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 Gastroenterology
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NCCN Guidelines Panel Disclosures
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Staging
This discussion is being updated to correspond with the newly updated algorithm.

Discussion

References

Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.
See NCCN Categories of Evidence and Consensus

These 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 these 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 makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2009.
Summary of the Guidelines updates

Summary changes in the 1.2010 version of the Rectal Cancer Guidelines from the 3.2009 version include:

Global changes
• PET scan changed to PET-CT scan throughout the Guidelines.

REC-3
• The category 2B recommendations have been removed from 5-FU ± leucovorin, FOLFOX, capecitabine, and bolus 5-FU +
  leucovorin + RT in the adjuvant setting. They are all now category 2A recommendations.
  (also applies to REC-4 and REC-5)
• The “category 2B for T2” recommendation was removed from transanal excision. This therapy is only recommended for T1, N0, as
  noted on REC-B.
• The recommendation for adjuvant chemotherapy was removed for T2, NX (margins negative) disease after transanal excision.
  Adjuvant treatment was clarified as 6 months of perioperative treatment recommended.

REC-5
• Footnote “p” modified to include consideration of BRAF testing as an option, if KRAS is non-mutated. (also applies to REC-6,
  REC-8 and REC-9)
• Footnote “q” is new to the page, “Patients with a known V600E BRAF mutation appear to be unlikely to benefit from anti-EGFR
  monoclonal antibodies.” (also applies to REC-9 and REC-10)
• Footnote “t” modified that RT is for patients at “increased” risk for pelvic recurrence (changed from “relative”).

REC-9
• If a patient remains unresectable after primary treatment, the recommendation of “observation” was removed.
  (also applies to REC-10)

REC-A 3 of 4
• New section added for BRAF testing.

REC-B 1 of 3
• The criteria of T2 for transanal excision was removed.
• Transabdominal resection - management principles: “endoscopy” was changed to “rigid proctoscopy” in second sub-bullet.
• Footnote “1” is a new reference to the page.

REC-B 2 of 3
• Bullet 8 modified to “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.”
Summary of the Guidelines updates

Summary changes in the 1.2010 version of the Rectal Cancer Guidelines from the 3.2009 version include:

**REC-C 1 of 2**
- FOLFOX 4 (Goldberg reference) regimen removed from the options for chemotherapy regimens.
- Simplified LV5FU2 (Andre reference) and weekly low dose leucovorin with 5-FU (Jager reference) added as a regimen options.
- Footnote modified relating to levoleucovorin, “While used in Europe, levoleucovorin is not approved for colorectal cancer in the United States. Leucovorin 400 mg/m2 is the equivalent of levoleucovorin 200 mg/m2.” (also applies for REC-E 4 of 6, and REC-E 5 of 6)

**REC-D**
- Bullet 7 - “if technically feasible” added.
- Bullet 8 - “concurrently with radiation therapy” replaced “as continuous infusion 5 to 7 days with radiation.”

**REC-E 1 of 6**
- Footnote “2” is new to the page, “PET-CT should not be used to monitor progress of therapy. CT with contrast or MRI is recommended. (also applies to REC-E 2 of 6)
- Footnote “9” is new to the page, “Patients with a known V600E BRAF mutation appear to be unlikely to benefit from anti-EGFR monoclonal antibodies.”

**REC-E 2 of 6**
- Panitumumab (KRAS WT gene only) was added as an option for patients not appropriate for intensive therapy with a category 2B designation.

**REC-E 3 of 6**
- Footnotes “2” and “9” are new to the page as noted above.
- Hecht reference in footnote “6” updated.

**REC-E 4 of 6**
- FOLFOX 4 (Goldberg reference) and FOLFIRI (Douillard reference) regimens removed from the options for chemotherapy regimens.

**REC-E 5 of 6**
- Bolus 5-FU/leucovorin (de Gramont reference) regimen removed from the options for chemotherapy regimens.
- Irinotecan dosing regimen changed from 4 weeks on and 2 weeks off, to 2 weeks on and 1 week off.

**REC-F 2 of 3**
- References 4-6, 8-9 added.
# Rectal Cancer

**CLINICAL PRESENTATION**

**Pedunculated polyp (adenoma [tubular, tubulovillous, or villous]) with invasive cancer**

- Pathology review<sup>b,c</sup>
- Colonoscopy
- Marking of cancerous polyp site (at time of colonoscopy or within 2 wks)

**FINDINGS**

- Single specimen, completely removed with favorable histological features<sup>d</sup> and clear margins (T1 only) → Observe
- Fragmented specimen or margin cannot be assessed or unfavorable histological features<sup>d</sup> → See Primary and Adjuvant Treatment (REC-3)

**Sessile polyp (Adenoma [tubular, tubulovillous, or villous]) with invasive cancer**

- Pathology review<sup>b,c</sup>
- Colonoscopy
- Marking of cancerous polyp site (at time of colonoscopy or within 2 wks)

**FINDINGS**

- Single specimen, completely removed with favorable histological features<sup>d</sup> and clear margins (T1 only) → Observe or See Primary Treatment on page REC-3
- Fragmented specimen or margin cannot be assessed or unfavorable histological features<sup>d</sup> → See Primary and Adjuvant Treatment (REC-3)

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<sup>a</sup> All patients with colon cancer should be counseled for family history. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP, see the NCCN Colorectal Cancer Screening Guidelines.

<sup>b</sup> Confirm the presence of invasive cancer (pT1). pTis has no biological potential to metastasize.

<sup>c</sup> 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.

<sup>d</sup> See Principles of Pathologic Review (REC-A) - Endoscopically removed malignant polyp.

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

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

**WORKUP**
- Biopsy
- Pathology review
- Colonoscopy
- Rigid proctoscopy
- Chest/abdominal/pelvic CT
- CEA
- Endorectal ultrasound or endorectal or pelvic MRI
- Enterostomal therapist as indicated for preoperative marking of site, teaching
- PET-CT scan is not routinely indicated

**CLINICAL STAGE**
- T1-2, N0e
  - See Primary Treatment (REC-3)
- T3, N0 or T any, N1-2
  - See Primary Treatment (REC-4)
- T4 and/or locally unresectable
  - See Primary Treatment (REC-4)
- T any, N any, M1
  - See Primary Treatment (REC-5)
- T any, N any, M1
  - See Primary Treatment (REC-6)

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All patients with colon cancer should be counseled for family history. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP, see the NCCN Colorectal Cancer Screening Guidelines.

T1-2, N0 should be based on assessment of endorectal ultrasound or MRI.

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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**Rectal Cancer**

**CLINICAL STAGE**

<table>
<thead>
<tr>
<th>T1-2, N0</th>
<th>Transabdominal resection</th>
<th>pT1-2, N0, M0</th>
<th>Observe</th>
<th>5-FU ± leucovorin or FOLFOX or capcitabine, then continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capcitabine/RT (category 2B), then 5-FU ± leucovorin or FOLFOX or capcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>or</td>
<td>Transanal excision, if appropriate</td>
<td>pT3, N0, M0 or pT1-3, N1-2</td>
<td>5-FU ± leucovorin or FOLFOX or capcitabine, then continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capcitabine/RT (category 2B), then 5-FU ± leucovorin or FOLFOX or capcitabine</td>
<td></td>
</tr>
<tr>
<td>T1, NX; Margins negative</td>
<td>Observe</td>
<td>pT1-2, N0, M0</td>
<td>Observe</td>
<td>5-FU ± leucovorin or FOLFOX or capcitabine, then continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capcitabine/RT (category 2B), then 5-FU ± leucovorin or FOLFOX or capcitabine</td>
</tr>
<tr>
<td>T1, NX with high risk features or T2, NX</td>
<td>Transabdominal resection</td>
<td>pT3, N0, M0 or pT1-3, N1-2</td>
<td>5-FU ± leucovorin or FOLFOX or capcitabine, then continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capcitabine/RT (category 2B), then 5-FU ± leucovorin or FOLFOX or capcitabine</td>
<td></td>
</tr>
</tbody>
</table>

**ADJUVANT TREATMENT**

(6 mo perioperative treatment preferred)

- **pT3, N0, M0 or pT1-3, N1-2**
  - Observe
  - **5-FU ± leucovorin or FOLFOX or capcitabine,** then continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capcitabine/RT (category 2B), then 5-FU ± leucovorin or FOLFOX or capcitabine

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

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

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*T1-2, N0 should be based on assessment of endorectal ultrasound or MRI.*

*See Principles of Surgery (REC-B).*

*High risk features include positive margins, lymphovascular invasion and poorly differentiated tumors.*

*See Principles of Adjuvant Therapy (REC-C).*

*See Principles of Radiation Therapy (REC-D).*

*The use of FOLFOX or capcitabine is an extrapolation from the available data in colon cancer. Trials are still pending in rectal cancer.*

Rectal Cancer

**Surveillance** (See REC-7)

- **T3, N0 or T any, N1-2**
  - Preoperative continuous 5-FU/RT (preferred) (category 1 for node positive disease) or bolus 5-FU + leucovorin/RT or capecitabine/RT (category 2B)
  - Transabdominal resection
  - Transabdominal resection
  - pT1–2, N0, M0
  - Observe
  - pT3, N0, M0, or pT1-3, N1-2
  - Reconsider:
    - 5-FU ± leucovorin (category 1) or FOLFOX or capecitabine
    - then continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capecitabine/RT (category 2B)
    - then 5-FU ± leucovorin or FOLFOX or capecitabine

- **T4 and/or locally unresectable**
  - Continuous IV 5-FU/RT or bolus 5-FU + leucovorin/RT or capecitabine/RT (category 2B)
  - Resection, if possible
  - Any T
  - 5-FU ± leucovorin (category 1) or FOLFOX or capecitabine

**ADJUVANT TREATMENT**

- 5-FU ± leucovorin (category 1) or FOLFOX or capecitabine

**CLINICAL STAGE**

**PRIMARY TREATMENT**

- **T3, N0 or T any, N1-2**
  - Preoperative continuous 5-FU/RT (preferred) (category 1 for node positive disease) or bolus 5-FU + leucovorin/RT or capecitabine/RT (category 2B)

- **T4 and/or locally unresectable**
  - Continuous IV 5-FU/RT or bolus 5-FU + leucovorin/RT or capecitabine/RT (category 2B)

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
<table>
<thead>
<tr>
<th>CLINICAL STAGE</th>
<th>PRIMARY TREATMENT</th>
<th>ADJUVANT THERAPY&lt;sup&gt;h,i&lt;/sup&gt; (resected metastatic disease) (6 mo perioperative treatment preferred)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Any, N Any, M1 Resectable synchronous metastases&lt;sup&gt;p&lt;/sup&gt;</td>
<td>Combination chemotherapy (2-3 months) FOLFIRI or FOLFOX or CapeOX ± bevacizumab&lt;sup&gt;r&lt;/sup&gt; or FOLFIRI or FOLFOX or CapeOX ± cetuximab [KRAS wild-type gene only]&lt;sup&gt;p,q&lt;/sup&gt; or Staged or synchronous resection of metastases&lt;sup&gt;f&lt;/sup&gt; and rectal lesion</td>
<td>Consider continuous IV 5-FU/pelvic RT or bolus 5-FU + leucovorin/pelvic RT or capecitabine/RT&lt;sup&gt;k&lt;/sup&gt;(category 2B)</td>
</tr>
<tr>
<td>or Continuous IV 5-FU/ pelvic RT or bolus 5-FU + leucovorin/pelvic RT or capecitabine/RT&lt;sup&gt;k&lt;/sup&gt; (category 2B)</td>
<td>Continuous IV 5-FU/pelvic RT or bolus 5-FU + leucovorin/pelvic RT or capecitabine/RT&lt;sup&gt;k&lt;/sup&gt; (category 2B)</td>
<td>Staged or synchronous resection of metastases&lt;sup&gt;f&lt;/sup&gt; and rectal lesion</td>
</tr>
<tr>
<td>Staged or synchronous resection of metastases&lt;sup&gt;f&lt;/sup&gt; and rectal lesion</td>
<td>pT1-2, N0, M1</td>
<td>Active chemotherapy regimen for advanced disease&lt;sup&gt;s&lt;/sup&gt; (See REC-E) (category 2B)</td>
</tr>
<tr>
<td>or pT3-4, Any N, M1 or Any T, N1-2, M1</td>
<td>5-FU ± leucovorin or FOLFOX&lt;sup&gt;j,o&lt;/sup&gt; or capecitabine&lt;sup&gt;j&lt;/sup&gt; then continuous 5-FU/RT&lt;sup&gt;t&lt;/sup&gt; or bolus 5-FU + leucovorin/RT&lt;sup&gt;t&lt;/sup&gt; or capecitabine/RT&lt;sup&gt;k,t&lt;/sup&gt; (category 2B), then 5-FU ± leucovorin or FOLFOX&lt;sup&gt;j,o&lt;/sup&gt; or capecitabine&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Active chemotherapy regimen for advanced disease&lt;sup&gt;s&lt;/sup&gt; (See REC-E) (category 2B)</td>
</tr>
</tbody>
</table>

<sup>f</sup>See Principles of Surgery (REC-B).
<sup>h</sup>See Principles of Adjuvant Therapy (REC-C).
<sup>i</sup>See Principles of Radiation Therapy (REC-D).
<sup>j</sup>The use of FOLFOX or capecitabine is an extrapolation from the available data in colon cancer. Trials are still pending in rectal cancer.
<sup>l</sup>An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery. See Principles of Pathologic Review (REC-A 3 of 4) - KRAS and BRAF Mutation Testing.
<sup>m</sup>Patients with a known V600E BRAF mutation appear to be unlikely to benefit from anti-EGFR monoclonal antibodies.
<sup>n</sup>The safety of administering bevacizumab pre or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. There should be at least a 6 wk interval between the last dose of bevacizumab and elective surgery. There is an increased risk of stroke and other arterial events especially in age ≥ 65. The use of bevacizumab may interfere with wound healing.
<sup>o</sup>FOLFOXIRI is not recommended in this setting.
<sup>p</sup>RT only recommended for patients at increased risk for pelvic recurrence.
**Clinical Stage**

- **Symptomatic**
  - T Any, N Any, M1
  - Unresectable synchronous metastases
  - or medically inoperable

  → Combination systemic chemotherapy or 5-FU/RT or Capecitabine/RT (category 2B) or Resection of involved rectal segment or Laser recanalization or Diverting colostomy or Stenting

→ [See Chemotherapy for Advanced or Metastatic Disease (REC-E)]

- **Asymptomatic**
  - See Chemotherapy for Advanced or Metastatic Disease (REC-E)

→ Reassess response to determine resectability

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

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{k} Data regarding the use of capecitabine/RT are limited and no phase III randomized data are available. Trials are pending. Kim J-Sang, Kim J-Sung, Cho, M et al Preoperative chemoradiation using oral capecitabine in locally advanced rectal cancer. Int J Radiation Oncology Biol Phys 2002;54(2):403-408.

