Overview of the management of rectal adenocarcinoma

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INTRODUCTION

Approximately 46,000 new cases of rectal cancer are diagnosed annually in the United States [1]. The vast majority of these are adenocarcinomas. Primary rectal squamous cell carcinomas, which are very rare, can be difficult to distinguish from anal cancers and are treated according to the same approach as anal cancer, with initial chemoradiotherapy (CRT; radiotherapy with concurrent fluoropyrimidine-based chemotherapy) rather than surgery. (See "Treatment of anal cancer", section on 'Rectal squamous cell cancers'.)

The optimal approach to treating rectal adenocarcinoma depends on several factors, of which the location in the rectum and the local disease extent are most important. For some patients with limited invasive cancer in a polyp who have no adverse features, polypectomy alone may suffice. At the other end of the spectrum, for others who have locally extensive, fixed, bulky tumors; extensive nodal disease; or extramural venous invasion on staging MRI a "total neoadjuvant approach" that includes four months of upfront chemotherapy and either long-course CRT or short-course radiotherapy prior to surgery may be pursued. (See 'Clinical T4, N2 disease, or other high-risk features' below.)

This topic review will provide an overview of the treatment for rectal cancer. Neoadjuvant CRT for potentially resectable adenocarcinomas, adjuvant therapy after resection of a primary rectal adenocarcinoma, staging and the staging workup, pretreatment local staging evaluation, surgical principles, and recommendations for post-treatment surveillance are discussed elsewhere, as is the management of rectal squamous cell cancers. (See "Neoadjuvant therapy

for rectal adenocarcinoma" and "Adjuvant therapy for resected rectal adenocarcinoma in patients not receiving neoadjuvant therapy" and "Pretreatment local staging evaluation for rectal cancer" and "Radical resection of rectal cancer" and "Post-treatment surveillance after colorectal cancer treatment" and "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Staging' and "Treatment of anal cancer", section on 'Rectal squamous cell cancers'.)

DIAGNOSIS AND STAGING

Most patients with rectal adenocarcinoma are diagnosed by colonoscopy after presenting with lower gastrointestinal tract bleeding; in some, the diagnosis is made by finding a lesion during a routine screening colonoscopy or incidentally on an imaging study performed for another reason. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Clinical presentation'.)

When viewed through the endoscope, the vast majority of rectal cancers are endoluminal masses that arise from the mucosa and protrude into the lumen. The mass may be exophytic or polypoid. Bleeding (oozing or frank bleeding) may be seen with lesions that are friable, necrotic, or ulcerated. A minority of neoplastic lesions are nonpolypoid and relatively flat or depressed.

If a mass is noted during colonoscopy, a biopsy should be performed. In other cases, the only finding may be a polyp or polyps. Endoscopic criteria that suggest malignancy in a polyp are outlined in the table (table 1). When they are identified, colorectal polyps should be removed as some types of polyps (particularly adenomatous polyps) are the precursors to invasive cancer. (See "Molecular genetics of colorectal cancer", section on 'The adenoma-carcinoma sequence'.)

There are two primary goals of polypectomy. The first is to completely remove all neoplastic tissue. The second is to provide a tissue sample that can be evaluated histologically. There are a number of techniques for endoscopic excision of colorectal polyps. The approach chosen will depend on the characteristics and location of the polyp, and the endoscopist's experience. Snare excision is commonly used for polyps >5 to 10 mm and offers the most complete removal of adenomatous tissue. Diminutive lesions (<5 mm) can be readily removed with either biopsy forceps or by snare polypectomy. (See "Overview of colon polyps".)

The optimal method for colonoscopic removal of large polyps (>10 mm) varies with the type of polyp. Large pedunculated polyps readily lend themselves to snare removal. Endoscopic mucosal resection (EMR), a technique whereby fluid is injected into the bowel wall to lift a flat or

a sessile polyp, allows resection of larger polyps. At times, large sessile adenomas (>2 to 3 cm) require piecemeal resection. When large polyps are present in the rectum, consideration should be given to referring the patient for a transanal endoscopic microsurgery (TEM (figure 1)) or transanal minimally invasive surgery (TAMIS) procedure as an alternative to endoscopic polypectomy, as there is a greater likelihood of removing the specimen in one piece, which allows an adequate assessment of the resection margins. (See "Endoscopic removal of large colon polyps" and "Transanal endoscopic surgery (TES)", section on 'Transanal minimally invasive surgery' and "Surgical treatment of rectal cancer", section on 'Local excision'.)

Whether or not polypectomy alone will be sufficient treatment for an individual malignant polyp depends on the histologic findings and the results of local staging. All patients with malignant polyps should be referred for local staging. (See 'Local imaging' below.)

The approach to management of malignant polyps, stratified according to clinical stage (which is derived from the biopsy and local staging evaluation), is discussed in more detail in the sections below. (See 'Management according to initial clinical stage' below.)

The pretreatment staging evaluation — The goal of the pretreatment staging evaluation is to assess the presence of distant metastatic disease and to determine the tumor location in the rectum and its local extent. An accurate assessment of location and local tumor extent is necessary prior to treatment to select the surgical approach and to identify those patients who are candidates for initial therapy (long-course chemoradiotherapy [CRT], short-course radiation therapy [RT] alone or short-course radiation followed by chemotherapy, or a combination of neoadjuvant chemotherapy and CRT) prior to surgery. In addition to a digital clinical examination (which may require an examination under anesthesia) and rigid proctoscopy, most patients with an invasive rectal cancer, possibly excepting those with limited malignancy in a polyp with favorable histologic features, should undergo preoperative local staging using either rectal magnetic resonance imaging (MRI; preferred) or transrectal ultrasound. (See "Pretreatment local staging evaluation for rectal cancer" and "Neoadjuvant therapy for rectal adenocarcinoma".)

Our approach to the staging algorithm is outlined in the algorithm, and described in detail in the following sections (algorithm 1).

TNM staging — Rectal cancers are staged using the tumor, node, metastasis (TNM) staging system from the joint American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC); the current (eighth edition, 2017) version is presented in the table (table 2) [2]. cTNM is the clinical classification (generally used for patients who are clinically staged before definitive surgical resection), and pTNM is the pathologic classification, which is

generally used after the pathologist has examined the final resection specimen. The "y" prefix is used for those cancers that are classified on the basis of a surgical specimen after neoadjuvant pretreatment (eg, ypTNM). The "r" prefix is used for recurrent tumors. The designation of the clinical stage of a rectal cancer generally rests upon the diagnostic biopsy, physical examination, and radiographic studies, such as computed tomography (CT), MRI, and transrectal ultrasound.

An important point is that pathologic T stage (pT) entails a resection of the primary tumor or excisional biopsy that is adequate to evaluate the highest pT category. A polypectomy specimen with complete removal of the lesion would fall under the pT1 category, but if lesion removal is incomplete, it is more correct to stage this as a clinical T1 (cT1) lesion or cTx if the margin cannot be determined.

Physical and endoscopic examination — Digital rectal examination (DRE) and proctoscopy are essential to the surgical decision-making process. On DRE, fixation of the lesion to the anal sphincter, its relationship to the anorectal ring (the collection of muscles that make up the sphincters), and fixation to both the rectal wall and the pelvic wall muscles (levators) can be assessed. Proctoscopy can accurately determine the distance between the distal tumor margin, the top of the anorectal ring, and the dentate line.

Adequate clinical assessment of local tumor extension may require an examination under anesthesia, especially when the patient cannot be examined because of pain. In some cases, a tumor that is considered unresectable by clinical or radiographic examination may appear amenable to curative resection when the patient is examined under anesthesia.

Imaging — Once the diagnosis is established, the local and distant extent of disease spread is determined to provide a framework for discussing therapy. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Clinical staging evaluation'.)

Local imaging — While preoperative CT of the abdomen and pelvis is imperative in planning the surgical procedure, imaging is imperfect, and it can underestimate the extent of adjacent local organ involvement. CT, in particular, can accurately identify locoregionally confined disease and the need for adjacent organ resection, but it is less helpful in predicting local tumor resectability [3]. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Locoregional staging for rectal cancer'.)

Thin-cut MRI with pelvic phased-array coil is the preferred imaging modality for evaluating the extent of the primary tumor as it will be able to provide information on the circumferential resection margin (CRM), as well as invasion to other organs and structures, and pelvic sidewall lymph nodes. MRI exceeds the capability of CT scan to locally stage the depth of transmural invasion, presence or absence of invasion into adjacent structures, and the presence of

perirectal nodal involvement for rectal cancers. (See "Pretreatment local staging evaluation for rectal cancer", section on 'Magnetic resonance imaging'.)

Endorectal or transrectal ultrasound is another alternative but may be limited by the bulkiness of the tumor and the lack of depth to assess invasion of other organs. Endoscopic ultrasound is particularly limited for posterior or posterolateral tumors, in whom the distance to the CRM cannot be estimated because neighboring structures that allow assessment of the CRM are lacking.

Whether all invasive rectal cancers require local staging is debated. Some adenomas with early invasive cancer (cT1 lesions) have a low (<2 percent) risk of lymphatic metastasis [4], and consensus-based guidelines from the National Comprehensive Cancer Network (NCCN) [5] suggest no imaging evaluation for single-specimen, completely resected pedunculated polyps with invasive cancer that have favorable histologic features and clear margins (pT1). (See 'Clinical/pathologic T1N0 amenable to endoscopic polypectomy or transanal excision' below and "Overview of colon polyps", section on 'High-grade dysplasia or cancer'.)

However, some factors, such as young age, may increase the risk of lymph node positivity in early stage rectal cancer [6]. Consensus-based guidelines from other expert groups, including the Practice Parameters Committee of the American College of Gastroenterology (ACG) and the European Society for Medical Oncology (ESMO), recommend performing either transrectal ultrasound or high-resolution MRI to determine the local tumor stage and assess for lymph node positivity for all patients with an invasive rectal cancer, including those with pT1 malignant polyps with favorable prognostic factors [7,8]. We agree with this approach, as reflected in the algorithm (algorithm 1).

The utility of MRI and endorectal ultrasound for local staging of rectal cancer is discussed in detail elsewhere. (See "Pretreatment local staging evaluation for rectal cancer", section on 'Imaging evaluation'.)

Evaluation for distant metastases — Consistent with guidelines from the NCCN [5] contrast-enhanced CT scan of the chest, abdomen, and pelvis is recommended for all patients with a new diagnosis of invasive rectal cancer except for those patients with a completely resected malignant polyp with no invasion beyond the submucosa (pT1N0), favorable histologic features, and clear margins. (See 'Clinical/pathologic T1N0 amenable to endoscopic polypectomy or transanal excision' below.)

