~~These data support limiting the subpopulation of colorectal cancers that should be tested for *NTRK* fusions to those with wild-type *KRAS*, *NRAS*, *BRAF*, and arguably to those that are MMR deficient (dMMR)/MSI-H~~ *NTRK fusions are more frequently found among patients with dMMR.*



Updates in Version 1.2022 of the NCCN Guidelines for Colon Cancer from Version 3.2021 include:

Systemic Therapy for Advanced or Metastatic Disease

COL-D 1 of 13

- ~~Patient appropriate for Intensive therapy recommended~~
 - Footnote d added to all FOLFOX, CAPEOX, and FOLFIRINOX regimens (applies to COL-D 2 of 13 through COL-D 6 of 13)
- ~~Patient NOT appropriate for Intensive therapy NOT recommended~~
 - The following Initial Therapy options removed: Fam-trastuzumab deruxtecan-nxki (HER2-amplified and *RAS* and *BRAF* WT)
- Cetuximab or panitumumab: restriction for left-sided tumors extended throughout all guideline settings. Qualification on this page as it is addressed in footnote g and COL-D 8 of 13 through COL-D 11 of 13

COL-D 2 of 13

- Subsequent Therapy
 - Footnote g added to all anti-EGFR based regimens (applies to COL-D 3 of 13 through COL-D 6 of 13)

COL-D 7 of 13

- Footnote d added: Discontinuation of oxaliplatin should be strongly considered after 3 to 4 months of therapy (or sooner for unacceptable neurotoxicity) while maintaining other agents until time of progression. Oxaliplatin may be reintroduced if it was discontinued for neurotoxicity rather than for disease progression.

COL-D 8 of 13

- Cetuximab every 2 week dosing noted as preferred (also applies to COL-D 9 of 13, COL-D 10 of 13)

COL-D 9 of 13

- Dosing added for FOLFIRINOX and modified FOLFIRINOX (references added to COL-D 12 of 13)
- Footnote ee added: FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of fluorouracil (3,200 mg/m² over 48 hours). Patients in the United States (U.S.) have been shown to have greater toxicity with fluorouracil. The dose of fluorouracil (2,400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.

Principles of Radiation and Chemoradiation Therapy

COL-E 1 of 2

- Treatment Information
 - ~~Bullet 1 modified: If radiation therapy is to be used, conformal external beam radiation should be routinely used and IMRT should be reserved only if preferred~~ for unique clinical situations such as reirradiation of previously treated patients with recurrent disease ~~and or~~ unique anatomical situations where IMRT facilitates the delivery of recommended target volume doses while respecting accepted normal tissue dose-volume constraints (eg, coverage of external iliac or inguinal lymph nodes or avoidance of small bowel).
- Target Volumes
 - Sub-bullet 2
 - ◊ Diamond 1 modified: Consider boost for close or positive margins *or unresectable* cases after evaluating the cumulative dose to adjacent organs at risk.
 - ◊ Diamond 2 modified: Small bowel dose should be limited to 4550 Gy.
 - Sub-bullet removed: If IORT is not available, additional 10–20 Gy external beam radiation therapy and/or brachytherapy could be considered to a limited volume.

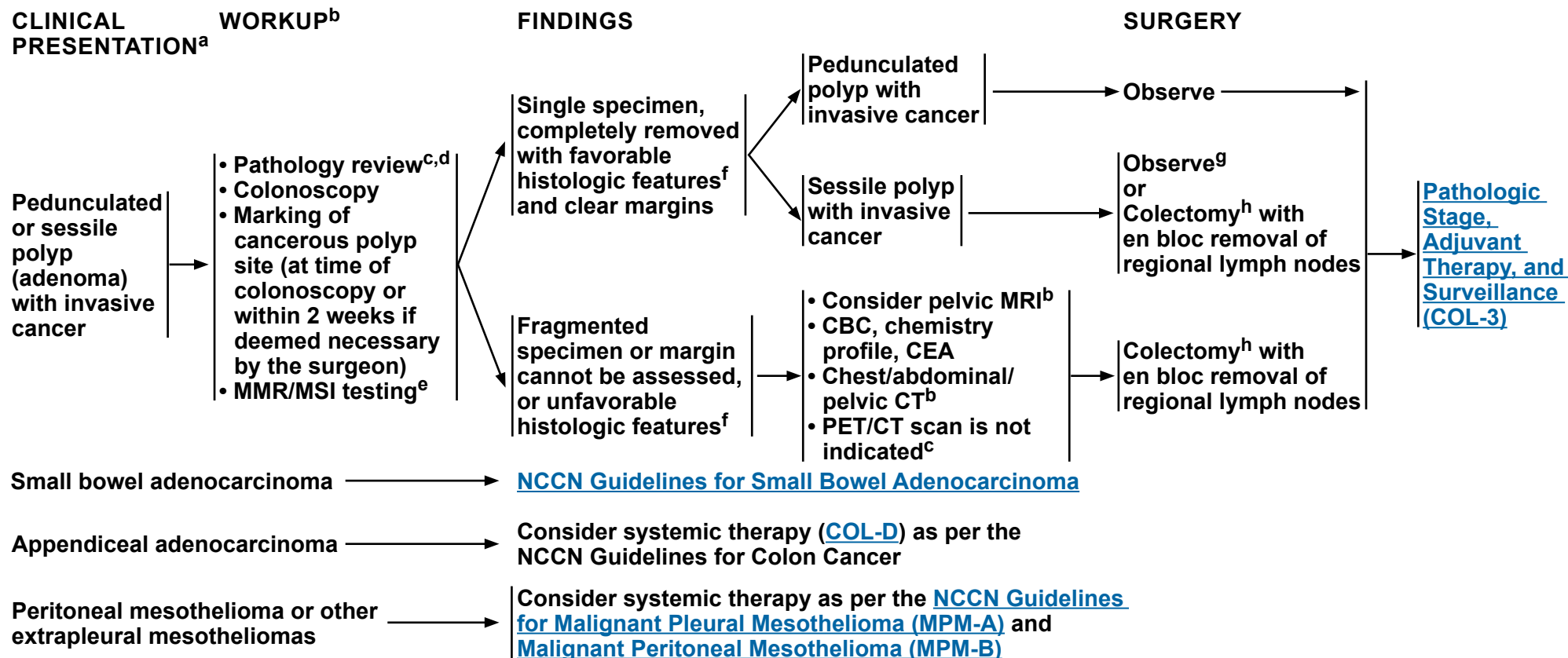
COL-E 2 of 2

- Supportive Care
 - Terminologies modified to be more inclusive of all sexual and gender identities.
 - Bullet 2 added: Patients of child bearing potential should be counseled about the effects of premature menopause and consideration should be given to referral for discussion of hormone replacement strategies.
 - Bullet 3 added: Patients of child bearing potential should be counseled that an irradiated uterus cannot carry a fetus to term.
 - Bullet 4 modified: Patients should be counseled on sexual dysfunction, *potential for future low testosterone levels*, and infertility risks and given information regarding sperm banking *or oocyte, egg, or ovarian tissue banking, as appropriate, prior to treatment*.



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^a All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP, see the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

^b [Principles of Imaging \(COL-A\)](#).

^c Confirm the presence of invasive cancer (pT1). pTis has no biological potential to metastasize.

^d It has not been established if molecular markers are useful in treatment determination (predictive markers) and prognosis. College of American Pathologists Consensus Statement 1999. Prognostic factors in colorectal cancer. Arch Pathol Lab Med 2000;124:979-994.

^e [Principles of Pathologic Review \(COL-B 4 of 8\)](#) - MSI or MMR Testing.

^f [Principles of Pathologic Review \(COL-B\)](#) - Endoscopically removed malignant polyp.

^g Observation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, hematogenous metastasis, but not lymph node metastasis) than polypoid malignant polyps. [Principles of Pathologic Review \(COL-B\)](#) - Endoscopically removed malignant polyp.

^h [Principles of Surgery \(COL-C 1 of 3\)](#).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

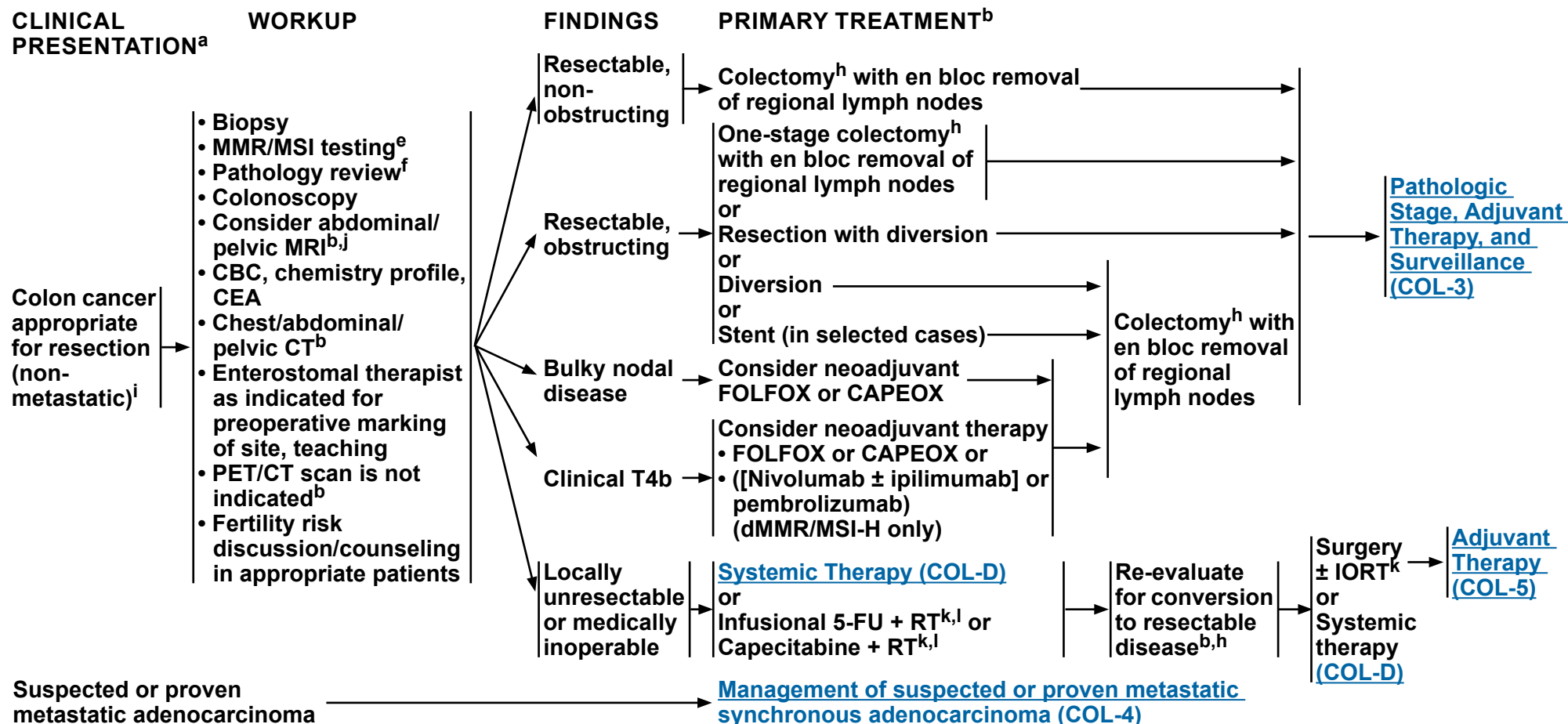


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^a All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected Lynch syndrome, FAP, and attenuated FAP, see the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

^b [Principles of Imaging \(COL-A\)](#).

^e [Principles of Pathologic Review \(COL-B 4 of 8\)](#) - MSI or MMR Testing.

^f [Principles of Pathologic Review \(COL-B\)](#) - Colon cancer appropriate for resection, pathologic stage, and lymph node evaluation.

^h [Principles of Surgery \(COL-C 1 of 3\)](#).

ⁱ For tools to aid optimal assessment and management of older adults with cancer, see the [NCCN Guidelines for Older Adult Oncology](#).

^j Consider an MRI to assist with the diagnosis of rectal cancer versus colon cancer (eg, low-lying sigmoid tumor). The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.

^k [Principles of Radiation and Chemoradiation Therapy \(COL-E\)](#).

^l Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

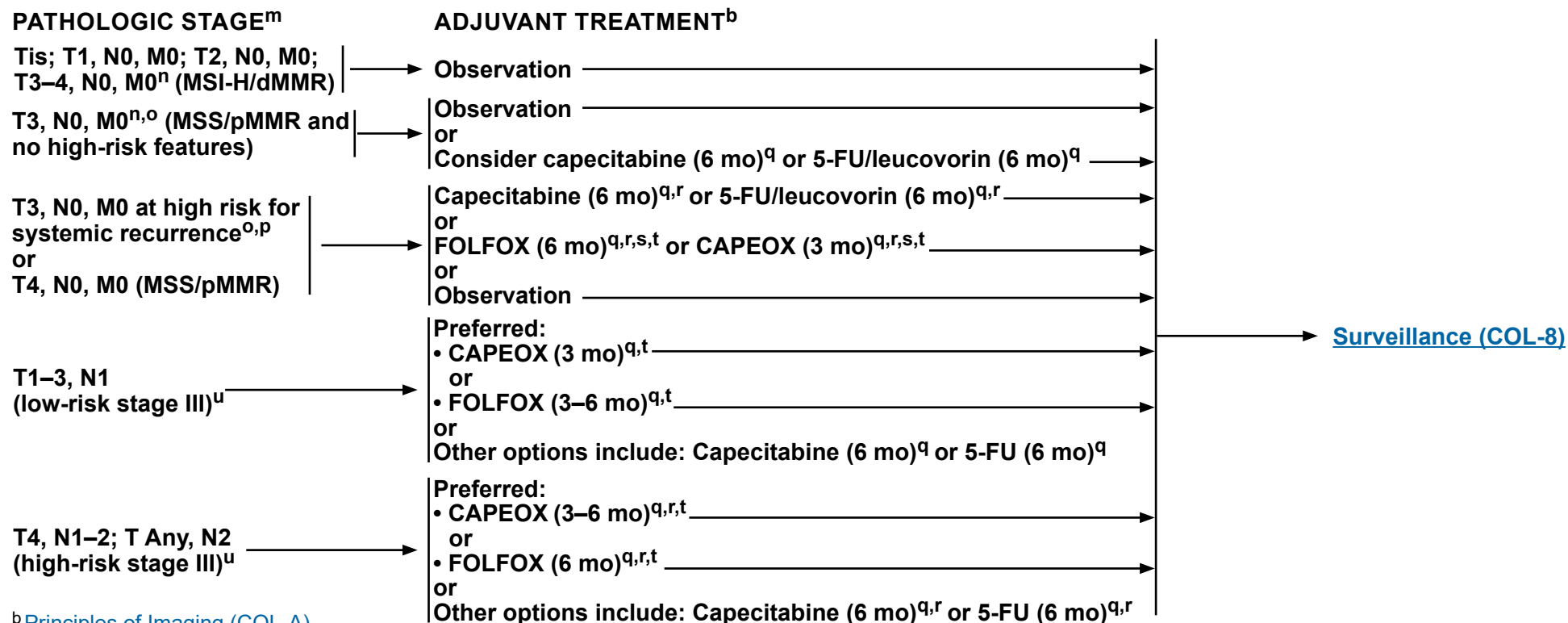
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^b [Principles of Imaging \(COL-A\)](#).^m [Principles of Pathologic Review \(COL-B\)](#).ⁿ [Principles of Risk Assessment for Stage II Disease \(COL-F\)](#).^o High-risk factors for recurrence (exclusive of those cancers that are microsatellite instability-high [MSI-H]): poorly differentiated/undifferentiated histology, lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, positive margins, or tumor budding. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.^p There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.^q [Principles of Adjuvant Therapy \(COL-G\)](#).^r Consider RT for T4 with penetration to a fixed structure.^r [Principles of Radiation and Chemoradiation Therapy \(COL-E\)](#).^s A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. Tournigand C, et al. J Clin Oncol 2012; 30:3353-3360.^t A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged 70 years and older has not been proven.^u While non-inferiority of 3 mo vs. 6 mo of CAPEOX has not been proven, 3 mo of CAPEOX numerically appeared similar to 6 mo of CAPEOX for 5-year overall survival (82.1% vs. 81.2%; HR, 0.96), with considerably less toxicity. (Andre T, et al. Lancet Oncol 2020;21:1620-1629). These results support the use of 3 mo of adjuvant CAPEOX over 6 mo in the vast majority of patients with stage III colon cancer. In patients with colon cancer, staged as T1–3, N1 (low-risk stage III), 3 mo of CAPEOX is non-inferior to 6 mo for disease-free survival; non-inferiority of 3 mo vs. 6 mo of FOLFOX has not been proven. In patients with colon cancer staged as T4, N1–2 or T any, N2 (high-risk stage III), 3 mo of FOLFOX is inferior to 6 mo for disease-free survival, whereas non-inferiority of 3 mo vs. 6 mo of CAPEOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 mo vs. 6 mo of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CAPEOX). Grothey A, et al. N Engl J Med 2018;378:1177-1188.**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



CLINICAL PRESENTATION

WORKUP

FINDINGS

Suspected or
proven metastatic
synchronous
adenocarcinoma
(any T, any N, M1)

- Colonoscopy
- Chest/abdominal/pelvic CT^b
- CBC, chemistry profile
- CEA
- Determination of tumor gene status for *RAS* and *BRAF* mutations and *HER2* amplifications (individually or as part of tissue- or blood-based next-generation sequencing [NGS] panel)^{v,w}
- Determination of tumor mismatch repair (MMR) or microsatellite instability (MSI) status^e (if not previously done)
- Biopsy, if clinically indicated
- Consider PET/CT scan (skull base to mid-thigh) if potentially surgically curable M1 disease in selected cases^b
 - ▶ Consider MRI of liver for liver metastases that are potentially resectable^b
- If potentially resectable, then multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary or lung metastases

Synchronous
liver only and/or
lung only
metastases

Resectable^h

[Treatment
and Adjuvant
Therapy \(COL-5\)](#)

Unresectable
(potentially
convertible^h or
unconvertible)

[Treatment
and Adjuvant
Therapy \(COL-6\)](#)

Synchronous
abdominal/peritoneal
metastases

[Primary Treatment
\(COL-7\)](#)

Synchronous
unresectable metastases
of other sites^x

[Systemic Therapy
\(COL-D\)](#)

^b [Principles of Imaging \(COL-A\)](#).

^e [Principles of Pathologic Review \(COL-B 4 of 8\)](#) - MSI or MMR Testing.

^h [Principles of Surgery \(COL-C 2 of 3\)](#).

^v [Principles of Pathologic Review \(COL-B 4 of 8\)](#) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing.

^w If known *RAS*/*RAF* mutation, *HER2* testing is not indicated. Tissue- or blood-based NGS panels have the ability to pick up rare and actionable mutations and fusions.

^x Consider colon resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

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TREATMENT

Resectable^h synchronous liver and/or lung metastases only

ADJUVANT TREATMENT^b (UP TO 6 MO PERIOPERATIVE TREATMENT) (resected metastatic disease)

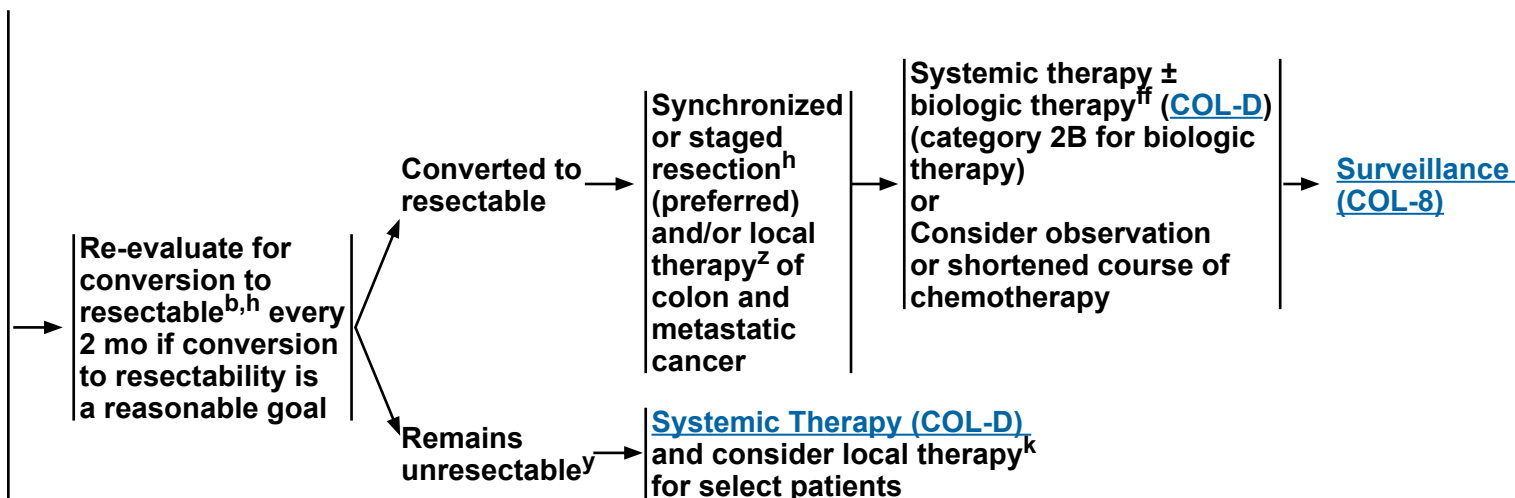
Synchronous or staged colectomy^y with liver or lung resection (preferred) and/or local therapy^z or
 Neoadjuvant therapy (for 2–3 mo) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFIRINOX (category 2B) followed by synchronous or staged colectomy^y and resection (preferred) and/or local therapy^z of metastatic disease or
 Colectomy,^y followed by chemotherapy (for 2–3 mo) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFIRINOX (category 2B) and staged resection (preferred) and/or local therapy^z of metastatic disease or
 Consider ([Nivolumab ± ipilimumab] or pembrolizumab [preferred]) (dMMR/MSI-H only)^{aa} followed by synchronous or staged colectomy^y and resection (preferred) and/or local therapy^z of metastatic disease

FOLFOX (preferred) or CAPEOX (preferred)
or
Capecitabine or 5-FU/leucovorin

[Surveillance \(COL-8\)](#)[Surveillance \(COL-8\)](#)^b [Principles of Imaging \(COL-A\)](#).^h [Principles of Surgery \(COL-C 2 of 3\)](#).^y Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.^z Resection is preferred over locally ablative procedures (eg, image-guided ablation or stereotactic body radiation therapy [SBRT]). However, these local techniques can be considered for liver or lung oligometastases ([COL-C](#) and [COL-E](#)).^{aa} Data are limited and the risk of early progression may be higher than with chemotherapy. Andre T, et al. N Engl J Med 2020;383:2207-2218.**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

**TREATMENT**
Unresectable^h synchronous liver
and/or lung metastases only

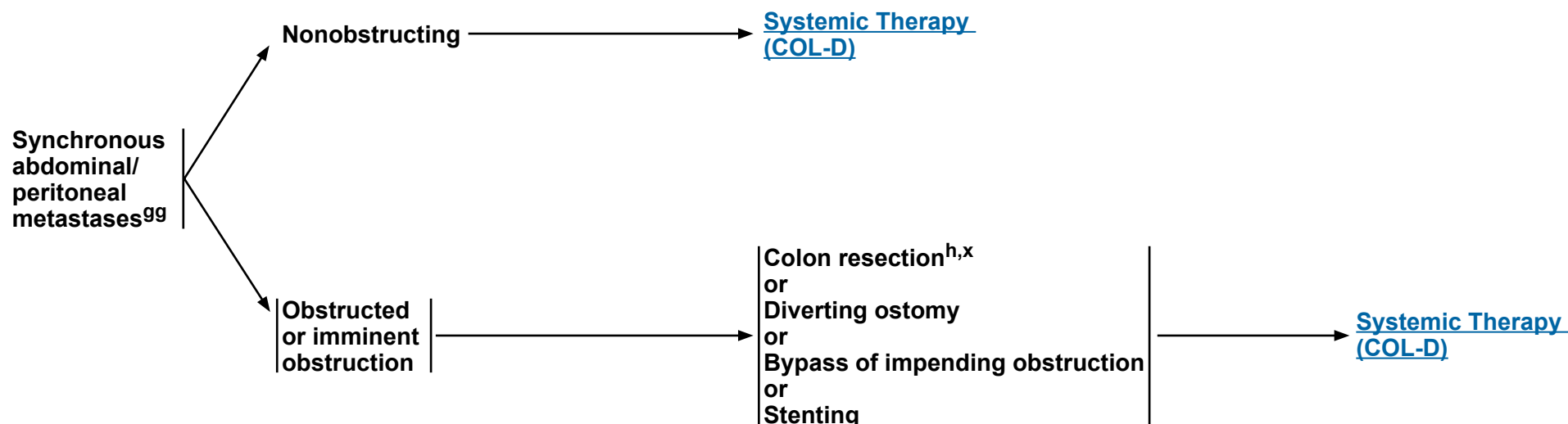
- **Systemic therapy**
 - FOLFIRI or FOLFOX or CAPEOX or FOLFIRINOX ± bevacizumab^{bb,cc} or
 - FOLFIRI or FOLFOX or FOLFIRINOX ± panitumumab or cetuximab^{dd} (category 2B for FOLFIRINOX combination) (*KRAS/NRAS/BRAF* WT gene only)^{v,ee} or
 - ([Nivolumab ± ipilimumab] or pembrolizumab [preferred]) (dMMR/MSI-H only)^{aa}
- **Consider colon resection^h only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms**

^b [Principles of Imaging \(COL-A\)](#).^h [Principles of Surgery \(COL-C 2 of 3\)](#).^k [Principles of Radiation and Chemoradiation Therapy \(COL-E\)](#).^v [Principles of Pathologic Review \(COL-B 4 of 8\)](#) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing.^y Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.^z Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases ([COL-C](#) and [COL-E](#)).^{aa} Data are limited and the risk of early progression may be higher than with chemotherapy. Andre T, et al. *N Engl J Med* 2020;383:2207-2218.^{bb} There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery and re-initiation of bevacizumab at least 6 to 8 weeks postoperatively. There is an increased risk of stroke and other arterial events, especially in those aged 65 years or older. The use of bevacizumab may interfere with wound healing.^{cc} An FDA-approved biosimilar is an appropriate substitute for bevacizumab.^{dd} There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.^{ee} Cetuximab or panitumumab should only be used for left-sided tumors. The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.^{ff} Biologic therapy is only appropriate for continuation of favorable response from conversion therapy.**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



FINDINGS

PRIMARY TREATMENT



^h [Principles of Surgery \(COL-C 2 of 3\)](#).

^x Consider colon resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

^{gg} Complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for select patients with limited peritoneal metastases for whom R0 resection can be achieved.

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PATHOLOGIC STAGE	SURVEILLANCE ^b		
Stage I →	Colonoscopy ^a at 1 y after surgery • If advanced adenoma, repeat in 1 y • If no advanced adenoma, ^{hh} repeat in 3 y, then every 5 y ⁱⁱ	Serial CEA elevation or documented recurrence → Workup and Treatment (COL-9)	
Stage II, III →	• History and physical examination every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • CEA ^{jj} every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • Chest/abdominal/pelvic CT every 6–12 mo (category 2B for frequency <12 mo) from date of surgery for a total of 5 y • Colonoscopy ^a in 1 y after surgery except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo ▶ If advanced adenoma, repeat in 1 y ▶ If no advanced adenoma, ^{hh} repeat in 3 y, then every 5 y ⁱⁱ • PET/CT scan is not indicated • Principles of Survivorship (COL-H)		
Stage IV →	• History and physical examination every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • CEA ^{jj} every 3–6 mo x 2 y, then every 6 mo for a total of 5 y • Chest/abdominal/pelvic CT scan every 3–6 mo (category 2B for frequency <6 mo) x 2 y, then every 6–12 mo for a total of 5 y • Colonoscopy ^a in 1 y after surgery except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo ▶ If advanced adenoma, repeat in 1 y ▶ If no advanced adenoma, ^{hh} repeat in 3 y, then every 5 y ⁱⁱ • Principles of Survivorship (COL-H)		

^a All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected Lynch syndrome, FAP, and attenuated FAP, see the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

^b [Principles of Imaging \(COL-A\)](#).

^{hh} Villous polyp, polyp >1 cm, or high-grade dysplasia.

ⁱⁱ Kahi CJ, et al. Gastroenterology 2016;150:758-768.

^{jj} If patient is a potential candidate for further intervention.

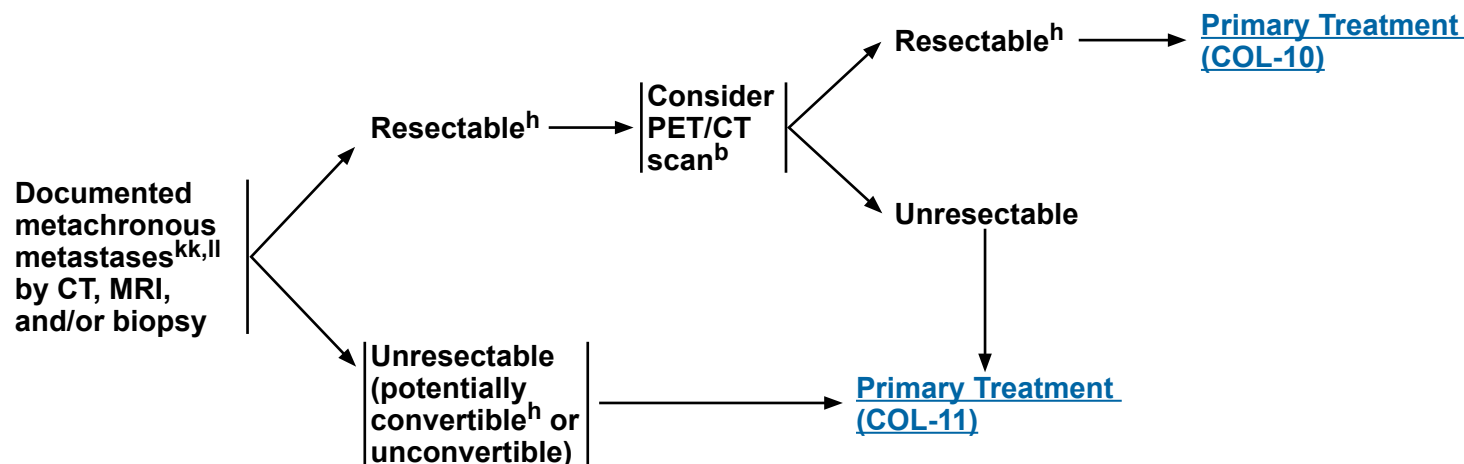
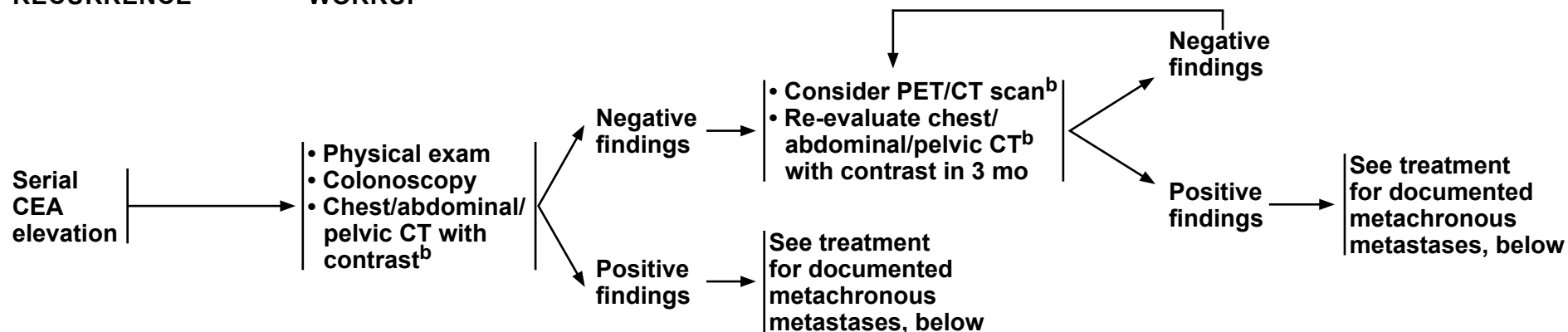
Note: All recommendations are category 2A unless otherwise indicated.

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RECURRENCE

WORKUP



^b [Principles of Imaging \(COL-A\)](#).

^h [Principles of Surgery \(COL-C 2 of 3\)](#).

^{kk} Determination of tumor gene status for *RAS* and *BRAF* mutations and *HER2* amplifications (individually or as part of tissue- or blood-based NGS panel). If known *RAS*/*RAF* mutation, *HER2* testing is not indicated. Determination of tumor MMR or MSI status (if not previously done). [Principles of Pathologic Review \(COL-B 4 of 8\)](#) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing. NGS panels have the ability to pick up rare and actionable mutations and fusions.

^{ll} Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.

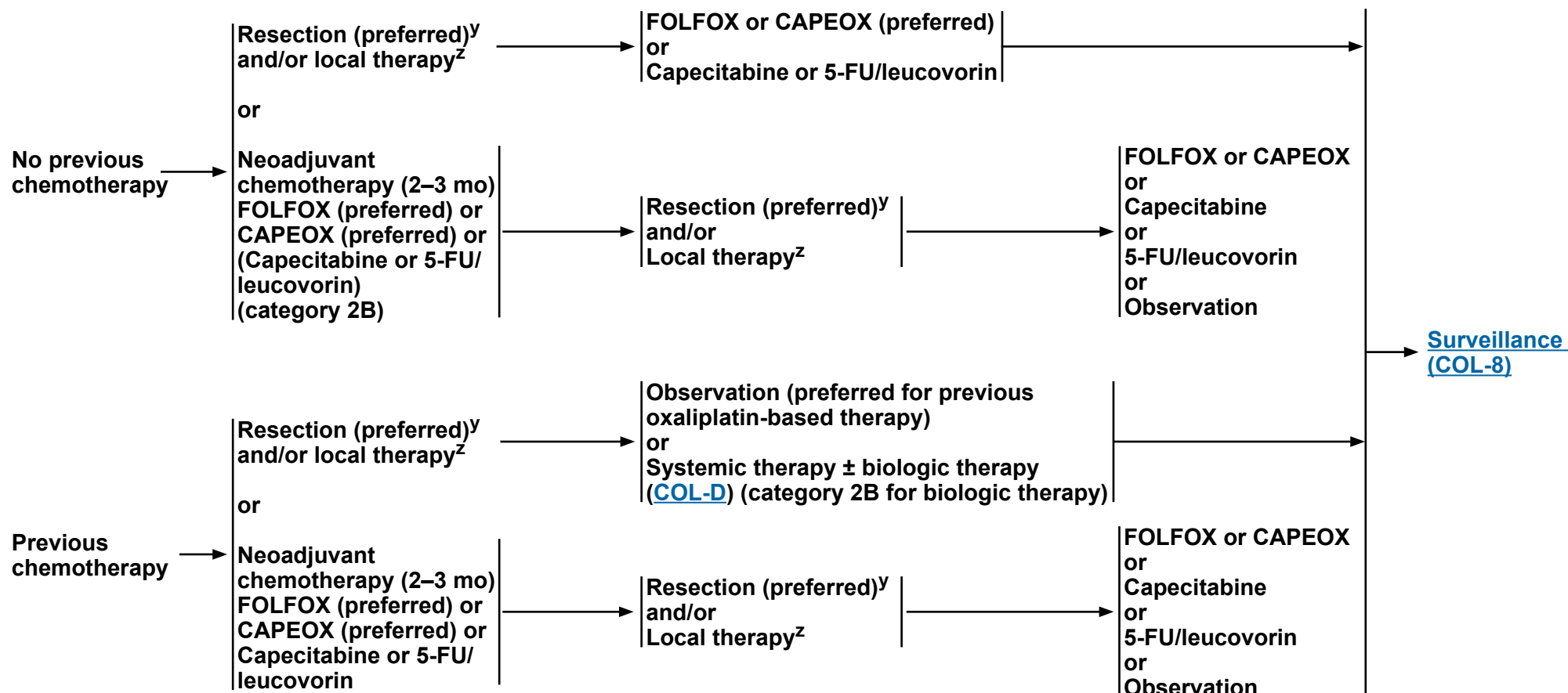
Note: All recommendations are category 2A unless otherwise indicated.

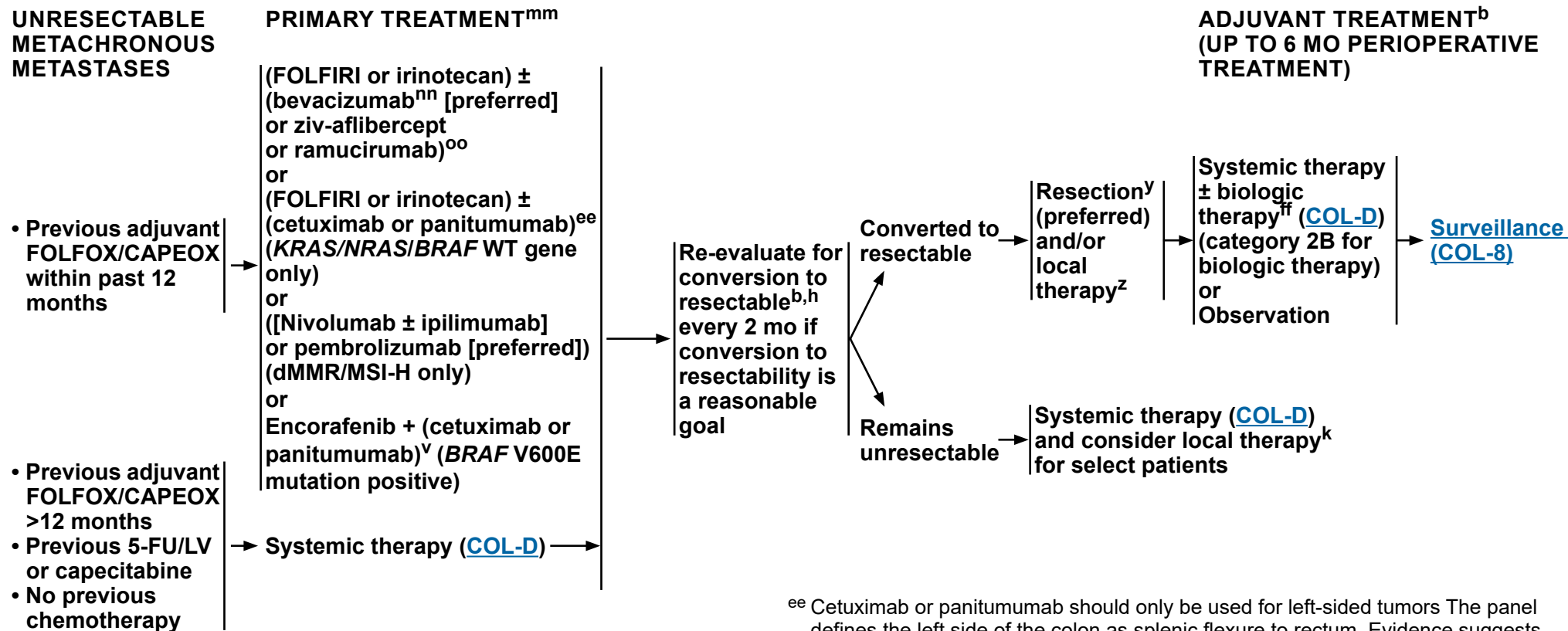
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NCCN Guidelines Version 1.2022

Colon Cancer

**RESECTABLE
METACHRONOUS
METASTASES****PRIMARY TREATMENT****ADJUVANT TREATMENT^b (UP TO 6 MO PERIOPERATIVE TREATMENT)**^b [Principles of Imaging \(COL-A\)](#).^y Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.^z Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases ([COL-C](#) and [COL-E](#)).**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

^b [Principles of Imaging \(COL-A\)](#).^h [Principles of Surgery \(COL-C 2 of 3\)](#).^k [Principles of Radiation and Chemoradiation Therapy \(COL-E\)](#).^v [Principles of Pathologic Review \(COL-B 4 of 8\)](#) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing.^y Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.^z Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases ([COL-C](#) and [COL-E](#)).^{ee} Cetuximab or panitumumab should only be used for left-sided tumors. The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.^{ff} Biologic therapy is only appropriate for continuation of favorable response from conversion therapy.^{mm} For infection risk, monitoring, and prophylaxis recommendations for targeted therapies, see INF-A in the [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#).ⁿⁿ An FDA-approved biosimilar is an appropriate substitute for bevacizumab.^{oo} Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



PRINCIPLES OF IMAGING¹⁻³

Initial Workup/Staging

- Chest, abdomen, and pelvic CT
 - ▶ Evaluate local extent of tumor or infiltration into surrounding structures.
 - ▶ Assess for distant metastatic disease to lungs, thoracic and abdominal lymph nodes, liver, peritoneal cavity, and other organs.
 - ▶ CT should be performed with intravenous iodinated contrast and oral contrast material unless contraindicated.
 - ▶ Intravenous contrast is not required for the chest CT (but usually given if performed with abdominal CT scan).
 - ▶ If IV iodinated contrast material is contraindicated because of significant contrast allergy, then MR examination of the abdomen and pelvis with IV gadolinium-based contrast agent (GBCA) can be obtained instead. In patients with chronic renal failure (glomerular filtration rate [GFR] <30 mL/min) who are not on dialysis, IV iodinated contrast material is also contraindicated, and IV GBCA can be administered in select cases using gadofosveset trisodium, gadoxetate disodium, gadobenate dimeglumine, or gadoteridol.
 - ▶ If iodinated and gadolinium contrast are both contraindicated due to significant allergy or chronic renal failure without dialysis, then consider MR without IV contrast or consider PET/CT imaging.
- Consider an abdominal/pelvic MRI to assist with the diagnosis of rectal cancer versus colon cancer (eg, low-lying sigmoid tumor). The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.
- Consider MRI of liver for liver metastases if potentially resectable.
- PET/CT is not routinely indicated.
 - ▶ PET/CT does not supplant a contrast-enhanced diagnostic CT or MR and should only be used to evaluate an equivocal finding on a contrast-enhanced CT or MR scan or in patients with strong contraindications to IV contrast administration.
 - ▶ Consider PET/CT (skull base to mid-thigh)
 - ◊ If potentially surgically curable M1 disease in selected cases.
 - ◊ In selected patients considered for image-guided liver-directed therapies (ie, ablation, radioembolization).⁴⁻⁸
- If liver-directed therapy or surgery is contemplated, a hepatic MRI with intravenous routine extracellular or hepatobiliary GBCA is preferred over CT to assess exact number and distribution of metastatic foci for local treatment planning.

Monitoring

- Chest, abdomen, and pelvic CT with contrast
 - ▶ Prior to adjuvant treatment to assess response to primary therapy or resection
 - ▶ During re-evaluation of conversion to resectable disease
- PET/CT can be considered for assessment of response and liver recurrence after image-guided liver-directed therapies (ie, ablation, radioembolization)

[Continued](#)

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PRINCIPLES OF IMAGING¹⁻³

Surveillance

- **Stage I disease**
 - ▶ **Imaging is not routinely indicated and should only be based on symptoms and clinical concern for recurrent/metastatic disease.**
- **Stage II & III disease**
 - ▶ **Chest, abdomen, and pelvic CT every 6 to 12 months (category 2B for frequency <12 months) for a total of 5 years.**
 - ▶ **PET/CT is not indicated.**
- **Stage IV disease**
 - ▶ **Chest, abdomen, and pelvic CT every 3 to 6 months (category 2B for frequency <6 months) x 2 years, then every 6 to 12 months for a total of 5 years.**
 - ▶ **PET/CT can be considered for assessment of response and liver recurrence after image-guided liver-directed therapies (ie, ablation, radioembolization) or serial CEA elevation during follow-up**

¹ Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* 2010;257:674-684.

² van Kessel CS, Buckens CF, van den Bosch MA, et al. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. *Ann Surg Oncol* 2012;19:2805-2813.

³ ACR Manual on Contrast Media v10.3 https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed May 25, 2017.

⁴ Mauri G, Gennaro N, De Beni S, et al. Real-time US- ¹⁸F-FDG-PET/CT image fusion for guidance of thermal ablation of ¹⁸F-FDG-PET-positive liver metastases: the added value of contrast enhancement. *Cardiovasc Intervent Radiol* 2019;42:60-68.

⁵ Sahin DA, Agcaoglu O, Chretien C, et al. The utility of PET/CT in the management of patients with colorectal liver metastases undergoing laparoscopic radiofrequency thermal ablation. *Ann Surg Oncol* 2012;19:850-855.

⁶ Shady W, Kishore S, Gavane S, et al. Metabolic tumor volume and total lesion glycolysis on FDG-PET/CT can predict overall survival after (90)Y radioembolization of colorectal liver metastases: a comparison with SUVmax, SUVpeak, and RECIST 1.0. *Eur J Radiol* 2016;85:1224-1231.

⁷ Shady W, Sotirchos VS, Do RK, et al. Surrogate imaging biomarkers of response of colorectal liver metastases after salvage radioembolization using 90Y-loaded resin microspheres. *AJR Am J Roentgenol* 2016;207:661-670.

⁸ Cornelis FH, Petre EN, Vakiani E, et al. Immediate postablation ¹⁸F-FDG injection and corresponding SUV are surrogate biomarkers of local tumor progression after thermal ablation of colorectal carcinoma liver metastases. *J Nucl Med* 2018;59:1360-1365.

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PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW

Endoscopically Removed Malignant Polyps

- A malignant polyp is defined as one with cancer invading through the muscularis mucosa and into the submucosa (pT1). pTis is not considered a “malignant polyp.”
- Favorable histologic features: grade 1 or 2, no angiolymphatic invasion, and negative margin of resection. There is no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as: 1) tumor <1 mm from the transected margin; 2) tumor <2 mm from the transected margin; and 3) tumor cells present within the diathermy of the transected margin.¹⁻⁴
- Unfavorable histologic features: grade 3 or 4, angiolymphatic invasion, or a “positive margin.” See the positive margin definition above. In several studies, tumor budding has been shown to be an adverse histologic feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.
- There is controversy as to whether malignant colorectal polyps with a sessile configuration can be successfully treated by endoscopic removal. The literature seems to indicate that endoscopically removed sessile malignant polyps have a significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than do pedunculated malignant polyps. However, when one closely looks at the data, configuration by itself is not a significant variable for adverse outcome, and endoscopically removed malignant sessile polyps with grade I or II histology, negative margins, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy.³⁻⁷

Colon Cancer Appropriate for Resection

- Histologic confirmation of primary colonic malignant neoplasm

Pathologic Stage

- The following parameters should be reported:
 - Grade of the cancer
 - Depth of penetration (T)
 - Number of lymph nodes evaluated and number positive (N)
 - Status of proximal, distal, radial, and mesenteric margins^{8,9} [See Staging \(ST-1\)](#)
 - Lymphovascular invasion^{10,11}
 - Perineural invasion (PNI)¹²⁻¹⁴
 - Tumor deposits¹⁵⁻¹⁸

[Pathologic Stage \(continued\) on COL-B \(2 of 8\)](#)

[Lymph Node Evaluation on COL-B \(3 of 8\)](#)

[KRAS, NRAS, and BRAF Mutation Testing on COL-B \(4 of 8\)](#)

[HER2-Testing and NTRK Fusions on COL-B \(5 of 8\)](#)

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[References](#)

**PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW****Pathologic Stage (continued)**

- **Radial (circumferential) margin evaluation** - The serosal surface (peritoneal) does not constitute a surgical margin. In colon cancer the circumferential (radial) margin represents the adventitial soft tissue closest to the deepest penetration of tumor, and is created surgically by blunt or sharp dissection of the retroperitoneal aspect. The radial margins should be assessed in all colonic segments with non-peritonealized surfaces. The circumferential resection margin corresponds to any aspect of the colon that is not covered by a serosal layer of mesothelial cells, and must be dissected from the retroperitoneum to remove the viscus. On pathologic examination it is difficult to appreciate the demarcation between a peritonealized surface and non-peritonealized surface. Therefore, the surgeon is encouraged to mark the area of non-peritonealized surface with a clip or suture. The mesenteric resection margin is the only relevant circumferential margin in segments completely encased by the peritoneum.^{10,11}
- **PNI** - The presence of PNI is associated with a significantly worse prognosis. In multivariate analysis, PNI has been shown to be an independent prognostic factor for cancer-specific, overall, and disease-free survival. For stage II carcinoma, those with PNI have a significantly worse 5-year disease-free survival compared to those without PNI (29% vs. 82%; $P = .0005$).¹²⁻¹⁴
- **Tumor deposits** - Irregular discrete tumor deposits in pericolic or perirectal fat away from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered peritumoral deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular invasion or, more rarely, PNI. Because these tumor deposits are associated with reduced disease-free and overall survival, their number should be recorded in the surgical pathology report. This poorer outcome has also been noted in patients with stage III carcinoma.¹⁵⁻¹⁸
- **Tumor budding** - In recent years, tumor budding has been identified as a new prognostic factor in colon cancer. Recently, there was an international consensus conference on tumor budding reporting.¹⁹ A tumor bud is defined as a single cell or a cluster of ≤ 4 cells detected by hematoxylin and eosin (H&E) at the advancing edge of the invasive carcinoma. The total number of buds should be reported from a selected hot spot measuring 0.785 mm (20x ocular in most microscopes/via a conversion factor). Budding is separated into three tiers: low tier (0–4 buds), intermediate tier (5–9 buds), and high tier (10 or more buds). Two recent studies^{20,21} using this scoring system have shown tumor budding to be an independent prognostic factor for stage II colon cancer. An ASCO guideline for stage II colon cancer designates tumor budding as an adverse (high-risk) factor.²² Several studies have shown that high-tier tumor budding in pT1 colorectal carcinomas, including malignant polyps, is associated with an increased risk of lymph node metastasis; however, methodologies for assessing tumor budding and tier were not uniform.²³⁻²⁷

[Endoscopically Removed Malignant Polyps and Colon Cancer Appropriate for Resection on COL-B \(1 of 8\)](#)**[Lymph Node Evaluation on COL-B \(3 of 8\)](#)****[KRAS, NRAS, and BRAF Mutation Testing on COL-B \(4 of 8\)](#)****[HER2 Testing and NTRK Fusions on COL-B \(5 of 8\)](#)****Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**[References](#)**

**PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW****Lymph Node Evaluation**

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately stage colon cancers.^{8,9,28} The literature lacks consensus as to what is the minimal number of lymph nodes to accurately identify stage II cancer. The minimal number of nodes has been reported as >7, >9, >13, >20, and >30.²⁹⁻³⁷ The number of lymph nodes retrieved can vary with patient age, gender, tumor grade, and tumor site.³⁰ For stage II (pN0) colon cancer, if fewer than 12 lymph nodes are initially identified, it is recommended that the pathologist go back to the specimen and resubmit more tissue of potential lymph nodes. If 12 lymph nodes are still not identified, a comment in the report should indicate that an extensive search for lymph nodes was undertaken. The pathologist should attempt to retrieve as many lymph nodes as possible. It has been shown that the number of negative lymph nodes is an independent prognostic factor for patients with stage IIIB and IIIC colon cancer.³⁸

Sentinel Lymph Node and Detection of Micrometastasis by Immunohistochemistry

- Examination of the lymph nodes (sentinel or routine) by intense histologic and/or immunohistochemical investigation helps to detect the presence of metastatic disease. The detection of single cells by immunohistochemistry (IHC) or by multiple H&E levels and/or clumps of tumor cells <0.2 mm are considered isolated tumor cells (pN0). The 8th edition of the AJCC Cancer Staging Manual and Handbook³⁹ defines clumps of tumor cells ≥0.2 mm but ≤2 mm in diameter or clusters of 10 to 20 tumor cells as micrometastasis and recommends that these micrometastases be considered as standard positive lymph nodes (pN+).
- At the present time the use of sentinel lymph nodes and detection of isolated tumor cells by IHC alone should be considered investigational, and results should be used with caution in clinical management decisions.⁴⁰⁻⁴⁹ Some studies have shown that the detection of IHC cytokeratin-positive cells in stage II (N0) colon cancer (defined by H&E) has a worse prognosis, while others have failed to show this survival difference. In some of these studies, what are presently defined as isolated tumor cells were considered to be micrometastases.⁴⁵⁻⁵⁰ A recent meta-analysis⁵¹ demonstrated that micrometastases (≥0.2 mm) are a significant poor prognostic factor. However, another recent multicenter prospective study of stage I or II disease (via H&E) had a 10% decrease in survival for IHC-detected isolated tumor cells, (<0.2 mm) but only in those with pT3–pT4 disease.⁵²

Endoscopically Removed Malignant Polyps and Colon Cancer Appropriate for Resection on COL-B (1 of 8)**Pathologic Stage on COL-B (2 of 8)****KRAS, NRAS, and BRAF Mutation Testing on COL-B (4 of 8)****HER2 Testing and NTRK Fusions on COL-B (5 of 8)**

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References

**PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW****Methods of Testing**

- The testing can be performed on formalin-fixed paraffin-embedded tissue (preferred) or blood-based assay.

KRAS, NRAS, and BRAF Mutation Testing

- All patients with metastatic colorectal cancer should have tumor genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of an NGS panel. Patients with any known *KRAS* mutation (exon 2, 3, 4) or *NRAS* mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab.⁵³⁻⁵⁵ *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a *BRAF* inhibitor.⁵⁶⁻⁵⁸
- *BRAF* V600E mutation testing via immunohistochemistry is also an option.
- Testing for *KRAS*, *NRAS*, and *BRAF* mutations should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform *high-complexity* clinical laboratory (molecular pathology) testing. No specific methodology is recommended (eg, sequencing, hybridization).
- The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS*, *NRAS*, and *BRAF* mutations are similar in both specimen types.⁵⁹

Microsatellite Instability or Mismatch Repair Testing

- Universal MMR^a or MSI^a testing is recommended in all newly diagnosed patients with colon cancer. [See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.](#)
- The presence of a *BRAF* V600E mutation in the setting of MLH1 absence would preclude the diagnosis of Lynch syndrome (LS) in the vast majority of cases. However, approximately 1% of cancers with *BRAF* V600E mutations (and loss of MLH1) are LS. Caution should be exercised in excluding cases with a strong family history from germline screening in the case of *BRAF* V600E mutations.⁶⁰
- Stage II MSI high (MSI-H) may have a good prognosis and do not benefit from 5-FU adjuvant therapy.⁶¹
- MMR or MSI testing should be performed only in CLIA-approved laboratories.
- Testing for MSI may be accomplished by polymerase chain reaction (PCR) or a validated NGS panel, the latter especially in patients with metastatic disease who require genotyping of *RAS* and *BRAF*.
- IHC refers to staining tumor tissue for protein expression of the four MMR genes known to be mutated in LS (MLH1, MSH2, MSH6, and PMS2). A normal IHC test implies that all four MMR proteins are normally expressed (retained). Loss (absence) of expression of one or more of the four DNA MMR proteins is often reported as abnormal or positive IHC. When IHC is reported as positive, caution should be taken to ensure that positive refers to absence of mismatch expression and not presence of expression. NOTE: Normal is the presence of positive protein staining (retained/intact) and abnormal is negative or loss of staining of protein. Loss of protein expression by IHC in any one of the MMR genes guides further genetic testing (mutation detection to the genes where the protein expression is not observed). Abnormal MLH1 IHC should be followed by tumor testing for *BRAF* V600E mutation or *MLH1* promoter methylation. The presence of *BRAF* V600E mutation or *MLH1* promoter methylation is consistent with sporadic cancer. However, caution should be exercised in excluding cases from germline screening based on *BRAF* V600E mutations in the setting of a strong family history.⁶⁰

HER2 Testing and NTRK Fusions on COL-B (5 of 8)

^a IHC for MMR and DNA analysis for MSI are different assays and measure different biological effects caused by deficient MMR function.

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References

**PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW****HER2 Testing**

- Diagnostic testing is via immunohistochemistry, fluorescence in situ hybridization (FISH), or NGS.
- Positive by immunohistochemistry is defined as: 3+ staining in more than 50% of tumor cells. 3+ staining is defined as an intense membrane staining that can be circumferential, basolateral, or lateral. Those that have a HER2 score of 2+ should be reflexed to FISH testing.⁶²⁻⁶⁴ HER2 amplification by FISH is considered positive when the HER2:CEP17 ratio is ≥ 2 in more than 50% of the cells.⁶²⁻⁶⁴ NGS is another methodology for testing for HER2 amplification.⁶⁵
- Anti-HER2 therapy is only indicated in HER2-amplified tumors that are also *RAS* and *BRAF* wild type.

NTRK Fusions

- *NTRK* fusions are extremely rare in colorectal carcinomas.⁶⁶ The overall incidence is approximately 0.35% in a cohort of 2314 colorectal carcinomas, with *NTRK* fusions confined to those tumors that are pan-wild type *KRAS*, *NRAS*, and *BRAF*. In one study of 8 colorectal cancers harboring *NTRK* fusions, 7 were found in the small subset that were dMMR (MLH-1)/MSI-H.⁶⁷ *NTRK* fusions are more frequently found among patients with dMMR.
- *NTRK* inhibitors have been shown to have activity **ONLY** in those cases with *NTRK* fusions, and **NOT** with *NTRK* point mutations.
- Methodologies for detecting *NTRK* fusions are IHC,⁶⁸ FISH, DNA-based NGS, and RNA-based NGS.^{66,69} In one study, DNA-based sequencing showed an overall sensitivity and specificity of 81.1% and 99.9%, respectively, for detection of *NTRK* fusions when compared to RNA-based sequencing and immunohistochemistry showed an overall sensitivity of 87.9% and specificity of 81.1%. Since approximately 1 in 5 tumors identified as having an *NTRK* fusion by IHC will be a false positive, tumors that test positive by IHC should be confirmed by RNA NGS. That same study commented that RNA-based sequencing appears to be the optimal way to approach *NTRK* fusions, because the splicing out of introns simplifies the technical requirements of adequate coverage and because detection of RNA-level fusions provides direct evidence of functional transcription.⁶⁹ However, selection of the appropriate assay for *NTRK* fusion detection depends on tumor type and genes involved, as well as consideration of other factors such as available material, accessibility of various clinical assays, and whether comprehensive genomic testing is needed concurrently.⁶⁹

[KRAS, NRAS, and BRAF Mutation Testing on COL-B \(4 of 8\)](#)

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References

**PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW – REFERENCES**

- ¹ Volk EE, Goldblum JR, Petras RE, et al. Management and outcome of patients with invasive carcinoma arising in colorectal polyps. *Gastroenterology* 1995;109:1801-1807.
- ² Cooper HS, Deppisch LM, Gourley WK, et al. Endoscopically removed malignant colorectal polyps: clinical pathological correlations. *Gastroenterology* 1995;108:1657-1665.
- ³ Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. *Gastroenterology* 2004;127:385-394.
- ⁴ Seitz U, Bohnacker S, Seewald S, et al. Is endoscopic polypectomy an adequate therapy for malignant colorectal polyps? Presentation of 114 patients and review of the literature. *Dis Colon Rectum* 2004;47:1789-1797.
- ⁵ Morson BC, Whiteway JE, Jones EA, et al. Histopathology and prognosis of malignant colorectal polyps treated by endoscopic polypectomy. *Gut* 1984;25:437-444.
- ⁶ Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 1985;89:328-336.
- ⁷ Netzer P, Binck J, Hammer B, et al. Significance of histological criteria for the management of patients with malignant colorectal polyps. *Scand J Gastroenterol* 1997;323:915-916.
- ⁸ Compton CC and Greene FL. The staging of colorectal cancer: 2004 and beyond. *Ca Cancer J Clin* 2004;54:295-308.
- ⁹ Compton CC, Fielding LP, Burgardt LJ, et al. Prognostic factors in colorectal cancer. College of American pathologists consensus statement. *Arch Pathol Lab Med* 2000;124:979-994.
- ¹⁰ Washington MK, Berlin J, Branton P, et al. Protocol for examination of specimens from patients with primary carcinoma of the colon and rectum. *Arch Pathol Lab Med* 2009;133:1539.
- ¹¹ Edge SB, Byrd D, Compton C, et al (eds). *AJCC Cancer Staging Manual* 7th Edition. Springer NY, 2010.
- ¹² Liebig C, Ayala G, Wilks J, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. *J Clin Oncol* 2009;27:5131-5137.
- ¹³ Fujita S, Shimoda T, Yoshimura K, et al. Prospective evaluation of prognostic factors in patients with colorectal cancer undergoing curative resection. *J Surg Oncol* 2003;84:127-131.
- ¹⁴ Quah HM. Identification of patients with high risk stage II colon cancer for adjuvant therapy. *Dis Colon Rect* 2008;51:53-507.
- ¹⁵ Goldstein NS and Turner JR. Percolonic tumor deposits in patients with T3N+M0: adenocarcinoma. *Cancer* 2000;88:2228-2238.
- ¹⁶ Ueno H, Mochizuki H, Hashiguchi Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. *J Clin Pathol* 2007;117:287-294.
- ¹⁷ Lo DS, Pollett A, Siu LL, et al. Prognostic significance of mesenteric tumor nodules in patients with stage III colorectal cancer. *Cancer* 2008;112:50-54.
- ¹⁸ Puppa G, Maisonneuve P, Sonzogni A, et al. Pathological assessment of pericolic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging. *Mod Pathol* 2007;20:843-855.
- ¹⁹ Lugli A, Kirsch R, Ajioka Y, et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. *Mod Pathol* 2017;30:1299-1311.
- ²⁰ Lee VWK, Chan KF. Tumor budding and poorly-differentiated cluster in prognostication in Stage II colon cancer. *Pathol Res Pract* 2018;214:402-407.
- ²¹ Romiti A, Roberto M, Marchetti P, et al. Study of histopathologic parameters to define the prognosis of stage II colon cancer. *Int J Colorectal Dis* 2019;34:905-913.
- ²² Costas-Chavarri A, Nandakumar G, Temin S, et al. Treatment of patients with early-stage colorectal cancer: ASCO Resource-Stratified Guideline. *J Glob Oncol* 2019;5:1-19.
- ²³ Koelzer VH, Zlobec I, Lugli A. Tumor budding in colorectal cancer – ready for diagnostic practice? *Hum Pathol* 2016;47:4-19.
- ²⁴ Bosch SL, Teerenstra S, de Wilt JH, et al. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. *Endoscopy* 2013;45:827-834.
- ²⁵ Brown IS, Bettington ML, Bettington A, et al. Adverse histological features in malignant colorectal polyps: a contemporary series of 239 cases. *J Clin Pathol* 2016;69:292-299.
- ²⁶ Backes Y, Elias SG, Groen JN, et al. Histologic factors associated with need for surgery in patients with pedunculated T1 colorectal carcinomas. *Gastroenterology* 2018;154:1647-1659.
- ²⁷ Pai RK, Chen YW, Jakubowski MA, et al. Colorectal carcinomas with submucosal invasion (pT1): analysis of histopathological and molecular factors predicting lymph node metastasis. *Mod Pathol* 2017;30:113-122.
- ²⁸ Sobin HL, and Greene FL. TNM classification. Clarification of number of regional lymph nodes for pN0. *Cancer* 2001;92:452.

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**PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW – REFERENCES**

- ²⁹ Le Voyer TE, Sigurdson ER, Hamlin AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol* 2003;21:2912-2919.
- ³⁰ Sarli L, Bader G, Lusco D, et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. *Eur J Cancer* 2005;41:272-279.
- ³¹ Swanson RS, Compton CC, Stewart AK, and Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. *Ann Surg Oncol* 2003;10:65-71.
- ³² Caplin S, Scerottini G-P, Bosman FT, Konstanda MT, Givel J-C. For patients with Duke's B (TNM stage II) colorectal carcinoma, examination of six or fewer lymph nodes is related to poor prognosis. *Cancer* 1998;83:666-672.
- ³³ Maurel J, Launoy G, Grosclaude P, et al. Lymph node harvest reporting in patients with carcinoma of the large bowel. A French population-based study. *Cancer* 1998;82:1482-1486.
- ³⁴ Pocard M, Panis Y, Malassagane B, et al. Assessing the effectiveness of mesorectal excision in rectal cancer. *Dis Colon Rectum* 1998;41:839-845.
- ³⁵ Joseph NE, Sigurdson ER, Hamlin AL, et al. Accuracy of determining nodal negativity in colorectal cancer on the basis of number of nodes retrieved on resection. *Ann of Surg Oncol* 2003;10:213-218.
- ³⁶ Goldstein NS. Lymph node recurrences from 2427 pT3 colorectal resection specimens spanning 45 years. Recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. *Am J Surg Pathol* 2002;26:179-189.
- ³⁷ Scott KWM and Grace RH. Detection of lymph node metastasis and colorectal carcinoma before and after fat clearance. *Br J Surg* 1989;76:1165-1167.
- ³⁸ Johnson PM, Porter GA, Ricciardi R and Baxter NN. Increasing negative lymph node count is independently associated with improved long term survival in stage IIIB and IIIC colon cancer. *J Clin Oncol* 2006;24:3570-3575.
- ³⁹ AJCC Cancer Staging Manual, 8th ed. Amin MB, Edge SB, Greene F, et al. (editors) Springer, New York, 2017.
- ⁴⁰ Turner RR, Nora DT, Trochas D, and Bilchik AJ. Colorectal carcinoma in nodal staging. Frequency and nature of cytokeratin positive cells in sentinel and nonsentinel lymph nodes. *Arch Pathol Lab Med* 2003;127:673-679.
- ⁴¹ Saha S, Van AG, Beutler T, et al. Sentinel lymph mapping techniques in colorectal cancer. *Sem Oncol* 2004;31:374-1381.
- ⁴² Wood TF, Nora DT, Morton DL, et al. One hundred consecutive cases of sentinel node mapping in early colorectal carcinoma. Detection of missed micrometastasis. *J Gastrointest Surg* 2002;6:322-330.
- ⁴³ Wiese DA, Sha S, Badin J, et al. Pathological evaluation of sentinel lymph nodes in colorectal carcinoma. *Arch Pathol Lab Med* 2000;124:1759-1763.
- ⁴⁴ Bertagnolli M, Miedema B, Redstone M, et al. Sentinel node staging of resectable colon cancer. Results of a multicenter study. *Ann Surg* 2004;240:624-630.
- ⁴⁵ Noura S, Yamamoto H, Ohnishi T, et al. Comparative detection of lymph node micrometastasis of stage II colorectal cancer by reverse transcriptase polymerase chain reaction in immunohistochemistry. *J Clin Oncol* 2002;20:4232-4241.
- ⁴⁶ Yasuda K, Adachi Y, Shiraishi N, et al. Pattern of lymph node micrometastasis and prognosis of patients with colorectal cancer. *Ann Surg Oncol* 2001;8:300-304.
- ⁴⁷ Noura S, Yamamoto H, Miyake Y, et al. Immunohistochemical assessment of localization of frequency of micrometastasis in lymph nodes of colorectal cancer. *Clin Cancer Research* 2002;8:759-767.
- ⁴⁸ Oberg A, Stenling R, Tavelin B, Lindmark G. Are lymph node micrometastasis of any clinical significance in Duke stages A and B colorectal cancer? *Dis Colon Rectum* 1998;41:1244-1249.
- ⁴⁹ Greenson JK, Isenhardt TCE, Rice R, et al. Identification of occult micrometastasis in pericolic lymph nodes of Duke's B colorectal cancer. Patient's using monoclonal antibodies against cytokeratin and CC49. Correlation with long term survival. *Cancer* 1994;73:563-569.
- ⁵⁰ Hermanek P, Hutter RVP, Sobin LH, Wittekind CH. Classification of isolated tumor cells and micrometastasis. *Cancer* 1999;86:2668-2673.
- ⁵¹ Sloothaak DA, Sahami S, van der Zaag-Loonen HJ, et al. The prognostic value of micrometastasis and isolated tumor cells in histologically negative lymph nodes of patients with colorectal cancer: a systematic review and meta-analysis. *Eur J Surg Oncol* 2014;40:263-269.
- ⁵² Protic M, Stojadinovic A, Nissam A, et al. Prognostic effect of ultra-staging node negative colon cancer without adjuvant therapy. A prospective National Cancer Institute-Sponsored Clinical Trial. *J Am Coll Surg* 2015;221:643-631.
- ⁵³ Lievre A, Bachatte J-B, Blige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with Cetuximab. *J Clin Oncol* 2008;26:374-379.

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7 OF 8

**PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW – REFERENCES**

- ⁵⁴ Amado IG, Wolf M, Peters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:1626-1634.
- ⁵⁵ Douillard JY, Oliner KS, Siena S, et al. Panitumumab--FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 2013;369:1023-1034.
- ⁵⁶ Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type *BRAF* is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 2008;26:5705-5712.
- ⁵⁷ Bokemeyer C, Cutsem EV, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials. *Eur J Cancer* 2012;48:1466-1475.
- ⁵⁸ Pietrantonio F, Petrelli F, Coinu A, et al. Predictive role of *BRAF* mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. *Eur J Cancer* 2015;51:587-594.
- ⁵⁹ Etienne-Gimeldi M-C, Formenta J-L, Francoual M, et al. KRAS mutations in treatment outcome in colorectal cancer in patients receiving exclusive fluoropyrimidine. *Clin Cancer Research* 2008;14:4830-4835.
- ⁶⁰ Parsons MT, Buchanan DD, Thompson B, et al. Correlation of tumor *BRAF* mutations and MLH-1 methylation with germline mismatch repair (MMR) gene mutation status: a literature review accessions utility of tumor features for MMR variant classification. *J Med Genet* 2012;49:151-157.
- ⁶¹ Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol* 2010;28:3219-3226.
- ⁶² Valtorta E, Martino C, Sartore-Bianchi A, et al. Assessment of a HER2 scoring system for colorectal cancer: results from a validation study. *Mod Pathol* 2015;28:1481-1491.
- ⁶³ Evaluation of Trastuzumab in Combination With Lapatinib or Pertuzumab in Combination With Trastuzumab-Emtansine to Treat Patients With HER2-positive Metastatic Colorectal Cancer (HERACLES). <https://clinicaltrials.gov/ct2/show/NCT03225937>
- ⁶⁴ Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2016;17:738-746.
- ⁶⁵ Cenaj O, Ligon AH, Hornick JL, et al. Detection of ERBB2 amplification by next-generation sequencing predicts HER2 expression in colorectal carcinoma. *Am J Clin Pathol* 2019;152:97-108.
- ⁶⁶ Solomon J, Hechtman JF. Detection of *NTRK* fusions: Merits and limitations of current diagnostic platforms. *Cancer Res* 2019;79:3163-3168.
- ⁶⁷ Cocco E, Benhamida J, Middha S, et al. Colorectal carcinomas containing hypermethylated MLH1 promotor and wild-type *BRAF/KRAS* are enriched for targetable kinase fusions. *Cancer Res* 2019;79:1047-1053.
- ⁶⁸ Hechtman JF, Benayed R, Hyman DM, et al. Pan-Trk immunohistochemistry is an efficient and reliable screen for the detection of *NTRK* fusions. *Am J Surg Pathol* 2017;41:1547-1551.
- ⁶⁹ Solomon JP, Linkov I, Rosado A, et al. *NTRK* fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. *Mod Pathol* 2020;33:38-46.

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PRINCIPLES OF SURGERY

Colectomy

- Lymphadenectomy

- ▶ Lymph nodes at the origin of feeding vessel(s) should be identified for pathologic examination.
 - ▶ Clinically positive lymph nodes outside the field of resection that are considered suspicious should be biopsied or removed, if possible.
 - ▶ Positive nodes left behind indicate an incomplete (R2) resection.
 - ▶ A minimum of 12 lymph nodes need to be examined to establish N stage.¹
- Minimally invasive approaches may be considered based on the following criteria²:
 - ▶ The surgeon has experience performing laparoscopically assisted colorectal operations.^{3,4}
 - ▶ Minimally invasive approaches are generally not indicated for locally advanced cancer or acute bowel obstruction or perforation from cancer.
 - ▶ Thorough abdominal exploration is required.⁵
 - ▶ Consider preoperative marking of lesion(s).
 - Management of patients with carrier status of known or clinically suspected LS.
 - ▶ Consider more extensive colectomy for patients with a strong family history of colon cancer or young age (<50 y).
[NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.](#)
 - Resection needs to be complete to be considered curative.

