



NCCN Clinical Practice Guidelines in Oncology™

Rectal Cancer

V.1.2007

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This manuscript is being updated to correspond with the newly updated algorithm.

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 Consensus: All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Consensus](#)

[Summary of Guidelines Updates](#)

Summary of the Guidelines updates

Summary of changes in the 1.2007 version of the Rectal Cancer Guidelines from the 2.2006 version include:

- [REC-1](#) is a new page to the guidelines discussing the management of malignant polyps.
- Chest CT replaced chest x-ray in the Workup section and proctoscopy was added ([REC-2](#)).
- Footnote "l" and "m" are new to page [REC-4](#).
- Footnote "q" is new to page [REC-5](#). Footnote "p" was modified to include patients greater than or equal to the age of 65 have an increased risk of stroke and other arterial events and the use of bevacizumab may interfere with wound healing.
- The H&P and CEA were changed from every 3 mo to every 3-6 mo for 2 y ([REC-7](#)).
- The recommended timing of colonoscopy was changed throughout the guidelines to at 3 y and then every 5 y for patients negative for polyps at the 1 y colonoscopy. Footnotes "v" and "w" are new to the page ([REC-7](#)).
- A new page was added to address the treatment recommendations for documented metachronous liver and/or lung metastases based upon the timing and type of previous therapy ([REC-9](#)).
- Principles of Pathologic Review is a new attachment ([REC-A](#)).
- Principles of Surgery ([REC-B](#))
 - The bullet regarding transanal microsurgery and the recommendation that surgery follow 5-10 weeks after neoadjuvant therapy are new to the page.
- Principles of Radiation Therapy ([REC-D](#))
 - The first bullet was modified to add "tumors involving anterior structures and the inguinal nodes should be included for tumors invading into the distal anal canal."
 - The fourth bullet regarding IMRT is new to the page.
- Chemotherapy for Advanced or Metastatic Disease ([REC-E](#)):
 - CapeOX was added as a treatment option wherever FOLFOX is listed as an option.
 - FOLFIRI + cetuximab and Irinotecan + cetuximab were added as treatment options with a category 2B designation after first progression following treatment on FOLFOX + bevacizumab or CapeOX + bevacizumab.
 - Panitumumab was added as a treatment option wherever cetuximab is listed as monotherapy.
 - IFL + bevacizumab and the Mayo Clinic 5-FU/LV regimens were removed as treatment recommendations for patients.
 - Capecitabine ± bevacizumab was added as a treatment option with a category 2B designation for patients who cannot tolerate intensive therapy.
 - Footnotes 2-4, 6, 8 and 12-15 are all new to the section to provide guidance for selecting therapy ([REC-E 2 of 5](#)).
 - Footnote 5 was modified to include the mention of the UGT1A1 test available but there are no guidelines established for use in clinical practice.
 - The simplified biweekly infusional 5-FU/LV regimen was added ([REC-E 4 of 5](#)).

CLINICAL PRESENTATION^a

WORKUP

FINDINGS

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

- Pathology review^{b,c}
- Colonoscopy
- Marking of cancerous polyp site (at time of colonoscopy or within 2 wks)

Single specimen, completely removed with favorable histological features^d and clear margins (T1 only)

Observe

Fragmented specimen or margin cannot be assessed or unfavorable histological features^d

[See Primary and Adjuvant Treatment \(REC-3\)](#)

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

- Pathology review^{b,c}
- Colonoscopy
- Marking of cancerous polyp site (at time of colonoscopy or within 2 wks)

Single specimen, completely removed with favorable histological features^d 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^d

[See Primary and Adjuvant Treatment \(REC-3\)](#)

^aAll 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](#).

^bConfirm the presence of invasive cancer (pT1). pT1s has no biological potential to metastasize.

^cIt 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.

^d[See Principles of Pathologic Review \(REC-A\)](#) - Endoscopically removed malignant polyp.

[Back to Other Clinical Presentations \(Table of Contents\)](#)

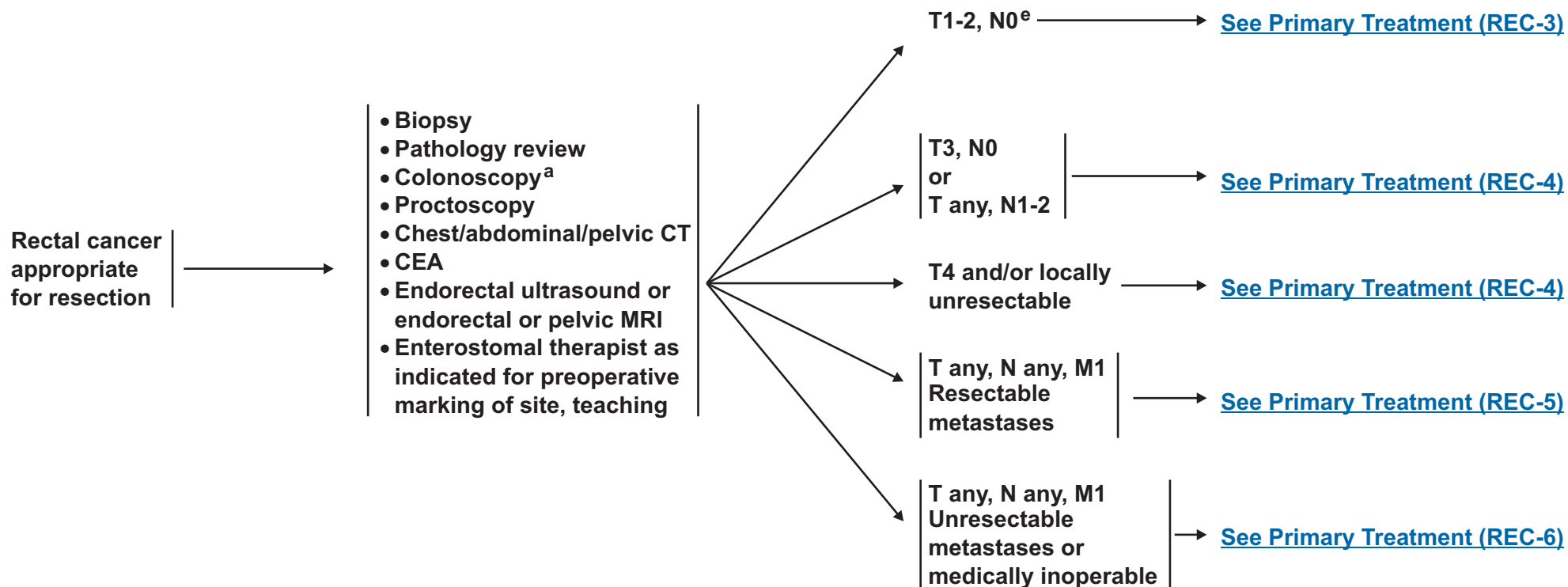
Note: All recommendations are category 2A unless otherwise indicated.