Pelvic CT is not needed in patients who have undergone pelvic MRI for staging. For patients with a contraindication to CT with intravenous (IV) contrast, contrast-enhanced MRI of the abdomen

and pelvis plus a non-contrast chest CT is an alternative. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Clinical staging evaluation'.)

Liver MRI may be needed to characterize the burden of hepatic metastases more accurately if oligometastatic disease is suspected. Positron emission tomography (PET) scans do not appear to add significant information to CT scans for routine preoperative staging of a newly diagnosed rectal cancer except for in the evaluation of patients who are thought to be candidates for resection of isolated liver metastases and those with an equivocal finding on contrast-enhanced CT scan. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Positron emission tomography scans'.)

Biopsy confirmation may be indicated for selected patients who have findings on either CT or PET that raise suspicion for distant metastases, if not well characterized during initial imaging, and especially if there is a question about the origin of the metastases (eg, in a patient with a history of lung or breast cancer).

Tumor markers — Circulating tumor markers, such as carcinoembryonic antigen (CEA), are not sufficiently sensitive or specific to be used for screening or as a diagnostic test for colorectal cancer. However, CEA levels do have value in the pretreatment staging and follow-up of patients with diagnosed colorectal cancer:

- Serum levels of CEA have prognostic utility in patients with newly diagnosed colorectal cancer. Patients with preoperative serum CEA >5 ng/mL have a worse prognosis, stage for stage, than those with lower levels. (See "Pathology and prognostic determinants of colorectal cancer", section on 'Preoperative serum CEA'.)

- Elevated preoperative CEA levels that do not normalize following surgical resection imply the presence of persistent disease and the need for further evaluation. Rarely, the elevated CEA levels will be due to a false positive elevation. (See "Post-treatment surveillance after colorectal cancer treatment", section on 'Carcinoembryonic antigen'.)

We recommend obtaining a serum CEA level preoperatively in most patients with rectal cancer to aid in post-treatment follow-up and in the assessment of prognosis. If serum CEA levels were not drawn preoperatively, they should be obtained in the immediate postoperative period. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Tumor markers'.)

OVERVIEW OF MANAGEMENT

Surgical approaches — Surgery is the only curative treatment for rectal cancer (algorithm 2). The principle components for a curative resection include performing a wide resection of the cancer by achieving histologically negative margins and performing a total mesorectal excision (TME) that includes resection of local lymph nodes with transabdominal procedures (eg, low anterior resection [LAR] or abdominoperineal resection [APR]).

Superficially invasive (T1), small rectal adenocarcinomas may be effectively managed with local excision, such as transanal excision, transanal endoscopic microsurgery (TEM), or transanal minimally invasive surgery (TAMIS) alone. (See 'Clinical/pathologic T1N0 amenable to endoscopic polypectomy or transanal excision' below and "Surgical treatment of rectal cancer", section on 'Local excision' and "Transanal endoscopic surgery (TES)".)

However, most patients have more deeply invasive tumors that do not meet the criteria for local excision. Such patients will require a transabdominal excision, and the specific techniques used depend on the extent and location of the tumor within the rectum [9,10] (see "Pretreatment local staging evaluation for rectal cancer" and "Surgical treatment of rectal cancer" and "Treatment of locally recurrent rectal adenocarcinoma"):

- Tumors in the upper and middle rectum can usually be managed with a sphincter-sparing procedure, such as LAR, provided that a curative resection can be achieved and adequate anorectal function preserved. (See "Surgical treatment of rectal cancer", section on 'Low anterior resection'.)

- Tumors in the lower rectum (ie, tumors within 5 cm of the anal verge (figure 2)) may require an APR if a curative resection cannot be achieved with sphincter-sparing procedures (see "Surgical treatment of rectal cancer", section on 'Abdominoperineal resection'). Alternatives to APR for patients with lower rectal tumor have evolved and include the following:

  - For selected patients with small lower rectal tumors, local excision techniques may offer local control and survival rates that are comparable to APR while preserving sphincter function. (See "Surgical treatment of rectal cancer", section on 'Local excision'.)

  - For patients with larger or more invasive lower rectal tumors, preoperative (neoadjuvant) radiation therapy (RT) and chemoradiotherapy (CRT) have been utilized to promote tumor regression in an attempt to convert a planned APR into a sphincter-sparing surgical procedure, such as LAR. (See 'Multidisciplinary management' below.)

- Locally advanced tumors involving adjacent pelvic organs or bony structures may require multivisceral resection (eg, pelvic exenteration), even as a part of multidisciplinary management that includes preoperative CRT with or without preoperative chemotherapy, or short-course radiation followed by chemotherapy. (See 'Clinical T4, N2 disease, or other high-risk features' below and 'Management of locally recurrent disease' below and "Surgical treatment of rectal cancer", section on 'Multivisceral resection'.)

For patients undergoing transabdominal surgery for rectal cancer, the proximal, distal, and radial surgical margins of resection must be histologically free of cancer to reduce the risk of a local recurrence. In addition, the surgeon should also perform an adequate TME. TME improves local control and patient survival while maintaining postoperative genitourinary function by preserving the pelvic autonomic nerves. The oncologic principles of transabdominal rectal surgery are further discussed elsewhere. (See "Radical resection of rectal cancer", section on 'Principles of radical resection'.)

Multidisciplinary management — All patients with invasive rectal cancer, with the possible exception of some patients with cT1N0 disease, should be discussed in multidisciplinary conference (surgery, radiation oncology, medical oncology, with joint review of radiology and pathology findings). (See 'Local imaging' above.)

Although surgical resection is the cornerstone of curative therapy for patients with potentially resectable rectal cancer, RT with concurrent fluoropyrimidine chemotherapy (termed CRT) has emerged as an important component of curative therapy for transmural or node-positive rectal cancers because local recurrences are more common than with colon primaries.

For patients who undergo initial surgery, postoperative (adjuvant) therapy (usually a combination of CRT and chemotherapy alone) is started approximately four to six weeks postoperatively for those with transmural (ie, T3 or T4) or node-positive tumors.

Currently, CRT is preferentially given preoperatively (neoadjuvant CRT) for the following patient groups:

- Clinically staged T3 or T4 (table 2), or node-positive tumors.
- Distal tumors, even if cT2N0, for which tumor regression may allow successful conversion of a planned APR into a sphincter-sparing surgical procedure.
- If the preoperative staging evaluation suggests invasion of the mesorectal fascia or a threatened circumferential resection margin.

As was demonstrated in the seminal German Rectal Cancer Study, the benefits of neoadjuvant, as compared with adjuvant, CRT include a superior sphincter preservation rate, a lower rate of anastomotic stenosis as a long-term complication of pelvic RT, and better local control while providing similar long-term survival. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Indications for neoadjuvant treatment' and "Neoadjuvant therapy for rectal adenocarcinoma", section on 'German Rectal Cancer Study Group trial'.)

At least in the United States, neoadjuvant CRT is generally administered over 5.5 weeks (1.8 Gy per day, five fractions per week) with concurrent infusional fluorouracil or daily oral capecitabine (long-course CRT). Two other types of neoadjuvant or induction therapy may be considered under specific circumstances:

- **Short-course RT alone** – Outside of the United States, short-course RT (25 Gy in five fractions over one week) has been adopted in many institutions as the standard preoperative approach for operable rectal cancer. Some institutions in the United States are now using short-course RT in selected patients, such as those who are thought unlikely to tolerate full-course CRT, or prior to rectal surgery in the setting of metastatic disease to minimize delays in initiation of systemic therapy. (See 'Distant metastases present' below.)

  However, at many institutions, long-course CRT is still considered the preferred approach for most patients, particularly for those with locally advanced, bulky tumors or extensive nodal disease. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Short-course radiotherapy'.)

- **Preoperative chemotherapy with selective, response-guided use of chemoradiation** – Preoperative chemotherapy followed by the response-guided use of CRT prior to surgical resection is an option for patients with T2N1M0, T3N0M0, or T3N1M0 rectal adenocarcinoma who are eligible for sphincter-sparing surgery. Most patients treated with this approach avoid CRT and are presumably spared from late radiation-associated toxicities. Further details are discussed separately. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Neoadjuvant chemotherapy and selective use of CRT'.)

- **Total neoadjuvant therapy** – Total neoadjuvant therapy (TNT) includes intensified induction therapy with chemotherapy (typically an oxaliplatin-based regimen, such as oxaliplatin plus short-term infusional fluorouracil and leucovorin [FOLFOX] (table 3)) plus RT (either long-course CRT or short-course RT) and then surgery. The chemotherapy can be given before or after long-course CRT or, as was done in the RAPIDO trial, short-course RT can be administered followed by chemotherapy prior to surgery. TNT may be considered for patients with locally advanced (eg, T4 (table 2)) or bulky primary tumors,

extensive (eg, N2 (table 2)) nodal disease, or other high-risk features such as a low-lying tumor, an involved or threatened mesorectal fascia, or extramural venous invasion. The rationale is that the likelihood of a positive margin at the time of surgery may be diminished if the patient experiences significant downstaging using a preoperative regimen that includes both CRT and chemotherapy. Further, there is a greater likelihood of completing systemic chemotherapy if given before surgery rather than after surgery due to postoperative morbidity and treatment-related toxicity. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Total neoadjuvant therapy for locally advanced tumors'.)

Following resection of patients with rectal adenocarcinoma who have received preoperative CRT, most oncologists recommend delivery of four months of additional chemotherapy, often with an oxaliplatin-based regimen, such as FOLFOX (six months is typically given to patients who received short-course preoperative RT alone). If patients received four months of preoperative chemotherapy as part of TNT, postoperative chemotherapy is omitted. (See "Adjuvant therapy after neoadjuvant therapy for rectal cancer", section on 'Benefit of postoperative chemotherapy' and "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Total neoadjuvant therapy for locally advanced tumors'.)

Role of intraoperative radiation therapy — At many centers in the United States, Europe, and Asia, intraoperative RT (IORT) has been used in conjunction with preoperative CRT and surgical resection for locally advanced tumors where the surgeon feels that there is a close or microscopic margin of resection. In general, IORT will not benefit patients with grossly positive margins of resection. Above all, in order to achieve good results, an optimal surgical procedure has to be performed as radiation or chemotherapy will not be able to make up for poor surgical technique.

Management according to initial clinical stage

Clinical/pathologic T1N0 amenable to endoscopic polypectomy or transanal excision — Our approach to the management of clinical T1N0 rectal cancer is outlined in the algorithm (algorithm 3), and described in detail in the following paragraphs. The approach to cT1 tumors that are not amenable to endoscopic or local excision is discussed below. (See 'Clinical T2N0 and cT1N0 not amenable to local excision' below.)