[Criteria for Resectability of Metastases and Locoregional Therapies Within Surgery on COL-C \(2 of 3\)](#)

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[References](#)

**PRINCIPLES OF SURGERY****CRITERIA FOR RESECTABILITY OF METASTASES AND LOCOREGIONAL THERAPIES WITHIN SURGERY****Liver**

- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.⁶
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.⁷
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.⁸⁻¹¹ Having a plan for a debulking resection (less than an R0 resection) is not recommended.⁷
- Patients with resectable metastatic disease and a primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.¹²
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches using preoperative portal vein embolization,¹³ staged liver resection,¹⁴ or yttrium-90 radioembolization¹⁵ can be considered.
- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- Arterially directed catheter therapy, and in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.
- Re-resection can be considered in selected patients.¹⁶

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.¹⁷⁻²⁰
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.²¹⁻²⁴
- Re-resection can be considered in selected patients.²⁵
- Ablative techniques may be considered alone or in conjunction with resection for resectable disease. All original sites of disease need to be amenable to ablation or resection.
- Ablative techniques can also be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.

Evaluation for Conversion to Resectable or Ablatable Disease

- Re-evaluation for resection and ablation should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.²⁶⁻²⁹
- Disease with a higher likelihood of being converted to resectable are those with initially convertible disease distributed within limited sites.
- When considering whether disease has been converted to resectable, all original sites need to be amenable to resection.³⁰
- Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.³¹

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References

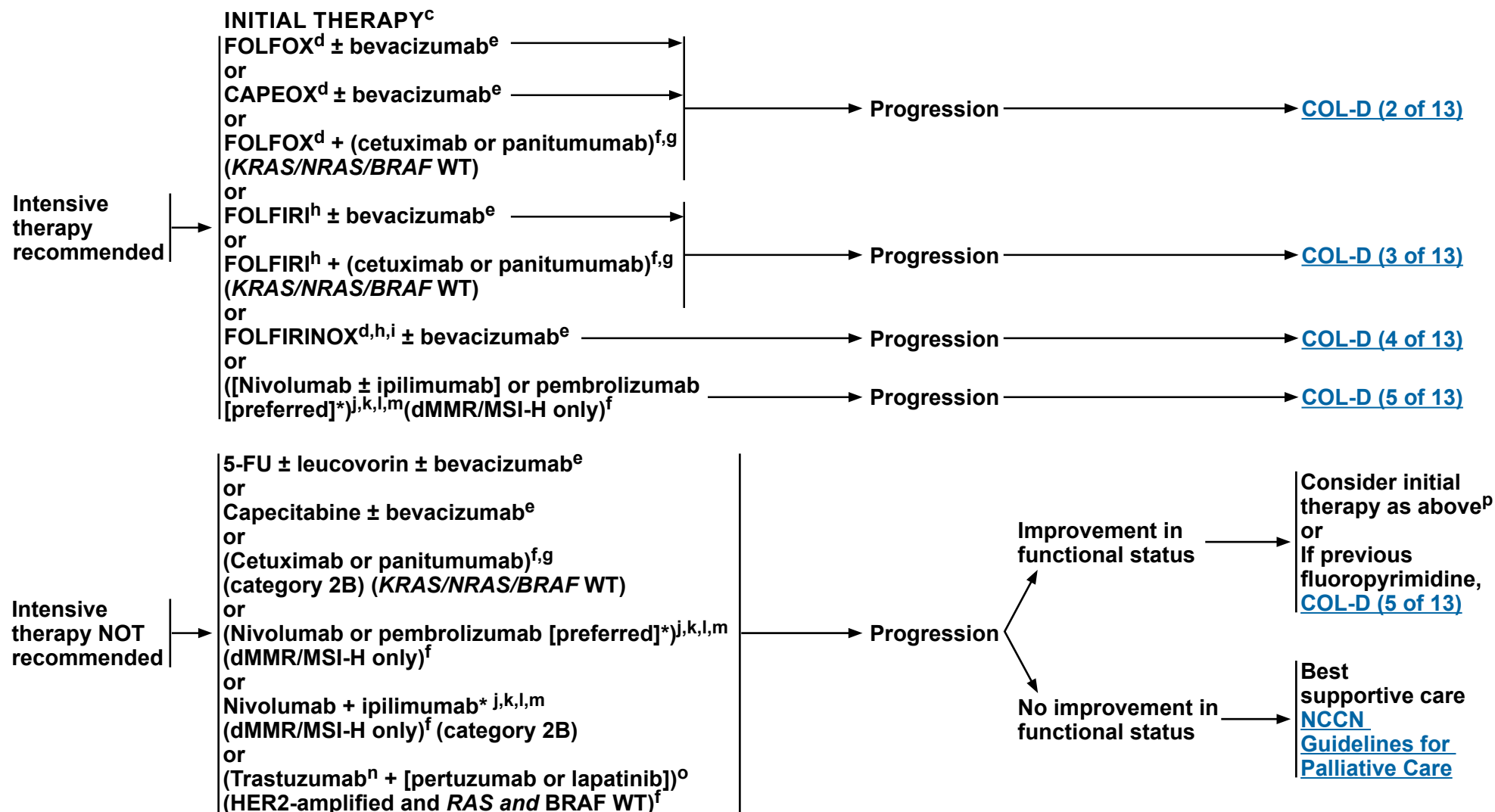
**PRINCIPLES OF SURGERY – REFERENCES**

- 1 LeVoyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol* 2003;21:2912-2919.
- 2 The Clinical Outcomes of Surgical therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004;350:2050-2059.
- 3 Wishner JD, Baker JW, Jr., Hoffman GC, et al. Laparoscopic-assisted colectomy. The learning curve. *Surg Endosc* 1995;9:1179-1183.
- 4 Nelson H, Weeks JC, Wieand HS. Proposed phase III trial comparing laparoscopic-assisted colectomy versus open colectomy for colon cancer. *J Natl Cancer Inst Monogr* 1995;51-56.
- 5 Ota DM, Nelson H, Weeks JC. Controversies regarding laparoscopic colectomy for malignant diseases. *Curr Opin Gen Surg* 1994;208-213.
- 6 Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004;239:818-825; discussion 825-827.
- 7 Charnsangavej C, Clary B, Fong Y, et al. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006;13:1261-1268.
- 8 Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. *J Clin Oncol* 1997;15:938-946.
- 9 Nordlinger B, Quilichini MA, Parc R, Hannoun L, Delva E, Huguet C. Surgical resection of liver metastases from colo-rectal cancers. *Int Surg* 1987;72:70-72.
- 10 Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999;230:309-318; discussion 318-321.
- 11 Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 2002;235:759-66.
- 12 Reddy SK, Pawlik TM, Zorzi D, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. *Ann Surg Oncol* 2007;14:3481-3491.
- 13 Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. *Ann Surg* 2008;247:451-455.
- 14 Adam R, Miller R, Pitombo M, et al. Two-stage hepatectomy approach for initially unresectable colorectal hepatic metastases. *Surg Oncol Clin N Am* 2007;16:525-536, viii.
- 15 Teo JY, Allen JC, Jr, Ng DC, et al. A systematic review of contralateral liver lobe hypertrophy after unilobar selective internal radiation therapy with Y90. *HPB (Oxford)* 2016;18:7-12.
- 16 Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. *Ann Surg* 1997;225:51-62.
- 17 McAfee MK, Allen MS, Trastek VF, Ilstrup DM, Deschamps C, Pairolero PC. Colorectal lung metastases: results of surgical excision. *Ann Thorac Surg* 1992;53:780-785; discussion 785-786.
- 18 Regnard JF, Grunenwald D, Spaggiari L, et al. Surgical treatment of hepatic and pulmonary metastases from colorectal cancers. *Ann Thorac Surg* 1998;66:214-218; discussion 218-219.
- 19 Inoue M, Kotake Y, Nakagawa K, Fujiwara K, Fukuhara K, Yasumitsu T. Surgery for pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg* 2000;70:380-383.
- 20 Sakamoto T, Tsubota N, Iwanaga K, Yuki T, Matsuoka H, Yoshimura M. Pulmonary resection for metastases from colorectal cancer. *Chest* 2001;119:1069-1072.
- 21 Rena O, Casadio C, Viano F, et al. Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience. *Eur J Cardiothorac Surg* 2002;21:906-912.
- 22 Irshad K, Ahmad F, Morin JE, Mulder DS. Pulmonary metastases from colorectal cancer: 25 years of experience. *Can J Surg* 2001;44:217-221.
- 23 Ambiru S, Miyazaki M, Ito H, et al. Resection of hepatic and pulmonary metastases in patients with colorectal carcinoma. *Cancer* 1998;82:274-278.
- 24 Yano T, Hara N, Ichinose Y, Yokoyama H, Miura T, Ohta M. Results of pulmonary resection of metastatic colorectal cancer and its application. *J Thorac Cardiovasc Surg* 1993;106:875-879.
- 25 Hendriks JM, Romijn S, Van Putte B, et al. Long-term results of surgical resection of lung metastases. *Acta Chir Belg* 2001;101:267-272.
- 26 Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann Surg Oncol* 2001;8:347-353.
- 27 Rivoire M, De Cian F, Meeus P, Negrier S, Sebban H, Kaemmerlen P. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. *Cancer* 2002;95:2283-2292.
- 28 Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006;24:2065-2072.
- 29 Pawlik TM, Olin K, Gleisner AL, et al. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. *J Gastrointest Surg* 2007;11:860-868.
- 30 Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 2006;24:3939-3945.
- 31 Bartlett DL, Berlin J, Lauwers GY, et al. Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol*. 2006;13:1284-1292.

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE^{a,b}



* Patients should be followed closely for 10 weeks to assess for response.

Footnotes [COL-D \(7 of 13\)](#)

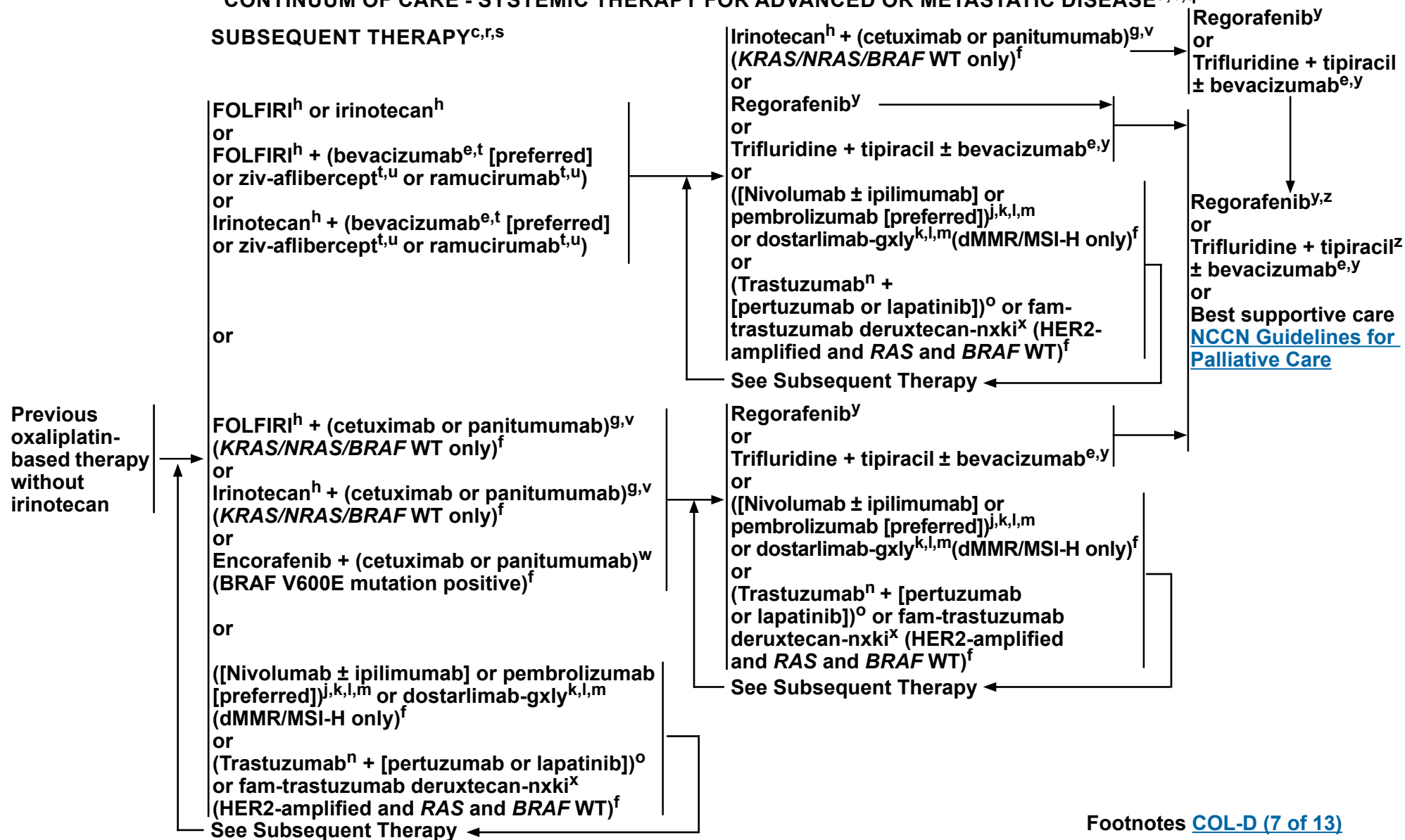
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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE^{a,b,q}

SUBSEQUENT THERAPY^{c,r,s}

Footnotes [COL-D \(7 of 13\)](#)

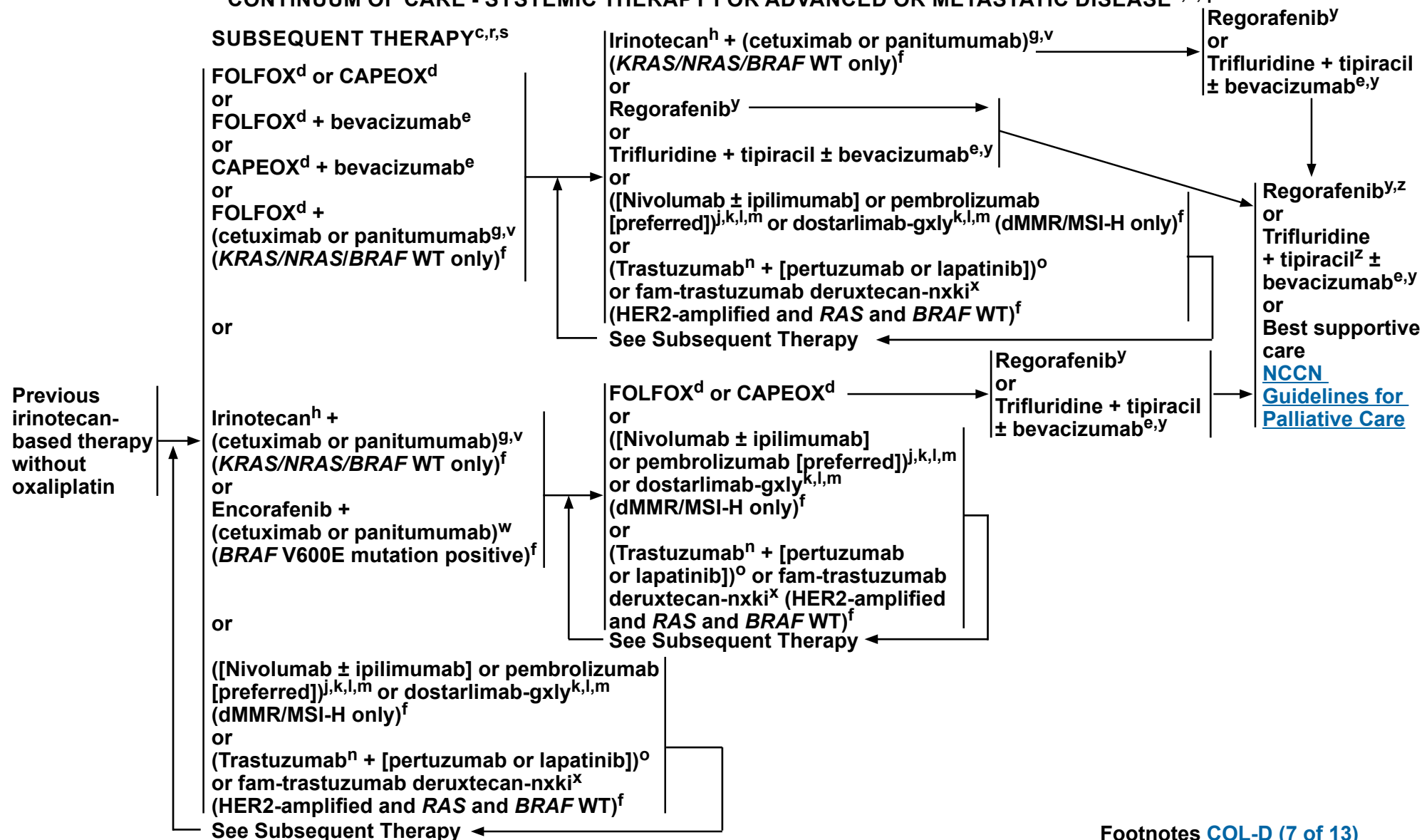
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SUBSEQUENT THERAPY^{c,r,s}

Footnotes [COL-D \(7 of 13\)](#)

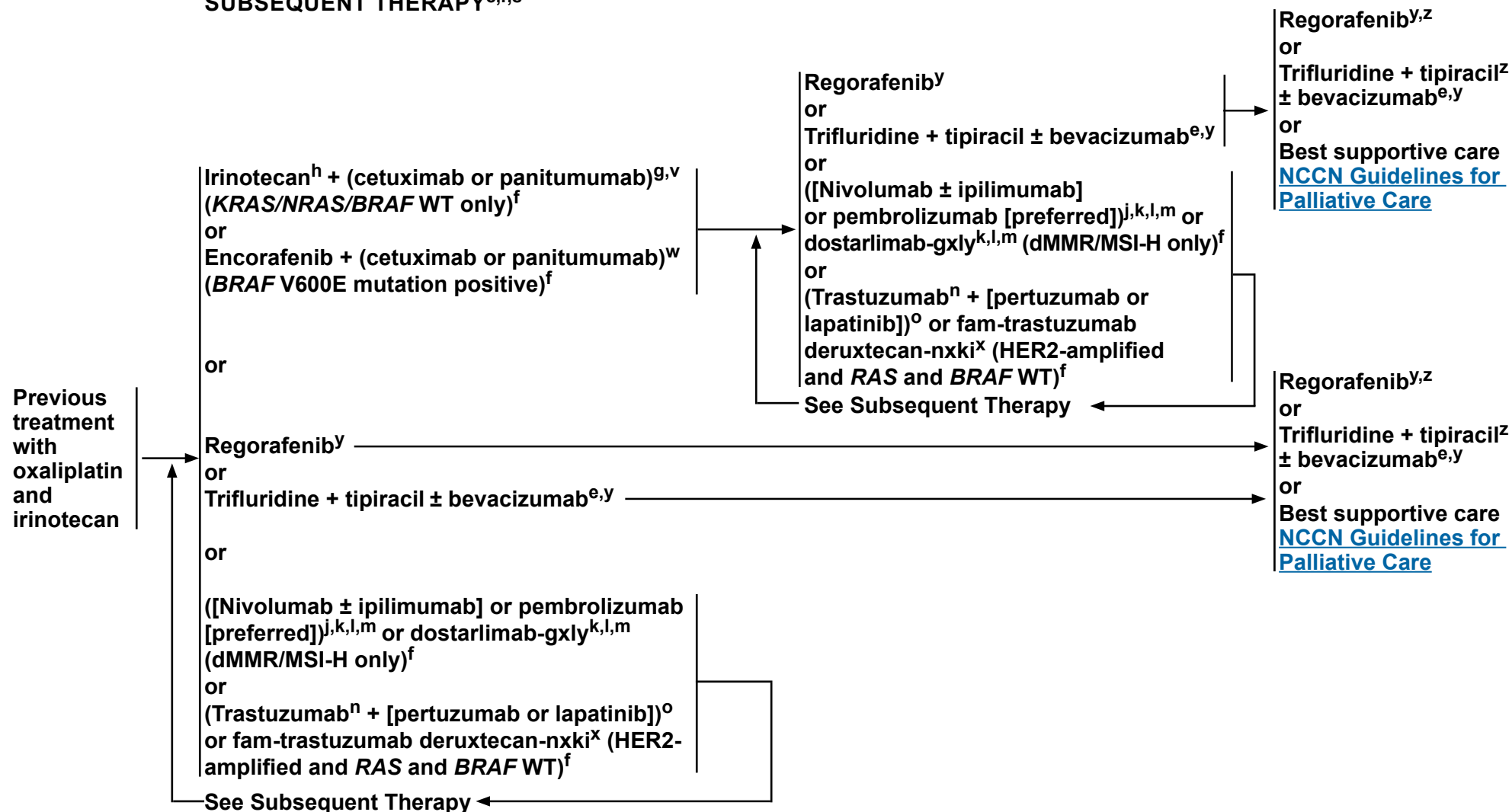
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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE^{a,b,q}

SUBSEQUENT THERAPY^{c,r,s}

Footnotes [COL-D \(7 of 13\)](#)

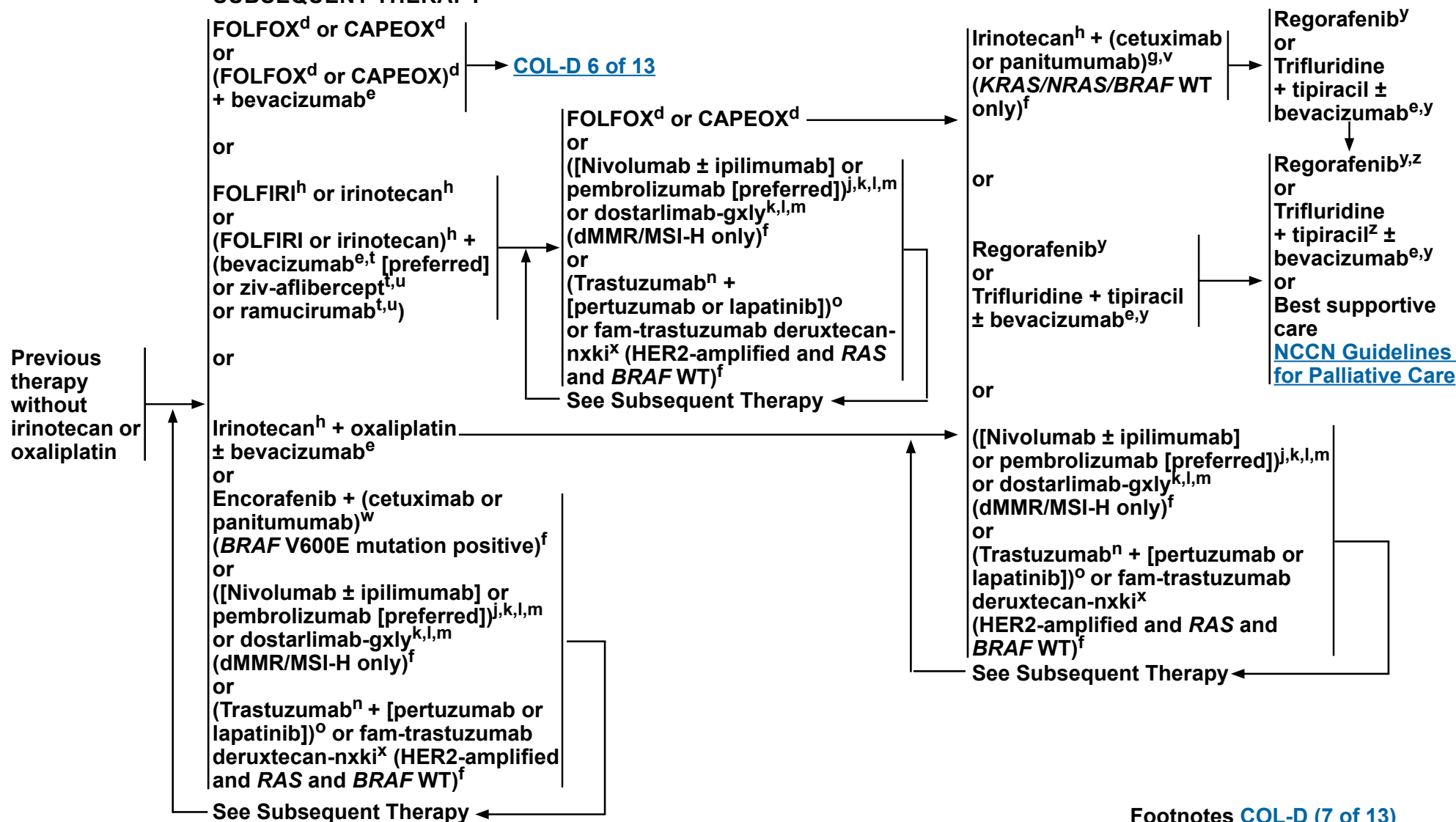
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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE^{a,b,q}

SUBSEQUENT THERAPY^{c,r,s}

Footnotes [COL-D \(7 of 13\)](#)

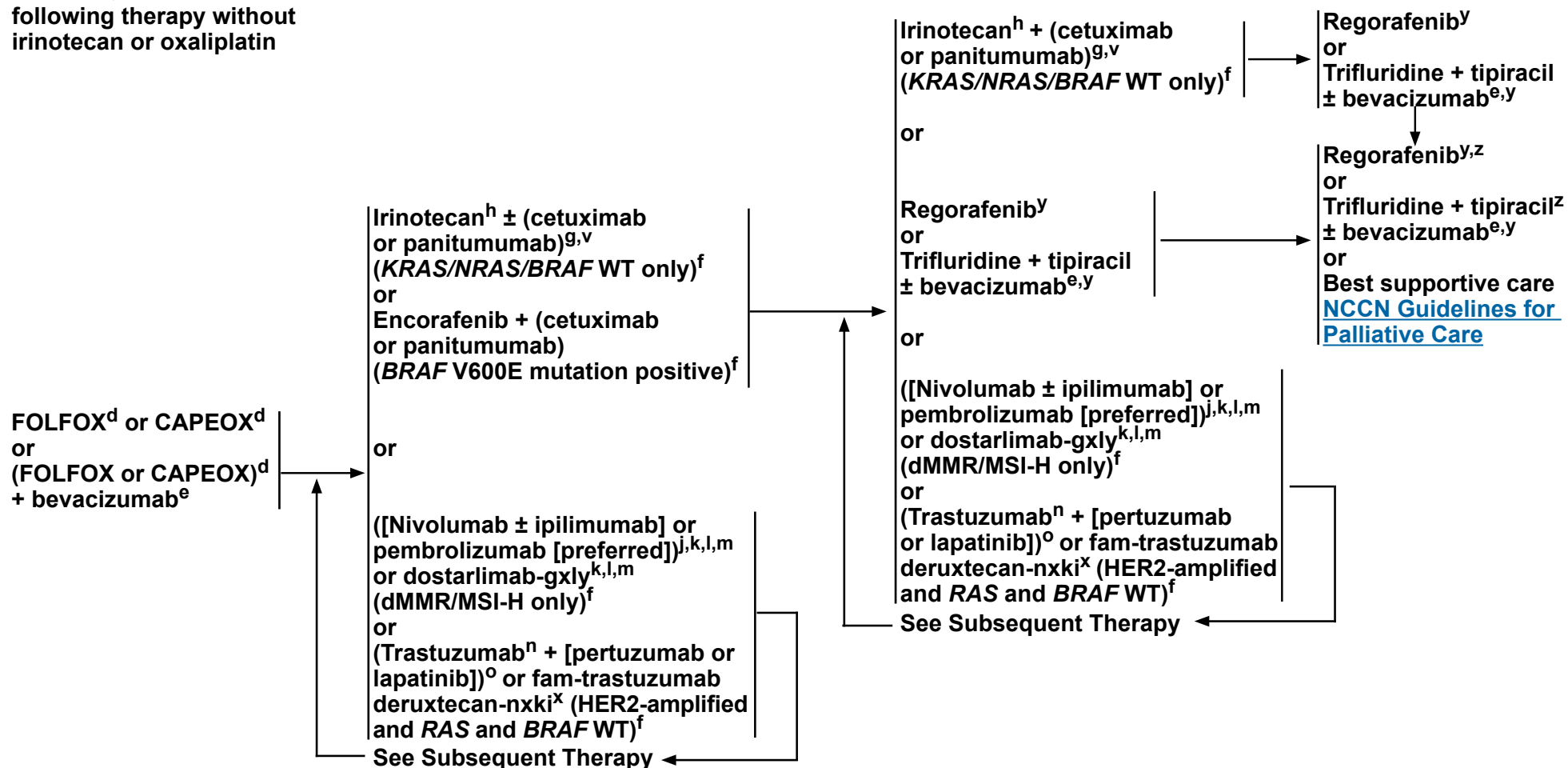
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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE^{a,b,q}

SUBSEQUENT THERAPY^{c,r,s}
 following therapy without
 irinotecan or oxaliplatin



Footnotes [COL-D \(7 of 13\)](#)

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**SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – FOOTNOTES**

^a For chemotherapy references, see [Chemotherapy Regimens and References \(COL-D \[8 of 13\]\)](#).

^b For infection risk, monitoring, and prophylaxis recommendations for targeted therapies, see INF-A in the [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#).

^c Chest/abdominal/pelvic CT with contrast or chest CT and abdominal/pelvic MRI with contrast to monitor progress of therapy. PET/CT should not be used. [Principles of Imaging \(COL-A\)](#).

^d Discontinuation of oxaliplatin should be strongly considered after 3 to 4 months of therapy (or sooner for unacceptable neurotoxicity) while maintaining other agents until time of progression. Oxaliplatin may be reintroduced if it was discontinued for neurotoxicity rather than for disease progression.

^e An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

^f [Principles of Pathologic Review \(COL-B 4 of 8\)](#).

^g Cetuximab or panitumumab should only be used for left-sided tumors. The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.

^h Irinotecan should be used with caution in patients with Gilbert syndrome or elevated serum bilirubin. There is a commercially available test for *UGT1A1*. Guidelines for use in clinical practice have not been established.

ⁱ FOLFIRINOX should be strongly considered for patients with excellent performance status.

^j Nivolumab ± ipilimumab are FDA approved for colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. However, a number of patients in the clinical trials had not received all three prior systemic therapies. Thirty-seven percent of patients received nivolumab monotherapy and 24% received ipilimumab/nivolumab combination therapy in first- or second-line, and 28% and 31% of patients had not received all three indicated prior therapies before treatment with nivolumab or ipilimumab/nivolumab, respectively.

^k [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

^l If disease response, consider discontinuing checkpoint inhibitor after 2 years of treatment.

^m If no previous treatment with a checkpoint inhibitor.

ⁿ An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

^o If no previous treatment with HER2 inhibitor.

^p The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.

^q Arterially directed catheter therapy, and in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/refractory disease and with predominant hepatic metastases. [Principles of Surgery \(COL-C\)](#).

^r Larotrectinib or entrectinib are treatment options for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.

^s If patients had therapy stopped for reasons other than progression (eg, cumulative toxicity, elective treatment break, patient preference), rechallenge is an option at time of progression.

^t Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

^u There are no data to suggest activity of FOLFIRI-ziv-aflibercept or FOLFIRI-ramucirumab in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept and ramucirumab have only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.

^v Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.

^w In the second-line setting for *BRAF* V600E mutation positive tumors, there is phase 3 evidence for better efficacy with targeted therapies over FOLFIRI.

^x Some activity was seen after a previous HER2-targeted regimen. May not be indicated in patients with underlying lung issues due to lung toxicity (2.6% report of deaths from interstitial lung disease).

^y Regorafenib or trifluridine + tipiracil with or without bevacizumab are treatment options for patients who have progressed through all available regimens.

^z If not previously given.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS****mFOLFOX 6^{1,2,3}****Oxaliplatin 85 mg/m² IV day 1^{aa}****Leucovorin 400 mg/m² IV day 1^{bb}****5-FU 400 mg/m² IV bolus on day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion****Repeat every 2 weeks****mFOLFOX 7⁴****Oxaliplatin 85 mg/m² IV day 1^{aa}****Leucovorin 400 mg/m² IV day 1^{bb}****5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)****IV continuous infusion****Repeat every 2 weeks****FOLFOX + bevacizumab^{5,e,dd}****Bevacizumab 5 mg/kg IV, day 1****Repeat every 2 weeks****FOLFOX + panitumumab⁶****(KRAS/NRAS/BRAF WT and left-sided tumors only)****Panitumumab 6 mg/kg IV over 60 minutes, day 1****Repeat every 2 weeks****FOLFOX + cetuximab⁷****(KRAS/NRAS/BRAF WT and left-sided tumors only)****Cetuximab 400 mg/m² IV over 2 hours first infusion,****followed by 250 mg/m² IV over 60 minutes weekly****or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks****(preferred for every 2 weeks)**^e An FDA-approved biosimilar is an appropriate substitute for bevacizumab.^{aa} Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.^{bb} Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².^{cc} The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.^{dd} Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).**CAPEOX⁸****Oxaliplatin 130 mg/m² IV day 1^{aa}****Capecitabine 1000^{cc} mg/m² twice daily PO for 14 days****Repeat every 3 weeks****CAPEOX + bevacizumab^{8,e,dd}****Oxaliplatin 130 mg/m² IV day 1^{aa}****Capecitabine 1000^{cc} mg/m² PO twice daily for 14 days****Bevacizumab 7.5 mg/kg IV day 1****Repeat every 3 weeks****FOLFIRI^{9,10}****Irinotecan 180 mg/m² IV over 30–90 minutes, day 1****Leucovorin^{bb} 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1****5-FU 400 mg/m² IV bolus day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion****Repeat every 2 weeks****FOLFIRI + bevacizumab^{11,e,dd}****Bevacizumab 5 mg/kg IV, day 1****Repeat every 2 weeks****FOLFIRI + cetuximab****(KRAS/NRAS/BRAF WT and left-sided tumors only)****Cetuximab 400 mg/m² IV over 2 hours first infusion,****followed by 250 mg/m² IV over 60 minutes weekly¹²****or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks¹³****(preferred for every 2 weeks)****Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**[Continued
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**SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS**

FOLFIRI + panitumumab¹⁴
(*KRAS/NRAS/BRAF* WT and left-sided tumors only)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ziv-aflibercept¹⁵
Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ramucirumab¹⁶
Ramucirumab 8 mg/kg over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRINOX^{17,ee}
Oxaliplatin 85 mg/m² IV day 1,^{aa} leucovorin 400 mg/m² IV over 2 hours on day 1, irinotecan 180 mg/m² IV over 30–90 minutes on day 1, fluorouracil 400 mg/m² IV push day 1, fluorouracil 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion.
Repeat every 2 weeks

Modified FOLFIRINOX^{18,ee}
Oxaliplatin 85 mg/m² IV on day 1,^{aa} leucovorin 400 mg/m² IV over 2 hours on day 1, irinotecan 150 mg/m² IV over 30–90 minutes on day 1, fluorouracil 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion. Repeat every 2 weeks

FOLFIRINOX or mFOLFIRINOX + bevacizumab^{19,e,dd}
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

^e An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

^{aa} Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.

^{dd} Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

^{ee} FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of fluorouracil (3,200 mg/m² over 48 hours). Patients in the United States (U.S.) have been shown to have greater toxicity with fluorouracil. The dose of fluorouracil (2,400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.

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FOLFIRINOX or mFOLFIRINOX + cetuximab²⁰
(*KRAS/NRAS/BRAF* WT and left-sided tumors only)
Cetuximab 500 mg/m² IV over 2 hours, day 1
Repeat every 2 weeks (preferred)
or Cetuximab 400 mg/m² IV over 2 hours first infusion, followed by 250 mg/m² IV over 60 minutes weekly

FOLFIRINOX or mFOLFIRINOX + panitumumab²⁰
(*KRAS/NRAS/BRAF* WT and left-sided tumors only)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

IROX²¹
Oxaliplatin 85 mg/m² IV,^{aa}
followed by irinotecan 200 mg/m² over 30–90 minutes every 3 weeks

IROX + bevacizumab^{e,dd}
Bevacizumab 7.5 mg/kg IV on day 1
Repeat every 3 weeks

**Bolus or infusional 5-FU/leucovorin
Roswell Park regimen²²**
Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m² IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks

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**SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS**

Simplified biweekly infusional 5-FU/LV (sLV5FU2)⁹
Leucovorin^{bb} 400 mg/m² IV over 2 hours on day 1,
followed by 5-FU bolus 400 mg/m² followed by 1200 mg/m²/day x 2
days (total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks
Weekly
Leucovorin 20 mg/m² IV over 2 hours on day 1, 5-FU 500 mg/m² IV
bolus injection 1 hour after the start of leucovorin. Repeat weekly²³
or
5-FU 2600 mg/m² by 24-hour infusion plus leucovorin 500 mg/m²
Repeat every week²³

Bolus or infusional 5-FU + bevacizumab^{e,dd}
Bevacizumab 5 mg/kg IV on day 1
Repeat every 2 weeks

Capecitabine^{24,cc}
Capecitabine 850–1250 mg/m² PO twice daily for 14 days
Repeat every 3 weeks

Capecitabine + bevacizumab^{25,e,dd}
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

Irinotecan
Irinotecan 125 mg/m² IV over 30–90 minutes, days 1 and 8
Repeat every 3 weeks^{26,27}
or Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 300–350 mg/m² IV over 30–90 minutes, day 1
Repeat every 3 weeks

Irinotecan + cetuximab
(KRAS/NRAS/BRAF WT and left-sided tumors only)
Cetuximab 400 mg/m² first infusion, followed by 250 mg/m² IV
weekly²⁸
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks¹³
(preferred for every 2 weeks)

Irinotecan + panitumumab^{14,29}
(KRAS/NRAS/BRAF WT and left-sided tumors only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Irinotecan + bevacizumab^{30,e,dd}
Irinotecan 180 mg/m² IV, day 1
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks
or
Irinotecan 300–350 mg/m² IV, day 1
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

Irinotecan + ramucirumab¹⁶
Ramucirumab 8 mg/kg IV over 60 minutes every 2 weeks

Irinotecan + ziv-aflibercept
Irinotecan 180 mg/m² IV, day 1
Ziv-aflibercept 4 mg/kg IV, day 1
Repeat every 2 weeks

Cetuximab (KRAS/NRAS/BRAF WT and left-sided tumors only)
Cetuximab 400 mg/m² first infusion, followed by 250 mg/m² IV
weekly²⁸
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks¹³
(preferred for every 2 weeks)

^e An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

^{cc} The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

^{dd} Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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**SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS****Panitumumab³¹****(*KRAS/NRAS/BRAF* WT and left-sided tumors only)****Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks****Regorafenib****Regorafenib 160 mg PO daily on days 1–21³²****or****First cycle: Regorafenib 80 mg PO daily on days 1–7, followed by 120 mg PO daily on days 8–14, followed by 160 mg PO daily on days 15–21³³****Subsequent cycles: Regorafenib 160 mg PO daily on days 1–21****Repeat every 28 days****Trifluridine + tipiracil ± bevacizumab^{e,34,35}****Trifluridine + tipiracil 35 mg/m² up to a maximum dose of 80 mg per dose (based on the trifluridine component)****PO twice daily days 1–5 and 8–12****Bevacizumab 5 mg/kg on days 1 and 15****Repeat every 28 days****Pembrolizumab³⁶ (dMMR/MSI-H only)****Pembrolizumab 2 mg/kg IV every 3 weeks****or Pembrolizumab 200 mg IV every 3 weeks****or Pembrolizumab 400 mg IV every 6 weeks****Nivolumab³⁷ (dMMR/MSI-H only)****Nivolumab 3 mg/kg every 2 weeks****or Nivolumab 240 mg IV every 2 weeks****or Nivolumab 480 mg IV every 4 weeks****Nivolumab + ipilimumab³⁸ (dMMR/MSI-H only)****Nivolumab 3 mg/kg (30-minute IV infusion) and ipilimumab 1 mg/kg (30-minute IV infusion) once every 3 weeks for four doses, followed by Nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 4 weeks****Dostarlimab-gxly³⁹ (dMMR/MSI-H only)****Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks****Trastuzumab^{ff} + pertuzumab⁴⁰****(HER2-amplified and *RAS* and *BRAF* WT)****Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, followed by 6 mg/kg IV every 21 days****Pertuzumab 840 mg IV loading dose on day 1 of cycle 1, followed by 420 mg IV every 21 days****Trastuzumab^{ff} + lapatinib⁴¹****(HER2-amplified and *RAS* and *BRAF* WT)****Trastuzumab 4 mg/kg IV loading dose on day 1 of cycle 1, followed by 2 mg/kg IV weekly****Lapatinib 1000 mg PO daily****Fam-trastuzumab deruxtecan-nxki⁴²****Fam-trastuzumab deruxtecan-nxki 6.4 mg/kg IV on day 1****Repeat every 21 days****Encorafenib + cetuximab⁴³⁻⁴⁵****(*BRAF* V600E mutation positive)****Encorafenib 300 mg PO daily****Cetuximab 400 mg/m² followed by 250 mg/m² weekly****Encorafenib + panitumumab⁴³⁻⁴⁵****(*BRAF* V600E mutation positive)****Encorafenib 300 mg PO daily****Panitumumab 6 mg/kg IV every 14 days****Larotrectinib⁴⁶ (*NTRK* gene fusion positive)****100 mg PO twice daily****Entrectinib⁴⁷ (*NTRK* gene fusion positive)****600 mg PO once daily**[References](#)^e An FDA-approved biosimilar is an appropriate substitute for bevacizumab.^{ff} An FDA-approved biosimilar is an appropriate substitute for trastuzumab.**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

**SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – REFERENCES**

- 1 deGramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced rectal cancer. *J Clin Oncol* 2000;18:2938-2947.
- 2 Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. *Br J Cancer* 2002;87:393-399.
- 3 Maindrault-Goebel F, deGramont A, Louvet C, et al. Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. *Ann Oncol* 2000;11:1477-1483.
- 4 Hochster HS, Grothey A, Hart L, et al. Improved time to treatment failure with an intermittent oxaliplatin strategy: results of CONcePT. *Ann Oncol* 2014;25:1172-1178.
- 5 Emmanouilides C, Sfakiotaki G, Androulakis N, et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. *BMC Cancer* 2007;7:91.
- 6 Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28:4697-4705.
- 7 Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: A randomized clinical trial. *JAMA* 2017;317:2392-2401.
- 8 Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008;26:2013-2019.
- 9 Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. *Eur J Cancer* 1999;35:1343-1347.
- 10 Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol* 2007;25:4779-4786.
- 11 Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomized, open-label, phase 3 trial. *Lancet Oncol* 2014;15:1065-1075.
- 12 Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351:337-345.
- 13 Martín-Martorell P, Roselló S, Rodríguez-Braun E, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. *Br J Cancer* 2008;99:455-458.
- 14 Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol* 2010;28:4706-4713.
- 15 Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012;30:3499-3506.
- 16 Tabernero J, Yoshino T, Cohn AL, et al. Ramucicirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomized, double-blind, multicentre, phase 3 study. *Lancet Oncol* 2015;16:499-508.
- 17 Conroy T, Bosset J-F, Etienne P-L, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *The Lancet Oncology* 2021;22:702-715.
- 18 Bennouna J, Andre T, Campion L, et al. Rationale and design of the IROCAS study: multicenter, international, randomized phase 3 trial comparing adjuvant modified (m) FOLFIRINOX to mFOLFOX6 in patients with high-risk stage III (pT4 and/or N2) colon cancer-A UNICANCER GI-PRODIGE Trial. *Clin Colorectal Cancer*. 2019;18:e69-e73.
- 19 Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol* 2015;16:1306-1315.
- 20 Cremolini C, Antoniotti C, Lonardi S, et al. Activity and safety of cetuximab plus modified FOLFOXIRI followed by maintenance with cetuximab or bevacizumab for RAS and BRAF wild-type metastatic colorectal cancer: A randomized phase 2 clinical trial. *JAMA Oncol* 2018;4:529-536.
- 21 Haller DG, Rothenberg ML, Wong AO, et al. Oxaliplatin plus irinotecan compared with irinotecan alone as second-line treatment after single agent fluoropyrimidine therapy for metastatic colorectal carcinoma. *J Clin Oncol* 2008;26:4544-4550.
- 22 Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Protocol C-03. *J Clin Oncol* 1993;11:1879-1887.

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**SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – REFERENCES**

- 23 Jäger E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. *J Clin Oncol* 1996;14:2274-2279.
- 24 Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001;19:4097-4106.
- 25 Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013;14:1077-1085.
- 26 Cunningham D, Pyrhonen S, James R, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *The Lancet* 1998;352:1413-1418.
- 27 Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. *J Clin Oncol* 2003;21:807-814.
- 28 Van Cutsem E, Tejpar S, Vanbeckevoort D, et al. Inpatient cetuximab dose escalation in metastatic colorectal cancer according to the grade of early skin reactions: The Randomized EVEREST Study. *J Clin Oncol* 2012;30:2861-2868.
- 29 Andre T, Blons H, Mabro M, et al. Panitumumab combined with irinotecan for patients with KRAS wild-type metastatic colorectal cancer refractory to standard chemotherapy: a GERCOR efficacy, tolerance, and translational molecular study. *Ann Oncol* 2013;24:412-419.
- 30 Yildiz R, Buyukberber S, Uner A, et al. Bevacizumab plus irinotecan-based therapy in metastatic colorectal cancer patients previously treated with oxaliplatin-based regimens. *Cancer Invest* 2010;28:33-37.
- 31 Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007;25:1658-1664.
- 32 Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381:303-312.
- 33 Bekaii-Saab TS, Ou F-S, Ahn DH, et al. Regorafenib-dose optimisation in patients with refractory metastatic colorectal cancer (reDOS): a randomised, multicentre, open-label, phase 2 study. *Lancet Oncol* 2019;20:1070-1082.
- 34 Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer (RECURSE). *N Engl J Med* 2015;372:1909-1919.
- 35 Pfeiffer PP, Yilmaz M, Moller S, et al. TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial. *Lancet Oncol* 2020;21:412-420.
- 36 Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;372:2509-2520.
- 37 Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair deficient/microsatellite instability-high colorectal cancer (CheckMate 142): results of an open-label, multicentre, phase 2 study. *Lancet Oncol* 2017;18:1182-1191.
- 38 Overman MJ, Lonardi S, Wong K et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol* 2018;36:773-779.
- 39 Berton D, Banerjee SN, Curigliano G, et al. Antitumor activity of dostarlimab in patients with mismatch repair-deficient/microsatellite instability-high tumors: A combined analysis of two cohorts in the GARNET study. *J Clin Oncol* 2021;39:15_suppl, 2564-2564.
- 40 Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol* 2019;20:518-530.
- 41 Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2016;17:738-746.
- 42 Siena S, Di Bartolomeo M, Raghav KPS, et al. A phase II, multicenter, open-label study of trastuzumab deruxtecan in patients with HER2-expressing metastatic colorectal cancer: DESTINY-CRC01. *J Clin Oncol* 2020;38(suppl; abstr 4000).
- 43 Van Cutsem E, Huijberts S, Grothey A, et al. Binimetinib, encorafenib, and cetuximab triplet therapy for patients with BRAF V600E-mutant metastatic colorectal cancer: Safety lead-in results from the phase III BEACON Colorectal Cancer Study. *J Clin Oncol* 2019;37:1460-1469.
- 44 Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. *N Engl J Med*. 2019;381:1632-1643.
- 45 Kopetz S, Grothey A, Van Cutsem E. et al. Encorafenib plus cetuximab with or without binimetinib for BRAF V600E-mutant metastatic colorectal cancer: Quality-of-life results from a randomized, three-arm, phase III study versus the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC) [abstract]. *J Clin Oncol* 2020;38(suppl 4;abstr 8).
- 46 Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 2018;378:731-739.
- 47 Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 2020;21:271-282.

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**PRINCIPLES OF RADIATION AND CHEMORADIATION THERAPY****General Principles**

- **Neoadjuvant radiation therapy with concurrent fluoropyrimidine-based chemotherapy may be considered for initially unresectable or medically inoperable non-metastatic T4 colon cancer to aid resectability.**
 - ▶ **Infusional 5-FU + RT¹**
5-FU 225 mg/m² IV over 24 hours 5 or 7 days/week during RT
 - ▶ **Capecitabine + RT^{2,3}**
Capecitabine 825 mg/m² PO twice daily 5 days/week during RT
 - ▶ **Bolus 5-FU/leucovorin + RT^{1,a}**
5-FU 400 mg/m² IV bolus + leucovorin 20 mg/m² IV bolus for 4 days during weeks 1 and 5 of RT
- **In patients with a limited number of liver or lung metastases, ablative radiotherapy to the metastatic site can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiation therapy, intensity-modulated radiation therapy (IMRT), or stereotactic body radiation therapy (SBRT).**

Treatment Information

- **IMRT is preferred for unique clinical situations such as reirradiation of previously treated patients with recurrent disease or unique anatomical situations where IMRT facilitates the delivery of recommended target volume doses while respecting accepted normal tissue dose-volume constraints (eg, coverage of external iliac or inguinal lymph nodes or avoidance of small bowel).**
- **Consider SBRT for patients with oligometastatic disease.**
- **Image-guided radiation therapy (IGRT) with kilovoltage (kV) imaging or cone-beam CT imaging should be routinely used during the course of treatment with IMRT and SBRT.**
- **Arterially directed catheter therapy, and in particular yttrium-90 microsphere-selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.**
- **Intraoperative radiation therapy (IORT), if available, may be considered for patients with T4 or recurrent cancers as an additional boost.**
- **Target Volumes**
 - ▶ **Radiation therapy fields should include the tumor bed, which should be defined by preoperative radiologic imaging and/or surgical clips.**
 - ▶ **Radiation doses should be: 45–50 Gy in 25–28 fractions.**
 - ◊ **Consider boost for close or positive margins or unresectable cases after evaluating the cumulative dose to adjacent organs at risk.**
 - ◊ **Small bowel dose should be limited to 50 Gy.**
 - ◊ **Large bowel, stomach, and liver are critical structures that should be evaluated on the dose-volume histogram (DVH).**
 - ◊ **Fluoropyrimidine-based chemotherapy should be delivered concurrently with radiation.**
- **Consider radiation treatment for T4 with penetration to a fixed structure after surgery.**

^a Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.[Continued](#)



PRINCIPLES OF RADIATION AND CHEMORADIATION THERAPY

Supportive Care

- Patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis, if applicable.
- Patients of child bearing potential should be counseled about the effects of premature menopause and consideration should be given to referral for discussion of hormone replacement strategies.
- Patients of child bearing potential should be counseled that an irradiated uterus cannot carry a fetus to term.
- Patients should be counseled on sexual dysfunction, potential for future low testosterone levels, and infertility risks and given information regarding sperm banking or oocyte, egg, or ovarian tissue banking, as appropriate, prior to treatment.

¹ Martenson JA Jr, Willett CG, Sargent DJ, et al. Phase III study of adjuvant chemotherapy and radiation therapy compared with chemotherapy alone in the surgical adjuvant treatment of colon cancer: results of intergroup protocol 0130. J Clin Oncol 2004;15:3277-3283.

² O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. J Clin Oncol 2014;32:1927-1934.

³ Hofheinz R, Wenz FK, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: A randomized, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579-588.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



PRINCIPLES OF RISK ASSESSMENT FOR STAGE II DISEASE^{1,2,3}

- Patient/physician discussion regarding the potential risks of therapy compared to potential benefits, including prognosis. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk characteristics, and patient preferences.
- When determining if adjuvant therapy should be administered, the following should be taken into consideration:
 - ▶ Number of lymph nodes analyzed after surgery (<12)
 - ▶ Poor prognostic features (eg, poorly differentiated histology [exclusive of those that are MSI-H]; lymphatic/vascular invasion; bowel obstruction; PNI; localized perforation; close, indeterminate, or positive margins)
 - ▶ Assessment of other comorbidities and anticipated life expectancy.
- The benefit of adjuvant chemotherapy does not improve survival by more than 5%.
- MSI or MMR testing ([see COL-B 4 of 8](#))

¹ Benson III AB, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;16:3408-3419.

² Figueredo A, Charette ML, Maroun J, et al. Adjuvant therapy for stage II colon cancer: a systematic review from the cancer care ontario program in evidence-based care's gastrointestinal cancer disease site group. J Clin Oncol 2004;16:3395-3407.

³ Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22:1797-1806.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**PRINCIPLES OF ADJUVANT THERAPY**

- CAPEOX or FOLFOX is superior to 5-FU/leucovorin for patients with stage III colon cancer.^{1,2}
- Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in patients with stage III colon cancer.³
- A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer.⁴ FOLFOX is reasonable for patients with stage II colon cancer with multiple high-risk factors and is not indicated for good- or average-risk patients with stage II colon cancer.
- A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged 70 years and older has not been proven.⁴
- While non-inferiority of 3 versus 6 months of CAPEOX has not been proven, 3 months of CAPEOX numerically appeared similar to 6 months of CAPEOX for 5-year overall survival (82.1% vs. 81.2%; HR, 0.96), with considerably less toxicity.⁵ These results support the use of 3 months of adjuvant CAPEOX over 6 months of adjuvant CAPEOX in the vast majority of patients with stage III colon cancer. In patients with colon cancer, staged as T1–3, N1 (low-risk stage III), 3 months of CAPEOX is non-inferior to 6 months of CAPEOX for disease-free survival; non-inferiority of 3 versus 6 months of FOLFOX has not been proven. In patients with colon cancer staged as T4, N1–2 or T any, N2 (high-risk stage III), 3 months of FOLFOX is inferior to 6 months of FOLFOX for disease-free survival, whereas non-inferiority of 3 versus 6 months of CAPEOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 versus 6 months of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CAPEOX) (Grothey A, et al. N Engl J Med 2018;378:1177-1188).⁶
- A pooled analysis of high-risk stage II patients in the IDEA collaboration did not show non-inferiority of 3 months compared to 6 months of adjuvant treatment. Similar to stage III, the duration of therapy was associated with a small (and not statistically significant) difference in disease-free survival (DFS) between 3 and 6 months of CAPEOX. There were significantly less grade 3–5 toxicities with 3 versus 6 months.⁷

[Principles of Adjuvant Therapy - Chemotherapy Regimens and References on COL-G \(2 of 2\)](#)

¹ Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-2351.

² Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109-3116.

³ Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696-2704.

⁴ Tournigand C, Andre T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. J Clin Oncol 2012;30:3353-3360.

⁵ André T, Meyerhardt J, Iveson T, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. Lancet Oncol 2020;21:1620-1629.

⁶ Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med 2018;378:1177-1188.

⁷ Iveson T, Sobrero AF, Yoshino T, et al. Prospective pooled analysis of four randomized trials investigating duration of adjuvant (adj) oxaliplatin-based therapy (3 vs 6 months {m} for patients (pts) with high-risk stage II colorectal cancer (CC) [abstract]. J Clin Oncol 2019;37:3501-3501.

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**PRINCIPLES OF ADJUVANT THERAPY - CHEMOTHERAPY REGIMENS AND REFERENCES****mFOLFOX 6****Oxaliplatin 85 mg/m² IV, day 1^a****Leucovorin 400 mg/m² IV, day 1^b****5-FU 400 mg/m² IV bolus on day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion.****Repeat every 2 weeks.^{1,2,3}****Capecitabine⁴****Capecitabine 1000–1250^c mg/m² PO twice daily for 14 days every 3 weeks x 24 weeks.****CAPEOX⁵****Oxaliplatin 130 mg/m² IV^a day 1****Capecitabine 1000^c mg/m² PO twice daily for 14 days every 3 weeks x 24 weeks.****5-FU/leucovorin**

- **Leucovorin 500 mg/m² given as a 2-hour infusion and repeated weekly x 6. 5-FU 500 mg/m² given bolus 1 hour after the start of leucovorin and repeated 6 x weekly. Every 8 weeks for 4 cycles.⁶**
- **Simplified biweekly infusional 5-FU/leucovorin (LV) (sLV5FU2)⁷**
Leucovorin 400^b mg/m² IV day 1, followed by 5-FU bolus 400 mg/m², followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion. Repeat every 2 weeks.

Footnotes

^a Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.

^b Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².

^c The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

References

- ¹ Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-2351.
- ² Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002;87:393-399.
- ³ Maindault-Goebel F, deGramont A, Louvet C, et al. Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. Ann Oncol 2000;11:1477-1483.
- ⁴ Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696-2704.
- ⁵ Schmoll HJ, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol 2007;25:102-109. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 2011;29:1465-1471.
- ⁶ Haller DG, Catalano PJ, Macdonald JS, Mayer RJ. Phase III study of fluorouracil, leucovorin and levamisole in high risk stage II and III colon cancer: final report of Intergroup 0089. J Clin Oncol 2005;23:8671-8678.
- ⁷ Andre T, Louvet C, Maindault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. Eur J Cancer 1999;35:1343-1347.

Note: All recommendations are category 2A unless otherwise indicated.

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**PRINCIPLES OF SURVIVORSHIP – Colorectal Long-term Follow-up Care****Colorectal Cancer Surveillance**

- Surveillance recommendations on [COL-8](#)
- Long-term surveillance should be carefully managed with routine good medical care and monitoring, including cancer screening, routine health care, and preventive care.
- Routine CEA monitoring and routine CT scanning are not recommended beyond 5 years.

Survivorship Care Planning

The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to patient.¹

- Develop survivorship care plan that includes:
 - ▶ Overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received.
 - ▶ Description of possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment.
 - ▶ Surveillance recommendations.
 - ▶ Delineate appropriate timing of transfer of care with specific responsibilities identified for primary care physician and oncologist.
 - ▶ Health behavior recommendations.

Management of Late/Long-term Sequelae of Disease or Treatment²⁻⁶

- For issues related to distress, pain, neuropathy, fatigue, or sexual dysfunction, see [NCCN Guidelines for Survivorship](#).
- For chronic diarrhea or incontinence
 - ▶ Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, pelvic floor rehabilitation, and protective undergarments.

- Management of an ostomy
 - ▶ Consider participation in an ostomy support group or coordination of care with a health care provider specializing in ostomy care (ie, ostomy nurse)
 - ▶ Screen for distress around body changes ([NCCN Guidelines for Distress Management](#)) and precautions around involvement with physical activity (see page SPA-C in the [NCCN Guidelines for Survivorship](#)).
- For oxaliplatin-induced neuropathy
 - ▶ Consider duloxetine for painful neuropathy only, not effective for numbness, tingling, or cold sensitivity.⁷
 - ▶ Consider non-pharmacologic therapies such as heat or acupuncture.
 - ▶ Pregabalin or gabapentin are not recommended.

Counseling Regarding Healthy Lifestyle and Wellness⁸
NCCN Guidelines for Survivorship

- Undergo all age- and gender-appropriate cancer and preventive health screenings as per national guidelines.
- Maintain a healthy body weight throughout life.
- Adopt a physically active lifestyle (at least 30 minutes of moderate-intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (ie, ostomy, neuropathy).
- Consume a healthy diet with emphasis on plant sources. Diet recommendations may be modified based on severity of bowel dysfunction.
- Consider daily aspirin 325 mg for secondary prevention.
- Eliminate or limit alcohol consumption, no more than 1 drink/day for women, and 2 drinks/day for men.
- Receive smoking cessation counseling as appropriate.

Additional health monitoring and immunizations should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.

References

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



PRINCIPLES OF SURVIVORSHIP – References

- ¹ Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C.:The National Academies Press; 2006.
- ² Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer. Cancer 2007;110:2075-2082.
- ³ Sprangers MAG, Taal BG, Aaronson NK, et al. Quality of life in colorectal cancer: stoma vs. nonstoma patients. Dis Colon Rectum 1995;38:361-369.
- ⁴ Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. Aliment Pharmacol Ther 2003;18:987-994.
- ⁵ DeSnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. Eur J Cancer 2006;15:244-251.
- ⁶ McGough C, Baldwin C, Frost C, Andreyev HJN. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. Br J Cancer 2004;90:2278-2287.
- ⁷ Lavoie Smith EM, Pang H, Cirincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy. JAMA 2013;309:1359-1367.
- ⁸ Kushi LH, Byers T, Doyle C, et al and The American Cancer Society 2006 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity CA Cancer J Clin 2006;56:254-281.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



American Joint Committee on Cancer (AJCC) TNM Staging Classification for Colon Cancer 8th ed., 2017

Table 1. Definitions for T, N, M

T Primary Tumor		N Regional Lymph Nodes	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastasis
Tis	Carcinoma <i>in situ</i> : intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)	N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥ 0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)	N1a	One regional lymph node is positive
T2	Tumor invades the muscularis propria	N1b	Two or three regional lymph nodes are positive
T3	Tumor invades through the muscularis propria into pericolorectal tissues	N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres** to adjacent organ or structure	N2	Four or more regional lymph nodes are positive
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)	N2a	Four to six regional lymph nodes are positive
T4b	Tumor directly invades* or adheres** to adjacent organs or structures	N2b	Seven or more regional lymph nodes are positive
		M Distant Metastasis	
		M0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists)
		M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
		M1a	Metastasis to one site or organ is identified without peritoneal metastasis
		M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
		M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

* Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (i.e., respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

** Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classification should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN prognostic factor should be used for perineural invasion.

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**American Joint Committee on Cancer (AJCC)**
TNM Staging System for Colon Cancer 8th ed., 2017**Table 2. Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
Stage IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.



NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference

Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.



NCCN Guidelines Version 1.2022 Colon Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Colon Cancer. Last updated September 10, 2021

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NCCN Guidelines Version 1.2022

Colon Cancer

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2020, an estimated 104,610 new cases of colon cancer and 43,340 cases of rectal cancer will occur. During the same year, an estimated 53,200 people will die of colon and rectal cancer combined.¹ Despite these high numbers, the incidence of colon and rectal cancers per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005 and, more recently, 38.7 in 2016.^{2,3} In addition, mortality from CRC has been decreasing for decades (since 1947 in women and since 1980 in men) and is currently down by more than 50% from peak mortality rates.^{1,3} These improvements in incidence of and mortality from CRC are thought to be a result of cancer prevention and earlier diagnosis through screening and better treatment modalities. Recent data show continued rapid declines in incidence among those aged 65 years or older, with a decrease of 3.3% annually between 2011 and 2016.³

Conversely, incidence has increased among those younger than 65 years, with a 1% annual increase in those aged 50 to 64 years and 2% annual increase in those younger than 50 years. CRC death rates also showed age-dependent trends, declining by 3% annually for those 65 years and older, compared to a 0.6% annual decline for individuals aged 50 to 64 years and a 1.3% annual increase for individuals younger than 50 years.³ A retrospective cohort study of the SEER CRC registry also found that the incidence of CRC in patients younger than 50 years has been increasing.⁴ The authors estimate that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for patients 20 to 34 years of age by 2030. The cause of this trend is currently unknown. One review suggests that CRC that occurs in young adult patients may be clinicopathologically and genetically different from CRC in older adults, although this has not been confirmed broadly. If cancer in this population

is different, there would be a need to develop specific treatment strategies for this population.⁵

This Discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer. These guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, perioperative treatment, patient surveillance, management of recurrent and metastatic disease, and survivorship. When reviewing these guidelines, clinicians should be aware of several things. First, these guidelines adhere to the TNM staging system (Table 1 in the algorithm).⁶ Furthermore, all recommendations are classified as category 2A except where noted in the text or algorithm. Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Colon Cancer, an electronic search of the PubMed database was performed to obtain key literature in the field of CRC, using the following search terms: (colon cancer) OR (colorectal cancer) OR (rectal cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.⁷

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.



NCCN Guidelines Version 1.2022

Colon Cancer

The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Risk Assessment

Approximately 20% of cases of colon cancer are associated with familial clustering, and first-degree relatives of patients with colorectal adenomas or invasive CRC are at increased risk for CRC.⁸⁻¹² Genetic susceptibility to CRC includes well-defined inherited syndromes, such as Lynch syndrome (also known as hereditary nonpolyposis CRC [HNPCC]) and familial adenomatous polyposis (FAP).¹³⁻¹⁵ Therefore, it is recommended that all patients with colon cancer be queried regarding their family history and considered for risk assessment, as detailed in the [NCCN Guidelines for Colorectal Cancer Screening](#). Results from a randomized controlled trial (RCT) suggest that most individuals without a personal history of CRC and with one first-degree relative with CRC diagnosed before age 50 years or two first-degree relatives with CRC diagnosed at any age can safely be screened with colonoscopy every 6 years.¹⁶

CRC is a heterogeneous disease. An international consortium recently reported a molecular classification, defining four different subtypes: CMS1 (MSI Immune), hypermutated, microsatellite unstable (see *Lynch Syndrome* and *Microsatellite Instability*, below), with strong immune activation; CMS2 (Canonical), epithelial, chromosomally unstable, with marked WNT and MYC signalling activation; CMS3 (Metabolic), epithelial, with evident metabolic dysregulation; and CMS4 (Mesenchymal),

prominent transforming growth factor β activation, stromal invasion, and angiogenesis.¹⁷ However, this classification is not yet recommended in clinical practice.

Lynch Syndrome

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all CRC cases.^{13,14,18,19} This hereditary syndrome results from germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Although identifying a germline mutation in an MMR gene through sequencing is definitive for Lynch syndrome, patients usually undergo selection by considering family history and performing an initial test on tumor tissue before sequencing. One of two different initial tests can be performed on CRC specimens to identify individuals who might have Lynch syndrome: 1) immunohistochemical (IHC) analysis for MMR protein expression, which is often diminished because of mutation; or 2) analysis for microsatellite instability (MSI), which results from MMR deficiency and is detected as changes in the length of repetitive DNA elements in tumor tissue caused by the insertion or deletion of repeated units.²⁰ Testing the *BRAF* gene for mutation is indicated when IHC shows that *MLH1* expression is absent in the tumor. The presence of a *BRAF* mutation indicates that *MLH1* expression is down-regulated through somatic methylation of the promoter region of the gene and not through a germline mutation.²⁰ Testing for *MLH1* promoter methylation may also be used to determine this.

Many NCCN Member Institutions and other comprehensive cancer centers now perform IHC and sometimes MSI testing on all newly diagnosed colorectal and endometrial cancers regardless of family history to determine which patients should have genetic testing for Lynch syndrome.²¹⁻²⁴ The cost effectiveness of this approach, referred to as universal or reflex testing, has been confirmed for CRC, and this approach



has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group at the Centers for Disease Control and Prevention (CDC)²⁵⁻²⁷ and by the American Society for Clinical Pathology (ASCP), College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and ASCO in a guideline on molecular biomarkers for CRC.²⁸ The U.S. Multi-Society Task Force on Colorectal Cancer also recommends universal genetic testing of tumors of all patients with newly diagnosed CRC, as does the American Gastroenterological Association.^{29,30} The Cleveland Clinic recently reported on its experiences implementing such a screening approach.³¹

The NCCN Colon/Rectal Cancer Panel endorses universal MMR or MSI testing of all patients with a personal history of colon or rectal cancer to identify individuals with Lynch syndrome. This testing is also relevant for adjuvant therapy planning for stage II disease and treatment selection in stage IV disease (see *Microsatellite Instability* and *Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease in the First-Line and Non-First-Line Settings*, below). An infrastructure needs to be in place to handle the screening results in either case. A more detailed discussion is available in the [NCCN Guidelines for Colorectal Cancer Screening](#).

The Role of Vitamin D in CRC

Prospective studies have suggested that vitamin D deficiency may contribute to CRC incidence and/or that vitamin D supplementation may decrease CRC risk.³²⁻³⁸ Furthermore, several prospective studies have shown that low vitamin D levels are associated with increased mortality of patients with CRC.³⁹⁻⁴² In fact, a systematic review and meta-analysis of five studies totaling 2330 patients with CRC compared the outcomes of patients in the highest and lowest categories of vitamin D levels and found better overall survival (OS) (hazard ratio [HR], 0.71; 95% CI, 0.55–0.91) and disease-specific mortality (HR, 0.65; 95% CI, 0.49–0.86) in those with

higher vitamin D levels.⁴³ Another meta-analysis determined that the relationship between vitamin D levels and mortality is linear.⁴⁴

Results of a recent randomized, double-blind, placebo-controlled trial, however, showed that supplementation with vitamin D and/or calcium had no effect on the recurrence of colorectal adenomas within 3 to 5 years after removal of adenomas in 2259 participants.⁴⁵ A later analysis of the same study reported that the effect of vitamin D supplementation on recurrence of advanced adenomas varied significantly based on the genotype of the vitamin D receptor, indicating that only individuals with specific vitamin D receptor alleles may benefit from vitamin D supplementation for prevention of advanced adenomas.⁴⁶

Furthermore, no study has yet definitively shown that vitamin D supplementation improves outcomes in patients with CRC. Several studies have reported that supplementation did not improve survival.⁴⁷⁻⁴⁹ In addition, while the randomized, double-blind, phase II SUNSHINE trial reported a longer progression-free survival (PFS) for previously untreated metastatic CRC (mCRC) patients randomized to standard treatment plus high-dose vitamin D supplementation compared to those randomized to standard treatment plus low-dose vitamin D supplementation (13.0 months vs. 11.0 months), this difference was not significant (HR, 0.64; 95% CI, 0–0.90; $P = .02$).⁵⁰ There was also no significant difference between high- and standard-dose vitamin D supplementation for overall response rate (ORR) or OS. In a 2010 report, the Institute of Medicine (now known as the National Academy of Medicine) concluded that data supporting a role for vitamin D were only conclusive in bone health, and not in cancer and other diseases.⁵¹ Citing this report and the lack of level 1 evidence, the panel does not currently recommend routine screening for vitamin D deficiency or supplementation of vitamin D in patients with CRC.