{p} Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). See Principles of Pathologic Review (REC-A 3 of 4) - KRAS and BRAF Mutation Testing.

See Chemotherapy for Advanced or Metastatic Disease (REC-E).
SURVEILLANCE

- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA\textsuperscript{v} every 3-6 mo for 2 y, then every 6 mo for a total of 5 y for T2 or greater lesions
- Chest/abdominal/pelvic CT annually x 3 y for patients at high risk for recurrence\textsuperscript{w,x}
- Colonoscopy in 1 y 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,\textsuperscript{y} repeat in 3 y, then every 5 y\textsuperscript{z}
- Consider proctoscopy every 6 mo x 5 y for patients status post LAR\textsuperscript{aa}
- PET-CT scan is not routinely recommended
- See Principles of Survivorship (REC-F)

\textsuperscript{v}If patient is a potential candidate for resection of isolated metastasis.
\textsuperscript{x}CT scan may be useful for patients at high risk for recurrence (eg, lymphatic or venous invasion by tumor, or poorly differentiated tumors).
\textsuperscript{y}Villous polyp, polyp > 1 cm, or high grade dysplasia.
\textsuperscript{aa}Patients with rectal cancer should also undergo limited endoscopic evaluation of the rectal anastomosis to identify local recurrence. Optimal timing for surveillance is not known. No specific data clearly support rigid versus flexible proctoscopy. The utility of routine endoscopic ultrasound for early surveillance is not defined.

Note: All recommendations are category 2A unless otherwise indicated.
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RECURRENCE | WORKUP | TREATMENT
--- | --- | ---
Serial CEA elevation | - Physical exam
- Colonoscopy
- Chest/abdominal/pelvic CT
- Consider PET-CT scan | Consider PET-CT scan
Reevaluate chest/abdominal/pelvic CT in 3 mo
See treatment for Documented metachronous metastases REC-9

Isolated pelvic/anastomotic recurrence | Preoperative continuous 5-FU IV + RT, if not given previously | Resection, if feasible ± IORT

Documented metachronous metastases by CT, MRI, and/or biopsy | See treatment for Documented metachronous metastases REC-9

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

\[^1\] See Principles of Radiation Therapy (REC-D).
\[^P\] Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). See Principles of Pathologic Review (REC-A 3 of 4) - KRAS and BRAF Mutation Testing.
**PRIMARY TREATMENT**

- **Resectable**
  - Documented metachronous metastases by CT, MRI and/or biopsy
  - FOLFIRI ± bevacizumab or FOLFIRI ± cetuximab (KRAS WT gene only)
  - Previous adjuvant FOLFOX within past 12 months
  - Previous adjuvant FOLFOX > 12 months
  - Previous 5-FU/LV or capcitabine
  - No previous chemotherapy
  - Re-evaluate for conversion to resectable every 2 mo if conversion to resectability is a reasonable goal

- **Unresectable (potentially convertible or unconvertible)**
  - Active chemotherapy regimen
  - Converted to resectable
  - Resection
  - Active chemotherapy regimen

- **Active chemotherapy regimen**
  - Observation

---

*fSee Principles of Surgery (REC-B).*

*p Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). See Principles of Pathologic Review (REC-A 3 of 4) - KRAS and BRAF Mutation Testing.*

*q Patients with a known V600E BRAF mutation appear to be unlikely to benefit from anti-EGFR monoclonal antibodies.*

*bb Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.*

*cc 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.*

*dd Total perioperative therapy should be considered for a maximum of 6 months.*
Rectal Cancer

**PRIMARY TREATMENT**

Resection\(^{cc}\) → Active chemotherapy regimen\(^{dd}\) (See REC-E)  
—or Neoadjuvant chemotherapy (2-3 mo) (See REC-E)

Response → Repeat initial chemotherapy

Resection\(^{cc}\) → No response

Resection\(^{cc}\) or Neoadjuvant chemotherapy (2-3 mo) (See REC-E)

Response → Repeat initial chemotherapy

Response → Observation

Response → Observation

**No previous chemotherapy**

Resectable\(^{f}\)

Resectable\(^{f,bb}\) metachronous metastases → Consider PET-CT scan

Unresectable

Active chemotherapy regimen ( ) \(^{dd}\) See REC-E

Repeat initial chemotherapy

Re-evaluate for conversion to resectable\(^{f}\) every 2 mo if conversion to resectability is a reasonable goal

Converted to resectable\(^{f}\)

Active chemotherapy regimen (See REC-E)

Unresectable

No previous chemotherapy

Resectable\(^{f}\)

Resectable\(^{f,bb}\) metachronous metastases

Unresectable

Active chemotherapy regimen ( ) \(^{dd}\) See REC-E

Repeat initial chemotherapy

Response → Observation

Response → Observation

**Previous chemotherapy**

Resection\(^{cc}\)

Response → Repeat initial chemotherapy

Response → Observation

Response → Observation

**Previous adjuvant FOLFOX within past 12 months**

FOLFIRI ± bevacizumab or FOLFIRI ± cetuximab (KRAS WT gene only)\(^{p,q}\)

Active chemotherapy regimen (See REC-E)

Re-evaluate for conversion to resectable\(^{f}\) every 2 mo if conversion to resectability is a reasonable goal

Converted to resectable\(^{f}\)

Active chemotherapy regimen (See REC-E)

Unresectable

**Active chemotherapy regimen** ( ) \(^{dd}\) See REC-E

Response → Repeat initial chemotherapy

Response → Observation

Response → Observation

**No previous chemotherapy**

Resectable\(^{f}\)

Resectable\(^{f,bb}\) metachronous metastases → Consider PET-CT scan

Unresectable

Active chemotherapy regimen ( ) \(^{dd}\) See REC-E

Repeat initial chemotherapy

Response → Observation

Response → Observation

**Previous adjuvant FOLFOX > 12 months**

Previous 5-FU/LV or capcitabine

No previous chemotherapy

Active chemotherapy regimen (See REC-E)

Repeat initial chemotherapy

Response → Observation

Response → Observation

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

\(^{f}\) See Principles of Surgery (REC-B).

\(^{p}\) Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing. See Principles of Pathologic Review (REC-A 3 of 4) - KRAS and BRAF Mutation Testing.

\(^{q}\) Patients with a known V600E BRAF mutation appear to be unlikely to benefit from anti-EGFR monoclonal antibodies.

\(^{bb}\) Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.

\(^{cc}\) 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.

\(^{dd}\) Total perioperative therapy should be considered for a maximum of 6 months.
PRINCIPLES OF PATHOLOGIC REVIEW (1 of 4)

Endoscopically removed malignant polyps

- A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). pTIS is not considered a “malignant polyp.”
- Favorable histological features: grade 1 or 2, no angiolympathic 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, 3) tumor cells present within the diathermy of the transected margin.¹-⁴
- Unfavorable histological features: grade 3 or 4, or angiolympathic invasion, or a “positive margin.” See above for definition of a positive margin.

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 outcome (residual disease, recurrent disease, mortality, hematogenous metastasis, but not lymph node metastasis) than do polypoid 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 margin, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy.³-⁷

Transanal excision

- Favorable histopathological features: < 3 cm size, T1, grade I or II, no lymphatic or venous invasion, negative margins.⁸,⁹
- Unfavorable histopathological features: > 3 cm in size, T1, with grade III, or lymphovascular invasion, or positive margin.⁸-¹⁰

Rectal cancer appropriate for resection

- Histological confirmation of primary malignant rectal neoplasm.

Pathological stage

- The following parameters should be reported.
  - Grade of the cancer
  - Depth of penetration, (T) the T stage is based on viable tumor. Acellular mucin pools are not considered residual tumor in those cases treated with neoadjuvant therapy.
  - Number of lymph nodes evaluated and number positive (N). Acellular mucin pools are not considered residual tumor in those cases treated with neoadjuvant therapy.
  - Status of proximal, distal, and circumferential (radial) margins.¹¹-¹²
  - A positive circumferential resection margin (CRM) has been defined as < 1 mm or < 2 mm depending on the publication¹³-¹⁴

See Staging (ST-1)
PRINCIPLES OF PATHOLOGIC REVIEW (2 of 4)

Lymph node evaluation

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately identify stage II colorectal cancers.\(^{11,12,15}\) 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, >30.\(^{16-23}\) Most of these studies have combined rectal and colon cancers and reflect those cases with surgery as the initial treatment. Two studies confined only to rectal cancer have reported 14 and > 10 lymph nodes as the minimal number to accurately identify stage II rectal cancer.\(^{19,22}\) The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade and tumor site.\(^{16}\) For stage II (pN0) colon cancer, if less 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 mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than those treated by surgery alone (13 vs 19, p < 0.05, 7 vs 10, p < 0.001).\(^{24,25}\) If 12 lymph nodes is considered the number needed to accurately stage, stage II tumors, then only 20% of cases treated with neoadjuvant therapy had adequate lymph node sampling.\(^{25}\) To date the number of lymph nodes needed to accurately stage neoadjuvant treated cases is unknown. However, it is not known what is the clinical significance of this in the neoadjuvant setting as postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.

Sentinel lymph node and detection of micrometastasis by immunohistochemistry

- Examination of the sentinel lymph node allows an intense histological and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. Studies in the literature have been reported using multiple H & E sections and/or immunohistochemistry (IHC) to detect cytokeratin positive cells. While studies to date seem promising, there is no uniformity in the definition of what constitutes "true metastatic carcinoma." Confusion arises when isolated tumors cells (ITC) have been considered micrometastatic disease in contraindication to true micrometastasis (tumor aggregates > 0.2 mm to < 2 mm in size). The significance of detection of single cells by IHC alone is controversial. Some studies have considered these to be micrometastases, however, "consensus" recommends these to be considered ITC and not micrometastatic disease.\(^{26-28}\) While the 6th edition of the AJCC Cancer Staging\(^ {29}\) manual considers "tumor clusters" < 0.2 mm as isolated tumor cells (pN0) and not metastatic carcinoma, some have challenged this. Some investigators believe that size should not effect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (eg, glandular differentiation, distension of sinus, or stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.\(^ {30}\) Hermanek et al\(^ {31}\) proposed isolated tumor cells to be defined as single tumor cells or small clusters (never more than a few cells clumped together) without evidence of extrasinusoidal stromal proliferation or reaction and no contact with or invasion of the vessel (lymphatic) wall. 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 these studies, ITC were considered micrometastasis.\(^ {32-36}\)

- At the present time the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational and results used with caution in clinical management decisions.\(^ {26-28,32-36}\)

See Malignant polyp, rectal cancer appropriate for resection, and pathological stage on page 1 of 4 REC-A

See KRAS and BRAF Mutation Testing page 3 of 4 REC-A

See footnotes on page 4 of 4 REC-A
KRAS Mutation Testing

- Mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of response to therapy with antibodies targeted to the epidermal growth factor receptor.\textsuperscript{37,38}

- Testing for Mutations in Codons 12 and 13 should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA – 88) as qualified to perform high complex clinical laboratory (molecular pathology) testing. No specific methodology is recommended (sequencing, hybridization, etc.).

- The testing can be performed on formalin fixed paraffin embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis as literature has shown that the KRAS mutations are similar in both specimen types.\textsuperscript{39}

BRAF Mutation Testing

- Recent small studies suggest that patients with wt KRAS and a BRAF mutation are unlikely to respond to therapy with antibodies targeted to the epidermal growth factor receptor.\textsuperscript{40,41}

- Testing for the BRAF V600E mutation can be performed on formalin fixed paraffin embedded tissues. This is usually performed by PCR amplification and direct DNA sequence analysis. This testing should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) and qualified to perform highly complex clinical laboratory (molecular pathology) testing.

Evaluation of Mesorectum (TME)

- The pathologist should evaluate the quality (completeness) of the mesorectum (only for low rectal cancer - distal 2/3).\textsuperscript{42-44}
15 Sobin HL and Green EFL. TNM classification. Clarification of number of regional lymph node for PNO. Cancer 2001;1;92:452.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

**Transanal excision:**

- **Criteria**
  - < 30% circumference of bowel
  - < 3 cm in size
  - Margin clear (> 3 mm)
  - Mobile, nonfixed
  - Within 8 cm of anal verge
  - T1 only
  - Endoscopically removed polyp with cancer or indeterminate pathology
  - No lymphovascular (LVI) or perineural invasion
  - Well to moderately differentiated
  - No evidence of lymphadenopathy on pretreatment imaging

- When the lesion can be adequately identified in the rectum, transanal microsurgery may be used.

**Transabdominal Resection:** Abdominoperineal resection or low anterior resection or coloanal anastomosis using total mesorectal excision.