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

CLINICAL
PRESENTATION

WORKUP

CLINICAL STAGE

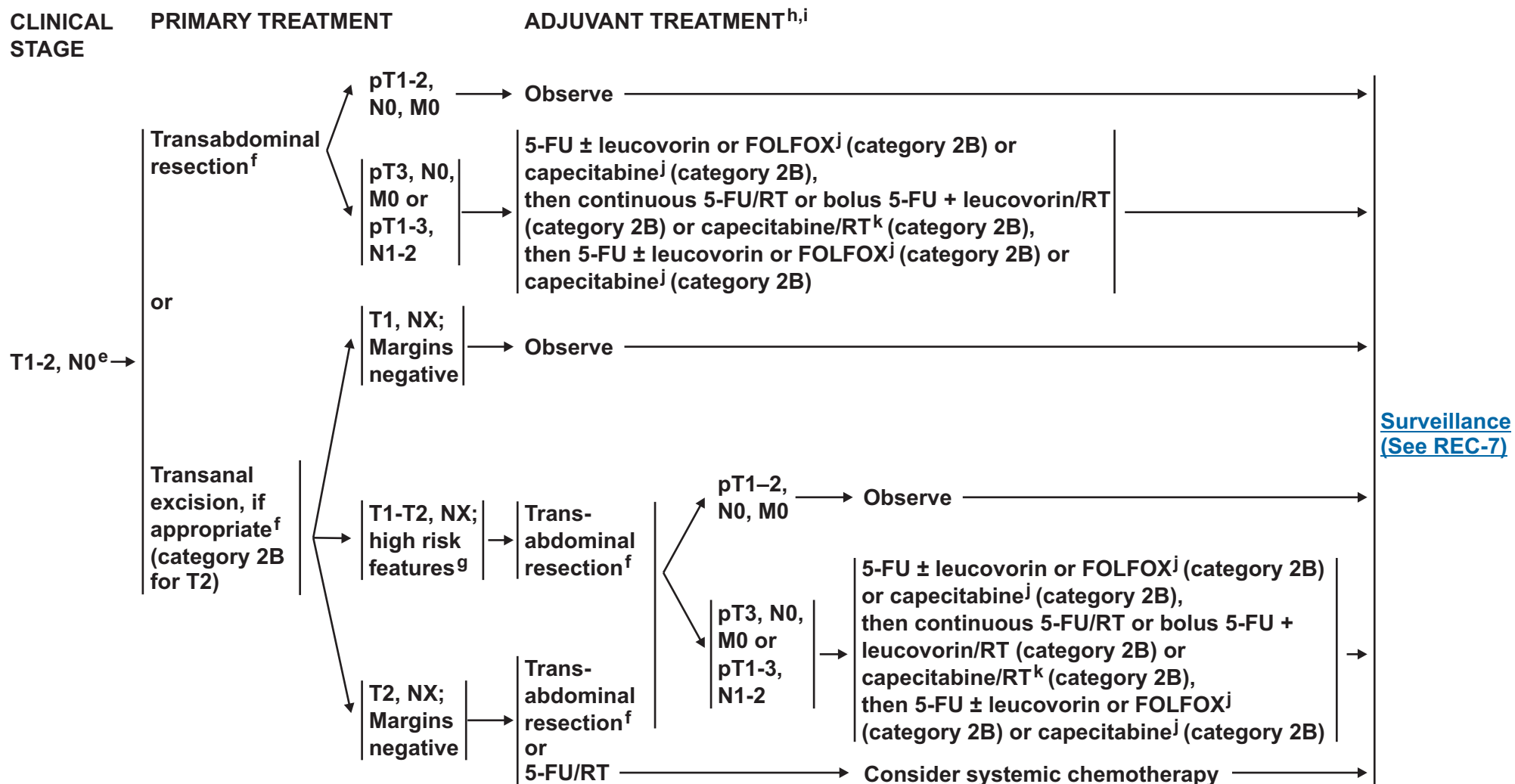


^aAll patients with colon cancer should be counseled for family history. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP, see the [NCCN Colorectal Cancer Screening Guidelines](#).

^eT1-2, N0 should be based on assessment of endorectal ultrasound or MRI.

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^eT1-2, N0 should be based on assessment of endorectal ultrasound or MRI.

^f[See Principles of Surgery \(REC-B\).](#)

^gHigh risk features include positive margins, lymphovascular invasion and poorly differentiated tumors.

^h[See Principles of Adjuvant Therapy \(REC-C\).](#)

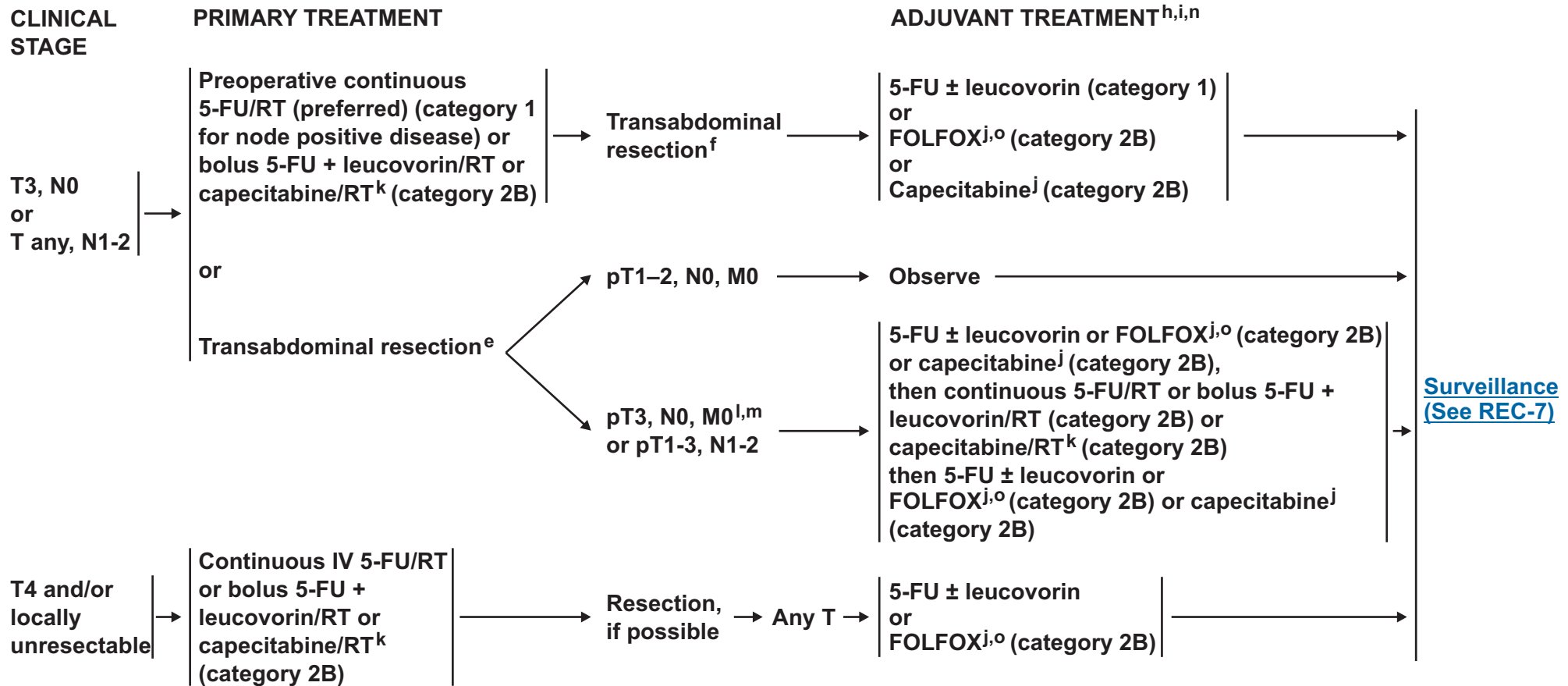
ⁱ[See Principles of Radiation Therapy \(REC-D\).](#)

^jThe use of FOLFOX or capecitabine is an extrapolation from the available data in colon cancer. Trials are still pending in rectal cancer.