Other Risk Factors for CRC

It is well-recognized that individuals with inflammatory bowel disease (ie, ulcerative colitis, Crohn's disease) are at an increased risk for CRC.⁵²⁻⁵⁴ Other possible risk factors for the development of CRC include smoking, the consumption of red and processed meats, alcohol consumption, diabetes mellitus, low levels of physical activity, metabolic syndrome, and obesity/high body mass index (BMI).^{53,55-70} In fact, in the EPIC cohort of almost 350,000 individuals, those who adhered to five healthy lifestyle factors (healthy weight, physical activity, non-smoking, limited alcohol consumption, and healthy diet) had an HR for the development of CRC of 0.63 (95% CI, 0.54–0.74) compared with those who adhered to 1 or fewer of the factors.⁷¹ Other large studies support the conclusion that adherence to healthy lifestyle factors can reduce the risk of CRC.^{72,73}

Some data suggest that consumption of dairy may lower risk for the development of CRC.^{70,74,75} However, a recent systematic review and meta-analysis of 15 cohort studies (>900,000 subjects; >5200 cases of CRC) only found an association between risk for colon cancer in men and the consumption of nonfermented milk.⁷⁶ No association was seen for rectal cancer in men or for colon or rectal cancer in women, and no association was seen for either cancer in either gender with consumption of solid cheese or fermented milk. Large cohort studies and meta-analyses suggest that other dietary factors may also lower the risk for CRC, including the consumption of fish and legumes.⁷⁷⁻⁷⁹ Furthermore, the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) may also decrease the risk for CRC.⁸⁰⁻⁸⁵ In fact, the USPSTF recommends that adults aged 50 to 59 years with a 10-year cardiovascular disease risk greater than or equal to 10% and a life expectancy of 10 years or more and without an increased bleeding risk take low-dose aspirin daily for at least 10 years for the primary prevention of both cardiovascular disease and CRC.⁸⁶

In addition, some data suggest that smoking, metabolic syndrome, obesity, and red/processed meat consumption are associated with a poor prognosis.^{57,87-91} Conversely, post-diagnosis fish consumption may be associated with a better prognosis.⁹² A family history of CRC increases risk while improving prognosis.⁹³ Data on the effect of dairy consumption on prognosis after diagnosis of CRC are conflicting.^{94,95}

The relationship between diabetes and CRC is complex. Whereas diabetes and insulin use may increase the risk of developing CRC, treatment with metformin appears to decrease risk, at least in women.⁹⁶⁻¹⁰⁵ Results of a small randomized study suggest that 1 year of low-dose metformin in non-diabetic patients with previously resected colorectal adenomas or polyps may reduce the likelihood of subsequent adenomas or polyps.¹⁰⁶ In addition, although patients with CRC and diabetes appear to have a worse prognosis than those without diabetes,^{107,108} patients with CRC and diabetes treated with metformin seem to have a survival benefit over those not treated with metformin.^{104,109,110} The data regarding the effects of metformin on CRC incidence and mortality, however, are not completely consistent, with some studies seeing no effect.^{111,112}

Staging

Staging in colon cancer is based on the TNM (tumor, node, metastases) system. The TNM categories reflect very similar survival outcomes for rectal and colon cancer; these diseases therefore share the same staging system.⁶

In the 8th edition of the AJCC Staging Manual, T1 tumors involve the submucosa; T2 tumors penetrate through the submucosa into the muscularis propria; T3 tumors penetrate through the muscularis propria; T4a tumors directly penetrate to the surface of the visceral peritoneum; and T4b tumors directly invade or are adherent to other organs or structures.⁶ The T component of colon cancer staging is very important in



prognostication, because analyses have shown that patients with T4,N0 tumors have a lower survival than those with T1–2,N1–2 tumors.^{113–115} Furthermore, in an analysis of 109,953 patients with invasive colon cancer included in the SEER colon cancer database from 1992 to 2004, the relative 5-year survival rate (ie, 5-year survival corrected by age-related morbidity) was considerably higher (79.6%) for node-negative patients with T4a compared with node-negative patients with T4b tumors (58.4%).¹¹⁶

Regional lymph node classification includes N1a (1 positive lymph node); N1b (2–3 positive lymph nodes), N2a (4–6 positive nodes); and N2b (7 or more positive nodes). In addition, tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis (ie, satellite tumor nodules) have been classified as N1c. Within each T stage, survival is inversely correlated with N stage (N0, N1a, N1b, N2a, and N2b).⁶

Metastatic disease is classified as M1a when metastases that are limited to only one site/solid organ (including to lymph nodes outside the primary tumor regional drainage area) are positive. M1b is used for metastases to multiple distant sites or solid organs, exclusive of peritoneal carcinomatosis. The 8th edition of the AJCC Cancer Staging Manual includes the M1c category for peritoneal carcinomatosis with or without blood-borne metastasis to visceral organs.⁶ Patients with peritoneal metastases have a shorter PFS and OS than those without peritoneal involvement.¹¹⁷

Pathology

CRCs are usually staged after surgical exploration of the abdomen and pathologic examination of the surgical specimen. Some of the criteria that should be included in the report of the pathologic evaluation include the following: grade of the cancer; depth of penetration and extension to

adjacent structures (T); number of regional lymph nodes evaluated; number of positive regional lymph nodes (N); an assessment of the presence of distant metastases to other organs, to the peritoneum or an abdominal structure, or in non-regional lymph nodes (M); the status of proximal, distal, radial, and mesenteric margins; lymphovascular invasion; perineural invasion (PNI); and tumor deposits.^{6,118–126} The prefixes “p” and “yp” used in TNM staging denote “pathologic staging” and “pathologic staging after neoadjuvant therapy and surgery,” respectively.⁶

Margins

In colon cancer, the radial margin (or circumferential resection margin, CRM) represents the adventitial soft tissue closest to the deepest penetration of the tumor. It is created surgically by blunt or sharp dissection of the retroperitoneal aspect, and it corresponds to any aspect of the colon that is not covered by a serosal layer of mesothelial cells.⁶ It must be dissected from the retroperitoneum to remove the viscus. The serosal (peritoneal) surface does not constitute a surgical margin. The radial margins should be assessed in all colonic segments with non-peritonealized surfaces. In segments of the colon that are completely encased by peritoneum, such as the transverse colon, the mesenteric resection margin is the only relevant radial margin.⁶ On pathologic examination, it is difficult to appreciate the demarcation between the peritonealized surface and the non-peritonealized surface. The surgeon is therefore encouraged to mark the area of non-peritonealized surface with a clip or suture.⁶ In a study of 608 patients with rectal cancer, a positive radial margin was shown to be a negative prognostic factor for both local recurrence and OS.¹²⁷ Patients with CRM-positive resections had a 38.2% local recurrence rate, whereas those with CRM-negative resections had a 10.0% local recurrence rate.¹²⁷



Lymph Nodes

The number of lymph nodes evaluated is important to note on the pathology report. A secondary analysis of patients from the Intergroup Trial INT-0089 showed that an increase in the number of lymph nodes examined was associated with increased survival for patients with both node-negative and node-positive disease.¹²⁸ In addition, results from population-based studies show an association between improvement in survival and examination of greater than or equal to 12 lymph nodes.^{129,130} The mechanism for this correlation is poorly understood. It has been hypothesized that the analysis of more lymph nodes would result in more accurate staging and thus better tailored treatments, but recent results suggest that this idea is not correct.¹³¹⁻¹³³ Instead it is likely that other factors associated with lymph node harvest are important for the survival advantage. For instance, the extent and quality of surgical resection can have an impact on the node harvest.¹³⁴ The number of regional lymph nodes retrieved from a surgical specimen also varies with age of the patient, gender, and tumor grade or site.^{128,129,135,136} In addition, it has been suggested that lymph nodes in patients with a strong anti-cancer immune response are easier to find, and that such patients have an improved prognosis.¹³⁷ Another possibility is that the underlying tumor biology affects lymph node yield and prognosis in parallel. For instance, MSI and wild-type *KRAS/BRAF* have been associated with both improved prognosis and increased lymph node retrieval.^{138,139}

Regardless of the mechanism for the observed correlation, the panel recommends examination of a minimum of 12 lymph nodes. This recommendation is supported by CAP¹⁴⁰ and the 8th edition of the AJCC Cancer Staging Manual,⁶ which also specify pathologic examination of a minimum of 12 lymph nodes. Notably, emerging evidence suggests that a greater number of nodes may need to be examined in some situations, particularly for T4 lesions, to provide an adequate assessment of disease stage.¹⁴¹ For stage II (pN0) colon cancer, it is recommended that the

pathologist go back to the specimen and submit more tissue of potential lymph nodes if fewer than 12 nodes were initially identified. Patients considered to have N0 disease but for whom fewer than 12 nodes have been examined are suboptimally staged and should be considered to be at higher risk.

The ratio of positive lymph nodes to the total number of lymph nodes examined is also being evaluated for possible prognostic impact. Case series have suggested cutoffs of 0.1, 0.2, or 0.25 as lymph node ratios that are prognostic for OS or PFS.¹⁴²⁻¹⁴⁵ A systematic review and meta-analysis of 33 studies that included greater than 75,000 patients with node-positive CRC concluded that a higher lymph node ratio was significantly associated with shorter OS and disease-free survival (DFS).¹⁴⁶ Analysis of the SEER database, however, suggests that the lymph node ratio does not adequately represent the different effects of both the number of positive lymph nodes and the number of lymph nodes examined.¹⁴⁷

The potential benefit of sentinel lymph node evaluation for colon cancer has mostly been associated with providing more accurate staging of nodal pathology through detection of micrometastatic disease in the sentinel node(s).¹⁴⁸ Results of studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify small foci of tumor cells and the identification of particular tumor antigens through IHC have been reported.¹⁴⁸⁻¹⁵³

There is also a potential benefit of assessing regional lymph nodes for micrometastases and isolated tumor cells.^{151,154-157} The 8th edition of the AJCC Cancer Staging Manual considers clusters of 10 to 20 tumor cells, or clumps of tumor that measure at least 0.2 mm in diameter, but smaller than 2 mm, in diameter to be micrometastases.⁶ Such micrometastases have been shown to be a poor prognostic factor. One study of 312 consecutive patients with pN0 disease found that positive cytokeratin



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staining was associated with a higher risk of recurrence.¹⁵⁸ Relapse occurred in 14% of patients with positive nodes compared to 4.7% of those with negative nodes (HR, 3.00; 95% CI, 1.23–7.32; $P = .013$). A 2012 systematic review and meta-analysis came to a similar conclusion, finding decreased survival in patients with pN0 tumors with IHC or reverse transcriptase polymerase chain reaction (RT-PCR) evidence of tumor cells in regional nodes.¹⁵⁹ A 2014 meta-analysis also found that the presence of micrometastases increases the likelihood of disease recurrence.¹⁶⁰

Tumor Deposits

Tumor deposits, also called extranodal tumor deposits, peritumoral deposits, or satellite nodules, are irregular discrete tumor deposits in the pericolic or perirectal fat that show no evidence of residual lymph node tissue, but are within the lymphatic drainage of the primary tumor. They are not counted as lymph nodes replaced by tumor. Most of these tumor deposits are thought to arise from lymphovascular invasion or, occasionally, PNI.^{161,162} The number of tumor deposits should be recorded in the pathology report, because they have been shown to be associated with reductions in DFS and OS.^{125,126,163,164} Multivariate survival analysis in one study showed that patients with pN0 tumors without satellite nodules had a 91.5% 5-year survival rate compared with a 37.0% 5-year survival rate for patients with pN0 tumors and the presence of satellite nodules ($P < .0001$).¹²⁶

Perineural Invasion

Several studies have shown that the presence of PNI is associated with a significantly worse prognosis.^{122-124,163,165-168} For example, one retrospective analysis of 269 consecutive patients who had colorectal tumors resected at one institution found a four-fold greater 5-year survival in patients without PNI versus patients whose tumors invaded nearby neural structures.¹²³ Multivariate analysis of patients with stage II rectal cancer showed that patients with PNI have a significantly worse 5-year

DFS compared with those without PNI (29% vs. 82%; $P = .0005$).¹²⁴ Similar results were seen for patients with stage III disease.¹²² A meta-analysis that included 58 studies and 22,900 patients also found that PNI is associated with a worse 5-year OS (relative risk [RR], 2.09; 95% CI, 1.68–2.61) and 5-year DFS (RR, 2.35; 95% CI, 1.66–3.31).¹⁶⁶ PNI is therefore included as a high-risk factor for systemic recurrence.

Tumor Budding

Tumor budding is defined as the presence of a single cell or a cluster of four or fewer neoplastic cells as detected by H&E staining at the advancing edge of an invasive carcinoma. As specified by the 2016 International Tumor Budding Consensus Conference (ITBCC), the total number of buds should be reported from a selected hot spot measuring 0.785 mm².¹⁶⁹ Budding is separated into three tiers: low (0–4 buds), intermediate (5–9 buds), and high (≥ 10 buds).

Several studies have shown that high-grade tumor budding in pT1 colorectal cancer or malignant polyps is associated with an increased risk of lymph node metastasis, although the methodologies for assessing tumor budding were not uniform.¹⁷⁰⁻¹⁷⁴ Studies have also supported tumor budding as an independent prognostic factor for stage II colon cancer. A retrospective study that assessed tumor budding in 135 stage II colon cancer specimens according to ITBCC criteria found that tumor budding correlated with survival outcomes.¹⁷⁵ Disease-specific survival (DSS) was 89% for low-tier tumor budding, 73% for intermediate-tier, and 52% for high-tier ($P = .001$). Another retrospective study evaluated 174 stage II colon cancer specimens for tumor budding.¹⁷⁶ This study also used the ITBCC criteria and found tumor budding to be independently associated with DSS ($P = .01$); specifically, 5-year DSS was 96% for low-tier tumor budding compared to 92% for high-tier for all patients. The difference was even more dramatic for those patients who received no adjuvant chemotherapy. For these patients, 5-year DSS was 98% for low-tier tumor



budding versus 80% for high-tier ($P = .008$). Tumor budding is therefore included as a high-risk factor for recurrence and may inform decisions related to adjuvant therapy.

Adenocarcinomas of the Small Bowel and Appendix

For recommendations on the management of small bowel adenocarcinoma, see the [NCCN Guidelines for Small Bowel Adenocarcinoma](#).

Adenocarcinomas of the appendix are rare cancers for which no NCCN Guidelines exist. Data on treatment of appendiceal adenocarcinomas are quite limited. Most patients receive debulking surgery with systemic or intraperitoneal therapy (intraperitoneal therapy is discussed further in *Peritoneal Carcinomatosis*, below). Case series have shown that combination systemic therapy in patients with advanced disease can result in response rates similar to those seen in advanced CRC.¹⁷⁷⁻¹⁷⁹ A recent analysis of the NCCN Outcomes Database found that fluoropyrimidine-based therapy is the most commonly administered systemic therapy at NCCN Member Institutions.¹⁸⁰ Among 99 patients with a recorded best response, the response rate was 39%, with a median PFS of 1.2 years.

Acknowledging the lack of high-level data, the panel recommends that adenocarcinomas of the appendix be treated with systemic therapy according to these NCCN Guidelines for Colon Cancer.

Clinical Presentation and Treatment of Nonmetastatic Disease

Workup and Management of the Malignant Polyp

A malignant polyp is defined as one with cancer invading the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated the submucosa and are therefore not considered capable of regional nodal metastasis.¹¹⁹ The panel recommends marking the polyp

site during colonoscopy or within 2 weeks of the polypectomy if deemed necessary by the surgeon. Testing for MMR/MSI should be done during the initial workup to help with diagnosis of Lynch syndrome and inform treatment decision-making if adjuvant therapy is later indicated.

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or adenoma, physicians should review the pathology and consult with the patient.¹⁸¹ In patients with invasive cancer in a pedunculated or sessile polyp (adenoma), no additional surgery is required if the polyp has been completely resected and has favorable histologic features.^{182,183} Favorable histologic features include lesions of grade 1 or 2, no angiolymphatic invasion, and a negative resection margin. However, in addition to the option of observation, the panel includes the option of colectomy in patients with a completely removed, single-specimen, sessile polyp with favorable histologic features and clear margins. This option is included because the literature seems to indicate that patients with sessile polyps may have a significantly greater incidence of adverse outcomes, including disease recurrence, mortality, and hematogenous metastasis compared with those with pedunculated polyps. This increased incidence likely occurs because of the high probability of a positive margin after endoscopic removal.¹⁸⁴⁻¹⁸⁶

If the polyp specimen is fragmented, the margins cannot be assessed; if the specimen shows unfavorable histopathology, additional workup including complete blood count (CBC), chemistry profile, carcinoembryonic antigen (CEA) determination, chest/abdominal/pelvic CT, and consideration of pelvic MRI should be performed to better assess for local staging and extent of disease (see *Workup and Management of Invasive Nonmetastatic Colon Cancer* for more details on this workup). If appropriate following workup, colectomy with en bloc removal of lymph nodes is recommended.^{181,187-189} Laparoscopic surgery is an option.¹⁹⁰ Unfavorable histopathologic features for malignant polyps include grade 3



or 4, angiolymphatic invasion, or a positive margin of resection.^{172,191} Notably, no consensus currently exists as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as the presence of tumor within 1 to 2 mm of the transected margin or the presence of tumor cells within the diathermy of the transected margin.^{181,192-194} In addition, several studies have shown that tumor budding is an adverse histologic feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.¹⁹⁵⁻¹⁹⁸

All patients who have malignant polyps removed by transanal excision or transabdominal resection should undergo total colonoscopy to rule out other synchronous polyps, and should subsequently undergo appropriate follow-up surveillance endoscopy. Adjuvant chemotherapy is not recommended for patients with stage I lesions.

Workup and Management of Invasive Nonmetastatic Colon Cancer

Patients who present with invasive colon cancer appropriate for resection require a complete staging workup, including biopsy, pathologic tissue review, total colonoscopy, CBC, chemistry profile, CEA determination, and baseline CT scans of the chest, abdomen, and pelvis.¹⁹⁹ Testing for MMR/MSI should be done at diagnosis to help with detection of Lynch syndrome and to inform treatment decision-making if adjuvant therapy is indicated. CT should be with IV and oral contrast. If the CT of the abdomen and pelvis is inadequate or if CT with IV contrast is contraindicated, an abdominal/pelvic MRI with contrast plus a non-contrast chest CT should be considered. The chest CT can identify lung metastases, which occur in approximately 4% to 9% of patients with colon and rectal cancer.²⁰⁰⁻²⁰² One series of 378 patients found that resection of pulmonary metastases resulted in 3-year recurrence-free survival of 28% and 3-year OS of 78%.²⁰³ Fertility risks should be discussed with appropriate patients prior to treatment and referral for and/or counseling

on fertility preservation options should be done if indicated (see the [NCCN Guidelines for Adolescent and Young Adult Oncology](#) for more information on this topic).

The consensus of the panel is that a PET/CT scan is not indicated at baseline for preoperative workup. In fact, PET/CT scans are usually done without contrast and multiple slicing and do not obviate the need for a contrast-enhanced diagnostic CT scan. If, however, abnormalities are seen on CT or MRI scan that are considered suspicious but inconclusive for metastases, then a PET/CT scan may be considered to further delineate that abnormality, if this information will change management. A PET/CT scan is not indicated for assessing subcentimeter lesions, because these are routinely below the level of PET/CT detection.

For resectable colon cancer that is causing overt obstruction, one-stage colectomy with en bloc removal of regional lymph nodes, resection with diversion, or diversion or stent (in selected cases) followed by colectomy are options. Stents are generally reserved for cases of distal lesions in which a stent can allow decompression of the proximal colon with later elective colostomy with primary anastomosis.²⁰⁴ A meta-analysis found that oncologic outcomes were similar for surgery and for stenting followed by elective surgery.²⁰⁵ This result was supported by the ESCO trial, an RCT from Europe that reported similar outcomes between colonic stenting as a bridge to surgery compared to emergency surgery for malignant colon obstruction.²⁰⁶ Another meta-analysis of comparative studies compared colectomy to diversion followed by colectomy.²⁰⁷ Although 30-day mortality and morbidity were the same between the groups, the diversion group was less likely to have a permanent colostomy (OR, 0.22; 95% CI, 0.11–0.46). Preoperative stoma education and marking of the site by an enterostomal therapist have been shown to improve outcomes and are therefore recommended for patients who are expected to receive a stoma following surgery.²⁰⁸⁻²¹⁰



If the cancer is locally unresectable or the patient is medically inoperable, systemic therapy or chemoradiation is recommended, possibly with the goal of converting the lesion to a resectable state.

Surgical Management

For resectable non-metastatic colon cancer, the preferred surgical procedure is colectomy with en bloc removal of the regional lymph nodes.^{211,212} The extent of colectomy should be based on the tumor location, resecting the portion of the bowel and arterial arcade containing the regional lymph nodes. Other nodes, such as those at the origin of the vessel feeding the tumor (ie, apical lymph node), and suspicious lymph nodes outside the field of resection, should also be biopsied or removed if possible. Resection must be complete to be considered curative, and positive lymph nodes left behind indicate an incomplete (R2) resection.²¹³

There has been some recent attention focused on the quality of colectomy.²¹⁴ A retrospective observational study found a possible OS advantage for surgery in the mesocolic plane over surgery in the muscularis propria plane.²¹⁵ A comparison of resection techniques by expert surgeons in Japan and Germany showed that complete mesocolic excision (CME) with central vascular ligation resulted in greater mesentery and lymph node yields than the Japanese D3 high tie surgery.²¹⁶

Differences in outcomes were not reported. A retrospective, population-based study in Denmark also supports the benefit of a CME approach in patients with stage I–III colon cancer, with a significant difference in 4-year DFS ($P = .001$) between those undergoing CME resection (85.8%; 95% CI, 81.4–90.1) and those undergoing conventional resection (75.9%, 95% CI, 72.2–79.7).²¹⁷ A systematic review found that four of nine prospective studies reported improved lymph node harvest and survival with CME compared with non-CME colectomy; the other studies reported improved specimen quality.²¹⁸

Minimally Invasive Approaches to Colectomy

Laparoscopic colectomy is an option in the surgical management of colon cancer.²¹⁹⁻²²² In a small European randomized trial (Barcelona), the laparoscopic approach seemed to be associated with some modest survival advantage, significantly faster recovery, and shorter hospital stays.²²³ More recently, a similar but larger trial (COLOR trial) of 1248 patients with colon cancer randomly assigned to curative surgery with either a conventional open approach or laparoscopic-assisted surgery showed a nonsignificant absolute difference of 2.0% in 3-year DFS favoring open colectomy.²²⁴ Non-inferiority of the laparoscopic approach could not be established because of study limitations. Ten-year outcomes of the COLOR trial also showed similar rates of DFS, OS, and recurrence between open and laparoscopic surgery.²²⁵ In the CLASICC study of 794 patients with CRC, no statistically significant differences in 3-year rates of OS, DFS, and local recurrence were observed between these surgical approaches.²²⁶ Long-term follow-up of participants in the CLASICC trial showed that the lack of differences in outcomes between arms continued over a median 62.9 months.²²⁷

In another trial (COST study) of 872 patients with colon cancer randomly assigned to undergo either open or laparoscopic-assisted colectomy for curable colon cancer, similar 5-year recurrence and 5-year OS rates were seen after a median of 7 years follow-up.^{228,229} A similar RCT in Australia and New Zealand also found no differences in disease outcomes.²³⁰ In addition, results of several recent meta-analyses have supported the conclusion that the two surgical approaches provide similar long-term outcomes with respect to local recurrence and survival in patients with colon cancer.²³¹⁻²³⁶ Factors have been described that may confound conclusions drawn from randomized studies comparing open colectomy with laparoscopic-assisted surgery for colon cancer.^{237,238}



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A subanalysis of results from the COLOR trial evaluating short-term outcomes (eg, conversion rate to open colectomy, number of lymph nodes collected, number of complications) based on hospital case volume indicated that these outcomes were statistically significantly more favorable when laparoscopic surgery was performed at hospitals with high case volumes.²³⁹ A meta-analysis of 18 studies (6153 patients) found a lower rate of cardiac complications with laparoscopic colectomy compared with open resection.²⁴⁰ Analyses of large national databases also support the benefits of the laparoscopic approach.^{241,242}

In recent years, perioperative care has improved, with reductions in the average length of hospital stay and complication rates after surgery.^{243,244} The multicenter, randomized, controlled EnROL trial therefore compared conventional and laparoscopic colectomy with an enhanced recovery program in place.²⁴⁵ Outcomes were the same in both arms, with the exception of median length of hospital stay, which was significantly shorter in the laparoscopic group (5 days vs. 7 days; $P = .033$).

Robotic colectomy has been compared to the laparoscopic approach, mostly with observational cohort studies.²⁴⁶⁻²⁴⁹ In general, the robotic approach appears to result in longer operating times and is more expensive but may be associated with less blood loss, shorter time to recovery of bowel function, shorter hospital stays, and lower rates of complications and infections.

The panel recommends that minimally invasive colectomy be considered only by surgeons experienced in the techniques. A thorough abdominal exploration is required as part of the procedure. Routine use of minimally invasive colon resection is generally not recommended for tumors that are acutely obstructed or perforated or tumors that are clearly locally invasive into surrounding structures (ie, T4). Patients at high risk for prohibitive abdominal adhesions should not have minimally invasive colectomy, and

those who are found to have prohibitive adhesions during exploration should be converted to an open procedure.^{190,250,251}

Adjuvant Chemotherapy for Resectable Colon Cancer

Choices for adjuvant therapy for patients with resected, nonmetastatic colon cancer depend on the stage of disease:

- Patients with stage I disease and patients with MSI-high [MSI-H], stage II disease do not require any adjuvant therapy.
- Patients with low-risk stage II disease that is microsatellite-stable (MSS) or MMR-proficient (pMMR) can be observed without adjuvant therapy or considered for capecitabine or 5-FU/leucovorin (LV). Based on results of the MOSAIC trial,²⁵²⁻²⁵⁴ and the possible long-term sequelae of oxaliplatin-based chemotherapy, the panel does not consider FOLFOX (infusional 5-FU, LV, oxaliplatin) to be an appropriate adjuvant therapy option for patients with stage II disease without high-risk features.
- Patients with stage II disease that is MSS/pMMR and at high risk for systemic recurrence, defined as those with poor prognostic features, including T4 tumors (stage IIB/IIC); poorly differentiated/undifferentiated histology; lymphovascular invasion; PNI; tumor budding; bowel obstruction; lesions with localized perforation or close, indeterminate, or positive margins; or inadequately sampled nodes (<12 lymph nodes), can be considered for 6 months of adjuvant chemotherapy with 5-FU/LV, capecitabine, or FOLFOX, or 3 months of adjuvant chemotherapy with CAPEOX (capecitabine and oxaliplatin).^{120,255} Observation without adjuvant therapy is also an option in this population. The factors in decision-making for stage II adjuvant therapy are discussed in more detail below.



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- For patients with low-risk (T1–3, N1) stage III disease, the preferred adjuvant treatment options are 3 months of CAPEOX²⁵⁶⁻²⁵⁸ or 3 to 6 months of FOLFOX.^{252-254,258} Other treatment options include 6 months of single-agent capecitabine²⁵⁹ or 5-FU/LV in patients for whom oxaliplatin therapy is believed to be inappropriate.²⁶⁰⁻²⁶³
- For patients with high-risk (T4, N1–2 or any T, N2) stage III disease, the preferred adjuvant treatment options are 6 months of FOLFOX²⁵²⁻²⁵⁴ or 3 to 6 months of CAPEOX.²⁵⁶⁻²⁵⁸ Other treatment options include 6 months of single-agent capecitabine²⁵⁹ or 5-FU/LV in patients for whom oxaliplatin therapy is believed to be inappropriate.²⁶⁰⁻²⁶³

Population and institutional studies have shown that patients with resected colon cancer treated with adjuvant therapy have a survival advantage over those not treated with adjuvant therapy.²⁶⁴⁻²⁶⁶ For example, patients from the National Cancer Database with stage III or high-risk stage II disease treated according to these NCCN Guidelines had a survival advantage over patients whose treatment did not adhere to these guidelines.²⁶⁴ A retrospective cohort study of 852 patients with any stage of colon or rectal cancer treated at Memorial University Medical Center in Savannah, Georgia similarly found that concordance with the recommendations in these NCCN Guidelines resulted in a lower risk of death.²⁶⁶

Endpoints for Adjuvant Chemotherapy Clinical Trials

The Adjuvant Colon Cancer End Points (ACCENT) collaborative group evaluated the appropriateness of various endpoints for adjuvant chemotherapy trials in colon cancer. Results of an analysis of individual patient data from 20,898 patients in 18 randomized colon adjuvant clinical trials by the ACCENT group suggested that DFS after 2 and 3 years follow-up are appropriate endpoints for clinical trials involving treatment of colon cancer with 5-FU–based chemotherapy in the adjuvant setting.²⁶⁷ An

update of this analysis showed that most relapses occur within 2 years after surgery, and that recurrence rates were less than 1.5% per year and less than 0.5% per year after 5 and 8 years, respectively.²⁶⁸ More recently, however, a further update of the data suggested that the association between 2- or 3-year DFS and 5-year OS was reduced when patient survival after recurrence was hypothetically prolonged to match the current time to survival from recurrence seen with modern combination therapies (2 years), and that more than 5 years may now be required to evaluate the effect of adjuvant therapies on OS.²⁶⁹ Further confirmation of this result comes from a new analysis by the ACCENT group of data from 12,676 patients undergoing combination therapies from six trials.²⁷⁰ This study determined that 2- and 3-year DFS correlated with 5- and 6-year OS in patients with stage III disease but not in those with stage II disease. In all patients, the correlation of DFS to OS was strongest at 6-year follow-up, suggesting that at least 6 years are required for adequate assessment of OS in modern adjuvant colon cancer trials.²⁷⁰

Adjuvant Chemotherapy in Stage II Disease

The impact of adjuvant chemotherapy for patients with stage II colon cancer has been addressed in several clinical trials and practice-based studies.^{120,252-255} Results from a 2015 meta-analysis of 25 high-quality studies showed that 5-year DFS in patients with stage II colon cancer who did not receive adjuvant therapy was 81.4% (95% CI, 75.4–87.4), whereas it was 79.3% (95% CI, 75.6–83.1) for patients with stage II colon cancer treated with adjuvant chemotherapy.²⁷¹ On the other hand, for patients with stage III colon cancer, the 5-year DFS was 49.0% (95% CI, 23.2–74.8) and 63.6% (95% CI, 59.3–67.9) in those treated without and with adjuvant chemotherapy, respectively. These results suggest that the benefit of adjuvant therapy is greater in patients at higher risk because of nodal status. In contrast to results from most other trials, the QUASAR trial indicated a small but statistically significant survival benefit for patients with stage II disease treated with 5-FU/LV compared to patients not



receiving adjuvant therapy (RR of recurrence at 2 years, 0.71; 95% CI, 0.54–0.92; $P = .01$).²⁷² In this trial, however, approximately 64% of patients had fewer than 12 lymph nodes sampled, and thus actually may have been patients with higher risk disease who were more likely to benefit from adjuvant therapy.²⁷³

The benefit of oxaliplatin in adjuvant therapy for patients with stage II colon cancer has also been addressed. Results from a recent post-hoc exploratory analysis of the MOSAIC trial did not show a significant DFS benefit of FOLFOX over 5-FU/LV for patients with stage II disease at a follow-up of 6 years (HR, 0.84; 95% CI, 0.62–1.14; $P = .258$).²⁷⁴ After longer follow-up, no difference in 10-year OS was observed in the stage II subpopulation (79.5% vs. 78.4%; HR, 1.00; $P = .98$).²⁵⁴ In addition, patients with high-risk stage II disease (ie, disease characterized by at least one of the following: T4 tumor; tumor perforation; bowel obstruction; poorly differentiated tumor; venous invasion; <10 lymph nodes examined) receiving FOLFOX did not have improved DFS compared with those receiving infusional 5-FU/LV (HR, 0.72; 95% CI, 0.50–1.02; $P = .063$). Furthermore, no OS benefit was seen in the stage II population overall or in the stage II population with high-risk features. Similar results were seen in the C-07 trial, which compared FLOX to 5-FU/LV in patients with stage II and III disease.²⁷⁵ Results of a large population-based study also support the lack of benefit of the addition of oxaliplatin to adjuvant regimens for patients with stage II colon cancer.²⁷⁶

Clinical trial results are supported by data from the community setting. Using the SEER databases, a 2002 analysis of outcomes of patients with stage II disease based on whether or not they had received adjuvant chemotherapy showed no statistically significant difference in 5-year OS between the groups (78% vs. 75%, respectively), with an HR for survival of 0.91 (95% CI, 0.77–1.09) when patients receiving adjuvant treatment were compared with untreated patients.²⁷⁷ In contrast, a 2016 analysis of

153,110 patients with stage II colon cancer from the National Cancer Database found that adjuvant treatment was associated with improved survival (HR, 0.76; $P < .001$) even after adjustment for comorbidity and unplanned hospital readmissions.²⁷⁶ Results of another population-level analysis from the Netherlands published in 2016 suggest that the benefit of adjuvant therapy in patients with stage II colon cancer may be limited to those with pT4 tumors.²⁷⁸

Decision-making regarding the use of adjuvant therapy for patients with stage II disease should incorporate patient/physician discussions individualized for the patient, and should include explanations of the specific characteristics of the disease and its prognosis and the evidence related to the efficacy and possible toxicities associated with treatment, centering on patient choice.^{255,279,280} Observation and participation in a clinical trial are options that should be considered. Patients with average-risk stage II colon cancer have a very good prognosis, so the possible benefit of adjuvant therapy is small. Patients with high-risk features, on the other hand, traditionally have been considered more likely to benefit from adjuvant chemotherapy. However, the current definition of high-risk stage II colon cancer is clearly inadequate, because many patients with high-risk features do not have a recurrence while some patients deemed to be average-risk do.²⁸¹ Furthermore, no data point to features that are predictive of benefit from adjuvant chemotherapy, and no data correlate risk features and selection of chemotherapy in patients with high-risk stage II disease.

Overall, the NCCN Panel supports the conclusion of a 2004 ASCO Panel and believes that it is reasonable to accept the relative benefit of adjuvant therapy in stage III disease as indirect evidence of benefit for stage II disease, especially for those with high-risk features.²⁵⁵ Additional information that may influence adjuvant therapy decisions for stage II and/or stage III disease (MSI, multigene assays, and the influence of



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patient age) is discussed below. Research into additional possible predictive markers may allow for more informed decision-making in the future.^{282,283}

Microsatellite Instability

MSI is an important piece of information to consider when deciding whether to use adjuvant chemotherapy in patients with stage II disease. Mutation of MMR genes or modifications of these genes (eg, methylation) can result in MMR protein deficiency and MSI (see *Risk Assessment*, above).²⁸⁴ Tumors showing the presence of MSI are classified as either MSI-H or MSI-Low (MSI-L), depending on the extent of instability in the markers tested, whereas tumors without this characteristic are classified as MSS.²⁸⁵ Patients determined to have defective MMR (dMMR) status are biologically the same population as those with MSI-H status.

Germline mutations in the MMR genes *MLH1*, *MSH2*, *MSH6*, and/or *PMS2* or *EpCAM* are found in individuals with Lynch syndrome, which is responsible for 2% to 4% of colon cancer cases.^{13,14,18,19} Somatic MMR defects have been reported to occur in approximately 19% of colorectal tumors,²⁸⁶ whereas others have reported somatic hypermethylation of the *MLH1* gene promoter, which is associated with *MLH1* gene inactivation, in as many as 52% of colon tumors.²⁸⁷

Data from the PETACC-3 trial showed that tumor specimens characterized as MSI-H are more common in stage II disease than in stage III disease (22% vs. 12%, respectively; $P < .0001$).²⁸⁸ In another large study, the percentage of stage IV tumors characterized as MSI-H was only 3.5%.²⁸⁹ These results suggest that MSI-H (ie, dMMR) tumors have a decreased likelihood to metastasize. In fact, substantial evidence shows that in patients with stage II disease, a deficiency in MMR protein expression or MSI-H tumor status is a prognostic marker of a more favorable outcome.²⁹⁰⁻²⁹² In contrast, the favorable impact of dMMR on outcomes

seems to be more limited in stage III colon cancer and may vary with primary tumor location.^{290,293}

Some of these same studies also show that a deficiency in MMR protein expression or MSI-H tumor status may be a predictive marker of decreased benefit and possibly a detrimental impact from adjuvant therapy with a fluoropyrimidine alone in patients with stage II disease.^{291,292,294} A retrospective study involving long-term follow-up of patients with stage II and III disease evaluated according to MSI tumor status showed that those characterized as MSI-L or MSS had improved outcomes with 5-FU adjuvant therapy. However, patients with tumors characterized as MSI-H did not show a statistically significant benefit from 5-FU after surgery, instead exhibiting a lower 5-year survival rate than those undergoing surgery alone.²⁹¹ Similarly, results from another retrospective study of pooled data from adjuvant trials by Sargent et al²⁹² showed that in tumors characterized as dMMR, adjuvant 5-FU chemotherapy seemed to be detrimental in patients with stage II disease, but not in those with stage III disease.

In contrast to the findings of Sargent et al,²⁹² however, a recent study of 1913 patients with stage II CRC from the QUASAR study, half of whom received adjuvant chemotherapy, showed that although dMMR was prognostic (the recurrence rate of dMMR tumors was 11% vs. 26% for pMMR tumors), it did not predict benefit or detrimental impact of chemotherapy.²⁷³ A recent study of patients in the CALGB 9581 and 89803 trials came to a similar conclusion.²⁹⁵ MMR status was prognostic but not predictive of benefit or detrimental impact of adjuvant therapy (irinotecan plus bolus 5-FU/LV [IFL regimen]) in patients with stage II colon cancer.

The panel recommends universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer to identify individuals with Lynch syndrome (see *Lynch Syndrome*, above), to inform use of



immunotherapy in patients with metastatic disease (see *Biomarkers for Systemic Therapy*, below), and to inform decisions for patients with stage II disease. Patients with stage II MSI-H tumors may have a good prognosis and do not benefit from 5-FU adjuvant therapy, and adjuvant therapy should not be given to patients with low-risk stage II MSI-H tumors. It should be noted that poorly differentiated histology is not considered a high-risk feature for patients with stage II disease whose tumors are MSI-H.

Multigene Assays, Immunoscore, and Circulating Tumor DNA (ctDNA)

Several assays have been developed in hopes of providing prognostic and predictive information to aid in decisions regarding adjuvant therapy in patients with stage II or III colon cancer.

Oncotype DX colon cancer assay quantifies the expression of seven recurrence-risk genes and five reference genes as a prognostic classifier of low, intermediate, or high likelihood of recurrence.²⁹⁶ Clinical validation in patients with stage II and III colon cancer from QUASAR²⁹⁷ and National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07²⁹⁸ trials showed that recurrence scores are prognostic for recurrence, DFS, and OS in stage II and III colon cancer, but are not predictive of benefit to adjuvant therapy. For the low, intermediate, and high recurrence risk groups, recurrence at 3 years was 12%, 18%, and 22%, respectively.²⁹⁷ Multivariate analysis showed that recurrence scores were related to recurrence independently from TNM staging, MMR status, tumor grade, and number of nodes assessed in both stage II and III disease. Similar results were found in a recent prospectively designed study that tested the correlation between recurrence score using the Oncotype DX colon cancer assay and the risk of recurrence in patients from the CALGB 9581 trial (stage II disease).²⁹⁹ An additional prospectively designed clinical validation study in patients from the NSABP C-07 trial found that the assay results correlated with recurrence, DFS, and OS.²⁹⁸ This study also found

some evidence that patients with higher recurrence scores may derive more absolute benefit from oxaliplatin, although the authors noted that the recurrence score is not predictive of oxaliplatin efficacy in that it does not identify patients who will or will not benefit from oxaliplatin treatment. An additional study validated the recurrence score in patients with stage II/III colon cancer treated with surgery alone.³⁰⁰

ColoPrint quantifies the expression of 18 genes as a prognostic classifier of low versus high recurrence risk.³⁰¹ In a set of 206 patients with stage I through III CRC, the 5-year relapse-free survival (RFS) rates were 87.6% (95% CI, 81.5%–93.7%) and 67.2% (95% CI, 55.4%–79.0%) for those classified as low and high risk, respectively. In patients with stage II disease in particular, the HR for recurrence between the high and low groups was 3.34 ($P = .017$).³⁰¹ This assay was further validated in a pooled analysis of 416 patients with stage II disease, 301 of whom were assessed as a T3/MSS subset.³⁰² In the T3/MSS subset, patients classified as low risk and high risk had a 5-year risk of relapse (survival until first event of recurrence or death from cancer) of 22.4% and 9.9%, respectively (HR, 2.41; $P = .005$). As with the Oncotype DX colon cancer assay, recurrence risk determined by ColoPrint is independent of other risk factors, including T stage, perforation, number of nodes assessed, and tumor grade. This assay is being further validated for its ability to predict 3-year relapse rates in patients with stage II colon cancer in a prospective trial (NCT00903565).

ColDx is a microarray-based multigene assay that uses 634 probes to identify patients with stage II colon cancer at high risk of recurrence.³⁰³ In a 144-sample independent validation set, the HR for identification of patients with high-risk disease was 2.53 (95% CI, 1.54–4.15; $P < .001$) for recurrence and 2.21 (95% CI, 1.22–3.97; $P = .0084$) for cancer-related death. A cohort study of patients in the C9581 trial found that patients with stage II colon cancer identified as high risk by ColDx had a shorter



recurrence-free interval than those identified as low-risk (multivariable HR, 2.13; 95% CI, 1.3–3.5; $P < .01$).³⁰⁴ Similar to the other assays described here, the recurrence risk determined by ColDx is independent of other risk factors.

An international study led by the Society for Immunotherapy of Cancer aimed to validate Immunoscore, a scoring system reported as percentiles of CD3+ and CD8+ immune cell densities in prespecified regions of the tumor sample by dedicated software, for the assay's prognostic value in patients with stage III colon cancer as well as its predictive value for efficacy of adjuvant chemotherapy in these patients.³⁰⁵ This study reported that patients with the highest Immunoscore showed the lowest risk of recurrence; 3-year recurrence-free survival rates were 56.9%, 65.9% and 76.4% for low, medium, and high Immunoscore (HR [high vs. low], 0.48; 95% CI, 0.32–0.71; $P = .0003$). A high Immunoscore also correlated with prolonged time to recurrence, OS, and DFS (all $P < .001$). The benefit of adjuvant chemotherapy was also associated with a high Immunoscore for both high-risk ($P = .0015$) and low-risk ($P = .0011$) tumors. The same was not true for tumors with a low Immunoscore ($P > .12$).

Post-surgical ctDNA has also been studied as a marker for an elevated risk of recurrence in stage I–III colon cancer. A prospective, multicenter study of 130 patients with stage I–III colon cancer detected ctDNA by multiplex, PCR-based next-generation sequencing (NGS).³⁰⁶ Thirty days after surgery, patients with positive ctDNA assays were seven times more likely to experience disease relapse than patients who were ctDNA-negative (HR, 7.2; 95% CI, 2.7–19.0; $P < .001$). Likewise, after adjuvant chemotherapy, patients with ctDNA-positive assays were 17 times more likely to have disease relapse (HR, 17.5; 95% CI, 5.4–56.5; $P < .001$). Another prospective study of 150 patients with localized colon cancer detected ctDNA with NGS following surgery.³⁰⁷ In this study, detection of ctDNA was also associated with poorer DFS (HR, 17.56; log rank $P =$

.0014 for ctDNA post-surgery and HR, 11.33; log rank $P = .0001$ for ctDNA in serial plasma samples during follow-up). Other studies have reported similar results.³⁰⁸

In summary, the information from these tests can further inform the risk of recurrence over other risk factors, but the panel questions the value added. Furthermore, evidence of predictive value in terms of the potential benefit of chemotherapy is lacking. Therefore, the panel believes that there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy. ESMO has released similar recommendations regarding these assays, stating that their role in predicting chemotherapy benefit is uncertain.³⁰⁹ The NCCN Panel encourages enrollment in clinical trials to help with the generation of additional data on these assays.

Adjuvant Chemotherapy in Elderly Patients

Adjuvant chemotherapy usage declines with the age of the patient.³¹⁰ Questions regarding the safety and efficacy of chemotherapy in older patients have been difficult to answer, because older patients are underrepresented in clinical trials. Some data speaking to these questions have been reviewed.^{311–313}

Population studies have found that adjuvant therapy is beneficial in older patients. A retrospective analysis of 7263 patients from the linked SEER-Medicare Databases found a survival benefit for the use of 5-FU/LV in patients 65 years or older with stage III disease (HR, 0.70; $P < .001$).³¹⁴ Another analysis of 5489 patients aged greater than or equal to 75 years diagnosed with stage III colon cancer between 2004 and 2007 from four datasets, including the SEER-Medicare Databases and the NCCN Outcomes Database, showed a survival benefit for adjuvant chemotherapy in this population (HR, 0.60; 95% CI, 0.53–0.68).³¹⁰ This study also looked specifically at the benefit of the addition of oxaliplatin to adjuvant therapy in these older stage III patients, and found only a small, non-significant



benefit. Analysis of almost 12,000 patients from the ACCENT database also found a reduced benefit to the addition of oxaliplatin to fluoropyrimidines in the adjuvant setting in patients aged greater than or equal to 70 years.³¹⁵

Subset analyses of major adjuvant therapy trials also show a lack of benefit to the addition of oxaliplatin in older patients. Subset analysis of the NSABP C-07 trial showed that the addition of oxaliplatin to 5-FU/LV gave no survival benefit in patients aged greater than or equal to 70 years with stage II or III colon cancer ($n = 396$), with a trend towards decreased survival (HR, 1.18; 95% CI, 0.86–1.62).²⁷⁵ Similarly, in a subset analysis of the MOSAIC trial, 315 patients aged 70 to 75 years with stage II or III colon cancer derived no benefit from the addition of oxaliplatin (OS HR, 1.10; 95% CI, 0.73–1.65).²⁷⁴

However, a recent pooled analysis of individual patient data from the NSABP C-08, XELOXA, X-ACT, and AVANT trials found that DFS (HR, 0.77; 95% CI, 0.62–0.95; $P = .014$) and OS (HR, 0.78; 95% CI, 0.61–0.99; $P = .045$) were improved with adjuvant CAPEOX or FOLFOX over 5-FU/LV in patients 70 years of age or older.³¹⁶ Likewise, a subgroup analysis of the phase III TOSCA trial (part of the IDEA collaboration) found that once the multivariable analysis was corrected for sex, performance status, tumor site, grade, treatment, treatment duration, and dose reduction, there was no significant difference in relapse-free interval between patients 70 years of age or older compared to those younger than 70 years when treated with oxaliplatin-based adjuvant therapy (HR, 1.19; 95% CI, 0.98–1.44; $P = .082$).³¹⁷

As for the risks of adjuvant therapy in elderly patients, a pooled analysis of 37,568 patients from adjuvant trials in the ACCENT database found that the likelihood of early mortality after adjuvant treatment increased with age in a nonlinear fashion ($P < .001$).³¹⁸ For instance, the ORs for 30-day mortality for patients aged 70 years and aged 80 years compared to

patients aged 60 years were 2.58 (95% CI, 1.88–3.54) and 8.61 (95% CI, 5.34–13.9), respectively. Patients aged 50 years, on the other hand, had a corresponding OR of 0.72 (95% CI, 0.47–1.10). However, the absolute risk of early mortality was very small, even for elderly patients (30-day mortality for 80-year-olds was 1.8%).

Overall, the benefit and toxicities of 5-FU/LV as adjuvant therapy seem to be similar in older and younger patients. However, the panel cautions that a benefit for the addition of oxaliplatin to 5-FU/LV in patients aged 70 years and older has not been proven in stage II or stage III colon cancer.

Timing of Adjuvant Therapy

A systematic review and meta-analysis of 10 studies involving more than 15,000 patients examined the effect of timing of adjuvant therapy after resection.³¹⁹ Results of this analysis showed that each 4-week delay in chemotherapy results in a 14% decrease in OS, indicating that adjuvant therapy should be administered as soon as the patient is medically able. These results are consistent with other similar analyses. In addition, a retrospective study of 7794 patients with stage II or III colon cancer from the National Cancer Database found that a delay of more than 6 weeks between surgery and adjuvant therapy reduced survival after adjustment for clinical-, tumor-, and treatment-related factors.³²⁰ Another retrospective study of 6620 patients with stage III colon cancer from the Netherlands Cancer Registry also found that starting adjuvant therapy after 8 weeks beyond resection was associated with worse survival.³²¹ However, some critics have pointed out that this type of analysis is biased by confounding factors such as comorbidities, which are likely to be higher in patients with a longer delay before initiation of chemotherapy.³²² In fact, the registry study found that patients who started therapy after 8 weeks were more likely to be older than 65 years, have had an emergency resection, and/or have a prolonged postoperative admission.³²¹



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Leucovorin Shortage

A shortage of LV recently existed in the United States. No specific data are available to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levoleucovorin, which is commonly used in Europe. A dose of 200 mg/m² of levoleucovorin is equivalent to 400 mg/m² of standard LV. Use of levoleucovorin should only be considered during times of LV shortage since levoleucovorin is substantially more expensive than LV.

Another option is for practices or institutions to use lower doses of LV for all doses in all patients, because the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg of LV was associated with similar survival and 3-year recurrence rates as 25 mg of LV when given with bolus 5-FU as adjuvant therapy to patients after R0 resections for CRC.³²³ Another study showed no difference in response rate or survival in patients with mCRC receiving bolus 5-FU with either high-dose (500 mg/m²) or low-dose (20 mg/m²) LV.³²⁴ Furthermore, the Mayo Clinic and North Central Cancer Treatment Group (NCCTG) determined that no therapeutic difference was seen between the use of high-dose (200 mg/m²) or low-dose (20 mg/m²) LV with bolus 5-FU in the treatment of advanced CRC, although the 5-FU doses were different in the treatment arms.³²⁵ Finally, if none of the above options is available, treatment without LV would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

Adjuvant FOLFOX and Infusional 5-FU/LV

The European MOSAIC trial compared the efficacy of FOLFOX and 5-FU/LV in the adjuvant setting in 2246 patients with completely resected stage II and III colon cancer. Although this initial trial was performed with

FOLFOX4, mFOLFOX6 has been the control arm for all recent and current National Cancer Institute (NCI) adjuvant studies for CRC, and the panel believes that mFOLFOX6 is the preferred FOLFOX regimen for adjuvant and metastatic treatments. Results of this study have been reported with median follow-ups of up to 9.5 years.²⁵²⁻²⁵⁴ For patients with stage III disease, DFS at 5 years was 58.9% in the 5-FU/LV arm and 66.4% in the FOLFOX arm ($P = .005$), and 10-year OS of patients with stage III disease receiving FOLFOX was statistically significantly increased compared with those receiving 5-FU/LV (67.1% vs. 59.0%; HR, 0.80; $P = .016$).²⁵⁴ Although the incidence of grade 3 peripheral sensory neuropathy was 12.4% for patients receiving FOLFOX and only 0.2% for patients receiving 5-FU/LV, long-term safety results showed a gradual recovery for most of these patients. However, neuropathy was present in 15.4% of examined patients at 4 years (mostly grade 1), suggesting that oxaliplatin-induced neuropathy may not be completely reversible in some patients.²⁵³

An analysis of five observational data sources, including the SEER-Medicare and NCCN Outcomes Databases, showed that the addition of oxaliplatin to 5-FU/LV gave a survival advantage to the general stage III colon cancer population treated in the community.³²⁶ Another population-based analysis found that the harms of oxaliplatin in the medicare population with stage III colon cancer were reasonable, even in patients aged 75 years or older.³²⁷ In addition, a pooled analysis of individual patient data from four RCTs revealed that the addition of oxaliplatin to capecitabine or 5-FU/LV improved outcomes in patients with stage III colon cancer.³²⁸ Furthermore, analysis of data from 12,233 patients in the ACCENT database of adjuvant colon cancer trials supports the benefit of oxaliplatin in patients with stage III disease.³²⁹

Adjuvant Capecitabine and CAPEOX

Single-agent oral capecitabine as adjuvant therapy for patients with stage III colon cancer was shown to be at least equivalent to bolus 5-FU/LV



(Mayo Clinic regimen) with respect to DFS and OS, with respective HRs of 0.87 (95% CI, 0.75–1.00; $P < .001$) and 0.84 (95% CI, 0.69–1.01; $P = .07$) in the X-ACT trial.²⁵⁹ Final results of this trial were recently reported.³³⁰

After a median follow-up of 6.9 years, the equivalencies in DFS and OS were maintained in all subgroups, including those 70 years of age or older.

Capecitabine was also assessed as adjuvant therapy for stage III colon cancer in combination with oxaliplatin (CAPEOX) in the NO16968 trial and showed an improved 3-year DFS rate compared with bolus 5-FU/LV (66.5% vs. 70.9%).^{256,257} Final results of this trial showed that OS at 7 years was improved in the CAPEOX arm compared with the 5-FU/LV arm (73% vs. 67%; HR, 0.83; 95% CI, 0.70–0.99; $P = .04$).³³¹ Another phase III trial compared CAPEOX to mFOLFOX6 in 408 patients with stage III or high-risk stage II colon cancer.³³² No significant differences were seen in 3-year DFS and 3-year OS. In addition, a pooled analysis of individual patient data from four RCTs revealed that the addition of oxaliplatin to capecitabine or 5-FU/LV improved outcomes in patients with stage III colon cancer.³²⁸

Duration of Adjuvant Therapy

The IDEA collaboration investigated whether limiting adjuvant treatment to 3 months of FOLFOX or CAPEOX—which would markedly decrease the incidence of neuropathy—would compromise oncologic outcomes. IDEA included 12,834 patients in an international effort that pooled data from six concurrently conducted, randomized phase III trials to assess the noninferiority of 3 months compared with 6 months of adjuvant FOLFOX or CAPEOX in patients with stage III colon cancer.²⁵⁸ The median follow-up was 39 months. Importantly, grade 3+ neurotoxicity rates were lower in the 3 months versus 6 months treatment arms (3% vs. 16% for FOLFOX; 3% vs. 9% for CAPEOX; $P < .0001$), as were grade 2 neurotoxicity rates (14% vs. 32% for FOLFOX; 12% vs. 36% for CAPEOX; $P < .0001$). Grade 2 and

grade 3/4 diarrhea rates were also lower with the shorter duration of therapy ($P < .0001$ for FOLFOX; $P = .01$ for CAPEOX).

The primary endpoint of 3-year DFS did not meet the prespecified cutoff for noninferiority in the overall population, despite the small absolute difference of 0.9% (74.6% for 3 months vs. 75.5% for 6 months; HR, 1.07; 95% CI, 1.00–1.15), which is of questionable clinical significance.

However, noninferiority was observed within certain subgroups.

Specifically, in the low-risk (T1–3, N1) subgroup, the DFS for 3 months of CAPEOX was noninferior to 6 months of CAPEOX (HR, 0.85; 95% CI, 0.71–1.01), whereas noninferiority could not be proven for 3 months versus 6 months of FOLFOX (HR, 1.10; 95% CI, 0.96–1.26). In the high-risk (T4 and/or N2) subgroup, DFS for 3 months of FOLFOX was inferior to 6 months of FOLFOX (HR, 1.20; 95% CI, 1.07–1.35), whereas noninferiority could not be proven for the 3-month to 6-month comparison with CAPEOX (HR, 1.02; 95% CI, 0.89–1.17).

Results of the final analysis of IDEA were reported after an overall median survival follow-up of 72 months.³³³ In the final analysis, 5-year OS was 82.4% for 3 months of therapy compared to 82.8% for 6 months (HR, 1.02; 95% CI, 0.95–1.11; $P = .058$). The 5-year DFS was 69.1% for 3 months versus 70.8% for 6 months (HR, 1.08; 95% CI, 1.01–1.15; $P = .22$). The HR for 5-year OS was 0.96 for CAPEOX (3 months vs. 6 months) and 1.07 for FOLFOX (3 months vs. 6 months). Likewise, long-term DFS HRs were 0.98 for CAPEOX (3 months vs. 6 months) and 1.16 for FOLFOX (3 months vs. 6 months). The authors of this study concluded that, while the differences in OS did not meet the statistical assumptions for noninferiority, the overall 0.4% difference in 5-year OS should be placed in clinical context, especially considering the marked reduction in toxicity associated with the shorter duration of therapy.

A pooled analysis of patients with high-risk stage II colon cancer in the IDEA collaboration failed to show non-inferiority of 3 months compared to



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6 months of adjuvant treatment based on 5-year DFS (80.7% for 3 months vs. 84.0% for 6 months; HR, 1.18; 80% CI, 1.05–1.31). Similar to stage III, the duration of therapy was associated with a small, not statistically significant, difference in 5-year DFS between 3 and 6 months of CAPEOX (81.7% vs. 82.0%). There were significantly less grade 3–5 toxicities with 3 months versus 6 months (26% vs. 40%; $P < .0001$).³³⁴ Two of the published trials within the IDEA collaboration reported similar results for high-risk stage II disease. For the TOSCA trial, 5-year RFS was found to be similar between 3 and 6 months of CAPEOX, while the difference was more pronounced between 3 and 6 months of FOLFOX (8.56% difference favoring 6 months of FOLFOX).³³⁵ In the Hellenic Oncology Research Group (HORG)-IDEA trial, 3-year DFS was 76.7% for 3 months versus 79.3% for 6 months of FOLFOX (HR, 1.21; 95% CI, 0.54–2.70) and 85.4% for 3 months versus 83.8% for 6 months of CAPEOX (HR, 0.99; 95% CI, 0.59–1.67).³³⁶

ACHIEVE was another phase III trial that investigated similar questions regarding duration of adjuvant therapy for 1313 Asian patients with stage III colon cancer.³³⁷ The results of ACHIEVE were consistent with IDEA, finding that the incidence of long-lasting peripheral neuropathy was significantly lower with 3 months of adjuvant therapy compared to 6 months (9.7% vs. 24.3% after 3 years; $P < .001$). DFS rates were similar between the 3- and 6-month arms (HR, 0.95; 95% CI, 0.76–1.20).

Based on these data, 3 months of CAPEOX or 3 to 6 months of FOLFOX are listed in the guidelines as preferred adjuvant therapy options for patients with low-risk stage III colon cancer. Three to 6 months of CAPEOX or 6 months of FOLFOX are listed as preferred adjuvant therapy options for patients with high-risk stage III colon cancer. Six months of infusional 5-FU/LV or single-agent capecitabine are included as other adjuvant therapy options for low- or high-risk stage III colon cancer. For stage II colon cancer at high risk for systemic recurrence, the

recommended options for adjuvant treatment are 6 months of capecitabine, 5-FU/LV, or FOLFOX or 3 months of CAPEOX. Observation may also be an appropriate option for high-risk stage II disease. In this population, no adjuvant treatment option is preferred over the others.

Adjuvant Regimens Not Recommended

Other adjuvant regimens studied for the treatment of early-stage colon cancer include 5-FU–based therapies incorporating irinotecan. The CALGB 89803 trial evaluated the IFL regimen versus 5-FU/LV alone in stage III colon cancer.³³⁸ No improvement in either OS ($P = .74$) or DFS ($P = .84$) was observed for patients receiving IFL compared with those receiving 5-FU/LV. However, IFL was associated with a greater degree of neutropenia, neutropenic fever, and death.^{338,339} Similar results were observed in a randomized phase III trial comparing bolus 5-FU/LV with the IFL regimen in stage II/III colon cancer.³⁴⁰ In addition, FOLFIRI (infusional 5-FU/LV/irinotecan) has not been shown to be superior to 5-FU/LV in the adjuvant setting.^{341,342} Thus, data do not support the use of irinotecan-containing regimens in the treatment of stage II or III colon cancer.

In the NSABP C-08 trial comparing 6 months of mFOLFOX6 with 6 months of mFOLFOX6 with bevacizumab plus an additional 6 months of bevacizumab alone in patients with stage II or III colon cancer, no statistically significant benefit in 3-year DFS was seen with the addition of bevacizumab (HR, 0.89; 95% CI, 0.76–1.04; $P = .15$).³⁴³ Similar results were seen after a median follow-up of 5 years.³⁴⁴ The results of the phase III AVANT trial evaluating bevacizumab in the adjuvant setting in a similar protocol also failed to show a benefit associated with bevacizumab in the adjuvant treatment of stage II or III CRC, and in fact showed a trend toward a detrimental effect to the addition of bevacizumab.^{345,346} Furthermore, results of the open-label, randomized phase III QUASAR 2 trial showed that bevacizumab had no benefit in the adjuvant colorectal



setting when added to capecitabine.³⁴⁷ Therefore, bevacizumab has no role in the adjuvant treatment of stage II or III colon cancer.

The NCCTG Intergroup phase III trial N0147 assessed the addition of cetuximab to FOLFOX in the adjuvant treatment of stage III colon cancer. In patients with wild-type or mutant *KRAS*, cetuximab provided no added benefit and was associated with increases in grade 3/4 adverse events (AEs).³⁴⁸ In addition, all subsets of patients treated with cetuximab experienced increases in grade 3/4 AEs. The open-label, randomized, phase III PETACC-8 trial also compared FOLFOX with and without cetuximab.³⁴⁹ Analysis of the wild-type *KRAS* exon 2 subset found that DFS was similar in both arms (HR, 0.99; 95% CI, 0.76–1.28), while AEs (ie, rash, diarrhea, mucositis, infusion-related reactions) were more common in the cetuximab group. However, a more recent analysis of PETACC-8 that looked at mutations in *KRAS*, *NRAS*, and *BRAF* found that patients with *RAS* wild-type/*BRAF* wild-type tumors had a non-significant trend towards improved DFS (HR, 0.76) for the addition of cetuximab to FOLFOX.³⁵⁰ Therefore, cetuximab also has no role in the adjuvant treatment of colon cancer at this time, but further trials may define a subset of patients who might benefit from cetuximab in the adjuvant setting.

A randomized phase III trial (NSABP C-07) compared the efficacy of FLOX with that of bolus 5-FU/LV in 2407 patients with stage II or III colon cancer. While FLOX showed significantly higher rates of 4- and 7-year DFS,^{275,351} no statistically significant differences in OS or colon-cancer-specific mortality were observed when the arms were compared. Furthermore, survival after disease recurrence was significantly shorter in the group receiving oxaliplatin (HR, 1.20; 95% CI, 1.00–1.43; *P* = .0497).²⁷⁵ Grade 3 neurotoxicity, diarrhea, and dehydration were higher with FLOX than with 5-FU/LV,²⁷⁵ and, when cross-study comparisons were made, the incidence of grade 3/4 diarrhea seemed to be considerably higher with FLOX than

with FOLFOX. For example, rates of grade 3/4 diarrhea were 10.8% and 6.6% for patients receiving FOLFOX and infusional 5-FU/LV in the MOSAIC trial,²⁵² whereas 38% and 32% of patients were reported to have grade 3/4 diarrhea in the NSABP C-07 trial when receiving FLOX and bolus 5-FU/LV.³⁵¹ For these reasons, FLOX is no longer recommended as adjuvant treatment for colon cancer.

Perioperative Chemoradiation

Neoadjuvant or adjuvant radiation therapy (RT) delivered concurrently with 5-FU-based chemotherapy may be considered for very select patients with disease characterized as T4 tumors penetrating to a fixed structure or for patients with recurrent disease.³⁵² RT fields should include the tumor bed as defined by preoperative radiologic imaging and/or surgical clips. Intraoperative RT (IORT), if available, should be considered for these patients as an additional boost.^{353,354} If IORT is not available, an additional 10 to 20 Gy of external beam RT (EBRT) and/or brachytherapy could be considered to a limited volume.

Chemoradiation can also be given to patients with locally unresectable disease or who are medically inoperable. In such cases, surgery with or without IORT can then be considered or additional lines of systemic therapy can be given.

If RT is to be used, conformal beam radiation should be the routine choice; intensity-modulated RT (IMRT), which uses computer-assisted inverse treatment planning to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,³⁵⁵ or stereotactic body RT (SBRT; also called stereotactic ablative radiotherapy [SABR]) should be considered for unique clinical situations, such as reirradiation of previously treated patients with recurrent disease or anatomical situations where IMRT facilitates the delivery of recommended target volume doses while respecting accepted normal tissue dose-volume constraints.³⁵⁶



Neoadjuvant Therapy for Resectable Colon Cancer

For bulky nodal disease or clinical T4b, neoadjuvant treatment with FOLFOX or CAPEOX may be considered prior to surgery. The randomized phase III FOxTROT trial is assessing whether this approach improves DFS (NCT00647530). Results from the feasibility phase of the trial were reported in 2012.³⁵⁷ One hundred fifty patients with T3 (with ≥ 5 mm invasion beyond the muscularis propria) or T4 tumors were randomly assigned to three cycles of preoperative therapy (5-FU/LV/oxaliplatin), surgery, and nine additional cycles of the same therapy or to surgery with 12 cycles of the same therapy given postoperatively. Preoperative therapy resulted in significant downstaging compared with postoperative therapy ($P = .04$), with acceptable toxicity. A 2019 abstract reported more mature data from 1052 patients on the FOxTROT trial.³⁵⁸ Histologic regression was seen in 59% of patients who received neoadjuvant therapy, including 4% pathologic complete responses. Neoadjuvant therapy also resulted in marked histologic downstaging as well as a decrease in incomplete resections compared to postoperative therapy (5% vs. 10%; $P = .001$). The 2-year rate of relapse or persistent disease (2-year failure rate) also improved with neoadjuvant therapy, although this difference was not statistically significant (14% vs. 18%; HR, 0.77; $P = .11$). These results support the feasibility of neoadjuvant therapy as a treatment option for colon cancer.

Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with CRC develop colorectal metastases,³⁵⁹⁻³⁶¹ and 80% to 90% of these patients have unresectable metastatic liver disease.^{360,362-365} Metastatic disease most frequently develops metachronously after treatment for locoregional CRC, with the liver being the most common site of involvement.³⁶⁶ However, 20% to 34% of patients with CRC present with synchronous liver metastases.^{365,367} Some evidence indicates that synchronous metastatic colorectal liver disease is associated with a more disseminated disease

state and a worse prognosis than metastatic colorectal liver disease that develops metachronously. In a retrospective study of 155 patients who underwent hepatic resection for colorectal liver metastases, patients with synchronous liver metastases had more sites of liver involvement ($P = .008$) and more bilobar metastases ($P = .016$) than patients diagnosed with metachronous liver metastases.³⁶⁸

It has been estimated that more than half of patients who die of CRC have liver metastases at autopsy, with metastatic liver disease being the cause of death in most patients.³⁶⁹ Reviews of autopsy reports of patients who died from CRC showed that the liver was the only site of metastatic disease in one-third of patients.³⁶⁴ Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.^{360,370} Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of more than 3 tumors, and a disease-free interval of less than 12 months, have been associated with a poor prognosis in patients with CRC.^{367,371-375}

Other groups, including ESMO, have established guidelines for the treatment of mCRC.³⁷⁶ The NCCN recommendations are discussed below.

Surgical Management of Colorectal Metastases

Studies of selected patients undergoing surgery to remove colorectal liver metastases have shown that cure is possible in this population and should be the goal for a substantial number of these patients.^{360,377} Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,^{372,375} and a recent meta-analysis reported a median 5-year survival of 38%.³⁷⁸ In addition, retrospective analyses and meta-analyses have shown that patients with solitary liver metastases have a 5-year OS rate as high as 71% following resection.³⁷⁹⁻³⁸¹ Therefore, decisions relating to patient suitability, or potential suitability, and subsequent selection for metastatic colorectal surgery are critical



junctures in the management of metastatic colorectal liver disease (discussed further in *Determining Resectability*).³⁸²

Colorectal metastatic disease sometimes occurs in the lung.³⁵⁹ Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases.^{203,383,384} A series of 378 patients found that resection of pulmonary metastases resulted in 3-year recurrence-free survival of 28% and 3-year OS of 78%.²⁰³ Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases,³⁸⁵⁻³⁸⁹ and an analysis of patients who underwent hepatic resection followed by subsequent pulmonary resection showed positive outcomes.³⁹⁰

Evidence supporting resection of extrahepatic metastases in patients with mCRC is limited. In a recent retrospective analysis of patients undergoing concurrent complete resection of hepatic and extrahepatic disease, the 5-year survival rate was lower than in patients without extrahepatic disease, and virtually all patients who underwent resection of extrahepatic metastases experienced disease recurrence.^{391,392} However, a recent international analysis of 1629 patients with colorectal liver metastases showed that 16% of the 171 patients (10.4%) who underwent concurrent resection of extrahepatic and hepatic disease remained disease-free at a median follow-up of 26 months, suggesting that concurrent resection may be of significant benefit in well-selected patients (ie, those with a smaller total number of metastases).³⁸⁹ A recent systematic review concluded similarly that carefully selected patients might benefit from this approach.³⁹³

Data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken.³⁹⁴⁻³⁹⁹ However, in a retrospective analysis, 5-year survival was shown to decrease with each subsequent curative-intent surgery, and the presence of extrahepatic

disease at the time of surgery was independently associated with a poor prognosis.³⁹⁵ In a more recent retrospective analysis of 43 patients who underwent repeat hepatectomy for recurrent disease, 5-year OS and PFS rates were reported to be 73% and 22%, respectively.³⁹⁴ A recent meta-analysis of 27 studies including fewer than 7200 patients found that those with longer disease-free intervals; those whose recurrences were solitary, smaller, or unilobular; and those lacking extrahepatic disease derived more benefit from repeat hepatectomy.⁴⁰⁰ Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.^{384,398,401}

Patients with a resectable primary colon tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection, as discussed below in *Resectable Synchronous Liver or Lung Metastases*. For patients presenting with unresectable metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic therapy is the preferred initial maneuver (discussed further in *Unresectable Synchronous Liver or Lung Metastases*).⁴⁰²

Local Therapies for Metastases

The standard of care for patients with resectable metastatic disease is surgical resection. Image-guided ablation has historically been used for non-surgical patients⁴⁰³⁻⁴⁰⁵ but is also indicated for small metastases that can be treated with margins, in combination with surgery or alone, as long as all visible disease is treated.⁴⁰⁶ SBRT is a reasonable option for patients who cannot be resected or ablated, as discussed in subsequent paragraphs.^{363,407,408} Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins⁴⁰⁵ or safely treated by SBRT. In select patients with liver-only or liver-dominant metastatic disease that cannot be resected or ablated, other local, arterially directed treatment options may be offered.⁴⁰⁹⁻⁴¹¹



A meta-analysis of 90 studies concluded that hepatic arterial infusion chemotherapy (HAIC), yttrium-90 microsphere radioembolization, and transcatheter arterial chemoembolization (TACE) have similar efficacy in patients with unresectable colorectal hepatic metastases.⁴¹² Local therapies are described in more detail below. The exact role and timing of using non-extirpative local therapies in the treatment of colorectal metastases remains controversial.

Hepatic Arterial Infusion

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery (ie, HAIC) is an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone through HAIC and intravenous 5-FU with or without LV was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.^{364,413} The study was not powered for long-term survival, but a trend (not significant) was seen toward better long-term outcomes in the group receiving HAIC at later follow-up periods.^{364,414} Several other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAIC was compared with systemic chemotherapy, although most have not shown a survival benefit of HAIC.³⁶⁴ Results of some studies also suggest that HAIC may be useful in the conversion of patients from an unresectable to a resectable status.^{415,416}

Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAIC.³⁷⁷ Limitations on the use of HAIC include the potential for biliary toxicity³⁶⁴ and the requirement of specific technical expertise. Panel consensus is that HAIC should be considered selectively, and only at institutions with extensive

experience in both the surgical and medical oncologic aspects of the procedure.

Arterially Directed Embolic Therapy

Transhepatic Arterial Chemoembolization

TACE involves hepatic artery catheterization to locally deliver chemotherapy followed by arterial occlusion.⁴¹⁰ A randomized trial compared the arterial delivery of irinotecan-loaded drug-eluting beads (DEBIRI) and reported an OS benefit (22 months vs. 15 months; $P = .031$) of DEBIRI when compared to systemic FOLFIRI.⁴¹⁷ A 2013 meta-analysis identified five observational studies and one randomized trial and concluded that, although DEBIRI appears to be safe and effective for patients with unresectable colorectal liver metastases, additional trials are needed.⁴¹⁸ A more recent trial randomized 30 patients with colorectal liver metastases to FOLFOX/bevacizumab and 30 patients to FOLFOX/bevacizumab/DEBIRI.⁴¹⁹ DEBIRI resulted in an improvement in the primary outcome measure of response rate (78% vs. 54% at 2 months; $P = .02$).

Doxorubicin-eluting beads have also been studied; the most robust data supporting their effectiveness come from several phase II trials in hepatocellular carcinoma.⁴²⁰⁻⁴²⁵ A 2013 systematic review concluded that data are not strong enough to recommend TACE for the treatment of colorectal liver metastases except as part of a clinical trial.⁴²⁶

Radioembolization

A prospective, randomized, phase III trial of 44 patients showed that radioembolization combined with chemotherapy can lengthen time to progression in patients with liver-limited mCRC following progression on initial therapy (2.1 vs. 4.5 months; $P = .03$).⁴²⁷ The effect on the primary endpoint of time to liver progression was more pronounced (2.1 vs. 5.5 months; $P = .003$). Treatment of liver metastases with yttrium-90 glass



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radioembolization in a prospective, multicenter, phase II study resulted in a median PFS of 2.9 months for patients with colorectal primaries who were refractory to standard treatment.⁴²⁸ In the refractory setting, a CEA level greater than or equal to 90 and lymphovascular invasion at the time of primary resection were negative prognostic factors for OS.⁴²⁹ Additional risk factors include tumor volume and liver replacement by disease as well as albumin and bilirubin levels, performance status, and the presence of extrahepatic disease for both glass⁴³⁰ and resin⁴³¹ microspheres. Several large case series have been reported for yttrium-90 radioembolization in patients with refractory unresectable colorectal liver metastases, and the technique appears to be safe with some clinical benefit.^{430,432,433} Median survival after radioembolization in the chemorefractory setting has been reported from 9 to 15.1 months.⁴²⁸⁻⁴³³ Survival at 1 year from radioembolization of heavily pretreated patients varies considerably based on the accumulation of risk factors such as extrahepatic disease, large tumor size, poor differentiation, higher CEA and ALT, and lower albumin levels.⁴³¹

Results from the phase III randomized controlled SIRFLOX trial (yttrium-90 resin microspheres with FOLFOX +/- bevacizumab vs. FOLFOX +/- bevacizumab) were reported.⁴³⁴ The trial assessed the safety and efficacy of yttrium-90 radioembolization as first-line therapy in 530 patients with colorectal liver metastases. Although the primary endpoint was not met, with PFS in the FOLFOX +/- bevacizumab arm at 10.2 months versus 10.7 months in the FOLFOX/yttrium-90 arm (HR, 0.93; 95% CI, 0.77–1.12; $P = .43$), a prolonged liver PFS was demonstrated for the study arm (20.5 months for the FOLFOX/yttrium-90 arm vs. 12.6 months for the chemotherapy only arm; HR, 0.69; 95% CI, 0.55–0.90; $P = .002$).