- **Management Principles**
  - The treating surgeon should perform a rigid proctoscopy before initiating treatment
  - Removal of primary tumor with adequate margins
  - Laparoscopic surgery is not recommended outside of a clinical trial
  - Treatment of draining lymphatics by total mesorectal excision
  - Restoration of organ integrity, if possible
  - Surgery should be 5-10 weeks following full dose 5 1/2 wk neoadjuvant chemoradiation

See Criteria for Resectability of Metastases on page 2 of 3 REC-B

Liver

- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of adequate hepatic function is required.\(^1,2\)
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.\(^3-5\) Plan for a debulking resection (less than an R0 resection) is not recommended.
- Patients with resectable metastatic disease and 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.
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization or staged liver resections can be considered.
- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.\(^6\)
- Ablative techniques may be considered alone or in conjunction with resection.\(^6\) All original sites of disease need to be amenable to ablation or resection.
- Some institutions use intra-arterial embolization in select patients with chemotherapy resistant/refractory disease, without obvious systemic disease, with predominant hepatic metastases (category 3).
- 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.\(^7\)

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.\(^8-11\)
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.\(^12-15\)
- Re-resection can be considered in selected patients.\(^16\)
- Ablative techniques can be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.

Evaluation for conversion to resectable disease

- Re-evaluation for resection should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.\(^17-20\)
- 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.\(^21\) Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.\(^22\)
Adjuvant therapy for rectal cancer consists of regimens that include both concurrent chemotherapy/RT and adjuvant chemotherapy. The chemotherapy/RT may be administered either pre or postoperatively. A total of 6 months of perioperative treatment is preferred.

**Postoperative adjuvant chemotherapy for patients receiving preoperative chemotherapy/RT:**

- Simplified biweekly infusional 5-FU/LV (sLV5FU2)\(^1\)
  
  Leucovorin 400 mg/m\(^2\) IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m\(^2\) and then 1200 mg/m\(^2\)/day x 2 days (total 2400 mg/m\(^2\) over 46-48 hours)\(^\dagger\) continuous infusion. Repeat every 2 weeks.

- Leucovorin 20 mg/m\(^2\) IV over 2 hours on day 1, 5-FU 500 mg/m\(^2\) IV bolus injection 1h after the start of leucovorin. Repeat weekly.\(^2\)

**Postoperative adjuvant regimens for patients not receiving preoperative therapy:**

- 5-FU + leucovorin x 1 cycle, then concurrent chemotherapy/RT (see below for regimens), then 5-FU/leucovorin x 2 cycles\(^3\)
  
  - 5-FU 500 mg/m\(^2\) IV bolus injection once a wk after the start of the leucovorin infusion, once a wk for 6 wks + leucovorin 500 mg/m\(^2\) IV over 2 h once a wk for 6 wks. A cycle is comprised of 6 wks followed by 2 wks of rest.

- mFOLFOX 6
  
  Oxaliplatin 85 mg/m\(^2\) IV over 2 hours, day 1, leucovorin\(^\ast\) 400 mg/m\(^2\) IV over 2 hours, day 1, 5-FU 400 mg/m\(^2\) IV bolus on day 1, then 1200 mg/m\(^2\)/day x 2 days (total 2400 mg/m\(^2\) over 46-48 hours)\(^\dagger\) continuous infusion.\(^4\) Repeat every 2 weeks to a total of 6 mo perioperative therapy.

- Capecitabine\(^5\)
  
  Capecitabine 1250 mg/m\(^2\) twice daily days 1-14 every 3 wks to a total of 6 mo perioperative therapy.

**Dosing Schedules for concurrent chemotherapy/RT:**

- XRT + continuous infusion 5-FU\(^6\)
  
  5-FU 225 mg/m\(^2\) over 24 h 7 d/wk during XRT

- XRT + 5-FU/leucovorin\(^7\)
  
  5-FU 400 mg/m\(^2\) IV bolus + leucovorin 20 mg/m\(^2\) IV bolus for 4 d during wk 1 and 5 of XRT

- XRT + Capecitabine\(^8,9\) (category 2B)
  
  Capecitabine 825 mg/m\(^2\) twice daily 5 or 7 d/wk + XRT x 5 wks

\(^\ast\)While used in Europe, levoleucovorin is not approved for colorectal cancer in the United States. Leucovorin 400 mg/m\(^2\) is the equivalent dose of levoleucovorin 200 mg/m\(^2\).

\(^\dagger\)NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m\(^2\)/day NOT 2400 mg/m\(^2\) over 48 hours) to minimize medication errors.
PRINCIPLES OF ADJUVANT THERAPY (2 of 2)

REFERENCES


Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
• Radiation therapy fields should include the tumor or tumor bed, with a 2-5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.
• Multiple radiation therapy fields should be used (generally a 3 or 4 field technique). Positioning and other techniques to minimize the volume of small bowel in the fields should be encouraged.
• For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.
• Intensity modulated radiotherapy (IMRT) should only be used in the setting of a clinical trial.
• Radiation doses:
  > 45-50 Gy in 25-28 fractions to the pelvis.
  > For resectable cancers, after 45 Gy a tumor bed boost with a 2 cm margin of 5.4 Gy in 3 fractions could be considered for preoperative radiation and 5.4-9.0 Gy in 3-5 fractions for postoperative radiation.
  > Small bowel dose should be limited to 45 Gy.
• Intraoperative radiotherapy (IORT), if available, should be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers. If IORT is not available, 10-20 Gy external beam radiation to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.
• For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.
• 5-fluorouracil based chemotherapy should be delivered concurrently with radiation therapy.
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 1 of 6)

**Initial therapy**
- FOLFOX³ ± bevacizumab or CapeOX⁴ ± bevacizumab⁵,⁶ or
- FOLFOX³ or CapeOX⁴ ± cetuximab⁶,⁷ (KRAS wild-type [WT] gene only)⁸,⁹ or
- FOLFIRI¹⁰ + bevacizumab⁵,⁶ or
- FOLFIRI¹⁰ ± cetuximab⁶,⁷ (KRAS WT gene only)⁸,⁹ or
- 5-FU/leucovorin¹¹ + bevacizumab⁵,⁶,¹² or
- FOLFOXIRI¹³ (category 2B)

**Therapy after First Progression**
- FOLFIRI¹⁰ or
- Irinotecan¹⁰
- FOLFIRI + cetuximab⁶,¹⁴-¹⁶ (category 2B) (KRAS WT gene only)⁸,⁹ or
- Cetuximab⁶,¹⁴-¹⁶ (KRAS WT gene only)⁸,⁹ + irinotecan¹⁰ (category 2B)
- FOLFOX³ or CapeOX⁴ or
- Cetuximab (KRAS WT gene only)⁶,⁸,⁹,¹⁴-¹⁶ + irinotecan,¹⁰ patients not able to tolerate combination, consider single agent cetuximab⁶,⁸,⁹,¹³-¹⁵ (KRAS WT gene only) or panitumumab⁶,⁸,⁹,¹⁵-¹⁷ (KRAS WT gene only) (not as combination)
- Clinical trial or best supportive care¹⁸

**Therapy after Second Progression**
- Clinical trial or best supportive care¹⁸
- FOLFOX² or CapeOX³
- Cetuximab (KRAS WT gene only)⁶,⁸,⁹,¹⁴-¹⁶ + irinotecan,¹⁰ patients not able to tolerate combination, consider single agent cetuximab⁶,⁸,⁹,¹³-¹⁵ (KRAS WT gene only) or panitumumab⁶,⁸,⁹,¹⁵-¹⁷ (KRAS WT gene only) (not as combination)
- Irinotecan¹⁰
- Cetuximab (KRAS WT gene only)⁶,⁸,⁹,¹⁴-¹⁶ + irinotecan,¹⁰ patients not able to tolerate combination, consider single agent cetuximab⁶,⁸,⁹,¹³-¹⁵ (KRAS WT gene only) or panitumumab⁶,⁸,⁹,¹⁵-¹⁷ (KRAS WT gene only) (not as combination)

Patient not appropriate for intensive therapy, see REC-E 2 of 6

See footnotes on page REC-E 3 of 6

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 2 of 6)

Initial therapy

Patient not appropriate for intensive therapy² →

Capecitabine¹⁹ ± bevacizumab →

or

Infusional 5-FU + leucovorin ± bevacizumab →

or

Cetuximab (KRAS wild-type gene only)⁸,⁹ (category 2B) →

or

Panitumumab (KRAS wild-type gene only)⁸,⁹ (category 2B) →

Improvement in functional status → Consider Initial Therapy as REC-E 1 of 6²⁰

No improvement in functional status → Best supportive care

See NCCN Palliative Care Guidelines

See footnotes on page REC-E 3 of 6
CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 3 of 6)

1. For chemotherapy references, see Chemotherapy Regimens and References (REC-E pages 4 - 6).
2. PET-CT should not be used to monitor progress of therapy. CT with contrast or MRI is recommended.
3. Discontinuation of oxaliplatin should be strongly considered from FOLFOX or CapeOX after 3-4 months of therapy (or sooner if significant neurotoxicity develops ≥ grade 2) with other drugs maintained (fluoropyrimidine + bevacizumab) until time of tumor progression. Oxaliplatin may be reintroduced if it was discontinued previously for neurotoxicity rather than disease progression. 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.
4. 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. Some data suggest 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. The relative efficacy of CapeOX with lower starting doses of capecitabine has not been addressed in large scale randomized trials. For good performance status patients, the 1000 mg/m² twice daily dose is the recommended starting dose, with close monitoring in the first cycle for toxicity, and dose adjustments as indicated.
5. There are no prospective data to support continuation of bevacizumab with a second-line regimen after progression on a bevacizumab-containing first line regimen, and such continuation of bevacizumab beyond progression is not recommended. If bevacizumab is not used in initial therapy, it may be appropriate to consider, if there is no contraindication to therapy. There is an increased risk of stroke and other arterial events especially in age ≥ 65. The use of bevacizumab may interfere with wound healing.
7. If cetuximab is used as initial therapy, then neither cetuximab nor panitumumab should be used in second or subsequent lines of therapy.
8. See Principles of Pathologic Review (REC-A 3 of 4) - KRAS and BRAF Mutation Testing.
9. Patients with a known V600E BRAF mutation appear to be unlikely to benefit from anti-EGFR monoclonal antibodies.
10. Irinotecan should be used with caution and with decreased doses in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for UGT1A1. Guidelines for use in clinical practice have not been established.
11. Infusional 5-FU is preferred.
12. A treatment option for patients not able to tolerate oxaliplatin or irinotecan.
13. Data are not mature for the addition of biologic agents to FOLFOXIRI.
14. Cetuximab is indicated in combination with irinotecan-based therapy or as single agent therapy for patients who cannot tolerate irinotecan.
15. EGFR testing has no demonstrated predictive value, and therefore routine EGFR testing is not recommended. No patient should be included or excluded from cetuximab or panitumumab therapy on the basis of EGFR test results.
16. There are no data, nor is there a compelling rationale, to support the use of panitumumab after clinical failure on cetuximab, or the use of cetuximab after clinical failure on panitumumab. As such, the use of one of these agents after therapeutic failure on the other is not recommended.
17. There are no data to support the combination of panitumumab with chemotherapy.
18. Single agent or combination therapy with capecitabine, mitomycin, or gemcitabine has not been shown to be effective in this setting.
19. Patients with diminished creatinine clearance may require dose modification of capecitabine.
20. The use of single agent capecitabine as a salvage therapy after failure on a fluoropyrimidine-containing regimen has been shown to be ineffective, and this is therefore not recommended.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 4 of 6)

CHEMOTHERAPY REGIMENS

FOLFOX
mFOLFOX 6
Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)† continuous infusion
Repeat every 2 weeks¹

CapeOX¹,²
Oxaliplatin 130 mg/m² day 1, Capecitabine 850-1000 mg/m² twice daily for 14 days
Repeat every 3 weeks

FOLFIRI³
Irinotecan 180 mg/m² IV over 30-90 minutes, day 1
Leucovorin 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)† continuous infusion
Repeat every 2 weeks

Bevacizumab + 5-FU containing regimens:⁴-⁶
Bevacizumab 5 mg/kg IV every 2 weeks +
5-FU and Leucovorin
or FOLFOX⁷
or FOLFIRI
Bevacizumab 7.5 mg/kg IV every 3 weeks + CapeOX²
Bevacizumab may be safely given at a rate of 0.5 mg/kg/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes)

*While used in Europe, levoleucovorin is not approved for colorectal cancer in the United States. Leucovorin 400 mg/m² is the equivalent dose of levoleucovorin 200 mg/m².

†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m² over 48 hours) to minimize medication errors.