^kData regarding the use of capecitabine/RT is 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.

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

^h See Principles of Adjuvant Therapy (REC-C).

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

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^l The use of agents other than fluoropyrimidines are not recommended concurrently with RT.

^m For patients with proximal T3, N0 disease with clear margins and favorable prognostic features, the incremental benefit of RT is likely to be small. Consider chemotherapy.

ⁿ Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.

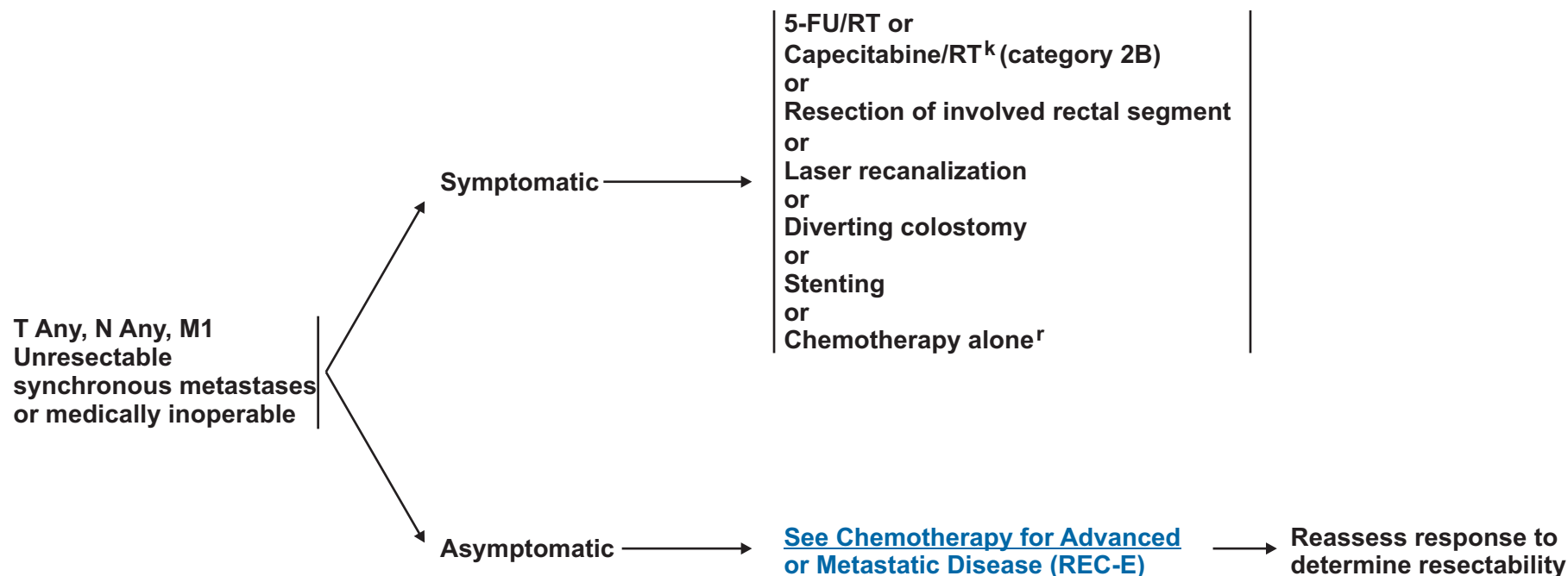
^o An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.

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CLINICAL STAGE

PRIMARY TREATMENT



^kData regarding the use of capecitabine/RT is 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.

^r[See Chemotherapy for Advanced or Metastatic Disease \(REC-E\).](#)

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SURVEILLANCE

- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA^s 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^{t,u}
- Colonoscopy in 1 y:
 - ▶ If abnormal, repeat in 1 y
 - ▶ If negative for polyps, repeat in 3 y, then every 5 y^v
 - ▶ If no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo.
- Consider proctoscopy every 6 mo x 5 y for patients status post LAR^w
- PET scan is not routinely recommended

Serial CEA elevation or documented recurrence

[See Workup and Treatment \(REC-8\)](#)

^sIf patient is a potential candidate for resection of isolated metastasis.

^tDesch CE, Benson III AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of the American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2005;23(33):8512-8519.

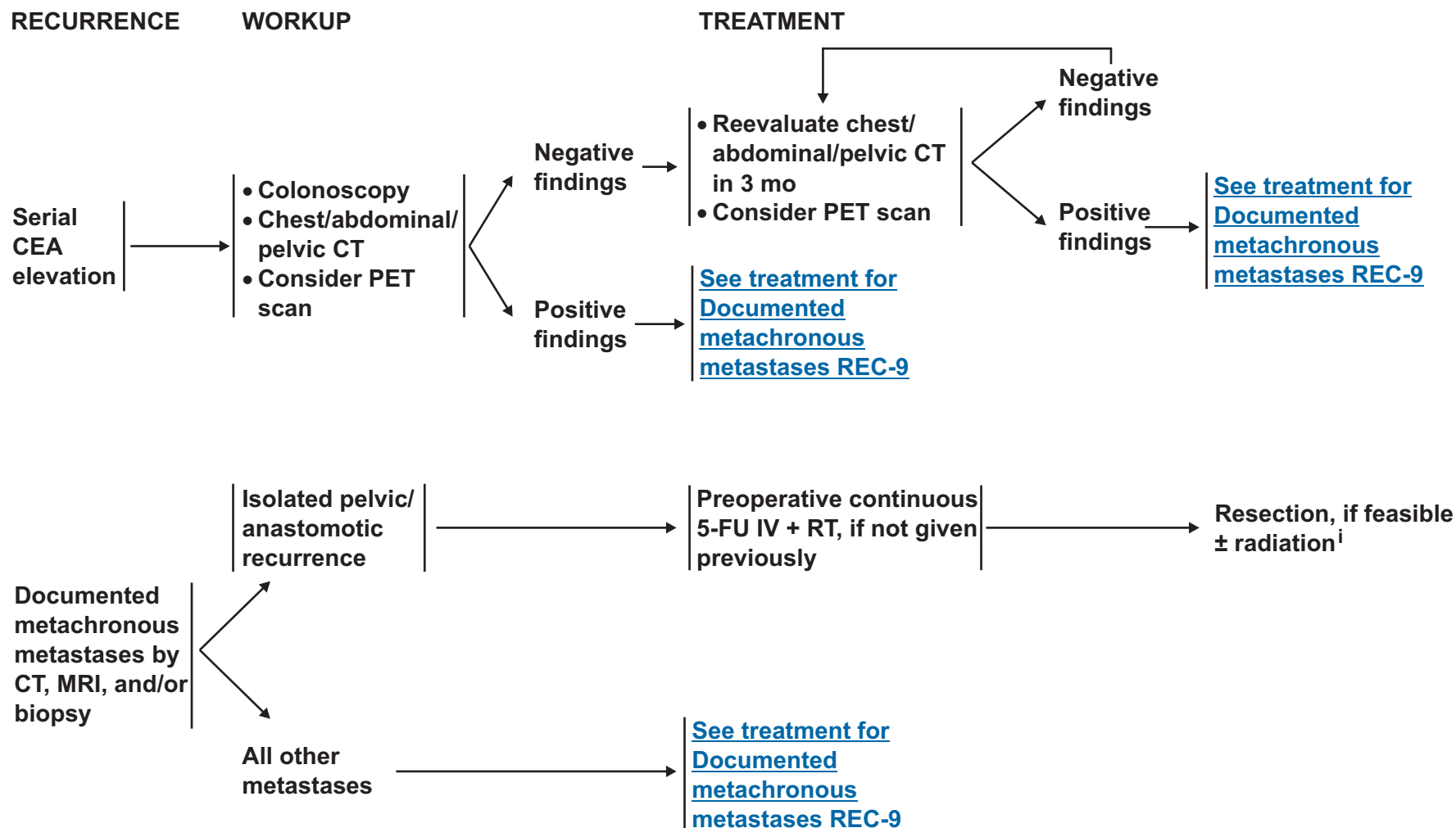
^uCT scan may be useful for patients at high risk for recurrence (eg, lymphatic or venous invasion by tumor, or poorly differentiated tumors).