The FOXFIRE and FOXFIRE Global studies were performed in the same manner as the SIRFLOX trial with the intention to compile all data and allow assessment of oncologic outcomes in a larger cohort.⁴³⁵ Pooled data

from 1103 patients in these three prospective trials showed similar findings as in the SIRFLOX trial with prolongation of the liver PFS in the group treated by radioembolization but no difference in OS and PFS. Of interest was the finding of a median OS benefit with radioembolization plus chemotherapy compared to chemotherapy alone in the subgroup of patients with right-sided primary origin (22.0 vs. 17.1 months; HR, 0.641; $P = .008$).⁴³⁶ Based on these data, further investigation is needed to identify the role of radioembolization at earlier stages of disease in patients with right-sided primary origin.

Whereas very little data show any impact on patient survival and the data supporting its efficacy are limited, toxicity with radioembolization is relatively low.^{434,437-439} Consensus amongst panel members is that arterially directed catheter therapy and, in particular, yttrium-90 microsphere selective internal radiation is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

Tumor Ablation

Resection is the standard approach for the local treatment of resectable metastatic disease. However, patients with liver or lung oligometastases can also be considered for tumor ablation therapy, particularly in cases that may not be optimal for resection.^{440,441} Ablative techniques include radiofrequency ablation (RFA),^{405,442} microwave ablation (MWA), cryoablation, and electro-coagulation (irreversible electroporation).⁴⁴³ There is extensive evidence on the use of RFA as a reasonable treatment option for non-surgical candidates and for recurrent disease after hepatectomy with small liver metastases that can be treated with clear margins.^{405,442,444-446}

A small number of older retrospective studies have compared RFA and resection in the treatment of liver or lung metastases.^{380,447-450} Most of these studies have shown RFA to be relatively inferior to resection in



terms of rates of local recurrence and 5-year OS.^{447,451} Whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are from patient selection bias, lack of treatment assessment based on the ability to achieve margins, technologic limitations of RFA, or a combination of these factors remains unclear.⁴⁴⁹

A 2012 phase II trial randomized 119 patients to receive systemic treatment alone (FOLFOX with or without bevacizumab) or systemic treatment plus RFA, with or without resection.⁴⁵² No difference in OS was initially seen, but PFS was improved at 3 years in the RFA group (27.6% vs. 10.6%; HR, 0.63; 95% CI, 0.42–0.95; $P = .025$). A subsequent analysis following prolonged follow-up of the same population in this phase II RCT showed that OS was improved in the combined modality arm (HR, 0.58; 95% CI, 0.38–0.88, $P = .01$), with a 3-, 5-, and 8-year OS of 56.9%, 43.1%, and 35.9% for the combined modality arm compared to 55.2%, 30.3%, and 8.9% for the chemotherapy alone arm.⁴⁰⁶ This study documented a long-term survival benefit for patients receiving RFA in addition to chemotherapy compared to those treated by chemotherapy only.

Data on ablative techniques other than RFA are growing.^{441,453-460} However, in a comparison of RFA with MWA, outcomes were similar with no local tumor progression for metastases ablated with margins greater than 10 mm (A0) and a relatively better control of perivascular tumors with the use of MWA ($P = .021$).⁴⁶⁰ Similarly, two recent studies and a position paper by a panel of experts indicated that ablation may provide acceptable oncologic outcomes for selected patients with small liver metastases that can be ablated with sufficient margins.^{404,405,448} In the same way, a 2018 systematic review confirmed that MWA provides oncologic outcomes similar to resection.⁴⁶¹ Recent publications indicated that the significance of margin creation is particularly important for *RAS*-mutant metastases.⁴⁶²⁻

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Regarding pulmonary ablation, a large prospective database of two French cancer centers that enrolled 566 consecutive patients with 1,037 lung metastases (the majority colorectal in origin) received initial treatment with RFA and 136 patients (24%) underwent repeat RFA.⁴⁶⁵ PFS rates at years 1 through 4 were 40.2%, 23.3%, 16.4%, and 13.1%, respectively. Five-year OS after RFA in CRC pulmonary ablation ranged from 40.7% to 67.5% depending on risk factors. MWA has been used increasingly within the latest years with a recent report indicating no local progression for small tumors ablated with margins of at least 5 mm.⁴⁶⁶

A recent multicenter, prospective phase II study (SOLSTICE) included 128 patients with 224 metastatic lung tumors that were targeted by pulmonary cryoablation.⁴⁶⁷ In this trial, investigators demonstrated a local response of the ablated tumor at 1 and 2 years of 85.1% and 77.2%, respectively. With the use of a second cryoablation for recurrent tumor, 1-year and 2-year local tumor control reached 91.1% and 84.4%, respectively. In this study, 1- and 2-year survival rates were 97.6% and 86.6%, respectively. The grade 3 and grade 4 complication rates were low, at 4.7% and 0.6%.

An emergent indication for ablation is the discontinuation of chemotherapy while controlling oligometastatic pulmonary disease.^{466,468} The median chemotherapy-free survival (time interval between ablation and resuming chemotherapy or death without chemotherapy) was 12.2 months. Patients with no extrapulmonary metastases had a longer median chemotherapy-free survival compared to those without (20.9 vs. 9.2 months).⁴⁶⁸

Resection or ablation (either alone or in combination with resection) should be reserved for patients with metastatic disease that is entirely amenable to local therapy with adequate margins. Use of surgery, ablation, or the combination of both modalities, with the goal of less-than-complete eradication of all known sites of disease is not recommended other than in the scope of a clinical trial.



Liver- or Lung-Directed External Beam Radiation

EBRT to the metastatic site can be considered in highly selected cases in which the patient has a limited number of metastases, including the liver or lung; or the patient is symptomatic; or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in place of surgical resection. The possible techniques include three-dimensional conformal RT (CRT), SBRT,^{363,407,408,469} and IMRT, which uses computer-assisted inverse treatment planning to focus radiation to the tumor site and potentially decrease toxicity to healthy tissue.^{355,470-473}

While colorectal cancer has been shown to be a relatively radioresistant histology,^{474,475} multiple studies have demonstrated effective local control with minimal toxicity using SBRT in the treatment of liver^{470,476} and lung^{477,478} metastases. In addition, data on the benefit of using SBRT to treat multiple metastatic lesions are emerging. A recent randomized phase II trial with multiple cancer types, including a small number of CRC origin, and up to five metastatic lesions in different organs demonstrated an improvement in OS with the addition of SBRT to standard-of-care treatment.⁴⁷⁹ In patients with liver- or lung-limited disease that is not amenable to complete resection or ablation, SBRT may be considered as local therapy in centers with expertise. SBRT for the treatment of extrahepatic disease can be considered in select cases, or as part of a clinical trial.

Peritoneal Carcinomatosis

Approximately 17% of patients with mCRC have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of metastasis. Patients with peritoneal metastases generally have a shorter PFS and OS than those without peritoneal involvement.^{117,480} The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative, and primarily consists of systemic therapy (see *Systemic Therapy for Advanced or Metastatic Disease*) with palliative surgery or

stenting if needed for obstruction or impending obstruction.⁴⁸¹⁻⁴⁸³ If an R0 resection can be achieved, however, surgical resection of isolated peritoneal disease may be considered at experienced centers. The panel cautions that the use of bevacizumab in patients with colon or rectal stents is associated with a possible increased risk of bowel perforation.^{484,485}

Cytoreductive Debulking with Hyperthermic Intraperitoneal Chemotherapy

Several surgical series and retrospective analyses have addressed the role of cytoreductive surgery (ie, peritoneal stripping surgery) in combination with perioperative hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis without extra-abdominal metastases.⁴⁸⁶⁻⁴⁹⁵ In an RCT of this approach, Verwaal et al randomized 105 patients to either standard therapy (5-FU/LV with or without palliative surgery) or to aggressive cytoreductive surgery and HIPEC with mitomycin C; postoperative 5-FU/LV was given to 33 of 47 patients.⁴⁹⁶ OS was 12.6 months in the standard arm and 22.3 months in the HIPEC arm ($P = .032$). However, treatment-related morbidity was high, and the mortality was 8% in the HIPEC group, mostly related to bowel leakage. In addition, long-term survival does not seem to be improved by this treatment as seen by follow-up results.⁴⁹⁷ Importantly, this trial was performed without oxaliplatin, irinotecan, or molecularly targeted agents. Some experts have argued that the OS difference seen might have been much smaller if these agents had been used (ie, the control group would have had better outcomes).⁴⁹⁸

Other criticisms of the Verwaal trial have been published.⁴⁹⁸ One important point is that the trial included patients with peritoneal carcinomatosis of appendiceal origin, a group that has seen greater benefit with the cytoreductive surgery/HIPEC approach.^{487,491,499,500} A retrospective multicenter cohort study reported median OS times of 30 and 77 months for patients with peritoneal carcinomatosis of colorectal origin and appendiceal origin, respectively, treated with HIPEC or with cytoreductive



surgery and early postoperative intraperitoneal chemotherapy.⁴⁹¹ The median OS time for patients with pseudomyxoma peritonei, which arises from mucinous appendiceal carcinomas, was not reached at the time of publication. A recent retrospective international registry study reported 10- and 15-year survival rates of 63% and 59%, respectively, in patients with pseudomyxoma peritonei from mucinous appendiceal carcinomas treated with cytoreductive surgery and HIPEC.⁵⁰¹ HIPEC was not shown to be associated with improvements in OS in this study, whereas completeness of cytoreduction was. Thus, for patients with pseudomyxoma peritonei, optimal treatment is still unclear.⁵⁰²

More recently, an ASCO 2018 abstract reported results from the randomized, phase III multicenter, PRODIGE 7 trial of 265 patients with colorectal peritoneal carcinomatosis.⁵⁰³ Patients in this trial received standard treatment of systemic chemotherapy before and/or after cytoreductive surgery and were randomized to standard treatment plus HIPEC with oxaliplatin or standard treatment alone. This study reported no significant difference in OS, with a median OS of 41.7 months in the HIPEC arm versus 41.2 months in the non-HIPEC arm (HR, 1.00; 95% CI, 0.73–1.37) and no significant difference in RFS, with a median RFS of 13.1 months with HIPEC versus 11.1 months without (HR, 0.90; 95% CI, 0.69–1.90). While the morbidity rates did not differ significantly at 30 days, the 60-day grade 3–5 morbidity rate was significantly higher in the HIPEC arm (24.1% vs. 13.6%, $P = .030$).

The individual components of the HIPEC approach have not been well studied. In fact, studies in rats have suggested that the hyperthermia component of the treatment is irrelevant.⁵⁰⁴ Results of a retrospective cohort study also suggest that heat may not affect outcomes from the procedure.⁴⁸⁸ In addition, a randomized trial compared systemic 5-FU/oxaliplatin to cytoreductive surgery and intraperitoneal 5-FU without heat.⁵⁰⁵ Although terminated prematurely because of poor accrual,

analysis suggested that the cytoreductive surgery plus IPEC approach may have been superior to the systemic therapy approach (2-year OS, 54% vs. 38%; $P = .04$) for patients with resectable colorectal peritoneal metastases.

In addition, significant morbidity and mortality are associated with this procedure. A 2006 meta-analysis of two RCTs and 12 other studies reported morbidity rates ranging from 23% to 44% and mortality rates ranging from 0% to 12%.⁴⁹⁵ Furthermore, recurrences after the procedure are very common.⁵⁰⁶ Whereas the risks are reportedly decreasing with time (ie, recent studies report 1%–5% mortality rates at centers of excellence^{492,498}), the benefits of the approach have not been definitively shown, and HIPEC remains very controversial.⁵⁰⁷⁻⁵¹⁰

There are also limited data to inform the use of perioperative systemic therapy before or after resection of peritoneal metastases. An observational cohort study from the Netherlands Cancer Registry used data from 393 patients with isolated synchronous CRC peritoneal metastases to investigate the potential benefit of adjuvant chemotherapy.⁵¹¹ This study found that following complete cytoreductive surgery and HIPEC, adjuvant systemic chemotherapy was associated with improved median OS compared to active surveillance (39.2 vs. 24.8 months; adjusted HR, 0.66; 95% CI, 0.49–0.88; $P = .006$). The CAIRO6 study is an ongoing randomized, parallel-group Dutch trial of 80 patients with isolated resectable peritoneal CRC metastases who were randomized to cytoreductive surgery with HIPEC, plus or minus perioperative systemic therapy.⁵¹² From the pilot portion of this trial, comparable proportions of patients completed cytoreductive surgery/HIPEC (89% vs. 86%) and had major postoperative morbidity (22% vs. 33%) between the perioperative systemic therapy and control arms, respectively. Grade ≥ 3 systemic therapy-related toxicity was observed in 35% of patients and ORR were



28% (radiologic response) and 37% (pathologic response) following neoadjuvant therapy.

The panel currently believes that complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. However, the significant morbidity and mortality associated with HIPEC, as well as the conflicting data on clinical efficacy, make this approach very controversial.

Determining Resectability

The consensus of the panel is that patients diagnosed with potentially resectable mCRC should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (ie, with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status. The criteria for determining patient suitability for resection of metastatic disease are the likelihood of achieving complete resection of all evident disease with negative surgical margins and maintaining adequate liver reserve.⁵¹³⁻⁵¹⁶ When the remnant liver is insufficient in size based on cross-sectional imaging volumetrics, preoperative portal vein embolization of the involved liver can be done to expand the future liver remnant.⁵¹⁷ It should be noted that size alone is rarely a contraindication to resection of a tumor. Resectability differs fundamentally from endpoints that focus more on palliative measures. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease.⁵¹⁸ Resection should not be undertaken unless complete removal of all known tumor is realistically possible (R0 resection), because incomplete resection or debulking (R1/R2 resection) has not been shown to be beneficial.^{361,513}

The role of PET/CT in determining resectability of patients with mCRC is discussed in *Workup and Management of Synchronous Metastatic Disease*, below.

Conversion to Resectability

The majority of patients diagnosed with metastatic colorectal disease have unresectable disease. However, for those with liver-limited unresectable disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished, preoperative systemic therapy is being increasingly considered in highly selected cases in an attempt to downsize colorectal metastases and convert them to a resectable status. Patients presenting with large numbers of metastatic sites within the liver or lung are unlikely to achieve an R0 resection simply on the basis of a favorable response to therapy, as the probability of complete eradication of a metastatic deposit by systemic therapy alone is low. These patients should be regarded as having unresectable disease not amenable to conversion therapy. In some highly selected cases, however, patients with significant response to conversion therapy can be converted from unresectable to resectable status.⁴⁵¹

Any active metastatic systemic regimen can be used in an attempt to convert a patient's unresectable status to a resectable status, because the goal is not specifically to eradicate micrometastatic disease, but rather to obtain the optimal size regression of the visible metastases. An important point to keep in mind is that irinotecan- and oxaliplatin-based chemotherapeutic regimens may cause liver steatohepatitis and sinusoidal liver injury, respectively.⁵¹⁹⁻⁵²³ Studies have reported that chemotherapy-associated liver injury (including severe sinusoidal dilatation and steatohepatitis) is associated with morbidity and complications following hepatectomy for colorectal liver metastases.^{519,520,523,524} To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable.



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Colon Cancer

Some of the trials addressing various conversion therapy regimens are discussed below.

In the study by Pozzo et al, it was reported that chemotherapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%) of the patients with initially unresectable liver metastases to undergo liver resection.⁵¹⁵ The median time to progression was 14.3 months, with all of these patients alive at a median follow-up of 19 months. In a phase II study conducted by the NCCTG,³⁶² 42 patients with unresectable liver metastases were treated with FOLFOX. Twenty-five patients (60%) had tumor reduction and 17 patients (40%; 68% of the responders) were able to undergo resection after a median period of 6 months of chemotherapy. In another study, 1104 patients with initially unresectable colorectal liver metastases were treated with chemotherapy, which included oxaliplatin in the majority of cases, and 138 patients (12.5%) classified as “good responders” underwent secondary hepatic resection.³⁷¹ The 5-year DFS rate for these 138 patients was 22%. In addition, results from a retrospective analysis of 795 previously untreated patients with mCRC enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%; 2 of the 24 had lung metastases) were able to undergo curative resection after treatment.⁵²⁵ The median OS time in this group was 42.4 months.

In addition, first-line FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI (infusional 5-FU, LV, irinotecan) in two randomized clinical trials in patients with unresectable disease.^{526,527} In both studies, FOLFOXIRI led to an increase in R0 secondary resection rates: 6% versus 15%, $P = .033$ in the Gruppo Oncologico Nord Ovest (GONO) trial⁵²⁶; and 4% versus 10%, $P = .08$ in the Gastrointestinal Committee of the HORG trial.⁵²⁷ In a follow-up study of the GONO trial, the 5-year survival rate was higher in the group receiving

FOLFOXIRI (15% vs. 8%), with a median OS of 23.4 versus 16.7 months ($P = .026$).⁵²⁸

More recent favorable results of randomized clinical trials evaluating FOLFIRI, FOLFOX, or FOLFOXIRI in combination with anti-epidermal growth factor receptor (EGFR) inhibitors for the purpose of conversion of unresectable disease to resectable disease have been reported. For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.⁵²⁹ Retrospective analysis showed that in both treatment arms combined resectability increased from 32% to 60% after chemotherapy in patients with wild-type *KRAS* exon 2 with the addition of cetuximab ($P < .0001$). Final analysis of this trial showed that the median OS of the entire cohort was 35.7 months (95% CI, 27.2–44.2 months), with no difference between the arms.⁵³⁰ Another recent RCT compared chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab to chemotherapy alone in patients with unresectable colorectal cancer metastatic to the liver.⁵³¹ The primary endpoint was the rate of conversion to resectability based on evaluation by a multidisciplinary team. After evaluation, 20 of 70 (29%) patients in the cetuximab arm and 9 of 68 (13%) patients in the control arm were determined to be eligible for curative-intent hepatic resection. R0 resection rates were 25.7% in the cetuximab arm and 7.4% in the control arm ($P < .01$). In addition, surgery improved the median survival time compared to unresected participants in both arms, with longer survival in patients receiving cetuximab (46.4 vs. 25.7 months; $P = .007$ for the cetuximab arm and 36.0 vs. 19.6 months; $P = .016$ for the control arm).

The randomized, phase II VOLFI trial compared the efficacy and safety of mFOLFOXIRI in combination with panitumumab to FOLFOXIRI alone in patients with *RAS* wild-type, primarily non-resectable mCRC.⁵³² Of the cohort with unresectable, potentially convertible metastases, 75% were ultimately converted to resectable with FOLFOXIRI + panitumumab



compared to 36.4% with FOLFOXIRI alone. ORR was also improved in the combination compared to FOLFOXIRI alone while PFS was similar between the two treatments and OS showed a trend in favor of the combination. A recent meta-analysis of four RCTs concluded that the addition of cetuximab or panitumumab to chemotherapy significantly increased the response rate, the R0 resection rate (from 11%–18%; RR, 1.59; $P = .04$), and PFS, but not OS in patients with wild-type *KRAS* exon 2-containing tumors.⁵³³ The randomized, phase III TRIPLETE study will compare mFOLFOXIRI plus panitumumab to mFOLFOX6 plus panitumumab as initial therapy for patients with unresectable *RAS* and *BRAF* wild-type mCRC.⁵³⁴

The role of bevacizumab in the patient with unresectable disease, whose disease is felt to be potentially convertible to resectability with a reduction in tumor size, has also been studied. Data seem to suggest that bevacizumab modestly improves the response rate to irinotecan-based regimens.^{535,536} Thus, when an irinotecan-based regimen is selected for an attempt to convert unresectable disease to resectability, the use of bevacizumab would seem to be an appropriate consideration. The data on use of bevacizumab with oxaliplatin-based therapy in the conversion to resectability setting are mixed. On one hand, a 1400-patient, randomized, double-blind, placebo-controlled trial of CAPEOX or FOLFOX with or without bevacizumab showed absolutely no benefit in terms of response rate or tumor regression for the addition of bevacizumab, as measured by both investigators and an independent radiology review committee.⁵³⁷ On the other hand, the randomized BECOME trial of 241 patients with initially unresectable *RAS* mutant CRC liver metastases showed improvement in the resectability of liver metastases as well as response rates and survival with mFOLFOX6 plus bevacizumab compared to mFOLFOX6 alone.⁵³⁸ R0 resection rates were 22.3% in the bevacizumab combo versus 5.8% with mFOLFOX6 alone ($P < .01$). Because it is not known in advance whether

resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable.

When systemic therapy is planned for patients with initially unresectable disease, the panel recommends that a surgical re-evaluation be planned 2 months after initiation of therapy, and that those patients who continue to receive systemic therapy undergo surgical re-evaluation every 2 months thereafter.^{523,539-541} Reported risks associated with chemotherapy include the potential for development of liver sinusoidal dilatation, steatosis, or steatohepatitis.^{519,524,542} To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable.

Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease

The panel recommends that a course of an active systemic therapy regimen for metastatic disease, administered for a total perioperative treatment time of approximately 6 months, be considered for most patients undergoing liver or lung resection to increase the likelihood that residual microscopic disease will be eradicated (category 2B for the use of biologic agents in the perioperative metastatic setting). Although systemic therapy can be given before, between, or after resections, the total duration of perioperative systemic therapy should not exceed 6 months. A 2012 meta-analysis identified three randomized clinical trials comparing surgery alone to surgery plus systemic therapy with 642 evaluable patients with colorectal liver metastases.⁵⁴³ The pooled analysis showed a benefit of chemotherapy in PFS (pooled HR, 0.75; CI, 0.62–0.91; $P = .003$) and DFS (pooled HR, 0.71; CI, 0.58–0.88; $P = .001$), but not in OS (pooled HR, 0.74; CI, 0.53–1.05; $P = .088$). Another meta-analysis published in 2015 combined data on 1896 patients from 10 studies and also found that perioperative chemotherapy improved DFS (HR, 0.81; 95% CI, 0.72–0.91; $P = .0007$) but not OS (HR, 0.88; 95% CI, 0.77–1.01; $P = .07$) in patients



with resectable colorectal liver metastases.⁵⁴⁴ Additional recent meta-analyses have also failed to observe a statistically significant OS benefit with the addition of adjuvant chemotherapy in resectable mCRC.⁵⁴⁵⁻⁵⁴⁷

A pooled analysis of the phase III TRIBE and TRIBE2 studies compared upfront FOLFOXIRI plus bevacizumab to chemotherapy doublets (FOLFOX or FOLFIRI) plus bevacizumab for oligometastatic mCRC.⁵⁴⁸ In agreement with the primary outcomes from these studies, the benefits of using the chemotherapy triplet compared to the doublet were retained in the patient population that had oligometastatic disease, with interaction *P* scores above significance for PFS, OS, and ORR outcome measures. Therefore, the authors of this study conclude that FOLFOXIRI provides a benefit for oligometastatic CRC, including when used as upfront treatment in conjunction with locoregional treatments, such as resection. Furthermore, an analysis of individual patient data from five trials that compared upfront FOLFOXIRI plus bevacizumab to doublet chemotherapy plus bevacizumab reported a higher R0 resection rate in the FOLFOXIRI arm.⁵⁴⁹ Based on the limited data that are available, as well as their own institutional practice patterns, the NCCN Panel has included FOLFOXIRI as an option for neoadjuvant treatment of resectable mCRC. The recommendation's category 2B rating reflects the relative scarcity of data supporting this treatment option.

While there are a lack of data in this setting, the panel considers pembrolizumab or nivolumab, as a monotherapy or in combination with ipilimumab, as options for neoadjuvant therapy of resectable dMMR/MSI-H mCRC. While there are no clinical trial data supporting this approach, a few case studies have reported notable responses to pembrolizumab and nivolumab when used as a neoadjuvant therapy for dMMR advanced or mCRC.⁵⁵⁰⁻⁵⁵² The panel notes that special caution should be taken to monitor for signs of progression, which could potentially cause a previously resectable tumor to become unresectable. While this is a

concern for any regimen being used as neoadjuvant therapy in the resectable mCRC setting, the risk is possibly higher with immunotherapy compared to traditional chemotherapy options.

The choice of regimen in the perioperative setting depends on several factors, including the chemotherapy history of the patient, whether disease is synchronous or metachronous, and the response rates and safety/toxicity issues associated with the regimens, as outlined in the guidelines. Biologics are not recommended in the perioperative metastatic setting, with the exception of initial therapy in unresectable patients who may be converted to a resectable state.

The optimal sequencing of systemic therapy and resection remains unclear. Patients with resectable disease may undergo resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neoadjuvant plus postoperative) systemic therapy can be used.^{553,554}

Potential advantages of preoperative therapy include: earlier treatment of micrometastatic disease, determination of responsiveness to therapy (which can be prognostic and help in planning postoperative therapy), and avoidance of local therapy for those patients with early disease progression. Potential disadvantages include missing the “window of opportunity” for resection because of the possibility of disease progression or achievement of a complete response, thereby making it difficult to identify areas for resection.^{364,555,556} In fact, results from recent studies of patients with CRC receiving preoperative therapy indicated that viable cancer was still present in most of the original sites of metastases when these sites were examined pathologically despite achievement of a complete response as evaluated on CT scan.⁵⁵⁶⁻⁵⁵⁸ Therefore, during treatment with preoperative systemic therapy, frequent evaluations must be undertaken and close communication must be maintained among medical oncologists, radiologists, surgeons, and patients so that a



treatment strategy can be developed that optimizes exposure to the preoperative regimen and facilitates an appropriately timed surgical intervention.⁵¹⁹

Other reported risks associated with the preoperative therapy approach include the potential for development of liver steatohepatitis and sinusoidal liver injury when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively.⁵¹⁹⁻⁵²³ To reduce the development of hepatotoxicity, the neoadjuvant period is usually limited to 2 to 3 months, and patients should be carefully monitored by a multidisciplinary team.

Systemic Therapy for Advanced or Metastatic Disease

The current management of disseminated metastatic colon cancer involves various active drugs, either in combination or as single agents. The choice of therapy is based on consideration of the goals of therapy, the type and timing of prior therapy, the mutational profile of the tumor, and the differing toxicity profiles of the constituent drugs. Although the specific regimens listed in the guideline are designated according to whether they pertain to initial therapy, therapy after first progression, or therapy after second progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete.⁵⁵⁹ For example, if oxaliplatin is administered as a part of an initial treatment regimen but is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the remainder of the treatment regimen would still be considered initial therapy.

Principles to consider at the start of therapy include: 1) preplanned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive; and 2) plans for adjusting therapy for patients who experience certain toxicities. For example,

decisions related to therapeutic choices after first progression of disease should be based, in part, on the prior therapies received (ie, exposing the patient to a range of cytotoxic agents). Furthermore, an evaluation of the efficacy and safety of these regimens for a patient must take into account not only the component drugs, but also the doses, schedules, and methods of administration of these agents, and the potential for surgical cure and the performance status of the patient.

Sequencing and Timing of Therapies

Few studies have addressed the sequencing of therapies in advanced metastatic disease. Prior to the use of targeted agents, several studies randomized patients to different schedules.⁵⁶⁰⁻⁵⁶³ The data from these trials suggest that there is little difference in clinical outcomes if intensive therapy is given in first line or if less intensive therapy is given first followed by more intensive combinations.

Results from a randomized study to evaluate the efficacy of FOLFIRI and FOLFOX regimens as initial therapy and to determine the effect of using sequential therapy with the alternate regimen after first progression showed neither sequence to be significantly superior with respect to PFS or median OS.⁵⁶³ A combined analysis of data from seven recent phase III clinical trials in advanced CRC provided support for a correlation between an increase in median survival and administration of all of the three cytotoxic agents (ie, 5-FU/LV, oxaliplatin, irinotecan) at some point in the continuum of care.⁵⁶⁴ Furthermore, OS was not found to be associated with the order in which these drugs were received.

A study of 6286 patients from nine trials that evaluated the benefits and risks associated with intensive first-line treatment in the setting of mCRC treatment showed similar therapeutic efficacy for patients with a performance status of 2 or 1 or less as compared with control groups. However, the risks of certain gastrointestinal (GI) toxicities were significantly increased for patients with a performance status of 2.⁵⁶⁵



Overall, the panel does not consider one regimen to be preferable over another as initial therapy for metastatic disease. The panel also does not indicate a preference for biologic agents used as part of initial therapy (ie, bevacizumab, cetuximab, panitumumab, none).

Therapy Retreatment/Rechallenge

Due to few efficacious options in later lines of therapy, there has been considerable interest in the possibility of retreating with a systemic therapy used during an earlier line of treatment. Most studies that have reported on this approach have been retrospective, detailing institutional experiences retreating with chemotherapeutics⁵⁶⁶⁻⁵⁶⁸ or targeted therapies (eg, EGFR inhibitors)^{566,569-573} and concluded that a retreatment approach was feasible, based on response and/or toxicity data. However, these studies were mainly small and did not differentiate between patients who stopped therapy due to progression compared to other reasons, limiting the quality of these data. The randomized FIRE-4 trial (NCT02934529) is currently under recruitment and will seek to address this question.

Therefore, until stronger data become available, the panel agrees that for patients who had therapy stopped for a reason other than progression (eg, use as adjuvant therapy, cumulative toxicity, treatment break, patient preference), rechallenge with this therapy would be an option. However, based on the current lack of evidence, retreatment with a therapy following progression on that regimen is not recommended.

Maintenance Therapy

Interest in the use of a maintenance therapy approach after first-line treatment of unresectable mCRC is growing. In general, this approach involves intensive first-line therapy, followed by less intensive therapy until progression in patients with good response to initial treatment.

The CAIRO3 study was an open-label, phase III, multicenter RCT assessing maintenance therapy with capecitabine/bevacizumab versus

observation in 558 patients with mCRC and with stable disease or better after first-line treatment with CAPEOX/bevacizumab.⁵⁷⁴ Following first progression, both groups were to receive CAPEOX/bevacizumab again until second progression (PFS2). After a median follow-up of 48 months, the primary endpoint of PFS2 was significantly better in the maintenance arm (8.5 months vs. 11.7 months; HR, 0.67; 95% CI, 0.56–0.81; $P < .0001$), with 54% of patients overall receiving CAPEOX/bevacizumab the second time. Quality of life was not affected by maintenance therapy, although 23% of patients in the maintenance group developed hand-foot syndrome during the maintenance period. A non-significant trend towards improved OS was seen in the maintenance arm (18.1 months vs. 21.6 months; adjusted HR, 0.83; 95% CI, 0.68–1.01; $P = .06$). A molecular subgroup analysis of CAIRO3 showed that the capecitabine/bevacizumab maintenance strategy was effective across all mutational subgroups (*RAS/BRAF* wild-type, *RAS* mutant, and *BRAF* V600E), although the benefit of maintenance was most pronounced for patients with *RAS/BRAF* wild-type or *BRAF* V600E mutation-positive tumors.⁵⁷⁵

The AIO 0207 trial was an open-label, non-inferiority, randomized phase III trial that randomized 472 patients whose disease did not progress on induction FOLFOX/bevacizumab or CAPEOX/bevacizumab to no maintenance therapy or to maintenance therapy with fluoropyrimidine/bevacizumab or with bevacizumab alone.⁵⁷⁶ The planned protocol included re-introduction of primary therapy after first progression. The primary endpoint was time to failure of strategy, defined as time from randomization to second progression, death, and initiation of treatment with a new drug. After a medium follow-up of 17 months, the median time to failure of strategy was 6.4 months (95% CI, 4.8–7.6) for the no treatment group, 6.9 months (95% CI, 6.1–8.5) for the fluoropyrimidine/bevacizumab group, and 6.1 months (95% CI, 5.3–7.4) for the bevacizumab alone group. Compared with fluoropyrimidine/bevacizumab, bevacizumab alone was non-inferior,



whereas the absence of maintenance therapy was not. However, only about one third of trial participants received the re-induction therapy, thus limiting the interpretation of results. OS was one of the secondary endpoints of the trial, and no relevant difference was seen between the arms.

PRODIGE 9 was a randomized phase III trial that investigated the effect of bevacizumab maintenance compared to no treatment during chemotherapy-free intervals following induction chemotherapy with 12 cycles of FOLFIRI plus bevacizumab. Median tumor control duration was 15 months in both groups. PFS was 9.2 and 8.9 months and OS was 21.7 and 22.0 months for bevacizumab maintenance and no treatment, respectively. Therefore, this study concluded that bevacizumab maintenance did not improve outcomes.⁵⁷⁷

The randomized phase III non-inferiority SAKK 41/06 trial addressed the question of continuing bevacizumab alone as maintenance therapy after chemotherapy plus bevacizumab in first-line therapy.⁵⁷⁸ The primary endpoint of time to progression was not met (4.1 months for bevacizumab continuation vs. 2.9 months for no continuation; HR, 0.74; 95% CI, 0.58–0.96), and no difference in OS was observed (25.4 months vs. 23.8 months; HR, 0.83; 95% CI, 0.63–1.1; $P = .2$). Therefore, non-inferiority for treatment holidays versus bevacizumab maintenance therapy was not demonstrated.

The GERCOR DREAM trial (OPTIMOX3) was an international, open-label, phase III study that randomized patients with mCRC without disease progression on bevacizumab-based therapy to maintenance therapy with bevacizumab or bevacizumab plus erlotinib.⁵⁷⁹ Intention-to-treat (ITT) analysis revealed an advantage in PFS (5.4 vs. 4.9 months; stratified HR, 0.81; 95% CI, 0.66–1.01; $P = .06$) and OS (24.9 vs. 22.1 months; stratified HR, 0.79; 95% CI, 0.63–0.99; $P = .04$) with combination therapy. A smaller randomized trial, however, showed no difference in PFS or OS between

bevacizumab and bevacizumab/erlotinib maintenance therapy in patients with *KRAS* wild-type tumors.⁵⁸⁰ A meta-analysis identified three randomized trials (682 patients) and concluded that maintenance therapy with bevacizumab/erlotinib significantly increases OS and PFS, with manageable toxicity.⁵⁸¹

Another phase III trial investigated the role of capecitabine in the maintenance phase, after initial treatment with FOLFOX or CAPEOX.⁵⁸² PFS, the primary endpoint, was 6.4 months in the capecitabine maintenance group and 3.4 months in the group that was observed until progression (HR, 0.54; 95% CI, 0.42–0.70; $P < .001$). A non-statistically significant difference in the median OS was also seen (HR, 0.85; 95% CI, 0.64–1.11; $P = .2247$). Toxicities associated with the capecitabine maintenance therapy were acceptable.

A systematic review and network meta-analysis of 12 randomized clinical trials comprising 5540 patients with mCRC concluded that a maintenance strategy with a fluoropyrimidine, with or without bevacizumab, led to a significant improvement in PFS, but not in OS.⁵⁸³ Given the PFS benefit seen in some studies, but the probable lack of OS benefit, maintenance therapy may be discussed as part of shared decision-making with patients with observation as an acceptable alternative.

Biosimilars

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing biologic therapy.⁵⁸⁴⁻⁵⁹⁰ Several biosimilars are now available in the U.S. market, including biosimilars to two biologics that are recommended in the NCCN Guidelines for Colon Cancer: bevacizumab and trastuzumab. The NCCN Panel has agreed that an FDA-approved biosimilar may be substituted for either bevacizumab or trastuzumab wherever these therapies are recommended within the NCCN Guidelines for Colon Cancer.



Biomarkers for Systemic Therapy

As the role of targeted therapy for treatment of advanced or mCRC has become increasingly prominent, the NCCN Panel has expanded its recommendations regarding biomarker testing. Currently, determination of tumor gene status for *KRAS/NRAS* and *BRAF* mutations, as well as HER2 amplifications and MSI/MMR status (if not previously done), are recommended for patients with mCRC. Testing may be carried out for individual genes or as part of an NGS panel, although no specific methodology is recommended. NGS panels have the advantage of being able to pick up rare and actionable genetic alterations, such as neurotrophic tyrosine receptor kinase (*NTRK*) fusions. Specific information about each of these biomarkers may be found in the sections below.

KRAS and NRAS Mutations

The MAPK pathway of RAS/RAF/MEK/ERK is downstream of EGFR; mutations in components of this pathway are now established to be strong negative predictive markers, essentially precluding efficacy of these therapies. A sizable body of literature has shown that tumors with a mutation in exons 2, 3, or 4 of either the *KRAS* or *NRAS* genes are essentially insensitive to cetuximab or panitumumab therapy.⁵⁹¹⁻⁶⁰¹ The panel therefore strongly recommends *RAS* (*KRAS/NRAS*) genotyping of tumor tissue (either primary tumor or metastasis) in all patients with mCRC. Patients with known *KRAS* or *NRAS* mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. ASCO released a Provisional Clinical Opinion Update on extended *RAS* testing in patients with mCRC that is consistent with the NCCN Panel's recommendations.⁶⁰² A guideline on molecular biomarkers for CRC developed by the ASCP, CAP, AMP, and ASCO also recommends *RAS* testing consistent with the NCCN recommendations.²⁸

The recommendation for *RAS* testing, at this point, is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of *RAS* status is appropriate to plan for the treatment continuum, so that the information may be obtained in a non-time-sensitive manner and the patient and provider can discuss the implications of a *RAS* mutation, if present, while other treatment options still exist. Note that because anti-EGFR agents have no role in the management of stage I, II, or III disease, *RAS* genotyping of CRCs at these earlier stages is not recommended.

KRAS mutations are early events in CRC formation, and therefore a very tight correlation exists between mutation status in the primary tumor and the metastases.⁶⁰³⁻⁶⁰⁵ For this reason, *RAS* genotyping can be performed on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of *RAS* genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable.

The panel recommends that *KRAS*, *NRAS*, and *BRAF* gene testing be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.⁶⁰⁶ No specific testing methodology is recommended.⁶⁰⁷ The three genes can be tested individually or as part of an NGS panel.

Results are mixed as far as the prognostic value of *KRAS* mutations. In the Alliance N0147 trial, patients with *KRAS* exon 2 mutations experienced a shorter DFS than patients without such mutations.⁶⁰⁸ At this time, however, the test is not recommended for prognostic reasons.

A retrospective study by De Roock et al⁶⁰⁹ raised the possibility that codon 13 mutations (G13D) in *KRAS* may not be absolutely predictive of non-response. Another retrospective study showed similar results.⁵⁹⁸ However,



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more recent retrospective analysis of three randomized controlled phase III trials concluded that patients with *KRAS* G13D mutations were unlikely to respond to panitumumab.⁶¹⁰ Results from a prospective phase II single-arm trial assessed the benefit of cetuximab monotherapy in 12 patients with refractory mCRC whose tumors contained *KRAS* G13D mutations.⁶¹¹ The primary endpoint of 4-month progression-free rate was not met (25%), and no responses were seen. Preliminary results of the AGITG phase II ICE CREAM trial also failed to see a benefit of cetuximab monotherapy in patients with *KRAS* G13D mutations.⁶¹² However, partial responses were reported after treatment with irinotecan plus cetuximab in 9% of this irinotecan-refractory population. A meta-analysis of eight RCTs came to the same conclusion: that tumors with *KRAS* G13D mutations are no more likely to respond to EGFR inhibitors than tumors with other *KRAS* mutations.⁶¹³ The panel believes that patients with any known *KRAS* mutation, including G13D, should not be treated with cetuximab or panitumumab.

In the AGITG MAX study, 10% of patients with wild-type *KRAS* exon 2 had mutations in *KRAS* exons 3 or 4 or in *NRAS* exons 2, 3, and 4.⁶¹⁴ In the PRIME trial, 17% of 641 patients without *KRAS* exon 2 mutations were found to have mutations in exons 3 and 4 of *KRAS* or mutations in exons 2, 3, and 4 of *NRAS*. A predefined retrospective subset analysis of data from PRIME revealed that PFS (HR, 1.31; 95% CI, 1.07–1.60; $P = .008$) and OS (HR, 1.21; 95% CI, 1.01–1.45; $P = .04$) were decreased in patients with any *KRAS* or *NRAS* mutation who received panitumumab plus FOLFOX compared to those who received FOLFOX alone.⁶⁰⁰ These results show that panitumumab does not benefit patients with *KRAS* or *NRAS* mutations and may even have a detrimental effect in these patients.

Updated analysis of the FIRE-3 trial (discussed in *Cetuximab or Panitumumab vs. Bevacizumab in First-line Therapy*, below) has been published.⁶¹⁵ When all *RAS* (*KRAS*/*NRAS*) mutations were considered,

PFS was significantly worse in patients with *RAS*-mutant tumors receiving FOLFIRI plus cetuximab than in patients with *RAS*-mutant tumors receiving FOLFIRI plus bevacizumab (6.1 months vs. 12.2 months; $P = .004$). On the other hand, patients with *KRAS*/*NRAS* wild-type tumors showed no difference in PFS between the regimens (10.4 months vs. 10.2 months; $P = .54$). This result indicates that cetuximab likely has a detrimental effect in patients with *KRAS* or *NRAS* mutations.

The FDA indication for panitumumab was updated to state that panitumumab is not indicated for the treatment of patients with *KRAS* or *NRAS* mutation-positive disease in combination with oxaliplatin-based chemotherapy.⁶¹⁶ The NCCN Colon/Rectal Cancer Panel believes that *RAS* mutation status should be determined at diagnosis of stage IV disease. Patients with any known *RAS* mutation should not be treated with either cetuximab or panitumumab.

BRAF V600E Mutations

Although mutations in *RAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *RAS* still do not respond to these therapies. Therefore, studies have addressed factors downstream of *RAS* as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5% to 9% of CRCs are characterized by a specific mutation in the *BRAF* gene (V600E).^{617,618} *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *RAS* mutations.⁶¹⁷⁻⁶¹⁹ Activation of the protein product of the non-mutated *BRAF* gene occurs downstream of the activated *KRAS* protein in the EGFR pathway. The mutated *BRAF* protein product is believed to be constitutively active,⁶²⁰⁻⁶²² thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

Limited data from unplanned retrospective subset analyses of patients with mCRC treated in the first-line setting suggest that although a *BRAF* V600E mutation confers a poor prognosis regardless of treatment, patients



with disease characterized by this mutation may receive some benefit from the addition of cetuximab to front-line therapy.^{618,623} A planned subset analysis of the PRIME trial also found that mutations in *BRAF* indicated a poor prognosis but were not predictive of benefit to panitumumab added to FOLFOX in first-line treatment of mCRC.⁶⁰⁰ On the other hand, results from the randomized phase III Medical Research Council (MRC) COIN trial suggest that cetuximab may have no effect or even a detrimental effect in patients with *BRAF*-mutated tumors treated with CAPEOX or FOLFOX in the first-line setting.⁶¹⁹

In subsequent lines of therapy, retrospective evidence suggests that mutated *BRAF* is a marker of resistance to anti-EGFR therapy in the non-first-line setting of metastatic disease.⁶²⁴⁻⁶²⁶ A retrospective study of 773 primary tumor samples from patients with chemotherapy-refractory disease showed that *BRAF* mutations conferred a significantly lower response rate to cetuximab (2/24; 8.3%) compared with tumors with wild-type *BRAF* (124/326; 38.0%; $P = .0012$).⁶²⁷ Furthermore, data from the multicenter randomized controlled PICCOLO trial are consistent with this conclusion, with a suggestion of harm seen for the addition of panitumumab to irinotecan in the non-first-line setting in the small subset of patients with *BRAF* mutations.⁶²⁸

A meta-analysis published in 2015 identified nine phase III trials and one phase II trial that compared cetuximab or panitumumab with standard therapy or best supportive care including 463 patients with metastatic colorectal tumors with *BRAF* mutations (first-line, second-line, or refractory settings).⁶²⁹ The addition of an EGFR inhibitor did not improve PFS (HR, 0.88; 95% CI, 0.67–1.14; $P = .33$), OS (HR, 0.91; 95% CI, 0.62–1.34; $P = .63$), or ORR (RR, 1.31; 95% CI, 0.83–2.08; $P = .25$) compared with control arms. Similarly, another meta-analysis identified seven RCTs and found that cetuximab and panitumumab did not improve PFS (HR, 0.86;

95% CI, 0.61–1.21) or OS (HR, 0.97; 95% CI, 0.67–1.41) in patients with *BRAF* mutations.⁶³⁰

In addition to its role as a predictive marker for *BRAF*-targeted therapy, it is clear that mutations in *BRAF* are a strong prognostic marker.^{288,618,619,631-}

⁶³⁶ A prospective analysis of tissues from patients with stage II and III colon cancer enrolled in the PETACC-3 trial showed that the *BRAF* mutation is prognostic for OS in patients with MSI-L or MSS tumors (HR, 2.2; 95% CI, 1.4–3.4; $P = .0003$).²⁸⁸ Moreover, an updated analysis of the CRYSTAL trial showed that patients with metastatic colorectal tumors carrying a *BRAF* mutation have a worse prognosis than those with the wild-type gene.⁶¹⁸ Additionally, *BRAF* mutation status predicted OS in the AGITG MAX trial, with an HR of 0.49 (95% CI, 0.33–0.73; $P = .001$).⁶³² The OS for patients with *BRAF* mutations in the COIN trial was 8.8 months, while those with *KRAS* exon 2 mutations and wild-type *KRAS* exon 2 tumors had OS times of 14.4 months and 20.1 months, respectively.⁶¹⁹ In addition, a secondary analysis of the N0147 and C-08 trials found that *BRAF* mutations were significantly associated with worse survival after recurrence of resected stage III colon cancer, with a stronger association for primary tumors located in the distal colon.⁶³⁷ Results from a recent systematic review and meta-analysis of 21 studies, including 9885 patients, suggest that *BRAF* mutation may accompany specific high-risk clinicopathologic characteristics.⁶³⁸ In particular, an association was observed between *BRAF* mutation and proximal tumor location (OR, 5.22; 95% CI, 3.80–7.17; $P < .001$), T4 tumors (OR, 1.76; 95% CI, 1.16–2.66; $P = .007$), and poor differentiation (OR, 3.82; 95% CI, 2.71–5.36; $P < .001$).

Overall, the panel believes that evidence increasingly suggests that *BRAF* V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely, unless given as part of a *BRAF* inhibitor regimen (see *Encorafenib Plus Cetuximab or Panitumumab for BRAF V600E Mutation-Positive Disease in*



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the *Non–First-line Setting*, below). The panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis⁶³⁹) at diagnosis of stage IV disease. Testing for the *BRAF* V600E mutation can be performed on formalin-fixed paraffin-embedded tissues and is usually performed by PCR amplification and direct DNA sequence analysis. Allele-specific PCR, NGS, or IHC are other acceptable methods for detecting this mutation.

HER2 Amplification/Overexpression

HER2 is a member of the same family of signaling kinase receptors as EGFR and has been successfully targeted in breast cancer in both the advanced and adjuvant settings. HER2 is rarely amplified/overexpressed in CRC (approximately 3% overall), but the prevalence is higher in *RAS/BRAF*–wild type tumors (reported at 5%–14%).^{640,641} Specific molecular diagnostic methods have been proposed for HER2 testing in CRC,⁶⁴² and HER2-targeted therapies are now recommended as subsequent therapy options in patients with tumors that are *RAS/BRAF* wild-type and have HER2 overexpression (see *Systemic Therapy Options for HER2-Amplified Disease*, below).^{640,643} Based on this, the NCCN Guidelines recommend testing for HER2 amplifications for patients with mCRC. If the tumor is already known to have a *KRAS/NRAS* or *BRAF* mutation, HER2 testing is not indicated. As HER2-targeted therapies are still under investigation, enrollment in a clinical trial is encouraged.

Evidence does not support a prognostic role of HER2 overexpression.⁶⁴⁴ In addition to its role as a predictive marker for HER2-targeted therapy, initial results indicate HER2 amplification/overexpression may be predictive of resistance to EGFR-targeting monoclonal antibodies.^{641,645,646}

For example, in a cohort of 98 patients with *RAS/BRAF*–wild type mCRC, median PFS on therapy without an EGFR inhibitor was similar regardless of HER2 status.⁶⁴⁶ However, in therapy with an EGFR inhibitor, the PFS was significantly shorter in those with HER2 amplification compared with

those without HER2 amplification (2.8 months vs. 8.1 months; HR, 7.05; 95% CI, 3.4–14.9; $P < .001$).

dMMR/MSI-H Status

The percentage of stage IV colorectal tumors characterized as MSI-H (dMMR) ranged from 3.5% to 5.0% in clinical trials and was 6.5% in the Nurses' Health Study and Health Professionals Follow-up Study.^{289,647,648} dMMR tumors contain thousands of mutations, which can encode mutant proteins with the potential to be recognized and targeted by the immune system. However, programmed death-ligands 1 and 2 (PD-L1 and PD-L2) on tumor cells can suppress the immune response by binding to programmed cell death protein 1 (PD-1) receptor on T-effector cells. This system evolved to protect the host from an unchecked immune response. Many tumors upregulate PD-L1 and thus evade the immune system.⁶⁴⁹ It was therefore hypothesized that dMMR tumors may be sensitive to PD-1 inhibitors. Subsequently, this hypothesis was confirmed in clinical trials, leading to the addition of recommendations for checkpoint inhibitors for dMMR/MSI-H disease (see *Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease in the First-Line and Non-First-Line Settings*, below). The NCCN Guidelines recommend universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer. In addition to its role as a predictive marker for immunotherapy use in the advanced CRC setting, MMR/MSI status can also help to identify individuals with Lynch syndrome (see *Lynch Syndrome*, above), and to inform adjuvant therapy decisions for patients with stage II disease (see *Microsatellite Instability under Adjuvant Chemotherapy for Resectable Colon Cancer*, above).

NTRK Fusions

Three *NTRK* genes encode the tropomyosin receptor kinase (TRK) proteins. TRK expression is primarily in the nervous system where these kinases help to regulate pain, perception of movement/position, appetite,



and memory. *NTRK* gene fusions lead to overexpression of the TRK fusion protein, resulting in constitutively active downstream signaling.⁶⁵⁰ Recent studies have estimated that about 0.2% to 1% of CRCs carry *NTRK* gene fusions.^{651,652} A study of 2314 CRC specimens, of which 0.35% had *NTRK* fusions, found that *NTRK* fusions were limited to cancers that were wild-type for *KRAS*, *NRAS*, and *BRAF*. Furthermore, a majority of the CRCs harboring *NTRK* fusions were also MMR-deficient.⁶⁵³ These results may support limiting testing for *NTRK* fusions to those with wild-type *KRAS*, *NRAS*, and *BRAF*. TRK inhibitors are treatment options for patients with mCRC that is *NTRK* gene fusion-positive (see *Larotrectinib or Entrectinib for NTRK Fusion-Positive Disease in the Non-First-Line Setting*, below).

Tumor Mutational Burden (TMB)

TMB measures the total amount of somatic coding mutations within a given coding area of the tumor genome and can be quantified using NGS techniques.⁶⁵⁴ Research has identified TMB as a potential biomarker for response to immunotherapy and pembrolizumab has been FDA-approved for patients with unresectable or metastatic, TMB-high (TMB-H) solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.⁶⁵⁵ TMB-H is defined in the label as 10 or more mutations/megabase by an FDA-approved test. This approval was based off results of the phase 2, KEYNOTE-158 study that enrolled patients with advanced solid tumors.⁶⁵⁶ Patients with TMB-H tumors who were treated with pembrolizumab had an ORR of 29% compared to 6% of those with non-TMB-H tumors. However, of the 796 patients who were evaluated for efficacy on this study, none had colorectal cancers. An abstract on the phase II TAPUR basket study reported results for 27 patients with TMB-H advanced CRC who were treated with pembrolizumab.⁶⁵⁷ One partial response and seven cases with stable disease for at least 16 weeks were reported, for a disease control rate of 28% and an ORR of 4%.

Based on the limited data in the colorectal cancer population, the NCCN Panel does not currently recommend TMB biomarker testing, unless measured as part of a clinical trial.

Severe Fluoropyrimidine-Associated Toxicity

Dihydropyrimidine dehydrogenase is the enzyme that catabolizes fluoropyrimidines.^{658,659} Individuals with certain variants of the dihydropyrimidine dehydrogenase gene, *DPYD*, have a significantly elevated risk for severe, life-threatening toxicity after a standard dose of fluoropyrimidine because these variants result in a truncated protein and prolonged systemic exposure to fluoropyrimidine.⁶⁶⁰⁻⁶⁶⁴ Pretreatment *DPYD* testing of all patients has the potential to identify the estimated 1% to 2% of the population with truncating alleles that may herald an increased risk of severe toxicity.⁶⁶⁵ These patients could receive dose reductions or could be offered non-fluoropyrimidine regimens, although it is not certain that every one of these patients is at risk.⁶⁵⁹ Two prospective studies have shown *DPYD* genotyping and fluoropyrimidine dose individualization to be feasible in clinical practice, improve patient safety, and be cost effective.⁶⁶⁶⁻⁶⁶⁸ In a prospective study, 22 patients with the *DPYD**2A variant allele (of 2038 patients screened; 1.1%) were given a fluoropyrimidine dose reduction of 17% to 91% (median 48%).⁶⁶⁸ Results showed a significant reduction in the risk of grade ≥3 toxicity compared with historic controls (28% vs. 73%; $P < .001$). None of the patients died from drug toxicity, compared with a 10% death rate in the historical control group. Another prospective study identified 85 patients with any of the four *DPYD* variant alleles (8% of 1103 patients screened) who received an initial fluoropyrimidine dose reduction of either 25% or 50% depending on the specific allele.⁶⁶⁷ This study reported that the RR of severe fluoropyrimidine-related toxicity was reduced for genotype-guided dosing for all studied alleles compared to the historical cohorts. However, because fluoropyrimidines are a pillar of therapy in CRC and it is not known with certainty that given *DYPD* variants are necessarily associated



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with this risk, universal pretreatment *DPYD* genotyping remains controversial and the NCCN Panel does not support it at this time.

Regimens Not Recommended

The consensus of the panel is that infusional 5-FU regimens seem to be less toxic than bolus regimens and that any bolus regimen of 5-FU is inappropriate when administered with either irinotecan or oxaliplatin. Therefore, the panel no longer recommends using the IFL regimen (which was shown to be associated with increased mortality and decreased efficacy relative to FOLFIRI in the BICC-C trial^{535,669} and inferior to FOLFOX in the Intergroup trial⁶⁷⁰) at any point in the therapy continuum. 5-FU in combination with irinotecan or oxaliplatin should be administered via an infusional biweekly regimen,²⁶¹ or capecitabine can be used with oxaliplatin.⁶⁷¹

The Dutch CAIRO trial showed promising results for the use of capecitabine/irinotecan (CapelRI) in the first-line treatment of mCRC.⁵⁶¹ However, in the American BICC-C trial, CapelRI showed worse PFS than FOLFIRI (5.8 vs. 7.6 months; $P = .015$), and was considerably more toxic with higher rates of severe vomiting, diarrhea, and dehydration.⁵³⁵ In this trial, the CapelRI arm was discontinued. The EORTC study 40015 also compared FOLFIRI with CapelRI and was discontinued after enrollment of only 85 patients because seven deaths were determined to be treatment-related (five in the CapelRI arm).⁶⁷² Several European studies have assessed the safety and efficacy of CapelRI in combination with bevacizumab (CapelRI/Bev) in the first-line metastatic setting. A small Spanish study of 46 patients who received CapelRI/Bev showed encouraging results with good tolerability.⁶⁷³ A similar trial by the Spanish group found similar results in 77 patients.⁶⁷⁴ Preliminary results from a randomized phase II study conducted in France were presented in 2009, showing a manageable toxicity profile for CapelRI/Bev in this setting.⁶⁷⁵ Additionally, a randomized phase III HeCOG trial compared CapelRI/Bev

and FOLFIRI/Bev in the first-line metastatic setting and found no significant differences in efficacy between the regimens.⁶⁷⁶ Despite the differing toxicity profiles reported, the toxicities seemed to be reasonable in both arms. Finally, a randomized phase II study of the AIO colorectal study group compared CAPEOX plus bevacizumab with a modified CapelRI regimen plus bevacizumab and found similar 6-month PFS and similar toxicities.⁶⁷⁷ Because of the concerns about the toxicity of the CapelRI combination, which may differ between American and European patients, the panel does not recommend CapelRI or CapelRI/Bev for the first-line treatment of mCRC.

Other drug combinations that have produced negative results in phase III trials for the treatment of advanced CRC include sunitinib plus FOLFIRI, cetuximab plus brivanib, erlotinib plus bevacizumab, cediranib plus FOLFOX/CAPEOX, and atezolizumab plus cobimetinib.⁶⁷⁸⁻⁶⁸² These regimens are not recommended for the treatment of patients with CRC.

Results from two randomized phase III trials have shown that combination therapy with more than one biologic agent is not associated with improved outcomes and can cause increased toxicity.^{683,684} In the PACCE trial, the addition of panitumumab to a regimen containing oxaliplatin- or irinotecan-based chemotherapy plus bevacizumab was associated with significantly shorter PFS and higher toxicity in both *KRAS* exon 2 wild-type and mutant gene groups.⁶⁸³ Similar results were observed in the CAIRO2 trial with the addition of cetuximab to a regimen containing capecitabine, oxaliplatin, and bevacizumab.⁶⁸⁴ Therefore, the panel strongly recommends against the use of therapy involving the concurrent combination of an anti-EGFR agent (cetuximab or panitumumab) and an anti-vascular endothelial growth factor (VEGF) agent (bevacizumab).

**First-line Systemic Therapy***FOLFOX for First-line Therapy*

The phase III EORTC 40983 study, evaluating use of perioperative FOLFOX (6 cycles before and 6 cycles after surgery) for patients with resectable liver metastases, showed absolute improvements in 3-year PFS of 8.1% ($P = .041$) and 9.2% ($P = .025$) for all eligible patients and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.⁶⁸⁵ The partial response rate after preoperative FOLFOX was 40%, and operative mortality was less than 1% in both treatment groups. However, no difference in OS was seen between the groups, perhaps because second-line therapy was given to 77% of the patients in the surgery-only arm and 59% of the patients in the chemotherapy arm.⁶⁸⁶

The addition of bevacizumab is an option when FOLFOX is chosen as initial therapy,^{537,687} as is the addition of panitumumab or cetuximab for patients with disease characterized by wild-type *KRAS* exon 2 (see discussions on *Bevacizumab; Cetuximab and Panitumumab: KRAS, NRAS, and BRAF Status and Primary Tumor Sidedness; and Cetuximab or Panitumumab vs. Bevacizumab in First-line Therapy*, below).^{593,688,689} With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemotherapy without an additional biologic agent, panel consensus is that FOLFOX and CAPEOX can be used interchangeably. Results from a recent registry-based cohort analysis of greater than 2000 patients support the equivalence of these combinations.⁶⁹⁰

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.⁶⁹¹ Results of the OPTIMOX1 study showed that a “stop-and-go” approach using oxaliplatin-free intervals resulted in decreased neurotoxicity but did not affect OS in patients receiving FOLFOX as initial therapy for metastatic disease.⁶⁹² Other trials

have also addressed the question of treatment breaks, with or without maintenance therapy, and found that toxicity can be minimized with minimal or no effect on survival.⁶⁹³ A recent meta-analysis of RCTs also concluded that intermittent delivery of systemic therapy does not compromise OS compared to continuous treatment.⁶⁹⁴ Therefore, the panel recommends adjusting the schedule/timing of the administration of this drug as a means of limiting this AE. Discontinuation of oxaliplatin from FOLFOX or CAPEOX should be strongly considered after 3 months of therapy, or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained for the entire 6 months or until time of tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity.

In the phase II OPTIMOX2 trial, patients were randomized to receive either an OPTIMOX1 approach (discontinuation of oxaliplatin after 6 cycles of FOLFOX to prevent or reduce neurotoxicity with continuance of 5-FU/LV followed by reintroduction of oxaliplatin on disease progression) or an induction FOLFOX regimen (6 cycles) followed by discontinuation of all chemotherapy until tumor progression reached baseline, followed by reintroduction of FOLFOX.⁶⁹⁵ Results of the study showed no difference in OS for patients receiving the OPTIMOX1 approach compared with those undergoing an early, pre-planned, chemotherapy-free interval (median OS, 23.8 vs. 19.5 months; $P = .42$). However, the median duration of disease control, which was the primary endpoint of the study, reached statistical significance at 13.1 months in patients undergoing maintenance therapy and 9.2 months in patients with a chemotherapy-free interval ($P = .046$).⁶⁹⁵

The CONcePT trial also tested an intermittent oxaliplatin approach in patients with advanced CRC and found that it improved acute peripheral sensory neuropathy ($P = .037$) over continuous oxaliplatin.⁶⁹⁶ The addition



of oxaliplatin breaks also improved time to treatment failure (HR, 0.581; $P = .0026$) and time to tumor progression (HR, 0.533; $P = .047$).

Early data suggested that calcium/magnesium infusion might prevent oxaliplatin-related neurotoxicity.⁶⁹⁷⁻⁷⁰⁴ However, the phase III randomized, double-blind N08CB study, which randomized 353 patients with colon cancer receiving adjuvant FOLFOX to calcium/magnesium infusion or placebo, found that calcium/magnesium did not reduce cumulative sensory neurotoxicity.⁷⁰⁵ The panel therefore recommends against calcium/magnesium infusions for this purpose.

CAPEOX for First-line Therapy

The combination of capecitabine and oxaliplatin, known as CAPEOX or XELOX, has been studied as an active first-line therapy for patients with mCRC.⁷⁰⁶⁻⁷¹⁰ In a randomized phase III trial comparing CAPEOX and FOLFOX in 2034 patients, the regimens showed similar median PFS intervals of 8.0 and 8.5 months, respectively, and CAPEOX was determined to be noninferior to FOLFOX as first-line treatment of metastatic disease.⁷⁰⁶ Meta-analyses of RCTs also showed that CAPEOX and FOLFOX had similar benefits for patients with mCRC.^{711,712}

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy (see *FOLFOX*, above).⁷¹³ Discontinuation of oxaliplatin from FOLFOX or CAPEOX should be strongly considered after 3 months of therapy (the OPTIMOX1 approach⁶⁹²), or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained until tumor progression. A recent Turkish Oncology Group Trial showed that this stop-and-go approach is safe and effective in first-line therapy with CAPEOX/bevacizumab.⁷¹⁴ Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity. The panel recommends against the use of calcium/magnesium infusion to prevent oxaliplatin-related neurotoxicity.⁷⁰⁵

Regarding the toxicities associated with capecitabine use, the panel noted that: 1) patients with diminished creatinine clearance may accumulate levels of the drug, and therefore may require dose modification⁷¹⁵; 2) the incidence of hand-foot syndrome was increased for patients receiving capecitabine-containing regimens versus either bolus or infusional regimens of 5-FU/LV^{687,715}; and 3) North American patients may experience a higher incidence of AEs with certain doses of capecitabine compared with patients from other countries.⁷¹⁶ These toxicities may necessitate modifications in the dosing of capecitabine.^{687,715,717} Patients on capecitabine should be monitored closely so that dose adjustments can be made at the earliest signs of certain side effects, such as hand-foot syndrome. Interestingly, a recent analysis of patients from the AIO's KRK-0104 trial and the Mannheim rectal cancer trial found that capecitabine-related hand-foot skin reactions were associated with an improved OS (75.8 vs. 41.0 months; $P = .001$; HR, 0.56).⁷¹⁸

The addition of bevacizumab is an option if CAPEOX is chosen as initial therapy.^{537,687} With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemotherapy without an additional biologic agent, the consensus of the panel is that FOLFOX and CAPEOX can be used interchangeably. Results from a recent registry-based cohort analysis of greater than 2000 patients support the equivalence of these combinations.⁶⁹⁰

FOLFIRI for First-line Therapy

Evidence for the comparable efficacy for FOLFOX and FOLFIRI comes from a crossover study in which patients received either FOLFOX or FOLFIRI as initial therapy and were then switched to the other regimen at disease progression.⁵⁶³ Similar response rates and PFS times were obtained when these regimens were used as first-line therapy. Further support for this conclusion has come from results of a phase III trial comparing the efficacy and toxicity of FOLFOX and FOLFIRI regimens in



previously untreated patients with mCRC.⁷¹⁹ No differences were observed in response rate, PFS times, and OS between the treatment arms.

A randomized phase III study compared FOLFIRI to 5-FU/LV in first-line treatment of elderly patients with mCRC.⁷²⁰ In this population of patients, aged 75 years or older, grade 3–4 toxicities were increased with the addition of irinotecan (52.2% vs. 76.3%), without an improvement in PFS or OS.

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.^{721,722} Irinotecan is inactivated by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which is also involved in converting substrates such as bilirubin into more soluble forms through conjugation with certain glycosyl groups. Deficiencies in UGT1A1 can be caused by certain genetic polymorphisms and can result in conditions associated with accumulation of unconjugated hyperbilirubinemia, such as types I and II of the Crigler-Najjar and Gilbert syndromes. Thus, irinotecan should be used with caution and at a decreased dose in patients with Gilbert syndrome or elevated serum bilirubin. Similarly, certain genetic polymorphisms in the gene encoding for UGT1A1 can result in a decreased level of glucuronidation of the active metabolite of irinotecan, resulting in an accumulation of the drug and increased risk for toxicity,⁷²²⁻⁷²⁴ although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.⁷²⁴ Results from a dose-finding and pharmacokinetic study suggest that dosing of irinotecan should be individualized based on UGT1A1 genotype.⁷²⁵ The maximum tolerated dose of intravenous irinotecan every 3 weeks was 850 mg, 700 mg, and 400 mg in patients with the *1/*1, *1/*28, and *28/*28 genotypes, respectively.

Commercial tests are available to detect the UGT1A1*28 allele, which is associated with decreased gene expression and, hence, reduced levels of UGT1A1 expression. Also, a warning was added to the label for irinotecan

indicating that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28.⁷²¹ A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,⁷²⁴ although guidelines for use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing on patients who experience irinotecan toxicity is not recommended, because they will require a dose reduction regardless of the UGT1A1 test result.

Results from a recent phase IV trial in 209 patients with mCRC who received bevacizumab in combination with FOLFIRI as first-line therapy showed that this combination was as effective and well-tolerated as bevacizumab with other 5-FU-based therapies.⁷²⁶ A phase III trial in Japan also showed that FOLFIRI plus bevacizumab is non-inferior to mFOLFOX6 plus bevacizumab with regard to PFS.⁷²⁷ Therefore, the addition of bevacizumab to FOLFIRI is recommended as an option for initial therapy; alternatively, cetuximab or panitumumab (only for left-sided tumors characterized by wild-type *RAS/BRAF*) can be added to this regimen (see discussions on *Bevacizumab; Cetuximab and Panitumumab: KRAS, NRAS, and BRAF Status and Primary Tumor Sidedness; and Cetuximab or Panitumumab vs. Bevacizumab in First-line Therapy*, below).^{599,618,688,728,729}

Infusional 5-FU/LV and Capecitabine for First-line Therapy

For patients with impaired tolerance to aggressive initial therapy, the guidelines recommend infusional 5-FU/LV or capecitabine with or without bevacizumab as an option.^{261,671,687,730-732} Patients with metastatic cancer with no improvement in functional status after this less intensive initial therapy should receive best supportive care. Patients showing improvement in functional status should be treated with one of the options specified for initial therapy for advanced or metastatic disease. Toxicities associated with capecitabine use are discussed earlier (see *CAPEOX*).



In a pooled analysis of results from two randomized clinical trials involving patients with a potentially curative resection of liver or lung metastases randomly assigned to either postoperative systemic chemotherapy with 5-FU/LV or observation alone after surgery, the median PFS was 27.9 months in the chemotherapy arm and 18.8 months for those undergoing surgery alone (HR, 1.32; 95% CI, 1.00–1.76; $P = .058$), with no significant difference in OS.⁷³³

Results were recently published from the open-label phase III AVEX trial, in which 280 patients aged 70 years or older were randomized to capecitabine with or without bevacizumab.⁷³⁴ The trial met its primary endpoint, with the addition of bevacizumab giving a significantly improved median PFS (9.1 vs. 5.1 months; HR, 0.53; 95% CI, 0.41–0.69; $P < .0001$).

FOLFOXIRI for First-line Therapy

FOLFOXIRI is also listed as an option for initial therapy in patients with unresectable metastatic disease. Use of FOLFOXIRI compared with FOLFIRI as initial therapy for the treatment of metastatic disease has been investigated in two randomized phase III trials.^{526,527} In a trial by the GONO group, statistically significant improvements in PFS (9.8 vs. 6.9 months; HR, 0.63; $P = .0006$) and median OS (22.6 vs. 16.7 months; HR, 0.70; $P = .032$) were observed in the FOLFOXIRI arm,⁵²⁶ although no OS difference was seen between treatment arms in the HORG study (median OS was 19.5 and 21.5 months for FOLFIRI and FOLFOXIRI, respectively; $P = .337$).⁵²⁷ Both studies showed some increased toxicity in the FOLFOXIRI arm (eg, significant increases in neurotoxicity and neutropenia,⁵²⁶ diarrhea, alopecia, and neurotoxicity⁵²⁷), but no differences in the rate of toxic death were reported in either study. Long-term outcomes of the GONO trial with a median follow-up of 60.6 months were later reported.⁵²⁸ The improvements in PFS and OS were maintained.

The panel includes the possibility of adding bevacizumab to FOLFOXIRI for initial therapy of patients with unresectable metastatic disease. Results of the GONO group's phase III TRIBE trial showed that FOLFOXIRI/bevacizumab significantly increased PFS (12.1 vs. 9.7 months; HR, 0.75; 95% CI, 0.62–0.90; $P = .003$) and response rate (65% vs. 53%; $P = .006$) compared to FOLFIRI/bevacizumab in patients with unresectable mCRC.⁷³⁵ Subgroup analyses indicated that no benefit to the addition of oxaliplatin was seen in patients who received prior adjuvant therapy (64% of cases included oxaliplatin in the adjuvant regimen). Diarrhea, stomatitis, neurotoxicity, and neutropenia were significantly more prevalent in the FOLFOXIRI arm. In an updated analysis on the TRIBE trial, investigators reported the median OS at 29.8 months (95% CI, 26.0–34.3) in the FOLFOXIRI plus bevacizumab arm and 25.8 months (95% CI, 22.5–29.1) in the FOLFIRI plus bevacizumab arm (HR, 0.80; 95% CI, 0.65–0.98; $P = .03$).⁷³⁶

The randomized, phase III TRIBE2 compared first-line FOLFOXIRI plus bevacizumab to a sequential strategy of first-line FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab after progression in 679 patients with unresectable, previously untreated mCRC.⁷³⁷ The primary endpoint of median PFS was 19.2 months for FOLFOXIRI compared to 16.4 months for the sequential strategy (HR, 0.74; 95% CI, 0.63–0.88; $P = .0005$). Serious AEs were reported in 25% of patients in the FOLFOXIRI group compared to 17% in the sequential therapy group.