Some early invasive cancers that do not invade beyond the submucosa (either cT1N0 or pT1N0 after local staging (see 'TNM staging' above)) will be effectively treated with polypectomy alone. Complete en bloc polypectomy in one piece is necessary for adequate pathologic evaluation; particularly in the modern era of endoscopic submucosal dissection, piecemeal polypectomy

should be avoided so that the margin, depth of invasion, and other pathological characteristics can be determined. (See "Overview of colon polyps", section on 'Polypectomy' and "Endoscopic removal of large colon polyps".)

Accepted criteria for situations in which endoscopic management alone is **insufficient** for managing a malignant polyp include the following [11,12]:

- For both pedunculated and nonpedunculated (sessile) polyps:
  - Piecemeal excision.
  - Poorly differentiated histology.
  - Lymphovascular or perineural invasion.
  - Intermediate to high tumor budding (foci of isolated cancer cells or a cluster of five or fewer cancer cells at the invasive margin of the polyp). (See "Pathology and prognostic determinants of colorectal cancer", section on 'Tumor border and tumor budding'.)
  - Cancer at the resection margin or submucosal invasion depth ≥1 mm.

In addition, endoscopic excision alone is **insufficient** if:

- Local staging (MRI, ultrasound) reveals any suspicion for deeper invasion or positive lymph nodes.
- For patients with large (≥2 cm) pedunculated polyps, endoscopic excision alone is insufficient if there is any concern for the possibility of invasive disease, or if the size and location of the polyp are not amenable to endoscopic resection with a relatively low risk of complications.

  For malignant polyps that meet any of these criteria, surgical referral is appropriate.

Some patients who are not amenable to endoscopic resection alone will be amenable to local excision. The selection criteria for performing a local excision are largely based on retrospective reviews. Consensus-based recommendations from the National Comprehensive Cancer Network (NCCN) suggest that local excision be limited to the following groups (see "Surgical treatment of rectal cancer", section on 'Local excision'):

- Superficial T1 cancer, limited to the submucosa
- No radiographic evidence of metastatic disease to the regional nodes
- Tumor <3 cm in diameter

- Well-differentiated histology, no lymphovascular or perineural invasion
- Mobile, non-fixed
- Margin clear (>3 mm)
- Involving <30 percent of the bowel lumen circumference
- Patient is able to comply with frequent postoperative surveillance

According to revised guidelines for treatment of rectal cancer from the European Society for Medical Oncology (ESMO), cT1 rectal cancers are subclassified into three categories, sm1, sm2, and sm3, based on the depth of submucosal invasion. Data primarily from Japan showed that when the depth of submucosal invasion was <1000 micrometers (ie, sm1), the rate of nodal involvement was 0 to 1.8 percent, whereas the rate of nodal involvement was 12.8 to 13.8 percent when the depth of submucosal invasion was ≥1000 micrometers (ie, sm2 or sm3) [13]. Other data from the Mayo clinic support the view that sm3 level of invasion is associated with a high risk of nodal metastases [14]. Consequently, ESMO recommends local excision for cT1 rectal cancers that are sm1, but proctectomy with total mesorectal excision for sm2 or sm3 tumors [8].

These criteria are not absolute. At least in the United States, this distinction has not been consistently made by pathologists reviewing biopsy material, and the depth of submucosal invasion has not generally been considered to be a factor in selecting patients with cT1 disease for local excision. This is in part due to the fact that some of these polyps are excised in a piecemeal fashion, thus the depth of submucosal invasion cannot be adequately determined.

Furthermore, selected patients with clinical N0 tumors that are deeper than T1 can be treated with local excision if used in conjunction with CRT, administered preoperatively or postoperatively. (See 'Clinical T2N0 and cT1N0 not amenable to local excision' below and "Adjuvant therapy for resected rectal adenocarcinoma in patients not receiving neoadjuvant therapy", section on 'T2 rectal cancer after local excision'.)

An important point is that just because the tumor is amenable to local excision does not mean that it represents the best choice for surgical therapy. Transabdominal surgery may represent a better option for some patients, especially if they are young and fit for surgery.

For patients treated with local excision, further management depends on postsurgical staging:

- For completely resected pT1 invasive tumors with favorable prognostic criteria (well or moderately well differentiated, no lymphovascular or perineural invasion, no mucin production, negative margins of excision) and intraepithelial tumors (pTis) (table 2), post-treatment endoscopic surveillance alone is appropriate. (See 'Stage I disease' below.)

- For pT1 disease with adverse prognostic factors or ≥pT2 disease, in general, completion transabdominal surgery is the standard approach. If pT3 neoadjuvant therapy CRT should be considered prior to radical surgery. If the patient is a poor surgical candidate or refuses transabdominal surgery, postoperative RT or CRT followed by close post-treatment surveillance is an option. (See "Adjuvant therapy for resected rectal adenocarcinoma in patients not receiving neoadjuvant therapy", section on 'T2 rectal cancer after local excision' and 'Stage I disease' below.)

Clinical T2N0 and cT1N0 not amenable to local excision — Our approach to managing cT2 tumors, and cT1 tumors that are not amenable to local excision is outlined in the algorithm (algorithm 4).

For patients with cT1N0 tumors that cannot be managed with local excision, transabdominal surgery (LAR or APR) is usually advised, unless the patient refuses it, or has a medical comorbidity or severely limited life expectancy that precludes open surgery.

Clinical stage T2, node-negative disease (cT2N0) is associated with a sufficiently high risk of nodal metastases (10 percent or higher) that endoscopic resection alone is not considered adequate treatment, and most patients are referred for initial transabdominal surgery (LAR or APR) as the standard surgical treatment. In general, neoadjuvant CRT is not needed in this setting unless to improve the chances for a sphincter saving procedure rather than an abdominoperineal resection with a permanent colostomy.

Preoperative CRT followed by local transanal excision might be feasible as an alternative to total mesorectal excision in good responders with cT2N0 distal rectal cancer. However, this is not yet a standard approach, especially for patients with direct sphincter invasion. We agree with guidelines from the National Comprehensive Cancer Network (NCCN), and ESMO, which both consider that transabdominal surgery is the preferred approach in this setting unless the patient is at high surgical risk because of age, frailty, extensive comorbidity, or refuses transabdominal surgery [5,8]. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'T1-2N0 tumors' and "Transanal endoscopic surgery (TES)", section on 'T2N0 rectal cancer'.)

However, if the patient is a poor surgical candidate or refuses transabdominal surgery, initial CRT may be chosen. Following CRT, restaging evaluation is indicated with magnetic resonance imaging (MRI) or endoscopic ultrasound. Although definitive therapy would be transabdominal surgery, an alternative to transabdominal surgery for patients who continue to refuse surgery or are poor candidates, and for highly selected patients who appear to have a complete clinical response (ie, they are left with only a scar after neoadjuvant CRT) is full thickness local excision with close follow-up or a watch and wait approach with close follow-up. (See "Surgical treatment

of rectal cancer", section on 'Local excision' and 'Stage I disease' below and "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Nonoperative management (watch and wait)'.)

However, patients should be counseled that this is not yet a standard approach. If this approach is chosen and the final pathology after local excision is ypT2 (table 2) or margin-positive, most institutions would suggest that transabdominal surgery be readdressed although at least some phase II data suggest this might not be necessary for ypT2N0, margin-negative tumors [15].

For most patients who undergo initial transabdominal surgery with negative margins, postoperative adjuvant therapy is recommended if the final pathologic stage is pT3 or pN+ (table 2). However, updated guidelines for treatment of rectal cancer from ESMO recommend a selective approach, advocating postoperative CRT after primary surgery for patients who have unexpected adverse histopathological features [8]. (See "Adjuvant therapy for resected rectal adenocarcinoma in patients not receiving neoadjuvant therapy", section on 'Recommendations from expert groups'.)

Clinical T3-4, N0-2 or T2, N1-2 — Our approach to the management of cT3/4 or node-positive rectal cancer is outlined in the algorithm, and discussed in the sections below (algorithm 5).

The decision making process for treatment of patients with clinically staged transmural (T3-4 (table 2)) or node-positive rectal cancer is based on whether the pretreatment staging evaluation demonstrates metastatic disease or not, and if so, whether the metastatic disease is potentially resectable (typically isolated hepatic or pulmonary metastases) or categorically unresectable. (See "Potentially resectable colorectal cancer liver metastases: Integration of surgery and chemotherapy" and "Surgical resection of pulmonary metastases: Benefits, indications, preoperative evaluation, and techniques".)

No distant metastases

Clinical T3/4 or N1 — For patients presenting with locally advanced rectal adenocarcinomas, preoperative radiotherapy is preferred over initial surgery. Several options are available:

- In the United States, conventional fractionation CRT over 5.5 to 6 weeks using concurrent fluoropyrimidine-based chemotherapy is generally the preferred approach. Among the benefits of preoperative, as compared with postoperative, combined modality therapy are a superior sphincter preservation rate, a lower rate of anastomotic stenosis, and better local control while providing similar long-term survival. These data are discussed elsewhere. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Indications

for neoadjuvant treatment' and "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Long-course chemoradiation'.)

- Another option for patients with locally advanced but potentially resectable rectal adenocarcinoma is the short-course (five days) high-dose-rate "Swedish style" of preoperative RT. However, this approach has not gained popularity in the United States, where long-course preoperative CRT is generally preferred if the patient can tolerate it. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Short-course radiotherapy'.)

However, whether all patients with transmural rectal cancer without a threatened circumferential margin should undergo initial RT or CRT is controversial. Updated guidelines for treatment of rectal cancer from ESMO suggest that patients with a depth of invasion beyond the muscularis propria that is 5 mm or less are appropriate candidates for upfront surgery rather than neoadjuvant CRT, even if they are node positive, as long as the levators are not threatened, the mesorectal fascia is clear, and there is no extranodal extension [8]. This subject is discussed in detail elsewhere. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Contribution of depth of extramural penetration'.)

Most patients who are selected for neoadjuvant CRT or short-course RT also receive at least four months of postoperative adjuvant chemotherapy. (See "Adjuvant therapy after neoadjuvant therapy for rectal cancer", section on 'Benefit of postoperative chemotherapy'.)