^vRex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130(6):1865-71.

^wPatients 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.

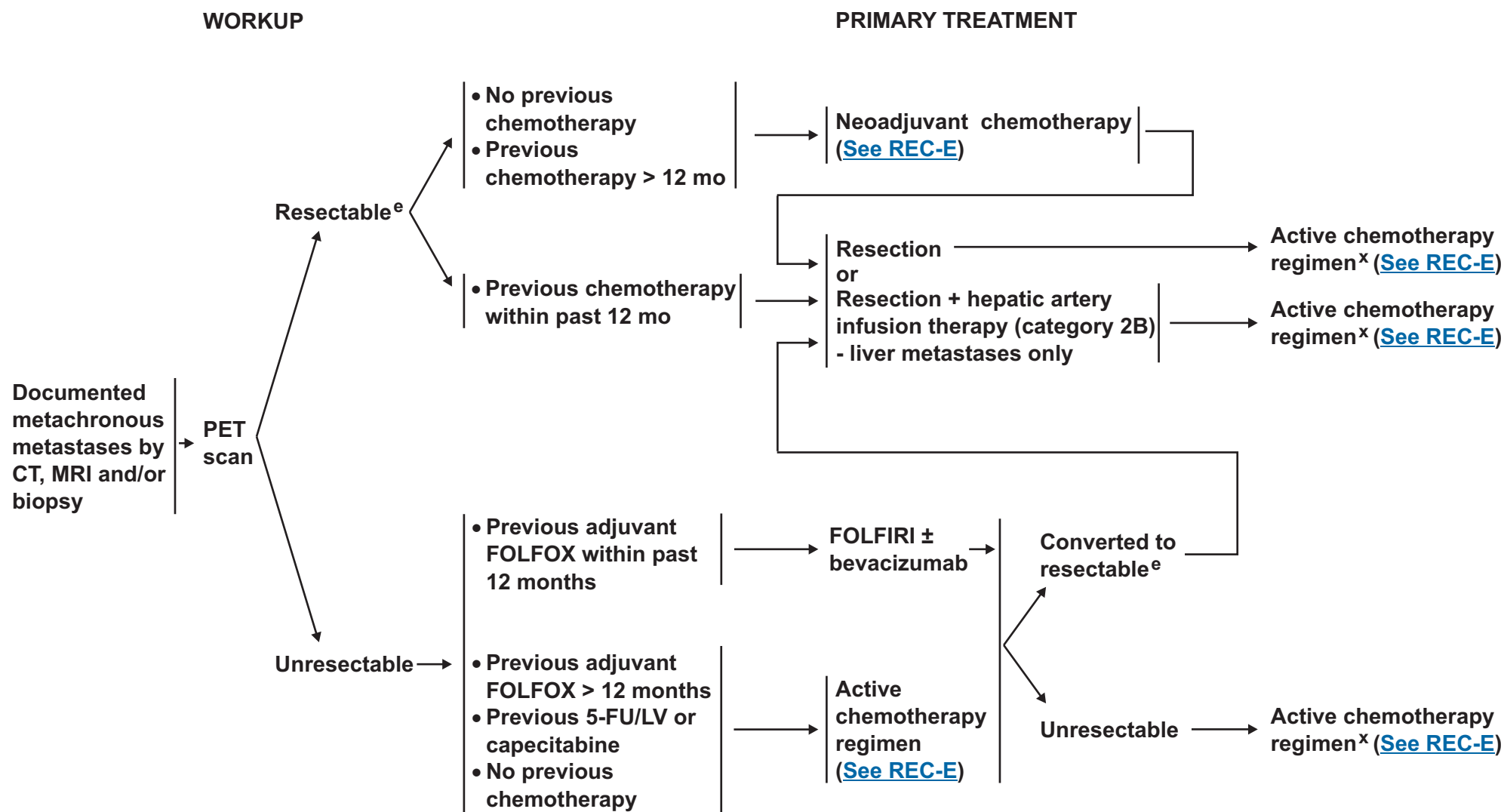
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ⁱ[See Principles of Radiation Therapy \(REC-D\).](#)

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^eSee Principles of Surgery (REC-B).

^xIf patient has seen all active chemotherapy regimens, observation is an option.

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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 3)

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 angiolymphatic invasion and negative margin of resection. There is no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as 1) tumor < 1 mm from the transected margin, 2) tumor < 2 mm from the transected margin, 3) tumor cells present within the diathermy of the transected margin.¹⁻⁴
- Unfavorable histological features grade 3 or 4, or angiolymphatic invasion, or a “positive margin.” See above for definition of a positive margin.

Transanal excision

- Favorable histopathological features: < 3 cm size, T1 or T2 (use caution in T2 due to high recurrence rate [see REC-B](#)), grade I or II, no lymphatic or venous invasion, negative margins.^{5,6}
- Unfavorable histopathological features: > 3 cm in size T1 or T2, with grade III, or lymphovascular invasion, or positive margin.⁵⁻⁷

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)
 - Status of proximal, distal, and circumferential (radial) margins⁸⁻⁹
 - A positive circumferential resection margin (CRM) has been defined as < 1 mm or < 2 mm depending on the publication¹⁰⁻¹¹ [See Staging \(ST-1\)](#)

[See Lymph node evaluation and sentinel lymph node on page 2 of 3 REC-A](#)

[See footnotes on page 3 of 3 REC-A](#)

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PRINCIPLES OF PATHOLOGIC REVIEW (2 of 3)

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 in those cases where surgery is the initial primary mode of treatment.^{8,9,14} 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, >30.¹⁵⁻²² 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.^{18,21} The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade and tumor site and the number of lymph nodes retrieved from rectal specimens are less than those from colon specimen.¹⁵ 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, $p < 0.001$).^{23,24} 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.²⁴ 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 post operative therapy is indicated in all patients who receive pre-operative therapy, regardless of the surgical pathology results
- Apical lymph node (at origin of feeding vessel) is defined as “most proximal lymph node within 1 cm of vessel ligation at apex of vascular pedicle.” The apical lymph node should be marked by the surgeon. Multivariate analysis has shown that involvement of the apical lymph node is significantly associated with an adverse outcome.^{25,26} In a previous AJCC/UICC staging system (4th edition, 1993) a positive apical lymph node was considered pN3.