Results from the randomized phase II OLIVIA trial, which compared mFOLFOX6/bevacizumab to FOLFOXIRI/bevacizumab in patients with unresectable colorectal liver metastases, were also reported.⁷³⁸ Improvement in R0 resection rate was seen in the FOLFOXIRI/bevacizumab arm (49% vs. 23%; 95% CI, 4%–48%) and in the primary endpoint of overall (R0/R1/R2) resection rate (61% vs. 49%; 95% CI, –11%–36%). Other phase II trials, including CHARTA and



STEAM, have also reported improved outcomes for FOLFOXIRI plus bevacizumab when compared to a chemotherapy doublet plus bevacizumab for first-line treatment of mCRC.^{739,740}

A pooled analysis of TRIBE and TRIBE2⁷⁴¹ and a meta-analysis of individual patient data from CHARTA, OLIVIA, STEAM, TRIBE, and TRIBE2⁵⁴⁹ reached similar conclusions as the clinical trials. These analyses concluded that first-line treatment with FOLFOXIRI plus bevacizumab yields significantly better outcomes, albeit at the expense of higher toxicity, compared to sequential treatment with chemotherapy doublets in combination with bevacizumab. Based on these results, the NCCN Panel strongly recommends first-line FOLFOXIRI for patients with excellent performance status who can withstand the higher toxicity of the triplet regimen.

Bevacizumab for First-line Therapy

Bevacizumab is a humanized monoclonal antibody that blocks the activity of VEGF, a factor that plays an important role in tumor angiogenesis.⁷⁴² The NCCN Panel notes that FDA-approved biosimilars may be substituted for bevacizumab wherever the therapy is recommended within these Guidelines (see *Biosimilars*, above, for more information). Pooled results from several randomized phase II studies have shown that the addition of bevacizumab to first-line 5-FU/LV improved OS in patients with unresectable mCRC compared with those receiving these regimens without bevacizumab.^{536,743,744} A combined analysis of the results of these trials showed that the addition of bevacizumab to 5-FU/LV was associated with a median survival of 17.9 versus 14.6 months for regimens consisting of 5-FU/LV or 5-FU/LV plus irinotecan without bevacizumab ($P = .008$).⁷³¹ A study of previously untreated patients receiving bevacizumab plus IFL also provided support for the inclusion of bevacizumab in initial therapy.⁵³⁶ In that pivotal trial, a longer survival time was observed with the use of bevacizumab (20.3 vs. 15.6 months; HR, 0.66; $P < .001$).

Results have also been reported from a large, head-to-head, randomized, double-blind, placebo-controlled, phase III study (NO16966) in which CAPEOX (capecitabine dose, 1000 mg/m², twice daily for 14 days) with bevacizumab or placebo was compared with FOLFOX with bevacizumab or placebo in 1400 patients with unresectable metastatic disease.⁵³⁷ The addition of bevacizumab to oxaliplatin-based regimens was associated with a more modest increase of 1.4 months in PFS compared with these regimens without bevacizumab (HR, 0.83; 97.5% CI, 0.72–0.95; $P = .0023$), and the difference in OS, which was also a modest 1.4 months, did not reach statistical significance (HR, 0.89; 97.5% CI, 0.76–1.03; $P = .077$).⁵³⁷ Researchers have suggested that differences observed in cross-study comparisons of NO16966 with other trials might be related to differences in the discontinuation rates and durations of treatment between trials, although these hypotheses are conjectural.⁵³⁷ However, in this 1400-patient randomized study, absolutely no difference in response rate was seen with and without bevacizumab, and this finding could not have been influenced by the early withdrawal rates, which would have occurred after the responses would have occurred. Results of subset analyses evaluating the benefit of adding bevacizumab to either FOLFOX or CAPEOX indicated that bevacizumab was associated with improvements in PFS when added to CAPEOX but not FOLFOX.⁵³⁷

The combination of FOLFIRI and bevacizumab in the first-line treatment of advanced CRC has been studied, although no RCTs have compared FOLFIRI with and without bevacizumab. A recent systematic review with a pooled analysis (29 prospective and retrospective studies, 3502 patients) found that the combination gave a response rate of 51.4%, a median PFS of 10.8 months (95% CI, 8.9–12.8), and a median OS of 23.7 months (95% CI, 18.1–31.6).⁷⁴⁵ FOLFOXIRI with bevacizumab is also an accepted combination (see *FOLFOXIRI*, above), although no RCTs have compared FOLFOXIRI with and without bevacizumab.



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A prospective observational cohort study (ARIES) included 1550 patients who received first-line therapy with bevacizumab with chemotherapy for mCRC and 482 patients treated with bevacizumab in second-line.⁷⁴⁶ Median OS was 23.2 months (95% CI, 21.2–24.8) for the first-line cohort and 17.8 months (95% CI, 16.5–20.7) in the second-line group. A similar cohort study (ETNA) of first-line bevacizumab use with irinotecan-based therapy reported a median OS of 25.3 months (95% CI, 23.3–27.0).⁷⁴⁷

Several meta-analyses have shown a benefit for the use of bevacizumab in first-line therapy for mCRC.^{748–756} A meta-analysis of six randomized clinical trials (3060 patients) that assessed the efficacy of bevacizumab in first-line treatment of mCRC found that bevacizumab gave a PFS (HR, 0.72; 95% CI, 0.66–0.78; $P < .00001$) and OS (HR, 0.84; 95% CI, 0.77–0.91; $P < .00001$) advantage.⁷⁵⁷ However, subgroup analyses showed that the advantage was limited to irinotecan-based regimens. In addition, a recent analysis of the SEER-Medicare database found that bevacizumab added a modest improvement to OS of patients with stage IV CRC diagnosed between 2002 and 2007 (HR, 0.85; 95% CI, 0.78–0.93).⁷⁵⁸ The survival advantage was not evident when bevacizumab was combined with oxaliplatin-based chemotherapy, but was evident in irinotecan-based regimens. Limitations of this analysis have been discussed,^{759,760} but, overall, the addition of bevacizumab to first-line chemotherapy appears to offer a modest clinical benefit.

Only limited data directly address whether bevacizumab should be used with chemotherapy in the perioperative treatment of resectable metastatic disease.⁷⁶¹ The randomized phase III HEPATICA trial, which closed prematurely due to poor accrual, found that global quality of life scores were higher in patients receiving CAPEOX plus bevacizumab than those receiving CAPEOX alone after resection of liver metastases, but no conclusions could be drawn regarding the primary endpoint of DFS.⁷⁶² Furthermore, data regarding the lack of efficacy of bevacizumab in the

adjuvant setting in stage II and III colon cancer^{343,345} have prompted some to reconsider the role of bevacizumab in the adjuvant setting of resectable colorectal metastases. However, the panel does not recommend the use of bevacizumab in the perioperative stage IV setting.

A meta-analysis of RCTs showed that the addition of bevacizumab to chemotherapy is associated with a higher incidence of treatment-related mortality than chemotherapy alone (RR, 1.33; 95% CI, 1.02–1.73; $P = .04$), with hemorrhage (23.5%), neutropenia (12.2%), and GI perforation (7.1%) being the most common causes of fatality.⁷⁶³ Venous thromboembolisms, on the other hand, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.⁷⁶⁴ Another meta-analysis showed that bevacizumab was associated with a significantly higher risk of hypertension, GI hemorrhage, and perforation, although the overall risk for hemorrhage and perforation is quite low.⁷⁶⁵ The risk of stroke and other arterial events is increased in patients receiving bevacizumab, especially in those aged 65 years or older. GI perforation is a rare but important side effect of bevacizumab therapy in patients with CRC.^{687,766} Extensive prior intra-abdominal surgery, such as peritoneal stripping, may predispose patients to GI perforation. A small cohort of patients with advanced ovarian cancer had an unacceptably high rate of GI perforation when treated with bevacizumab.⁷⁶⁷ This result illustrated that peritoneal debulking surgery may be a risk factor for GI perforation, whereas the presence of an intact primary tumor does not seem to increase the risk for GI perforation. The FDA recently approved a safety label warning of the risk for necrotizing fasciitis, sometimes fatal and usually secondary to wound healing complications, GI perforation, or fistula formation after bevacizumab use.⁷⁴²

Use of bevacizumab may interfere with wound healing.^{687,742,766} A retrospective evaluation of data from two randomized trials of 1132



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patients undergoing chemotherapy with or without bevacizumab as initial therapy for mCRC indicated that the incidence of wound healing complications was increased for the group of patients undergoing a major surgical procedure while receiving a bevacizumab-containing regimen compared with the group receiving chemotherapy alone while undergoing major surgery (13% vs. 3.4%, respectively; $P = .28$).⁷⁶⁶ However, when chemotherapy plus bevacizumab or chemotherapy alone was administered after surgery, with a delay between surgery and bevacizumab administration of at least 6 weeks, the incidence of wound healing complications in either group of patients was low (1.3% vs. 0.5%; $P = .63$). Similarly, results of a single-center, nonrandomized phase II trial of patients with potentially resectable liver metastases showed no increase in bleeding or wound complications when the bevacizumab component of CAPEOX plus bevacizumab therapy was stopped 5 weeks before surgery (ie, bevacizumab excluded from the sixth cycle of therapy).⁷⁶⁸ In addition, no significant differences in bleeding, wound, or hepatic complications were seen in a retrospective trial evaluating the effects of preoperative bevacizumab stopped at 8 weeks or less versus at more than 8 weeks before resection of liver colorectal metastases in patients receiving oxaliplatin- or irinotecan-containing regimens.⁷⁶⁹ The panel recommends an interval of at least 6 weeks (which corresponds to two half-lives of the drug⁷⁴²) between the last dose of bevacizumab and any elective surgery. Additionally, re-initiation of bevacizumab should be delayed at least 6 to 8 weeks postoperatively.

Preclinical studies suggested that cessation of anti-VEGF therapy might be associated with accelerated recurrence, more aggressive tumors on recurrence, and increased mortality. A recent retrospective meta-analysis of five placebo-controlled, randomized phase III trials including 4205 patients with metastatic colorectal, breast, renal, or pancreatic cancer found no difference in time to disease progression and mortality with discontinuation of bevacizumab versus discontinuation of placebo.⁷⁷⁰

Although this meta-analysis has been criticized,^{771,772} the results are supported by recent results from the NSABP Protocol C-08 trial.³⁴³ This trial included patients with stage II and stage III CRC, and no differences in recurrence, mortality, or mortality 2 years after recurrence were seen between patients receiving bevacizumab versus patients in the control arm. These results suggest that no “rebound effect” is associated with bevacizumab use.

Cetuximab or Panitumumab for First-line Therapy in KRAS/NRAS Wild-Type Disease

Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways. Panitumumab is a fully human monoclonal antibody, whereas cetuximab is a chimeric monoclonal antibody.^{616,773} Cetuximab and panitumumab have been studied in combination with FOLFIRI and FOLFOX as initial therapy options for treatment of mCRC. The randomized, phase II PLANET-TTD trial comparing patients treated with panitumumab plus either FOLFOX or FOLFIRI found no significant differences in efficacy between the two regimens.⁷⁷⁴

Recent meta-analyses of RCTs have concluded that EGFR inhibitors provide a clear clinical benefit in the treatment in patients with *RAS* wild-type mCRC.^{601,775} Patients with known *KRAS* or *NRAS* mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified (see *Biomarkers for Systemic Therapy, KRAS and NRAS Mutations*, above for more information). Individual trials are discussed below.

Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.^{616,773} Based on case reports and a small trial,



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administration of panitumumab seems to be feasible for patients experiencing severe infusion reactions to cetuximab.⁷⁷⁶⁻⁷⁷⁸ Skin toxicity is a side effect of both of these agents and is not considered part of the infusion reactions. The incidence and severity of skin reactions with cetuximab and panitumumab seem to be very similar. Furthermore, the presence and severity of skin rash in patients receiving either of these drugs have been shown to predict increased response and survival.^{597,599,779-782} A recent NCCN task force addressed the management of dermatologic and other toxicities associated with anti-EGFR inhibitors.⁷⁸³ Cetuximab and panitumumab have also been associated with a risk for venous thromboembolic and other serious AEs.^{784,785}

Based on the results of the PACCE and CAIRO2 trials, the panel strongly advises against the concurrent use of bevacizumab with either cetuximab or panitumumab (see *Bevacizumab*, above).^{683,684} Several trials that assessed EGFR inhibitors in combination with various chemotherapy agents are discussed below.

Cetuximab/Panitumumab and Primary Tumor Sidedness: A growing body of data has shown that the location of the primary tumor can be both prognostic and predictive of response to EGFR inhibitors in mCRC.⁷⁸⁶⁻⁷⁹⁴ For example, outcomes of 75 patients with mCRC treated with cetuximab, panitumumab, or cetuximab/irinotecan in first-line or subsequent lines of therapy at three Italian centers were analyzed based on sidedness of the primary tumor.⁷⁸⁷ No responses were seen in the patients with right-sided primary tumors compared with a response rate of 41% in those with left-sided primaries ($P = .003$). The median PFS was 2.3 and 6.6 months in patients with right-sided and left-sided tumors, respectively (HR, 3.97; 95% CI, 2.09–7.53; $P < .0001$).

The strongest evidence for the predictive value of primary tumor sidedness and response to EGFR inhibitors is in the first-line treatment of patients in the phase III CALGB/SWOG 80405 trial.⁷⁹¹ The study showed

that patients with *RAS* wild-type, right-sided primary tumors (cecum to hepatic flexure) had longer OS if treated with bevacizumab than if treated with cetuximab in first line (HR, 1.36; 95% CI, 0.93–1.99; $P = .10$), whereas patients with all *RAS* wild-type, left-sided primary tumors (splenic flexure to rectum) had longer OS if treated with cetuximab than if treated with bevacizumab (HR, 0.77; 95% CI, 0.59–0.99; $P = .04$).⁷⁹⁵ OS was prolonged with cetuximab versus bevacizumab in the left-sided primary group (39.3 months vs. 32.6 months) but shortened in the right-sided primary group (13.6 months vs. 29.2 months). Retrospective analyses of other contemporary studies have confirmed this finding.⁷⁹⁴

These and other data suggest that cetuximab and panitumumab confer little if any benefit to patients with mCRC if the primary tumor originated on the right side.^{786,787,789} The panel believes that primary tumor sidedness is a surrogate for the non-random distribution of molecular subtypes across the colon and that the ongoing analysis of genomic differences between right- and left-sided tumors⁷⁹⁶ will enable a better understanding of the biologic explanation of the observed difference in response to EGFR inhibitors. Until that time, only patients whose primary tumors originated on the left side of the colon (splenic flexure to rectum) should be offered cetuximab or panitumumab in the first-line treatment of metastatic disease. Evidence also suggests that sidedness is predictive of response to EGFR inhibitors in subsequent lines of therapy,^{786,787,789} but the panel awaits more definitive studies. Until such data are available, all patients with *RAS/BRAF* wild-type tumors can be considered for panitumumab or cetuximab in subsequent lines of therapy if neither was previously given.

Cetuximab with FOLFIRI: Use of cetuximab as initial therapy for metastatic disease was investigated in the CRYSTAL trial, in which patients were randomly assigned to receive FOLFIRI with or without cetuximab.⁵⁹⁹ Retrospective analyses of the subset of patients with known *KRAS* exon 2 tumor status showed a statistically significant improvement in median PFS



with the addition of cetuximab in the wild-type (9.9 vs. 8.7 months; HR, 0.68; 95% CI, 0.50–0.94; $P = .02$).⁵⁹⁹ The statistically significant benefit in PFS for patients with *KRAS* exon 2 wild-type tumors receiving cetuximab was confirmed in a recent publication of an updated analysis of the CRYSTAL data.⁶¹⁸ This recent study included a retrospective analysis of OS in the *KRAS* exon 2 wild-type population and found an improvement with the addition of cetuximab (23.5 vs. 20.0 months, $P = .009$). Importantly, the addition of cetuximab did not affect the quality of life of participants in the CRYSTAL trial.⁷⁹⁷ As has been seen with other trials, when DNA samples from the CRYSTAL trial were re-analyzed for additional *KRAS* and *NRAS* mutations, patients with *RAS* wild-type tumors derived a clear OS benefit (HR, 0.69; 95% CI, 0.54–0.88), whereas those with any *RAS* mutation did not (HR, 1.05; 95% CI, 0.86–1.28).⁷⁹⁸

Panitumumab with FOLFIRI: FOLFIRI with panitumumab is listed as an option for first-line therapy in mCRC based on extrapolation from data in second-line treatment.^{628,729,799,800}

Cetuximab with FOLFOX: Several trials have assessed the combination of FOLFOX and cetuximab in first-line treatment of mCRC. In a retrospective evaluation of the subset of patients with known tumor *KRAS* exon 2 status enrolled in the randomized phase II OPUS trial, addition of cetuximab to FOLFOX was associated with an increased objective response rate (61% vs. 37%; OR, 2.54; $P = .011$) and a very slightly lower risk of disease progression (7.7 vs. 7.2 months [a 15-day difference]; HR, 0.57; 95% CI, 0.36–0.91; $P = .016$) compared with FOLFOX alone in the subset of patients with *KRAS* exon 2 wild-type tumors.⁵⁹³ Although data supporting the statistically significant benefits in objective response rate and PFS for patients with tumors characterized by *KRAS* wild-type exon 2 were upheld in an update of this study, no median OS benefit was observed for the addition of cetuximab to chemotherapy (22.8 months in the cetuximab arm

vs. 18.5 months in the arm undergoing chemotherapy alone; HR, 0.85; $P = .39$).⁸⁰¹

Furthermore, in the recent randomized phase III MRC COIN trial, no benefit in OS (17.9 vs. 17.0 months; $P = .067$) or PFS (8.6 months in both groups; $P = .60$) was seen with the addition of cetuximab to FOLFOX or CAPEOX as first-line treatment of patients with locally advanced or mCRC and wild-type *KRAS* exon 2.⁶¹⁹ Exploratory analyses of the COIN trial, however, suggest that there may be a benefit to the addition of cetuximab in patients who received FOLFOX instead of CAPEOX.⁶¹⁹

Notably, more recent trials examining the efficacy of the addition of cetuximab to oxaliplatin-containing regimens in the first-line treatment of patients with advanced or mCRC and wild-type *KRAS* exon 2 have not shown any benefit. The addition of cetuximab to the Nordic FLOX regimen showed no benefit in OS or PFS in this population of patients in the randomized phase III NORDIC VII study of the Nordic Colorectal Cancer Biomodulation Group.⁸⁰²

However, results from the randomized phase III CALGB/SWOG 80405 trial of greater than 1000 patients (discussed in *Cetuximab or Panitumumab vs. Bevacizumab in First-line Therapy*, below) showed that the combination of FOLFOX with cetuximab can be effective in first-line treatment of mCRC.⁶⁸⁹ The phase III open-label, randomized TAILOR trial confirmed this result, reporting benefits in PFS (9.2 vs. 7.4 months; $P = .004$), OS (20.7 vs. 17.8 months; $P = .02$), and ORR (61.1% vs. 39.5%; $P < .001$) with first-line cetuximab plus FOLFOX compared to FOLFOX alone in patients with *RAS* wild-type mCRC.⁸⁰³ Therefore, the panel recommends cetuximab plus FOLFOX as an initial therapy option for *RAS/BRAF* wild-type patients with advanced or metastatic disease.

The New EPOC trial, which was stopped early because it met protocol-defined futility criteria, found a lack of benefit to cetuximab with



chemotherapy in the perioperative metastatic setting (>85% received FOLFOX or CAPEOX; patients with prior oxaliplatin received FOLFIRI).⁸⁰⁴ In fact, with less than half of expected events observed, PFS was significantly reduced in the cetuximab arm (14.8 vs. 24.2 months; HR, 1.50; 95% CI, 1.00–2.25; $P < .048$). A subsequent analysis of New EPOC, carried out 5 years after the last patient was recruited, reported a reduced median OS for chemotherapy plus cetuximab compared to chemotherapy alone (55.4 vs. 81.0 months; HR, 1.45; 95% CI, 1.02–2.05; $P = .036$).⁸⁰⁵ The panel thus cautions that cetuximab in the perioperative setting may harm patients. The panel therefore does not recommend the use of FOLFOX plus cetuximab in patients with resectable disease and should be used with caution in those with unresectable disease that could potentially be converted to a resectable status.

Panitumumab with FOLFOX: Panitumumab in combination with either FOLFOX^{600,688} or FOLFIRI⁷²⁸ has also been studied in the first-line treatment of patients with mCRC. Results from the large, open-label, randomized PRIME trial comparing panitumumab plus FOLFOX versus FOLFOX alone in patients with *KRAS/NRAS* wild-type advanced CRC showed a statistically significant improvement in PFS (HR, 0.72; 95% CI, 0.58–0.90; $P = .004$) and OS (HR, 0.77; 95% CI, 0.64–0.94; $P = .009$) with the addition of panitumumab.⁶⁰⁰ Therefore, the combination of FOLFOX and panitumumab remains an option as initial therapy for patients with advanced or metastatic disease. Importantly, the addition of panitumumab had a detrimental impact on PFS for patients with tumors characterized by mutated *KRAS/NRAS* in the PRIME trial (discussed further in *KRAS and NRAS Mutations within Biomarkers for Systemic Therapy*, above).⁶⁰⁰

Cetuximab or Panitumumab vs. Bevacizumab in First-line Therapy: The randomized, open-label, multicenter FIRE-3 trial from the German AIO group compared the efficacy of FOLFIRI plus cetuximab to FOLFIRI plus bevacizumab in first-line, *KRAS* exon 2 wild-type, metastatic disease.⁶¹⁵

This trial did not meet its primary endpoint of investigator-read objective response rate in the 592 randomized patients (62.0% vs. 58.0%; $P = .18$). PFS was nearly identical between the arms of the study, but a statistically significant improvement in OS was reported in the cetuximab arm (28.7 vs. 25.0 months; HR, 0.77; 95% CI, 0.62–0.96; $P = .017$). The panel has several criticisms of the trial, including the lack of third-party review and low rates of second-line therapy.^{806,807} While the rate of AEs was similar between the arms, more skin toxicity was observed in those receiving cetuximab.

Results of the phase III CALGB/SWOG 80405 trial, comparing FOLFOX/FOLFIRI with cetuximab or bevacizumab, were recently reported.⁶⁸⁹ In this study, patients with wild-type *KRAS* exon 2 received either FOLFOX (73%) or FOLFIRI (27%) and were randomized to receive cetuximab or bevacizumab. The primary endpoint of OS was equivalent between the arms, at 29.0 months in the bevacizumab arm versus 30.0 months in the cetuximab arm (HR, 0.88; 95% CI, 0.77–1.01; $P = .08$).

Results for the randomized multicenter phase II PEAK trial, which compared FOLFOX/panitumumab with FOLFOX/bevacizumab in first-line treatment of patients with wild-type *KRAS* exon 2, were also published.⁸⁰⁸ In the subset of 170 participants with wild-type *KRAS/NRAS* based on extended tumor analysis, PFS was better in the panitumumab arm (13.0 vs. 9.5 months; HR, 0.65; 95% CI, 0.44–0.96; $P = .03$). A trend towards improved OS was seen (41.3 vs. 28.9 months; HR, 0.63; 95% CI, 0.39–1.02; $P = .06$). The final analysis of the PEAK trial confirmed that FOLFOX/panitumumab showed a longer PFS compared to FOLFOX/bevacizumab in patients with wild-type *RAS* (12.8 vs. 10.1 months; HR, 0.68; 95% CI, 0.48–0.96; $P = .029$).⁸⁰⁹ Although these data are intriguing, definitive conclusions are hindered by the small sample size and limitations of subset analyses.⁸¹⁰



Economic analyses suggest that bevacizumab may be more cost-effective than EGFR inhibitors in first-line therapy for mCRC,⁸¹¹ although more recent analyses have shown the opposite.^{812,813}

At this time, the panel considers the addition of cetuximab, panitumumab, or bevacizumab to chemotherapy as equivalent choices in the first-line, *RAS/BRAF* wild-type, metastatic setting.

Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease in the First-Line Setting

The phase III, randomized open-label KEYNOTE-177 study evaluated the use of pembrolizumab compared to chemotherapy with or without bevacizumab or cetuximab as first-line therapy for 307 patients with MSI-H/dMMR mCRC.⁸¹⁴ Median PFS was found to be longer with pembrolizumab compared to chemotherapy (16.5 vs. 8.2 months; HR, 0.60; 95% CI, 0.45-0.80; $P = .0002$). Confirmed ORR was 43.8% with pembrolizumab versus 33.1% with chemotherapy. Grade ≥ 3 treatment-related AEs were reported in 22% of patients treated with pembrolizumab compared to 66% of those treated with chemotherapy.

Likewise, the phase II CheckMate-142 trial evaluated the role of nivolumab in combination with ipilimumab for first-line treatment of dMMR/MSI-H mCRC. A 2019 abstract on the phase II CheckMate-142 trial reported results for 45 patients with previously untreated MSI-H/dMMR mCRC.⁸¹⁵ ORR was found to be 60% (95% CI, 44.3%–74.3%), with a median follow-up of 13.8 months. After 19.9 months of follow-up, investigator-assessed ORR was 64% (95% CI, 49%–78%), disease control rate was 84% (95% CI, 71%–94%), and duration of response had not been reached. After 19.9 months of follow-up, 20% of patients had grade 3 or 4 treatment-related AEs and AEs led to discontinuation in 11% of patients. A 2020 abstract reported results from a longer follow-up of this same trial.⁸¹⁶ With a median follow-up of 29.0 months, the ORR increased to 69% and the CR rate was 13%. While median PFS and OS were not yet reached, 24-months rates

for these outcome measures were 74% and 79%, respectively. Treatment-related AE and discontinuation rates were similar to the earlier analysis. Additional results from CheckMate-142 (including nivolumab alone or in combination with ipilimumab as subsequent therapy) are discussed in *Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease in the Non-First-Line Setting*, below.

Based on these data, the panel recommends pembrolizumab or nivolumab, alone or in combination with ipilimumab, as first-line treatment options for patients with MSI-H/dMMR mCRC, whether or not they are eligible for intensive therapy. The recommendation for nivolumab plus ipilimumab for patients not appropriate for intensive therapy is category 2B due to concerns about potential toxicity from the combination therapy.

Second-line or Subsequent Systemic Therapy

Decisions regarding therapy after progression of metastatic disease depend on previous therapies. The panel recommends against the use of mitomycin, alfa-interferon, taxanes, methotrexate, pemetrexed, sunitinib, sorafenib, erlotinib, or gemcitabine, either as single agents or in combination, as therapy in patients exhibiting disease progression after treatment with standard therapies. These agents have not been shown to be effective in this setting. Furthermore, no objective responses were observed when single-agent capecitabine was administered in a phase II study of patients with CRC resistant to 5-FU.⁸¹⁷

The recommended therapy options after first progression for patients who have received prior therapy are dependent on the initial treatment regimen and are outlined in the guidelines.

Single-agent irinotecan administered after first progression has been shown to significantly improve OS relative to best supportive care⁸¹⁸ or infusional 5-FU/LV.⁸¹⁹ In the study of Rougier et al,⁸¹⁹ median PFS was 4.2 months for irinotecan versus 2.9 months for 5-FU ($P = .030$), whereas



Cunningham et al⁸¹⁸ reported a survival rate at 1 year of 36.2% in the group receiving irinotecan versus 13.8% in the supportive care group ($P = .0001$). A meta-analysis of five RCTs showed that there was no OS benefit to FOLFIRI over that obtained with irinotecan alone.⁸²⁰ Furthermore, no significant differences in OS were observed in the Intergroup N9841 trial when FOLFOX was compared with irinotecan monotherapy after first progression of mCRC.⁸²¹

A meta-analysis of randomized trials found that the addition of a targeted agent after first-line treatment improves outcomes but also increases toxicity.⁸²² Another meta-analysis showed an OS and PFS benefit to continuing an anti-angiogenic agent after progression on an anti-angiogenic agent in first-line.⁸²³ Data relating to specific biologic therapies are discussed below.

Cetuximab and Panitumumab in the Non–First-line Setting

For patients with wild-type *KRAS/NRAS/BRAF* who experienced progression on therapies *not* containing an EGFR inhibitor, cetuximab or panitumumab plus irinotecan, cetuximab or panitumumab plus FOLFIRI, or single-agent cetuximab or panitumumab⁵⁹⁵ is recommended. For patients with wild-type *KRAS/NRAS/BRAF* progressing on therapies that *did* contain an EGFR inhibitor, administration of an EGFR inhibitor is not recommended in subsequent lines of therapy. No data support switching to either cetuximab or panitumumab after failure of the other drug, and the panel recommends against this practice.

Panitumumab has been studied as a single agent in the setting of mCRC for patients with disease progression on oxaliplatin/irinotecan-based chemotherapy in an open-label phase III trial.⁸²⁴ In a retrospective analysis of the subset of patients in this trial with known *KRAS* exon 2 tumor status, the benefit of panitumumab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.⁵⁹¹ PFS was 12.3 weeks versus 7.3 weeks in favor of the panitumumab arm. Response

rates to panitumumab were 17% versus 0% in the wild-type and mutant arms, respectively.⁵⁹¹ A more recent phase III trial compared single-agent panitumumab to best supportive care in patients with wild-type *KRAS* exon 2 mCRC and disease progression on oxaliplatin- and irinotecan-based chemotherapy.⁸²⁵ The primary endpoint of OS was improved with panitumumab (10.0 months vs. 7.4 months; HR, 0.73; 95% CI, 0.57–0.93; $P < .01$).

Panitumumab has also been studied in combination therapy in the setting of progressing mCRC. Among patients with *KRAS* exon 2 wild-type tumors enrolled in the large Study 181 comparing FOLFIRI alone versus FOLFIRI plus panitumumab as second-line therapy for mCRC, addition of the biologic agent was associated with improvement in median PFS (5.9 vs. 3.9 months; HR, 0.73; 95% CI, 0.59–0.90; $P = .004$), although differences in OS between the arms did not reach statistical significance.⁷²⁹ These results were confirmed in the final results of Study 181.⁸⁰⁰ Furthermore, re-analysis of samples from the trial showed that the benefit of the combination was limited to participants with no *RAS* mutations.⁸²⁶ In addition, secondary analysis from the STEPP trial showed that panitumumab in combination with irinotecan-based chemotherapy in second-line therapy has an acceptable toxicity profile.⁷⁹⁹ The randomized multicenter PICCOLO trial, which assessed the safety and efficacy of irinotecan/panitumumab, did not meet its primary endpoint of improved OS in patients with wild-type *KRAS/NRAS* tumors.⁶²⁸

Cetuximab has been studied both as a single agent^{595,779,827,828} and in combination with irinotecan⁸²⁷ in patients experiencing disease progression on initial therapy not containing cetuximab or panitumumab for metastatic disease. Results of a large phase III study comparing irinotecan with or without cetuximab did not show a difference in OS, but showed significant improvement in response rate and in median PFS with irinotecan and cetuximab compared with irinotecan alone.⁸²⁹ Importantly,



KRAS status was not determined in this study and toxicity was higher in the cetuximab-containing arm (eg, rash, diarrhea, electrolyte imbalances).⁸²⁹

In a retrospective analysis of the subset of patients with known *KRAS* exon 2 tumor status receiving cetuximab monotherapy as second-line therapy,⁷⁷⁹ the benefit of cetuximab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.⁵⁹⁵ For those patients, median PFS was 3.7 versus 1.9 months (HR, 0.40; 95% CI, 0.30–0.54; $P < .001$) and median OS was 9.5 versus 4.8 months (HR, 0.55; 95% CI, 0.41–0.74; $P < .001$), in favor of the cetuximab arm.⁵⁹⁵

The randomized, multicenter, open-label, non-inferiority phase III ASPECCT trial compared single-agent cetuximab with single-agent panitumumab in the chemotherapy-refractory metastatic setting.⁸³⁰ The primary non-inferiority OS endpoint was reached, with a median OS of 10.4 months (95% CI, 9.4–11.6) with panitumumab and 10.0 months (95% CI, 9.3–11.0) with cetuximab (HR, 0.97; 95% CI, 0.84–1.11). The incidence of AEs was similar between the groups. The final analysis of ASPECCT came to the same conclusion, reporting a median OS of 10.2 months with panitumumab and 9.9 months with cetuximab (HR, 0.98; 95% CI, 0.82–1.07).⁸³¹

The randomized, multicenter, phase II SPIRITT trial randomized 182 patients with *KRAS* wild-type tumors whose disease progressed on first-line oxaliplatin-based therapy plus bevacizumab to FOLFIRI plus bevacizumab or FOLFIRI plus panitumumab.⁸³² No difference was seen in the primary endpoint of PFS between the arms (7.7 months in the panitumumab arm vs. 9.2 months in the bevacizumab arm; HR, 1.01; 95% CI, 0.68–1.50; $P = .97$).

Bevacizumab in the Non–First-line Setting

In the TML (ML18147) trial, patients with mCRC who progressed on regimens containing bevacizumab received second-line therapy consisting of a different chemotherapy regimen with or without bevacizumab.⁸³³ This study met its primary endpoint, with patients continuing on bevacizumab having a modest improvement in OS (11.2 months vs. 9.8 months; HR, 0.81; 95% CI, 0.69–0.94; $P = .0062$). Subgroup analyses from this trial found that these treatment effects were independent of *KRAS* exon 2 status.⁸³⁴

Similar results were reported from the GONO group's phase III randomized BEBYP trial, in which the PFS of patients who continued on bevacizumab plus a different chemotherapy regimen following progression on bevacizumab was 6.8 months compared to 5.0 months in the control arm (HR, 0.70; 95% CI, 0.52–0.95; $P = .001$).⁸³⁵ An improvement in OS was also seen in the bevacizumab arm (HR, 0.77; 95% CI, 0.56–1.06; $P = .04$). The EAGLE trial randomized 387 patients with disease progression following oxaliplatin-based therapy with bevacizumab to second-line therapy with FOLFIRI plus either 5 or 10 mg/kg bevacizumab.⁸³⁶ No difference was seen in PFS or time to treatment failure between the arms, indicating that 5 mg/kg of bevacizumab is an appropriate dose in second-line treatment of mCRC.

The continuation of bevacizumab following progression on bevacizumab was also studied in a community oncology setting through a retrospective analysis of 573 patients from the US Oncology iKnowMed electronic medical record system.⁸³⁷ Bevacizumab beyond progression was associated with a longer OS (HR, 0.76; 95% CI, 0.61–0.95) and a longer post-progression OS (HR, 0.74; 95% CI, 0.60–0.93) on multivariate analysis. Analyses of the ARIES observational cohort found similar results, with longer post-progression survival with continuation of bevacizumab (HR, 0.84; 95% CI, 0.73–0.97).⁸³⁸



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Overall, these data (along with data from the VELOUR trial, discussed below) show that the continuation of VEGF blockade in second-line therapy offers a very modest but statistically significant OS benefit. The panel added the continuation of bevacizumab to the second-line treatment options in the 2013 versions of the NCCN Guidelines for Colon and Rectal Cancers. It may be added to any regimen that does not contain another targeted agent. The panel recognizes the lack of data suggesting a benefit to bevacizumab with irinotecan alone in this setting, but believes that the option is acceptable, especially in patients whose disease progressed on a 5-FU– or capecitabine-based regimen. When an angiogenic agent is used in second-line therapy, bevacizumab is preferred over ziv-aflibercept and ramucirumab (discussed below), based on toxicity and/or cost.⁸³⁹ Beyond the second-line setting, bevacizumab may be combined with trifluridine-tipiracil [see *Trifluridine-Tipiracil (TAS-102)*, below, for more information].

It may also be appropriate to consider using bevacizumab with second-line therapy after progression on a first-line regimen that did not contain bevacizumab.⁸⁴⁰ However, there are no data to support adding bevacizumab to a regimen after progression on that same regimen. The randomized phase III ECOG E3200 study in patients who experienced progression through a first-line non-bevacizumab-containing regimen showed that the addition of bevacizumab to second-line FOLFOX modestly improved survival.⁸⁴⁰ Median OS was 12.9 months for patients receiving FOLFOX plus bevacizumab compared with 10.8 months for patients treated with FOLFOX alone ($P = .0011$).⁸⁴⁰ Use of single-agent bevacizumab is not recommended because it was shown to have inferior efficacy compared with the FOLFOX alone or FOLFOX plus bevacizumab treatment arms.⁸⁴⁰

Ziv-Aflibercept

Ziv-aflibercept is a recombinant protein that has part of the human VEGF receptors 1 and 2 fused to the Fc portion of human IgG1.⁸⁴¹ It is

designed to function as a VEGF trap to prevent activation of VEGF receptors and thus inhibit angiogenesis. The VELOUR trial tested second-line ziv-aflibercept in patients with mCRC that progressed after one regimen containing oxaliplatin. The trial met its primary endpoint with a small improvement in OS (13.5 months for FOLFIRI/ziv-aflibercept vs. 12.1 months for FOLFIRI/placebo; HR, 0.82; 95% CI, 0.71–0.94; $P = .003$).⁸⁴² A prespecified subgroup analysis from the VELOUR trial found that median OS in the ziv-aflibercept arm versus the placebo arm was 12.5 months (95% CI, 10.8–15.5) versus 11.7 months (95% CI, 9.8–13.8) in patients with prior bevacizumab treatment and 13.9 months (95% CI, 12.7–15.6) versus 12.4 months (95% CI, 11.2–13.5) in patients with no prior bevacizumab treatment.⁸⁴³

AEs associated with ziv-aflibercept treatment in the VELOUR trial led to discontinuation in 26.6% of patients compared to a 12.1% discontinuation in the placebo group.⁸⁴² The most common causes for discontinuation were asthenia/fatigue, infections, diarrhea, hypertension, and venous thromboembolic events.

Ziv-aflibercept has only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients. No data suggest activity of FOLFIRI plus ziv-aflibercept in patients who progressed on FOLFIRI plus bevacizumab or vice-versa, and no data suggest activity of single-agent ziv-aflibercept. Furthermore, the addition of ziv-aflibercept to FOLFIRI in first-line therapy of patients with mCRC in the phase II AFFIRM study had no benefit and increased toxicity.⁸⁴⁴ Thus, the panel added ziv-aflibercept as a second-line treatment option in combination with FOLFIRI or irinotecan only following progression on therapy not containing irinotecan. However, the panel prefers bevacizumab over ziv-aflibercept and ramucirumab (discussed below) in this setting, based on toxicity and/or cost.⁸³⁹



Ramucirumab

Another anti-angiogenic agent, ramucirumab, is a human monoclonal antibody that targets the extracellular domain of VEGF receptor 2 to block VEGF signaling.⁸⁴⁵ In the multicenter, phase III RAISE trial, 1072 patients with mCRC whose disease progressed on first-line therapy with fluoropyrimidine/oxaliplatin/bevacizumab were randomized to FOLFIRI with either ramucirumab or placebo.⁸⁴⁶ The primary endpoint of OS in the ITT population was met at 13.3 months and 11.7 months in the ramucirumab and placebo groups, respectively, for an HR of 0.84 (95% CI, 0.73–0.98; $P = .02$). PFS was also improved with the addition of ramucirumab, at 5.7 months and 4.5 months for the two arms (HR, 0.79; 95% CI, 0.70–0.90; $P < .0005$). A subgroup analysis of the RAISE trial subsequently reported similar efficacy and safety among patient subgroups with different *KRAS* mutation status, time to progression on first-line therapy, and age.⁸⁴⁷

Rates of discontinuation due to AEs in the RAISE trial were 11.5% in the ramucirumab arm and 4.5% in the placebo arm. The most common grade 3 or worse AEs were neutropenia, hypertension, diarrhea, and fatigue. In addition, a meta-analysis of six phase III trials showed that ramucirumab did not increase the risk of arterial thromboembolic events, venous thromboembolic events, high-grade bleeding, or high-grade GI bleeding compared to placebo controls.⁸⁴⁸ These results suggest that ramucirumab may be distinct among antiangiogenic agents in that it does not increase the risk of these events.

Considering the results of the RAISE trial, the panel added ramucirumab as a second-line treatment option in combination with FOLFIRI or irinotecan following progression on therapy not containing irinotecan. As with ziv-aflibercept, no data suggest activity of FOLFIRI plus ramucirumab in patients who progressed on FOLFIRI plus bevacizumab or vice-versa, and no data suggest activity of single-agent ramucirumab. When an

angiogenic agent is used in this setting, the panel prefers bevacizumab over ziv-aflibercept and ramucirumab, because of toxicity and/or cost.⁸³⁹

Encorafenib Plus Cetuximab or Panitumumab for BRAF V600E Mutation-Positive Disease in the Non–First-line Setting

A combination of the BRAF inhibitor, encorafenib, and the MEK inhibitor, binimetinib, with cetuximab has been investigated in the randomized, phase III BEACON trial for metastatic, *BRAF* V600E mutation-positive CRC.^{849,850} The safety lead-in of the BEACON trial showed promising efficacy results with an ORR of 48% (95% CI, 29.4%–67.5%) among the 29 patients included in the efficacy analysis. Among the 30 treated patients in the safety lead-in, the most common grade 3 or 4 AEs were fatigue (13%), anemia (10%), increased creatine phosphokinase (10%), increased aspartate transaminase (AST) (10%), and urinary tract infections (10%).⁸⁴⁹

Subsequently, the randomized portion of the BEACON trial reported similarly encouraging results, including a positive OS result.⁸⁵⁰ Within this portion of the study, 665 patients were randomized to receive either the triplet combination, an encorafenib and cetuximab doublet, or a control regimen of cetuximab plus either irinotecan or FOLFIRI. The final results of BEACON reported a median OS of 5.9 months, 9.3 months, and 9.3 months for the control, doublet, and triplet arms, respectively, after a median follow-up of 12.8 months.⁸⁵¹ The ORRs were 2%, 20%, and 27%, respectively, and grade 3 or higher AE rates were highest in the triplet arm, although the addition of binimetinib did not improve OS or ORR over the doublet. Quality-of-life assessments showed that the doublet and triplet regimens led to a similarly longer maintenance of quality of life compared with control. Based on this report, the NCCN Panel concluded that only the doublet regimen of encorafenib with either cetuximab or panitumumab should be recommended for patients with *BRAF* V600E-mutated mCRC.



Data exist on the use of cetuximab or panitumumab in combination with irinotecan and vemurafenib⁸⁵² or dabrafenib plus trametinib⁸⁵³ for *BRAF* V600E mutation-positive mCRC. However, based on superior data and/or lower toxicity with the encorafenib-containing doublets, the panel voted to not include recommendations for these regimens within the current version of the guidelines.

Systemic Therapy Options for HER2-Amplified Disease

Three different regimens are recommended by the panel as options for subsequent treatment of mCRC with HER2 amplifications: fam-trastuzumab deruxtecan-nxki (T-DXd) monotherapy or trastuzumab in combination with either pertuzumab or lapatinib. These regimens may also be appropriate for patients with previously untreated HER2-amplified mCRC who are not appropriate for intensive therapy. The NCCN Panel notes that FDA-approved biosimilars may be substituted for trastuzumab wherever the therapy is recommended within these Guidelines (see *Biosimilars*, above, for more information). The results of clinical trials supporting each of these regimens are detailed below.

Trastuzumab Plus Pertuzumab: A combination regimen of the HER2 inhibitors trastuzumab and pertuzumab was studied in a subset analysis of MyPathway, a phase IIa multiple basket study.⁸⁵⁴ This subset included 57 patients with previously treated, HER2-amplified mCRC who were treated with the combination of pertuzumab and trastuzumab. ORR was 32% (95% CI, 20%–45%), with 1 complete response and 17 partial responses. Thirty-seven percent of patients treated with trastuzumab plus pertuzumab had grade 3 or 4 AEs, with hypokalemia and abdominal pain being most common. Another phase II basket study, TAPUR, also investigated the combination of trastuzumab and pertuzumab in HER2-amplified mCRC.⁸⁵⁵ In this study, 28 patients with heavily pretreated, HER2-amplified advanced CRC were treated with the combination. Four partial responses and 10 cases of stable disease for at least 16 weeks were reported,

leading to a disease control rate of 50% and an ORR of 14%. Two patients had at least one grade 3 AE, including anemia, infusion reaction, and left ventricular dysfunction.

Trastuzumab Plus Lapatinib: The combination of trastuzumab plus the dual HER2/EGFR inhibitor, lapatinib, was studied in the multicenter, phase II HERACLES trial.⁶⁴⁰ This trial included 27 patients with previously treated, HER2-positive tumors that were treated with trastuzumab and lapatinib. ORR was 30% (95% CI, 14%–50%), with one complete response, seven partial responses, and 12 patients with stable disease. Twenty-two percent of patients treated with trastuzumab plus lapatinib had grade 3 AEs, including fatigue (four patients), skin rash (one patient), and increased bilirubin (one patient).⁶⁴⁰

T-DXd: The HER2-directed antibody and topoisomerase inhibitor conjugate was studied in the phase 2, multicenter DESTINY-CRC01 trial of 78 patients with HER2-expressing, *RAS/BRAF* wild-type unresectable and/or mCRC that had already progressed on at least two prior regimens.⁸⁵⁶ Patients were split into three cohorts based on the level of tumor HER2 expression (cohort A: IHC 3+ or IHC 2+/ISH+; cohort B: IHC 2+/ISH -; cohort C: IHC 1+). In cohort A, the primary endpoint of ORR was 45.3%, with one complete response and 23 partial responses. Median PFS in this group was 6.9 months, and median OS had not yet been reached. No responses were reported in cohorts B or C. Twenty point five percent of patients had received prior anti-HER2 therapy; for these patients ORR was 43.8%. Grade ≥3 treatment-emergent AEs occurred in 61.5% of patients, with decreased neutrophil count and anemia being most common. Of note, five patients on this trial developed interstitial lung disease related to T-DXd, including two deaths due to this complication (2.6% of all patients).



Pembrolizumab, Nivolumab, Ipilimumab, and Dostarlimab-gxly for dMMR/MSI-H Disease in the Non-First-line Setting

Pembrolizumab is a humanized, IgG4 monoclonal antibody that binds to PD-1 with high affinity, preventing its interaction with PD-L1 and PD-L2 and thus allowing immune recognition and response.⁶⁵⁵

A phase II study evaluated the activity of pembrolizumab in 11 patients with dMMR CRC, 21 patients with pMMR CRC, and nine patients with dMMR non-colorectal carcinomas.⁸⁵⁷ All patients had progressive metastatic disease; the patients in the colorectal arms had progressed through two to four previous therapies. The primary endpoints were the immune-related objective response rate and the 20-week immune-related PFS rate. The immune-related objective response rates were 40% (95% CI, 12%–74%) in the dMMR CRC group, 0% (95% CI, 0%–20%) in the pMMR CRC group, and 71% (95% CI, 29%–96%) in the dMMR non-colorectal group. The 20-week immune-related PFS rates were 78% (95% CI, 40–97), 11% (95% CI, 1–35), and 67% (95% CI, 22–96), respectively. These results indicate that MSI is a predictive marker for the effectiveness of pembrolizumab across tumor types. Furthermore, the median PFS and OS were not reached in the arm with dMMR CRC and were 2.2 and 5.0 months, respectively, in the pMMR CRC group (HR for disease progression or death, 0.10; $P < .001$). Another phase II study, KEYNOTE-164, investigated the efficacy of pembrolizumab in 124 patients with MSI-H/dMMR mCRC that had been treated with at least one previous line of therapy.⁸⁵⁸ The patients on this study were divided into two cohorts based on whether they had received 2 lines or more of therapy including fluoropyrimidine, oxaliplatin, and irinotecan (cohort A) or 1 or more lines of therapy (cohort B). ORR was reported as 33% for both cohorts, with the median duration of response not reached at the time of publication. Median PFS was 2.3 months and 4.1 months, for cohorts A and B, respectively. Median OS was 31.4 months for cohort A and had not been reached for cohort B. Treatment-related AEs of grade ≥ 3 occurred in 16%

of patients in cohort A and 13% in cohort B, with pancreatitis, fatigue, increased alanine aminotransferase, and increased lipase being most common.

Nivolumab is another humanized IgG4 PD-1 blocking antibody,⁸⁵⁹ which was studied with or without ipilimumab in patients with mCRC in the phase II, multi-cohort CheckMate-142 trial.^{860,861} One cohort of this trial included 74 patients with dMMR CRC who were treated with nivolumab. ORR for these patients was 31.1% (95% CI, 20.8–42.9) with 69% of patients having disease control for at least 12 weeks. Median duration of response had not yet been reached at the time of data collection. PFS and OS were 50% and 73%, respectively, at 1 year. Grade 3 or 4 drug-related AEs occurred in 20% of patients, with increased amylase and increased lipase being most common.⁸⁶¹ Another cohort of the CheckMate-142 included 119 patients with dMMR CRC who were treated with nivolumab in combination with ipilimumab. For this cohort, ORR was 55% (95% CI, 45.2–63.8) and the disease control rate for at least 12 weeks was 80%. PFS and OS were 71% and 85%, respectively, at 1 year. In addition, significant, clinically meaningful improvements were observed in patient-reported outcomes of functioning, symptoms, and quality of life. Grade 3 to 4 treatment-related AEs occurred in 32% of patients, but were manageable.⁸⁶⁰ An in-depth analysis of the safety profile of nivolumab plus ipilimumab on the CheckMate-142 trial reported that AEs predefined in the study protocol as being of special clinical interest (eg, endocrine, GI, hepatic, pulmonary, renal, and skin events) tended to occur early in treatment, were managed using evidence-based treatment algorithms, and resolved.⁸⁶²

A third humanized IgG4 PD-1 blocking antibody, dostarlimab-gxly, has been FDA-approved for the treatment of adult patients with dMMR recurrent or advanced solid tumors that have progressed on or following treatment and who have no satisfactory alternative treatment options.⁸⁶³



The safety and efficacy of dostarlimab-gxly was evaluated in the ongoing phase I GARNET study of patients with advanced solid tumors who had previously received systemic therapy for advanced disease.⁸⁶⁴ Cohort F of this trial enrolled patients with dMMR or POLEmut non-endometrial solid tumors, the majority of which were gastrointestinal cancers. Of the 106 patients in the efficacy analysis, confirmed ORR in dMMR cases was 38.7% (95% CI, 29.4–48.6), with 7.5% achieving complete response. For CRC specifically, the ORR was 36.2% (95% CI, 25.0–48.7). Treatment-related AEs were reported in 68.8% of 144 patients included in the safety analysis and 8.3% experiences at least one grade ≥ 3 AE. Increased lipase was most common and two patients discontinued dostarlimab-gxly due to a treatment-related AE.

Based on these data, the panel recommends pembrolizumab, nivolumab, nivolumab plus ipilimumab, or dostarlimab-gxly as subsequent-line treatment options in patients with metastatic dMMR/MSI-H CRC. These therapies are only options for patients who have not previously received a checkpoint inhibitor. Clinical trials are ongoing to confirm the benefit of these drugs in this setting.

Although PD-1 immune checkpoint inhibitors are generally well tolerated, serious adverse reactions—many immune-mediated—occur in as many as 21% to 41% of patients.^{857,860,861,865} The most common immune-mediated side effects are to the skin, liver, kidneys, GI tract, lungs, and endocrine systems.⁸⁶⁶⁻⁸⁶⁸ Pneumonitis, occurring in approximately 3% to 7% of patients on checkpoint inhibitor therapy, is one of the most serious side effects of PD-1 inhibitors.^{866,869-871}

Larotrectinib or Entrectinib for NTRK Fusion-Positive Disease in the Non-First-line Setting

Recent studies have estimated that about 0.2% to 1% of CRCs carry *NTRK* gene fusions.^{651,652} Two targeted therapies, larotrectinib and entrectinib, have been FDA-approved for the treatment of patients with

metastatic, unresectable solid tumors that have an *NTRK* gene fusion and no satisfactory alternative treatment options, regardless of the location of the primary tumor.^{872,873}

A pooled analysis of three studies (a phase I including adults, a phase I/II involving children, and the phase II NAVIGATE study involving adolescents and adults) studied the safety and efficacy of larotrectinib in 55 patients with *NTRK* gene fusion-positive tumors, including four patients with colon cancer.⁶⁵⁰ For the whole population, the ORR was 75% (95% CI, 61%–85%) by independent review and 80% (95% CI, 67%–90%) by investigator assessment,⁶⁵⁰ although the package insert cites a 25% ORR for colon tumors specifically.⁸⁷³ Larotrectinib was found to be well-tolerated as the majority (93%) of AEs were grades 1 or 2 and no treatment-related AEs of grades 3 or 4 occurred in more than 5% of patients.⁶⁵⁰ A subsequent analysis of these three studies included 159 patients, eight with colon cancer, and reported similar results compared to the earlier analysis.⁸⁷⁴ In this later analysis, the ORR was 79% (95% CI, 72%–85%) by investigator assessment with 16% complete responses. An analysis of 14 patients with GI cancer who were treated with larotrectinib in the NAVIGATE study reported a median PFS of 5.3 months (95% CI, 2.2–9.0) and a median OS of 33.4 months (95% CI, 2.8–36.5).⁸⁷⁵ Responses were ongoing for five patients, leading their results to be censored. Of the 8 patients with colon cancer, 50% showed a partial response and 50% had stable disease.

An integrated analysis of three global phase I/II studies (ALKA-372-001, STARTRK-1, and STARTRK-2) tested the efficacy and safety of entrectinib in 54 adult patients with advanced or metastatic *NTRK* gene fusion-positive solid tumors.⁸⁷⁶ For the whole population, ORR was 57% (95% CI, 43.2%–70.8%), median PFS was 11 months (95% CI, 8.0–14.9), and median OS was 21 months (95% CI, 14.9–not estimable) by independent review. Median duration of response was 10 months (95%



CI, 7.1—not estimable). Of the four patients with CRC on this study, one was recorded as having a response. Notably, a similar ORR (50% vs. 60%) was observed among those with central nervous system metastasis, indicating that entrectinib has activity in this population. Entrectinib was found to be well-tolerated as most treatment-related AEs were grade 1 or 2 and managed with dose reduction, leading few (4%) patients to discontinue therapy due to treatment-related AEs.

Based on these results the panel added larotrectinib and entrectinib as subsequent treatment options for patients with *NTRK* gene fusion-positive disease, acknowledging that these therapies will not be appropriate for most patients due to the rarity of the *NTRK* fusion in CRC.

Regorafenib

Regorafenib is a small-molecule inhibitor of multiple kinases (including VEGF receptors, fibroblast growth factor [FGF] receptors, platelet-derived growth factor [PDGF] receptors, BRAF, KIT, and RET) that are involved with various processes including tumor growth and angiogenesis.⁸⁷⁷ The phase III CORRECT trial randomized 760 patients who progressed on standard therapy to best supportive care with placebo or regorafenib.⁸⁷⁸ The trial met its primary endpoint of OS (6.4 months for regorafenib vs. 5.0 months for placebo; HR, 0.77; 95% CI, 0.64–0.94; $P = .005$). PFS was also significantly but modestly improved (1.9 months vs. 1.7 months; HR, 0.49; 95% CI, 0.42–0.58; $P < .000001$).

The randomized, double-blind, phase III CONCUR trial was performed in China, Hong Kong, South Korea, Taiwan, and Vietnam.⁸⁷⁹ Patients with progressive mCRC were randomized 2:1 to receive regorafenib or placebo after two or more previous treatment regimens. After a median follow-up of 7.4 months, the primary endpoint of OS was met in the 204 randomized patients (8.8 months in the regorafenib arm vs. 6.3 months in the placebo arm; HR, 0.55; 95% CI, 0.40–0.77; $P < .001$).

The most common grade 3 or higher AEs in the regorafenib arm of the CORRECT trial were hand-foot skin reaction (17%), fatigue (10%), hypertension (7%), diarrhea (7%), and rash/desquamation (6%).⁸⁷⁸ Severe and fatal liver toxicity occurred in 0.3% of 1100 patients treated with regorafenib across all trials.⁸⁷⁷ In a meta-analysis of four studies that included 1078 patients treated with regorafenib for CRC, GI stromal tumor (GIST), renal cell carcinoma, or hepatocellular carcinoma, the overall incidence of all-grade and high-grade hand-foot skin reactions was 60.5% and 20.4%, respectively.⁸⁸⁰ In the subset of 500 patients with CRC, the incidence of all-grade hand-foot skin reaction was 46.6%.

Other studies have also investigated regorafenib for treatment of refractory mCRC. The phase IIIb CONSIGN trial assessed the safety of regorafenib in 2872 patients from 25 countries with refractory mCRC.⁸⁸¹ The REBECCA study assessed the safety and efficacy of regorafenib in a cohort of 654 patients with mCRC within a compassionate use program.⁸⁸² The prospective, observational CORRELATE study assessed the safety and efficacy of regorafenib in 1037 patients with mCRC in real-world clinical practice.⁸⁸³ The safety and efficacy profiles of regorafenib in all of these trials were consistent with that seen in the CORRECT trial.

The randomized, phase II ReDOS trial investigated the use of an alternative dose schedule to reduce the toxicities related to regorafenib treatment.⁸⁸⁴ Of the 116 evaluable patients, the dose-escalation group had a higher percentage of patients who initiated cycle 3 of regorafenib (43%) compared to the standard dosing group (26%). Rates of several of the most common AEs were also lower among the dose-escalation group compared to the standard dosing group. Based on these results, the panel agreed that a dose-escalation strategy is an appropriate alternative approach for regorafenib dosing.

Regorafenib has only shown activity in patients who have progressed on all standard therapy. Therefore, the panel added regorafenib as an



additional line of therapy for patients with mCRC refractory to chemotherapy. It can be given before or after trifluridine-tipiracil; no data inform the best order of these therapies.

Trifluridine-Tipiracil (TAS-102)

Trifluridine-tipiracil is an oral combination drug, consisting of a cytotoxic thymidine analog, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride, which prevents the degradation of trifluridine. Early clinical studies of the drug in patients with CRC were promising.^{885,886}

Results of the double-blind, randomized, controlled, international phase III RECURSE trial were published in 2015,⁸⁸⁷ followed shortly thereafter by approval of trifluridine-tipiracil by the FDA.⁸⁸⁸ With 800 patients with mCRC who progressed through at least two prior regimens randomized 2:1 to receive trifluridine-tipiracil or placebo, the primary endpoint of OS was met (5.3 months vs. 7.1 months; HR, 0.68; 95% CI, 0.58–0.81; $P < .001$).⁸⁸⁷ Improvement was also seen in the secondary endpoint of PFS (1.7 months vs. 2.0 months; HR, 0.48; 95% CI, 0.41–0.57; $P < .001$). The most common AEs associated with trifluridine-tipiracil in RECURSE were neutropenia (38%), leukopenia (21%), and febrile neutropenia (4%); one drug-related death occurred.⁸⁸⁷ A postmarketing surveillance study did not reveal any unexpected safety signals⁸⁸⁹ and a subgroup analysis of the RECURSE trial reported similar efficacy and safety regardless of age, geographical origin, or *KRAS* mutation status.⁸⁹⁰

The combination of trifluridine-tipiracil and bevacizumab has also been studied in the non-first-line setting. C-TASK FORCE was an open-label, single-arm phase I/II study of trifluridine-tipiracil plus bevacizumab for patients with mCRC who had previously received a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF therapy, and an anti-EGFR therapy, if eligible.⁸⁹¹ Patients in this study had not been previously treated with regorafenib. The primary endpoint of PFS at 16 weeks was 42.9% and treatment-related serious AEs were reported in 12% of patients. Based on

the results from C-TASK FORCE, a randomized phase II trial of 93 patients was initiated to compare trifluridine-tipiracil with and without bevacizumab in this patient population.⁸⁹² On the phase II trial, previous treatment with a VEGF inhibitor and/or regorafenib were permitted, but not required for study eligibility. After a median follow-up of 10 months, the median PFS was 2.6 months for trifluridine-tipiracil alone compared to 4.6 months in combination with bevacizumab (HR, 0.45; 95% CI, 0.29–0.72; $P = .0015$). Toxicity was similar between the two groups, with serious AEs reported in 45% of patients who received trifluridine-tipiracil alone and 41% of those who received trifluridine-tipiracil in combination with bevacizumab. A retrospective study of 57 patients with refractory mCRC showed similar results, with an improved median OS for trifluridine-tipiracil with bevacizumab versus without (14.4 months vs. 4.5 months; $P < .001$).⁸⁹³

Based on these data, the panel added trifluridine-tipiracil, with or without bevacizumab, as a treatment option for patients who have progressed through standard therapies. It can be given before or after regorafenib; no data inform the best order of these therapies, although real-world data have shown that patients show better adherence to trifluridine-tipiracil compared to regorafenib.⁸⁹⁴ The 144 patients in RECURSE who had prior exposure to regorafenib obtained similar OS benefit from trifluridine-tipiracil (HR, 0.69; 95% CI, 0.45–1.05) as the 656 patients who did not (HR, 0.69; 95% CI, 0.57–0.83).

Workup and Management of Synchronous Metastatic Disease

The workup for patients in whom metastatic synchronous adenocarcinoma from the large bowel (eg, colorectal liver metastases) is suspected should include a total colonoscopy, CBC, chemistry profile, CEA determination, biopsy if indicated, and CT scan with intravenous contrast of the chest, abdomen, and pelvis.¹⁹⁹ MRI with intravenous contrast should be considered if CT is inadequate. The panel also recommends testing for



tumor *KRAS/NRAS* and *BRAF* gene status and HER2 amplifications at diagnosis of metastatic disease (see *Biomarkers for Systemic Therapy*, above). However, if the tumor is known to have a *RAS* or *BRAF* mutation, HER2 testing is not indicated, as amplification is very rare in this subset.^{640,641} NGS panels can be used to detect these biomarkers and have the advantage of also detecting other rare and actionable mutations (eg, *NTRK* fusions).

The panel strongly discourages the routine use of PET/CT scanning for staging, baseline imaging, or routine follow-up. However, the panel recommends consideration of a preoperative PET/CT scan at baseline in selected cases if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease. The purpose of this PET/CT scan is to evaluate for unrecognized metastatic disease that would preclude the possibility of surgical management. A recent randomized clinical trial of patients with resectable metachronous metastases assessed the role of PET/CT in the workup of potential curable disease.⁸⁹⁵ While there was no impact of PET/CT on survival, surgical management was changed in 8% of patients after PET/CT. For example, resection was not undertaken for 2.7% of patients because additional metastatic disease was identified (ie, bone, peritoneum/omentum, abdominal nodes). In addition, 1.5% of patients had more extensive hepatic resections and 3.4% had additional organ surgery. An additional 8.4% of patients in the PET/CT arm had false-positive results, many of which were investigated with biopsies or additional imaging. A meta-analysis of 18 studies including 1059 patients with hepatic colorectal metastases found that PET or PET/CT results changed management in 24% of patients.⁸⁹⁶

Patients with clearly unresectable metastatic disease should not have baseline PET/CT scans. The panel also notes that PET/CT scans should not be used to assess response to chemotherapy, because a PET/CT scan can become transiently negative after chemotherapy (eg, in the

presence of necrotic lesions).⁸⁹⁷ False-positive PET/CT scan results can occur in the presence of tissue inflammation after surgery or infection.⁸⁹⁷ An MRI with intravenous contrast can be considered as part of the preoperative evaluation of patients with potentially surgically resectable M1 liver disease. For example, an MRI with contrast may be of use when the PET and CT scan results are inconsistent with respect to the extent of disease in the liver.

The criterion of potential surgical cure includes patients with metastatic disease that is not initially resectable but for whom a surgical cure may become possible after preoperative chemotherapy. In most cases, however, the presence of extrahepatic disease will preclude the possibility of resection for cure; *conversion to resectability* for the most part refers to a patient with liver-only disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished with chemotherapy (see *Conversion to Resectability*, above).

Close communication among members of the multidisciplinary treatment team is recommended, including an upfront evaluation by a surgeon experienced in the resection of hepatobiliary or lung metastases.

Resectable Synchronous Liver or Lung Metastases

When patients present with CRC and synchronous liver metastases, resection of the primary tumor and liver can be performed in a simultaneous or staged approach.⁸⁹⁸⁻⁹⁰⁶ Historically, in the staged approach, the primary tumor was usually resected first. However, the approach of liver resection before resection of the primary followed by adjuvant chemotherapy is now well-accepted.^{899,901,907,908} In addition, emerging data suggest that chemotherapy, followed by resection of liver metastases before resection of the primary tumor, might be an effective approach in some patients, although more studies are needed.⁹⁰⁹⁻⁹¹⁶



If a patient with resectable liver or lung metastases is a candidate for surgery, the panel recommends the following options: 1) synchronous or staged colectomy with liver or lung resection^{366,374} followed by adjuvant chemotherapy (FOLFOX [preferred], CAPEOX [preferred], 5-FU/LV, or capecitabine^{257,685}); 2) neoadjuvant chemotherapy for 2 to 3 months (ie, FOLFOX [preferred],³⁶⁵ CAPEOX [preferred], FOLFIRI [category 2B], or FOLFOXIRI [category 2B]⁵⁴⁸) followed by synchronous or staged colectomy with liver or lung resection, then adjuvant chemotherapy; or 3) colectomy followed by chemotherapy (see neoadjuvant options above) and a staged resection of metastatic disease, then adjuvant chemotherapy. For dMMR/MSI-H disease, any of the checkpoint inhibitor regimens that are recommended for metastatic disease may also be used in the neoadjuvant setting. Overall, combined neoadjuvant and adjuvant treatments should not exceed 6 months.

In the case of liver metastases only, HAIC with or without systemic 5-FU/LV (category 2B) remains an option at centers with experience in the surgical and medical oncologic aspects of this procedure.

Unresectable Synchronous Liver or Lung Metastases

For patients with metastatic disease that is deemed to be potentially convertible (see *Conversion to Resectability*, above),⁹¹⁷ chemotherapy regimens with high response rates should be considered, and these patients should be reevaluated for resection after 2 months of preoperative chemotherapy and every 2 months thereafter while undergoing this therapy. If bevacizumab is included as a component of the conversion therapy, an interval of at least 6 weeks between the last dose of bevacizumab and surgery should be applied, with a 6- to 8-week postoperative period before re-initiation of bevacizumab. Patients with disease converted to a resectable state should undergo synchronized or staged resection of colon and metastatic cancer, including treatment with pre- and postoperative chemotherapy for a preferred total perioperative

therapy duration of 6 months. Recommended options for adjuvant therapy for these patients include active systemic therapy regimens for advanced or metastatic disease (category 2B for the use of biologic agents in this setting); observation or a shortened course of chemotherapy can also be considered for patients who have completed preoperative chemotherapy. In the case of liver metastases only, HAIC with or without systemic 5-FU/LV (category 2B) remains an option at centers with experience in the surgical and medical oncologic aspects of this procedure. Ablative therapy of metastatic disease, either alone or in combination with resection, can also be considered when all measurable metastatic disease can be treated (see *Management of Metastatic Disease*).

Patients with disease that is not responding to therapy should receive systemic therapy for advanced or metastatic disease with treatment selection based partly on whether the patient is an appropriate candidate for intensive therapy. Debulking surgery or ablation without curative intent is not recommended.

For patients with liver-only or lung-only disease that is deemed unresectable (see *Determining Resectability*, above), the panel recommends chemotherapy corresponding to initial therapy for metastatic disease (eg, FOLFIRI, FOLFOX, or CAPEOX chemotherapy alone or with bevacizumab; FOLFIRI or FOLFOX with panitumumab or cetuximab; FOLFOXIRI alone or with bevacizumab).

Results from one study suggest that there may be some benefit in both OS and PFS from resection of the primary in the setting of unresectable colorectal metastases.⁹¹⁸ Other systematic reviews and retrospective analyses also have shown a potential benefit.⁹¹⁸⁻⁹²⁴ Separate analyses of the SEER database and the National Cancer Database also identified a survival benefit of primary tumor resection in this setting.^{925,926}



On the other hand, a different analysis of the National Cancer Database came to the opposite conclusion.⁹²⁷ The randomized phase III JCOG1007 study also concluded that primary tumor resection followed by chemotherapy in patients with synchronous unresectable metastases conferred no survival benefit over chemotherapy alone.⁹²⁸ For the 160 patients enrolled in this study, median OS was 25.9 months with primary tumor resection plus chemotherapy compared to 26.7 months for chemotherapy alone. Median PFS was 10.4 and 12.1 months, respectively. Three patients on this study died following primary tumor resection due to postoperative complications. Furthermore, the prospective, multicenter phase II NSABP C-10 trial showed that patients with an asymptomatic primary colon tumor and unresectable metastatic disease who received mFOLFOX6 with bevacizumab experienced an acceptable level of morbidity without upfront resection of the primary tumor.⁹²⁹ The median OS was 19.9 months. Notably, symptomatic improvement in the primary is often seen with systemic chemotherapy even within the first 1 to 2 weeks.

Complications from the intact primary lesion are uncommon in this setting,⁴⁰² and its removal delays initiation of systemic chemotherapy. In fact, a systematic review concluded that resection of the primary does not reduce complications and does not improve OS.⁹³⁰ Another systematic review and meta-analysis identified five studies that compared open to laparoscopic palliative colectomies in this setting.⁹³¹ The laparoscopic approach resulted in shorter lengths of hospital stays ($P < .001$), fewer postoperative complications ($P = .01$), and lower estimated blood loss ($P < .01$).

Overall, the panel believes that the risks of surgery outweigh the possible benefits of resection of asymptomatic primary tumors in the setting of unresectable colorectal metastases. Routine palliative resection of a synchronous primary lesion should therefore only be considered if the

patient has an unequivocal imminent risk of obstruction, acute significant bleeding, perforation, or other significant tumor-related symptoms.

An intact primary is not a contraindication to bevacizumab use. The risk of GI perforation in the setting of bevacizumab is not decreased by removal of the primary tumor, because large bowel perforations, in general, and perforation of the primary lesion, in particular, are rare.

Synchronous Abdominal/Peritoneal Metastases

For patients with peritoneal metastases causing obstruction or that may cause imminent obstruction, palliative surgical options include colon resection, diverting colostomy, a bypass of impending obstruction, or stenting, followed by systemic therapy for advanced or metastatic disease.

The primary treatment of patients with nonobstructing metastases is chemotherapy. As mentioned above (see *Cytoreductive Debulking with Hyperthermic Intraperitoneal Chemotherapy*), the panel currently believes that the treatment of disseminated carcinomatosis with complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. However, the significant morbidity and mortality associated with HIPEC, as well as the conflicting data on clinical efficacy, make this approach very controversial.

Workup and Management of Metachronous Metastatic Disease

On documentation of metachronous, potentially resectable, metastatic disease with dedicated contrast-enhanced CT or MRI, characterization of the disease extent using PET/CT scan should be considered in select cases if a surgical cure of M1 disease is feasible. PET/CT is used at this juncture to promptly characterize the extent of metastatic disease, and to identify possible sites of extrahepatic disease that could preclude surgery.^{895,932,933} Specifically, Joyce et al⁹³² reported that the preoperative



PET changed or precluded curative-intent liver resection in 25% of patients. A recent randomized clinical trial assessed the role of PET/CT in the workup of patients with resectable metachronous metastases.⁸⁹⁵ While there was no impact of PET/CT on survival, surgical management was changed in 8% of patients after PET/CT. This trial is discussed in more detail in *Workup and Management of Synchronous Metastatic Disease*, above.

As with other conditions in which stage IV disease is diagnosed, a tumor analysis (metastases or original primary) for *KRAS/NRAS* and *BRAF* mutations and HER2 amplifications, as well as MSI/MMR testing if not previously done, should be performed to define whether targeted therapies can be considered among the potential options (see *Biomarkers for Systemic Therapy*).

Close communication between members of the multidisciplinary treatment team is recommended, including upfront evaluation by a surgeon experienced in the resection of hepatobiliary and lung metastases. The management of metachronous metastatic disease is distinguished from that of synchronous disease through also including an evaluation of the chemotherapy history of the patient and through the absence of colectomy.