Another area of controversy is whether patients who have a complete clinical response to neoadjuvant CRT should undergo immediate transabdominal surgery. There are increasing reports of excellent long-term disease-free survival and cure in patients who take the approach of watch and wait instead of immediate surgical resection. Most of these patients were treated with a combination of radiotherapy (either short-course or long-course CRT) plus neoadjuvant chemotherapy, an approach referred to as total neoadjuvant therapy (TNT). (See 'Clinical T4, N2 disease, or other high-risk features' below.)

In our view, surgical resection remains the standard approach after neoadjuvant therapy for patients who are medically operable, but patients who would otherwise require an APR may consider watchful waiting if they are followed by clinicians skilled in this practice and the patient understands the risk of tumor regrowth and salvage surgery results. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Avoidance of radical surgery'.)

Clinical T2N1 or T3N0-1 disease eligible for sphincter-sparing surgery — Neoadjuvant chemotherapy followed by the response-guided use of CRT prior to surgical resection is an option for patients with clinical T2N1M0, T3N0M0, or T3N1M0

adenocarcinoma who are eligible for sphincter-sparing surgery. Most patients treated with this approach avoid CRT and are presumably spared from late radiation-associated toxicities. Further details are discussed separately. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Neoadjuvant chemotherapy and selective use of CRT'.)

Clinical T4, N2 disease, or other high-risk features — TNT (ie, induction chemotherapy [preferably with an oxaliplatin-containing regimen, such as FOLFOX] followed by fluoropyrimidine-based concomitant CRT) is an appropriate alternative to initial CRT for patients with large bulky, locally unresectable tumors (ie, clinical T4 disease), clinical N2 disease, or other high-risk features such as a low-lying rectal tumor, an involved or threatened mesorectal fascia, or extramural venous invasion (EMVI) on staging MRI. For patients who receive four months of preoperative chemotherapy, postoperative adjuvant chemotherapy is omitted. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Total neoadjuvant therapy for locally advanced tumors'.)

Another approach to TNT is short-course RT followed by oxaliplatin-containing chemotherapy and then surgical resection. At least two trials have compared this approach with long-course CRT followed by surgery and adjuvant chemotherapy in patients with high-risk rectal cancer and both showed at least similar outcomes for short-course RT plus neoadjuvant chemotherapy, although the STELLAR trial also showed higher rates of acute treatment-related toxicity with the short-course approach. These data are described in more detail elsewhere. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Choice of strategy'.)

Distant metastases present — The management of patients who present with synchronous metastatic disease must be individualized. The two most important factors are whether the metastases are potentially resectable and whether the primary tumor is symptomatic or not. It is important that patients be assessed for patency of the rectal lumen before starting systemic chemotherapy treatment. These patients should be discussed in a multidisciplinary tumor board for optimal treatment planning. (See 'Multidisciplinary management' above.)

Potentially resectable metastases — If both the primary tumor and metastases are resectable, one approach is to start with systemic chemotherapy and then short-course RT to the primary and involved nodes followed by synchronous resection of the primary and the metastatic disease. Other acceptable approaches include short-course RT followed by chemotherapy followed by surgery, or chemotherapy followed by long-course CRT and then surgery. For most patients, we favor initial chemotherapy to allow the natural history of the metastatic disease to reveal itself. Furthermore, if there has been significant tumor downsizing with induction chemotherapy, chemoradiation may not be necessary and may be selectively

omitted. An important point is that the relative impact of chemotherapy and radiation in a patient with resectable synchronous metastatic disease has not been established, and efforts should focus on achieving margin-negative resections of both the primary site and metastases above all else. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Local treatment for patients with distant metastases'.)

Whether resection of the metastases is performed synchronously or in a staged fashion depends on multiple factors, including the extent of resection at both primary and metastatic sites and the general condition of the patient. There is no consensus as to the best approach. This subject is discussed in more detail elsewhere. (See "Hepatic resection for colorectal cancer liver metastasis", section on 'Synchronous colorectal liver metastases'.)

Unresectable metastases — The approach to patients with unresectable metastatic disease depends on whether the primary tumor is symptomatic or not:

- For patients with a symptomatic rectal primary tumor and synchronous, unresectable metastatic disease, alternatives include creation of a diverting stoma or palliative resection in patients presenting with impending obstruction, prior to initiation of systemic chemotherapy, to obtain fast relief from symptoms and to avoid complete bowel obstruction or perforation necessitating emergency surgery. Another option is placement of an intraluminal self-expanding metal stent, although in the rectum, this is less favored due to potential migration or erosion through the wall as the tumor responds to treatment. In addition, stents should not be utilized in the distal rectum because they are uncomfortable. For nonobstructing tumors, laser ablation or electrofulguration can be utilized. It is imperative that endoscopic evaluation of the lumen be performed periodically in patients with the primary tumor in place who are receiving systemic therapy for unresectable metastases. (See "Locoregional methods for management and palliation in patients who present with stage IV colorectal cancer", section on 'Symptomatic primary' and "Locoregional methods for management and palliation in patients who present with stage IV colorectal cancer", section on 'Nonsurgical palliative options' and "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Synchronous unresectable metastases'.)

- For patients with an asymptomatic primary, systemic chemotherapy is appropriate. Given the low likelihood of primary site complications requiring emergency surgery in patients treated with modern systemic chemotherapy, the relatively high risk of postoperative morbidity, and the lack of evidence that resection of the primary tumor improves survival, we pursue bowel resection only if there is imminent risk of obstruction. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic

approach" and "Locoregional methods for management and palliation in patients who present with stage IV colorectal cancer", section on 'Incurable metastatic disease'.)

Prognosis — Five-year overall survival rates, stratified according to 2010 American Joint Committee on Cancer (AJCC) tumor (T) stage at diagnosis for rectal cancer and derived from the Surveillance, Epidemiology, and End Results (SEER) database, are illustrated in the following figure (figure 3) [16]. However, these outcome estimates are problematic in two ways:

- The survival rates depict overall and not cancer-specific survival. Because the incidence of colorectal cancer increases with age, there are relevant risks of dying from causes other than colorectal cancer.

- Furthermore, in the case of rectal cancer, these survival estimates were derived from studies in which surgical resection was not preceded by neoadjuvant therapy. Outcomes are better in patients who undergo pathologic staging after preoperative treatment. Both a large institutional study [17] and a randomized phase III trial [18,19] demonstrate that complete eradication of the tumor, as detected by microscopic examination of the resected specimen, is associated with a better prognosis than an incomplete or poor response to neoadjuvant treatment (table 4). (See "Pathology and prognostic determinants of colorectal cancer", section on 'Tumor regression after neoadjuvant therapy'.)

These two issues were addressed in a series of 771 consecutive patients with stages I to IV rectal cancer who were undergoing resection between 1991 and 2008; 296 (38 percent) received some form of neoadjuvant therapy [20]. Ten-year cancer-specific survival rates for patients with stage I, II, III, and IV disease at the time of resection were 89, 80, 63, and 11 percent, respectively. Only approximately one-third of the observed deaths in patients with stages I to III disease were related to rectal cancer. In addition, a substantial number of deaths due to rectal cancer occurred between years 5 and 10 (5-year and 10-year cancer-specific survival 73 versus 66 percent), highlighting the importance of longer follow-up periods to avoid underestimating the real burden of rectal cancer. (See "Pathology and prognostic determinants of colorectal cancer" and "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Prognosis and extent of tumor regression'.)

Prognosis for patients with advanced (metastatic) colorectal cancer is highly variable and dependent on many factors, including age and performance status, site and number of metastases, molecular factors such as *RAS* or *BRAF* mutations and deficient DNA mismatch repair/microsatellite instability (MSI), eligibility for surgery or additional chemotherapy, and tumor location. Nomograms for overall and progression-free survival based on several of these clinicopathologic factors have been developed that can assist in aiding prognostication and

patient-physician communication; however, they do not include tumor location or MSI status and only apply to patients who are not candidates for or do not undergo metastasectomy [21].

GENETIC ISSUES

Although most colorectal cancers are sporadic, specific genetic disorders have been identified, most of which are autosomal dominant, that are associated with a very high risk of developing the disease. Familial adenomatous polyposis (FAP; 90 percent risk of colorectal cancer by the age of 45 in the absence of prophylactic colectomy) and Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]; lifetime risk of colorectal cancer 25 to 75 percent) are the most common of the familial colorectal cancer syndromes, but together these two conditions account for fewer than 5 percent of colorectal cancer cases. (See "Colorectal cancer: Epidemiology, risk factors, and protective factors", section on 'Hereditary CRC syndromes' and "Clinical manifestations and diagnosis of familial adenomatous polyposis" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis".)

Testing for deficient mismatch repair — Lynch syndrome is more common than FAP and accounts for approximately 2 to 3 percent of all colorectal adenocarcinomas. The term Lynch syndrome is now commonly used for families who have been genetically determined to have a disease-causing defect (inherited or, rarely, de novo) in one of the mismatch repair (MMR) genes. The biologic footprint of deficient MMR capacity is microsatellite instability (MSI), detected by polymerase chain reaction (PCR) or, indirectly, by the absence of MMR gene protein expression in the tumor, as detected by immunohistochemistry (IHC). However, absence of MMR proteins is not specific to Lynch syndrome; approximately 15 percent of sporadic tumors also have deficient mismatch repair, as evidenced by high levels of MSI or loss of expression of MMR proteins.

At most institutions, testing of all colorectal cancers is routinely used to help establish the diagnosis of Lynch syndrome as well as to identify those patients whose tumors may respond to immune checkpoint inhibitor immunotherapy.

Some institutions perform selective MSI testing and/or IHC testing for MMR proteins in colorectal cancers in young patients (diagnosed prior to age 50 years) or in those who meet the Bethesda criteria (table 5). However, increasingly, universal testing of all colorectal cancers for MSI and/or loss of MMR proteins by IHC is performed, a practice that is supported by guidelines from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and a United States Multi-Society Task Force on Colorectal Cancer [22-24]. In general:

- Absence of MSI and intact expression of all four MMR proteins on IHC rules out Lynch syndrome.

- For individuals with evidence of loss of expression of an MMR protein by IHC, further evaluation is based on the IHC results and is outlined in the suggested algorithm (algorithm 6).

  - Although over 90 percent of Lynch syndrome-related colorectal cancers will demonstrate MSI, 15 percent of sporadic colorectal cancers also have MSI. Thus, the finding of MSI in a colorectal cancer is not specific for Lynch syndrome. Absence of protein expression of MLH1 and PMS2, MLH1 alone, or PMS2 alone (which is rare) may be associated with either sporadic or inherited disease. If these two proteins are not expressed in a tumor, the next step is analysis of BRAF V600E mutation or analysis of methylation of the MLH1 promoter. The presence of a BRAF mutation suggests sporadic, rather than inherited, disease, and there is no need to refer for genetic testing. If there is methylation of the MLH1 promoter and no BRAF mutation, most likely the patient will have a sporadic tumor; however, 5 to 10 percent of these patients may harbor a germline mutation. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Indications for germline testing'.)