Sentinel lymph node and detection of micrometastasis by immunohistochemistry

- Examination of the sentinel lymph 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 tumor cells (ITC) have been considered micrometastatic disease in contradiction 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 micrometastasis, however, “consensus” recommends these to be considered ITC and not micrometastatic disease.²⁷⁻²⁹
- 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.³⁰⁻³⁴
- 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.²⁷⁻³⁶

[See Malignant polyp, rectal cancer appropriate for resection, and pathological stage on page 1 of 3 REC-A](#)

[See footnotes on page 3 of 3 REC-A](#)

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PRINCIPLES OF PATHOLOGIC REVIEW (3 of 3)
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PRINCIPLES OF SURGERY (1 of 3)

Transanal excision:• **Criteria**

- ▶ < 30% circumference of bowel
- ▶ < 3 cm in size
- ▶ Margin clear (> 3 mm)
- ▶ Mobile, nonfixed
- ▶ Within 8 cm of anal verge
- ▶ T1 or T2 (use caution in T2, due to high recurrence rate)
- ▶ Fragmented polyp with cancer, or indeterminate pathology (a full workup may be initiated if local excision reveals invasive cancer)
- ▶ 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 an endoscopy before initiating treatment.
- ▶ Removal of primary tumor with adequate margins.
- ▶ Laparoscopic surgery is not recommended outside of a clinical trial.
- ▶ Treatment of draining lymphatics.
- ▶ Restoration of organ integrity, if possible.
- ▶ Surgery should be 5-10 weeks following neoadjuvant therapy

• **Total mesorectal excision**

- ▶ Reduces positive radial margin rate.
- ▶ Extend 4-5 cm below distal edge of tumors for an adequate mesorectal excision. In distal rectal cancers (ie, < 5cm from anal verge), negative distal bowel wall margin of 1-2 cm may be acceptable, this must be confirmed to be tumor free by frozen section.
- ▶ Full rectal mobilization allows for a negative distal margin and adequate mesorectal excision.

• **Lymph node dissection^{1,2}**

- ▶ Biopsy or remove clinically suspicious nodes beyond the field of resection if possible.
- ▶ Extended resection not indicated in the absence of clinically suspected nodes.

[See Criteria for Resectability of Metastases on page 2 of 3 REC-B](#)

¹Gunderson LL, Sargent DJ, Tepper JB, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol 2004;22(10):1785-1796.

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PRINCIPLES OF SURGERY (2 of 3)
CRITERIA FOR RESECTABILITY OF METASTASESLiver

- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of adequate hepatic function is required.^{1,2}
- There should be no unresectable extrahepatic sites of disease.^{3,4,5}
- Re-evaluation for resection can be considered in otherwise unresectable patients after neoadjuvant therapy.^{6,7}
- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.⁸
- Ablative techniques should be considered in conjunction with resection in otherwise unresectable patients.⁸
- The primary tumor must have been resected for cure (R0).
- Re-resection can be considered in selected patients.⁹

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.¹⁰⁻¹³
- Resectable extrapulmonary metastases do not preclude resection.¹⁴⁻¹⁷
- The primary tumor must have been resected for cure (R0).
- Re-resection can be considered in selected patients.¹⁸

[See footnotes on page 3 of 3 REC-B](#)

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

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PRINCIPLES OF SURGERY (3 of 3)
CRITERIA FOR RESECTABILITY OF METASTASES - REFERENCES

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PRINCIPLES OF ADJUVANT THERAPY (1 of 2)

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.

Postoperative adjuvant chemotherapy for patients receiving preoperative chemotherapy/RT:

- 5-FU 380 mg/m²/day on days 1-5 ± leucovorin IV 20 mg/m² on days 1-5 every 28 days x 4 cycles¹
- 5-FU 500 mg/m² IV bolus injection 1 h after the start of leucovorin infusion, once a wk for 6 wks x 3 cycles
Leucovorin 500 mg/m² IV over 2 h once a wk for 6 weeks x 3 cycles²
 - ▶ A cycle is comprised of 6 wks followed by 2 wks of rest.

Postoperative adjuvant regimens for patients not receiving preoperative therapy:

- 5-FU + leucovorin x 1 cycle, then concurrent chemotherapy/XRT (see below for regimens), then 5-FU/leucovorin x 2 cycles²
 - ▶ 5-FU 500 mg/m² IV bolus injection one h after the start of the leucovorin infusion, once a wk for 6 wks + leucovorin 500 mg/m² IV over 2 h once a wk for 6 wks
 - ▶ A cycle is comprised of 6 wks followed by 2 wks of rest.
- 5-FU ± leucovorin x 2 cycles, then concurrent chemotherapy/RT (see below for regimens), then 5-FU ± leucovorin x 2 cycles¹
 - ▶ 5-FU 425 mg/m²/d and leucovorin 20 mg/m²/d, days 1-5 and 29-33 before RT. After RT, the regimen is 5-FU 380 mg/m²/d and leucovorin 20 mg/m²/d for 5 consecutive days x 2 cycles
- FOLFOX (category 2B)
 - ▶ FOLFOX 4
 - Oxaliplatin 85 mg/m² IV over 2 hours, day 1
 - Leucovorin 200 mg/m² IV over 2 hours, days 1 and 2
 - 5-FU 400 mg/m² IV bolus, then 600 mg/m² IV over 22 hours continuous infusion, days 1 and 2
 - Repeat every 2 weeks³
 - ▶ 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 weeks^{4,5}
- Capecitabine⁶ (category 2B)
 - ▶ Capecitabine 1250 mg/m² twice daily days 1-14 every 3 wks x 24 wks

*Leucovorin dose in Europe is 200 mg/m² of levo-leucovorin. Levo-leucovorin is not available in the United States. The equivalent dose of leucovorin is 400 mg/m².

**NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m²/day over 46 hours) to minimize medication errors.

Dosing Schedules for concurrent chemotherapy/RT:

- XRT + continuous infusion 5-FU⁷
 - ▶ 5-FU 225 mg/m² over 24 h 7 d/wk during XRT
- XRT + 5-FU/leucovorin¹
 - ▶ 5-FU 400 mg/m² IV bolus + leucovorin 20 mg/m² IV bolus for 4 d during wk 1 and 5 of XRT
- XRT + Capecitabine⁸ (category 2B)
 - ▶ Capecitabine 825 mg/m² twice daily 7 d/wk + XRT x 5 wks

[See footnotes on page 2 of 2 REC-C](#)

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.