‡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. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large scale randomized trials.
## CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 5 of 6)

### CHEMOTHERAPY REGIMENS

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Capecitabine</strong>&lt;sup&gt;8&lt;/sup&gt;</td>
<td>2000-2500 mg/m&lt;sup&gt;2&lt;/sup&gt;/day PO in two divided doses, days 1-14, followed by 7 days rest, Repeat every 3 weeks</td>
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<tr>
<td><strong>Bolus or infusional 5-FU/leucovorin</strong></td>
<td><strong>Roswell-Park regimen</strong></td>
</tr>
<tr>
<td><strong>Leucovorin 500 mg/m&lt;sup&gt;2&lt;/sup&gt; IV over 2 hours, days 1, 8, 15, 22, 29, and 36</strong></td>
<td><strong>5-FU 500 mg/m&lt;sup&gt;2&lt;/sup&gt; IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, 36, Repeat every 8 weeks</strong></td>
</tr>
<tr>
<td><strong>Simplified biweekly infusional 5-FU/LV (sLV5FU2)</strong></td>
<td><strong>Leucovorin 400 mg/m&lt;sup&gt;2&lt;/sup&gt; IV over 2 hours on day 1,</strong> followed by 5-FU bolus 400 mg/m&lt;sup&gt;2&lt;/sup&gt; and then 1200 mg/m&lt;sup&gt;2&lt;/sup&gt;/day x 2 days (total 2400 mg/m&lt;sup&gt;2&lt;/sup&gt; over 46-48 hours)&lt;sup&gt;†&lt;/sup&gt; continuous infusion, Repeat every 2 weeks</td>
</tr>
<tr>
<td><strong>Weekly</strong></td>
<td><strong>Leucovorin 20 mg/m&lt;sup&gt;2&lt;/sup&gt; IV over 2 hours on day 1,</strong> 5-FU 500 mg/m&lt;sup&gt;2&lt;/sup&gt; IV bolus injection 1h after the start of leucovorin. Repeat weekly,&lt;sup&gt;10&lt;/sup&gt; 5-FU 2600 mg/m&lt;sup&gt;2&lt;/sup&gt; by 24 h infusion plus leucovorin 500 mg/m&lt;sup&gt;2&lt;/sup&gt;, Repeat every week&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>FOLFOXIRI</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
<td><strong>Irinotecan 165 mg/m&lt;sup&gt;2&lt;/sup&gt; IV day 1,</strong> oxaliplatin 85 mg/m&lt;sup&gt;2&lt;/sup&gt; day 1,** leucovorin 400 mg/m&lt;sup&gt;2&lt;/sup&gt; day 1,** fluorouracil 3,200 mg/m&lt;sup&gt;2&lt;/sup&gt; over 48 h continuous infusion starting on day 1, Repeat every 2 weeks</td>
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<tr>
<td><strong>Irinotecan</strong></td>
<td><strong>Irinotecan 125 mg/m&lt;sup&gt;2&lt;/sup&gt; IV over 30-90 minutes,</strong> days 1, 8, Repeat every 3 weeks</td>
</tr>
<tr>
<td><strong>Irinotecan 300-350 mg/m&lt;sup&gt;2&lt;/sup&gt; IV over 30-90 minutes,</strong> day 1</td>
<td>Repeat every 3 weeks&lt;sup&gt;13,14&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Cetuximab (KRAS wild-type gene only) ± irinotecan</strong></td>
<td><strong>Cetuximab 400 mg/m&lt;sup&gt;2&lt;/sup&gt; 1st infusion,</strong> then 250 mg/m&lt;sup&gt;2&lt;/sup&gt; IV weekly or **Cetuximab 500 mg/m&lt;sup&gt;2&lt;/sup&gt; IV every 2 weeks&lt;sup&gt;16&lt;/sup&gt; ± **Irinotecan 300-350 mg/m&lt;sup&gt;2&lt;/sup&gt; IV every 3 weeks or **Irinotecan 180 mg/m&lt;sup&gt;2&lt;/sup&gt; IV every 2 weeks or **Irinotecan 125 mg/m&lt;sup&gt;2&lt;/sup&gt; every week for 4 weeks Every 6 weeks</td>
</tr>
<tr>
<td><strong>Cetuximab (KRAS wild-type gene only)</strong></td>
<td><strong>Panitumumab&lt;sup&gt;17&lt;/sup&gt; (KRAS wild-type gene only)</strong>&lt;br&gt;Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks</td>
</tr>
</tbody>
</table>

<sup>*</sup>While used in Europe, levoleucovorin is not approved for colorectal cancer in the United States. Leucovorin 400 mg/m<sup>2</sup> is the equivalent dose of levoleucovorin 200 mg/m<sup>2</sup>.  
<sup>†</sup>NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m<sup>2</sup>/day NOT 2400 mg/m<sup>2</sup> over 48 hours) to minimize medication errors.

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See footnotes on page 6 of 6 REC-E

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
CHEMOTHERAPY REFERENCES


2. European studies showing equivalent efficacy for CapeOX used at a higher dose; however, European patients consistently tolerate capcitabine with less toxicity than American patients.


Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Management of Late Sequelae of Disease or Treatment:

- **Chronic Diarrhea or Incontinence**
  - Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, and protective undergarments.
- **Oxaliplatin-Induced Neuropathy**
  - Consider the use of analgesics or referral to a pain specialist, for painful, persistent neuropathy.
- **Bone Health After Pelvic Radiation**
  - Consider monitoring of bone density or evaluation for pelvic fractures with pelvic pain if previously received pelvic radiation
- **Urogenital Dysfunction after Resection and/or Pelvic Radiation**
  - Screen for sexual dysfunction, erectile dysfunction, dyspareunia, and vaginal dryness
  - Screen for urinary incontinence, frequency, and urgency
  - Consider referral to urologist or gynecologist for persistent symptoms.

**Immunizations:**

- **Annual trivalent inactivated influenza vaccination**
- **Pneumococcal vaccination with revaccination as appropriate**

**Routine Health Monitoring and Screening:**

- **Cholesterol, blood pressure, and glucose monitoring**
- **Bone density testing as appropriate**
- **Routine dental examinations**
- **Routine sun protection**
- **Screening for depression as appropriate**

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5 DeSnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. European Journal of Cancer Care 2006;15) 244-51.


Counseling Regarding Healthy Lifestyle and Wellness: 6-9
- Screening and counseling to maintain a healthy weight.
- Screening for physical activity and counseling to adopt a physically active lifestyle (Recommended activity: at least 30 minutes or more of moderate to vigorous physical activity at least 5 days of the week).
- Screening and counseling for alcohol use.
- Screening and counseling for tobacco use with emphasis on smoking cessation.
- Counseling regarding healthy diet adoption, with emphasis on plant sources.

Prescription for Survivorship and Transfer of Care to Primary Care Physician: 10
(If primary physician will be assuming cancer surveillance responsibilities)
- Include overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received
- Describe possible clinical course, including expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment
- Include surveillance recommendations
- Delineate appropriate timing of transfer of care with specific responsibilities identified for PCP and Oncologist.

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**Staging**

**Table 1**

**American Joint Committee on Cancer (AJCC) TNM Staging System for Colorectal Cancer**

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Dukes*</th>
<th>MAC†</th>
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**Regional Lymph Nodes (N)**

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**Distant Metastasis (M)**

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**Stage Grouping**

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<th>M</th>
<th>Dukes*</th>
<th>MAC†</th>
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<td>Any T</td>
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**Histologic Grade (G)**

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<tr>
<td>G1</td>
<td>Well differentiated</td>
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<tr>
<td>G2</td>
<td>Moderately differentiated</td>
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<tr>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>G4</td>
<td>Undifferentiated</td>
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</tbody>
</table>

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the *AJCC Cancer Staging Manual, Sixth Edition* (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed written permission of Springer-Verlag New York on behalf of the AJCC.

†Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

‡Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa; for example, invasion of the sigmoid colon by a carcinoma of the cecum. Tumor that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumor is present in the adhesion, microscopically, the classification should be pT3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion.

§A tumor nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident), because there is a strong likelihood that it represents venous invasion.

¶Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

Note: The y prefix is to be used for those cancers that are classified after pretreatment, whereas the r prefix is to be used for those cancers that have recurred.
Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 08/12/09

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

In 2009 an estimated 40,870 new cases of rectal cancer will occur in the United States (23,580 cases in men; 17,290 cases in women). During the same year, it is estimated that 49,920 people will die from rectal and colon cancer.1 Although colorectal cancer is ranked as the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the U.S., mortality from colorectal cancer has decreased during the past 30 years. This decrease may be due to both earlier diagnosis through screening and better treatment modalities.

The recommendations in these clinical practice guidelines are classified as category 2A except where noted, meaning that there is uniform NCCN consensus, based on lower-level evidence (including clinical experience), that the recommendation is appropriate. The panel unanimously endorses patient participation in a clinical trial over standard or accepted therapy. This is especially true for cases of advanced disease and for patients with locally aggressive colorectal cancer who are receiving combined modality treatment. The clinical practice guidelines for managing rectal cancer overlap considerably with the NCCN Colon Cancer Guidelines. First-degree relatives of patients with newly diagnosed adenomas2 or invasive carcinoma3 are at increased risk for colorectal cancer. Therefore, all rectal cancer patients should be counseled regarding their family history as outlined in the NCCN Colorectal Screening Guidelines.

TNM Staging

The NCCN Rectal Cancer Guidelines adhere to the current TNM staging system as included in the 6th edition of the American Joint Committee on Cancer's (AJCC) Cancer Staging Manual (Table 1).4, 5 Stage I rectal cancer is defined as T1-T2, N0, M0. Stage II disease is subdivided into IIA (if the primary tumor is T3, N0, M0) and IIB (for T4, N0, M0 lesions). Stage III disease is subdivided into IIIA (T1-2, N1, M0), IIIB (T3-4, N1, M0), and IIIC (any T, N2, M0). Stage IV disease is defined as any T, any N, and the presence of one or more distant metastases (M1). The difference between N1 and N2 disease is the number of nodes involved: N1 lesions have 1 to 3 positive regional lymph nodes, whereas N2 tumors have 4 or more regional lymph nodes. In this version of the staging system, smooth metastatic nodules in the pericolic or perirectal fat are considered lymph node metastases and should be included in N staging. Irregularly contoured metastatic nodules in the peritumoral fat are considered vascular invasion. In addition, the 6th edition of the AJCC staging manual6 includes the suggestion that the surgeon mark the area of the specimen with the deepest tumor penetration so that the pathologist can directly evaluate the status of the resection margins. The surgeon is encouraged to score the completeness of the resection as (1) R0 for complete tumor resection with all margins negative; (2) R1 for incomplete tumor resection with microscopic involvement of a margin; and (3) R2 for incomplete tumor resection with gross residual tumor that was not resected.
Pathology

Pathologic staging information is provided by examination of the surgical specimen. Some of the information that should be detailed in the report of the pathologic evaluation of rectal cancer includes: 1) gross description of the tumor and specimen; 2) grade of the cancer; 3) depth of penetration and extension to adjacent structures (T); 4) number of regional lymph nodes evaluated and 5) number of positive regional lymph nodes (N); 6) the presence of distant metastases to other organs, the peritoneum of an abdominal structure, or non-regional lymph nodes (M) and 7) the status of proximal, distal, and circumferential (radial) margins.\(^5,7\) The prefixes “p” and “yp” used in TNM staging denote pathologic staging and pathologic staging following neoadjuvant therapy, respectively.\(^8\)

The circumferential margin or circumferential resection margin (CRM) is an important pathologic staging parameter in rectal cancer. Whereas the radial margin for resected segments of the colon that are completely encased by a peritonealized (serosal) surface is also referred to as the peritoneal margin, the CRM is very important in segments of the colon or rectum that are either not encased or only partially encased in peritoneum.\(^5\) The CRM is the closest radial margin between the deepest penetration of the tumor and the edge of resected soft tissue around the rectum (ie, the retroperitoneal or subperitoneal aspect of the tumor) and should be measured in millimeters. Identification of the CRM is determined through evaluation of the outer circumference of the rectal and mesorectal specimen which often requires inking of the outer surfaces and “bread-loaf” slicing of the specimen.\(^9\) A positive CRM has been defined as tumor within 1-2 mm from the transected margin.\(^10-13\) Accurate pathologic assessment of the CRM of resected rectal tumor specimens is very important since the CRM has been shown to be a strong predictor of both local recurrence and overall survival since the CRM has been shown to be a strong predictor of both local recurrence and overall survival, and should be measured in millimeters. Identification of the CRM is determined through evaluation of the outer circumference of the rectal and mesorectal specimen which often requires inking of the outer surfaces and “bread-loaf” slicing of the specimen.\(^9\) A positive CRM has been defined as tumor within 1-2 mm from the transected margin.\(^10-13\) Accurate pathologic assessment of the CRM of resected rectal tumor specimens is very important since the CRM has been shown to be a strong predictor of both local recurrence and overall survival, and should be measured in millimeters. Identification of the CRM is determined through evaluation of the outer circumference of the rectal and mesorectal specimen which often requires inking of the outer surfaces and “bread-loaf” slicing of the specimen.\(^9\) A positive CRM has been defined as tumor within 1-2 mm from the transected margin.\(^10-13\) Accurate pathologic assessment of the CRM of resected rectal tumor specimens is very important since the CRM has been shown to be a strong predictor of both local recurrence and overall survival, and should be measured in millimeters. Identification of the CRM is determined through evaluation of the outer circumference of the rectal and mesorectal specimen which often requires inking of the outer surfaces and “bread-loaf” slicing of the specimen.\(^9\) A positive CRM has been defined as tumor within 1-2 mm from the transected margin.\(^10-13\) Accurate pathologic assessment of the CRM of resected rectal tumor specimens is very important since the CRM has been shown to be a strong predictor of both local recurrence and overall survival, and should be measured in millimeters. Identification of the CRM is determined through evaluation of the outer circumference of the rectal and mesorectal specimen which often requires inking of the outer surfaces and “bread-loaf” slicing of the specimen.\(^9\) A positive CRM has been defined as tumor within 1-2 mm from the transected margin.\(^10-13\) Accurate pathologic assessment of the CRM of resected rectal tumor specimens is very important since the CRM has been shown to be a strong predictor of both local recurrence and overall survival, and should be measured in millimeters.

In a retrospective study of over 17,000 patients with rectal cancer, CRM was found to be a better predictor of local recurrence for patients who had received preoperative therapy when these patients were compared with patients undergoing surgery as initial therapy.\(^16\) Additional components of the pathological evaluation of the surgical specimen following a total mesorectal excision (TME) are described under Surgical Approaches.

The AJCC and College of American Pathologists (CAP) recommend evaluation of a minimum of 12 lymph nodes to accurately identify stage II colorectal cancers.\(^5,6\) The number of lymph nodes retrieved can vary with age of the patient, gender, and tumor grade or site.\(^17,18\) The extent and quality of surgical resection and pathologic review of the specimen can also have an impact on the node harvest.\(^19\) The literature lacks consensus regarding the minimal number of lymph nodes needed to accurately identify stage II rectal cancer. Most of these studies have combined rectal and colon cancers and reflect those cases with surgery as the initial treatment. Two studies confined only to rectal cancer have reported 14 and >10 lymph nodes as the minimal number to accurately identify stage II rectal cancer.\(^20,21\) Furthermore, the mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than those treated by surgery alone (13 vs 19, P<0.05; 7 vs 10, P≤0.0001).\(^22,23\) A recent retrospective analysis of data from patients with T3/T4 and/or lymph node-positive rectal cancer enrolled in the Intergroup 0114 trial showed lymph node ratio (LNR), the number of positive lymph nodes divided by the total number, to be a strong predictor of survival.\(^24\) Nevertheless, the panel does not consider determination of LNR to be a substitute for an adequate lymph node evaluation.