  - On the other hand, loss of expression of MSH2 alone, MSH2 in combination with MSH6, or MSH6 alone is highly specific for a disease-causing germline defect, and referral for genetic testing (for the genes corresponding to the absent proteins) is appropriate. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management".)

  - An important point is that IHC for presence of MMR proteins (particularly MSH6) may be unreliable on a rectal cancer for which neoadjuvant treatment has been administered [25,26]. Thus, if initial chemoradiotherapy (CRT) or short-course radiation therapy (RT) is planned, an attempt should be made to perform IHC testing on the pretreatment biopsy material.

Extracolonic cancers are very common in Lynch syndrome, particularly endometrial carcinomas, which may occur in up to 60 percent of female mutation carriers in some families. Other sites at increased risk of neoplasm formation include the ovary, stomach, small bowel, hepatobiliary system, brain, renal pelvis or ureter, and sebaceous glands of the skin, such as with sebaceous adenomas or carcinomas. Periodic screening is recommended by expert groups. (See "Lynch

syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management", section on 'General measures'.)

Treatment implications

- **Adjuvant setting** – Colorectal tumors that are deficient in MMR proteins (dMMR/MSI-H) have a relatively good prognosis, but they tend to be relatively refractory to fluoropyrimidines when used alone in the adjuvant setting. (See "Pathology and prognostic determinants of colorectal cancer", section on 'Mismatch repair deficiency'.)

- **Neoadjuvant setting** – Although data are limited, at least some reports note an excellent prognosis for dMMR/MSI-H rectal cancers and a pathologic complete tumor response rate (28 percent) following fluoropyrimidine-based CRT that seems comparable with that reported in other series [27], and this is a standard approach even for patients with dMMR/MSI-H tumors. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Long-course chemoradiation'.)

  Furthermore, patients with localized dMMR/MSI-H colorectal cancer may respond to neoadjuvant immunotherapy [28-31], and early data exploring the potential of immunotherapy to spare patients from the morbidity of subsequent surgery and RT are promising in locally advanced dMMR rectal cancer [32]. These data are discussed in detail elsewhere. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Neoadjuvant immunotherapy for dMMR tumors'.)

- **Metastatic disease** – The finding of dMMR/MSI-H colorectal cancer also identifies patients who might respond to immunotherapy using immune checkpoint inhibitors in the setting of metastatic disease. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Approach to later lines of systemic therapy", section on 'Microsatellite unstable/deficient mismatch repair tumors'.)

ADJUNCTIVE THERAPIES

The benefits of diet and exercise, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), vitamin D, and coffee consumption on cancer outcomes are discussed separately. (See "Adjunctive therapy for patients with resected early stage colorectal cancer: Diet, exercise, NSAIDs, and vitamin D", section on 'Vitamin D status'.)

POST-TREATMENT SURVEILLANCE

The purpose of surveillance after definitive therapy of rectal cancer is early identification of those patients who might potentially be cured by further surgical intervention and to screen for second primary cancers and polyps. Early diagnosis of an asymptomatic recurrence increases the likelihood of a complete surgical resection if potentially resectable recurrent disease is identified. Furthermore, several meta-analyses support a modest but significant survival benefit from an intensive surveillance strategy after resection of a colorectal cancer.

Stage II and III disease — Intensive postoperative surveillance is generally recommended for patients with resected stage II or III (table 2) cancers who would be considered candidates for aggressive treatment, including curative-intent surgery. In keeping with guidelines from the American Society of Clinical Oncology (ASCO) and others, the components of surveillance include the following (table 6):

- A clinical encounter with a physician every three to four months for the first three years and every six months during years 4 and 5. A history should be obtained at each visit, aimed at highlighting symptoms that could suggest cancer recurrence. The physical examination should include a rectal examination for those patients who have undergone low anterior resection (LAR) or a transanal excision for rectal cancer. (See "Post-treatment surveillance after colorectal cancer treatment", section on 'History and physical examination'.)

- A serum carcinoembryonic antigen (CEA) level should be obtained at each follow-up visit for at least the first three years after primary resection, even if preoperative CEA levels were normal. It is reasonable to eliminate CEA testing from the surveillance strategy in patients who would not be potentially eligible for resection if an early recurrence were documented. (See "Post-treatment surveillance after colorectal cancer treatment", section on 'Carcinoembryonic antigen'.)

- All patients should undergo a complete colonoscopy either before surgical resection or (for those with initially obstructing tumors) within a few months after resection to exclude synchronous polyps and cancer. (See "Post-treatment surveillance after colorectal cancer treatment", section on 'Perioperative colonoscopy'.)

- Repeat colonoscopy one year after primary resection to exclude new lesions and, if normal, subsequent follow-up intervals of three to five years are recommended, depending on the results of the prior colonoscopy. (See "Post-treatment surveillance after colorectal cancer treatment", section on 'Postoperative endoscopic surveillance' and "Post-treatment surveillance after colorectal cancer treatment", section on 'Guidelines from major groups'.)

- Although some disagree, ASCO guidelines suggest that patients who have undergone LAR for rectal cancer and who have not received radiation therapy (RT) undergo flexible proctosigmoidoscopy every six months for two to five years. This recommendation is controversial, however, and consensus-based guidelines from the National Comprehensive Cancer Network (NCCN) no longer recommend surveillance proctosigmoidoscopy in this population, with the exception of patients treated with transanal excision only. (See "Post-treatment surveillance after colorectal cancer treatment", section on 'Proctosigmoidoscopy'.)

- Annual surveillance computed tomography (CT) scans of the chest, abdomen, and pelvis should be performed for at least three years if the patient would be eligible for aggressive therapy, including curative-intent surgery. (See "Post-treatment surveillance after colorectal cancer treatment", section on 'Radiographic imaging'.)

Stage I disease — There is less consensus on the appropriate post-treatment surveillance strategy for patients with resected stage I rectal cancer, and recommendations vary, especially for patients undergoing only local excision for T1 disease [33]. We suggest the following approach, which parallels that for more advanced disease:

- Physical examination, including rectal examination (preferably by the surgeon) and serum CEA every three to four months for two years, then every six months through years 3 to 5.

- Flexible sigmoidoscopy every 6 to 12 months for up to five years if only a local excision was performed.

- Colonoscopy at one year postresection, then at year 4 postresection.

- Annual surveillance CT scans.

Guidelines from expert groups — Guidelines from a United States Multi-Society task force and the NCCN recommend periodic proctoscopy with or without endoscopic ultrasound (EUS) in this setting, with differences in the frequency of testing and the target population (table 6):

- The NCCN recommends testing with proctoscopy and either endorectal ultrasound or contrast-enhanced magnetic resonance imaging (MRI) every three to six months for the first two years, then every six months for a total of five years for patients who have undergone transanal excision only [5].

- Updated guidelines from a United States Multi-Society Task Force on Colorectal Cancer suggest flexible sigmoidoscopy (or EUS) every three to six months for the first two to three

years after surgery for the following groups who are at increased risk of a local recurrence [34]:

- Patients with localized rectal cancer who have undergone surgery without total mesorectal excision (TME)
- Patients who have undergone transanal local excision or endoscopic submucosal dissection alone
- Patients with locally advanced rectal cancer who did not receive neoadjuvant chemoradiotherapy and then a TME

Guidelines for post-treatment surveillance from ASCO do not cover stage I tumors [35]. Furthermore, guidelines from the European Society for Medical Oncology (ESMO) do not address the role of post-treatment proctosigmoidoscopy after treatment for rectal cancer, stating only that completion colonoscopy should be carried out within the first year if not done at the time of diagnostic workup and that colonoscopy with resection of colonic polyps be carried out every five years up to age 75; further clinical, laboratory, and radiological examinations should be restricted to patients with suspicious symptoms [8].

Resected stage IV disease — There are no data to guide recommendations for surveillance in patients with resected metastatic colorectal cancer, and guidelines are not available from most expert groups, including ASCO [35]. However, consensus-based NCCN guidelines [5] suggest following the same surveillance strategy as for resected stage II or III disease but with more frequent CT scanning (table 6). We agree with this approach.

Links to other society guidelines are provided elsewhere. (See 'Society guideline links' below.)

MANAGEMENT IN RESOURCE-CONSTRAINED SETTINGS

There are few data to guide the treatment strategy for colorectal cancer in resource-constrained settings. The American Society of Clinical Oncology (ASCO) has developed consensus-based guidelines for early detection and treatment of early stage (localized) colorectal cancer that stratify recommendations based on the available level of services (basic, limited, enhanced, and maximal (table 7)) [36-38].

Guidelines for treatment of patients with late-stage colorectal cancer are also available [39]. They include specific recommendations for initial diagnostic evaluation, systemic therapy in the first-line setting and beyond, surgical management of patients with potentially resectable disease, other liver-directed therapy options for late-stage disease and liver metastases, issues

specific to primary site radiation therapy in patients with metastatic disease, and post-treatment surveillance.

MANAGEMENT OF LOCALLY RECURRENT DISEASE

Management of locally recurrent rectal adenocarcinoma is a significant challenge. The choice of therapy depends on prior therapy, the local extent of the recurrence, and whether or not distant disease is present. (See "Treatment of locally recurrent rectal adenocarcinoma", section on 'Introduction'.)

The pretreatment evaluation should focus on an assessment of fitness for major surgical intervention, staging of the recurrence to ascertain the anatomy and the extent of local and distant disease, and histologic confirmation of the recurrence. All patients with suspected locally recurrent rectal cancer should undergo a full clinical staging evaluation to exclude the presence of distant metastatic disease, including a computed tomography (CT) of the torso (chest, abdomen, and pelvis) and an integrated positron emission tomography (PET)/CT scan. In addition to a digital clinical examination (which may require an examination under anesthesia) and full colonoscopy to evaluate the anastomotic site and assess the remainder of the large bowel for synchronous lesions, the preoperative evaluation of any patient with a locally recurrent rectal cancer should include rectal magnetic resonance imaging (MRI). Gynecologic or cystoscopic evaluation may be needed for selected patients. In addition, serum levels of the tumor marker carcinoembryonic antigen (CEA) should be obtained. (See "Treatment of locally recurrent rectal adenocarcinoma", section on 'Pretreatment evaluation'.)