PRINCIPLES OF ADJUVANT THERAPY (2 of 2)
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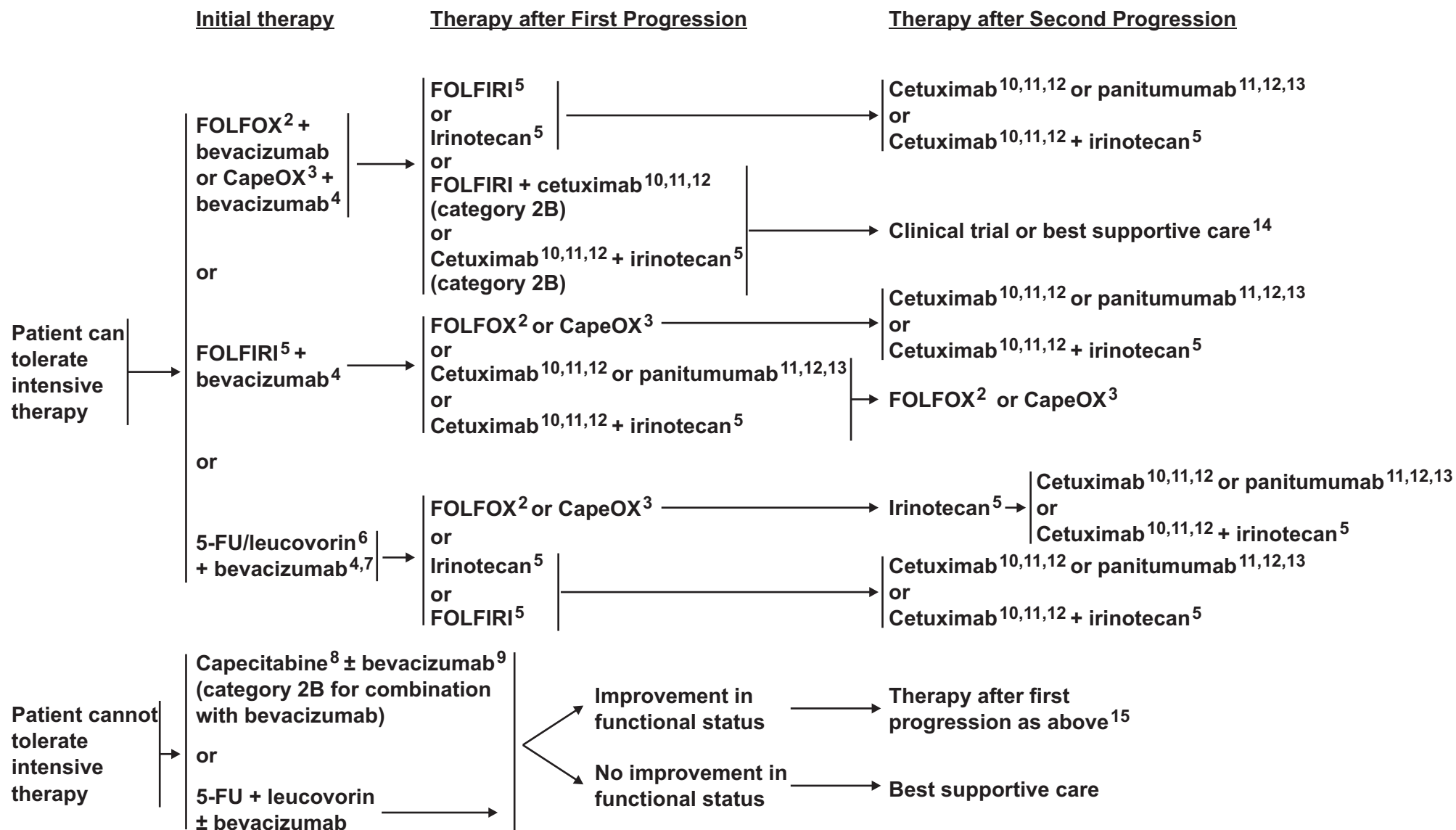
PRINCIPLES OF RADIATION THERAPY

- 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 and the inguinal nodes should be included for tumors invading into the distal anal canal.
- 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) or tomotherapy could be considered when there is a high risk of radiation-related normal tissue toxicity. Care should be taken to assure adequate tumor bed coverage.
- 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.
- 5-fluorouracil based chemotherapy should be delivered concurrently or as a bolus with radiation.

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CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 1 of 5)



[See footnotes on page REC-E 2 of 5](#)

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 2 of 5)

- ¹For chemotherapy references, [see Chemotherapy Regimens and References \(REC-E pages 3 - 5\)](#).
- ²Discontinuation of oxaliplatin is strongly considered from FOLFOX or CapeOX after 3 months of therapy or sooner if significant neurotoxicity develops (> grade 3) 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.
- ³The 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.
- ⁴There are no data to support continuation of bevacizumab with a second-line regimen after first progression on a bevacizumab-containing regimen and such use is not routinely recommended. If bevacizumab 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.
- ⁵Irinotecan 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.
- ⁶Infusional 5-FU is preferred. Bolus regimens of 5-FU are inappropriate as combination regimens with oxaliplatin or irinotecan.
- ⁷A treatment option for patients not able to tolerate oxaliplatin or irinotecan.
- ⁸Patients with diminished creatinine clearance may require dose modification of capecitabine.
- ⁹Routine use of bevacizumab + cetuximab is not recommended in patients with prior bevacizumab progression.
- ¹⁰Cetuximab is indicated in combination with irinotecan-based therapy or as single agent therapy for patients who cannot tolerate irinotecan.
- ¹¹EGFR 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.
- ¹²There 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.
- ¹³If cetuximab is used as a single agent, panitumumab could be substituted. There are no data to support the combination of panitumumab with irinotecan.
- ¹⁴Single agent or combination therapy with capecitabine, mitomycin, or gemcitabine has not been shown to be effective in this setting.
- ¹⁵The 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.

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 3 of 5)

CHEMOTHERAPY REGIMENS

FOLFOX**FOLFOX 4**

Oxaliplatin 85 mg/m² IV over 2 hours, day 1
 Leucovorin 200 mg/m² IV over 2 hours, days 1 and 2
 5-FU 400 mg/m² IV bolus, then 600 mg/m² IV over 22 hours continuous infusion, days 1 and 2
 Repeat every 2 weeks[†]

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 weeks^{2,3}

CapeOX^{3,4}

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

FOLFIRI^{5,6}

Irinotecan 180 mg/m² IV over 30-120 minutes, day 1
 Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, prior to 5-FU, days 1 and 2
 5-FU 400 mg/m² IV bolus, then 600 mg/m² IV over 22 hours continuous infusion, days 1 and 2
 Repeat every 2 weeks

Irinotecan 180 mg/m² IV over 30-120 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:^{7,8}

Bevacizumab 5mg/kg IV every 2 weeks +
 5-FU and Leucovorin
 or FOLFOX⁹
 or FOLFIRI
 Bevacizumab 7.5 mg/kg IV every 3 weeks + CapeOX⁴

*Leucovorin dose in Europe is 200 mg/m² of levo-leucovorin. Levo-leucovorin is not available in the United States.
 The equivalent dose of leucovorin is 400 mg/m².