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, or identification of particular tumor antigens...
through immunohistochemical (IHC) analysis have been reported.\textsuperscript{25,26} Although results of some of these studies seem promising, there is no uniformity in the definition of “true” clinically relevant metastatic carcinoma. Some studies have considered detection of single cells by IHC as well as isolated tumor cells (ITC) to be micrometastasis.\textsuperscript{27,28} In addition, results of one study demonstrated that, following neoadjuvant radiotherapy for rectal cancer, the sensitivity for the sentinel node procedure was only 40%.\textsuperscript{29} Presently, the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational and the results should be used with caution in clinical management decisions.

A sizable body of literature has demonstrated that mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of response to cetuximab or panitumumab therapy.\textsuperscript{30-40} Therefore, the panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer at the time of diagnosis of stage IV disease. The recommendation for KRAS testing at this point is not meant to indicate a preference regarding regimen selection in the first-line setting, but rather, this early establishment of KRAS status is appropriate in order 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 KRAS mutation, if present, while other treatment options still exist. KRAS mutations are early events in colorectal cancer formation, and there is a tight correlation between mutation status in the primary tumor and the metastases.\textsuperscript{41,42} For this reason, KRAS genotyping can be done on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of KRAS genotyping if an archived specimen from either the primary tumor or a metastasis is available. The panel recommends that KRAS 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.

Clinical Presentation and Treatment
Management of Polypoid Cancer
Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or villous adenoma, physicians should review pathology and consult with the patient.\textsuperscript{43} A malignant rectal polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore not considered to be capable of regional nodal metastasis.\textsuperscript{5} The panel recommends marking the cancerous polyp site at the time of colonoscopy or within 2 weeks. In patients with invasive cancer and adenoma (tubular, tubulovillous or villous), no additional surgery is required for pedunculated or sessile polyps, if the polyp has been completely resected with favorable histological features.\textsuperscript{43} Favorable histological 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 rectal surgery in patients with a completely-removed, single-specimen, sessile polyp with favorable histological features and clear margins because it has been reported that patients with sessile polyps have a 10% risk of lymph node metastases.\textsuperscript{44} For pedunculated and sessile polyps, unfavorable histopathological features are: grade 3 or 4, angiolymphatic invasion, or a positive margin of resection. It should be noted that there is currently no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as the presence of tumor within 1-2 mm from the transected margin and the presence of tumor cells within the diathermy of the transected margin.\textsuperscript{43,45-47} For a pedunculated or sessile polyp with fragmented specimen or margins that cannot be assessed or...
unfavorable pathology, either a transanal excision or a transabdominal resection is recommended (See section on Surgical Approaches used in the management of rectal cancer appropriate for resection). Results from a preoperative endoscopic ultrasound evaluation may provide additional information to guide choice of surgical approach, although the accuracy of this method to detect residual cancer is limited (see section on Clinical Evaluation/Staging, below). All patients who have resected polyps should undergo total colonoscopy to rule out other synchronous polyps, as well as appropriate follow-up surveillance endoscopy.

Management of Rectal Cancer

Rectal cancer has been defined as a cancerous lesion located within 12 cm of the anal verge by rigid proctoscopy. Some support for this definition comes from the study of Kapiteijn et al. which included a subgroup analysis of the risk of recurrence of rectal cancer based on tumor location. Univariate analyses indicated that local recurrence rates were low for patients who had tumors with an inferior margin of 10.1 cm or more from the anal verge, and that no significant differences between patients in this group receiving radiotherapy and surgery were observed when they were compared to those undergoing surgery alone. A recent retrospective review of patients with rectal or rectosigmoid cancer demonstrated that treatment options were impacted by whether the location of the rectal lesion was characterized by rigid proctoscopy or colonoscopy.

Determination of an optimal treatment plan for an individual patient with rectal cancer is a complex process. In addition to decisions relating to the intent of rectal cancer surgery (ie, curative or palliative), consideration must also be given to the likely functional results of treatment, including the probability of maintaining or restoring normal bowel function/anal continence, and preserving genitourinary functions. For patients with distal rectal cancer, in particular, the simultaneous achievement of the goals of cure and minimal impact on quality of life can be challenging. Furthermore, the risk of pelvic recurrence is higher in patients with rectal cancer compared to those with colon cancer, and locally recurrent rectal cancer has frequently been associated with a poor prognosis. Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy for selected patients which combines chemoradiation (chemoRT) with operative treatment as part of the treatment regimen is recommended.

Clinical Evaluation/Staging

The initial clinical workup of patients with rectal cancer provides important preoperative information on the clinical stage of disease. Since the clinical stage of the disease is used to direct decisions regarding choice of primary treatment, including surgical intent (eg, curative or palliative) and approaches, and whether to recommend preoperative chemoRT, the implications of either clinically understaging or over-staging rectal cancer can be substantial.

Patients who present with rectal cancer appropriate for resection require complete staging evaluation, including total colonoscopy to evaluate for synchronous lesions or other pathologic conditions of the colon and rectum, rigid proctoscopy to provide a determination of the location of the cancer (ie, measurement of the distance of the tumor from the anal verge should be performed by the responsible surgeon using rigid proctoscopy), and a complete physical examination, including assessment of performance status, to determine operative risk, carcinoembryonic antigen (CEA) determination, and baseline computed tomographic (CT) scans of the chest, abdomen and pelvis. The consensus of the panel is that a positron emission tomography (PET) scan is not routinely indicated at baseline in the absence of evidence of synchronous metastatic disease. In addition, the accessibility of rectal cancer to evaluation by certain imaging
modalities, such as endoscopic ultrasound and magnetic resonance imaging (MRI), makes possible preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases.\textsuperscript{56} Additional information regarding the extent of disease and the occurrence of distant metastases can be determined preoperatively through CT scans. Thus, endorectal ultrasound or endorectal or pelvic MRI, and CT scans of the chest, abdomen and pelvis are recommended for the preoperative staging of rectal cancer.

Results from a meta-analysis of 90 studies involving the accuracy of endoscopic ultrasound, MRI, and CT in preoperatively staging rectal cancer demonstrated that endoscopic ultrasound and MRI have similarly high sensitivities for evaluating the depth of tumor penetration into the muscularis propria (94%), although endoscopic ultrasound was found to be more specific than MRI in the evaluation of local tumor invasion (86% vs. 69%).\textsuperscript{57} Only a very limited number of studies using CT for the purpose of T-staging have been performed, and it is not currently considered to be an optimal method for staging the extent of tumor penetration.\textsuperscript{57,58} Accurate assessment of nodal status is one of the greatest challenges in the preoperative staging of rectal cancer. In the meta-analysis of Bipat et al.,\textsuperscript{57} the sensitivities and specificities of the 3 imaging modalities for accurately evaluating lymph node involvement were: CT (55% and 74%); endoscopic ultrasound (67% and 78%); and MRI (66% and 76%). Results from another recent meta-analysis of 84 articles, indicated that none of the 3 imaging modalities were significantly superior to another method with respect to an accurate determination of tumor N-stage.\textsuperscript{59} Disadvantages of endoscopic ultrasound and MRI include a high degree of operator dependence.\textsuperscript{57} An advantage of MRI is its ability to provide accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia. Hence, MRI evaluation of patients with more advanced rectal cancer has the potential to provide information useful in the prediction of the CRM prior to radical surgery.\textsuperscript{58-60}

Clinical staging is also based on histopathologic examination of the specimen obtained via biopsy or local excision (eg, excised polyps). Endoscopic biopsy specimens of the lesion should undergo careful pathology review for evidence of invasion into the muscularis mucosa. If removal of the rectum is contemplated, early consultation with an enterostomal therapist is recommended for preoperative marking of the site and patient teaching purposes.

**Surgical Approaches**

A variety of surgical approaches, depending on the location and extent of disease, are used to treat the primary rectal cancer lesion.\textsuperscript{61} These methods include local procedures, such as polypectomy, transanal excision and transanal microsurgery, and radical procedures involving a transabdominal resection (eg, low anterior resection [LAR], total mesorectal excision [TME] with coloanal anastomosis or abdominoperineal resection [APR]).

Transanal excision may be appropriate for selected early-stage cancers. Small (<3 cm), well to moderately differentiated small tumors that are within 8 cm of the anal verge and limited to less than 30% of the rectal circumference, and for which there is no evidence of nodal involvement (category 2A) can be approached with transanal excision with negative margins. Transanal endoscopic microsurgery (TEM) can facilitate excision of small tumors through the anus that are located higher up in the rectum. Both transanal excision and TEM involve a full thickness excision performed perpendicularly through the bowel wall into the perirectal fat. Negative (> 3 mm) deep and mucosal margins are required. Tumor fragmentation should be avoided. The excised specimen should be oriented and pinned before fixation and brought to the pathologist by the surgeon (ie, to facilitate an oriented histopathologic evaluation of the specimen). Advantages of a local procedure include minimal morbidity (eg, a sphincter-sparing procedure) and mortality and rapid postoperative recovery.\textsuperscript{53,62} If
pathologic examination reveals adverse features such as high grade, positive margins, lymphovascular invasion (LVI) or perineural invasion, a more radical resection is recommended. Data are limited on long-term patient outcomes, including risk of local recurrence, for patients undergoing local excision for T2 tumors. If these adverse features are present, a more radical resection is recommended.

Limitations of a transanal excision include the absence of pathologic staging of nodal involvement. Further, there is evidence to indicate that lymph node micrometastases are both more common in early rectal lesions and unlikely to be identified by endorectal ultrasound. These observations may underlie the findings of a recent retrospective study of 282 patients undergoing either transanal excision or radical resection for T1 rectal cancer during 1985-2004 which showed respective local recurrence rates of 13.2% and 2.7% for these 2 groups.

Patients with rectal cancer who do not meet requirements for local surgery should be treated with a transabdominal resection. Organ-preserving procedures which maintain sphincter function are preferable, but not possible, in all cases. For lesions in the mid to upper rectum, a low anterior resection (LAR) extended 4-5 cm below distal edge of tumor, followed by creation of a colorectal anastomosis, is the treatment of choice. Where creation of an anastomosis is not possible, colostomy is required.

Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer are limited. In the CLASICC trial comparing laparoscopically-assisted resection to open resection, nearly half of the 794 patients were diagnosed with rectal cancer. No significant differences in local recurrence, DFS, or overall survival were observed between the 2 groups of patients with rectal cancer based on surgical approach. However, factors which may confound conclusions drawn from randomized studies comparing open surgery to laparoscopically-assisted surgery for colorectal cancer have been described, and laparoscopic surgery for rectal cancer is not recommended by the panel outside of a clinical trial.

For low rectal lesions, abdominopereineal resection (APR) or total mesorectal excision (TME) with coloanal anastomosis is required. A TME involves an en bloc removal of the mesorectum, including associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia as a “tumor package” through sharp dissection and is designed to spare the autonomic nerves. In cases where anal function is intact and distal clearance is adequate, the TME may be followed by creation of a coloanal anastomosis. Pathologists play a key role in evaluating the surgical specimen following TME which includes a macroscopic assessment of both its external appearance/completeness and the CRM. Detailed descriptions of how the quality of the mesorectal specimens should be scored were provided in the Dutch Rectal Cancer Trial and these guidelines are endorsed by the NCCN panel.

An APR involves en bloc resection of the rectosigmoid, the rectum, and the anus, as well as the surrounding mesentery, mesorectum, and perianal soft tissue and necessitates creation of a colostomy. Whereas sphincter preservation may become possible in cases where initial tumor bulk prevented consideration of such surgery but exposure to the tumor is improved by chemoRT, an APR should be performed when tumor directly involves the anal sphincter or the levator muscles. Recent comparisons of the outcomes of patients undergoing an APR versus a LAR in the treatment of rectal cancer have shown those treated with an APR to have worse local control and overall survival.
Whether these differences can be attributed to the surgical procedure alone, to patient- and tumor-related characteristics, or some combination of these factors is presently unclear. However, results from a recent retrospective study of 3633 patients with T3-4 rectal cancer tumors included in 5 large European trials suggest that there is an association between the APR procedure itself and the increased risks of recurrence and death.73

The lymphatic drainage regions of rectal tumors are influenced by their position in the rectum. More distal tumors are more likely to be characterized by both upward and lateral lymphatic drainage whereas the likelihood of only upward mesorectal drainage is much higher for more proximal tumors.74 The TME approach is designed to radically remove lymphatic drainage regions of tumors located above the level of the levator muscles.75 The panel does not recommend extension of nodal dissection beyond the field of resection (eg, into the distribution of iliac lymph nodes) unless these nodes are clinically suspicious.

Neoadjuvant/Adjuvant Therapy
Neoadjuvant/adjuvant therapy of rectal cancer often includes locoregional treatment due to the relatively high risk of locoregional recurrence. This risk is associated with the close proximity of the rectum to pelvic structures and organs, the absence of a serosa surrounding the rectum, and technical difficulties associated with obtaining wide surgical margins at resection. In contrast, adjuvant treatment of colon cancer is more focused on preventing distant metastases since this disease is characterized by lower rates of local recurrence.

Combined-modality therapy consisting of surgery, radiation therapy (RT), and chemotherapy is recommended for the majority of patients with stage II (node-negative disease with tumor penetration through the muscle wall) or stage III rectal cancer (node-positive disease without distant metastasis). Use of perioperative pelvic RT in the treatment of patients with stage II/III rectal cancer continues to evolve. Concurrent fluoropyrimidine-based chemotherapy is recommended with radiation.