Complete radical resection is a prerequisite for cure. Aggressive surgical attempts to obtain microscopically negative margins are warranted due to the superior outcomes with microscopically complete (R0) resection. This may require an extensive operative procedure (eg, pelvic exenteration). (See "Treatment of locally recurrent rectal adenocarcinoma", section on 'Surgical resection'.)

Contraindications for radical surgery include:

- Nerve root involvement above the level of S1-2
- Proximal (S1,2) sacral invasion extending to the sacral promontory (relative contraindication)
- Involvement of the paraaortic lymph nodes (relative contraindication if the involved nodes are below the left renal vein)
- Tumor encasement of the external iliac vessels

- Extension of tumor through the greater sciatic notch
- Bilateral ureteral obstruction (relative contraindication)
- Unresectable extrapelvic disease
- Circumferential involvement of the pelvic wall

Distant metastases (typically to liver or lung) may or may not be a relative contraindication depending on the location and potential for curative resection. (See "Potentially resectable colorectal cancer liver metastases: Integration of surgery and chemotherapy" and "Surgical resection of pulmonary metastases: Outcomes by histology".)

For most patients, especially those who have not received prior pelvic radiation therapy (RT), combined modality therapy is recommended rather than surgery alone. (See "Treatment of locally recurrent rectal adenocarcinoma", section on 'Combined modality therapy'.)

For previously unirradiated patients, the same principles as guide preoperative therapy of primary locally advanced rectal adenocarcinoma are followed. Preoperative therapy with fluoropyrimidine-based, concurrent, long-course external beam RT followed by surgery six to eight weeks later and then four to six months of adjuvant chemotherapy is preferred rather than surgery followed by adjuvant therapy. For patients with bulky tumors or extensive nodal disease, another option is to start with up to four months of chemotherapy, followed by chemoradiotherapy and surgery. (See "Neoadjuvant therapy for rectal adenocarcinoma".)

For previously irradiated patients, pelvic reirradiation is feasible in selected patients and may permit surgical salvage and long-term survival. The dose of RT for reirradiation in this setting should be limited to 30 to 39 Gy. (See "Treatment of locally recurrent rectal adenocarcinoma", section on 'Previously irradiated patients'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Colorectal cancer".)

SUMMARY AND RECOMMENDATIONS

- **Diagnosis and staging**
  - Most patients with rectal cancer are diagnosed by colonoscopy after presenting with lower gastrointestinal tract bleeding; in some, the diagnosis is made during a routine

screening colonoscopy. (See 'Diagnosis and staging' above.)

- The goal of the pretreatment staging evaluation is to assess for distant metastases and to determine primary tumor location and local extent (algorithm 1) (see 'The pretreatment staging evaluation' above):

  - All patients with an invasive rectal cancer require preoperative local staging using either rectal magnetic resonance imaging (MRI; preferred) or transrectal endoscopic ultrasound. (See 'Local imaging' above.)

  - We use contrast-enhanced computed tomography (CT) scan of the chest and abdomen to evaluate for distant metastases in all patients, except if there is a completely resected malignant polyp with no invasion beyond the submucosa (pT1N0), favorable histologic features, and clear margins. If pelvic MRI is not performed, the CT scan should also include the pelvis. (See 'Evaluation for distant metastases' above.)

  - We obtain a serum carcinoembryonic antigen (CEA) level preoperatively in most patients with rectal cancer. (See 'Tumor markers' above.)

- **Management** – Multidisciplinary evaluation is required to optimize management (algorithm 2). (See 'Multidisciplinary management' above.)

  - **Surgical principles**

    - Polypectomy alone is adequate for some patients with limited invasive cancer in a polyp who have no adverse features(algorithm 3). Superficially invasive (cT1), small rectal adenocarcinomas that are not amenable to polypectomy alone may be effectively managed with local excision. (See 'Clinical/pathologic T1N0 amenable to endoscopic polypectomy or transanal excision' above.)

      For more deeply invasive tumors that do not meet the criteria for local excision, and those with cT1 tumors that are not amenable to local excision, transabdominal excision is the standard approach. Preoperative chemoradiotherapy (CRT) followed by local transanal excision might be feasible as an alternative to total mesorectal excision in good responders with cT2N0 distal rectal cancer. However, this is not yet a standard approach, especially for patients with direct sphincter invasion (algorithm 4). (See 'Clinical T2N0 and cT1N0 not amenable to local excision' above.)

- The specific surgical technique used for the resection of a rectal cancer depend on the extent and location of the tumor within the rectum (see 'Surgical approaches' above):

  A tumor in the upper and middle rectum can usually be managed with a sphincter-sparing procedure, such as low anterior resection (LAR), provided that negative margins can be achieved. (See "Surgical treatment of rectal cancer", section on 'Low anterior resection'.)

  Tumors in the lower rectum (ie, within 5 cm of the anal verge (figure 2)) may require an abdominal perineal resection (APR) if a negative distal margin cannot be achieved with sphincter-sparing procedures. (See "Surgical treatment of rectal cancer", section on 'Abdominoperineal resection'.)

- **Preoperative RT and chemotherapy**

  - Indications for preoperative CRT or RT include a clinically staged T3 or T4, or node-positive tumor, or one that is invading or threatening the circumferential margin (algorithm 5). (See 'Clinical T3/4 or N1' above.)

    For patients with transmural (T3-4) or node-positive disease, the specific approach to initial therapy varies according to the presence or absence of distant metastases:

    - **Conventional chemoradiation** – For patients without distant metastases, preoperative conventional fractionation CRT over 5.5 to 6 weeks using concurrent fluoropyrimidine-based chemotherapy is preferred over initial surgery if the patient can tolerate it. Short-course (five days), high-dose-rate “Swedish style” preoperative RT is acceptable and is the preferred approach at many institutions outside of the United States.

    - **Neoadjuvant chemotherapy with selective use of RT** – Preoperative chemotherapy followed by the response-guided use of CRT prior to surgical resection is an option for patients with clinical T2N1M0, T3N0M0, or T3N1M0 rectal adenocarcinoma who are eligible for sphincter-sparing surgery. Most patients treated with this approach avoid CRT and are presumably spared from late radiation-associated toxicities. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Neoadjuvant chemotherapy and selective use of CRT'.)

- **Total neoadjuvant therapy (TNT)** – TNT is an alternative approach for those with bulky, initially unresectable tumors (ie, clinical T4 disease), extensive nodal disease (ie, cN2 disease), or other high-risk features, such as a low-lying tumor, an involved or threatened mesorectal fascia, or extramural venous invasion. (See 'No distant metastases' above.)

  For patients with potentially resectable metastatic disease, one approach is to start with short-course RT to the primary and involved nodes followed by combination chemotherapy and then surgical resection of both the primary and the metastatic disease. Another approach is initial chemotherapy followed by long-course CRT and then resection. (See 'Potentially resectable metastases' above.)

- **Other approaches** – For symptomatic patients with unresectable metastatic disease options include surgical diversion, palliative resection, laser ablation or electrofulguration (for nonobstructing tumors), or short-course RT followed by systemic chemotherapy. For asymptomatic primary tumors, we only pursue treatment of the primary in the setting of imminent obstruction. (See 'Unresectable metastases' above.)

- **Post-treatment surveillance**

  - Intensive postoperative surveillance is generally recommended for patients with resected stage II or III (table 2) cancers who would be considered candidates for aggressive treatment, including curative-intent surgery, in the event of a disease recurrence. We follow published guidelines from ASCO (table 6). For patients with resected stage IV disease, we increase the frequency of surveillance CT to every six months. (See 'Post-treatment surveillance' above.)

  - For resected stage I disease, we follow the same post-treatment surveillance strategy as used for stage II disease, and do periodic flexible sigmoidoscopy for patients who are treated with transanal excision alone. (See 'Stage I disease' above.)

- **Genetic issues**

  - Lynch syndrome, an inherited condition with a very high risk of colorectal and other cancers, is characterized by a germline disease-causing defect in one of the mismatch repair (MMR) genes, the biologic footprint of which is microsatellite instability (MSI). Increasingly, universal testing of all colorectal cancers for MSI or loss of MMR proteins by immunohistochemistry (IHC) is performed.

Testing for MMR deficiency helps establish a diagnosis of Lynch syndrome and identifies patients who may respond to immunotherapy. Testing for presence of MMR proteins by IHC is unreliable on post-treatment rectal cancer, and if initial CRT or short-course RT is planned, an attempt should be made to perform IHC testing on the pretreatment biopsy material. (See 'Testing for deficient mismatch repair' above.)

- **Local recurrence** – Management of locally recurrent rectal adenocarcinoma is a significant challenge. The choice of therapy depends on prior therapy, the local extent of the recurrence, and whether or not distant disease is present. Complete surgical resection is a prerequisite for cure; however, outcomes are poor with surgery alone, and outcomes are better with combined modality therapy. (See 'Management of locally recurrent disease' above.)