[†]NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m²/day over 46 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.

[See footnotes on page 5 of 5 REC-E](#)

[See Additional Chemotherapy Regimens 4 of 5 REC-E](#)

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 4 of 5)

CHEMOTHERAPY REGIMENS

Capecitabine¹⁰

2000-2500 mg/m²/day PO in two divided doses, days 1-14,
followed by 7 days rest
Repeat every 3 weeks

**Bolus or infusional 5-FU/leucovorin
Roswell-Park regimen¹¹**

Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m² IV bolus 1 hour after start of Leucovorin,
days 1, 8, 15, 22, 29, 36
Repeat every 8 weeks

Biweekly¹²

Leucovorin* 400 mg/m² IV over 2 hours, days 1 and 2
5-FU 400 mg/m² IV bolus, then 600 mg/m² IV over 22 hours
continuous infusion, days 1 and 2
Repeat every 2 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)¹³

Leucovorin 400* mg/m² IV over 2 hours on day 1,
followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2
days (total 2400 mg/m² over 46-48 hours)[†] continuous infusion
Repeat every 2 weeks

Weekly¹⁴

Leucovorin 20 mg/m² as a 2 h infusion
5-FU 500 mg/m² bolus administered 1 h after LV infusion
Repeat every week

*Leucovorin dose in Europe is 200 mg/m² of levo-leucovorin. Levo-leucovorin is not available in the United States.
The equivalent dose of leucovorin is 400 mg/m².

[†]NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m²/day over 46 hours) to minimize medication errors.

Irinotecan^{15,16}

Irinotecan 125 mg/m² IV over 30-90 minutes, days 1, 8, 15, 22
Repeat every 6 weeks

Irinotecan 300-350 mg/m² IV over 30-90 minutes, day 1
Repeat every 3 weeks

Cetuximab ± irinotecan¹⁷

Cetuximab 400 mg/m² 1st infusion, then 250 mg/m²
weekly

±

Irinotecan
300-350 mg/m² IV every 3 weeks

or

180 mg/m² IV every 2 weeks

or

125 mg/m² every week for 4 weeks
Every 6 weeks

Panitumumab¹⁸

Panitumumab 6 mg/kg IV administered over 60
minutes every 2 weeks

[See footnotes on page 5 of 5 REC-E](#)

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 5 of 5)

CHEMOTHERAPY REFERENCES

- ¹Goldberg R, Sargent DJ, Morton RF et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; 22(1):23-30.
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Staging

Table 1

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

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ: intraepithelial or invasion of lamina propria†
- T1 Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues
- T4 Tumor directly invades other organs or structures, and/or perforates visceral peritoneum‡

Regional Lymph Nodes (N)§

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in 1 to 3 regional lymph nodes
- N2 Metastasis in 4 or more regional lymph nodes

Distant Metastasis (M)

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Stage Grouping

Stage	T	N	M	Dukes¶	MAC¶
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4	N0	M0	B	B3
IIIA	T1-T2	N1	M0	C	C1
IIIB	T3-T4	N1	M0	C	C2/C3
IIIC	Any T	N2	M0	C	C1/C2/C3
IV	Any T	Any N	M1	-	D

Histologic Grade (G)

- GX Grade cannot be assessed
- G1 Well differentiated
- G2 Moderately differentiated
- G3 Poorly differentiated
- G4 Undifferentiated

*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 pericorectal 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.

Manuscript This manuscript is being updated to correspond with the newly updated algorithm.

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

In 2005, an estimated 40,340 new cases of rectal cancer will occur in the United States (23,530 cases in men; 16,810 cases in women). During the same year, it is estimated that 56,290 people will die from rectal and colon cancer.¹ Although colorectal cancer is ranked as the third most frequently diagnosed cancer in men and women, mortality from rectal cancer has decreased during the past 30 years. This decrease may be because of 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 carcinoma 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, rectal cancer patients, especially those 50 years or younger, should be counseled regarding their family history as outlined in the NCCN Colorectal Screening Guidelines.

Staging

The NCCN Rectal Cancer Guidelines adhere to the current TNM staging system (Table 1).^{4,5} In this version of the staging system, smooth metastatic nodules in the pericolic or perirectal fat are considered lymph node metastases and should be counted in the N staging. Irregularly contoured metastatic nodules in the peritumoral fat are considered vascular invasion. Stage II is now subdivided into IIA (if the primary tumor is T3) and IIB (for T4 lesions). Stage III is subdivided into IIIA (T1-2, N1, M0), IIIB (T3-4, N1, M0), and IIIC (any T, N2, M0). In addition, the current staging suggests that the surgeon mark the area of the specimen with the deepest tumor penetration so that the pathologist can directly evaluate the radial margin. 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.

Clinical Evaluation

Rectal carcinoma should be fully staged. Endoscopic biopsy specimens of the lesion should undergo careful pathology review for evidence of invasion into the muscularis mucosa. If available, endorectal ultrasound, endorectal or pelvic magnetic resonance imaging (MRI) can assist the surgeon in determining the extent of disease.⁶ These modalities have been useful in assessing the depth of invasion and the lymph node status.⁷ Computed tomographic (CT) scans of the abdomen and pelvis are recommended because they might provide additional information about the extent of the disease. If removal of the rectum is contemplated, early consultation with an enterostomal therapist is recommended for preoperative marking of the site and for patient teaching purposes.

Treatment

Treatment of T1 and T2 Lesions With Favorable Characteristics

In selected T1 and T2 lesions without positive margins or adverse features (eg, no lymphovascular invasion [LVI] or perineural invasion; size less than 3 cm; well to moderately differentiated), local excision might give results comparable to anterior-posterior resection.⁸ Transanal excision is the preferred procedure for small tumors within 8 cm of the anal verge and limited to 30% of the rectal circumference (Category 2B for T2 tumors). Local recurrence rates for T2 lesions have been 25% when looking at several trials.⁹ Transabdominal resection should be used when lesions are not suitable for transanal surgery. If postsurgical pathology review after local excision reveals a poorly differentiated histology, positive margins, or LVI, then a transabdominal resection should be performed. A T2 lesion with negative margins and none of the poor prognostic factors can be treated with transabdominal resection or

adjuvant 5-fluorouracil/radiation therapy (5-fluorouracil/RT). Systemic chemotherapy should be considered as an adjuvant treatment. Laparoscopic surgery is not recommended outside of a clinical trial.