Patients with resectable disease are classified according to whether they have undergone previous chemotherapy. For patients who have resectable metastatic disease, treatment is resection with 6 months of perioperative chemotherapy (pre- or postoperative or a combination of both), with choice of regimens based on previous therapy. Locally ablative procedures can be considered instead of or in addition to resection in cases of liver or lung oligometastases (see *Local Therapies for Metastases*, above), but resection is preferred. For patients without a history of chemotherapy use, FOLFOX or CAPEOX is preferred, with capecitabine or 5-FU/LV as additional category 2B options. There are also

cases when perioperative chemotherapy is not recommended in resectable metachronous disease. In particular, patients with a history of previous chemotherapy and an upfront resection can be observed or may be given an active regimen for advanced disease (category 2B for the use of biologic agents in these settings). Observation is preferred if oxaliplatin-based therapy was previously administered.

Patients determined to have unresectable disease through cross-sectional imaging scan (including those considered potentially convertible) should receive an active systemic therapy regimen based on prior chemotherapy history (see *Second-line or Subsequent Systemic Therapy*, above). In the case of liver metastases only, HAIC with or without systemic 5-FU/LV (category 2B) is an option at centers with experience in the surgical and medical oncologic aspects of this procedure. Patients receiving palliative systemic therapy should be monitored with CT or MRI scans approximately every 2 to 3 months.

Endpoints for Advanced CRC Clinical Trials

In the past few years, there has been much debate over what endpoints are most appropriate for clinical trials in advanced CRC.⁹³⁴ Quality of life is an outcome that is rarely measured but of unquestioned clinical relevance.⁹³⁵ While OS is also of clear clinical relevance, it is often not used because large numbers of patients and long follow-up periods are required.⁹³⁵ PFS is often used as a surrogate, but its correlation with OS is inconsistent at best, especially when subsequent lines of therapy are administered.⁹³⁵⁻⁹³⁷ In 2011, The Grupo Español Multidisciplinar en Cancer Digestivo (GEMCAD) proposed particular aspects of clinical trial design to be incorporated into trials that use PFS as an endpoint.⁹³⁸

A recent study, in which individual patient data from three RCTs were pooled, tested endpoints that take into account subsequent lines of therapy: duration of disease control, which is the sum of PFS times of



each active treatment; and time to failure of strategy, which includes intervals between treatment courses and ends when the planned lines of treatment end (because of death, progression, or administration of a new agent).⁹³⁶ The authors found a better correlation between these endpoints and OS than between PFS and OS. Another alternative endpoint, time to tumor growth, has also been suggested to predict OS.^{939,940} Further evaluation of these and other surrogate endpoints is warranted.

Posttreatment Surveillance

After curative-intent surgery and adjuvant chemotherapy, if administered, post-treatment surveillance of patients with CRC is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and identify new metachronous neoplasms at a preinvasive stage. An analysis of data from 20,898 patients enrolled in 18 large, adjuvant, randomized trials showed that 80% of recurrences occurred in the first 3 years after surgical resection of the primary tumor,²⁶⁸ and a recent study found that 95% of recurrences occurred in the first 5 years.⁹⁴¹

Surveillance for Locoregional Disease

Advantages of more intensive follow-up of patients with stage II and/or stage III disease have been shown prospectively in several older studies⁹⁴²⁻⁹⁴⁴ and in multiple meta-analyses of RCTs designed to compare low- and high-intensity programs of surveillance.⁹⁴⁵⁻⁹⁵⁰ Intensive postoperative surveillance has also been suggested to be of benefit to patients with stage I and IIA disease.⁹⁵¹ Furthermore, a population-based report indicates increased rates of resectability and survival in patients treated for local recurrence and distant metastases of CRC in more recent years, thereby providing support for more intensive post-treatment follow-up in these patients.⁹⁵²

Results from the recent randomized controlled FACS trial of 1202 patients with resected stage I to III disease showed that intensive surveillance imaging or CEA screening resulted in an increased rate of curative-intent surgical treatment compared with a minimum follow-up group that only received testing if symptoms occurred, but no advantage was seen in the CEA and CT combination arm (2.3% in the minimum follow-up group, 6.7% in the CEA group, 8% in the CT group, and 6.6% in the CEA plus CT group).⁹⁵³ In this study, no mortality benefit to regular monitoring with CEA, CT, or both was observed compared with minimum follow-up (death rate, 18.2% vs. 15.9%; difference, 2.3%; 95% CI, -2.6%–7.1%). The authors concluded that any strategy of surveillance is unlikely to provide a large survival advantage over a symptom-based approach. The randomized COLOFOL trial of 2509 patients with stage II or III CRC looked at follow-up testing with CT of the thorax and abdomen and CEA screening, comparing a high-frequency surveillance approach (CT and CEA at 6, 12, 18, 24, and 36 months post-surgery) to a low-frequency approach (CT and CEA at 12 and 36 months post-surgery).⁹⁵⁴ This trial reported no significant difference in 5-year overall mortality or CRC-specific mortality between the two screening approaches.

The CEAwatch trial compared usual follow-up care to CEA measurements every two months, with imaging performed if CEA increases were seen twice, in 3223 patients at 11 hospitals treated for non-mCRC in the Netherlands.⁹⁵⁵ The intensive CEA surveillance protocol resulted in the detection of more recurrences and recurrences that could be treated with curative intent than usual follow-up, and the time to detection of recurrent disease was shorter. Another randomized trial of 1228 patients found that more intensive surveillance led to earlier detection of recurrences than a less intensive program (less frequent colonoscopy and liver ultrasound and the absence of an annual chest x-ray) but did not affect OS.⁹⁵⁶



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Colon Cancer

The randomized phase III PRODIGE 13 trial is comparing 5-year OS after intensive radiologic monitoring (abdominal ultrasound, chest/abdomen/pelvis CT, and CEA) with a lower intensity program (abdominal ultrasound and chest x-ray) in patients with resected stage II or III colon or rectal tumors.⁹⁵⁷ An abstract reporting results from 1995 patients on this trial concluded that the more intensive surveillance program did not provide any benefit in 5-year OS, but did result in more curative intent secondary surgeries for colon cancer. Surgical treatment of recurrence was performed in 40.9% of patients receiving minimal surveillance (no CT, no CEA), 66.3% of patients receiving lower intensity imaging plus CEA, 50.7% of patients receiving no CEA but higher intensity imaging, and 59.5% in the maximum surveillance group with both CEA and CT ($P = .0035$).⁹⁵⁸

Clearly, controversies remain regarding selection of optimal strategies for following up patients after potentially curative CRC surgery, and the panel's recommendations are based mainly on consensus. The panel endorses surveillance as a means to identify patients who are potentially curable of metastatic disease with surgical resection.

For patients with stage I disease, the panel believes that a less intensive surveillance schedule is appropriate because of the low risk of recurrence and the harms associated with surveillance. Possible harms include radiation exposure with repeated CT scans, psychological stress associated with surveillance visits and scans, and stress and risks from following up on false-positive results. Therefore, for patients with stage I disease, the panel recommends colonoscopy at 1 year after surgery. Repeat colonoscopy is recommended at 3 years, and then every 5 years thereafter, unless advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia) is found. In this case, colonoscopy should be repeated in 1 year.⁹⁵⁰

The following panel recommendations for post-treatment surveillance pertain to patients with stage II/III disease who have undergone successful treatment (ie, no known residual disease). History and physical examination should be given every 3 to 6 months for 2 years, and then every 6 months for a total of 5 years. A CEA test (also see *Managing an Increasing CEA Level*, below) is recommended at baseline and every 3 to 6 months for 2 years,⁹⁵⁹ then every 6 months for a total of 5 years for patients with stage III disease and those with stage II disease if the clinician determines that the patient is a potential candidate for aggressive curative surgery.^{945,959} Colonoscopy is recommended at approximately 1 year after resection (or at 3–6 months postresection if not performed preoperatively because of an obstructing lesion). Repeat colonoscopy is typically recommended at 3 years, and then every 5 years thereafter, unless follow-up colonoscopy indicates advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia), in which case colonoscopy should be repeated in 1 year.⁹⁵⁰ More frequent colonoscopies may be indicated in patients who present with colon cancer before 50 years of age. Chest, abdominal, and pelvic CT scan are recommended every 6 to 12 months (category 2B for more frequently than annually) for up to 5 years in patients with stage III disease and those with stage II disease at a high risk for recurrence.^{945,960} Routine CEA monitoring and CT scanning are not recommended beyond 5 years. Use of PET/CT to monitor for disease recurrence is not recommended.^{960,961} The CT that accompanies a PET/CT is usually a noncontrast CT, and therefore not of ideal quality for routine surveillance.

Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps, because data show that patients with a history of CRC have an increased risk of developing second cancers, particularly in the first 2 years after resection.^{950,962} Furthermore, use of post-treatment surveillance colonoscopy has not been shown to improve survival through the early detection of recurrence of the original CRC.⁹⁵⁰



The recommended frequency of post-treatment surveillance colonoscopies is higher (ie, annually) for patients with Lynch syndrome.²⁹

CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and liver.⁹⁴⁵ Hence, CT scan is not routinely recommended in asymptomatic patients who are not candidates for potentially curative resection of liver or lung metastases.^{945,960}

The ASCO Clinical Practice Guidelines Committee has endorsed the Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer from Cancer Care Ontario (CCO).^{963,964} These guidelines differ only slightly from the surveillance recommendations in these NCCN Guidelines for Colon Cancer. While ASCO/CCO recommend abdominal and chest CT annually for 3 years in patients with stage II and III disease, the NCCN Panel recommends semi-annual to annual scans for 5 years (category 2B for more frequent than annual scanning). The panel bases its recommendation on the fact that approximately 10% of patients will recur after 3 years.^{268,941} The American Society of Colon and Rectal Surgeons also released surveillance guidelines, which are also very similar to NCCN surveillance recommendations.⁹⁶⁵ One exception is the inclusion of intensive surveillance for patients with resected stage I colon or rectal cancer if the provider deems the patient to be at increased risk for recurrence.

Surveillance for Metastatic Disease

Patients who had resection of mCRC can undergo subsequent curative-intent resection of recurrent disease (see *Surgical Management of Colorectal Metastases*, above). A retrospective analysis of 952 patients who underwent resection at Memorial Sloan Kettering Cancer Center showed that 27% of patients with recurrent disease underwent curative-

intent resection and that 25% of those patients (6% of recurrences; 4% of the initial population) were free of disease for 36 months or more.⁹⁶⁶

Panel recommendations for surveillance of patients with stage IV CRC with no evidence of disease (NED) after curative-intent surgery and subsequent adjuvant treatment are similar to those listed for patients with stage II/III disease, except that certain evaluations are performed more frequently. Specifically, the panel recommends that these patients undergo contrast-enhanced CT scan of the chest, abdomen, and pelvis every 3 to 6 months in the first 2 years after adjuvant treatment (category 2B for frequency <6 months) and then every 6 to 12 months for up to a total of 5 years. CEA testing is recommended every 3 to 6 months for the first 2 years and then every 6 months for a total of 5 years, as in early-stage disease. Again, use of PET/CT scans for surveillance is not recommended. A recent analysis of patients with resected or ablated colorectal liver metastases found that the frequency of surveillance imaging did not correlate with time to second procedure or median survival duration.⁹⁶⁷ Those scanned once per year survived a median of 54 months versus 43 months for those scanned 3 to 4 times per year ($P = .08$), suggesting that annual scans may be sufficient in this population.

Managing an Increasing CEA Level

Managing patients with an elevated CEA level after resection should include colonoscopy; chest, abdominal, and pelvic CT scans; physical examination; and consideration of PET/CT scan. If imaging study results are normal in the face of a rising CEA, repeat CT scans are recommended every 3 months until either disease is identified or CEA level stabilizes or declines.

In a recent retrospective chart review at Memorial Sloan Kettering Cancer Center, approximately half of elevations in CEA levels after R0 resection of locoregional CRC were false positives, with most being single high



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readings or repeat readings in the range of 5 to 15 ng/mL.⁹⁶⁸ In this study, false-positive results greater than 15 ng/mL were rare, and all results greater than 35 ng/mL represented true positives. Following a systematic review and meta-analysis, the pooled sensitivity and specificity of CEA at a cutoff of 10 ng/mL were calculated at 68% (95% CI, 53%–79%) and 97% (95% CI, 90%–99%), respectively.^{969,970} In the first 2 years post-resection, a CEA cutoff of 10 ng/mL is estimated to detect 20 recurrences, miss 10 recurrences, and result in 29 false positives.

Panel opinion was divided on the usefulness of PET/CT scan in the scenario of an elevated CEA with negative, good-quality CT scans (ie, some panel members favored use of PET/CT in this scenario whereas others noted that the likelihood of PET/CT identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). A recent systematic review and meta-analysis found 11 studies (510 patients) that addressed the use of PET/CT in this setting.⁹⁷¹ The pooled estimates of sensitivity and specificity for the detection of tumor recurrence were 94.1% (95% CI, 89.4–97.1%) and 77.2% (95% CI, 66.4–85.9), respectively. Use of PET/CT scans in this scenario is permissible within these guidelines. The panel does not recommend a so-called blind or CEA-directed laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative,⁹⁷² nor does it recommend use of anti-CEA-radiolabeled scintigraphy.

Survivorship

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written.⁹⁷³ The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to the patient. The care plan should include an overall summary of treatments received, including surgeries, radiation treatments, and systemic therapies. The possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible

late sequelae of treatment should be described. Finally, surveillance and health behavior recommendations should be part of the care plan.

Disease preventive measures, such as immunizations; early disease detection through periodic screening for second primary cancers (eg, breast, cervical, or prostate cancers); and routine good medical care and monitoring are recommended (see the [NCCN Guidelines for Survivorship](#)). Additional health monitoring should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.⁹⁷⁴

Other recommendations include monitoring for late sequelae of colon cancer or the treatment of colon cancer, such as chronic diarrhea or incontinence (eg, patients with stoma).⁹⁷⁵⁻⁹⁸⁰ Other long-term problems common to CRC survivors include oxaliplatin-induced peripheral neuropathy, fatigue, insomnia, cognitive dysfunction, body image issues (especially as related to an ostomy), and emotional or social distress.⁹⁸¹⁻⁹⁸⁷ Specific management interventions to address these and other side effects are described in a review,⁹⁸⁸ and a survivorship care plan for patients with CRC have been published.⁹⁸⁹

The [NCCN Guidelines for Survivorship](#) provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment to aid health care professionals who work with survivors of adult-onset cancer in the post-treatment period, including those in specialty cancer survivor clinics and primary care practices. The NCCN Guidelines for Survivorship include many topics with potential relevance to survivors of CRC, including Anxiety, Depression, and Distress; Cognitive Dysfunction; Fatigue; Pain; Sexual Dysfunction; Healthy Lifestyles; and Immunizations. Concerns related to employment, insurance, and disability are also discussed. The American Cancer Society has also established guidelines for the care of survivors of CRC, including surveillance for



recurrence, screening for subsequent primary malignancies, the management of physical and psychosocial effects of cancer and its treatment, and promotion of healthy lifestyles.⁹⁷⁴

Healthy Lifestyles for Survivors of CRC

Evidence indicates that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy BMI, engaging in regular exercise, and making certain dietary choices are associated with improved outcomes and quality of life after treatment for colon cancer.

In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, DFS was found to be directly related to the amount of exercise in which the patients engaged.⁹⁹⁰ In addition, a study of a large cohort of men treated for stage I through III CRC showed an association between increased physical activity and lower rates of CRC-specific mortality and overall mortality.⁹⁹¹ More recent data support the conclusion that physical activity improves outcomes. In a cohort of more than 2000 survivors of non-mCRC, those who spent more time in recreational activity had a lower mortality than those who spent more leisure time sitting.⁹⁹² In addition, recent evidence suggests that both pre- and post-diagnosis physical activity decreases CRC mortality. Women enrolled in the Women's Health Initiative study who subsequently developed CRC had lower CRC-specific mortality (HR, 0.68; 95% CI, 0.41–1.13) and all-cause mortality (HR, 0.63; 95% CI, 0.42–0.96) if they reported high levels of physical activity.⁹⁹³ Similar results were seen in other studies and in recent meta-analyses of prospective studies.⁹⁹⁴⁻⁹⁹⁷

A retrospective study of patients with stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that patients with a BMI of 35 kg/m² or greater had an increased risk of disease recurrence and death.⁹⁹⁸ Data from the ACCENT database also found that pre-diagnosis BMI has a

prognostic impact on outcomes in patients with stage II/III CRC undergoing adjuvant therapy.⁹⁹⁹ An analysis of participants in the Cancer Prevention Study-II Nutrition Cohort who subsequently developed non-mCRC found that pre-diagnosis obesity but not post-diagnosis obesity was associated with higher all-cause and CRC-specific mortality.¹⁰⁰⁰ A meta-analysis of prospective cohort studies found that pre-diagnosis obesity was associated with increased CRC-specific and all-cause mortality.¹⁰⁰¹ Other analyses confirm the increased risk for recurrence and death in obese patients.^{89,1002-1005}

In contrast, pooled data from first-line clinical trials in the ARCAD database indicate that a low BMI may be associated with an increased risk of progression and death in the metastatic setting, whereas a high BMI may not be.¹⁰⁰⁶ In addition, results of one retrospective observational study of a cohort of 3408 patients with resected stage I to III CRC suggest that the relationship between mortality and BMI might be U shaped, with the lowest mortality for those with BMI 28 kg/m².¹⁰⁰⁷ However, several possible explanations for this so-called “obesity paradox” have been suggested.¹⁰⁰⁸ Overall, the panel believes that survivors of CRC should be encouraged to achieve and maintain a healthy body weight (see the [NCCN Guidelines for Survivorship](#)).

A diet consisting of more fruits, vegetables, poultry, and fish; less red meat; more whole grains; and fewer refined grains and concentrated sweets has been found to be associated with an improved outcome in terms of cancer recurrence or death.¹⁰⁰⁹ There is also some evidence that higher postdiagnosis intake of total milk and calcium may be associated with a lower risk of death in patients with stage I, II, or III CRC.⁹⁵ Recent analysis of the CALGB 89803 trial found that higher dietary glycemic load was also associated with an increased risk of recurrence and mortality in patients with stage III disease.¹⁰¹⁰ Another analysis of the data from CALGB 89803 found an association between high intake of sugar-



sweetened beverages and an increased risk of recurrence and death in patients with stage III colon cancer.¹⁰¹¹ The link between red and processed meats and mortality in survivors of non-mCRC has been further supported by recent data from the Cancer Prevention Study II Nutrition Cohort, in which survivors with consistently high intake had a higher risk of CRC-specific mortality than those with low intake (RR, 1.79; 95% CI, 1.11–2.89).⁸⁷

A discussion of lifestyle characteristics that may be associated with a decreased risk of colon cancer recurrence, such as those recommended by the American Cancer Society,¹⁰¹² also provides “a teachable moment” for the promotion of overall health, and an opportunity to encourage patients to make choices and changes compatible with a healthy lifestyle. In addition, a recent trial showed that telephone-based health behavior coaching had a positive effect on physical activity, diet, and BMI in survivors of CRC, suggesting that survivors may be open to health behavior change.¹⁰¹³

Therefore, survivors of CRC should be encouraged to maintain a healthy body weight throughout life; adopt a physically active lifestyle (at least 30 minutes of moderate-intensity activity on most days of the week); consume a healthy diet with emphasis on plant sources; eliminate or limit alcohol consumption to no more than 1 drink/day for women and 2 drinks/day for men; and quit smoking.¹⁰¹² Activity recommendations may require modification based on treatment sequelae (ie, ostomy, neuropathy), and diet recommendations may be modified based on the severity of bowel dysfunction.¹⁰¹⁴

Secondary Chemoprevention for CRC Survivors

Limited data suggest a link between post-colorectal-cancer-diagnosis statin use and increased survival.^{112,1015,1016} A meta-analysis that included four studies found that post-diagnosis statin use increased OS (HR, 0.76;

95% CI, 0.68–0.85; $P < .001$) and cancer-specific survival (HR, 0.70; 95% CI, 0.60–0.81; $P < .001$).¹⁰¹⁵

Abundant data show that low-dose aspirin therapy after a diagnosis of CRC decreases the risk of recurrence and death.¹⁰¹⁷⁻¹⁰²³ For example, a population-based, observational, retrospective cohort study of 23,162 patients with CRC in Norway found that post-diagnosis aspirin use was associated with improved CRC-specific survival (HR, 0.85; 95% CI, 0.79–0.92) and OS (HR, 0.95; 95% CI, 0.90–1.01).¹⁰¹⁷ Some evidence suggests that tumor mutations in *PIK3CA* may be predictive for response to aspirin, although the data are somewhat inconsistent and other predictive markers have also been suggested.^{1019,1024-1029} In addition, a meta-analysis of 15 RCTs showed that while non-aspirin NSAIDs were better for preventing recurrence, low-dose aspirin was safer and thereby had a more favorable risk-to-benefit profile.¹⁰³⁰

Based on these data, the panel believes that survivors of CRC can consider taking 325 mg aspirin daily to reduce their risk of recurrence and death. Importantly, aspirin may increase the risk of GI bleeding and hemorrhagic stroke, and these risks should be discussed with CRC survivors.¹⁰³¹

Summary

The panel believes that a multidisciplinary approach is necessary for managing CRC. The panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy.

The recommended surgical procedure for resectable colon cancer is an en bloc resection and adequate lymphadenectomy. Adequate pathologic assessment of the resected lymph nodes is important with a goal of evaluating at least 12 nodes. Adjuvant chemotherapy is recommended for patients with stage III disease and is also an option for some patients with high-risk stage II disease. The preferred regimens for adjuvant therapy, as



well as the recommended duration of therapy, depends on the pathologic stage of the tumor and the risk of recurrence. Patients with resectable T4b tumors or with bulky nodal disease may be treated with neoadjuvant systemic therapy prior to colectomy.

Patients with metastatic disease in the liver or lung should be considered for surgical resection if they are candidates for surgery and if all original sites of disease are amenable to resection (R0) and/or ablation. Six months of perioperative systemic therapy should be administered to patients with synchronous or metachronous resectable metastatic disease. When a response to chemotherapy would likely convert a patient from an unresectable to a resectable state (ie, conversion therapy), this therapy should be initiated.

The recommended post-treatment surveillance program for patients with resected disease includes serial CEA determinations; periodic chest, abdominal, and pelvic CT scans; colonoscopic evaluations; and a survivorship plan to manage long-term side effects of treatment, facilitate disease prevention, and promote a healthy lifestyle.

Recommendations for patients with disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at initiation of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression, including plans for adjusting therapy for patients who experience certain toxicities. In addition to fluoropyrimidine-, oxaliplatin-, and/or irinotecan-containing chemotherapy regimens, immunotherapy and targeted therapy regimens are becoming an increasingly important part of the mCRC treatment landscape. Combination of a biologic agent (eg, bevacizumab, cetuximab, panitumumab) with some of the chemotherapy regimens is an option, depending on available data. Systemic therapy options for patients with

progressive disease depend on the choice of initial therapy and biomarker status of the tumor.



References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31912902>.
2. Cheng L, Eng C, Nieman LZ, et al. Trends in colorectal cancer incidence by anatomic site and disease stage in the United States from 1976 to 2005. Am J Clin Oncol 2011;34:573-580. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21217399>.
3. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32133645>.
4. Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. JAMA Surg 2014;1-6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25372703>.
5. Weinberg BA, Marshall JL, Salem ME. The Growing Challenge of Young Adults With Colorectal Cancer. Oncology (Williston Park) 2017;31:381-389. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28516436>.
6. Amin MB, Edge SB, Greene F, et al., eds. AJCC Cancer Staging Manual, 8th ed. New York: Springer International Publishing; 2017.
7. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html. Accessed November 17, 2020.
8. Ahsan H, Neugut AI, Garbowski GC, et al. Family history of colorectal adenomatous polyps and increased risk for colorectal cancer. Ann Intern Med 1998;128:900-905. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9634428>.
9. Bonelli L, Martinez H, Conio M, et al. Family history of colorectal cancer as a risk factor for benign and malignant tumours of the large bowel. A case-control study. Int J Cancer 1988;41:513-517. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3356486>.
10. Hemminki K, Eng C. Clinical genetic counselling for familial cancers requires reliable data on familial cancer risks and general action plans. J Med Genet 2004;41:801-807. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15520403>.
11. Hemminki K, Chen B. Familial risk for colorectal cancers are mainly due to heritable causes. Cancer Epidemiol Biomarkers Prev 2004;13:1253-1256. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15247139>.
12. Quintero E, Carrillo M, Leoz ML, et al. Risk of advanced neoplasia in first-degree relatives with colorectal cancer: a large multicenter cross-sectional study. PLoS Med 2016;13:e1002008. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27138769>.
13. Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008;26:5783-5788. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18809606>.
14. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003;348:919-932. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12621137>.
15. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol 2006;101:385-398. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16454848>.
16. Hennink SD, van der Meulen-de Jong AE, Wolterbeek R, et al. Randomized comparison of surveillance intervals in familial colorectal cancer. J Clin Oncol 2015;33:4188-4193. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26527788>.
17. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350-1356. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26457759>.



18. Aaltonen LA, Salovaara R, Kristo P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. *N Engl J Med* 1998;338:1481-1487. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9593786>.

19. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). *N Engl J Med* 2005;352:1851-1860. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15872200>.

20. Hendriks YM, de Jong AE, Morreau H, et al. Diagnostic approach and management of Lynch syndrome (hereditary nonpolyposis colorectal carcinoma): a guide for clinicians. *CA Cancer J Clin* 2006;56:213-225. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16870997>.

21. Beamer LC, Grant ML, Espenschied CR, et al. Reflex immunohistochemistry and microsatellite instability testing of colorectal tumors for Lynch syndrome among US cancer programs and follow-up of abnormal results. *J Clin Oncol* 2012;30:1058-1063. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22355048>.

22. Burt RW. Who should have genetic testing for the Lynch syndrome? *Ann Intern Med* 2011;155:127-128. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21768586>.

23. Ward RL, Hicks S, Hawkins NJ. Population-based molecular screening for Lynch syndrome: implications for personalized medicine. *J Clin Oncol* 2013;31:2554-2562. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23733757>.

24. Matloff J, Lucas A, Polydorides AD, Itzkowitz SH. Molecular tumor testing for Lynch syndrome in patients with colorectal cancer. *J Natl Compr Canc Netw* 2013;11:1380-1385. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24225971>.

25. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genet*

Med 2009;11:35-41. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19125126>.

26. Ladabaum U, Wang G, Terdiman J, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. *Ann Intern Med* 2011;155:69-79. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21768580>.

27. Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genet Med* 2009;11:42-65. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19125127>.

28. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. *J Mol Diagn* 2017;19:187-225. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28185757>.

29. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. *Am J Gastroenterol* 2014;109:1159-1179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25070057>.

30. Rubenstein JH, Enns R, Heidelbaugh J, et al. American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome. *Gastroenterology* 2015;149:777-782. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26226577>.

31. Heald B, Plesec T, Liu X, et al. Implementation of universal microsatellite instability and immunohistochemistry screening for diagnosing lynch syndrome in a large academic medical center. *J Clin Oncol* 2013;31:1336-1340. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23401454>.



32. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. *Lancet Diabetes Endocrinol* 2014;2:76-89. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24622671>.

33. Chung M, Lee J, Terasawa T, et al. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 2011;155:827-838. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22184690>.

34. Gorham ED, Garland CF, Garland FC, et al. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. *Am J Prev Med* 2007;32:210-216. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17296473>.

35. Lappe JM, Travers-Gustafson D, Davies KM, et al. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;85:1586-1591. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17556697>.

36. Ma Y, Zhang P, Wang F, et al. Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. *J Clin Oncol* 2011;29:3775-3782. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21876081>.

37. Ekmekcioglu C, Haluza D, Kundi M. 25-Hydroxyvitamin D Status and Risk for Colorectal Cancer and Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Epidemiological Studies. *Int J Environ Res Public Health* 2017;14. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28134804>.

38. McCullough ML, Zoltick ES, Weinstein SJ, et al. Circulating Vitamin D and Colorectal Cancer Risk: An International Pooling Project of 17 Cohorts. *JNCI: Journal of the National Cancer Institute* 2018:djy087-djy087. Available at: <http://dx.doi.org/10.1093/jnci/djy087>.

39. Fedirko V, Riboli E, Tjonneland A, et al. Prediagnostic 25-hydroxyvitamin D, VDR and CASR polymorphisms, and survival in patients with colorectal cancer in western European populations. *Cancer*

Epidemiol Biomarkers Prev 2012;21:582-593. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22278364>.

40. Ng K, Meyerhardt JA, Wu K, et al. Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer. *J Clin Oncol* 2008;26:2984-2991. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18565885>.

41. Zgaga L, Theodoratou E, Farrington SM, et al. Plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer. *J Clin Oncol* 2014;32:2430-2439. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25002714>.

42. Yuan C, Sato K, Hollis BW, et al. Plasma 25-Hydroxyvitamin D Levels and Survival in Patients with Advanced or Metastatic Colorectal Cancer: Findings from CALGB/SWOG 80405 (Alliance). *Clin Cancer Res* 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31548349>.

43. Maalmi H, Ordonez-Mena JM, Schottker B, Brenner H. Serum 25-hydroxyvitamin D levels and survival in colorectal and breast cancer patients: systematic review and meta-analysis of prospective cohort studies. *Eur J Cancer* 2014;50:1510-1521. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24582912>.

44. Ou B, Zhao J, Guan S, Lu A. Plasma 25-hydroxyvitamin D levels and survival of colorectal cancer patients: a meta-analysis. *Eur J Cancer* 2015;51:786-788. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25746389>.

45. Baron JA, Barry EL, Mott LA, et al. A trial of calcium and vitamin D for the prevention of colorectal adenomas. *N Engl J Med* 2015;373:1519-1530. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26465985>.

46. Barry EL, Peacock JL, Rees JR, et al. Vitamin D Receptor Genotype, Vitamin D3 Supplementation, and Risk of Colorectal Adenomas: A Randomized Clinical Trial. *JAMA Oncol* 2017;3:628-635. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27978548>.



47. Lewis C, Xun P, He K. Vitamin D supplementation and quality of life following diagnosis in stage II colorectal cancer patients: a 24-month prospective study. *Support Care Cancer* 2016;24:1655-1661. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26408324>.
48. Jeffreys M, Redaniel MT, Martin RM. The effect of pre-diagnostic vitamin D supplementation on cancer survival in women: a cohort study within the UK Clinical Practice Research Datalink. *BMC Cancer* 2015;15:670. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26458897>.
49. Urashima M, Ohdaira H, Akutsu T, et al. Effect of Vitamin D Supplementation on Relapse-Free Survival Among Patients With Digestive Tract Cancers: The AMATERASU Randomized Clinical Trial. *Jama* 2019;321:1361-1369. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30964526>.
50. Ng K, Nimeiri HS, McCleary NJ, et al. Effect of High-Dose vs Standard-Dose Vitamin D3 Supplementation on Progression-Free Survival Among Patients With Advanced or Metastatic Colorectal Cancer: The SUNSHINE Randomized Clinical Trial. *Jama* 2019;321:1370-1379. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30964527>.
51. Ross AC, Taylor CL, Yaktine AL, Valle HBD, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): National Academies Press (US); 2011.
52. Beaugerie L, Svrcek M, Seksik P, et al. Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. *Gastroenterology* 2013;145:166-175 e168. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23541909>.
53. Johnson CM, Wei C, Ensor JE, et al. Meta-analyses of colorectal cancer risk factors. *Cancer Causes Control* 2013;24:1207-1222. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23563998>.
54. Lutgens MW, van Oijen MG, van der Heijden GJ, et al. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis* 2013;19:789-799. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23448792>.
55. Cheng J, Chen Y, Wang X, et al. Meta-analysis of prospective cohort studies of cigarette smoking and the incidence of colon and rectal cancers. *Eur J Cancer Prev* 2014;24:6-15. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24722538>.
56. De Bruijn KM, Arends LR, Hansen BE, et al. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. *Br J Surg* 2013;100:1421-1429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24037561>.
57. Esposito K, Chiodini P, Capuano A, et al. Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis. *Endocrine* 2013;44:634-647. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23546613>.
58. Kitahara CM, Berndt SI, de Gonzalez AB, et al. Prospective investigation of body mass index, colorectal adenoma, and colorectal cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *J Clin Oncol* 2013;31:2450-2459. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23715565>.
59. Klatsky AL, Li Y, Nicole Tran H, et al. Alcohol intake, beverage choice, and cancer: a cohort study in a large kaiser permanente population. *Perm J* 2015;19:28-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25785639>.
60. Keum N, Greenwood DC, Lee DH, et al. Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. *J Natl Cancer Inst* 2015;107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25618901>.
61. Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ*



2016;354:i3857. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/27510511>.

62. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer--viewpoint of the IARC Working Group. *N Engl J Med* 2016;375:794-798. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/27557308>.

63. Luo W, Cao Y, Liao C, Gao F. Diabetes mellitus and the incidence and mortality of colorectal cancer: a meta-analysis of 24 cohort studies. *Colorectal Dis* 2012;14:1307-1312. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23046351>.

64. Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. *PLoS One* 2013;8:e53916. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23349764>.

65. Magalhaes B, Peleteiro B, Lunet N. Dietary patterns and colorectal cancer: systematic review and meta-analysis. *Eur J Cancer Prev* 2012;21:15-23. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21946864>.

66. Moore SC, Lee IM, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med* 2016;176:816-825. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/27183032>.

67. Parajuli R, Bjerkaas E, Tverdal A, et al. The increased risk of colon cancer due to cigarette smoking may be greater in women than men. *Cancer Epidemiol Biomarkers Prev* 2013;22:862-871. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23632818>.

68. Schmid D, Leitzmann MF. Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. *J Natl Cancer Inst* 2014;106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24935969>.

69. Shen D, Mao W, Liu T, et al. Sedentary behavior and incident cancer: a meta-analysis of prospective studies. *PLoS One* 2014;9:e105709. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25153314>.

70. Vieira AR, Abar L, Chan DSM, et al. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. *Ann Oncol* 2017;28:1788-1802. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28407090>.

71. Aleksandrova K, Pischon T, Jenab M, et al. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. *BMC Med* 2014;12:168. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25319089>.

72. Song M, Giovannucci E. Preventable incidence and mortality of carcinoma associated with lifestyle factors among white adults in the United States. *JAMA Oncol* 2016;2:1154-1161. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/27196525>.

73. Kohler LN, Garcia DO, Harris RB, et al. Adherence to diet and physical activity cancer prevention guidelines and cancer outcomes: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2016;25:1018-1028. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27340121>.

74. Keum N, Aune D, Greenwood DC, et al. Calcium intake and colorectal cancer risk: dose-response meta-analysis of prospective observational studies. *Int J Cancer* 2014;135:1940-1948. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24623471>.

75. Murphy N, Norat T, Ferrari P, et al. Consumption of dairy products and colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *PLoS One* 2013;8:e72715. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24023767>.

76. Ralston RA, Truby H, Palermo CE, Walker KZ. Colorectal cancer and nonfermented milk, solid cheese, and fermented milk consumption: a systematic review and meta-analysis of prospective studies. *Crit Rev Food Sci Nutr* 2014;54:1167-1179. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24499149>.



77. Orlich MJ, Singh PN, Sabate J, et al. Vegetarian dietary patterns and the risk of colorectal cancers. *JAMA Intern Med* 2015;175:767-776. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25751512>.

78. Yu XF, Zou J, Dong J. Fish consumption and risk of gastrointestinal cancers: a meta-analysis of cohort studies. *World J Gastroenterol* 2014;20:15398-15412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25386090>.

79. Zhu B, Sun Y, Qi L, et al. Dietary legume consumption reduces risk of colorectal cancer: evidence from a meta-analysis of cohort studies. *Sci Rep* 2015;5:8797. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25739376>.

80. Cao Y, Nishihara R, Wu K, et al. Population-wide impact of long-term use of aspirin and the risk for cancer. *JAMA Oncol* 2016;2:762-769. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26940135>.

81. Chan AT, Giovannucci EL, Meyerhardt JA, et al. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA* 2005;294:914-923. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16118381>.

82. Flossmann E, Rothwell PM, British Doctors Aspirin T, the UKTIAAT. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 2007;369:1603-1613. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17499602>.

83. Friis S, Poulsen AH, Sorensen HT, et al. Aspirin and other non-steroidal anti-inflammatory drugs and risk of colorectal cancer: a Danish cohort study. *Cancer Causes Control* 2009;20:731-740. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19122977>.

84. Friis S, Riis AH, Erichsen R, et al. Low-dose aspirin or nonsteroidal anti-inflammatory drug use and colorectal cancer risk: a population-based, case-control study. *Ann Intern Med* 2015;163:347-355. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26302241>.

85. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet* 2010;376:1741-1750. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20970847>.

86. Bibbins-Domingo K, Force USPST. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2016;164:836-845. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27064677>.

87. McCullough ML, Gapstur SM, Shah R, et al. Association between red and processed meat intake and mortality among colorectal cancer survivors. *J Clin Oncol* 2013;31:2773-2782. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23816965>.

88. Phipps AI, Shi Q, Newcomb PA, et al. Associations between cigarette smoking status and colon cancer prognosis among participants in North Central Cancer Treatment group phase III trial N0147. *J Clin Oncol* 2013;31:2016-2023. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23547084>.

89. Sinicrope FA, Foster NR, Yoon HH, et al. Association of obesity with DNA mismatch repair status and clinical outcome in patients with stage II or III colon carcinoma participating in NCCTG and NSABP adjuvant chemotherapy trials. *J Clin Oncol* 2012;30:406-412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22203756>.

90. Walter V, Jansen L, Hoffmeister M, Brenner H. Smoking and survival of colorectal cancer patients: systematic review and meta-analysis. *Ann Oncol* 2014;25:1517-1525. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24692581>.

91. Yang B, Jacobs EJ, Gapstur SM, et al. Active smoking and mortality among colorectal cancer survivors: the Cancer Prevention Study II nutrition cohort. *J Clin Oncol* 2015;33:885-893. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25646196>.



92. Song M, Zhang X, Meyerhardt JA, et al. Marine omega-3 polyunsaturated fatty acid intake and survival after colorectal cancer diagnosis. *Gut* 2016;66:1790-1796. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27436272>.

93. Morris EJ, Penegar S, Whitehouse LE, et al. A retrospective observational study of the relationship between family history and survival from colorectal cancer. *Br J Cancer* 2013;108:1502-1507. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23511565>.

94. Dik VK, Murphy N, Siersema PD, et al. Prediagnostic intake of dairy products and dietary calcium and colorectal cancer survival-results from the EPIC cohort study. *Cancer Epidemiol Biomarkers Prev* 2014;23:1813-1823. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24917183>.

95. Yang B, McCullough ML, Gapstur SM, et al. Calcium, vitamin D, dairy products, and mortality among colorectal cancer survivors: the Cancer Prevention Study-II Nutrition cohort. *J Clin Oncol* 2014;32:2335-2343. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24958826>.

96. Bu WJ, Song L, Zhao DY, et al. Insulin therapy and the risk of colorectal cancer in patients with type 2 diabetes: a meta-analysis of observational studies. *Br J Clin Pharmacol* 2014;78:301-309. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25099257>.

97. Cardel M, Jensen SM, Pottegard A, et al. Long-term use of metformin and colorectal cancer risk in type II diabetics: a population-based case-control study. *Cancer Med* 2014;3:1458-1466. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25091592>.

98. Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. *World J Gastroenterol* 2015;21:6026-6031. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26019469>.

99. Karlstad O, Starup-Linde J, Vestergaard P, et al. Use of insulin and insulin analogs and risk of cancer - systematic review and meta-analysis of observational studies. *Curr Drug Saf* 2013;8:333-348. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24215311>.

100. Rokkas T, Portincasa P. Colon neoplasia in patients with type 2 diabetes on metformin: A meta-analysis. *Eur J Intern Med* 2016;33:60-66. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27318643>.

101. Sehdev A, Shih YC, Vekhter B, et al. Metformin for primary colorectal cancer prevention in patients with diabetes: a case-control study in a US population. *Cancer* 2015;121:1071-1078. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25424411>.

102. Singh S, Singh H, Singh PP, et al. Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2013;22:2258-2268. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24042261>.

103. Zhang ZJ, Li S. The prognostic value of metformin for cancer patients with concurrent diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2014;16:707-710. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24460896>.

104. He XK, Su TT, Si JM, Sun LM. Metformin is associated with slightly reduced risk of colorectal cancer and moderate survival benefits in diabetes mellitus: A meta-analysis. *Medicine (Baltimore)* 2016;95:e2749. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26886616>.

105. Nie Z, Zhu H, Gu M. Reduced colorectal cancer incidence in type 2 diabetic patients treated with metformin: a meta-analysis. *Pharm Biol* 2016;54:2636-2642. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27159666>.

106. Higurashi T, Hosono K, Takahashi H, et al. Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicentre double-blind, placebo-controlled, randomised phase 3 trial. *Lancet Oncol* 2016;17:475-483. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26947328>.

107. Mills KT, Bellows CF, Hoffman AE, et al. Diabetes mellitus and colorectal cancer prognosis: a meta-analysis. *Dis Colon Rectum*



2013;56:1304-1319. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24105007>.

108. Zhu B, Wu X, Wu B, et al. The relationship between diabetes and colorectal cancer prognosis: A meta-analysis based on the cohort studies. PLoS One 2017;12:e0176068. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28423026>.

109. Mei ZB, Zhang ZJ, Liu CY, et al. Survival benefits of metformin for colorectal cancer patients with diabetes: a systematic review and meta-analysis. PLoS One 2014;9:e91818. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24647047>.

110. Meng F, Song L, Wang W. Metformin improves overall survival of colorectal cancer patients with diabetes: A meta-analysis. J Diabetes Res 2017;2017:5063239. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28271076>.

111. Kowall B, Stang A, Rathmann W, Kostev K. No reduced risk of overall, colorectal, lung, breast, and prostate cancer with metformin therapy in diabetic patients: database analyses from Germany and the UK. Pharmacoepidemiol Drug Saf 2015;24:865-874. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26132313>.

112. Zanders MM, van Herk-Sukel MP, Vissers PA, et al. Are metformin, statin and aspirin use still associated with overall mortality among colorectal cancer patients with diabetes if adjusted for one another? Br J Cancer 2015;113:403-410. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26180924>.

113. Hari DM, Leung AM, Lee JH, et al. AJCC Cancer Staging Manual 7th edition criteria for colon cancer: do the complex modifications improve prognostic assessment? J Am Coll Surg 2013;217:181-190. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23768788>.

114. Chu QD, Zhou M, Medeiros K, Peddi P. Positive surgical margins contribute to the survival paradox between patients with stage IIB/C (T4N0) and stage IIIA (T1-2N1, T1N2a) colon cancer. Surgery

2016;160:1333-1343. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/27425043>.

115. Kim MJ, Jeong SY, Choi SJ, et al. Survival paradox between stage IIB/C (T4N0) and stage IIIA (T1-2N1) colon cancer. Ann Surg Oncol 2015;22:505-512. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25145501>.

116. Gunderson LL, Jessup JM, Sargent DJ, et al. Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol 2010;28:264-271. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19949014>.

117. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. J Clin Oncol 2012;30:263-267. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22162570>.

118. Compton CC. Updated protocol for the examination of specimens from patients with carcinomas of the colon and rectum, excluding carcinoid tumors, lymphomas, sarcomas, and tumors of the vermiform appendix: a basis for checklists. Cancer Committee. Arch Pathol Lab Med 2000;124:1016-1025. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10888778>.

119. Compton CC, Greene FL. The staging of colorectal cancer: 2004 and beyond. CA Cancer J Clin 2004;54:295-308. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15537574>.

120. Compton CC, Fielding LP, Burgart LJ, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000;124:979-994. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10888773>.

121. Nissan A, Stojadinovic A, Shia J, et al. Predictors of recurrence in patients with T2 and early T3, N0 adenocarcinoma of the rectum treated by surgery alone. J Clin Oncol 2006;24:4078-4084. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16943525>.



122. Fujita S, Shimoda T, Yoshimura K, et al. Prospective evaluation of prognostic factors in patients with colorectal cancer undergoing curative resection. *J Surg Oncol* 2003;84:127-131. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14598355>.

123. Liebig C, Ayala G, Wilks J, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. *J Clin Oncol* 2009;27:5131-5137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19738119>.

124. Quah HM, Chou JF, Gonen M, et al. Identification of patients with high-risk stage II colon cancer for adjuvant therapy. *Dis Colon Rectum* 2008;51:503-507. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18322753>.

125. Lo DS, Pollett A, Siu LL, et al. Prognostic significance of mesenteric tumor nodules in patients with stage III colorectal cancer. *Cancer* 2008;112:50-54. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18008365>.

126. Ueno H, Mochizuki H, Hashiguchi Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. *Am J Clin Pathol* 2007;127:287-294. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17210518>.

127. Birbeck KF, Macklin CP, Tiffin NJ, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg* 2002;235:449-457. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11923599>.

128. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol* 2003;21:2912-2919. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12885809>.

129. Bilimoria KY, Palis B, Stewart AK, et al. Impact of tumor location on nodal evaluation for colon cancer. *Dis Colon Rectum* 2008;51:154-161. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18172729>.

130. Lykke J, Roikjaer O, Jess P. The relation between lymph node status and survival in Stage I-III colon cancer: results from a prospective nationwide cohort study. *Colorectal Dis* 2013;15:559-565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23061638>.

131. Budde CN, Tsikitis VL, Deveney KE, et al. Increasing the number of lymph nodes examined after colectomy does not improve colon cancer staging. *J Am Coll Surg* 2014;218:1004-1011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24661856>.

132. Parsons HM, Tuttle TM, Kuntz KM, et al. Association between lymph node evaluation for colon cancer and node positivity over the past 20 years. *JAMA* 2011;306:1089-1097. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21917579>.

133. Storli K, Sondenaa K, Furnes B, et al. Improved lymph node harvest from resected colon cancer specimens did not cause upstaging from TNM stage II to III. *World J Surg* 2011;35:2796-2803. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21879420>.

134. Wong SL, Ji H, Hollenbeck BK, et al. Hospital lymph node examination rates and survival after resection for colon cancer. *JAMA* 2007;298:2149-2154. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18000198>.

135. Nedrebo BS, Soreide K, Nesbakken A, et al. Risk factors associated with poor lymph node harvest after colon cancer surgery in a national cohort. *Colorectal Dis* 2013;15:e301-308. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23582027>.

136. Sarli L, Bader G, Iusco D, et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. *Eur J Cancer* 2005;41:272-279. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15661553>.

137. Wong SL. Lymph node evaluation in colon cancer: assessing the link between quality indicators and quality. *JAMA* 2011;306:1139-1141. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21917585>.



138. Belt EJ, te Velde EA, Krijgsman O, et al. High lymph node yield is related to microsatellite instability in colon cancer. *Ann Surg Oncol* 2012;19:1222-1230. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21989661>.

139. Berg M, Guriby M, Nordgard O, et al. Influence of microsatellite instability, KRAS and BRAF mutations on lymph node harvest in stage I-III colon cancers. *Mol Med* 2013;19:286-293. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23979710>.

140. Kakar S, Shi C, Berho ME, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. College of American Pathologists 2017. Available at: <http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folgers/WebContent/pdf/cp-gilower-colonrectum-17protocol-4010.pdf>.

141. Gonen M, Schrag D, Weiser MR. Nodal staging score: a tool to assess adequate staging of node-negative colon cancer. *J Clin Oncol* 2009;27:6166-6171. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19901106>.

142. Gill S, Haince JF, Shi Q, et al. Prognostic value of molecular detection of lymph node metastases after curative resection of stage II colon cancer: a systematic pooled data analysis. *Clin Colorectal Cancer* 2015;14:99-105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25619805>.

143. Ramos-Esquivel A, Juarez M, Gonzalez I, et al. Prognosis impact of the lymph node ratio in patients with colon adenocarcinoma: a single-centre experience. *J Gastrointest Cancer* 2014;45:133-136. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24382601>.

144. Sabbagh C, Mauvais F, Cosse C, et al. A lymph node ratio of 10% is predictive of survival in stage III colon cancer: a French regional study. *Int Surg* 2014;99:344-353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25058763>.

145. Sugimoto K, Sakamoto K, Tomiki Y, et al. Proposal of new classification for stage III colon cancer based on the lymph node ratio:

analysis of 4,172 patients from multi-institutional database in Japan. *Ann Surg Oncol* 2015;22:528-534. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25160735>.

146. Zhang MR, Xie TH, Chi JL, et al. Prognostic role of the lymph node ratio in node positive colorectal cancer: a meta-analysis. *Oncotarget* 2016;7:72898-72907. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27662659>.

147. Gleisner AL, Mogal H, Dodson R, et al. Nodal status, number of lymph nodes examined, and lymph node ratio: what defines prognosis after resection of colon adenocarcinoma? *J Am Coll Surg* 2013;217:1090-1100. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24045143>.

148. Redston M, Compton CC, Miedema BW, et al. Analysis of micrometastatic disease in sentinel lymph nodes from resectable colon cancer: results of Cancer and Leukemia Group B Trial 80001. *J Clin Oncol* 2006;24:878-883. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16418493>.

149. Bertagnolli M, Miedema B, Redston M, et al. Sentinel node staging of resectable colon cancer: results of a multicenter study. *Ann Surg* 2004;240:624-628. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15383790>.

150. Saha S, Dan AG, Beutler T, et al. Sentinel lymph node mapping technique in colon cancer. *Semin Oncol* 2004;31:374-381. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15190495>.

151. Turner RR, Nora DT, Trocha SD, Bilchik AJ. Colorectal carcinoma nodal staging. Frequency and nature of cytokeratin-positive cells in sentinel and nonsentinel lymph nodes. *Arch Pathol Lab Med* 2003;127:673-679. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12741889>.

152. Wiese DA, Saha S, Badin J, et al. Pathologic evaluation of sentinel lymph nodes in colorectal carcinoma. *Arch Pathol Lab Med* 2000;124:1759-1763. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11100053>.



153. Wood TF, Nora DT, Morton DL, et al. One hundred consecutive cases of sentinel lymph node mapping in early colorectal carcinoma: detection of missed micrometastases. *J Gastrointest Surg* 2002;6:322-329; discussion 229-330. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12022982>.

154. Noura S, Yamamoto H, Miyake Y, et al. Immunohistochemical assessment of localization and frequency of micrometastases in lymph nodes of colorectal cancer. *Clin Cancer Res* 2002;8:759-767. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11895906>.

155. Noura S, Yamamoto H, Ohnishi T, et al. Comparative detection of lymph node micrometastases of stage II colorectal cancer by reverse transcriptase polymerase chain reaction and immunohistochemistry. *J Clin Oncol* 2002;20:4232-4241. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12377967>.

156. Yasuda K, Adachi Y, Shiraishi N, et al. Pattern of lymph node micrometastasis and prognosis of patients with colorectal cancer. *Ann Surg Oncol* 2001;8:300-304. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11352302>.

157. Protic M, Stojadinovic A, Nissan A, et al. Prognostic effect of ultra-staging node-negative colon cancer without adjuvant chemotherapy: a prospective National Cancer Institute-sponsored clinical trial. *J Am Coll Surg* 2015;221:643-651; quiz 783-645. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26213360>.

158. Mescoli C, Albertoni L, Pucciarelli S, et al. Isolated tumor cells in regional lymph nodes as relapse predictors in stage I and II colorectal cancer. *J Clin Oncol* 2012;30:965-971. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22355061>.

159. Rahbari NN, Bork U, Motschall E, et al. Molecular detection of tumor cells in regional lymph nodes is associated with disease recurrence and poor survival in node-negative colorectal cancer: a systematic review and meta-analysis. *J Clin Oncol* 2012;30:60-70. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22124103>.

160. Sloothak DA, Sahami S, van der Zaag-Loonen HJ, et al. The prognostic value of micrometastases and isolated tumour cells in histologically negative lymph nodes of patients with colorectal cancer: a systematic review and meta-analysis. *Eur J Surg Oncol* 2014;40:263-269. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24368050>.

161. Goldstein NS, Turner JR. Pericolonic tumor deposits in patients with T3N+MO colon adenocarcinomas: markers of reduced disease free survival and intra-abdominal metastases and their implications for TNM classification. *Cancer* 2000;88:2228-2238. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10820343>.

162. Puppa G, Maisonneuve P, Sonzogni A, et al. Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging. *Mod Pathol* 2007;20:843-855. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17491597>.

163. Mayo E, Llanos AA, Yi X, et al. Prognostic value of tumour deposit and perineural invasion status in colorectal cancer patients: a SEER-based population study. *Histopathology* 2016;69:230-238. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26802566>.

164. Ueno H, Mochizuki H. Clinical significance of extrabowel skipped cancer infiltration in rectal cancer. *Surg Today* 1997;27:617-622. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9306563>.

165. Al-Sukhni E, Attwood K, Gabriel EM, et al. Lymphovascular and perineural invasion are associated with poor prognostic features and outcomes in colorectal cancer: A retrospective cohort study. *Int J Surg* 2016;37:42-49. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27600906>.

166. Knijn N, Mogk SC, Teerenstra S, et al. Perineural invasion is a strong prognostic factor in colorectal cancer: a systematic review. *Am J Surg Pathol* 2016;40:103-112. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26426380>.

167. Yang Y, Huang X, Sun J, et al. Prognostic value of perineural invasion in colorectal cancer: a meta-analysis. *J Gastrointest Surg*



2015;19:1113-1122. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25663635>.

168. Yun JA, Kim HC, Kim SH, et al. Prognostic significance of perineural invasion in stage IIA colon cancer. ANZ J Surg 2014;86:1007-1013.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25113398>.

169. Lugli A, Kirsch R, Ajioka Y, et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol 2017;30:1299-1311. Available at:

<https://pubmed.ncbi.nlm.nih.gov/28548122/>.

170. Pai RK, Cheng YW, Jakubowski MA, et al. Colorectal carcinomas with submucosal invasion (pT1): analysis of histopathological and molecular factors predicting lymph node metastasis. Mod Pathol 2017;30:113-122. Available at:

<https://pubmed.ncbi.nlm.nih.gov/27713420/>.

171. Koelzer VH, Zlobec I, Lugli A. Tumor budding in colorectal cancer--ready for diagnostic practice? Hum Pathol 2016;47:4-19. Available at:

<https://pubmed.ncbi.nlm.nih.gov/26476568/>.

172. Bosch SL, Teerenstra S, de Wilt JH, et al. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy 2013;45:827-834.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23884793>.

173. Backes Y, Elias SG, Groen JN, et al. Histologic Factors Associated With Need for Surgery in Patients With Pedunculated T1 Colorectal Carcinomas. Gastroenterology 2018;154:1647-1659. Available at:

<https://pubmed.ncbi.nlm.nih.gov/29366842/>.

174. Brown IS, Bettington ML, Bettington A, et al. Adverse histological features in malignant colorectal polyps: a contemporary series of 239 cases. J Clin Pathol 2016;69:292-299. Available at:

<https://pubmed.ncbi.nlm.nih.gov/26424814/>.

175. Lee VWK, Chan KF. Tumor budding and poorly-differentiated cluster in prognostication in Stage II colon cancer. Pathol Res Pract 2018;214:402-407. Available at:

<https://pubmed.ncbi.nlm.nih.gov/29487008/>.

176. Romiti A, Roberto M, Marchetti P, et al. Study of histopathologic parameters to define the prognosis of stage II colon cancer. Int J Colorectal Dis 2019;34:905-913. Available at:

<https://pubmed.ncbi.nlm.nih.gov/30915540/>.

177. Farquharson AL, Pranesh N, Witham G, et al. A phase II study evaluating the use of concurrent mitomycin C and capecitabine in patients with advanced unresectable pseudomyxoma peritonei. Br J Cancer 2008;99:591-596. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18682713>.

178. Lieu CH, Lambert LA, Wolff RA, et al. Systemic chemotherapy and surgical cytoreduction for poorly differentiated and signet ring cell adenocarcinomas of the appendix. Ann Oncol 2012;23:652-658. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21653683>.

179. Shapiro JF, Chase JL, Wolff RA, et al. Modern systemic chemotherapy in surgically unresectable neoplasms of appendiceal origin: a single-institution experience. Cancer 2010;116:316-322. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19904805>.

180. Tejani MA, Ter Veer A, Milne D, et al. Systemic therapy for advanced appendiceal adenocarcinoma: an analysis from the NCCN Oncology Outcomes Database for Colorectal Cancer. J Natl Compr Canc Netw 2014;12:1123-1130. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25099444>.

181. Cooper HS, Deppisch LM, Gourley WK, et al. Endoscopically removed malignant colorectal polyps: clinicopathologic correlations. Gastroenterology 1995;108:1657-1665. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/7768369>.



182. Markowitz AJ, Winawer SJ. Management of colorectal polyps. CA Cancer J Clin 1997;47:93-9112. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9074488>.

183. Yoshii S, Nojima M, Nosho K, et al. Factors associated with risk for colorectal cancer recurrence after endoscopic resection of T1 tumors. Clin Gastroenterol Hepatol 2014;12:292-302 e293. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23962552>.

184. Cooper HS. Surgical pathology of endoscopically removed malignant polyps of the colon and rectum. Am J Surg Pathol 1983;7:613-623. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6638257>.

185. Cooper HS. Pathologic issues in the treatment of endoscopically removed malignant colorectal polyps. J Natl Compr Canc Netw 2007;5:991-996. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17977505>.

186. Hassan C, Zullo A, Risio M, et al. Histologic risk factors and clinical outcome in colorectal malignant polyp: a pooled-data analysis. Dis Colon Rectum 2005;48:1588-1596. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15937622>.

187. Belderbos TD, Leenders M, Moons LM, Siersema PD. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. Endoscopy 2014;46:388-402. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24671869>.

188. Cranley JP, Petras RE, Carey WD, et al. When is endoscopic polypectomy adequate therapy for colonic polyps containing invasive carcinoma? Gastroenterology 1986;91:419-427. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3721127>.

189. Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology 1985;89:328-336. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/4007423>.

190. Ota DM, Nelson H, Weeks JC. Controversies regarding laparoscopic colectomy for malignant diseases. Curr Opin Gen Surg 1994;208-213. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7583971>.

191. Mou S, Soetikno R, Shimoda T, et al. Pathologic predictive factors for lymph node metastasis in submucosal invasive (T1) colorectal cancer: a systematic review and meta-analysis. Surg Endosc 2013;27:2692-2703. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23392988>.

192. Seitz U, Bohnacker S, Seewald S, et al. Is endoscopic polypectomy an adequate therapy for malignant colorectal adenomas? Presentation of 114 patients and review of the literature. Dis Colon Rectum 2004;47:1789-1796. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15622570>.

193. Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology 2004;127:385-394. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15300569>.

194. Volk EE, Goldblum JR, Petras RE, et al. Management and outcome of patients with invasive carcinoma arising in colorectal polyps. Gastroenterology 1995;109:1801-1807. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7498644>.

195. Choi JY, Jung SA, Shim KN, et al. Meta-analysis of predictive clinicopathologic factors for lymph node metastasis in patients with early colorectal carcinoma. J Korean Med Sci 2015;30:398-406. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25829807>.

196. Choi DH, Sohn DK, Chang HJ, et al. Indications for subsequent surgery after endoscopic resection of submucosally invasive colorectal carcinomas: a prospective cohort study. Dis Colon Rectum 2009;52:438-445. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19333043>.

197. Park KJ, Choi HJ, Roh MS, et al. Intensity of tumor budding and its prognostic implications in invasive colon carcinoma. Dis Colon Rectum 2005;48:1597-1602. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15937624>.



198. Rogers AC, Winter DC, Heeney A, et al. Systematic review and meta-analysis of the impact of tumour budding in colorectal cancer. *Br J Cancer* 2016;115:831-840. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27599041>.

199. Balthazar EJ, Megibow AJ, Hulnick D, Naidich DP. Carcinoma of the colon: detection and preoperative staging by CT. *AJR Am J Roentgenol* 1988;150:301-306. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3257314>.

200. Choi DJ, Kwak JM, Kim J, et al. Preoperative chest computerized tomography in patients with locally advanced mid or lower rectal cancer: its role in staging and impact on treatment strategy. *J Surg Oncol* 2010;102:588-592. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20607759>.

201. Grossmann I, Avenarius JK, Mastboom WJ, Klaase JM. Preoperative staging with chest CT in patients with colorectal carcinoma: not as a routine procedure. *Ann Surg Oncol* 2010;17:2045-2050. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20151212>.

202. Qiu M, Hu J, Yang D, et al. Pattern of distant metastases in colorectal cancer: a SEER based study. *Oncotarget* 2015;6:38658-38666. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26484417>.

203. Onaitis MW, Petersen RP, Haney JC, et al. Prognostic factors for recurrence after pulmonary resection of colorectal cancer metastases. *Ann Thorac Surg* 2009;87:1684-1688. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19463577>.

204. Huang X, Lv B, Zhang S, Meng L. Preoperative colonic stents versus emergency surgery for acute left-sided malignant colonic obstruction: a meta-analysis. *J Gastrointest Surg* 2014;18:584-591. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24170606>.

205. Matsuda A, Miyashita M, Matsumoto S, et al. Comparison of long-term outcomes of colonic stent as "bridge to surgery" and emergency surgery for malignant large-bowel obstruction: a meta-analysis. *Ann Surg*

Oncol 2015;22:497-504. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25120255>.

206. Arezzo A, Balague C, Targarona E, et al. Colonic stenting as a bridge to surgery versus emergency surgery for malignant colonic obstruction: results of a multicentre randomised controlled trial (ESCO trial). *Surg Endosc* 2017;31:3297-3305. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27924392>.

207. Amelung FJ, Mulder CL, Verheijen PM, et al. Acute resection versus bridge to surgery with diverting colostomy for patients with acute malignant left sided colonic obstruction: Systematic review and meta-analysis. *Surg Oncol* 2015;24:313-321. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26690820>.

208. Chaudhri S, Brown L, Hassan I, Horgan AF. Preoperative intensive, community-based vs. traditional stoma education: a randomized, controlled trial. *Dis Colon Rectum* 2005;48:504-509. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15768181>.

209. Baykara ZG, Demir SG, Karadag A, et al. A multicenter, retrospective study to evaluate the effect of preoperative stoma site marking on stomal and peristomal complications. *Ostomy Wound Manage* 2014;60:16-26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24807019>.

210. Bass EM, Del Pino A, Tan A, et al. Does preoperative stoma marking and education by the enterostomal therapist affect outcome? *Dis Colon Rectum* 1997;40:440-442. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9106693>.

211. Cohen AM. Surgical considerations in patients with cancer of the colon and rectum. *Semin Oncol* 1991;18:381-387. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1713712>.

212. West NP, Hohenberger W, Weber K, et al. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. *J Clin Oncol* 2010;28:272-278. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19949013>.



213. Berger AC, Sigurdson ER, LeVoyer T, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. J Clin Oncol 2005;23:8706-8712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16314630>.

214. Madoff RD. Defining quality in colon cancer surgery. J Clin Oncol 2012;30:1738-1740. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22473171>.

215. West NP, Morris EJ, Rotimi O, et al. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. Lancet Oncol 2008;9:857-865. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18667357>.

216. West NP, Kobayashi H, Takahashi K, et al. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol 2012;30:1763-1769. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22473170>.

217. Bertelsen CA, Neuenschwander AU, Jansen JE, et al. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. Lancet Oncol 2015;16:161-168. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25555421>.

218. Kontovounisios C, Kinross J, Tan E, et al. Complete mesocolic excision in colorectal cancer: a systematic review. Colorectal Dis 2015;17:7-16. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25283236>.

219. Lee JK, Delaney CP, Lipman JM. Current state of the art in laparoscopic colorectal surgery for cancer: Update on the multi-centric international trials. Ann Surg Innov Res 2012;6:5. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22846394>.

220. Morneau M, Boulanger J, Charlebois P, et al. Laparoscopic versus open surgery for the treatment of colorectal cancer: a literature review and recommendations from the Comité de l'évolution des pratiques en

oncologie. Can J Surg 2013;56:297-310. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24067514>.

221. Theophilus M, Platell C, Spilsbury K. Long-term survival following laparoscopic and open colectomy for colon cancer: a meta-analysis of randomized controlled trials. Colorectal Dis 2014;16:O75-81. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24206016>.

222. Wang CL, Qu G, Xu HW. The short- and long-term outcomes of laparoscopic versus open surgery for colorectal cancer: a meta-analysis. Int J Colorectal Dis 2014;29:309-320. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24445673>.

223. Lacy AM, Garcia-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002;359:2224-2229. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12103285>.

224. Buunen M, Veldkamp R, Hop WCJ, et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. Lancet Oncol 2009;10:44-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19071061>.

225. Deijen CL, Vasmel JE, de Lange-de Klerk ESM, et al. Ten-year outcomes of a randomised trial of laparoscopic versus open surgery for colon cancer. Surg Endosc 2017;31:2607-2615. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27734203>.

226. Jayne DG, Guillou PJ, Thorpe H, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. J Clin Oncol 2007;25:3061-3068. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17634484>.

227. Green BL, Marshall HC, Collinson F, et al. Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg 2013;100:75-82. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23132548>.



NCCN Guidelines Version 1.2022

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228. Laparoscopically assisted colectomy is as safe and effective as open colectomy in people with colon cancer Abstracted from: Nelson H, Sargent D, Wieand HS, et al; for the Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004; 350: 2050-2059. *Cancer Treat Rev* 2004;30:707-709. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15541580>.

229. Fleshman J, Sargent DJ, Green E, et al. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. *Ann Surg* 2007;246:655-662. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17893502>.

230. Bagshaw PF, Allardyce RA, Frampton CM, et al. Long-term outcomes of the australasian randomized clinical trial comparing laparoscopic and conventional open surgical treatments for colon cancer: the Australasian Laparoscopic Colon Cancer Study trial. *Ann Surg* 2012;256:915-919. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23154392>.

231. Bonjer HJ, Hop WCJ, Nelson H, et al. Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. *Arch Surg* 2007;142:298-303. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17372057>.

232. Di B, Li Y, Wei K, et al. Laparoscopic versus open surgery for colon cancer: a meta-analysis of 5-year follow-up outcomes. *Surg Oncol* 2013;22:e39-43. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23643698>.

233. Jackson TD, Kaplan GG, Arena G, et al. Laparoscopic versus open resection for colorectal cancer: a metaanalysis of oncologic outcomes. *J Am Coll Surg* 2007;204:439-446. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17324779>.

234. Kuhry E, Schwenk W, Gaupset R, et al. Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials. *Cancer Treat Rev* 2008;34:498-504. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18468803>.

235. Ohtani H, Tamamori Y, Arimoto Y, et al. A meta-analysis of the short- and long-term results of randomized controlled trials that compared laparoscopy-assisted and open colectomy for colon cancer. *J Cancer* 2012;3:49-57. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22315650>.

236. Rondelli F, Trastulli S, Avenia N, et al. Is laparoscopic right colectomy more effective than open resection? A meta-analysis of randomized and nonrandomized studies. *Colorectal Dis* 2012;14:e447-469. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22540533>.

237. Kienle P, Weitz J, Koch M, Buchler MW. Laparoscopic surgery for colorectal cancer. *Colorectal Dis* 2006;8 Suppl 3:33-36. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16813591>.

238. Wagman LD. Laparoscopic and open surgery for colorectal cancer: reaching equipoise? *J Clin Oncol* 2007;25:2996-2998. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17634477>.

239. Kuhry E, Bonjer HJ, Haglind E, et al. Impact of hospital case volume on short-term outcome after laparoscopic operation for colonic cancer. *Surg Endosc* 2005;19:687-692. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15798899>.

240. Schipphorst AH, Verweij NM, Pronk A, et al. Non-surgical complications after laparoscopic and open surgery for colorectal cancer - A systematic review of randomised controlled trials. *Eur J Surg Oncol* 2015;41:1118-1127. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25980746>.

241. Zheng Z, Jemal A, Lin CC, et al. Comparative effectiveness of laparoscopy vs open colectomy among nonmetastatic colon cancer patients: an analysis using the National Cancer Data Base. *J Natl Cancer Inst* 2015;107. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25663688>.

242. Huscher CG, Bretagnol F, Corcione F. Laparoscopic colorectal cancer resection in high-volume surgical centers: long-term outcomes



NCCN Guidelines Version 1.2022

Colon Cancer

from the LAPCOLON group trial. World J Surg 2015;39:2045-2051. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25820910>.

243. Nelson G, Kiyang LN, Crumley ET, et al. Implementation of enhanced recovery after surgery (ERAS) across a provincial healthcare system: the ERAS Alberta colorectal surgery experience. World J Surg 2016;40:1092-1103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26928854>.

244. Varadhan KK, Lobo DN, Ljungqvist O. Enhanced recovery after surgery: the future of improving surgical care. Crit Care Clin 2010;26:527-547, x. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20643305>.

245. Kennedy RH, Francis EA, Wharton R, et al. Multicenter randomized controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme: EnROL. J Clin Oncol 2014;32:1804-1811. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24799480>.

246. Chang YS, Wang JX, Chang DW. A meta-analysis of robotic versus laparoscopic colectomy. J Surg Res 2015;195:465-474. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25770742>.

247. Lim S, Kim JH, Baek SJ, et al. Comparison of perioperative and short-term outcomes between robotic and conventional laparoscopic surgery for colonic cancer: a systematic review and meta-analysis. Ann Surg Treat Res 2016;90:328-339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27274509>.

248. Trastulli S, Cirocchi R, Desiderio J, et al. Robotic versus laparoscopic approach in colonic resections for cancer and benign diseases: systematic review and meta-analysis. PLoS One 2015;10:e0134062. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26214845>.

249. Zarak A, Castillo A, Kichler K, et al. Robotic versus laparoscopic surgery for colonic disease: a meta-analysis of postoperative variables. Surg Endosc 2015;29:1341-1347. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25847139>.

250. Nelson H, Weeks JC, Wieand HS. Proposed phase III trial comparing laparoscopic-assisted colectomy versus open colectomy for colon cancer. J Natl Cancer Inst Monogr 1995;51-56. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7577206>.

251. Wishner JD, Baker JW, Hoffman GC, et al. Laparoscopic-assisted colectomy. The learning curve. Surg Endosc 1995;9:1179-1183. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8553229>.

252. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-2351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15175436>.

253. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109-3116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19451431>.

254. Andre T, de Gramont A, Vernerey D, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. J Clin Oncol 2015;33:4176-4187. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26527776>.

255. Benson AB, 3rd, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;22:3408-3419. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15199089>.

256. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 2011;29:1465-1471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21383294>.

257. Schmoll HJ, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol 2007;25:102-109. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17194911>.



258. Grothey A, Sobrero AF, Shields AF, et al. Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. *N Engl J Med* 2018;378:1177-1188. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29590544>.

259. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005;352:2696-2704. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15987918>.

260. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. *Lancet* 1995;345:939-944. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7715291>.

261. Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. *GERCOR. Eur J Cancer* 1999;35:1343-1347. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10658525>.

262. Haller DG, Catalano PJ, Macdonald JS, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. *J Clin Oncol* 2005;23:8671-8678. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16314627>.

263. Wolmark N, Rockette H, Mamounas E, et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. *J Clin Oncol* 1999;17:3553-3559. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10550154>.

264. Boland GM, Chang GJ, Haynes AB, et al. Association between adherence to National Comprehensive Cancer Network treatment guidelines and improved survival in patients with colon cancer. *Cancer* 2013;119:1593-1601. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23280510>.

265. Booth CM, Nanji S, Wei X, et al. Use and effectiveness of adjuvant chemotherapy for stage III colon cancer: a population-based study. *J Natl*

Compr Canc Netw 2016;14:47-56. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26733554>.

266. Hines RB, Barrett A, Twumasi-Ankrah P, et al. Predictors of guideline treatment nonadherence and the impact on survival in patients with colorectal cancer. *J Natl Compr Canc Netw* 2015;13:51-60. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25583769>.

267. Sargent DJ, Wieand HS, Haller DG, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. *J Clin Oncol* 2005;23:8664-8670. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16260700>.

268. Sargent D, Sobrero A, Grothey A, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. *J Clin Oncol* 2009;27:872-877. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19124803>.

269. de Gramont A, Hubbard J, Shi Q, et al. Association between disease-free survival and overall survival when survival is prolonged after recurrence in patients receiving cytotoxic adjuvant therapy for colon cancer: simulations based on the 20,800 patient ACCENT data set. *J Clin Oncol* 2010;28:460-465. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20008641>.