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Topic 106743 Version 47.0

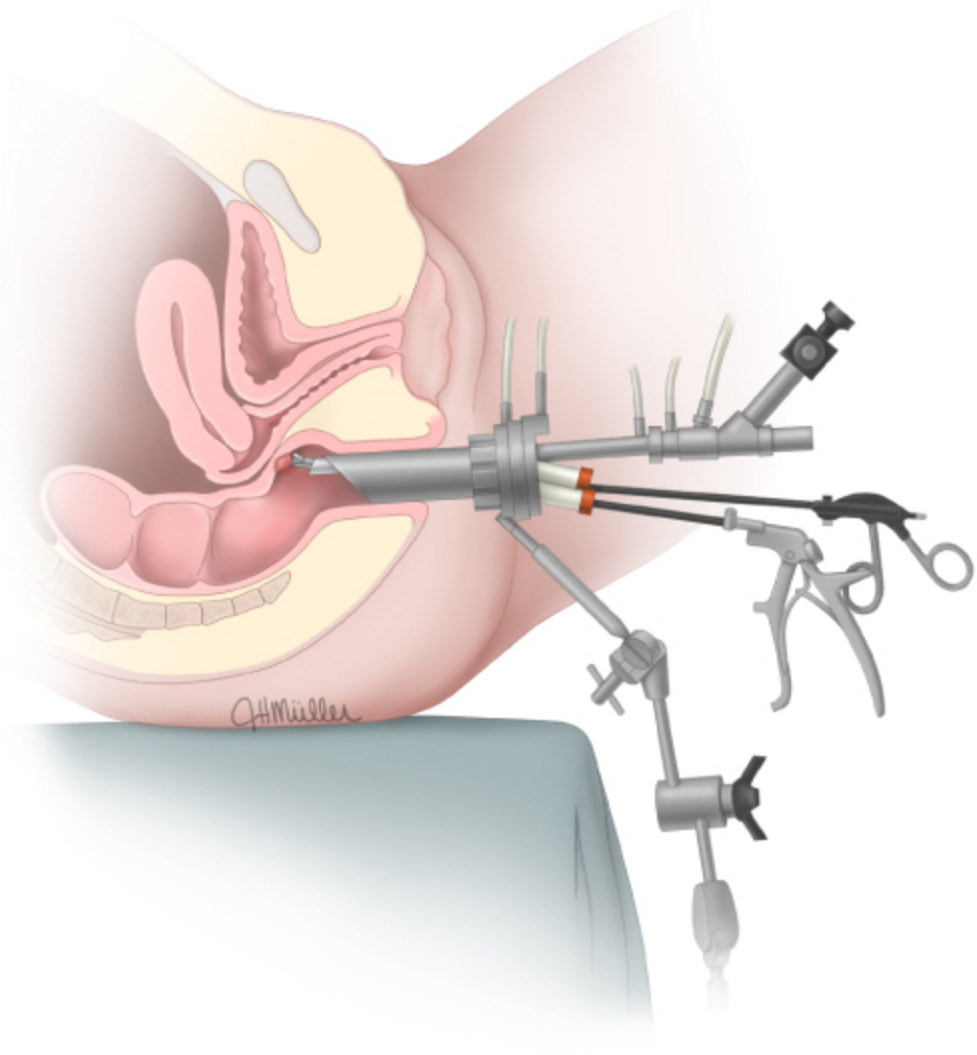
GRAPHICS

Endoscopic criteria suggesting malignancy of a polyp

Firm consistency
Adherence
Ulceration
Friability

Graphic 68868 Version 1.0

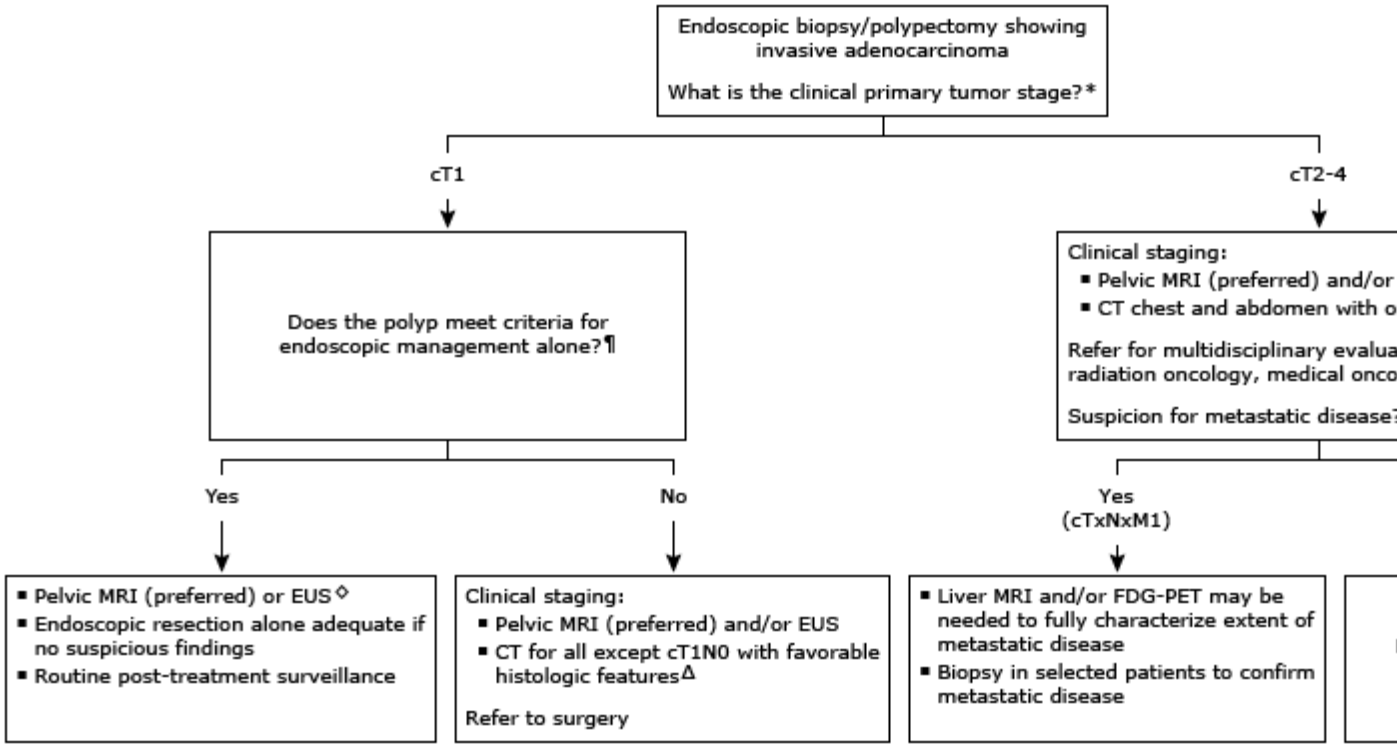
Transanal endoscopic microsurgery



This figure depicts the placement of the operating endoscope and cutting instrument used for the local excision of a rectal lesion.

Graphic 58698 Version 1.0

Staging workup of newly diagnosed rectal cancer



This is an overview of our approach to staging workup of newly diagnosed nonmetastatic rectal adenocarcir used in conjunction with other UpToDate content on rectal adenocarcinoma.

MRI: magnetic resonance imaging; EUS: endoscopic ultrasound; CT: computed tomography; FDG-PET: fluorc positron emission tomography.

* T1 tumors invade through the muscularis mucosa. Tumors that invade the muscularis propria or beyond a

¶ Endoscopic excision alone is NOT appropriate for malignant polyps with any of the following:

- For both pedunculated and nonpedunculated polyps:
  - Piecemeal resection
  - Poorly differentiated histology
  - Lymphovascular invasion
  - Tumor budding (foci of isolated cancer cells or a cluster of five or fewer cancer cells at the invasive
- For pedunculated polyps, a positive margin variably defined as:
  - Cancer present at the resection margin
  - Cancer within 1 mm of resection margin
  - Cancer within 2 mm of resection margin
- For nonpedunculated polyps:
  - Cancer at resection margin
  - Submucosal invasion depth ≥1 mm

Δ CT is appropriate for all except those with clinical T1N0 cancers with favorable histologic features.

- If pelvic MRI has been done, we perform CT of the chest and abdomen
- If pelvic MRI has not been done, we perform CT of the chest, abdomen, and pelvis

◇ Practice Parameters Committee of the American College of Gastroenterology (ACG) and the European Soc Oncology (ESMO), recommend performing either transrectal ultrasound or high-resolution MRI to determin stage and assess for lymph node positivity for all patients with an invasive rectal cancer, including those witl polyps with favorable prognostic factors.

Graphic 131308 Version 1.0

Colorectal cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres¶ to adjacent organ or structure
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades* or adheres¶ to adjacent organs or structures
* Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (ie, respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina). ¶ Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classification should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN prognostic factor should be used for perineural invasion.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative

N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the: ▪ Subserosa ▪ Mesentery ▪ Nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis by imaging, etc; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists.)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Prognostic stage groups

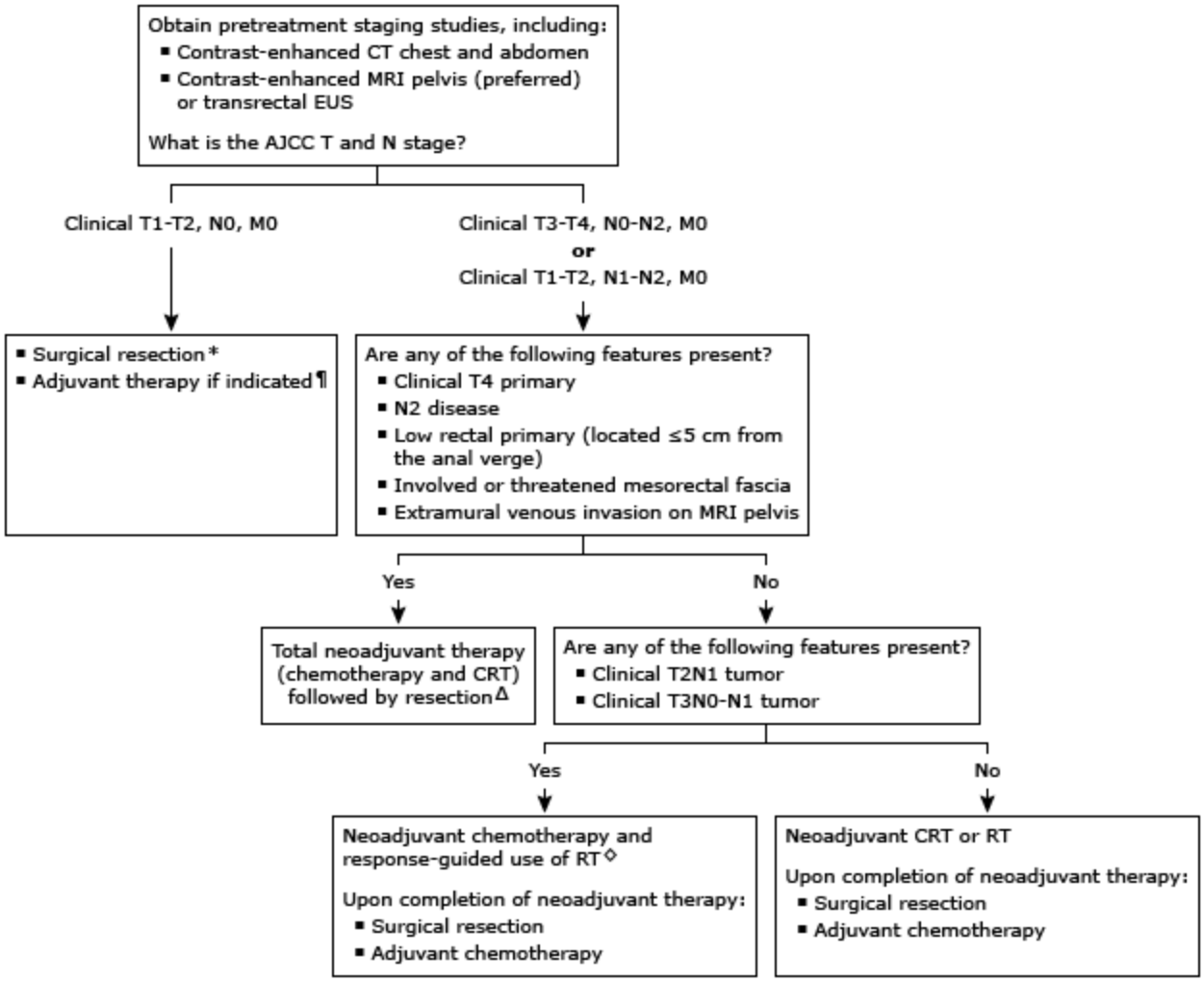
When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1-T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3-T4a	N1/N1c	M0	IIIB
T2-T3	N2a	M0	IIIB
T1-T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC

T3-T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

TNM: Tumor, Node, Metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 111438 Version 10.0

Initial treatment of pMMR/MSS, non-metastatic rectal adenocarcinoma



The initial management of locally advanced (clinical T3-4 or node-positive) pMMR/MSS rectal adenocarcinoma is presented here. The diagnosis must be pathologically confirmed on biopsy, and imaging and clinical studies should show no evidence of distant metastatic disease. Multidisciplinary treatment input is necessary from surgical oncology, radiation oncology, and medical oncology. For further details and evidence, refer to UpToDate content on the management of rectal adenocarcinoma.