Treatment of Invasive Carcinoma

For patients with T1 to T2 lesions not amenable to local excision, a radical resection is required. For lesions in the mid to upper rectum, a low anterior resection is the treatment of choice. For low rectal lesions, abdominoperineal resection or coloanal anastomosis is required. To decrease the risk of local recurrence, patients should undergo optimal pelvic dissection with sharp mesorectal excision, including mesentery distal to the tumor as an intact unit.¹⁰ Node-negative T1 and T2 lesions are treated with transabdominal resection or transanal excision (category 2B for T2), if appropriate. 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 postoperative adjuvant chemotherapy with 5-fluorouracil with or without leucovorin or FOLFOX (category 2B) or capecitabine (category 2B), followed by concurrent 5-fluorouracil (continuous infusion or bolus) and RT, along with leucovorin/RT or capecitabine/RT (category 2B), then 5-fluorouracil with or without leucovorin or FOLFOX (infusional 5-fluorouracil/leucovorin/oxaliplatin (category 2B) or capecitabine (category 2B). The use of FOLFOX or capecitabine is an extrapolation from the data available for colon cancer. Trials are still pending in rectal cancer. No phase III randomized data is available yet for capecitabine/RT. In the Intergroup Trial 0114, all patients received 6 cycles of postoperative chemotherapy plus concurrent RT during cycles 3 and 4. 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 chemotherapy.¹¹ In addition, the Mayo/NCCTG 86-47-51 trial showed that administration of infusional 5-fluorouracil during pelvic irradiation was more effective than bolus 5-fluorouracil.¹² As a result, continuous infusional 5-fluorouracil plus radiotherapy or bolus 5-fluorouracil plus radiotherapy is an acceptable chemoradiation regimen.

Preoperative therapy decreases the volume of the primary tumor and thus enhances sphincter preservation.^{13,14} 5-fluorouracil-based chemoradiation therapy has been shown to improve sphincter preservation and produces pathological complete remissions in rectal cancer patients. EORTC 22921 phase III trial evaluated the addition of chemotherapy to preoperative RT and the efficacy of postoperative chemotherapy for improving survival in T3-T4 resectable rectal cancer.¹⁵ Addition of 5-fluorouracil with leucovorin to preoperative RT significantly reduced the tumor size, pTN stage and lymphatic, vascular and perineural (LVN) invasion rates. Phase I-II trials have demonstrated the safety and efficacy of concurrent combination of RT and capecitabine in locally advanced rectal cancer.¹⁶⁻¹⁸ Chemoradiation with capecitabine was well tolerated with no toxicity or mild to moderate toxicity in majority of patients and produced comparable results to those obtained with continuous infusion of 5-fluorouracil and RT.

Patients with resectable T3, N0 or any T, N1-2 lesions should be treated with preoperative combined-modality therapy or transabdominal resection. Preoperative continuous infusional 5-fluorouracil/RT is the preferred treatment option (category 1 for node positive disease). Alternative regimens include bolus 5-fluorouracil with leucovorin/RT or capecitabine/RT (category 2B). Patients who receive preoperative radiotherapy should receive postoperative

adjuvant chemotherapy with 5-fluorouracil with or without leucovorin (category 1 for T3, N0 or any T, N1-2 tumors) or infusional 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX, category 2B) or capecitabine (category 2B). Patients with T4 and/or locally unresectable disease are treated with preoperative continuous infusional 5-fluorouracil/RT or bolus 5-fluorouracil with leucovorin/RT or capecitabine/RT (category 2B). If possible, resection should be considered following preoperative chemotherapy.

Adjuvant therapy is recommended for rectal cancer patients after local excision to decrease local recurrence rates.¹⁹ Postoperative therapy is indicated for all patients who have received preoperative chemotherapy, regardless of the surgical pathology results. The guidelines panel recommends both concurrent chemoradiation therapy and chemotherapy as adjuvant treatment options.

Surveillance and Management of Advanced Metastatic Disease

Patients with stage IV disease (any T, any N, M1) with resectable metastases should undergo staged or synchronous resection of metastases and rectal lesion. Alternatively, they can be treated with continuous infusional 5-fluorouracil/pelvic RT or bolus 5-fluorouracil with leucovorin/pelvic RT or capecitabine/RT (category 2B) OR combination chemotherapy (FOLFOX or FOLFIRI with or without bevacizumab, or IFL with bevacizumab) prior to resection.

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-fluorouracil/RT or capecitabine/RT (category 2B), resection of the involved rectal segment or laser canalization or diverting colostomy or stenting.

The approach to monitoring and surveillance of patients with rectal carcinoma is essentially the same as for colon cancer. Patients with suspected recurrence based on increasing carcinoembryonic antigen (CEA) or those with documented metastases by CT, MRI and/or biopsy should have a positron-emission tomography scan, especially if surgery is under consideration for resectable organ-confined lesion. Isolated pelvic/anastomotic recurrence is managed by preoperative chemoradiation with infusional 5-FU, if not given previously, followed by resection. Patients with unresectable or multiple lesions are treated according to their performance status (PS). PS 0-2 patients are given chemotherapy for advanced or metastatic disease. Best supportive care is the option for those with PS \geq 3.

Salvage chemotherapy treatments for metastatic or recurrent rectal cancer are similar to the recommendations for colon cancer. Patients with good performance status and ability to tolerate intensive therapy should be considered for the first-line therapy with FOLFOX or FOLFIRI in combination with bevacizumab,^{20,21} 5-fluorouracil/leucovorin with bevacizumab,²²⁻²⁴ bolus 5-fluorouracil/leucovorin/irinotecan (IFL) with bevacizumab,²⁵⁻²⁷ CapOX with bevacizumab (category 2B).^{28,29}

Current data do not support the use of bevacizumab in second or third line regimens after progression on a first line bevacizumab containing regimen. Single agent bevacizumab, or the addition of bevacizumab to a regimen that has failed, have not been shown to be active in colorectal cancer, and such uses are not recommended. Elderly patients are at increased risk of stroke and other arterial events. The use of bevacizumab increases the risk of bleeding. Because weekly bolus 5-fluorouracil/leucovorin/irinotecan may cause severe gastrointestinal toxicity, patients on this regimen

should be carefully monitored during the first 60 days of therapy.³⁰

The recommended second-line therapy includes FOLFOX, FOLFIRI, irinotecan as a single agent³¹ or in combination with cetuximab³². Cetuximab is indicated in combination with irinotecan for patients refractory to irinotecan-based chemotherapy. Irinotecan should not be used in patients with Gilbert's disease or elevated serum bilirubin. EGFR testing has no demonstrated predictive value, and therefore routine EGFR testing is not recommended. No patient should be included or excluded from cetuximab therapy on the basis of EGFR test results.

Patients who are unable to tolerate intensive therapy should be offered capecitabine,³³ or bolus or infusional 5-fluorouracil/leucovorin with or without bevacizumab^{34,35} or protracted intravenous 5-fluorouracil with or without leucovorin.³⁶ Metastatic cancer patients with no improvement in functional status should receive best supportive care.

Summary

The NCCN Rectal Cancer Guidelines panel believes that a multidisciplinary approach is necessary for treating patients with colorectal cancer. Patients with T1 or T2 lesions that are node-negative by endorectal ultrasound and who meet carefully defined criteria can be managed with a transabdominal resection or transanal excision. Abdominal peritoneal resection or low anterior resection with total mesorectal excision is appropriate for all other rectal lesions. Either preoperative chemoradiation or postoperative chemoradiotherapy is standard for patients with suspected or proven serosal invasion (pT3) and/or regional node involvement. Patients with recurrent localized disease should be considered for

resection with or without radiotherapy. Chemotherapy regimens (FOLFOX, FOFIRI, 5-fluorouracil/leucovorin, IFL, CapOX or irinotecan) with or without bevacizumab/cetuximab should be considered for patients with distant metastasis. The panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy.

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