270. Sargent D, Shi Q, Yothers G, et al. Two or three year disease-free survival (DFS) as a primary end-point in stage III adjuvant colon cancer trials with fluoropyrimidines with or without oxaliplatin or irinotecan: Data from 12,676 patients from MOSAIC, X-ACT, PETACC-3, C-06, C-07 and C89803. *Eur J Cancer* 2011;47:990-996. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21257306>.

271. Bockelman C, Engelmann BE, Kaprio T, et al. Risk of recurrence in patients with colon cancer stage II and III: a systematic review and meta-analysis of recent literature. *Acta Oncol* 2015;54:5-16. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25430983>.



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272. Gray R, Barnwell J, McConkey C, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007;370:2020-2029. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18083404>.

273. Hutchins G, Southward K, Handley K, et al. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. *J Clin Oncol* 2011;29:1261-1270. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21383284>.

274. Tournigand C, Andre T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. *J Clin Oncol* 2012;30:3353-3360. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22915656>.

275. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 2011;29:3768-3774. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21859995>.

276. Casadaban L, Rauscher G, Aklilu M, et al. Adjuvant chemotherapy is associated with improved survival in patients with stage II colon cancer. *Cancer* 2016;122:3277-3287. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27417445>.

277. Schrag D, Rifas-Shiman S, Saltz L, et al. Adjuvant chemotherapy use for Medicare beneficiaries with stage II colon cancer. *J Clin Oncol* 2002;20:3999-4005. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12351597>.

278. Verhoeff SR, van Erning FN, Lemmens VE, et al. Adjuvant chemotherapy is not associated with improved survival for all high-risk factors in stage II colon cancer. *Int J Cancer* 2016;139:187-193. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26914273>.

279. Pahlman LA, Hohenberger WM, Matzel K, et al. Should the benefit of adjuvant chemotherapy in colon cancer be re-evaluated? *J Clin Oncol*

2016;34:1297-1299. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26903571>.

280. Sargent DJ, Andre T, Grothey A. Further evaluating the benefit of adjuvant chemotherapy for colon cancer. *J Clin Oncol* 2016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27528725>.

281. Benson AB, 3rd, Hamilton SR. Path toward prognostication and prediction: an evolving matrix. *J Clin Oncol* 2011;29:4599-4601. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22067398>.

282. Dalerba P, Sahoo D, Paik S, et al. CDX2 as a prognostic biomarker in stage II and stage III colon cancer. *N Engl J Med* 2016;374:211-222. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26789870>.

283. Tie J, Wang Y, Tomasetti C, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. *Sci Transl Med* 2016;8:346ra392. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27384348>.

284. Markowitz SD, Bertagnolli MM. Molecular origins of cancer: molecular basis of colorectal cancer. *N Engl J Med* 2009;361:2449-2460. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20018966>.

285. Kim GP, Colangelo LH, Wieand HS, et al. Prognostic and predictive roles of high-degree microsatellite instability in colon cancer: a National Cancer Institute-National Surgical Adjuvant Breast and Bowel Project Collaborative Study. *J Clin Oncol* 2007;25:767-772. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17228023>.

286. Halvarsson B, Anderson H, Domanska K, et al. Clinicopathologic factors identify sporadic mismatch repair-defective colon cancers. *Am J Clin Pathol* 2008;129:238-244. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18208804>.

287. Cunningham JM, Christensen ER, Tester DJ, et al. Hypermethylation of the hMLH1 promoter in colon cancer with microsatellite instability. *Cancer Res* 1998;58:3455-3460. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9699680>.



288. Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. *J Clin Oncol* 2010;28:466-474. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20008640>.

289. Koopman M, Kortman GAM, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. *Br J Cancer* 2009;100:266-273. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19165197>.

290. Klingbiel D, Saridaki Z, Roth AD, et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. *Ann Oncol* 2015;26:126-132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25361982>.

291. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 2003;349:247-257. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12867608>.

292. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol* 2010;28:3219-3226. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20498393>.

293. Sinicrope FA, Mahoney MR, Smyrk TC, et al. Prognostic impact of deficient DNA mismatch repair in patients with stage III colon cancer from a randomized trial of FOLFOX-based adjuvant chemotherapy. *J Clin Oncol* 2013;31:3664-3672. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24019539>.

294. Kim JE, Hong YS, Kim HJ, et al. Defective mismatch repair status was not associated with DFS and OS in stage II colon cancer treated with adjuvant chemotherapy. *Ann Surg Oncol* 2015;22 Suppl 3:S630-637. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26271397>.

295. Bertagnolli MM, Redston M, Compton CC, et al. Microsatellite instability and loss of heterozygosity at chromosomal location 18q: prospective evaluation of biomarkers for stages II and III colon cancer--a study of CALGB 9581 and 89803. *J Clin Oncol* 2011;29:3153-3162. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21747089>.

296. O'Connell MJ, Lavery I, Yothers G, et al. Relationship between tumor gene expression and recurrence in four independent studies of patients with stage II/III colon cancer treated with surgery alone or surgery plus adjuvant fluorouracil plus leucovorin. *J Clin Oncol* 2010;28:3937-3944. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20679606>.

297. Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. *J Clin Oncol* 2011;29:4611-4619. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22067390>.

298. Yothers G, O'Connell MJ, Lee M, et al. Validation of the 12-gene colon cancer recurrence score in NSABP C-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin. *J Clin Oncol* 2013;31:4512-4519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24220557>.

299. Venook AP, Niedzwiecki D, Lopatin M, et al. Biologic determinants of tumor recurrence in stage II colon cancer: validation study of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581. *J Clin Oncol* 2013;31:1775-1781. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23530100>.

300. Yamanaka T, Oki E, Yamazaki K, et al. 12-gene recurrence score assay stratifies the recurrence risk in stage II/III colon cancer with surgery alone: the SUNRISE study. *J Clin Oncol* 2016;34:2906-2913. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27325854>.

301. Salazar R, Roepman P, Capella G, et al. Gene expression signature to improve prognosis prediction of stage II and III colorectal cancer. *J Clin*



Oncol 2011;29:17-24. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21098318>.

302. Kopetz S, Tabernero J, Rosenberg R, et al. Genomic classifier ColoPrint predicts recurrence in stage II colorectal cancer patients more accurately than clinical factors. *Oncologist* 2015;20:127-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25561511>.

303. Kennedy RD, Bylesjo M, Kerr P, et al. Development and independent validation of a prognostic assay for stage II colon cancer using formalin-fixed paraffin-embedded tissue. *J Clin Oncol* 2011;29:4620-4626. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22067406>.

304. Niedzwiecki D, Frankel WL, Venook AP, et al. Association between results of a gene expression signature assay and recurrence-free interval in patients with stage II colon cancer in Cancer and Leukemia Group B 9581 (Alliance). *J Clin Oncol* 2016;34:3047-3053. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27432924>.

305. Mlecnik B, Bifulco C, Bindea G, et al. Multicenter International Society for Immunotherapy of Cancer Study of the Consensus Immunoscore for the Prediction of Survival and Response to Chemotherapy in Stage III Colon Cancer. *J Clin Oncol* 2020;JCO1903205. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32897827>.

306. Reinert T, Henriksen TV, Christensen E, et al. Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients With Stages I to III Colorectal Cancer. *JAMA Oncol* 2019;5:1124-1131. Available at: <https://pubmed.ncbi.nlm.nih.gov/31070691/>.

307. Tarazona N, Gimeno-Valiente F, Gambardella V, et al. Targeted next-generation sequencing of circulating-tumor DNA for tracking minimal residual disease in localized colon cancer. *Ann Oncol* 2019;30:1804-1812. Available at: <https://pubmed.ncbi.nlm.nih.gov/31562764/>.

308. Tie J, Cohen JD, Wang Y, et al. Circulating Tumor DNA Analyses as Markers of Recurrence Risk and Benefit of Adjuvant Therapy for Stage III Colon Cancer. *JAMA Oncol* 2019;5:1710-1717. Available at: <https://pubmed.ncbi.nlm.nih.gov/31621801/>.

309. Argiles G, Tabernero J, Labianca R, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020;31:1291-1305. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32702383>.

310. Sanoff HK, Carpenter WR, Sturmer T, et al. Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *J Clin Oncol* 2012;30:2624-2634. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22665536>.

311. Dotan E, Browner I, Hurria A, Denlinger C. Challenges in the management of older patients with colon cancer. *J Natl Compr Canc Netw* 2012;10:213-224; quiz 225. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22308516>.

312. McCleary NJ, Dotan E, Browner I. Refining the chemotherapy approach for older patients with colon cancer. *J Clin Oncol* 2014;32:2570-2580. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25071118>.

313. Muss HB, Bynum DL. Adjuvant chemotherapy in older patients with stage III colon cancer: an underused lifesaving treatment. *J Clin Oncol* 2012;30:2576-2578. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22665545>.

314. Hanna NN, Onukwugha E, Choti MA, et al. Comparative analysis of various prognostic nodal factors, adjuvant chemotherapy and survival among stage III colon cancer patients over 65 years: an analysis using surveillance, epidemiology and end results (SEER)-Medicare data. *Colorectal Dis* 2012;14:48-55. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21689262>.

315. McCleary NJ, Meyerhardt JA, Green E, et al. Impact of age on the efficacy of newer adjuvant therapies in patients with stage II/III colon cancer: findings from the ACCENT database. *J Clin Oncol* 2013;31:2600-2606. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23733765>.

316. Haller DG, O'Connell MJ, Cartwright TH, et al. Impact of age and medical comorbidity on adjuvant treatment outcomes for stage III colon cancer: a pooled analysis of individual patient data from four randomized,



controlled trials. *Ann Oncol* 2015;26:715-724. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25595934>.

317. Rosati G, Galli F, Lonardi S, et al. Oxaliplatin plus fluoropyrimidines as adjuvant therapy for colon cancer in elderly patients: A subgroup analysis from TOSCA trial [abstract]. *Annals of Oncology* 2020;31:S410-S411. Available at: <https://doi.org/10.1016/j.annonc.2020.08.510>.

318. Cheung WY, Renfro LA, Kerr D, et al. Determinants of early mortality among 37,568 patients with colon cancer who participated in 25 clinical trials from the Adjuvant Colon Cancer Endpoints Database. *J Clin Oncol* 2016;34:1182-1189. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26858337>.

319. Biagi JJ, Raphael MJ, Mackillop WJ, et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. *JAMA* 2011;305:2335-2342. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21642686>.

320. Sun Z, Adam MA, Kim J, et al. Determining the optimal timing for initiation of adjuvant chemotherapy after resection for stage II and III colon cancer. *Dis Colon Rectum* 2016;59:87-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26734965>.

321. Bos AC, van Erning FN, van Gestel YR, et al. Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer. *Eur J Cancer* 2015;51:2553-2561. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26360411>.

322. Sargent D, Grothey A, Gray R. Time to initiation of adjuvant chemotherapy and survival in colorectal cancer. *JAMA* 2011;306:1199; author reply 1200. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21934049>.

323. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group. *Lancet* 2000;355:1588-1596. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10821362>.

324. Jager E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. *J Clin Oncol* 1996;14:2274-2279. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8708717>.

325. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. A Mayo Clinic/North Central Cancer Treatment Group study. *Cancer* 1989;63:1026-1030. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2465076>.

326. Sanoff HK, Carpenter WR, Martin CF, et al. Comparative effectiveness of oxaliplatin vs non-oxaliplatin-containing adjuvant chemotherapy for stage III colon cancer. *J Natl Cancer Inst* 2012;104:211-227. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22266473>.

327. Sanoff HK, Carpenter WR, Freburger J, et al. Comparison of adverse events during 5-fluorouracil versus 5-fluorouracil/oxaliplatin adjuvant chemotherapy for stage III colon cancer: A population-based analysis. *Cancer* 2012;118:4309-4320. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22294436>.

328. Schmoll HJ, Twelves C, Sun W, et al. Effect of adjuvant capecitabine or fluorouracil, with or without oxaliplatin, on survival outcomes in stage III colon cancer and the effect of oxaliplatin on post-relapse survival: a pooled analysis of individual patient data from four randomised controlled trials. *Lancet Oncol* 2014;15:1481-1492. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25456367>.

329. Shah MA, Renfro LA, Allegra CJ, et al. Impact of patient factors on recurrence risk and time dependency of oxaliplatin benefit in patients with colon cancer: analysis from modern-era adjuvant studies in the Adjuvant Colon Cancer End Points (ACCENT) database. *J Clin Oncol* 2016;34:843-853. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26811529>.

330. Twelves C, Scheithauer W, McKendrick J, et al. Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary



evidence of a pharmacodynamic marker of efficacy. *Ann Oncol* 2012;23:1190-1197. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21896539>.

331. Schmoll HJ, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the NO16968 randomized controlled phase III trial. *J Clin Oncol* 2015;33:3733-3740. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26324362>.

332. Pectasides D, Karavasilis V, Papaxoinis G, et al. Randomized phase III clinical trial comparing the combination of capecitabine and oxaliplatin (CAPOX) with the combination of 5-fluorouracil, leucovorin and oxaliplatin (modified FOLFOX6) as adjuvant therapy in patients with operated high-risk stage II or stage III colorectal cancer. *BMC Cancer* 2015;15:384. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25956750>.

333. Sobrero AF, Andre T, Meyerhardt JA, et al. Overall survival (OS) and long-term disease-free survival (DFS) of three versus six months of adjuvant (adj) oxaliplatin and fluoropyrimidine-based therapy for patients (pts) with stage III colon cancer (CC): Final results from the IDEA (International Duration Evaluation of Adj chemotherapy) collaboration [abstract]. *Journal of Clinical Oncology* 2020;38:4004-4004. Available at:

https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.4004.

334. Iveson T, Sobrero AF, Yoshino T, et al. Prospective pooled analysis of four randomized trials investigating duration of adjuvant (adj) oxaliplatin-based therapy (3 vs 6 months {m}) for patients (pts) with high-risk stage II colorectal cancer (CC) [abstract]. *Journal of Clinical Oncology* 2019;37:3501-3501. Available at:

https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.3501.

335. Petrelli F, Labianca R, Zaniboni A, et al. Assessment of Duration and Effects of 3 vs 6 Months of Adjuvant Chemotherapy in High-Risk Stage II Colorectal Cancer: A Subgroup Analysis of the TOSCA Randomized Clinical Trial. *JAMA Oncol* 2020;6:547-551. Available at:

<https://pubmed.ncbi.nlm.nih.gov/32053133/>.

336. Souglakos J, Boukovinas I, Kakolyris S, et al. Three- versus six-month adjuvant FOLFOX or CAPOX for high-risk stage II and stage III colon cancer patients: the efficacy results of Hellenic Oncology Research Group (HORG) participation to the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) project. *Ann Oncol* 2019;30:1304-1310. Available at:

<https://pubmed.ncbi.nlm.nih.gov/31228203/>.

337. Yoshino T, Yamanaka T, Oki E, et al. Efficacy and Long-term Peripheral Sensory Neuropathy of 3 vs 6 Months of Oxaliplatin-Based Adjuvant Chemotherapy for Colon Cancer: The ACHIEVE Phase 3 Randomized Clinical Trial. *JAMA Oncol* 2019;5:1574-1581. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/31513248>.

338. Saltz LB, Niedzwiecki D, Hollis D, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. *J Clin Oncol* 2007;25:3456-3461. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17687149>.

339. Rothenberg ML, Meropol NJ, Poplin EA, et al. Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 2001;19:3801-3807. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11559717>.

340. Papadimitriou CA, Papakostas P, Karina M, et al. A randomized phase III trial of adjuvant chemotherapy with irinotecan, leucovorin and fluorouracil versus leucovorin and fluorouracil for stage II and III colon cancer: a Hellenic Cooperative Oncology Group study. *BMC Med* 2011;9:10. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21281463>.

341. Van Cutsem E, Labianca R, Bodoky G, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. *J Clin Oncol* 2009;27:3117-3125. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19451425>.

342. Ychou M, Raoul JL, Douillard JY, et al. A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon



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cancer (FNCLCC Accord02/FFCD9802). *Ann Oncol* 2009;20:674-680. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19179549>.

343. Allegra CJ, Yothers G, O'Connell MJ, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. *J Clin Oncol* 2011;29:11-16. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20940184>.

344. Allegra CJ, Yothers G, O'Connell MJ, et al. Bevacizumab in stage II-III colon cancer: 5-year update of the National Surgical Adjuvant Breast and Bowel Project C-08 trial. *J Clin Oncol* 2013;31:359-364. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23233715>.

345. de Gramont A, Van Cutsem E, Schmoll HJ, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. *Lancet Oncol* 2012;13:1225-1233. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23168362>.

346. Andre T, Vernerey D, Im SA, et al. Bevacizumab as adjuvant treatment of colon cancer: updated results from the S-AVANT phase III study by the GERCOR Group. *Ann Oncol* 2020;31:246-256. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31959341>.

347. Kerr RS, Love S, Segelov E, et al. Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial. *Lancet Oncol* 2016;17:1543-1557. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27660192>.

348. Alberts SR, Sargent DJ, Nair S, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. *JAMA* 2012;307:1383-1393. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22474202>.

349. Taieb J, Tabernero J, Mini E, et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial.

Lancet Oncol 2014;15:862-873. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24928083>.

350. Taieb J, Balogoun R, Le Malicot K, et al. Adjuvant FOLFOX +/- cetuximab in full RAS and BRAF wildtype stage III colon cancer patients. *Ann Oncol* 2017;28:824-830. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28031175>.

351. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol* 2007;25:2198-2204. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17470851>.

352. Ludmir EB, Arya R, Wu Y, et al. Role of Adjuvant Radiotherapy in Locally Advanced Colonic Carcinoma in the Modern Chemotherapy Era. *Ann Surg Oncol* 2016;23:856-862. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26480849>.

353. Cantero-Munoz P, Urien MA, Ruano-Ravina A. Efficacy and safety of intraoperative radiotherapy in colorectal cancer: A systematic review. *Cancer Lett* 2011;306:121-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21414718>.

354. Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: systematic review and meta-analysis of techniques, long-term outcomes, and complications. *Surg Oncol* 2013;22:22-35. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23270946>.

355. Hong TS, Ritter MA, Tome WA, Harari PM. Intensity-modulated radiation therapy: emerging cancer treatment technology. *Br J Cancer* 2005;92:1819-1824. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15856036>.

356. Bae BK, Kang MK, Kim JC, et al. Simultaneous integrated boost intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy in preoperative concurrent chemoradiotherapy for locally advanced rectal cancer. *Radiat Oncol J* 2017;35:208-216. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29037023>.



357. Foxtrot Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. *Lancet Oncol* 2012;13:1152-1160. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23017669>.

358. Seymour MT, Morton D, Investigators obotIFT. FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer [abstract]. *Journal of Clinical Oncology* 2019;37:3504-3504. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.3504.

359. Lee WS, Yun SH, Chun HK, et al. Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. *Int J Colorectal Dis* 2007;22:699-704. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17109105>.

360. Van Cutsem E, Nordlinger B, Adam R, et al. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur J Cancer* 2006;42:2212-2221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16904315>.

361. Yoo PS, Lopez-Soler RI, Longo WE, Cha CH. Liver resection for metastatic colorectal cancer in the age of neoadjuvant chemotherapy and bevacizumab. *Clin Colorectal Cancer* 2006;6:202-207. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17026789>.

362. Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005;23:9243-9249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16230673>.

363. Dawood O, Mahadevan A, Goodman KA. Stereotactic body radiation therapy for liver metastases. *Eur J Cancer* 2009;45:2947-2959. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19773153>.

364. Kemeny N. Management of liver metastases from colorectal cancer. *Oncology (Williston Park)* 2006;20:1161-1176, 1179; discussion 1179-

1180, 1185-1166. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17024869>.

365. Muratore A, Zorzi D, Bouzari H, et al. Asymptomatic colorectal cancer with un-resectable liver metastases: immediate colorectal resection or up-front systemic chemotherapy? *Ann Surg Oncol* 2007;14:766-770. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17103261>.

366. Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. *J Clin Oncol* 1997;15:938-946. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9060531>.

367. Hayashi M, Inoue Y, Komeda K, et al. Clinicopathological analysis of recurrence patterns and prognostic factors for survival after hepatectomy for colorectal liver metastasis. *BMC Surg* 2010;10:27. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20875094>.

368. Tsai M-S, Su Y-H, Ho M-C, et al. Clinicopathological features and prognosis in resectable synchronous and metachronous colorectal liver metastasis. *Ann Surg Oncol* 2007;14:786-794. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17103254>.

369. Foster JH. Treatment of metastatic disease of the liver: a skeptic's view. *Semin Liver Dis* 1984;4:170-179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6205450>.

370. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994;343:1405-1410. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7515134>.

371. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004;240:644-657; discussion 657-648. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15383792>.

372. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg*



2002;235:759-766. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/12035031>.

373. Elias D, Liberale G, Vernerey D, et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. *Ann Surg Oncol* 2005;12:900-909. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16184442>.

374. Fong Y, Salo J. Surgical therapy of hepatic colorectal metastasis. *Semin Oncol* 1999;26:514-523. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/10528899>.

375. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005;241:715-722. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/15849507>.

376. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016;27:1386-1422. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/27380959>.

377. Venook AP. The Kemeny article reviewed management of liver metastases from colorectal cancer: review 2. *Oncology* 2006;20. Available at: <http://www.cancernetwork.com/display/article/10165/108033>.

378. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012;4:283-301. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23152705>.

379. Aloia TA, Vauthey JN, Loyer EM, et al. Solitary colorectal liver metastasis: resection determines outcome. *Arch Surg* 2006;141:460-466; discussion 466-467. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16702517>.

380. Hur H, Ko YT, Min BS, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver

metastases. *Am J Surg* 2009;197:728-736. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18789428>.

381. Lee WS, Yun SH, Chun HK, et al. Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis. *J Clin Gastroenterol* 2008;42:945-949. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18438208>.

382. Charnsangavej C, Clary B, Fong Y, et al. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006;13:1261-1268. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16947009>.

383. Gonzalez M, Poncet A, Combescure C, et al. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. *Ann Surg Oncol* 2013;20:572-579. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23104709>.

384. Gonzalez M, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: systematic review and meta-analysis. *Future Oncol* 2015;11:31-33. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/25662325>.

385. Brouquet A, Vauthey JN, Contreras CM, et al. Improved survival after resection of liver and lung colorectal metastases compared with liver-only metastases: a study of 112 patients with limited lung metastatic disease. *J Am Coll Surg* 2011;213:62-69. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21700179>.

386. Hadden WJ, de Reuver PR, Brown K, et al. Resection of colorectal liver metastases and extra-hepatic disease: a systematic review and proportional meta-analysis of survival outcomes. *HPB (Oxford)* 2016;18:209-220. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/27017160>.

387. Headrick JR, Miller DL, Nagorney DM, et al. Surgical treatment of hepatic and pulmonary metastases from colon cancer. *Ann Thorac Surg* 2001;71:975-979. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11269484>.



388. Marin C, Robles R, Lopez Conesa A, et al. Outcome of strict patient selection for surgical treatment of hepatic and pulmonary metastases from colorectal cancer. *Dis Colon Rectum* 2013;56:43-50. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23222279>.

389. Pulitano C, Bodingbauer M, Aldrighetti L, et al. Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. *Ann Surg Oncol* 2011;18:1380-1388. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21136180>.

390. Wiegering A, Riegel J, Wagner J, et al. The impact of pulmonary metastasectomy in patients with previously resected colorectal cancer liver metastases. *PLoS One* 2017;12:e0173933. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28328956>.

391. Carpizo DR, Are C, Jarnagin W, et al. Liver resection for metastatic colorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. *Ann Surg Oncol* 2009;16:2138-2146. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19495884>.

392. Carpizo DR, D'Angelica M. Liver resection for metastatic colorectal cancer in the presence of extrahepatic disease. *Ann Surg Oncol* 2009;16:2411-2421. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19554376>.

393. Chua TC, Saxena A, Liauw W, et al. Hepatectomy and resection of concomitant extrahepatic disease for colorectal liver metastases--a systematic review. *Eur J Cancer* 2012;48:1757-1765. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22153217>.

394. Andreou A, Brouquet A, Abdalla EK, et al. Repeat hepatectomy for recurrent colorectal liver metastases is associated with a high survival rate. *HPB (Oxford)* 2011;13:774-782. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21999590>.

395. de Jong MC, Mayo SC, Pulitano C, et al. Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: results from an international multi-institutional analysis. *J Gastrointest*

Surg 2009;13:2141-2151. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19795176>.

396. Homayounfar K, Bleckmann A, Conradi LC, et al. Metastatic recurrence after complete resection of colorectal liver metastases: impact of surgery and chemotherapy on survival. *Int J Colorectal Dis* 2013;28:1009-1017. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23371333>.

397. Neeff HP, Drognitz O, Holzner P, et al. Outcome after repeat resection of liver metastases from colorectal cancer. *Int J Colorectal Dis* 2013;28:1135-1141. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23468250>.

398. Salah S, Watanabe K, Park JS, et al. Repeated resection of colorectal cancer pulmonary oligometastases: pooled analysis and prognostic assessment. *Ann Surg Oncol* 2013;20:1955-1961. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23334254>.

399. Wurster EF, Tenckhoff S, Probst P, et al. A systematic review and meta-analysis of the utility of repeated versus single hepatic resection for colorectal cancer liver metastases. *HPB (Oxford)* 2017;19:491-497. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28347640>.

400. Luo LX, Yu ZY, Huang JW, Wu H. Selecting patients for a second hepatectomy for colorectal metastases: An systemic review and meta-analysis. *Eur J Surg Oncol* 2014;40:1036-1048. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24915859>.

401. Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. *Ann Surg* 1997;225:51-60; discussion 60-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8998120>.

402. Poultides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol* 2009;27:3379-3384. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19487380>.



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Colon Cancer

403. Gillams A, Goldberg N, Ahmed M, et al. Thermal ablation of colorectal liver metastases: a position paper by an international panel of ablation experts, the interventional oncology sans frontieres meeting 2013. *Eur Radiol* 2015;25:3438-3454. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25994193>.

404. Solbiati L, Ahmed M, Cova L, et al. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. *Radiology* 2012;265:958-968. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23091175>.

405. Shady W, Petre EN, Gonen M, et al. Percutaneous radiofrequency ablation of colorectal cancer liver metastases: factors affecting outcomes—a 10-year experience at a single center. *Radiology* 2015;142:489. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26267832>.

406. Ruers T, Van Coevorden F, Punt CJ, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. *J Natl Cancer Inst* 2017;109. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28376151>.

407. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. *J Clin Oncol* 2009;27:1585-1591. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19255313>.

408. Rusthoven KE, Kavanagh BD, Cardenas H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* 2009;27:1572-1578. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19255321>.

409. Alsina J, Choti MA. Liver-directed therapies in colorectal cancer. *Semin Oncol* 2011;38:561-567. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21810515>.

410. Johnston FM, Mavros MN, Herman JM, Pawlik TM. Local therapies for hepatic metastases. *J Natl Compr Canc Netw* 2013;11:153-160. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23411382>.

411. Park J, Chen YJ, Lu WP, Fong Y. The evolution of liver-directed treatments for hepatic colorectal metastases. *Oncology (Williston Park)* 2014;28:991-1003. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25403632>.

412. Zacharias AJ, Jayakrishnan TT, Rajeev R, et al. Comparative effectiveness of hepatic artery based therapies for unresectable colorectal liver metastases: a meta-analysis. *PLoS One* 2015;10:e0139940. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26448327>.

413. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999;341:2039-2048. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10615075>.

414. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005;352:734-735. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15716576>.

415. Chan DL, Alzahrani NA, Morris DL, Chua TC. Systematic review and meta-analysis of hepatic arterial infusion chemotherapy as bridging therapy for colorectal liver metastases. *Surg Oncol* 2015;24:162-171. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26133575>.

416. Levi FA, Boige V, Hebbar M, et al. Conversion to resection of liver metastases from colorectal cancer with hepatic artery infusion of combined chemotherapy and systemic cetuximab in multicenter trial OPTILIV. *Ann Oncol* 2016;27:267-274. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26578731>.

417. Fiorentini G, Aliberti C, Tilli M, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. *Anticancer Res* 2012;32:1387-1395. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22493375>.

418. Richardson AJ, Laurence JM, Lam VW. Transarterial chemoembolization with irinotecan beads in the treatment of colorectal



liver metastases: systematic review. J Vasc Interv Radiol 2013;24:1209-1217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23885916>.

419. Martin RC, 2nd, Scoggins CR, Schreeder M, et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. Cancer 2015;121:3649-3658. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26149602>.

420. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33:41-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19908093>.

421. Martin RC, Howard J, Tomalty D, et al. Toxicity of irinotecan-eluting beads in the treatment of hepatic malignancies: results of a multi-institutional registry. Cardiovasc Intervent Radiol 2010;33:960-966. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20661569>.

422. Pawlik TM, Reyes DK, Cosgrove D, et al. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol 2011;29:3960-3967. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21911714>.

423. Reyes DK, Vossen JA, Kamel IR, et al. Single-center phase II trial of transarterial chemoembolization with drug-eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States. Cancer J 2009;15:526-532. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20010173>.

424. van Malenstein H, Maleux G, Vandecaveye V, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie 2011;34:368-376. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21734423>.

425. Vogl TJ, Lammer J, Lencioni R, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with

PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. AJR Am J Roentgenol 2011;197:W562-570. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21940527>.

426. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Transarterial (chemo)embolisation versus no intervention or placebo intervention for liver metastases. Cochrane Database Syst Rev 2013;4:CD009498. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23633373>.

427. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol 2010;28:3687-3694. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20567019>.

428. Benson AB, 3rd, Geschwind JF, Mulcahy MF, et al. Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. Eur J Cancer 2013;49:3122-3130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23777743>.

429. Sofocleous CT, Violari EG, Sotirchos VS, et al. Radioembolization as a salvage therapy for heavily pretreated patients with colorectal cancer liver metastases: factors that affect outcomes. Clin Colorectal Cancer 2015;14:296-305. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26277696>.

430. Hickey R, Lewandowski RJ, Prudhomme T, et al. 90Y radioembolization of colorectal hepatic metastases using glass microspheres: safety and survival outcomes from a 531-patient multicenter study. J Nucl Med 2016;57:665-671. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26635340>.

431. Kurilova I, Beets-Tan RG, Flynn J, et al. Factors Affecting Oncologic Outcomes of 90Y Radioembolization of Heavily Pre-Treated Patients With Colon Cancer Liver Metastases. Clin Colorectal Cancer 2019;18:8-18. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30297264>.



432. Kennedy AS, Ball D, Cohen SJ, et al. Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for (90)Y resin microspheres. *J Gastrointest Oncol* 2015;6:134-142. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25830033>.
433. Saxena A, Meteling B, Kapoor J, et al. Is yttrium-90 radioembolization a viable treatment option for unresectable, chemorefractory colorectal cancer liver metastases? A large single-center experience of 302 patients. *Ann Surg Oncol* 2015;22:794-802. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25323474>.
434. van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. *J Clin Oncol* 2016;34:1723-1731. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26903575>.
435. Wasan HS, Gibbs P, Sharma NK, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. *Lancet Oncol* 2017;18:1159-1171. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28781171>.
436. Gibbs P, Heinemann V, Sharma NK, et al. Effect of Primary Tumor Side on Survival Outcomes in Untreated Patients With Metastatic Colorectal Cancer When Selective Internal Radiation Therapy Is Added to Chemotherapy: Combined Analysis of Two Randomized Controlled Studies. *Clin Colorectal Cancer* 2018;17:e617-e629. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30033117>.
437. Rosenbaum CE, Verkooijen HM, Lam MG, et al. Radioembolization for treatment of salvage patients with colorectal cancer liver metastases: a systematic review. *J Nucl Med* 2013;54:1890-1895. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24071510>.
438. Saxena A, Bester L, Shan L, et al. A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. *J Cancer Res Clin Oncol* 2014;140:537-547. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24318568>.
439. Townsend A, Price T, Karapetis C. Selective internal radiation therapy for liver metastases from colorectal cancer. *Cochrane Database Syst Rev* 2009;CD007045. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19821394>.
440. Abdalla EK, Vauthey J-N, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004;239:818-825. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15166961>.
441. Correa-Gallego C, Gonen M, Fischer M, et al. Perioperative complications influence recurrence and survival after resection of hepatic colorectal metastases. *Ann Surg Oncol* 2013;20:2477-2484. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23608971>.
442. Wang X, Sofocleous CT, Erinjeri JP, et al. Margin size is an independent predictor of local tumor progression after ablation of colon cancer liver metastases. *Cardiovasc Intervent Radiol* 2013;36:166-175. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22535243>.
443. Scheffer HJ, Vroomen LG, Nielsen K, et al. Colorectal liver metastatic disease: efficacy of irreversible electroporation--a single-arm phase II clinical trial (COLDFIRE-2 trial). *BMC Cancer* 2015;15:772. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26497813>.
444. Elias D, De Baere T, Smayra T, et al. Percutaneous radiofrequency thermoablation as an alternative to surgery for treatment of liver tumour recurrence after hepatectomy. *Br J Surg* 2002;89:752-756. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12027986>.
445. Sofocleous CT, Petre EN, Gonen M, et al. CT-guided radiofrequency ablation as a salvage treatment of colorectal cancer hepatic metastases



developing after hepatectomy. J Vasc Interv Radiol 2011;22:755-761. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21514841>.

446. Sucandy I, Cheek S, Golas BJ, et al. Longterm survival outcomes of patients undergoing treatment with radiofrequency ablation for hepatocellular carcinoma and metastatic colorectal cancer liver tumors. HPB (Oxford) 2016;18:756-763. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27593593>.

447. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg 2009;250:440-448. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19730175>.

448. Gillams A, Khan Z, Osborn P, Lees W. Survival after radiofrequency ablation in 122 patients with inoperable colorectal lung metastases. Cardiovasc Interv Radiol 2013;36:724-730. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23070108>.

449. Gleisner AL, Choti MA, Assumpcao L, et al. Colorectal liver metastases: recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. Arch Surg 2008;143:1204-1212. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19075173>.

450. Reuter NP, Woodall CE, Scoggins CR, et al. Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent? J Gastrointest Surg 2009;13:486-491. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18972167>.

451. Abdalla EK. Commentary: Radiofrequency ablation for colorectal liver metastases: do not blame the biology when it is the technology. Am J Surg 2009;197:737-739. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18789420>.

452. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized

EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 2012;23:2619-2626. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22431703>.

453. Bala MM, Riemsma RP, Wolff R, Kleijnen J. Microwave coagulation for liver metastases. Cochrane Database Syst Rev 2013;10:CD010163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24122576>.

454. Bala MM, Riemsma RP, Wolff R, Kleijnen J. Cryotherapy for liver metastases. Cochrane Database Syst Rev 2013;6:CD009058. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23740609>.

455. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Percutaneous ethanol injection for liver metastases. Cochrane Database Syst Rev 2013;5:CD008717. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23728679>.

456. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Electro-coagulation for liver metastases. Cochrane Database Syst Rev 2013;5:CD009497. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23728692>.

457. Cirocchi R, Trastulli S, Boselli C, et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. Cochrane Database Syst Rev 2012;6:CD006317. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22696357>.

458. Weng M, Zhang Y, Zhou D, et al. Radiofrequency ablation versus resection for colorectal cancer liver metastases: a meta-analysis. PLoS One 2012;7:e45493. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23029051>.

459. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol 2010;28:493-508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19841322>.

460. Shady W, Petre EN, Do KG, et al. Percutaneous Microwave versus Radiofrequency Ablation of Colorectal Liver Metastases: Ablation with Clear Margins (A0) Provides the Best Local Tumor Control. J Vasc Interv



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Radiol 2018;29:268-275.e261. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/29203394>.

461. Meijerink MR, Puijk RS, van Tilborg A, et al. Radiofrequency and Microwave Ablation Compared to Systemic Chemotherapy and to Partial Hepatectomy in the Treatment of Colorectal Liver Metastases: A Systematic Review and Meta-Analysis. Cardiovasc Intervent Radiol 2018;41:1189-1204. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/29666906>.

462. Calandri M, Yamashita S, Gazzera C, et al. Ablation of colorectal liver metastasis: Interaction of ablation margins and RAS mutation profiling on local tumour progression-free survival. Eur Radiol 2018;28:2727-2734. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29417253>.

463. Odisio BC, Yamashita S, Huang SY, et al. Local tumour progression after percutaneous ablation of colorectal liver metastases according to RAS mutation status. Br J Surg 2017;104:760-768. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/28240361>.

464. Shady W, Petre EN, Vakiani E, et al. Kras mutation is a marker of worse oncologic outcomes after percutaneous radiofrequency ablation of colorectal liver metastases. Oncotarget 2017;8:66117-66127. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/29029497>.

465. de Baere T, Auperin A, Deschamps F, et al. Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases. Ann Oncol 2015;26:987-991. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/25688058>.

466. Kurilova I, Gonzalez-Aguirre A, Beets-Tan RG, et al. Microwave Ablation in the Management of Colorectal Cancer Pulmonary Metastases. Cardiovasc Intervent Radiol 2018;41:1530-1544. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/29845348>.

467. Callstrom MR, Woodrum DA, Nichols FC, et al. Multicenter Study of Metastatic Lung Tumors Targeted by Interventional Cryoablation Evaluation (SOLSTICE). J Thorac Oncol 2020;15:1200-1209. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/32151777>.

468. Fonck M, Perez JT, Catena V, et al. Pulmonary Thermal Ablation Enables Long Chemotherapy-Free Survival in Metastatic Colorectal Cancer Patients. Cardiovasc Intervent Radiol 2018;41:1727-1734. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29766240>.

469. Agolli L, Bracci S, Nicosia L, et al. Lung metastases treated with stereotactic ablative radiation therapy in oligometastatic colorectal cancer patients: outcomes and prognostic factors after long-term follow-up. Clin Colorectal Cancer 2016;16:58-64. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/27522627>.

470. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: A pooled analysis. Cancer 2011;117:4060-4069. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21432842>.

471. Meyer J, Czito B, Yin F-F, Willett C. Advanced radiation therapy technologies in the treatment of rectal and anal cancer: intensity-modulated photon therapy and proton therapy. Clin Colorectal Cancer 2007;6:348-356. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17311699>.

472. Topkan E, Onal HC, Yavuz MN. Managing liver metastases with conformal radiation therapy. J Support Oncol 2008;6:9-13, 15. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18257395>.

473. ACR Practice Parameter for Intensity Modulated Radiation Therapy (IMRT). The American College of Radiology; 2016. Available at: <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/IMRT-RO.pdf>. Accessed November 17, 2020.

474. Ahmed KA, Scott JG, Arrington JA, et al. Radiosensitivity of Lung Metastases by Primary Histology and Implications for Stereotactic Body Radiation Therapy Using the Genomically Adjusted Radiation Dose. J Thorac Oncol 2018;13:1121-1127. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/29733909>.

475. Ahmed KA, Caudell JJ, El-Haddad G, et al. Radiosensitivity Differences Between Liver Metastases Based on Primary Histology



Suggest Implications for Clinical Outcomes After Stereotactic Body Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2016;95:1399-1404. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27319288>.

476. Joo JH, Park JH, Kim JC, et al. Local Control Outcomes Using Stereotactic Body Radiation Therapy for Liver Metastases From Colorectal Cancer. *Int J Radiat Oncol Biol Phys* 2017;99:876-883. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29063852>.

477. Siva S, MacManus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastases: a systematic review. *J Thorac Oncol* 2010;5:1091-1099. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20479693>.

478. Helou J, Thibault I, Poon I, et al. Stereotactic Ablative Radiation Therapy for Pulmonary Metastases: Histology, Dose, and Indication Matter. *Int J Radiat Oncol Biol Phys* 2017;98:419-427. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28463162>.

479. Palma DA, Olson R, Harrow S, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. *J Clin Oncol* 2020;38:2830-2838. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32484754>.

480. Franko J, Shi Q, Meyers JP, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *Lancet Oncol* 2016;17:1709-1719. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27743922>.

481. Klaver YL, Leenders BJ, Creemers GJ, et al. Addition of biological therapies to palliative chemotherapy prolongs survival in patients with peritoneal carcinomatosis of colorectal origin. *Am J Clin Oncol* 2013;36:157-161. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22314003>.

482. Takahashi H, Okabayashi K, Tsuruta M, et al. Self-expanding metallic stents versus surgical intervention as palliative therapy for obstructive

colorectal cancer: a meta-analysis. *World J Surg* 2015;39:2037-2044. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25894403>.

483. van Hooft JE, van Halsema EE, Vanbiervliet G, et al. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Gastrointest Endosc* 2014;80:747-761 e741-775. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25436393>.

484. Cennamo V, Fuccio L, Mutri V, et al. Does stent placement for advanced colon cancer increase the risk of perforation during bevacizumab-based therapy? *Clin Gastroenterol Hepatol* 2009;7:1174-1176. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19631290>.

485. Small AJ, Coelho-Prabhu N, Baron TH. Endoscopic placement of self-expandable metal stents for malignant colonic obstruction: long-term outcomes and complication factors. *Gastrointest Endosc* 2010;71:560-572. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20189515>.

486. Baratti D, Kusamura S, Pietrantonio F, et al. Progress in treatments for colorectal cancer peritoneal metastases during the years 2010-2015. A systematic review. *Crit Rev Oncol Hematol* 2016;100:209-222. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26867984>.

487. Chua TC, Pelz JO, Kerscher A, et al. Critical analysis of 33 patients with peritoneal carcinomatosis secondary to colorectal and appendiceal signet ring cell carcinoma. *Ann Surg Oncol* 2009;16:2765-2770. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19641972>.

488. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol* 2010;28:63-68. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19917863>.

489. Esquivel J, Sticca R, Sugarbaker P, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement.



Society of Surgical Oncology. Ann Surg Oncol 2007;14:128-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17072675>.

490. Goere D, Malka D, Tzanis D, et al. Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? Ann Surg 2013;257:1065-1071. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23299520>.

491. Glehen O, Gilly FN, Boutitie F, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer 2010;116:5608-5618. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20737573>.

492. Haslinger M, Francescutti V, Attwood K, et al. A contemporary analysis of morbidity and outcomes in cytoreduction/hyperthermic intraperitoneal chemoperfusion. Cancer Med 2013;2:334-342. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23930210>.

493. Kwakman R, Schrama AM, van Olmen JP, et al. Clinicopathological parameters in patient selection for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer metastases: A meta-analysis. Ann Surg 2016;263:1102-1111. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26756756>.

494. Tabrizian P, Shrager B, Jibara G, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: outcomes from a single tertiary institution. J Gastrointest Surg 2014;18:1024-1031. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24577736>.

495. Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol 2006;24:4011-4019. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16921055>.

496. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737-3743. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14551293>.

497. Verwaal VJ, Bruin S, Boot H, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008;15:2426-2432. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18521686>.

498. Sugarbaker PH, Ryan DP. Cytoreductive surgery plus hyperthermic perioperative chemotherapy to treat peritoneal metastases from colorectal cancer: standard of care or an experimental approach? Lancet Oncol 2012;13:e362-369. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22846841>.

499. El Halabi H, Gushchin V, Francis J, et al. The role of cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) in patients with high-grade appendiceal carcinoma and extensive peritoneal carcinomatosis. Ann Surg Oncol 2012;19:110-114. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21701929>.

500. Shaib WL, Martin LK, Choi M, et al. Hyperthermic intraperitoneal chemotherapy following cytoreductive surgery improves outcome in patients with primary appendiceal mucinous adenocarcinoma: a pooled analysis from three tertiary care centers. Oncologist 2015;20:907-914. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26070916>.

501. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol 2012;30:2449-2456. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22614976>.

502. Faris JE, Ryan DP. Controversy and consensus on the management of patients with pseudomyxoma peritonei. Curr Treat Options Oncol



2013;14:365-373. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23934509>.

503. Quenet F, Elias D, Roca L, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7 [abstract]. J Clin Oncol 2018;36:suppl; abstr LBA3503. Available at:

<https://meetinglibrary.asco.org/record/158740/abstract>.

504. Klaver YL, Hendriks T, Lomme RM, et al. Hyperthermia and intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis: an experimental study. Ann Surg 2011;254:125-130. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21502859>.

505. Cashin PH, Mahteme H, Spang N, et al. Cytoreductive surgery and intraperitoneal chemotherapy versus systemic chemotherapy for colorectal peritoneal metastases: A randomised trial. Eur J Cancer 2016;53:155-162. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26751236>.

506. van Oudheusden TR, Nienhuijs SW, Luyer MD, et al. Incidence and treatment of recurrent disease after cytoreductive surgery and intraperitoneal chemotherapy for peritoneally metastasized colorectal cancer: A systematic review. Eur J Surg Oncol 2015;41:1269-1277. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26175345>.

507. Esquivel J. Colorectal cancer with peritoneal metastases: a plea for cooperation between medical and surgical oncologists. Oncology (Williston Park) 2015;29:521-522. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26178340>.

508. Loggie BW, Thomas P. Gastrointestinal cancers with peritoneal carcinomatosis: surgery and hyperthermic intraperitoneal chemotherapy. Oncology (Williston Park) 2015;29:515-521. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26178339>.

509. McRee AJ, O'Neil BH. The role of HIPEC in gastrointestinal malignancies: controversies and conclusions. Oncology (Williston Park) 2015;29:523-524, C523. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26178341>.

510. O'Dwyer S, Verwaal VJ, Sugarbaker PH. Evolution of treatments for peritoneal metastases from colorectal cancer. J Clin Oncol 2015;33:2122-2123. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25897165>.

511. Rovers KP, Bakkers C, van Erning FN, et al. Adjuvant Systemic Chemotherapy vs Active Surveillance Following Up-front Resection of Isolated Synchronous Colorectal Peritoneal Metastases. JAMA Oncol 2020;6:e202701. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32672798>.

512. Rovers K, Bakkers C, Nienhuijs S, et al. Safety, feasibility, tolerability, and preliminary efficacy of perioperative systemic therapy for resectable colorectal peritoneal metastases: Pilot phase of a randomised trial (CAIRO6) [abstract]. Annals of Oncology 2020;31:S243. Available at:

<https://doi.org/10.1016/j.annonc.2020.04.081>.

513. Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. Surg Oncol Clin N Am 2003;12:165-192. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12735137>.

514. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist 2008;13:51-64. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18245012>.

515. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. Ann Oncol 2004;15:933-939. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15151951>.

516. Vauthey J-N, Zorzi D, Pawlik TM. Making unresectable hepatic colorectal metastases resectable--does it work? Semin Oncol 2005;32:118-122. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16399448>.

517. Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Ann Surg 2008;247:451-455. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18376189>.



518. Folprecht G, Grothey A, Alberts S, et al. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005;16:1311-1319. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15870084>.

519. Bilchik AJ, Poston G, Curley SA, et al. Neoadjuvant chemotherapy for metastatic colon cancer: a cautionary note. *J Clin Oncol* 2005;23:9073-9078. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16361615>.

520. Choti MA. Chemotherapy-associated hepatotoxicity: do we need to be concerned? *Ann Surg Oncol* 2009;16:2391-2394. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19554374>.

521. Kishi Y, Zorzi D, Contreras CM, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. *Ann Surg Oncol* 2010;17:2870-2876. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20567921>.

522. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol* 2004;15:460-466. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14998849>.

523. Vauthey J-N, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006;24:2065-2072. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16648507>.

524. Zhao J, van Mierlo KMC, Gomez-Ramirez J, et al. Systematic review of the influence of chemotherapy-associated liver injury on outcome after partial hepatectomy for colorectal liver metastases. *Br J Surg* 2017;104:990-1002. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28542731>.

525. Delaunoy T, Alberts SR, Sargent DJ, et al. Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741. *Ann Oncol* 2005;16:425-429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15677624>.

526. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007;25:1670-1676. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17470860>.

527. Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer* 2006;94:798-805. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16508637>.

528. Masi G, Vasile E, Loupakakis F, et al. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. *J Natl Cancer Inst* 2011;103:21-30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21123833>.

529. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 2010;11:38-47. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19942479>.

530. Folprecht G, Gruenberger T, Bechstein W, et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). *Ann Oncol* 2014;25:1018-1025. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24585720>.

531. Ye LC, Liu TS, Ren L, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J Clin Oncol* 2013;31:1931-1938. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23569301>.

532. Modest DP, Martens UM, Riera-Knorrenschild J, et al. FOLFOXIRI Plus Panitumumab As First-Line Treatment of RAS Wild-Type Metastatic Colorectal Cancer: The Randomized, Open-Label, Phase II VOLFI Study



(AIO KRK0109). J Clin Oncol 2019;37:3401-3411. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31609637>.

533. Petrelli F, Barni S. Resectability and outcome with anti-EGFR agents in patients with KRAS wild-type colorectal liver-limited metastases: a meta-analysis. Int J Colorectal Dis 2012;27:997-1004. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22358385>.

534. Borelli B, Moretto R, Lonardi S, et al. TRIPLETE: a randomised phase III study of modified FOLFOXIRI plus panitumumab versus mFOLFOX6 plus panitumumab as initial therapy for patients with unresectable RAS and BRAF wild-type metastatic colorectal cancer. ESMO Open 2018;3:e000403. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30018814>.

535. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-4786. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17947725>.

536. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-2342. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15175435>.

537. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013-2019. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18421054>.

538. Tang W, Ren L, Liu T, et al. Bevacizumab Plus mFOLFOX6 Versus mFOLFOX6 Alone as First-Line Treatment for RAS Mutant Unresectable Colorectal Liver-Limited Metastases: The BECOME Randomized Controlled Trial. J Clin Oncol 2020;38:3175-3184. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32749938>.

539. Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001;8:347-353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11352309>.

540. Pawlik TM, Olin K, Gleisner AL, et al. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. J Gastrointest Surg 2007;11:860-868. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17492335>.

541. Rivoire M, De Cian F, Meeus P, et al. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. Cancer 2002;95:2283-2292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12436433>.

542. van Mierlo KM, Zhao J, Kleijnen J, et al. The influence of chemotherapy-associated sinusoidal dilatation on short-term outcome after partial hepatectomy for colorectal liver metastases: A systematic review with meta-analysis. Surg Oncol 2016;25:298-307. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27566036>.

543. Ciliberto D, Prati U, Roveda L, et al. Role of systemic chemotherapy in the management of resected or resectable colorectal liver metastases: a systematic review and meta-analysis of randomized controlled trials. Oncol Rep 2012;27:1849-1856. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22446591>.

544. Wang ZM, Chen YY, Chen FF, et al. Peri-operative chemotherapy for patients with resectable colorectal hepatic metastasis: A meta-analysis. Eur J Surg Oncol 2015;41:1197-1203. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26094113>.

545. Araujo RL, Gonen M, Herman P. Chemotherapy for patients with colorectal liver metastases who underwent curative resection improves long-term outcomes: systematic review and meta-analysis. Ann Surg Oncol 2015;22:3070-3078. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25586244>.



NCCN Guidelines Version 1.2022

Colon Cancer

546. Khoo E, O'Neill S, Brown E, et al. Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases. *HPB (Oxford)* 2016;18:485-493. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27317952>.

547. Brandi G, De Lorenzo S, Nannini M, et al. Adjuvant chemotherapy for resected colorectal cancer metastases: Literature review and meta-analysis. *World J Gastroenterol* 2016;22:519-533. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26811604>.

548. Moretto R, Rossini D, Zucchelli G, et al. Oligometastatic colorectal cancer: prognosis, role of locoregional treatments and impact of first-line chemotherapy-a pooled analysis of TRIBE and TRIBE2 studies by Gruppo Oncologico del Nord Ovest. *Eur J Cancer* 2020;139:81-89. Available at: <https://pubmed.ncbi.nlm.nih.gov/32979645/>.

549. Cremolini C, Antoniotti C, Stein A, et al. Individual Patient Data Meta-Analysis of FOLFOXIRI Plus Bevacizumab Versus Doublets Plus Bevacizumab as Initial Therapy of Unresectable Metastatic Colorectal Cancer. *J Clin Oncol* 2020;Jco2001225. Available at: <https://pubmed.ncbi.nlm.nih.gov/32816630/>.

550. Zhang J, Cai J, Deng Y, Wang H. Complete response in patients with locally advanced rectal cancer after neoadjuvant treatment with nivolumab. *Oncoimmunology* 2019;8:e1663108. Available at: <https://pubmed.ncbi.nlm.nih.gov/31741760/>.

551. Demisse R, Damle N, Kim E, et al. Neoadjuvant Immunotherapy-Based Systemic Treatment in MMR-Deficient or MSI-High Rectal Cancer: Case Series. *J Natl Compr Canc Netw* 2020;18:798-804. Available at: <https://pubmed.ncbi.nlm.nih.gov/32634770/>.

552. Baimas-George M, Baker E, Kamionek M, et al. A Complete Pathological Response to Pembrolizumab following ex vivo Liver Resection in a Patient with Colorectal Liver Metastases. *Chemotherapy* 2018;63:90-94. Available at: <https://pubmed.ncbi.nlm.nih.gov/29621772/>.

553. Araujo R, Gonen M, Allen P, et al. Comparison between perioperative and postoperative chemotherapy after potentially curative hepatic

resection for metastatic colorectal cancer. *Ann Surg Oncol* 2013;20:4312-4321. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23897009>.

554. Bilchik AJ, Poston G, Adam R, Choti MA. Prognostic variables for resection of colorectal cancer hepatic metastases: an evolving paradigm. *J Clin Oncol* 2008;26:5320-5321. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18936470>.

555. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2005;23:2038-2048. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15774795>.

556. van Vledder MG, de Jong MC, Pawlik TM, et al. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? *J Gastrointest Surg* 2010;14:1691-1700. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20839072>.

557. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 2006;24:3939-3945. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16921046>.

558. Bischof DA, Clary BM, Maithel SK, Pawlik TM. Surgical management of disappearing colorectal liver metastases. *Br J Surg* 2013;100:1414-1420. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24037559>.

559. Goldberg RM, Rothenberg ML, Van Cutsem E, et al. The continuum of care: a paradigm for the management of metastatic colorectal cancer. *Oncologist* 2007;12:38-50. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17227899>.

560. Ducreux M, Malka D, Mendiboure J, et al. Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-05): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2011;12:1032-1044. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21903473>.



NCCN Guidelines Version 1.2022

Colon Cancer

561. Koopman M, Antonini NF, Douma J, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007;370:135-142. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17630036>.

562. Seymour MT, Maughan TS, Ledermann JA, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007;370:143-152. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17630037>.

563. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229-237. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14657227>.

564. Grothey A, Sargent D, Goldberg RM, Schmoll H-J. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004;22:1209-1214. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15051767>.

565. Sargent DJ, Kohne CH, Sanoff HK, et al. Pooled safety and efficacy analysis examining the effect of performance status on outcomes in nine first-line treatment trials using individual data from patients with metastatic colorectal cancer. *J Clin Oncol* 2009;27:1948-1955. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19255311>.

566. Nielsen DL, Palshof JA, Larsen FO, et al. A systematic review of salvage therapy to patients with metastatic colorectal cancer previously treated with fluorouracil, oxaliplatin and irinotecan +/- targeted therapy. *Cancer Treat Rev* 2014;40:701-715. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24731471>.

567. Costa T, Nunez J, Felismino T, et al. REOX: Evaluation of the Efficacy of Retreatment With an Oxaliplatin-containing Regimen in Metastatic Colorectal Cancer: A Retrospective Single-center Study. *Clin*

Colorectal Cancer 2017;16:316-323. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28392022>.

568. Besora S, Santos C, Izquierdo C, et al. Rechallenge with oxaliplatin and peripheral neuropathy in colorectal cancer patients. *J Cancer Res Clin Oncol* 2018;144:1793-1801. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29955956>.

569. Tanioka H, Asano M, Yoshida R, et al. Cetuximab retreatment in patients with metastatic colorectal cancer who exhibited a clinical benefit in response to prior cetuximab: A retrospective study. *Oncol Lett* 2018;16:3674-3680. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30127977>.

570. Mauri G, Pizzutilo EG, Amatu A, et al. Retreatment with anti-EGFR monoclonal antibodies in metastatic colorectal cancer: Systematic review of different strategies. *Cancer Treat Rev* 2019;73:41-53. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30616224>.

571. Liu X, George GC, Tsimberidou AM, et al. Retreatment with anti-EGFR based therapies in metastatic colorectal cancer: impact of intervening time interval and prior anti-EGFR response. *BMC Cancer* 2015;15:713. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26474549>.

572. Kajitani T, Makiyama A, Arita S, et al. Anti-Epidermal Growth Factor Receptor Antibody Readministration in Chemorefractory Metastatic Colorectal Cancer. *Anticancer Res* 2017;37:6459-6468. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29061833>.

573. Cremolini C, Rossini D, Dell'Aquila E, et al. Rechallenge for Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer With Acquired Resistance to First-line Cetuximab and Irinotecan: A Phase 2 Single-Arm Clinical Trial. *JAMA Oncol* 2019;5:343-350. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30476968>.

574. Simkens LH, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal



Cancer Group. Lancet 2015;385:1843-1852. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25862517>.

575. Goey KKH, Elias SG, van Tinteren H, et al. Maintenance treatment with capecitabine and bevacizumab versus observation in metastatic colorectal cancer: updated results and molecular subgroup analyses of the phase 3 CAIRO3 study. Ann Oncol 2017;28:2128-2134. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28911067>.

576. Hegewisch-Becker S, Graeven U, Lerchenmuller CA, et al. Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (AIO 0207): a randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol 2015;16:1355-1369. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26361971>.

577. Aparicio T, Ghiringhelli F, Boige V, et al. Bevacizumab Maintenance Versus No Maintenance During Chemotherapy-Free Intervals in Metastatic Colorectal Cancer: A Randomized Phase III Trial (PRODIGE 9). J Clin Oncol 2018;36:674-681. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29346040>.

578. Koeberle D, Betticher DC, von Moos R, et al. Bevacizumab continuation versus no continuation after first-line chemotherapy plus bevacizumab in patients with metastatic colorectal cancer: a randomized phase III non-inferiority trial (SAKK 41/06). Ann Oncol 2015;26:709-714. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25605741>.

579. Tournigand C, Chibaudel B, Samson B, et al. Bevacizumab with or without erlotinib as maintenance therapy in patients with metastatic colorectal cancer (GERCOR DREAM; OPTIMOX3): a randomised, open-label, phase 3 trial. Lancet Oncol 2015;16:1493-1505. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26474518>.

580. Hagman H, Frodin JE, Berglund A, et al. A randomized study of KRAS-guided maintenance therapy with bevacizumab, erlotinib or metronomic capecitabine after first-line induction treatment of metastatic colorectal cancer: the Nordic ACT2 trial. Ann Oncol 2016;27:140-147. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26483047>.

581. Xu W, Gong Y, Kuang M, et al. Survival benefit and safety of bevacizumab in combination with erlotinib as maintenance therapy in patients with metastatic colorectal cancer: a meta-analysis. Clin Drug Investig 2016;37:155-165. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27665469>.

582. Luo HY, Li YH, Wang W, et al. Single-agent capecitabine as maintenance therapy after induction of XELOX (or FOLFOX) in first-line treatment of metastatic colorectal cancer: randomized clinical trial of efficacy and safety. Ann Oncol 2016;27:1074-1081. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26940686>.

583. Sonbol MB, Mountjoy LJ, Firwana B, et al. The Role of Maintenance Strategies in Metastatic Colorectal Cancer: A Systematic Review and Network Meta-analysis of Randomized Clinical Trials. JAMA Oncol 2020;6:e194489. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31855256>.

584. U. S. Food & Drug Administration. Package Insert. MVASI™ (bevacizumab-awwb) injection, for intravenous use. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761028s004bl.pdf. Accessed November 17, 2020.

585. U. S. Food & Drug Administration. Package Insert. ZIRABEV™ (bevacizumab-bvzr) injection, for intravenous use. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761099s000bl.pdf. Accessed November 17, 2020.

586. U.S. Food & Drug Administration. Package Insert. HERZUMA® (trastuzumab-pkrb) for injection, for intravenous use. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761091s001s002lbl.pdf. Accessed November 17, 2020.

587. U.S. Food & Drug Administration. Package Insert. KANJINTI™ (trastuzumab-anns) for injection, for intravenous use. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761073Orig1s000lbl.pdf. Accessed November 17, 2020.



588. U.S. Food & Drug Administration. Package Insert. OGIvRI (trastuzumab-dkst) for injection, for intravenous use. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761074s004bl.pdf. Accessed November 17, 2020.

589. U.S. Food & Drug Administration. Package Insert. ONTRUZANT (trastuzumab-dttb) for injection, for intravenous use. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761100s000bl.pdf. Accessed November 17, 2020.

590. U.S. Food & Drug Administration. Package Insert. TRAZIMERA™ (trastuzumab-qyyp) for injection, for intravenous use. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761081s000bl.pdf. Accessed November 17, 2020.

591. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-1634. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18316791>.

592. Baselga J, Rosen N. Determinants of RASistance to anti-epidermal growth factor receptor agents. J Clin Oncol 2008;26:1582-1584. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18316790>.

593. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009;27:663-671. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19114683>.

594. De Roock W, Piessevaux H, De Schutter J, et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol 2008;19:508-515. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17998284>.

595. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757-1765. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18946061>.

596. Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007;25:3230-3237. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17664471>.

597. Lievre A, Bachet J-B, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008;26:374-379. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18202412>.

598. Tejpar S, Celik I, Schlichting M, et al. Association of KRAS G13D tumor mutations with outcome in patients with metastatic colorectal cancer treated with first-line chemotherapy with or without cetuximab. J Clin Oncol 2012;30:3570-3577. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22734028>.

599. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408-1417. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19339720>.

600. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-1034. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24024839>.

601. Sorich MJ, Wiese MD, Rowland A, et al. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Ann Oncol 2015;26:13-21. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25115304>.

602. Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS gene mutation testing in metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy: American Society of Clinical Oncology provisional clinical opinion update 2015. J Clin Oncol 2016;34:179-185. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26438111>.



NCCN Guidelines Version 1.2022

Colon Cancer

603. Artale S, Sartore-Bianchi A, Veronese SM, et al. Mutations of KRAS and BRAF in primary and matched metastatic sites of colorectal cancer. *J Clin Oncol* 2008;26:4217-4219. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18757341>.

604. Etienne-Grimaldi M-C, Formento J-L, Francoual M, et al. K-Ras mutations and treatment outcome in colorectal cancer patients receiving exclusive fluoropyrimidine therapy. *Clin Cancer Res* 2008;14:4830-4835. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18676755>.

605. Knijn N, Mekenkamp LJ, Klomp M, et al. KRAS mutation analysis: a comparison between primary tumours and matched liver metastases in 305 colorectal cancer patients. *Br J Cancer* 2011;104:1020-1026. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21364579>.

606. Wang HL, Lopategui J, Amin MB, Patterson SD. KRAS mutation testing in human cancers: the pathologist's role in the era of personalized medicine. *Adv Anat Pathol* 2010;17:23-32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20032635>.

607. Monzon FA, Ogino S, Hammond MEH, et al. The role of KRAS mutation testing in the management of patients with metastatic colorectal cancer. *Arch Pathol Lab Med* 2009;133:1600-1606. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19792050>.

608. Yoon HH, Tougeron D, Shi Q, et al. KRAS codon 12 and 13 mutations in relation to disease-free survival in BRAF-wild-type stage III colon cancers from an adjuvant chemotherapy trial (N0147 alliance). *Clin Cancer Res* 2014;20:3033-3043. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24687927>.

609. De Roock W, Jonker DJ, Di Nicolantonio F, et al. Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. *JAMA* 2010;304:1812-1820. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20978259>.

610. Peeters M, Douillard JY, Van Cutsem E, et al. Mutant KRAS codon 12 and 13 alleles in patients with metastatic colorectal cancer: assessment

as prognostic and predictive biomarkers of response to panitumumab. *J Clin Oncol* 2013;31:759-765. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23182985>.

611. Schirripa M, Loupakakis F, Lonardi S, et al. Phase II study of single-agent cetuximab in KRAS G13D mutant metastatic colorectal cancer. *Ann Oncol* 2015;26:2503. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26371285>.

612. Segelov E, Thavaneswaran S, Waring PM, et al. Response to cetuximab with or without irinotecan in patients with refractory metastatic colorectal cancer harboring the KRAS G13D mutation: Australasian Gastro-Intestinal Trials Group ICECREAM study. *J Clin Oncol* 2016;34:2258-2264. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27114605>.

613. Rowland A, Dias MM, Wiese MD, et al. Meta-analysis comparing the efficacy of anti-EGFR monoclonal antibody therapy between KRAS G13D and other KRAS mutant metastatic colorectal cancer tumours. *Eur J Cancer* 2016;55:122-130. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26812186>.

614. Price TJ, Bruhn MA, Lee CK, et al. Correlation of extended RAS and PIK3CA gene mutation status with outcomes from the phase III AGITG MAX STUDY involving capecitabine alone or in combination with bevacizumab plus or minus mitomycin C in advanced colorectal cancer. *Br J Cancer* 2015;112:963-970. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25742472>.

615. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:1065-1075. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25088940>.

616. U.S. Food & Drug Administration. Package Insert. Vectibix® (Panitumumab). 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125147s2071/bl.pdf. Accessed November 17, 2020.



617. Tol J, Nagtegaal ID, Punt CJA. BRAF mutation in metastatic colorectal cancer. *N Engl J Med* 2009;361:98-99. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19571295>.

618. Van Cutsem E, Kohne CH, Lang I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 2011;29:2011-2019. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21502544>.

619. Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011;377:2103-2114. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21641636>.

620. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature* 2002;417:949-954. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12068308>.

621. Ikenoue T, Hikiba Y, Kanai F, et al. Functional analysis of mutations within the kinase activation segment of B-Raf in human colorectal tumors. *Cancer Res* 2003;63:8132-8137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14678966>.

622. Wan PT, Garnett MJ, Roe SM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell* 2004;116:855-867. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15035987>.

623. Bokemeyer C, Cutsem EV, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials. *Eur J Cancer* 2012;48:1466-1475. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22446022>.

624. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic

colorectal cancer. *J Clin Oncol* 2008;26:5705-5712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19001320>.

625. Laurent-Puig P, Cayre A, Manceau G, et al. Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. *J Clin Oncol* 2009;27:5924-5930. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19884556>.

626. Loupakakis F, Ruzzo A, Cremolini C, et al. KRAS codon 61, 146 and BRAF mutations predict resistance to cetuximab plus irinotecan in KRAS codon 12 and 13 wild-type metastatic colorectal cancer. *Br J Cancer* 2009;101:715-721. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19603018>.

627. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol* 2010;11:753-762. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20619739>.

628. Seymour MT, Brown SR, Middleton G, et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. *Lancet Oncol* 2013;14:749-759. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23725851>.

629. Pietrantonio F, Petrelli F, Coinu A, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. *Eur J Cancer* 2015;51:587-594. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25673558>.

630. Rowland A, Dias MM, Wiese MD, et al. Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer. *Br J Cancer* 2015;112:1888-1894. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25989278>.

631. Chen D, Huang JF, Liu K, et al. BRAFV600E mutation and its association with clinicopathological features of colorectal cancer: a



systematic review and meta-analysis. PLoS One 2014;9:e90607. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24594804>.

632. Price TJ, Hardingham JE, Lee CK, et al. Impact of KRAS and BRAF gene mutation status on outcomes from the phase III AGITG MAX trial of capecitabine alone or in combination with bevacizumab and mitomycin in advanced colorectal cancer. J Clin Oncol 2011;29:2675-2682. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21646616>.

633. Safaee Ardekani G, Jafarnejad SM, Tan L, et al. The prognostic value of BRAF mutation in colorectal cancer and melanoma: a systematic review and meta-analysis. PLoS One 2012;7:e47054. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23056577>.

634. Samowitz WS, Sweeney C, Herrick J, et al. Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancers. Cancer Res 2005;65:6063-6069. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16024606>.

635. Saridaki Z, Papadatos-Pastos D, Tzardi M, et al. BRAF mutations, microsatellite instability status and cyclin D1 expression predict metastatic colorectal patients' outcome. Br J Cancer 2010;102:1762-1768. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20485284>.

636. Xu Q, Xu AT, Zhu MM, et al. Predictive and prognostic roles of BRAF mutation in patients with metastatic colorectal cancer treated with anti-epidermal growth factor receptor monoclonal antibodies: A meta-analysis. J Dig Dis 2013;14:409-416. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23615046>.

637. Sinicrope FA, Shi Q, Allegra CJ, et al. Association of DNA mismatch repair and mutations in BRAF and KRAS with survival after recurrence in stage III colon cancers : A secondary analysis of 2 randomized clinical trials. JAMA Oncol 2017;3:472-480. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28006055>.

638. Clancy C, Burke JP, Kalady MF, Coffey JC. BRAF mutation is associated with distinct clinicopathological characteristics in colorectal cancer: a systematic review and meta-analysis. Colorectal Dis

2013;15:e711-718. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24112392>.

639. Santini D, Spoto C, Loupakakis F, et al. High concordance of BRAF status between primary colorectal tumours and related metastatic sites: implications for clinical practice. Ann Oncol 2010;21:1565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20573852>.

640. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol 2016;17:738-746. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27108243>.

641. Sartore-Bianchi A, Amatu A, Porcu L, et al. HER2 Positivity Predicts Unresponsiveness to EGFR-Targeted Treatment in Metastatic Colorectal Cancer. Oncologist 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30952821>.

642. Valtorta E, Martino C, Sartore-Bianchi A, et al. Assessment of a HER2 scoring system for colorectal cancer: results from a validation study. Mod Pathol 2015;28:1481-1491. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26449765>.

643. Hainsworth JD, Meric-Bernstam F, Swanton C, et al. Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study. J Clin Oncol 2018;36:536-542. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29320312>.

644. Wu SW, Ma CC, Li WH. Does overexpression of HER-2 correlate with clinicopathological characteristics and prognosis in colorectal cancer? Evidence from a meta-analysis. Diagn Pathol 2015;10:144. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26276145>.

645. Martin V, Landi L, Molinari F, et al. HER2 gene copy number status may influence clinical efficacy to anti-EGFR monoclonal antibodies in



metastatic colorectal cancer patients. *Br J Cancer* 2013;108:668-675. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23348520>.

646. Raghav K, Loree JM, Morris JS, et al. Validation of HER2 Amplification as a Predictive Biomarker for Anti-Epidermal Growth Factor Receptor Antibody Therapy in Metastatic Colorectal Cancer. *JCO Precision Oncology* 2019;1-13. Available at: <https://ascopubs.org/doi/abs/10.1200/PO.18.00226>.

647. Lochhead P, Kuchiba A, Imamura Y, et al. Microsatellite instability and BRAF mutation testing in colorectal cancer prognostication. *J Natl Cancer Inst* 2013;105:1151-1156. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23878352>.

648. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. *Clin Cancer Res* 2014;20:5322-5330. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25139339>.

649. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443-2454. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22658127>.

650. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med* 2018;378:731-739. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29466156>.

651. Gatalica Z, Xiu J, Swensen J, Vranic S. Molecular characterization of cancers with NTRK gene fusions. *Mod Pathol* 2019;32:147-153. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30171197>.

652. Okamura R, Boichard A, Kato S, et al. Analysis of NTRK Alterations in Pan-Cancer Adult and Pediatric Malignancies: Implications for NTRK-Targeted Therapeutics. *JCO Precis Oncol* 2018;2018. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30637364>.

653. Cocco E, Benhamida J, Middha S, et al. Colorectal Carcinomas Containing Hypermethylated MLH1 Promoter and Wild-Type BRAF/KRAS Are Enriched for Targetable Kinase Fusions. *Cancer Res* 2019;79:1047-1053. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30643016>.

654. Fancello L, Gandini S, Pelicci PG, Mazzarella L. Tumor mutational burden quantification from targeted gene panels: major advancements and challenges. *J Immunother Cancer* 2019;7:183. Available at: <https://pubmed.ncbi.nlm.nih.gov/31307554/>.