Ionizing radiation to the pelvis provides local tumoricidal therapy. Putative advantages to preoperative radiation are related to both tumor response and normal tissue.76,77 Reducing tumor volume may facilitate resection and increase the likelihood of a sphincter-sparing procedure. Irradiating tissue that is surgery-naïve and thus better oxygenated may result in increased sensitivity to RT. Preoperative radiation can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by post-surgical adhesions. Preoperative radiation that includes structures that will be resected increases the likelihood that an anastomosis with healthy colon can be performed (ie, the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected). One disadvantage of using preoperative RT is the possibility of over-treating early-stage tumors which do not require adjuvant radiation.77-79 Improvements in preoperative staging techniques, such as endoscopic ultrasound and CT scans, allow for more accurate staging, although the risk of over-staging disease has not been eliminated.80

The results of the Swedish Rectal Cancer Trial evaluating the use of short course (5 day) RT administered preoperatively for resectable rectal cancer showed a survival advantage and a decreased rate of local recurrence with this approach compared with surgery alone.81 However, whereas a number of other studies investigating the effectiveness of preoperative RT or postoperative RT in patients with rectal cancer staged as T1-3 have demonstrated improvements in local control of disease, overall survival was not shown to be significantly affected.51,82,83 In a multicenter, randomized study of 1350 patients with stage II/III rectal cancer comparing short course preoperative RT with a postoperative approach which included chemoRT in selected patients (ie, those with a positive CRM following resection) and no RT in
patients without evidence of residual disease following surgery indicated that patients in the preoperative RT arm had significantly lower local recurrence rates and a 6% absolute improvement in 3-year disease-free survival (DFS) \( (P=0.03) \). No difference in overall survival has been observed between the 2 arms of the study. Currently, however, short course RT for the treatment of rectal cancer is not widely practiced in the U.S.

A number of randomized trials have evaluated the effectiveness of chemoRT administered either preoperatively following clinical evaluation/staging (eg, T3-4 by endoscopic ultrasound) or postoperatively following pathologic staging of rectal cancer as T3 and/or N1-2. Putative benefits of addition of chemotherapy concurrent with either pre- or postoperative RT include local RT sensitization and systemic control of disease (ie, eradication of micrometastases), whereas preoperative chemoRT also has the potential to increase rates of pathologic complete response and sphincter preservation. In a study of patients with T3/4 rectal cancer without evidence of distant metastases who were randomly assigned to receive either preoperative RT alone or preoperative concurrent chemoRT with 5-FU/LV, no difference in overall survival or sphincter preservation was observed in the 2 groups, although patients receiving chemoRT were significantly more likely to exhibit a pathologic complete response (11.4% vs 3.6%; \( P<0.05 \)) and grade 3/4 toxicity (14.6% vs 2.7%; \( P<0.05 \)) and less likely to exhibit local recurrence of disease (8.1% vs 16.5%; \( P<0.05 \)). These conclusions have been supported in a recent systematic review which included 4 randomized controlled trials.

A large prospective, randomized trial from The German Rectal Cancer Study Group compared preoperative versus postoperative chemoRT in the treatment of clinical stage II/III rectal cancer. Results of this study indicated that preoperative therapy was associated with a significant reduction in local recurrence (6% vs 13%; \( P=0.006 \)) and treatment-associated toxicity, although overall survival was similar in the 2 groups. Preliminary results of a phase III trial that included an evaluation of the addition of chemotherapy to preoperative RT in patients with T3-T4 resectable rectal cancer demonstrated that use of 5-FU/LV chemotherapy enhanced the tumorcidal effect of RT when the 2 approaches were used concurrently. Significant reductions in tumor size, pTN stage, and lymphatic, vascular and perineural invasion rates were observed with use of combined-modality therapy compared with use of RT and surgery without chemotherapy. More mature results from this trial which included 4 treatment groups (preoperative RT; preoperative chemoRT; preoperative RT plus postoperative chemotherapy; and preoperative chemoRT plus postoperative chemotherapy) indicated that no significant differences in overall survival were associated with adding 5-FU-based chemotherapy preoperatively or postoperatively. Although local recurrence rates were significantly lower in the groups receiving RT followed by chemotherapy, concurrent chemoRT, or concurrent chemoRT plus chemotherapy compared to the group receiving preoperative RT alone, the addition of chemotherapy after concurrent chemoRT did not significantly impact local recurrence rates. In subsequent exploratory analyses of data from the group of patients in this trial who underwent complete tumor resection without evidence of distant disease before or at surgery, those patients with disease characterized as ypT0-2 showed significant benefit from adjuvant chemotherapy with respect to DFS and overall survival. These findings may indicate that patients are more likely to benefit from adjuvant therapy if their disease can be downstaged by chemoRT.

Whereas reports from at least one of these studies has indicated that preoperative chemoRT is associated with increased rates of sphincter preservation in rectal cancer patients, this conclusion has not been supported by 2 recent meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.
Although combined-modality therapy has been associated with decreased rates of local recurrence of rectal cancer, it is also associated with increased toxicity (eg, radiation-induced injury, hematologic toxicities, etc.) relative to surgery alone. It has been suggested that some patients with disease at lower risk of local recurrence (eg, proximal rectal cancer staged as T3, N0, M0, characterized by clear margins and favorable prognostic features) may be adequately treated with surgery and adjuvant chemotherapy.

Nevertheless, results from a recent retrospective analysis showed the risk of locoregional recurrence to be significantly higher in patients with pT3N0 rectal cancer who did not undergo RT. In addition, 22% of 188 patients clinically staged with T3N0 rectal cancer by either EUS or MRI who subsequently received preoperative chemoRT had positive lymph nodes following pathologic review of the surgical specimens according to results of a recent retrospective multicenter study.

With respect to the type of chemotherapy administered concurrently with RT, results from the Intergroup 0114 trial, showed bolus 5-FU as part of adjuvant therapy for rectal cancer to be noninferior to bolus 5-FU plus LV. After a median follow-up of 4 years, neither the rate of local control nor survival differed among 3 different combinations of modulated 5-fluorouracil (5-FU) chemotherapy. The equivalence of bolus 5-FU/LV and infusional 5-FU in concurrent chemorT for rectal cancer is supported by the results of a phase III trial (median follow-up of 5.7 years) in which similar outcomes with respect to overall survival and relapse-free survival were observed when a continuous infusion of 5-FU or bolus 5-FU plus LV was administered concurrently with postoperative RT, although hematologic toxicity was greater in the group of patients receiving bolus 5-FU. However, results from an earlier trial from the North Central Cancer Treatment Group (NCCTG) showed that postoperative administration of continuous infusion 5-FU during pelvic irradiation was associated with longer overall survival when compared to bolus 5-FU. Most of the patients in this study had node-positive disease.

Postoperative chemoRT regimens commonly employ a “sandwich” approach – whereby chemotherapy (typically 5-FU based) is administered before and after the chemoRT regimen. The use of FOLFOX or capecitabine chemotherapy before and after postoperative chemoRT is an extrapolation of the available data in colon cancer.

With respect to administration of RT, multiple RT fields should include the tumor or tumor bed with a 2-5 cm margin, presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures as well as consideration of inclusion of the inguinal nodes for tumors invading into the distal anal canal. Recommended doses of radiation are typically 45-50 Gy, with the exceptions of unresectable cancers where doses higher than 54 Gy may be required, and irradiation of the small bowel where the dose should be limited to 45 Gy. Intensity modulated radiotherapy (IMRT) which uses computer-imaging to focus RT to the tumor site and potentially decrease toxicity to normal tissue, should be used in the context of a clinical trial only. As an additional boost, intraoperative radiotherapy (IORT) which involves direct exposure of tumors to RT during surgery while removing normal structures from the field of treatment should be considered preoperatively for patients with T4 tumors or recurrent cancers to facilitate resection.

Coordination of preoperative therapy, surgery and adjuvant chemotherapy is important. For patients treated with preoperative chemoRT, the panel recommends an interval of 5-10 weeks following completion of full dose 5 ½ week chemoRT prior to performance of surgical resection in order to allow patient recuperation from chemoRT-associated toxicities. Although longer intervals from completion of chemoRT to surgery have been shown to be associated with an increase in pathologic complete response rates, it is unclear...
whether this is associated with clinical benefit. Nevertheless, when longer intervals are clinically necessary, they do not appear to increase the blood loss, time associated with surgery, or positive margin rate.  

Adjuvant chemotherapy of approximately 4 months duration is recommended for all patients with stage II/III rectal cancer following neoadjuvant chemoRT/surgery regardless of the surgical pathology results, although few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer and its role is not well defined. Evaluation of adjuvant chemotherapy with 5-FU/LV alone versus postoperative RT followed by adjuvant chemotherapy with 5-FU/LV in patients with stage II/III rectal cancer in the National Surgical Breast and Bowel Project (NSABP) R-02 trial showed a significant decrease in local recurrence rate in the group receiving adjuvant chemotherapy after RT compared to the group receiving adjuvant chemotherapy alone.  

However, no benefit of adding 5-FU-based adjuvant chemotherapy to preoperative chemoRT with respect to rate of local recurrence was observed in the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Group Trial 22921 (hazard ratio=0.87; 95% CI, 0.72-1.04; P=0.13) when the DFS of patients receiving adjuvant chemotherapy following preoperative RT (+/- 5-FU-based chemotherapy) was compared to DFS of patients who underwent preoperative RT (+/- 5-FU-based chemotherapy) but did not receive adjuvant 5-FU-based chemotherapy.  

However, patients responding to preoperative chemoRT had a survival benefit with adjuvant chemotherapy.

Most of the support for use of FOLFOX or capecitabine as adjuvant chemotherapy in rectal cancer is an extrapolation from the data available for colon cancer. The phase III ECOG E3201 trial is investigating the effect of adding either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) to 5-FU/LV-based adjuvant chemotherapy administered to stage II/III rectal cancer patients following either preoperative or postoperative chemoRT. Early reports indicate that adjuvant FOLFOX can be safely used in this patient population. Nevertheless, the duration of treatment with adjuvant FOLFOX in rectal cancer is still unclear. In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX. Some justification for the use of a shorter course of adjuvant FOLFOX in rectal cancer (ie, 4 months) can be provided when preoperative chemoRT is administered. In addition, the NSABP-07 trial demonstrated similar DFS benefits to those reported in the MOSAIC trial with only 9 cycles of an oxaliplatin-containing adjuvant regimen.  

A summary of ongoing clinical trials in early-stage rectal cancer has been presented.

**Treatment of Nonmetastatic Rectal Cancer**

**Recommendations for patients with T1 and T2 lesions**

Node-negative T1 and T2 lesions are treated with transabdominal resection or transanal excision (category 2B for T2), if appropriate. This recommendation is category 2B for node-negative T2 tumors since local recurrence rates of 11% to 45% have been observed for T2 lesions following local excision alone. In selected lesions that are staged by endoscopic ultrasound or MRI as T1-2, N0 and without adverse pathologic features (eg, no lymphovascular invasion [LVI] or perineural invasion; size less than 3 cm; well to moderately differentiated), local excision with negative margins may give results comparable to transabdominal resection. No additional therapy is recommended for patients with well-differentiated T1 cancers. If pathology review after local excision reveals a poorly differentiated histology, positive margins, or LVI, then a transabdominal re-resection should be performed. T2 cancers excised with negative margins and no poor prognostic factors should be treated with transabdominal resection or adjuvant 5-FU/RT. Systemic chemotherapy should be considered as an adjuvant treatment for those patients who receive adjuvant...
chemoradiation without additional surgery in order to avoid the risk of undertreatment as the lymph node status is unknown.

For patients with T1 to T2 lesions not amenable to local excision, a transabdominal resection is required. No adjuvant therapy is indicated for patients with pathologic findings of T1 or T2 lesions. Patients with pathologic lymph node-negative T3 lesions (pT3, N0, M0) or pathologic lymph node-positive lesions (pT1-3, N1-2) should receive a “sandwich regimen” consisting of adjuvant chemotherapy with 5-FU with or without LV or FOLFOX (category 2B) or capecitabine (category 2B), followed by concurrent 5-FU/RT (continuous infusion [category 2A] or bolus infusion along with LV [category 2B]) or capecitabine/RT (category 2B), then 5-FU with or without LV or FOLFOX (category 2B) or capecitabine (category 2B). The panel recommends approximately postoperative therapy for a total duration of approximately 6 months. For patients with pathologic evidence of proximal T3, N0, M0 disease with clear margins and favorable prognostic features following an upfront resection, the incremental benefit of RT is likely to be small and chemotherapy alone can be considered, although most patients are not likely to be part of this subset.

Recommendations for patients with T3 lesions and lesions with nodal involvement
Patients clinically staged as having resectable T3, N0 or any T, N1-2 lesions should initially be treated with preoperative combined-modality therapy. Upfront surgery should be reserved for patients with medical contraindications to chemoRT. Preoperative continuous infusional 5-FU/RT is the preferred treatment option (category 1 for node positive disease). Alternative regimens include bolus 5-FU/LV/RT (category 2A) or capecitabine/RT (category 2B). Patients who receive preoperative radiotherapy should undergo transabdominal resection 5-10 weeks following completion of neoadjuvant therapy. The panel recommends approximately 6 months total duration of pre- and postoperative chemotherapy (regardless of surgical pathology results) with 5-FU with or without LV (category 1 for T3, N0 or Tany, N1-2 tumors) or FOLFOX (category 2B) or capecitabine (category 2B).

Patients with disease characterized as T3, N0 or T any, N1-2 disease initially treated by transabdominal resection with subsequent pathologic staging of disease as pT1-2, N0, M0 can be followed with observation only. Patients with disease staged as pT3, N0, M0 or pT1-3, N1-2, M0 following initial treatment by transabdominal resection should receive approximately 6 months postoperative chemotherapy with 5-FU with or without LV or FOLFOX (category 2B) or capecitabine (category 2B), followed by concurrent 5-FU/RT (5-FU as continuous infusion [category 2A] or bolus infusion with LV [category 2B]) or capecitabine/RT (category 2B), then 5-FU with or without LV (category 2A) or FOLFOX (category 2B) or capecitabine (category 2B). For some patients with pathologic evidence of proximal T3, N0, M0 disease with clear margins and favorable prognostic features following transabdominal resection, the incremental benefit RT is likely is small and chemotherapy alone can be considered, although this subset of patients is small.

Recommendations for patients with T4 lesions and/or locally unresectable disease
Patients with T4 and/or locally unresectable disease are treated with preoperative continuous infusional 5-FU/RT (category 2A) or bolus 5-FU with LV/RT (category 2A) or capecitabine/RT (category 2B). If possible, resection should be considered following preoperative chemoRT. Adjuvant therapy to complete 6 months with either 5-FU with or without LV (category 2A), FOLFOX (category 2B) or capecitabine (category 2B) is recommended regardless of the surgical pathology results.

Treatment of Metastatic Disease
Approximately 50%-60% of patients diagnosed with colorectal cancer will develop colorectal metastases.119,120 Patients with stage IV (any T,
any N, M1) colorectal cancer or recurrent disease can present with synchronous liver or lung metastases or abdominal peritoneal metastases. Approximately 15%-25% of patients with colorectal cancer present with synchronous liver metastases, although 80%-90% of these patients are initially evaluated to have unresectable metastatic liver disease. Metastatic disease more frequently develops metachronously following treatment for colorectal cancer, with the liver as a common site of involvement. There is some evidence to indicate that synchronous metastatic colorectal liver disease is associated with a more disseminated disease state and a worse prognosis than metastatic colorectal disease that develops metachronously. In one 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=0.008) and more bilobar metastases (P=0.016) when compared with patients diagnosed with metachronous liver metastases. For patients presenting with synchronous metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver. It has been estimated that over one-half of patients who die of colorectal cancer have liver metastases at autopsy, and that metastatic liver disease is the cause of death in the majority of these patients. Results from reviews of autopsy reports of patients dying from colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients. Furthermore, rates of 5-year survival for patients with metastatic liver disease not undergoing surgery have been shown to be quite low in a number of studies. However, studies of selected patients undergoing surgery to remove colorectal liver metastases have demonstrated that cure is possible in this population and should be the goal for many patients with colorectal metastatic liver disease. Recent reports have shown 5-year survival rates following resection of hepatic colorectal metastases exceeding 50%. 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. The criteria for determining patient suitability for resection, or surgical cure, of metastatic disease are evolving, with the emphasis being increasingly placed on the likelihood of achieving negative surgical margins while maintaining adequate liver reserve, as opposed to other criteria, such as the number of liver metastases present. Resectability differs fundamentally from endpoints which focus more on palliative measures of treatment such as response and DFS. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease, since partial liver resection or debulking has not been shown to be beneficial. Approaches used in the surgical treatment of liver metastases include simultaneous resections of colorectal cancer and synchronous liver metastases, preoperative portal vein embolization for the purpose of increasing the volume and function of the portion of the liver which will remain postsurgically, hepatic resection performed in 2 stages for bilobar disease. Resection is the standard of care for the local treatment of metastatic disease that is initially resectable or converted to a potentially curable status following chemotherapy. However, some patients in this group who cannot undergo resection due to comorbidity, location of the metastatic lesion(s) (ie, adjacent to a major hepatic vein or the vena cava) or an estimate of inadequate liver volume following resection may be candidates for ablation therapy. A number of retrospective studies have compared radiofrequency ablation (RFA) and liver resection in the treatment of liver metastases, although RFA has not been well studied in this setting. Most of these studies have shown RFA to be inferior to resection with respect to rates of local recurrence and 5-year overall survival. It is presently unclear whether the differences in
outcome observed for patients with liver metastases treated with RFA versus resection alone are due to patient selection bias, technological limitations of RFA or a combination of these two factors. Nevertheless, the panel does not consider RFA to be a substitute for resection in patients with completely resectable disease. In addition, resection or RFA (either alone or in combination with resection) should be reserved for patients with disease that is completely amenable to local therapy. Use of either surgery, RFA, or the combination of the two “debulking procedures” with a goal of less than complete resection/ablation of all known sites of disease is not recommended.

The consensus of the panel is that patients diagnosed with potentially resectable metastatic colorectal cancer should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (i.e., with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status.

The majority of patients diagnosed with metastatic colorectal disease are initially classified as unresectable disease. For those with liver-limited unresectable disease, however, preoperative chemotherapy is being increasingly employed to downsize colorectal metastases in order to convert these lesions to a resectable status (i.e., conversion chemotherapy); it has also been administered to patients with metastatic disease determined to be resectable (i.e., neoadjuvant therapy). Potential advantages of this approach include: earlier treatment of micrometastatic disease; determination of responsiveness to chemotherapy (which can be prognostic and help plan postoperative therapy; and avoidance of local therapy in those who progress early. Potential disadvantages include: chemotherapy-induced liver injury; and missing the “window of opportunity” for resection through the possibility of either disease progression; or achievement of a complete response, thereby making it difficult to identify areas for resection. Furthermore, results from a study of colorectal cancer patients receiving preoperative chemotherapy indicated that cancer cells were 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. It is therefore essential that during treatment with preoperative chemotherapy, frequent evaluations are undertaken and close communication is maintained between medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed which optimizes exposure to the preoperative regimen and facilitates an appropriately-timed surgical intervention. When preoperative chemotherapy is planned for patients with initially unresectable disease, the panel recommends that a surgical re-evaluation should be planned 2 months after initiation of preoperative chemotherapy, and that those patients who continue to receive preoperative chemotherapy undergo surgical re-evaluation every 2 months thereafter.

Certain clinicopathologic factors, such as the presence of extrahepatic metastases and a disease-free interval of < 12 months, have been associated with a poor prognosis in patients with colorectal cancer, although the ability of these factors to predict outcome following resection may be limited. However, decision-making relating to whether to offer preoperative chemotherapy begins with an initial evaluation of the degree of resectability of metastatic disease. Benefits of initial surgery in patients with clearly resectable disease characterized by generally favorable prognostic characteristics may outweigh the benefits of downsizing the disease with neoadjuvant chemotherapy. Alternatively, preoperative chemotherapy would be more appropriate in patients with borderline resectable or initially unresectable but potentially convertible following response to chemotherapy. In addition, preoperative chemotherapy may be more beneficial in patients who have not been exposed to prior chemotherapy or who have not received prior chemotherapy in the previous 12 months.
The most important benefit of the preoperative approach is the potential to convert patients with initially unresectable metastatic disease to a resectable state. In the study of Pozzo et al, it was reported that preoperative therapy 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.\(^\text{134}\) 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 North Central Cancer Treatment Group (NCCTG),\(^\text{123}\) 44 patients with unresectable liver metastases were treated with FOLFOX4. 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 of 1439 initially unresectable patients with colorectal liver disease, 1104 patients were treated with chemotherapy and 335 patients (23%) were able to undergo primary hepatic resection. Of the 1104 patients receiving chemotherapy, 138 patients (12.5%) classified as “good responders” underwent secondary hepatic resection following preoperative chemotherapy which included oxaliplatin in the majority of cases.\(^\text{156}\) The 5-year survival rate for these 138 patients overall was 33%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%) were able to undergo curative liver resection following treatment.\(^\text{157}\) The median overall survival time in this group was 42.4 months.

The choice of chemotherapy regimen in the preoperative setting is dependent on a number of factors including whether the patient has resectable or potentially convertible metastatic disease, and the response rates and safety/toxicity issues associated with the regimens. Although the benefits of preoperative or postoperative chemotherapy for patients with liver metastases have not yet been fully validated in randomized clinical trials, a recent European Organization for Research and Treatment of Cancer (EORTC) phase III study evaluating use of perioperative FOLFOX4 (6 cycles before and 6 cycles after surgery) for patients with initially resectable liver metastases demonstrated absolute improvements in 3-year progression-free survival (PFS) of 8.1% (P=0.041) and 9.2% (P=0.025) for all eligible patients and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.\(^\text{158}\) The partial response rate after preoperative FOLFOX was 40% and operative mortality was <1% in both treatment groups.

There have been recent reports of randomized clinical trials evaluating preoperative FOLFIRI or FOLFOX as conversion therapies in combination with anti-EGFR inhibitors.\(^\text{159,160}\) However, a number of randomized studies have investigated the efficacy and safety of FOLFOX, CapeOX, or FOLFIRI with and without bevacizumab or cetuximab in the first-line treatment of patients with metastatic colorectal cancer (see section on Chemotherapy for Advanced or Metastatic Disease in NCCN Colon Cancer Guidelines). In addition, first-line FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI in 2 randomized clinical trials.\(^\text{161,162}\) Significantly improved rates of response and overall survival were reported for patients in the FOLFOXIRI arm of one of the studies,\(^\text{162}\) but not in the other.\(^\text{161}\)

The efficacy of bevacizumab in combination with FOLFOX and FOLFIRI (infusional 5-FU, LV, irinotecan) in the treatment of unresectable metastatic disease (see section on Chemotherapy for Advanced or Metastatic Disease in NCCN Colon Cancer Guidelines) has led to its use in combination with these regimens in the preoperative setting, although the safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU-based regimens has not been adequately evaluated. A retrospective evaluation of data from
2 randomized trials of 1132 patients receiving chemotherapy with or without bevacizumab as initial therapy for metastatic colorectal cancer 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 when this population was compared to the group receiving chemotherapy alone while undergoing major surgery (13% vs 3.4%, respectively; P=0.28). However, when chemotherapy plus bevacizumab or chemotherapy alone was administered prior to surgery, the incidence of wound healing complications in either group of patients was low (1.3% vs 0.5%; P=0.63). The panel recommends at least a 6 week interval (which corresponds to 2 half-lives of the drug) between the last dose of bevacizumab and elective surgery. Further support for this recommendation comes from results of a single center, nonrandomized phase II trial of patients with potentially resectable liver metastases which showed no increase in bleeding or wound complications when the bevacizumab component of CapeOX plus bevacizumab therapy was stopped 5 weeks prior to surgery (ie, bevacizumab excluded from the 6th cycle of therapy). In addition, no significant differences in bleeding, wound, or hepatic complications were observed in a retrospective trial evaluating effects of preoperative bevacizumab stopped ≤ 8 weeks vs. > 8 weeks prior to resection of liver colorectal metastases for patients receiving oxaliplatin- or irinotecan-containing regimens.

Other reported risks associated with the preoperative approach include the potential for development of liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered. To limit the development of hepatotoxicity, it is therefore recommended that surgery should be performed as soon as possible after the patient becomes resectable and usually not more than 3-4 months following initiation of preoperative treatment.

As mentioned above, colorectal metastatic disease can also occur in the lung. Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases. Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in selected cases. The goal of treatment of most abdominal/peritoneal metastases is palliative, rather than curative.

It is important to note that some of the treatment approaches for patients diagnosed with rectal cancer and potentially resectable synchronous lung or liver metastases differ relative to those for patients diagnosed with stage IV colon cancer characterized as potentially resectable metastatic disease. In particular, initial treatment options for potentially resectable rectal cancer include: preoperative chemoRT directed toward treatment of the primary cancer; preoperative combination chemotherapy regimen plus a biologic agent to target metastatic disease; and a surgical approach (ie, staged or synchronous resection of metastases and rectal lesion). Advantages of an initial chemoRT approach include a possible decreased risk of pelvic failure following surgery although preoperative pelvic RT may decrease tolerance to systemic bevacizumab-containing adjuvant regimens, thereby limiting subsequent treatment of systemic disease. However, data to guide decisions regarding optimal treatment approaches in this population of patients are very limited. Of note, patients with stage II/III rectal cancer enrolled in a large randomized trial evaluating the effect of adding chemotherapy to preoperative RT were found to be three times more likely to develop distant metastases than local recurrence of disease after a median follow-up of over 5 years.

Only limited data exist regarding the efficacy of adjuvant chemotherapy following resection for metastatic colorectal liver or lung disease. Nevertheless, the panel recommends administration of a course of an active systemic chemotherapy regimen for metastatic disease for some
patients following liver or lung resection who have received preoperative chemoRT or no preoperative therapy following staged or synchronous resection of metastases and rectal lesion in order to increase the likelihood that residual microscopic disease will be eradicated for a total perioperative treatment time of approximately 6 months. Postoperative chemoRT is recommended for patients with synchronous metastases who have not received prior chemoRT and who are at higher risk for pelvic recurrence following staged or synchronous resection of metastases and rectal lesion (ie, patients with disease staged as pT3-4, Any N, or Any T,N1-2).

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent administration of chemotherapy directed to the liver metastases through the hepatic artery (ie, HAI) is listed in the guidelines as an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine (with dexamethasone and with or without LV) by HAI in addition to systemic chemotherapy was shown to be superior to systemic chemotherapy alone with respect to 2-year survival and time to progression of hepatic disease. However, the difference in survival between the 2 arms of the study was not significant at later follow-up periods. A number of other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAI therapy was compared with systemic chemotherapy, although most have not shown a survival benefit of HAI therapy. Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI. However, limitations on the use of HAI therapy include the potential for biliary toxicity, and the requirement for specific technical expertise. The consensus of the panel is that HAI therapy should be considered only at institutions with extensive experience in both the surgical and medical oncologic aspects of the procedure.

Finally, a number of liver-directed therapies are available for the treatment of unresectable metastatic disease in highly select patients, although their role in the treatment of colorectal metastases is controversial. These therapies include arterial radioembolization with yttrium-90 microspheres, arterial chemoembolization, and conformal radiation therapy. Use of intra-arterial embolization is a category 3 recommendation for select patients with predominant hepatic metastases, and conformal external beam radiation therapy is not recommended unless the patient is symptomatic or it is used in the setting of a clinical trial. (See sections on Recommendations for the Treatment of Synchronous Metastases/Unresectable Disease and Recommendations for the Treatment of Metachronous Metastases.

Locally recurrent rectal cancer is characterized by isolated pelvic/anastomotic recurrence of disease. In a single-center study at MD Anderson, rates of 5-year local recurrence were reported to be low (ie, 5-year locoregional control rate of 91%) for patients with rectal cancer treated with surgery and either RT or chemoRT, and 78% of recurrences occurred in the low pelvic and presacral regions. In a study of 43 consecutive patients with advanced pelvic recurrence of colorectal cancer who had not undergone prior RT, treatment with 5 weeks of 5-FU by continuous infusion concurrent with RT enabled the majority of patients (77%) to undergo re-resection with curative intent.