655. U.S. Food & Drug Administration. Package Insert. KEYTRUDA® (pembrolizumab) injection, for intravenous use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s0881.pdf. Accessed November 17, 2020.

656. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* 2020. Available at: <https://pubmed.ncbi.nlm.nih.gov/32919526/>.

657. Meiri E, Garrett-Mayer E, Halabi S, et al. Pembrolizumab (P) in patients (Pts) with colorectal cancer (CRC) with high tumor mutational burden (HTMB): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study [abstract]. *Journal of Clinical Oncology* 2020;38:133-133. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.133.

658. Mattison LK, Soong R, Diasio RB. Implications of dihydropyrimidine dehydrogenase on 5-fluorouracil pharmacogenetics and pharmacogenomics. *Pharmacogenomics* 2002;3:485-492. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12164772>.

659. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther* 2018;103:210-216. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29152729>.



660. Lee AM, Shi Q, Pavey E, et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). *J Natl Cancer Inst* 2014;106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25381393>.

661. Morel A, Boisdron-Celle M, Fey L, et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. *Mol Cancer Ther* 2006;5:2895-2904. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17121937>.

662. Meulendijks D, Henricks LM, Sonke GS, et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. *Lancet Oncol* 2015;16:1639-1650. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26603945>.

663. Terrazzino S, Cargnin S, Del Re M, et al. DPYD IVS14+1G>A and 2846A>T genotyping for the prediction of severe fluoropyrimidine-related toxicity: a meta-analysis. *Pharmacogenomics* 2013;14:1255-1272. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23930673>.

664. Lunenburg C, Henricks LM, Guchelaar HJ, et al. Prospective DPYD genotyping to reduce the risk of fluoropyrimidine-induced severe toxicity: Ready for prime time. *Eur J Cancer* 2016;54:40-48. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26716401>.

665. Deenen MJ, Cats A, Severens JL, et al. Reply to T. Magnes et al. *J Clin Oncol* 2016;34:2434-2435. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27161961>.

666. Henricks LM, Lunenburg C, de Man FM, et al. A cost analysis of upfront DPYD genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy. *Eur J Cancer* 2019;107:60-67. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30544060>.

667. Henricks LM, Lunenburg C, de Man FM, et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with

cancer: a prospective safety analysis. *Lancet Oncol* 2018;19:1459-1467. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30348537>.

668. Deenen MJ, Meulendijks D, Cats A, et al. Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. *J Clin Oncol* 2016;34:227-234. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26573078>.

669. Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. *J Clin Oncol* 2008;26:689-690. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18235136>.

670. Goldberg RM, Sargent DJ, Morton RF, et al. Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial. *J Clin Oncol* 2006;24:3347-3353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16849748>.

671. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001;19:4097-4106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11689577>.

672. Kohne CH, De Greve J, Hartmann JT, et al. Irinotecan combined with infusional 5-fluorouracil/folinic acid or capecitabine plus celecoxib or placebo in the first-line treatment of patients with metastatic colorectal cancer. EORTC study 40015. *Ann Oncol* 2008;19:920-926. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18065406>.

673. Garcia-Alfonso P, Munoz-Martin AJ, Alvarez-Suarez S, et al. Bevacizumab in combination with biweekly capecitabine and irinotecan, as first-line treatment for patients with metastatic colorectal cancer. *Br J Cancer* 2010;103:1524-1528. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20978503>.



674. Garcia-Alfonso P, Chaves M, Munoz A, et al. Capecitabine and irinotecan with bevacizumab 2-weekly for metastatic colorectal cancer: the phase II AVAXIRI study. *BMC Cancer* 2015;15:327. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25925749>.

675. Ducreux M, Adenis A, Pignon JP, et al. Efficacy and safety of bevacizumab-based combination regimens in patients with previously untreated metastatic colorectal cancer: final results from a randomised phase II study of bevacizumab plus 5-fluorouracil, leucovorin plus irinotecan versus bevacizumab plus capecitabine plus irinotecan (FNCLCC ACCORD 13/0503 study). *Eur J Cancer* 2013;49:1236-1245. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23352604>.

676. Pectasides D, Papaxoinis G, Kalogeras K, et al. XELIRI-bevacizumab versus FOLFIRI-bevacizumab as first-line treatment in patients with metastatic colorectal cancer: a Hellenic Cooperative Oncology Group phase III trial with collateral biomarker analysis. *BMC Cancer* 2012;12:271. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22748098>.

677. Schmiegel W, Reinacher-Schick A, Arnold D, et al. Capecitabine/irinotecan or capecitabine/oxaliplatin in combination with bevacizumab is effective and safe as first-line therapy for metastatic colorectal cancer: a randomized phase II study of the AIO colorectal study group. *Ann Oncol* 2013;24:1580-1587. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23463625>.

678. Hoff PM, Hochhaus A, Pestalozzi BC, et al. Cediranib plus FOLFOX/CAPOX versus placebo plus FOLFOX/CAPOX in patients with previously untreated metastatic colorectal cancer: a randomized, double-blind, phase III study (HORIZON II). *J Clin Oncol* 2012;30:3596-3603. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22965965>.

679. Siu LL, Shapiro JD, Jonker DJ, et al. Phase III randomized, placebo-controlled study of cetuximab plus brivanib alaninate versus cetuximab plus placebo in patients with metastatic, chemotherapy-refractory, wild-type K-RAS colorectal carcinoma: the NCIC clinical trials group and AGITG CO.20 trial. *J Clin Oncol* 2013;31:2477-2484. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23690424>.

680. Carrato A, Swieboda-Sadlej A, Staszewska-Skurczynska M, et al. Fluorouracil, leucovorin, and irinotecan plus either sunitinib or placebo in metastatic colorectal cancer: a randomized, phase III trial. *J Clin Oncol* 2013;31:1341-1347. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23358972>.

681. Johnsson A, Hagman H, Frodin JE, et al. A randomized phase III trial on maintenance treatment with bevacizumab alone or in combination with erlotinib after chemotherapy and bevacizumab in metastatic colorectal cancer: the Nordic ACT Trial. *Ann Oncol* 2013;24:2335-2341. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23788755>.

682. Eng C, Kim TW, Bendell J, et al. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol* 2019;20:849-861. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31003911>.

683. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* 2009;27:672-680. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19114685>.

684. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 2009;360:563-572. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19196673>.

685. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008;371:1007-1016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18358928>.

686. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013;14:1208-1215. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24120480>.



687. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. *J Clin Oncol* 2008;26:3523-3529. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18640933>.

688. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28:4697-4705. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20921465>.

689. Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. *Jama* 2017;317:2392-2401. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28632865>.

690. Buchler T, Pavlik T, Melichar B, et al. Bevacizumab with 5-fluorouracil, leucovorin, and oxaliplatin versus bevacizumab with capecitabine and oxaliplatin for metastatic colorectal carcinoma: results of a large registry-based cohort analysis. *BMC Cancer* 2014;14:323. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24884897>.

691. Kidwell KM, Yothers G, Ganz PA, et al. Long-term neurotoxicity effects of oxaliplatin added to fluorouracil and leucovorin as adjuvant therapy for colon cancer: results from National Surgical Adjuvant Breast and Bowel Project trials C-07 and LTS-01. *Cancer* 2012;118:5614-5622. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22569841>.

692. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer--a GERCOR study. *J Clin Oncol* 2006;24:394-400. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16421419>.

693. Seymour M. Conceptual approaches to metastatic disease. *Ann Oncol* 2012;23 Suppl 10:x77-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22987997>.

694. Berry SR, Cosby R, Asmis T, et al. Continuous versus intermittent chemotherapy strategies in metastatic colorectal cancer: a systematic review and meta-analysis. *Ann Oncol* 2014;26:477-485. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25057174>.

695. Chibaudel B, Maindrault-Goebel F, Lledo G, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. *J Clin Oncol* 2009;27:5727-5733. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19786657>.

696. Hochster HS, Grothey A, Hart L, et al. Improved time to treatment failure with an intermittent oxaliplatin strategy: results of CONCEPT. *Ann Oncol* 2014;25:1172-1178. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24608198>.

697. Gamelin L, Boisdron-Celle M, Delva R, et al. Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-Fluorouracil and leucovorin for advanced colorectal cancer. *Clin Cancer Res* 2004;10:4055-4061. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15217938>.

698. Gamelin L, Boisdron-Celle M, Morel A, et al. Oxaliplatin-related neurotoxicity: interest of calcium-magnesium infusion and no impact on its efficacy. *J Clin Oncol* 2008;26:1188-1189; author reply 1189-1190. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18309961>.

699. Grothey A, Nikcevic DA, Sloan JA, et al. Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7. *J Clin Oncol* 2011;29:421-427. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21189381>.

700. Hochster HS, Grothey A, Childs BH. Use of calcium and magnesium salts to reduce oxaliplatin-related neurotoxicity. *J Clin Oncol*



2007;25:4028-4029. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17664456>.

701. Knijn N, Tol J, Koopman M, et al. The effect of prophylactic calcium and magnesium infusions on the incidence of neurotoxicity and clinical outcome of oxaliplatin-based systemic treatment in advanced colorectal cancer patients. *Eur J Cancer* 2010;47:369-374. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21067912>.

702. Kurniali PC, Luo LG, Weitberg AB. Role of calcium/ magnesium infusion in oxaliplatin-based chemotherapy for colorectal cancer patients. *Oncology (Williston Park)* 2010;24:289-292. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20394142>.

703. Wen F, Zhou Y, Wang W, et al. Ca/Mg infusions for the prevention of oxaliplatin-related neurotoxicity in patients with colorectal cancer: a meta-analysis. *Ann Oncol* 2013;24:171-178. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22898039>.

704. Wu Z, Ouyang J, He Z, Zhang S. Infusion of calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in colorectal cancer: A systematic review and meta-analysis. *Eur J Cancer* 2012;48:1791-1798. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22542974>.

705. Loprinzi CL, Qin R, Dakhil SR, et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). *J Clin Oncol* 2014;32:997-1005. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24297951>.

706. Cassidy J, Clarke S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008;26:2006-2012. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18421053>.

707. Cassidy J, Tabernero J, Twelves C, et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal

cancer. *J Clin Oncol* 2004;22:2084-2091. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15169795>.

708. Cassidy J, Clarke S, Diaz-Rubio E, et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. *Br J Cancer* 2011;105:58-64. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21673685>.

709. Ducreux M, Bennouna J, Hebbar M, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. *Int J Cancer* 2011;128:682-690. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20473862>.

710. Porschen R, Arkenau H-T, Kubicka S, et al. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. *J Clin Oncol* 2007;25:4217-4223. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17548840>.

711. Guo Y, Xiong BH, Zhang T, et al. XELOX vs. FOLFOX in metastatic colorectal cancer: An updated meta-analysis. *Cancer Invest* 2016;34:94-104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26864862>.

712. Zhang C, Wang J, Gu H, et al. Capecitabine plus oxaliplatin compared with 5-fluorouracil plus oxaliplatin in metastatic colorectal cancer: Meta-analysis of randomized controlled trials. *Oncol Lett* 2012;3:831-838. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22741002>.

713. U.S. Food & Drug Administration. Package Insert. ELOXATIN (oxaliplatin) injection for intravenous use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021759s023bl.pdf. Accessed November 17, 2020.

714. Yalcin S, Uslu R, Dane F, et al. Bevacizumab + capecitabine as maintenance therapy after initial bevacizumab + XELOX treatment in previously untreated patients with metastatic colorectal cancer: phase III 'Stop and Go' study results--a Turkish Oncology Group Trial. *Oncology*



2013;85:328-335. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24247559>.

715. U.S. Food & Drug Administration. Package Insert. XELODA® (capecitabine) tablets, for oral use. 2019. Available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020896s042bl.pdf. Accessed November 17, 2020.

716. Haller DG, Cassidy J, Clarke SJ, et al. Potential regional differences for the tolerability profiles of fluoropyrimidines. *J Clin Oncol* 2008;26:2118-2123. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18445840>.

717. Schmoll H-J, Arnold D. Update on capecitabine in colorectal cancer. *Oncologist* 2006;11:1003-1009. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17030642>.

718. Hofheinz RD, Heinemann V, von Weikersthal LF, et al. Capecitabine-associated hand-foot-skin reaction is an independent clinical predictor of improved survival in patients with colorectal cancer. *Br J Cancer* 2012;107:1678-1683. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23033005>.

719. Colucci G, Gebbia V, Paoletti G, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005;23:4866-4875. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15939922>.

720. Aparicio T, Lavau-Denes S, Phelip JM, et al. Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001-02). *Ann Oncol* 2016;27:121-127. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26487578>.

721. Package Insert. Camptosar® (Irinotecan) Injection, intravenous infusion. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020571s051bl.pdf. Accessed November 17, 2020.

722. Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004;22:1382-1388. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15007088>.

723. Liu X, Cheng D, Kuang Q, et al. Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians. *Pharmacogenomics J* 2014;14:120-129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23529007>.

724. O'Dwyer PJ, Catalano RB. Uridine diphosphate glucuronosyltransferase (UGT) 1A1 and irinotecan: practical pharmacogenomics arrives in cancer therapy. *J Clin Oncol* 2006;24:4534-4538. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17008691>.

725. Innocenti F, Schilsky RL, Ramirez J, et al. Dose-finding and pharmacokinetic study to optimize the dosing of irinotecan according to the UGT1A1 genotype of patients with cancer. *J Clin Oncol* 2014;32:2328-2334. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24958824>.

726. Sobrero A, Ackland S, Clarke S, et al. Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer. *Oncology* 2009;77:113-119. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19628950>.

727. Yamazaki K, Nagase M, Tamagawa H, et al. Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G). *Ann Oncol* 2016;27:1539-1546. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27177863>.

728. Kohne CH, Hofheinz R, Mineur L, et al. First-line panitumumab plus irinotecan/5-fluorouracil/leucovorin treatment in patients with metastatic colorectal cancer. *J Cancer Res Clin Oncol* 2012;138:65-72. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21960318>.

729. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI)



compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol* 2010;28:4706-4713. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20921462>.

730. Hurwitz HI, Fehrenbacher L, Hainsworth JD, et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. *J Clin Oncol* 2005;23:3502-3508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15908660>.

731. Kabbinavar FF, Hambleton J, Mass RD, et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005;23:3706-3712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15867200>.

732. Van Cutsem E, Hoff PM, Harper P, et al. Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. *Br J Cancer* 2004;90:1190-1197. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15026800>.

733. Mitry E, Fields ALA, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol* 2008;26:4906-4911. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18794541>.

734. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013;14:1077-1085. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24028813>.

735. Loupakakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014;371:1609-1618. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25337750>.

736. Cremolini C, Loupakakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of

patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol* 2015;16:1306-1315. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26338525>.

737. Cremolini C, Antoniotti C, Rossini D, et al. Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol* 2020;21:497-507. Available at: <https://pubmed.ncbi.nlm.nih.gov/32164906/>.

738. Gruenberger T, Bridgewater J, Chau I, et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. *Ann Oncol* 2015;26:702-708. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25538173>.

739. Schmoll H-J, Meinert FM, Cygon F, et al. "CHARTA": FOLFOX/Bevacizumab vs. FOLFOXIRI/Bevacizumab in advanced colorectal cancer—Final results, prognostic and potentially predictive factors from the randomized Phase II trial of the AIO [abstract]. *Journal of Clinical Oncology* 2017;35:3533-3533. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.3533.

740. Hurwitz HI, Tan BR, Reeves JA, et al. Phase II Randomized Trial of Sequential or Concurrent FOLFOXIRI-Bevacizumab Versus FOLFOX-Bevacizumab for Metastatic Colorectal Cancer (STEAM). *Oncologist* 2019;24:921-932. Available at: <https://pubmed.ncbi.nlm.nih.gov/30552157/>.

741. Rossini D, Lonardi S, Antoniotti C, et al. Treatments after progression to first-line FOLFOXIRI and bevacizumab in metastatic colorectal cancer: a pooled analysis of TRIBE and TRIBE2 studies by GONO. *Br J Cancer* 2020. Available at: <https://pubmed.ncbi.nlm.nih.gov/33024268/>.

742. U.S. Food & Drug Administration. Package Insert. AVASTIN® (bevacizumab) injection, for intravenous use 2020. Available at:



https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125085s336bl.pdf. Accessed November 17, 2020.

743. Kabbinar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* 2003;21:60-65. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12506171>.

744. Kabbinar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol* 2005;23:3697-3705. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15738537>.

745. Petrelli F, Borronovo K, Cabiddu M, et al. FOLFIRI-bevacizumab as first-line chemotherapy in 3500 patients with advanced colorectal cancer: a pooled analysis of 29 published trials. *Clin Colorectal Cancer* 2013;12:145-151. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23763824>.

746. Hurwitz HI, Bekaii-Saab TS, Bendell JC, et al. Safety and effectiveness of bevacizumab treatment for metastatic colorectal cancer: final results from the Avastin((R)) Registry - Investigation of Effectiveness and Safety (ARIES) observational cohort study. *Clin Oncol (R Coll Radiol)* 2014;26:323-332. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24686090>.

747. Fourrier-Reglat A, Smith D, Rouyer M, et al. Survival outcomes of bevacizumab in first-line metastatic colorectal cancer in a real-life setting: results of the ETNA cohort. *Target Oncol* 2013;9:311-319. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24307007>.

748. Botrel TE, Clark LG, Paladini L, Clark OA. Efficacy and safety of bevacizumab plus chemotherapy compared to chemotherapy alone in previously untreated advanced or metastatic colorectal cancer: a systematic review and meta-analysis. *BMC Cancer* 2016;16:677. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27558497>.

749. Cao Y, Tan A, Gao F, et al. A meta-analysis of randomized controlled trials comparing chemotherapy plus bevacizumab with chemotherapy alone in metastatic colorectal cancer. *Int J Colorectal Dis* 2009;24:677-685. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19184059>.

750. Hu W, Xu W, Liao X, He H. Bevacizumab in combination with first-line chemotherapy in patients with metastatic colorectal cancer: a meta-analysis. *Minerva Chir* 2015;70:451-458. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26013763>.

751. Hurwitz HI, Tebbutt NC, Kabbinar F, et al. Efficacy and safety of bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trials. *Oncologist* 2013;18:1004-1012. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23881988>.

752. Loupakis F, Bria E, Vaccaro V, et al. Magnitude of benefit of the addition of bevacizumab to first-line chemotherapy for metastatic colorectal cancer: meta-analysis of randomized clinical trials. *J Exp Clin Cancer Res* 2010;29:58. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20504361>.

753. Lv C, Wu S, Zheng D, et al. The efficacy of additional bevacizumab to cytotoxic chemotherapy regimens for the treatment of colorectal cancer: an updated meta-analysis for randomized trials. *Cancer Biother Radiopharm* 2013;28:501-509. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23768086>.

754. Qu CY, Zheng Y, Zhou M, et al. Value of bevacizumab in treatment of colorectal cancer: A meta-analysis. *World J Gastroenterol* 2015;21:5072-5080. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25945023>.

755. Welch S, Spithoff K, Rumble RB, Maroun J. Bevacizumab combined with chemotherapy for patients with advanced colorectal cancer: a systematic review. *Ann Oncol* 2010;21:1152-1162. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19942597>.

756. Zhang G, Zhou X, Lin C. Efficacy of chemotherapy plus bevacizumab as first-line therapy in patients with metastatic colorectal cancer: a meta-



analysis and up-date. Int J Clin Exp Med 2015;8:1434-1445. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25785152>.

757. Macedo LT, da Costa Lima AB, Sasse AD. Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups. BMC Cancer 2012;12:89. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22414244>.

758. Meyerhardt JA, Li L, Sanoff HK, et al. Effectiveness of bevacizumab with first-line combination chemotherapy for Medicare patients with stage IV colorectal cancer. J Clin Oncol 2012;30:608-615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22253466>.

759. Hartmann H, Muller J, Marschner N. Is there a difference in demography and clinical characteristics in patients treated with and without bevacizumab? J Clin Oncol 2012;30:3317-3318; author reply 3318. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22649139>.

760. Hurwitz HI, Lyman GH. Registries and randomized trials in assessing the effects of bevacizumab in colorectal cancer: is there a common theme? J Clin Oncol 2012;30:580-581. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22253468>.

761. Cui CH, Huang SX, Qi J, et al. Neoadjuvant chemotherapy (NCT) plus targeted agents versus NCT alone in colorectal liver metastases patients: A systematic review and meta-analysis. Oncotarget 2015;6:44005-44018. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26515604>.

762. Snoeren N, van Hillegersberg R, Schouten SB, et al. Randomized phase III study to assess efficacy and safety of adjuvant CAPOX with or without bevacizumab in patients after resection of colorectal liver metastases: HEPATICA study. Neoplasia 2017;19:93-99. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28088688>.

763. Ranpura V, Hapani S, Wu S. Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis. JAMA 2011;305:487-494. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21285426>.

764. Hurwitz HI, Saltz LB, Van Cutsem E, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. J Clin Oncol 2011;29:1757-1764. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21422411>.

765. Dai F, Shu L, Bian Y, et al. Safety of bevacizumab in treating metastatic colorectal cancer: a systematic review and meta-analysis of all randomized clinical trials. Clin Drug Investig 2013;33:779-788. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23979925>.

766. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J Surg Oncol 2005;91:173-180. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16118771>.

767. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 2007;25:5180-5186. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18024865>.

768. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. J Clin Oncol 2008;26:1830-1835. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18398148>.

769. Reddy SK, Morse MA, Hurwitz HI, et al. Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases. J Am Coll Surg 2008;206:96-9106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18155574>.

770. Miles D, Harbeck N, Escudier B, et al. Disease course patterns after discontinuation of bevacizumab: pooled analysis of randomized phase III trials. J Clin Oncol 2011;29:83-88. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21098326>.



771. Miles DW. Reply to P. Potemski. J Clin Oncol 2011;29:e386. Available at: <http://jco.ascopubs.org/content/29/13/e386.full>.

772. Potemski P. Is the postprogression survival time really not shortened in the bevacizumab-containing arms of phase III clinical trials? J Clin Oncol 2011;29:e384-385. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21422432>.

773. U.S. Food & Drug Administration. Package Insert. Erbitux® (cetuximab) injection, for intravenous use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125084s275bl.pdf. Accessed November 17, 2020.

774. Carrato A, Abad A, Massuti B, et al. First-line panitumumab plus FOLFOX4 or FOLFIRI in colorectal cancer with multiple or unresectable liver metastases: A randomised, phase II trial (PLANET-TTD). Eur J Cancer 2017;81:191-202. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28633089>.

775. Pietrantonio F, Cremolini C, Petrelli F, et al. First-line anti-EGFR monoclonal antibodies in panRAS wild-type metastatic colorectal cancer: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2015;96:156-166. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26088456>.

776. Helbling D, Borner M. Successful challenge with the fully human EGFR antibody panitumumab following an infusion reaction with the chimeric EGFR antibody cetuximab. Ann Oncol 2007;18:963-964. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17488734>.

777. Heun J, Holen K. Treatment with panitumumab after a severe infusion reaction to cetuximab in a patient with metastatic colorectal cancer: a case report. Clin Colorectal Cancer 2007;6:529-531. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17553202>.

778. Resch G, Schaberl-Moser R, Kier P, et al. Infusion reactions to the chimeric EGFR inhibitor cetuximab--change to the fully human anti-EGFR monoclonal antibody panitumumab is safe. Ann Oncol 2011;22:486-487. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21239398>.

779. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357:2040-2048. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18003960>.

780. Petrelli F, Borgonovo K, Barni S. The predictive role of skin rash with cetuximab and panitumumab in colorectal cancer patients: a systematic review and meta-analysis of published trials. Target Oncol 2013;8:173-181. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23321777>.

781. Stintzing S, Kapaun C, Laubender RP, et al. Prognostic value of cetuximab-related skin toxicity in metastatic colorectal cancer patients and its correlation with parameters of the epidermal growth factor receptor signal transduction pathway: results from a randomized trial of the GERMAN AIO CRC Study Group. Int J Cancer 2013;132:236-245. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22644776>.

782. Van Cutsem E, Tejpar S, Vanbeckevoort D, et al. Inpatient cetuximab dose escalation in metastatic colorectal cancer according to the grade of early skin reactions: the randomized EVEREST study. J Clin Oncol 2012;30:2861-2868. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22753904>.

783. Burtneess B, Anadkat M, Basti S, et al. NCCN Task Force Report: management of dermatologic and other toxicities associated with EGFR inhibition in patients with cancer. J Natl Compr Canc Netw 2009;7 Suppl 1:5-5. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19470276>.

784. Petrelli F, Cabiddu M, Borgonovo K, Barni S. Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials. Ann Oncol 2012;23:1672-1679. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22241897>.

785. Zhang D, Ye J, Xu T, Xiong B. Treatment related severe and fatal adverse events with cetuximab in colorectal cancer patients: a meta-analysis. J Chemother 2013;25:170-175. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23783142>.

786. Brule SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of



benefit from cetuximab in NCIC CO.17. *Eur J Cancer* 2015;51:1405-1414. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25979833>.

787. Moretto R, Cremolini C, Rossini D, et al. Location of primary tumor and benefit from anti-epidermal growth factor receptor monoclonal antibodies in patients with RAS and BRAF wild-type metastatic colorectal cancer. *Oncologist* 2016;21:988-994. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27382031>.

788. Loupakakis F, Yang D, Yau L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst* 2015;107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25713148>.

789. Chen KH, Shao YY, Chen HM, et al. Primary tumor site is a useful predictor of cetuximab efficacy in the third-line or salvage treatment of KRAS wild-type (exon 2 non-mutant) metastatic colorectal cancer: a nationwide cohort study. *BMC Cancer* 2016;16:327. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27221731>.

790. Warschkow R, Sulz MC, Marti L, et al. Better survival in right-sided versus left-sided stage I - III colon cancer patients. *BMC Cancer* 2016;16:554. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27464835>.

791. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1^o) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance) [abstract]. *ASCO Meeting Abstracts* 2016;34:3504. Available at: <http://meetinglibrary.asco.org/content/161936-176>.

792. Yahagi M, Okabayashi K, Hasegawa H, et al. The worse prognosis of right-sided compared with left-sided colon cancers: A systematic review and meta-analysis. *J Gastrointest Surg* 2016;20:648-655. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26573851>.

793. Wang F, Bai L, Liu TS, et al. Right-sided colon cancer and left-sided colorectal cancers respond differently to cetuximab. *Chin J Cancer* 2015;34:384-393. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26111811>.

794. Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol* 2017;28:1713-1729. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28407110>.

795. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1^o) tumor location on overall survival (OS) and progression free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of all RAS wt patients on CALGB / SWOG 80405 (Alliance) [abstract]. *ESMO Congress* 2016. Available at:

796. Yaeger R, Chatila WK, Lipsyc MD, et al. Clinical Sequencing Defines the Genomic Landscape of Metastatic Colorectal Cancer. *Cancer Cell* 2018;33:125-136.e123. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29316426>.

797. Lang I, Kohne CH, Folprecht G, et al. Quality of life analysis in patients with KRAS wild-type metastatic colorectal cancer treated first-line with cetuximab plus irinotecan, fluorouracil and leucovorin. *Eur J Cancer* 2013;49:439-448. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23116683>.

798. Van Cutsem E, Lenz HJ, Kohne CH, et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. *J Clin Oncol* 2015;33:692-700. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25605843>.

799. Mitchell EP, Piperdi B, Lacouture ME, et al. The efficacy and safety of panitumumab administered concomitantly with FOLFIRI or Irinotecan in second-line therapy for metastatic colorectal cancer: the secondary analysis from STEPP (Skin Toxicity Evaluation Protocol With Panitumumab) by KRAS status. *Clin Colorectal Cancer* 2011;10:333-339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22000810>.

800. Peeters M, Price TJ, Cervantes A, et al. Final results from a randomized phase 3 study of FOLFIRI {+/-} panitumumab for second-line treatment of metastatic colorectal cancer. *Ann Oncol* 2014;25:107-116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24356622>.



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801. Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann Oncol* 2011;22:1535-1546. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21228335>.

802. Tveit KM, Guren T, Glimelius B, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. *J Clin Oncol* 2012;30:1755-1762. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22473155>.

803. Qin S, Li J, Wang L, et al. Efficacy and Tolerability of First-Line Cetuximab Plus Leucovorin, Fluorouracil, and Oxaliplatin (FOLFOX-4) Versus FOLFOX-4 in Patients With RAS Wild-Type Metastatic Colorectal Cancer: The Open-Label, Randomized, Phase III TAILOR Trial. *J Clin Oncol* 2018;Jco2018783183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30199311>.

804. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol* 2014;15:601-611. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24717919>.

805. Bridgewater JA, Pugh SA, Maishman T, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2020;21:398-411. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32014119>.

806. Modest DP, Stintzing S, von Weikersthal LF, et al. Impact of subsequent therapies on outcome of the FIRE-3/AIO KRK0306 trial: first-line therapy with FOLFIRI plus cetuximab or bevacizumab in patients with KRAS wild-type tumors in metastatic colorectal cancer. *J Clin Oncol* 2015;33:3718-3726. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26261259>.

807. O'Neil BH, Venook AP. Trying to understand differing results of FIRE-3 and 80405: does the first treatment matter more than others? *J Clin*

Oncol 2015;33:3686-3688. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26324365>.

808. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. *J Clin Oncol* 2014;32:2240-2247. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24687833>.

809. Rivera F, Karthaus M, Hecht JR, et al. Final analysis of the randomised PEAK trial: overall survival and tumour responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal carcinoma. *Int J Colorectal Dis* 2017;32:1179-1190. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28424871>.

810. Wolpin BM, Bass AJ. Managing advanced colorectal cancer: have we reached the PEAK with current therapies? *J Clin Oncol* 2014;32:2200-2202. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24934780>.

811. Riesco-Martinez MC, Berry SR, Ko YJ, et al. Cost-effectiveness analysis of different sequences of the use of epidermal growth factor receptor inhibitors for wild-type KRAS unresectable metastatic colorectal cancer. *J Oncol Pract* 2016;12:e710-723. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27143148>.

812. Graham CN, Christodouloupoulou A, Knox HN, et al. A within-trial cost-effectiveness analysis of panitumumab compared with bevacizumab in the first-line treatment of patients with wild-type RAS metastatic colorectal cancer in the US. *J Med Econ* 2018;1-9. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30091652>.

813. Shankaran V, Ortendahl JD, Purdum AG, et al. Cost-Effectiveness of Cetuximab as First-line Treatment for Metastatic Colorectal Cancer in the United States. *Am J Clin Oncol* 2018;41:65-72. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26398184>.



NCCN Guidelines Version 1.2022

Colon Cancer

814. Andre T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med* 2020;383:2207-2218. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33264544>.

815. Lenz H-J, Lonardi S, Zagonel V, et al. Nivolumab (NIVO) + low-dose ipilimumab (IPI) as first-line (1L) therapy in microsatellite instability-high/DNA mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Clinical update [abstract]. *Journal of Clinical Oncology* 2019;37:3521-3521. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.3521.

816. Lenz H-J, Lonardi S, Zagonel V, et al. Nivolumab (NIVO) + low-dose ipilimumab (IPI) as first-line (1L) therapy in microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Two-year clinical update [abstract]. *Journal of Clinical Oncology* 2020;38:4040-4040. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.4040.

817. Hoff PM, Pazdur R, Lassere Y, et al. Phase II study of capecitabine in patients with fluorouracil-resistant metastatic colorectal carcinoma. *J Clin Oncol* 2004;22:2078-2083. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15169794>.

818. Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998;352:1413-1418. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9807987>.

819. Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998;352:1407-1412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9807986>.

820. Wulaningsih W, Wardhana A, Watkins J, et al. Irinotecan chemotherapy combined with fluoropyrimidines versus irinotecan alone for overall survival and progression-free survival in patients with advanced

and/or metastatic colorectal cancer. *Cochrane Database Syst Rev* 2016;2:CD008593. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26869023>.

821. Kim GP, Sargent DJ, Mahoney MR, et al. Phase III noninferiority trial comparing irinotecan with oxaliplatin, fluorouracil, and leucovorin in patients with advanced colorectal carcinoma previously treated with fluorouracil: N9841. *J Clin Oncol* 2009;27:2848-2854. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19380443>.

822. Segelov E, Chan D, Shapiro J, et al. The role of biological therapy in metastatic colorectal cancer after first-line treatment: a meta-analysis of randomised trials. *Br J Cancer* 2014;111:1122-1131. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25072258>.

823. Hofheinz RD, Ronellenfitsch U, Kubicka S, et al. Treatment with antiangiogenic drugs in multiple lines in patients with metastatic colorectal cancer: meta-analysis of randomized trials. *Gastroenterol Res Pract* 2016;2016:9189483. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27656206>.

824. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007;25:1658-1664. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17470858>.

825. Kim TW, Elme A, Kusic Z, et al. A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type KRAS or RAS metastatic colorectal cancer. *Br J Cancer* 2016;115:1206-1214. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27736842>.

826. Peeters M, Oliner K, Price TJ, et al. Analysis of KRAS/NRAS mutations in a phase 3 study of panitumumab with FOLFIRI compared with FOLFIRI alone as second-line treatment for metastatic colorectal cancer. *Clin Cancer Res* 2015;21:5469-5479. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26341920>.



827. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351:337-345. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15269313>.

828. Saltz LB, Meropol NJ, Loehrer PJ, et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* 2004;22:1201-1208. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14993230>.

829. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:2311-2319. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18390971>.

830. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol* 2014;15:569-579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24739896>.

831. Price T, Kim TW, Li J, et al. Final results and outcomes by prior bevacizumab exposure, skin toxicity, and hypomagnesaemia from ASPECCT: randomized phase 3 non-inferiority study of panitumumab versus cetuximab in chemorefractory wild-type KRAS exon 2 metastatic colorectal cancer. *Eur J Cancer* 2016;68:51-59. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27716478>.

832. Hecht JR, Cohn A, Dakhil S, et al. SPIRITT: a randomized, multicenter, phase II study of panitumumab with FOLFIRI and bevacizumab with FOLFIRI as second-line treatment in patients with unresectable wild type KRAS metastatic colorectal cancer. *Clin Colorectal Cancer* 2015;14:72-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25982297>.

833. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013;14:29-37. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23168366>.

834. Kubicka S, Greil R, Andre T, et al. Bevacizumab plus chemotherapy continued beyond first progression in patients with metastatic colorectal cancer previously treated with bevacizumab plus chemotherapy: ML18147 study KRAS subgroup findings. *Ann Oncol* 2013;24:2342-2349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23852309>.

835. Masi G, Salvatore L, Boni L, et al. Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. *Ann Oncol* 2015;26:724-730. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25600568>.

836. Iwamoto S, Takahashi T, Tamagawa H, et al. FOLFIRI plus bevacizumab as second-line therapy in patients with metastatic colorectal cancer after first-line bevacizumab plus oxaliplatin-based therapy: the randomized phase III EAGLE study. *Ann Oncol* 2015;26:1427-1433. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25908603>.

837. Cartwright TH, Yim YM, Yu E, et al. Survival outcomes of bevacizumab beyond progression in metastatic colorectal cancer patients treated in US community oncology. *Clin Colorectal Cancer* 2012;11:238-246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22658457>.

838. Grothey A, Flick ED, Cohn AL, et al. Bevacizumab exposure beyond first disease progression in patients with metastatic colorectal cancer: analyses of the ARIES observational cohort study. *Pharmacoepidemiol Drug Saf* 2014;23:726-734. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24830357>.

839. Goldstein DA, El-Rayes BF. Considering Efficacy and Cost, Where Does Ramucirumab Fit in the Management of Metastatic Colorectal Cancer? *Oncologist* 2015;20:981-982. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26265225>.

840. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007;25:1539-1544. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17442997>.



NCCN Guidelines Version 1.2022

Colon Cancer

841. U.S. Food & Drug Administration. Package Insert. ZALTRAP® (ziv-aflibercept) injection for intravenous infusion. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125418s0471bl.pdf. Accessed November 17, 2020.

842. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012;30:3499-3506. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22949147>.

843. Tabernero J, Van Cutsem E, Lakomy R, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. *Eur J Cancer* 2014;50:320-331. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24140268>.

844. Folprecht G, Pericay C, Saunders MP, et al. Oxaliplatin and 5-FU/folinic acid (modified FOLFOX6) with or without aflibercept in first-line treatment of patients with metastatic colorectal cancer: the AFFIRM study. *Ann Oncol* 2016;27:1273-1279. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27091810>.

845. U.S. Food & Drug Administration. Package Insert. CYRAMZA (ramucirumab) injection, for intravenous use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125477s0371bl.pdf. Accessed November 17, 2020.

846. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol* 2015;16:499-508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25877855>.

847. Obermannova R, Van Cutsem E, Yoshino T, et al. Subgroup analysis in RAISE: a randomized, double-blind phase III study of irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) plus ramucirumab or placebo in patients

with metastatic colorectal carcinoma progression. *Ann Oncol* 2016;27:2082-2090. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27573561>.

848. Arnold D, Fuchs CS, Tabernero J, et al. Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab. *Ann Oncol* 2017;28:2932-2942. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28950290>.

849. Van Cutsem E, Huijberts S, Grothey A, et al. Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E-Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study. *J Clin Oncol* 2019;37:1460-1469. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30892987>.

850. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. *N Engl J Med* 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31566309>.

851. Kopetz S, Grothey A, Cutsem EV, et al. Encorafenib plus cetuximab with or without binimetinib for BRAF V600E-mutant metastatic colorectal cancer: Quality-of-life results from a randomized, three-arm, phase III study versus the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC) [abstract]. *J Clin Oncol* 2020;38; suppl 4:8. Available at: <https://meetinglibrary.asco.org/record/181898/abstract>.

852. Kopetz S, McDonough SL, Lenz H-J, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406) [abstract]. *J Clin Oncol* 2017;35 (suppl):3505. Available at: http://abstracts.asco.org/199/AbstView_199_194502.html.

853. Corcoran RB, Andre T, Atreya CE, et al. Combined BRAF, EGFR, and MEK Inhibition in Patients with BRAF(V600E)-Mutant Colorectal Cancer. *Cancer Discov* 2018;8:428-443. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29431699>.



NCCN Guidelines Version 1.2022

Colon Cancer

854. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol* 2019;20:518-530. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30857956>.

855. Gupta R, Garrett-Mayer E, Halabi S, et al. Pertuzumab plus trastuzumab (P+T) in patients (Pts) with colorectal cancer (CRC) with ERBB2 amplification or overexpression: Results from the TAPUR Study [abstract]. *Journal of Clinical Oncology* 2020;38:132-132. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.132.

856. Siena S, Bartolomeo MD, Raghav KPS, et al. A phase II, multicenter, open-label study of trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): DESTINY-CRC01 [abstract]. *Journal of Clinical Oncology* 2020;38:4000-4000. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.4000.

857. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;372:2509-2520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26028255>.

858. Le DT, Kim TW, Van Cutsem E, et al. Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164. *J Clin Oncol* 2020;38:11-19. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31725351>.

859. U.S. Food & Drug Administration. Package Insert. OPDIVO (nivolumab) injection, for intravenous use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125554s0711bl.pdf. Accessed November 17, 2020.

860. Overman MJ, Lonardi S, Wong KYM, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. *J Clin Oncol* 2018;36:773-779. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29355075>.

861. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol* 2017;18:1182-1191. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28734759>.

862. Morse MA, Overman MJ, Hartman L, et al. Safety of Nivolumab plus Low-Dose Ipilimumab in Previously Treated Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer. *Oncologist* 2019;24:1453-1461. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31147488>.

863. U.S. Food & Drug Administration. Package Insert. JEMPERLI (dostarlimab-gxly) injection, for intravenous use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761223s000bl.pdf. Accessed August 31, 2021.

864. Andre T, Berton D, Curigliano G, et al. Safety and efficacy of anti-PD-1 antibody dostarlimab in patients (pts) with mismatch repair-deficient (dMMR) solid cancers: Results from GARNET study [abstract]. *Journal of Clinical Oncology* 2021;39:9-9. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.3_suppl.9.

865. Sul J, Blumenthal GM, Jiang X, et al. FDA approval summary: pembrolizumab for the treatment of patients with metastatic non-small cell lung cancer whose tumors express programmed death-ligand 1. *Oncologist* 2016;21:643-650. Available at: <http://theoncologist.alphamedpress.org/content/21/5/643.short>.

866. Lewis C. Programmed death-1 inhibition in cancer with a focus on non-small cell lung cancer: rationale, nursing implications, and patient management strategies. *Clin J Oncol Nurs* 2016;20:319-326. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27206299>.

867. Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016;60:190-209. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27085692>.



868. Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016;60:210-225. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27084345>.

869. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol* 2016;35:709-717. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27646942>.

870. Nishino M, Chambers ES, Chong CR, et al. Anti-PD-1 inhibitor-related pneumonitis in non-small cell lung cancer. *Cancer Immunol Res* 2016;4:289-293. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26865455>.

871. Nishino M, Sholl LM, Hodi FS, et al. Anti-PD-1-related pneumonitis during cancer immunotherapy. *N Engl J Med* 2015;373:288-290. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26176400>.

872. U.S. Food & Drug Administration. Package Insert. ROZLYTREK (entrectinib) capsules, for oral use. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212725s000bl.pdf. Accessed November 17, 2020.

873. U.S. Food & Drug Administration. Package Insert. VITRAKVI® (larotrectinib) capsules, for oral use. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210861s000bl.pdf. Accessed November 17, 2020.

874. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol* 2020;21:531-540. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32105622>.

875. Berlin J, Hong DS, Deeken JF, et al. Efficacy and safety of larotrectinib in patients with TRK fusion gastrointestinal cancer [abstract]. *Journal of Clinical Oncology* 2020;38:824-824. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.824.

876. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 2020;21:271-282. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31838007>.

877. U.S. Food & Drug Administration. Package Insert. STIVARGA (regorafenib) tablets, for oral use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203085s013bl.pdf. Accessed November 17, 2020.

878. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381:303-312. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23177514>.

879. Li J, Qin S, Xu R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2015;16:619-629. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25981818>.

880. Belum VR, Wu S, Lacouture ME. Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: a meta-analysis. *Invest New Drugs* 2013;31:1078-1086. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23700287>.

881. Van Cutsem E, Martinelli E, Cascinu S, et al. Regorafenib for Patients with Metastatic Colorectal Cancer Who Progressed After Standard Therapy: Results of the Large, Single-Arm, Open-Label Phase IIIb CONSIGN Study. *Oncologist* 2018. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30190299>.

882. Adenis A, de la Fouchardiere C, Paule B, et al. Survival, safety, and prognostic factors for outcome with Regorafenib in patients with metastatic colorectal cancer refractory to standard therapies: results from a multicenter study (REBACCA) nested within a compassionate use program. *BMC Cancer* 2016;16:412. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27389564>.



NCCN Guidelines Version 1.2022

Colon Cancer

883. Ducreux M, Petersen LN, Ohler L, et al. Safety and effectiveness of regorafenib in patients with metastatic colorectal cancer in routine clinical practice in the prospective, observational CORRELATE study. *Eur J Cancer* 2019;123:146-154. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31698328>.

884. Bekaii-Saab TS, Ou FS, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. *Lancet Oncol* 2019;20:1070-1082. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31262657>.

885. Bendell JC, Rosen LS, Mayer RJ, et al. Phase 1 study of oral TAS-102 in patients with refractory metastatic colorectal cancer. *Cancer Chemother Pharmacol* 2015;76:925-932. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26370544>.

886. Yoshino T, Mizunuma N, Yamazaki K, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol* 2012;13:993-1001. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22951287>.

887. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 2015;372:1909-1919. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25970050>.

888. U.S. Food & Drug Administration. Package Insert. LONSURF (trifluridine and tipiracil) tablets, for oral use. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207981s009bl.pdf. Accessed November 17, 2020.

889. Yoshino T, Uetake H, Fujita N, et al. TAS-102 safety in metastatic colorectal cancer: results from the first postmarketing surveillance study. *Clin Colorectal Cancer* 2016;15:e205-e211. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27324983>.

890. Van Cutsem E, Mayer RJ, Laurent S, et al. The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo

with best supportive care in patients with metastatic colorectal cancer. *Eur J Cancer* 2018;90:63-72. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29274618>.

891. Kuboki Y, Nishina T, Shinozaki E, et al. TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. *Lancet Oncol* 2017;18:1172-1181. Available at: <https://pubmed.ncbi.nlm.nih.gov/28760399/>.

892. Pfeiffer P, Yilmaz M, Möller S, et al. TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial. *Lancet Oncol* 2020;21:412-420. Available at: <https://pubmed.ncbi.nlm.nih.gov/31999946/>.

893. Fujii H, Matsushashi N, Kitahara M, et al. Bevacizumab in Combination with TAS-102 Improves Clinical Outcomes in Patients with Refractory Metastatic Colorectal Cancer: A Retrospective Study. *Oncologist* 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31748337>.

894. Patel AK, Barghout V, Yenikomshian MA, et al. Real-World Adherence in Patients with Metastatic Colorectal Cancer Treated with Trifluridine plus Tipiracil or Regorafenib. *Oncologist* 2020;25:e75-e84. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31591140>.

895. Moulton CA, Gu CS, Law CH, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. *JAMA* 2014;311:1863-1869. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24825641>.

896. Maffione AM, Lopci E, Bluemel C, et al. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. *Eur J Nucl Med Mol Imaging* 2015;42:152-163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25319712>.



897. Delbeke D, Martin WH. PET and PET-CT for evaluation of colorectal carcinoma. *Semin Nucl Med* 2004;34:209-223. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15202102>.

898. Adam R, Miller R, Pitombo M, et al. Two-stage hepatectomy approach for initially unresectable colorectal hepatic metastases. *Surg Oncol Clin N Am* 2007;16:525-536. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17606192>.

899. Baltatzis M, Chan AK, Jegatheeswaran S, et al. Colorectal cancer with synchronous hepatic metastases: systematic review of reports comparing synchronous surgery with sequential bowel-first or liver-first approaches. *Eur J Surg Oncol* 2016;42:159-165. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26733368>.

900. Chen J, Li Q, Wang C, et al. Simultaneous vs. staged resection for synchronous colorectal liver metastases: a metaanalysis. *Int J Colorectal Dis* 2011;26:191-199. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20669024>.

901. Feng Q, Wei Y, Zhu D, et al. Timing of hepatectomy for resectable synchronous colorectal liver metastases: for whom simultaneous resection is more suitable--a meta-analysis. *PLoS One* 2014;9:e104348. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25093337>.

902. Lykoudis PM, O'Reilly D, Nastos K, Fusai G. Systematic review of surgical management of synchronous colorectal liver metastases. *Br J Surg* 2014;101:605-612. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24652674>.

903. Mayo SC, Pulitano C, Marques H, et al. Surgical management of patients with synchronous colorectal liver metastasis: a multicenter international analysis. *J Am Coll Surg* 2013;216:707-716; discussion 716-708. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23433970>.

904. Reddy SK, Pawlik TM, Zorzi D, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. *Ann Surg Oncol* 2007;14:3481-3491. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17805933>.

905. Slessor AA, Simillis C, Goldin R, et al. A meta-analysis comparing simultaneous versus delayed resections in patients with synchronous colorectal liver metastases. *Surg Oncol* 2013;22:36-47. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23253399>.

906. Worni M, Mantyh CR, Akushevich I, et al. Is there a role for simultaneous hepatic and colorectal resections? A contemporary view from NSQIP. *J Gastrointest Surg* 2012;16:2074-2085. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22972010>.

907. Kelly ME, Spolverato G, Le GN, et al. Synchronous colorectal liver metastasis: a network meta-analysis review comparing classical, combined, and liver-first surgical strategies. *J Surg Oncol* 2015;111:341-351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25363294>.

908. Reddy SK, Zorzi D, Lum YW, et al. Timing of multimodality therapy for resectable synchronous colorectal liver metastases: a retrospective multi-institutional analysis. *Ann Surg Oncol* 2009;16:1809-1819. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18979139>.

909. Brouquet A, Mortenson MM, Vauthey JN, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? *J Am Coll Surg* 2010;210:934-941. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20510802>.

910. de Jong MC, van Dam RM, Maas M, et al. The liver-first approach for synchronous colorectal liver metastasis: a 5-year single-centre experience. *HPB (Oxford)* 2011;13:745-752. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21929676>.

911. De Rosa A, Gomez D, Brooks A, Cameron IC. "Liver-first" approach for synchronous colorectal liver metastases: is this a justifiable approach? *J Hepatobiliary Pancreat Sci* 2013;20:263-270. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23325126>.

912. Jegatheeswaran S, Mason JM, Hancock HC, Siriwardena AK. The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: a systematic review. *JAMA Surg*



2013;148:385-391. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23715907>.

913. Lam VW, Laurence JM, Pang T, et al. A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases. *HPB (Oxford)* 2014;16:101-108. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23509899>.

914. Mentha G, Roth AD, Terraz S, et al. 'Liver first' approach in the treatment of colorectal cancer with synchronous liver metastases. *Dig Surg* 2008;25:430-435. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19212115>.

915. Mentha G, Majno P, Terraz S, et al. Treatment strategies for the management of advanced colorectal liver metastases detected synchronously with the primary tumour. *Eur J Surg Oncol* 2007;33 Suppl 2:S76-83. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18006267>.

916. Van Dessel E, Fierens K, Pattyn P, et al. Defining the optimal therapy sequence in synchronous resectable liver metastases from colorectal cancer: a decision analysis approach. *Acta Chir Belg* 2009;109:317-320. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19943586>.

917. Bartlett DL, Berlin J, Lauwers GY, et al. Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006;13:1284-1292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16955384>.

918. Faron M, Pignon JP, Malka D, et al. Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials. *Eur J Cancer* 2015;51:166-176. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25465185>.

919. Ishihara S, Nishikawa T, Tanaka T, et al. Benefit of primary tumor resection in stage IV colorectal cancer with unresectable metastasis: a multicenter retrospective study using a propensity score analysis. *Int J Colorectal Dis* 2015;30:807-812. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25922146>.

920. Karoui M, Roudot-Thoraval F, Mesli F, et al. Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a multicentric study. *Dis Colon Rectum* 2011;54:930-938. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21730780>.

921. Venderbosch S, de Wilt JH, Teerenstra S, et al. Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: retrospective analysis of two randomized studies and a review of the literature. *Ann Surg Oncol* 2011;18:3252-3260. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21822557>.

922. Ahmed S, Shahid RK, Leis A, et al. Should noncurative resection of the primary tumour be performed in patients with stage iv colorectal cancer? A systematic review and meta-analysis. *Curr Oncol* 2013;20:e420-441. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24155639>.

923. Anwar S, Peter MB, Dent J, Scott NA. Palliative excisional surgery for primary colorectal cancer in patients with incurable metastatic disease. Is there a survival benefit? A systematic review. *Colorectal Dis* 2012;14:920-930. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21899714>.

924. Clancy C, Burke JP, Barry M, et al. A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival. *Ann Surg Oncol* 2014;21:3900-3908. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24849523>.

925. Tarantino I, Warschkow R, Worni M, et al. Prognostic relevance of palliative primary tumor removal in 37,793 metastatic colorectal cancer patients: a population-based, propensity score-adjusted trend analysis. *Ann Surg* 2015;262:112-120. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25373464>.

926. Gulack BC, Nussbaum DP, Keenan JE, et al. Surgical resection of the primary tumor in stage IV colorectal cancer without metastasectomy is associated with improved overall survival compared with



chemotherapy/radiation therapy alone. Dis Colon Rectum 2016;59:299-305. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26953988>.

927. Alawadi Z, Phatak UR, Hu CY, et al. Comparative effectiveness of primary tumor resection in patients with stage IV colon cancer. Cancer 2016;123:1124-1133. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27479827>.

928. Kanemitsu Y, Shitara K, Mizusawa J, et al. A randomized phase III trial comparing primary tumor resection plus chemotherapy with chemotherapy alone in incurable stage IV colorectal cancer: JCOG1007 study (iPACS) [abstract]. Journal of Clinical Oncology 2020;38:7-7. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.7.

929. McCahill LE, Yothers G, Sharif S, et al. Primary mFOLFOX6 plus bevacizumab without resection of the primary tumor for patients presenting with surgically unresectable metastatic colon cancer and an intact asymptomatic colon cancer: definitive analysis of NSABP trial C-10. J Clin Oncol 2012;30:3223-3228. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22869888>.

930. Cirocchi R, Trastulli S, Abraha I, et al. Non-resection versus resection for an asymptomatic primary tumour in patients with unresectable Stage IV colorectal cancer. Cochrane Database Syst Rev 2012;8:CD008997. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22895981>.

931. Yang TX, Billah B, Morris DL, Chua TC. Palliative resection of the primary tumour in patients with Stage IV colorectal cancer: systematic review and meta-analysis of the early outcome after laparoscopic and open colectomy. Colorectal Dis 2013;15:e407-419. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23895669>.

932. Joyce DL, Wahl RL, Patel PV, et al. Preoperative positron emission tomography to evaluate potentially resectable hepatic colorectal metastases. Arch Surg 2006;141:1220-1226; discussion 1227. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17178965>.

933. Pelosi E, Deandreis D. The role of 18F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) in the management of patients with colorectal cancer. Eur J Surg Oncol 2007;33:1-6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17126522>.

934. Gill S, Berry S, Biagi J, et al. Progression-free survival as a primary endpoint in clinical trials of metastatic colorectal cancer. Curr Oncol 2011;18 Suppl 2:S5-S10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21969810>.

935. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? J Clin Oncol 2012;30:1030-1033. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22370321>.

936. Chibaudel B, Bonnetain F, Shi Q, et al. Alternative end points to evaluate a therapeutic strategy in advanced colorectal cancer: evaluation of progression-free survival, duration of disease control, and time to failure of strategy--an Aide et Recherche en Cancerologie Digestive Group Study. J Clin Oncol 2011;29:4199-4204. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21969501>.

937. Shi Q, de Gramont A, Grothey A, et al. Individual patient data analysis of progression-free survival versus overall survival as a first-line end point for metastatic colorectal cancer in modern randomized trials: findings from the analysis and research in cancers of the digestive system database. J Clin Oncol 2015;33:22-28. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25385741>.

938. Carrera G, Garcia-Albeniz X, Ayuso JR, et al. Design and endpoints of clinical and translational trials in advanced colorectal cancer. a proposal from GROUP Espanol Multidisciplinar en Cancer Digestivo (GEMCAD). Rev Recent Clin Trials 2011;6:158-170. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21241233>.

939. Claret L, Gupta M, Han K, et al. Evaluation of tumor-size response metrics to predict overall survival in Western and Chinese patients with first-line metastatic colorectal cancer. J Clin Oncol 2013;31:2110-2114. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23650411>.



940. Sharma MR, Gray E, Goldberg RM, et al. Resampling the N9741 trial to compare tumor dynamic versus conventional end points in randomized phase II trials. *J Clin Oncol* 2015;33:36-41. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25349295>.

941. Seo SI, Lim SB, Yoon YS, et al. Comparison of recurrence patterns between ≤ 5 years and > 5 years after curative operations in colorectal cancer patients. *J Surg Oncol* 2013;108:9-13. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23754582>.

942. Pietra N, Sarli L, Costi R, et al. Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. *Dis Colon Rectum* 1998;41:1127-1133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9749496>.

943. Rodriguez-Moranta F, Salo J, Arcusa A, et al. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. *J Clin Oncol* 2006;24:386-393. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16365182>.

944. Secco GB, Fardelli R, Gianquinto D, et al. Efficacy and cost of risk-adapted follow-up in patients after colorectal cancer surgery: a prospective, randomized and controlled trial. *Eur J Surg Oncol* 2002;28:418-423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12099653>.

945. Desch CE, Benson AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol* 2005;23:8512-8519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16260687>.

946. Figueredo A, Rumble RB, Maroun J, et al. Follow-up of patients with curatively resected colorectal cancer: a practice guideline. *BMC Cancer* 2003;3:26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14529575>.

947. Pita-Fernandez S, Alhayek-Ai M, Gonzalez-Martin C, et al. Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis.

Ann Oncol 2015;26:644-656. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25411419>.

948. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *BMJ* 2002;324:813-813. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11934773>.

949. Mokhles S, Macbeth F, Farewell V, et al. Meta-analysis of colorectal cancer follow-up after potentially curative resection. *Br J Surg* 2016;103:1259-1268. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27488593>.

950. Kahi CJ, Boland CR, Dominitz JA, et al. Colonoscopy surveillance after colorectal cancer resection: recommendations of the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2016;150:758-768 e711. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26892199>.

951. Tsikitis VL, Malireddy K, Green EA, et al. Postoperative surveillance recommendations for early stage colon cancer based on results from the clinical outcomes of surgical therapy trial. *J Clin Oncol* 2009;27:3671-3676. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19564531>.

952. Guyot F, Faivre J, Manfredi S, et al. Time trends in the treatment and survival of recurrences from colorectal cancer. *Ann Oncol* 2005;16:756-761. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15790673>.

953. Primrose JN, Perera R, Gray A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA* 2014;311:263-270. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24430319>.

954. Wille-Jorgensen P, Syk I, Smedh K, et al. Effect of More vs Less Frequent Follow-up Testing on Overall and Colorectal Cancer-Specific Mortality in Patients With Stage II or III Colorectal Cancer: The COLOFOL Randomized Clinical Trial. *Jama* 2018;319:2095-2103. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29800179>.



955. Verberne CJ, Zhan Z, van den Heuvel E, et al. Intensified follow-up in colorectal cancer patients using frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging: Results of the randomized "CEAwatch" trial. *Eur J Surg Oncol* 2015;41:1188-1196. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26184850>.

956. Rosati G, Ambrosini G, Barni S, et al. A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma. *Ann Oncol* 2016;27:274-280. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26578734>.

957. Lepage C, Phelip JM, Cany L, et al. Effect of 5 years of imaging and CEA follow-up to detect recurrence of colorectal cancer: The FFCD PRODIGE 13 randomised phase III trial. *Dig Liver Dis* 2015;47:529-531. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25933809>.

958. Lepage C, Phelip JM, Cany L, et al. Effect of 5 years of imaging and CEA follow-up to detect recurrence of colorectal cancer (CRC) - PRODIGE 13 a FFCD phase III trial [abstract]. *Annals of Oncology* 2020;31:S410. Available at: <https://doi.org/10.1016/j.annonc.2020.08.509>.

959. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006;24:5313-5327. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17060676>.

960. Pfister DG, Benson AB, 3rd, Somerfield MR. Clinical practice. Surveillance strategies after curative treatment of colorectal cancer. *N Engl J Med* 2004;350:2375-2382. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15175439>.

961. Patel K, Hadar N, Lee J, et al. The lack of evidence for PET or PET/CT surveillance of patients with treated lymphoma, colorectal cancer, and head and neck cancer: a systematic review. *J Nucl Med* 2013;54:1518-1527. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23776200>.

962. Green RJ, Metlay JP, Propert K, et al. Surveillance for second primary colorectal cancer after adjuvant chemotherapy: an analysis of

Intergroup 0089. *Ann Intern Med* 2002;136:261-269. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11848723>.

963. Meyerhardt JA, Mangu PB, Flynn PJ, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: american society of clinical oncology clinical practice guideline endorsement. *J Clin Oncol* 2013;31:4465-4470. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24220554>.

964. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer. *Cancer Care Ontario*; 2016. Available at: <https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/256>. Accessed November 17, 2020.

965. Steele SR, Chang GJ, Hendren S, et al. Practice guideline for the surveillance of patients after curative treatment of colon and rectal cancer. *Dis Colon Rectum* 2015;58:713-725. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26163950>.

966. Butte JM, Gonen M, Allen PJ, et al. Recurrence after partial hepatectomy for metastatic colorectal cancer: potentially curative role of salvage repeat resection. *Ann Surg Oncol* 2015;22:2761-2771. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25572686>.

967. Hyder O, Dodson RM, Mayo SC, et al. Post-treatment surveillance of patients with colorectal cancer with surgically treated liver metastases. *Surgery* 2013;154:256-265. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23889953>.

968. Litvka A, Cercek A, Segal N, et al. False-positive elevations of carcinoembryonic antigen in patients with a history of resected colorectal cancer. *J Natl Compr Canc Netw* 2014;12:907-913. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24925201>.

969. Nicholson BD, Shinkins B, Pathiraja I, et al. Blood CEA levels for detecting recurrent colorectal cancer. *Cochrane Database Syst Rev* 2015:CD011134. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26661580>.



970. Nicholson BD, Shinkins B, Mant D. Blood measurement of carcinoembryonic antigen level for detecting recurrence of colorectal cancer. *JAMA* 2016;316:1310-1311. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27673308>.

971. Lu YY, Chen JH, Chien CR, et al. Use of FDG-PET or PET/CT to detect recurrent colorectal cancer in patients with elevated CEA: a systematic review and meta-analysis. *Int J Colorectal Dis* 2013;28:1039-1047. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23407908>.

972. Martin EW, Minton JP, Carey LC. CEA-directed second-look surgery in the asymptomatic patient after primary resection of colorectal carcinoma. *Ann Surg* 1985;202:310-317. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/4037904>.

973. Hewitt M, Greenfield S, Stovall E, eds. From Cancer Patient to Cancer Survivor: Lost in Transition. Committee on Cancer Survivorship: Improving Care and Quality of Life, Institute of Medicine and National Research Council: National Academy of Sciences; 2006. Available at: <http://www.nap.edu/catalog/11468.html>.

974. El-Shami K, Oeffinger KC, Erb NL, et al. American Cancer Society Colorectal Cancer Survivorship Care Guidelines. *CA Cancer J Clin* 2015;65:428-455. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26348643>.

975. Desnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. *Eur J Cancer Care (Engl)* 2006;15:244-251. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16882120>.

976. Downing A, Morris EJ, Richards M, et al. Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis. *J Clin Oncol* 2015;33:616-624. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25559806>.

977. Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. *Aliment Pharmacol*

Ther 2003;18:987-994. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14616164>.

978. McGough C, Baldwin C, Frost G, Andreyev HJ. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. *Br J Cancer* 2004;90:2278-2287. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15162154>.

979. Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer: patient-reported symptoms 4 years after diagnosis. *Cancer* 2007;110:2075-2082. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17849466>.

980. Sprangers MA, Taal BG, Aaronson NK, te Velde A. Quality of life in colorectal cancer. Stoma vs. nonstoma patients. *Dis Colon Rectum* 1995;38:361-369. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7720441>.

981. Hong KS, Oh BY, Kim EJ, et al. Psychological attitude to self-appraisal of stoma patients: prospective observation of stoma duration effect to self-appraisal. *Ann Surg Treat Res* 2014;86:152-160. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24761424>.

982. Jansen L, Herrmann A, Stegmaier C, et al. Health-related quality of life during the 10 years after diagnosis of colorectal cancer: a population-based study. *J Clin Oncol* 2011;29:3263-3269. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21768465>.

983. Lynch BM, Steginga SK, Hawkes AL, et al. Describing and predicting psychological distress after colorectal cancer. *Cancer* 2008;112:1363-1370. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18318044>.

984. Mols F, Beijers T, Lemmens V, et al. Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: results from the population-based PROFILES registry. *J Clin Oncol* 2013;31:2699-2707. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23775951>.



985. Thong MS, Mols F, Wang XS, et al. Quantifying fatigue in (long-term) colorectal cancer survivors: a study from the population-based patient reported outcomes following initial treatment and long term evaluation of survivorship registry. *Eur J Cancer* 2013;49:1957-1966. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23453750>.

986. Vardy JL, Dhillon HM, Pond GR, et al. Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal, controlled study. *J Clin Oncol* 2015;33:4085-4092. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26527785>.

987. Wright P, Downing A, Morris EJ, et al. Identifying social distress: a cross-sectional survey of social outcomes 12 to 36 months after colorectal cancer diagnosis. *J Clin Oncol* 2015;33:3423-3430. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26282636>.

988. Denlinger CS, Barsevick AM. The challenges of colorectal cancer survivorship. *J Natl Compr Canc Netw* 2009;7:883-893; quiz 894. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19755048>.

989. Faul LA, Shibata D, Townsend I, Jacobsen PB. Improving survivorship care for patients with colorectal cancer. *Cancer Control* 2010;17:35-43. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20010517>.

990. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol* 2006;24:3535-3541. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16822843>.

991. Meyerhardt JA, Giovannucci EL, Ogino S, et al. Physical activity and male colorectal cancer survival. *Arch Intern Med* 2009;169:2102-2108. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20008694>.

992. Campbell PT, Patel AV, Newton CC, et al. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. *J Clin Oncol* 2013;31:876-885. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23341510>.

993. Kuiper JG, Phipps AI, Neuhouwer ML, et al. Recreational physical activity, body mass index, and survival in women with colorectal cancer. *Cancer Causes Control* 2012;23:1939-1948. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23053793>.

994. Arem H, Pfeiffer RM, Engels EA, et al. Pre- and postdiagnosis physical activity, television viewing, and mortality among patients with colorectal cancer in the National Institutes of Health-AARP Diet and Health Study. *J Clin Oncol* 2015;33:180-188. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25488967>.

995. Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. Association between physical activity and mortality in colorectal cancer: A meta-analysis of prospective cohort studies. *Int J Cancer* 2013;133:1905-1913. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23580314>.

996. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Ann Oncol* 2014;25:1293-1311. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24644304>.

997. Wu W, Guo F, Ye J, et al. Pre- and post-diagnosis physical activity is associated with survival benefits of colorectal cancer patients: a systematic review and meta-analysis. *Oncotarget* 2016;7:52095-52103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27437765>.

998. Dignam JJ, Polite BN, Yothers G, et al. Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. *J Natl Cancer Inst* 2006;98:1647-1654. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17105987>.

999. Sinicrope FA, Foster NR, Yothers G, et al. Body mass index at diagnosis and survival among colon cancer patients enrolled in clinical trials of adjuvant chemotherapy. *Cancer* 2013;119:1528-1536. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23310947>.

1000. Campbell PT, Newton CC, Dehal AN, et al. Impact of body mass index on survival after colorectal cancer diagnosis: the Cancer Prevention



Study-II Nutrition Cohort. J Clin Oncol 2012;30:42-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22124093>.

1001. Lee J, Meyerhardt JA, Giovannucci E, Jeon JY. Association between body mass index and prognosis of colorectal cancer: a meta-analysis of prospective cohort studies. PLoS One 2015;10:e0120706. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25811460>.

1002. Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA, et al. Metabolic dysfunction, obesity, and survival among patients with early-stage colorectal cancer. J Clin Oncol 2016. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27601537>.

1003. Daniel CR, Shu X, Ye Y, et al. Severe obesity prior to diagnosis limits survival in colorectal cancer patients evaluated at a large cancer centre. Br J Cancer 2016;114:103-109. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26679375>.

1004. Doleman B, Mills KT, Lim S, et al. Body mass index and colorectal cancer prognosis: a systematic review and meta-analysis. Tech Coloproctol 2016;20:517-535. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27343117>.

1005. Laake I, Larsen IK, Selmer R, et al. Pre-diagnostic body mass index and weight change in relation to colorectal cancer survival among incident cases from a population-based cohort study. BMC Cancer 2016;16:402. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27387027>.

1006. Renfro LA, Loupakis F, Adams RA, et al. Body mass index is prognostic in metastatic colorectal cancer: pooled analysis of patients from first-line clinical trials in the ARCAD database. J Clin Oncol 2016;34:144-150. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26503203>.

1007. Kroenke CH, Neugebauer R, Meyerhardt J, et al. Analysis of body mass index and mortality in patients with colorectal cancer using causal diagrams. JAMA Oncol 2016;2:1137-1145. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27196302>.

1008. Renehan AG, Sperrin M. The obesity paradox and mortality after colorectal cancer: a causal conundrum. JAMA Oncol 2016;2:1127-1129. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27195485>.

1009. Meyerhardt JA, Niedzwiecki D, Hollis D, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA 2007;298:754-764. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17699009>.

1010. Meyerhardt JA, Sato K, Niedzwiecki D, et al. Dietary glycemic load and cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Natl Cancer Inst 2012;104:1702-1711. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23136358>.

1011. Fuchs MA, Sato K, Niedzwiecki D, et al. Sugar-sweetened beverage intake and cancer recurrence and survival in CALGB 89803 (Alliance). PLoS One 2014;9:e99816. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24937507>.

1012. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:242-274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22539238>.

1013. Hawkes AL, Chambers SK, Pakenham KI, et al. Effects of a telephone-delivered multiple health behavior change intervention (CanChange) on health and behavioral outcomes in survivors of colorectal cancer: a randomized controlled trial. J Clin Oncol 2013;31:2313-2321. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23690410>.

1014. Sun V, Grant M, Wendel CS, et al. Dietary and behavioral adjustments to manage bowel dysfunction after surgery in long-term colorectal cancer survivors. Ann Surg Oncol 2015;22:4317-4324. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26159443>.

1015. Cai H, Zhang G, Wang Z, et al. Relationship between the use of statins and patient survival in colorectal cancer: a systematic review and meta-analysis. PLoS One 2015;10:e0126944. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26030771>.



1016. Cardwell CR, Hicks BM, Hughes C, Murray LJ. Statin use after colorectal cancer diagnosis and survival: a population-based cohort study. *J Clin Oncol* 2014;32:3177-3183. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25092779>.

1017. Bains SJ, Mahic M, Myklebust TA, et al. Aspirin as secondary prevention in patients with colorectal cancer: an unselected population-based study. *J Clin Oncol* 2016;34:2501-2508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27247217>.

1018. Bastiaannet E, Sampieri K, Dekkers OM, et al. Use of aspirin postdiagnosis improves survival for colon cancer patients. *Br J Cancer* 2012;106:1564-1570. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22454078>.

1019. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. *JAMA* 2009;302:649-658. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19671906>.

1020. Goh CH, Leong WQ, Chew MH, et al. Post-operative aspirin use and colorectal cancer-specific survival in patients with stage I-III colorectal cancer. *Anticancer Res* 2014;34:7407-7414. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25503181>.

1021. Li P, Wu H, Zhang H, et al. Aspirin use after diagnosis but not prediagnosis improves established colorectal cancer survival: a meta-analysis. *Gut* 2015;64:1419-1425. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25239119>.

1022. McCowan C, Munro AJ, Donnan PT, Steele RJ. Use of aspirin post-diagnosis in a cohort of patients with colorectal cancer and its association with all-cause and colorectal cancer specific mortality. *Eur J Cancer* 2013;49:1049-1057. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23182687>.

1023. Ng K, Meyerhardt JA, Chan AT, et al. Aspirin and COX-2 inhibitor use in patients with stage III colon cancer. *J Natl Cancer Inst* 2015;107:345. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25432409>.

1024. Domingo E, Church DN, Sieber O, et al. Evaluation of PIK3CA mutation as a predictor of benefit from nonsteroidal anti-inflammatory drug therapy in colorectal cancer. *J Clin Oncol* 2013;31:4297-4305. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24062397>.

1025. Elwood PC, Morgan G, Pickering JE, et al. Aspirin in the treatment of cancer: reductions in metastatic spread and in mortality: a systematic review and meta-analyses of published studies. *PLoS One* 2016;11:e0152402. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27096951>.

1026. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. *N Engl J Med* 2012;367:1596-1606. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23094721>.

1027. Nan H, Hutter CM, Lin Y, et al. Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants. *JAMA* 2015;313:1133-1142. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25781442>.

1028. Reimers MS, Bastiaannet E, Langley RE, et al. Expression of HLA class I antigen, aspirin use, and survival after a diagnosis of colon cancer. *JAMA Intern Med* 2014;174:732-739. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24687028>.

1029. Paleari L, Puntoni M, Clavarezza M, et al. PIK3CA mutation, aspirin use after diagnosis and survival of colorectal cancer: a systematic review and meta-analysis of epidemiological studies. *Clin Oncol (R Coll Radiol)* 2016;28:317-326. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26712086>.

1030. Dulai PS, Singh S, Marquez E, et al. Chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia: systematic review and network meta-analysis. *Bmj* 2016;355:i6188. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27919915>.

1031. Whitlock EP, Burda BU, Williams SB, et al. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the



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Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2022 Colon Cancer

U.S. Preventive Services Task Force. Ann Intern Med 2016;164:826-835.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27064261>.