Recommendations for Treatment of Synchronous Metastases/Resectable Disease
As part of the pre-treatment work-up, the panel recommends tumor KRAS gene status testing for all patients with metastatic colorectal cancer at the time of diagnosis of metastatic disease (see discussion of KRAS testing on MS-3).
Initial treatment options for patients with stage IV disease (any T, any N, M1) with resectable liver or lung metastases include: combination chemotherapy for 2-3 months (eg, FOLFOX, CapeOX, or FOLFIRI regimens with or without bevacizumab or cetuximab for KRAS wild-type tumors only); staged or synchronous resection of metastases and rectal lesion; treatment with continuous infusional 5-FU/pelvic RT (category 2A) or bolus 5-FU with LV/pelvic RT (category 2A) or capecitabine/RT (category 2B); or 2-3 months of upfront combination chemotherapy with FOLFOX, CapeOX, or FOLFIRI regimens with or without bevacizumab or cetuximab (KRAS wild-type tumors only) followed by chemoRT. The impetus for inclusion of the latter option is upfront systemic treatment with a goal of early eradication of micrometastases followed by consolidating chemoRT for local control of disease prior to surgery. For the 3 groups of patients receiving neoadjuvant therapy, surgery should be performed 5-10 weeks following completion of such treatment.

Adjuvant therapy for patients undergoing initial surgery is dependent on pathologic staging of disease. For patients undergoing initial surgical treatment, the panel recommends that those at higher risk for pelvic failure relative to systemic disease (eg, disease pathologically staged as pT3-4, Any N or Any T, N1-2) undergo postoperative chemoRT using the “sandwich” approach (ie, chemotherapy followed by concurrent chemoRT followed by chemotherapy for 6 months total duration). The panel acknowledged that not all patients with rectal cancer and resectable liver or lung metastases need to be treated with chemoRT. For example, in the population of patients with pT1-2,N0 disease, the competing risk of distant metastases is considered to be higher than that of locoregional recurrence. Therefore, the panel recommends that these patients receive an active adjuvant chemotherapy regimen (for 6 months) for advanced disease, with the exception of FOLFOXIRI. Adjuvant therapy recommendations for patients who have received neoadjuvant chemoRT only is as described for patients with pT1-2,N0 disease (except total duration of pre- plus postoperative chemotherapy should be 6 months), whereas patients who have undergone preoperative bevacizumab- or cetuximab (KRAS wild-type tumors only)-containing therapy should receive postoperative chemoRT as described above for patients with pT3-4, Any N, or Any T, N1-2 disease (except total duration of pre- plus postoperative chemotherapy should be 6 months). Those patients undergoing preoperative bevacizumab- or cetuximab-containing therapy followed by preoperative chemoRT should not receive postoperative chemotherapy.

Recommendations for Treatment of Synchronous Metastases/Unresectable Disease
Patients with any unresectable or medically inoperable metastases are treated according to whether they are symptomatic or asymptomatic. Symptomatic patients are treated with chemotherapy alone or combined modality therapy with 5-FU/RT or capecitabine/RT (category 2B), resection of the involved rectal segment or laser canalization or diverting colostomy or stenting. Primary treatment should be followed by an active chemotherapy regimen for metastatic disease.

For patients with asymptomatic liver or lung disease that is deemed to be unresectable, the panel recommends chemotherapy corresponding to initial therapy for metastatic disease (eg, choice of FOLFIRI, FOLFOX, or CapeOX chemotherapy with or without bevacizumab or cetuximab [KRAS wild-type tumors only], or the same chemotherapy regimens with or without cetuximab [KRAS wild-type tumors only], or FOLFOXIRI [category 2B for FOLFOXIRI]) to attempt to render these patients candidates for resection. Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease, and these patients should be re-evaluated for resection after 2 months of preoperative chemotherapy and every 2 months thereafter while undergoing such therapy.
Primary treatment of unresectable synchronous liver or lung metastases by palliative surgery to remove the primary tumor should be considered only if the patient has an unequivocal imminent risk of obstruction or acute significant bleeding. It should be noted that symptomatic improvement in the primary is often seen with first-line systemic chemotherapy, even within the first one to two weeks, and routine palliative resection of a synchronous primary lesion should not be done in the absence of overt, serious symptoms. Complications from the primary lesion are uncommon in these circumstances, and its removal delays initiation of systemic chemotherapy. An intact primary is not a contraindication to bevacizumab use. The risk of gastrointestinal perforation in the setting of bevacizumab is not decreased by removal of the primary tumor, as large bowel perforations, in general, and perforation of the primary lesion, in particular, are rare (see section on Chemotherapy for Advanced or Metastatic Disease in the NCCN Colon Cancer Guidelines).

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 Treatment of Metastatic Disease). Post-treatment follow-up for patients classified as stage IV and no evidence of disease (NED) is described in the section on Post-Treatment Surveillance.

Patients with unresectable metastatic disease not responding to preoperative therapy should receive chemotherapy for advanced or metastatic disease with treatment selection based, in part, on whether the patient is or is not an appropriate candidate for intensive therapy.

There was no consensus of the panel regarding the use of liver-directed therapies such as arterial radioembolization therapy and arterial chemoembolization therapy. For select patients with chemotherapy resistant/refractory disease characterized by predominant liver metastases and no obvious systemic disease, use of these interventions was supported by some panel members but not others (category 3). The consensus of the panel is that conformal external radiation therapy should not be used unless the patient is symptomatic or it is administered in the context of a clinical trial.

**Recommendations for Treatment of Metachronous Metastases**

Routine use of PET to monitor for disease recurrence is not recommended. It should be noted that the CT that accompanies a “PET/CT” is a non-contrast CT, and thus not of ideal quality for routine surveillance. Upon documentation on dedicated contrast-enhanced CT or MRI of metachronous metastases in which disease is or may become potentially resectable, characterization of the extent of disease by PET scan is recommended. PET is used at this juncture to promptly characterize the extent of metastatic disease, and to identify possible sites of extrahepatic disease which could preclude surgery. As with other first identifications of metastatic disease, a tumor sample (metastases or original primary) should be sent for KRAS genotyping in order to define whether anti-EGFR agents can be considered in the list of potential options for this patient (see discussion of KRAS testing on MS-2 – MS-3). 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 further distinguished from that of synchronous disease by also including an evaluation of the chemotherapy history of the patient, and by the absence of transabdominal resection. Resectable patients are classified according to whether they have received no previous chemotherapy or prior chemotherapy within or prior to the previous 12 months. For patients who have not received prior chemotherapy and who have resectable metastatic disease, primary treatment options include initial resection followed by chemotherapy with an active
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Patients receiving palliative chemotherapy should be monitored with CT or MRI scans approximately every 2-3 months. PET scans are not recommended for routine monitoring of the progression of metastatic disease.

Isolated pelvic/anastomotic recurrence is optimally managed by preoperative RT and concurrent infusional 5-FU, if full course RT was not given previously. Resection followed by the option of IORT should be considered if it can be safely delivered. However, debulking, resulting in gross residual cancer, is discouraged. Patients with unresectable lesions are treated according to their ability to tolerate therapy. The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative. The panel currently considers the treatment of disseminated carcinomatosis with cytoreductive surgery (ie, peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy to be investigational and does not endorse such therapy outside of a clinical trial. However, the panel recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities.

Chemotherapy for Advanced or Metastatic Disease
The continuum of care approach to the management of patients with metastatic rectal cancer is the same as described for patients with metastatic colon cancer. Please refer to the corresponding section in the Colon Cancer Guidelines – Chemotherapy for Advanced or Metastatic Disease.

Post-Treatment Surveillance
The approach to monitoring and surveillance of patients with rectal cancer is similar to that described for colon cancer with the addition of proctoscopy to evaluate the rectal anastomosis for local recurrence for patients who have undergone an LAR. Anastomotic recurrence of rectal...
cancer has a much more favorable prognosis than local recurrence at other locations in the pelvis, although the optimal timing for surveillance of the rectal anastomosis is not known.

Following curative-intent surgery, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and to identify new metachronous neoplasms at a preinvasive stage. Advantages of more intensive follow-up of Stage II and/or Stage III patients have been demonstrated prospectively in several studies and in 3 recent meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance. Other recent studies impacting on the issue of post-treatment surveillance of colorectal cancer include results from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials which demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor, and a population-based report indicating increased rates of resectability and survival in patients treated for local recurrence and distant metastases of colorectal cancer, thereby providing support for more intensive post-treatment follow-up in these patients. Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery.

The following panel recommendations for post-treatment surveillance pertain to patients with stage I-stage III disease who have undergone successful treatment (i.e. no known residual disease): history and physical examination every 3-6 months for 2 years, and then every 6 months for a total of 5 years; and a CEA test at baseline and every 3-6 months for the next 5 years for patients with disease staged as T2 or greater. Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps since data show that patients with a history of colorectal cancer have an increased risk of developing second cancers, particularly in the first 2 years following resection. Furthermore, use of post-treatment surveillance colonoscopy has not been shown to improve survival through the early detection of recurrence of the original colorectal cancer. CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and the liver. Hence, CT scan is not routinely recommended in patients who are not candidates for
potentially curative resection of liver or lung metastases. Post-treatment PET scan is not routinely recommended for surveillance of patients with resected early-stage colorectal cancer to detect recurrence of the original cancer.\textsuperscript{189,192} Furthermore, PET scan is not routinely recommended to detect metastatic disease in the absence of other evidence of such disease.\textsuperscript{192}

Post-treatment surveillance also includes a survivorship care plan involving disease preventive measures such as immunizations against influenza and pneumococcal infections at prescribed intervals and regular dental care, and early disease detection through periodic screening for second primary cancers (eg, breast, cervical, or prostate cancers) and routine health monitoring to screen for comorbid conditions including psychosocial distress associated with rectal cancer and its treatment.

Other recommendations include monitoring for late sequelae of rectal cancer or the treatment of rectal cancer, such as: chronic diarrhea or incontinence (eg, patients with stoma)\textsuperscript{199}; persistent neuropathy - a well known side effect of oxaliplatin treatment\textsuperscript{99}; and pelvic pain/pelvic fractures; and urogenital dysfunction following resection or pelvic irradiation.\textsuperscript{200-203} Specific management interventions to address these side effects are described in a recent review.\textsuperscript{204}

There is also evidence to indicate that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy body mass index (BMI), engaging in regular exercise, and making certain dietary choices are associated with improved outcomes following treatment for colon cancer. For example, 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 $\geq 35$ kg/m$^2$ had an increased risk of disease recurrence and death.\textsuperscript{205} In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, disease-free survival was found to be directly dependent on how much exercise these patients received.\textsuperscript{206} Furthermore, a diet consisting of more fruits, vegetables, poultry and fish, and less red meat, as well as diets higher in whole grains and lower in refined grains and concentrated sweets was found to be associated with an improved outcome in terms of cancer recurrence or death.\textsuperscript{207} A discussion of lifestyle characteristics which may be associated with a decreased risk of colorectal cancer recurrence 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.

Managing an Increasing Carcinoembryonic Antigen Level

Managing patients with an elevated CEA level after resection should include colonoscopy, chest, abdominal, and pelvic CT scans, and consideration of a PET scan. If imaging study results are normal in the face of a rising CEA, a PET scan should be performed with repeat CT scans recommended every 3 months or until either disease is identified or CEA stabilizes or declines. The opinion of the panel on the usefulness of PET scan in the scenario of an elevated CEA with negative, good-quality CT scans was divided (ie, some panel members favored use of PET in this scenario while others noted that the likelihood of PET identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). Use of PET 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,\textsuperscript{208} nor is the use of anti-CEA-radiolabeled scintigraphy

Summary

The NCCN Rectal Cancer Guidelines panel believes that a multidisciplinary approach, including representation from gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology is necessary for treating patients with rectal
cancer. Adequate pathologic assessment of the resected lymph nodes is important with a goal of evaluating at least 12 nodes when possible. Patients with very early stage tumors lesions that are node-negative by endorectal ultrasound or endorectal or pelvic MRI and who meet carefully defined criteria can be managed with a transanal excision. A transabdominal resection is appropriate for all other rectal lesions. Preoperative chemoRT is preferred for the majority of patients with suspected or proven T3/T4 disease and/or regional node involvement and adjuvant chemotherapy is recommended. Patients with recurrent localized disease should be considered for resection with or without radiotherapy.

A patient with metastatic disease in the liver or lung should be considered for surgical resection if he or she is a candidate for surgery and if complete resection (R0) or ablation can be achieved. Preoperative chemotherapy can be considered as initial therapy in patients with synchronous or metachronous resectable metastatic disease (ie, neoadjuvant therapy) or when a response to chemotherapy may convert a patient from an unresectable to resectable state (ie, conversion therapy). Other options for patients with resectable synchronous metastases are initial treatment with chemoRT or chemotherapy with or without bevacizumab or cetuximab (KRAS wild type tumor only) followed by consolidating chemoRT. Resection should be followed by adjuvant therapy based on prior therapy received. The recommended post-treatment surveillance program for rectal cancer patients includes serial CEA determinations, as well as periodic chest, abdominal and pelvic CT scans, and periodic evaluations by colonoscopy and proctoscopy.

Recommendations for patients with previously untreated disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at the start 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. Recommended initial therapy options for advanced or metastatic disease depend on whether or not the patient is appropriate for intensive therapy. The more intensive initial therapy options include FOLFOX, FOLFIRI, CapeOX, and FOLFOXIRI (category 2B). Addition of a biologic agent (eg, bevacizumab or cetuximab) is either recommended, or listed as an option, in combination with some of these regimens, depending on available data. Chemotherapy options for patients with progressive disease are dependent on the choice of initial therapy. The panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy.
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