AJCC: American Joint Committee on Cancer; CT: computed tomography; CRT: chemoradiation; EUS: endoscopic ultrasound; M: metastasis; MRI: magnetic resonance imaging; MSS: microsatellite stable; N: node; pMMR: proficient mismatch repair; RT: radiation therapy; T: tumor.

* Clinical T1N0 and clinical T2N0 tumors are primarily managed with surgical resection (ie, transanal local excision, transabdominal resection).

Neoadjuvant CRT is an alternative for patients with a primary distal tumor who decline resection or are poor surgical candidates.

¶ Adjuvant therapy is indicated for clinical T1-2, N0 tumors treated with transabdominal resection that subsequently demonstrate pathologic T3-4 or pathologic N1-2 disease on

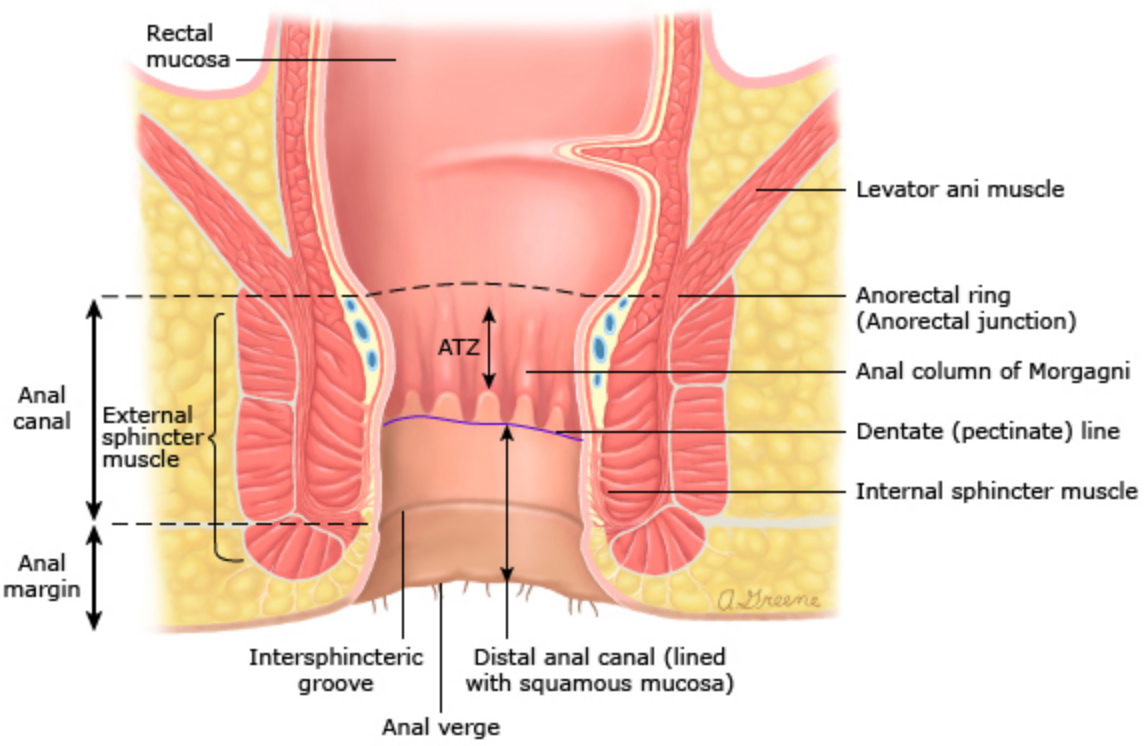
postoperative pathology.

Δ Patients with a complete clinical response to total neoadjuvant therapy may be offered surveillance without further surgery.

◇ Neoadjuvant chemotherapy plus response-guided use of RT allows most patients to omit RT and avoid its late toxicities. Patients treated with neoadjuvant chemotherapy who have a clinical response of 20% or greater for the primary tumor can omit RT and proceed directly to surgical resection, whereas those with a clinical response of less than 20% receive neoadjuvant CRT or RT prior to surgery.

Graphic 138397 Version 3.0

Anatomy of the anus and rectum



The anal canal is 2.5 to 4.0 cm long and begins superiorly where the rectal ampulla is narrowed by the anorectal ring. This palpable muscular ring is formed by fusion of the puborectalis muscle (part of the levator ani muscle complex) with the more inferior internal and external anal canal sphincters.

The external anal canal sphincter ends just distally to the internal anal canal sphincter; the intersphincteric groove is the palpable plane that can be palpated between the termination of the two sphincters. The presence of the intersphincteric groove coincides roughly with the anal verge, which marks the distal portion of the anal canal. The perianus or anal margin extends 5 cm laterally from the anal verge and is characterized by the presence of hair follicles and glands.

The interior of the anal canal can be divided into proximal and distal portions by an irregular line formed by the anal valves called the dentate (or pectinate) line (colored purple in the diagram). The portions of the anal canal proximal and distal to the dentate line have different origins of arterial supply, nerve innervation, and venous lymphatic drainage. The squamo-columnar junction (SCJ) lies within the proximal portion of the anal canal and marks the transition between rectal columnar epithelium to anal squamous epithelium. The exact position of the SCJ changes with time due to replacement of columnar epithelium with squamous epithelium in a process known as squamous metaplasia. The anal transformation zone (ATZ) is the zone where all aspects of squamous metaplasia are currently found and/or have occurred. The ATZ is marked by the SCJ proximally and extends distally to approximately the level of the dentate line.

Graphic 62539 Version 16.0

Modified FOLFOX6 chemotherapy for gastrointestinal cancer[1,2]

Cycle length: 14 days.

Drug	Dose and route	Administration	Given on days
Oxaliplatin	85 mg/m^2 IV*	Dilute with 500 mL D5W¶ and administer over two hours (on days 1 and 15, oxaliplatin and leucovorin can be administered concurrently in separate bags using a Y-connector). Shorter oxaliplatin administration schedules (eg, 1 mg/m^2 per minute) appear to be safe.[3]	Day 1
Leucovorin$^\Delta$	400 mg/m^2 IV$^\diamond$	Dilute with 250 mL D5W¶ and administer over two hours concurrent with oxaliplatin.	Day 1
Fluorouracil (FU)	400 mg/m^2 IV bolus	Slow IV push over five minutes (administer immediately after leucovorin).	Day 1
FU	2400 mg/m^2 IV	Dilute with 500 to 1000 mL D5W¶ and administer over 46 hours (begin immediately after FU IV bolus). To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS.¶	Day 1

Pretreatment considerations:

Emesis risk	▪ MODERATE. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Prophylaxis for infusion reactions	▪ There is no standard premedication regimen. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Oxaliplatin and FU are classified as irritants, but oxaliplatin can cause significant tissue damage; avoid extravasation. ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.

Infection prophylaxis	▪ Primary prophylaxis with G-CSF is not justified (estimated risk of febrile neutropenia <5%[2]). ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or kidney dysfunction	▪ A lower starting dose of oxaliplatin may be needed for severe kidney impairment.[4] A lower starting dose of FU may be needed for patients with liver impairment.[5] ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents.
Maneuvers to prevent acute neurotoxicity	▪ Counsel patients to avoid exposure to cold during and for approximately 72 hours after each infusion. Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity. ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.
Cardiac issues	▪ QT prolongation and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin.

Monitoring parameters:

- CBC with differential and platelet count prior to each treatment.
- Assess electrolytes (especially potassium and magnesium) and liver and kidney function prior to each treatment.
- Assess changes in neurologic function prior to each treatment.

Suggested dose modifications for toxicity:

Myelotoxicity	▪ Delay treatment cycle by one week for ANC <1500/microL, or platelets <75,000/microL on the day of treatment. If treatment is delayed for two weeks or delayed for one week on two separate occasions, eliminate FU bolus. With the second occurrence, reduce infusional FU by 20% and reduce oxaliplatin dose from 85 to 65 mg/m^2.

Neurologic toxicity	▪ For grade 2 symptoms lasting longer than seven days, decrease oxaliplatin dose by 20%. Discontinue oxaliplatin for grade 3 paresthesias/dysesthesias. The US Prescribing Information recommends a dose reduction in oxaliplatin (to 75 mg/m^2 in patients treated in the adjuvant setting and to 65 mg/m^2 in patients with advanced disease) for persistent grade 2 neurosensory events that do not resolve and discontinuation for persistent grade 3 neurosensory events.[4] ▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[5]
Diarrhea	▪ Withhold treatment for grade 2 or worse diarrhea, and restart at a 20% lower dose of all agents after complete resolution. The US Prescribing Information recommends dose reduction of oxaliplatin (to 75 mg/m^2 in patients treated in the adjuvant setting and to 65 mg/m^2 for patients treated for advanced disease), as well as a reduction of bolus FU and infusional FU after recovery from grade 3 or 4 diarrhea during the prior cycle.[4,5] ▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency. ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
Cardiopulmonary toxicity	▪ Oxaliplatin has rarely been associated with pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded. ▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents. ▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[5]
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; D5W: 5% dextrose in water; NS: normal saline; G-CSF: granulocyte-colony stimulating factors; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle); ECG: electrocardiogram; CBC: complete blood count; ANC: absolute neutrophil count; DPD: dihydropyrimidine dehydrogenase.

* Many centers routinely infuse oxaliplatin through a central venous line because of local pain with infusion into a peripheral vein.

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Δ Leucovorin dose is given for d,l-racemic mixture.[6] Use half the dose for LEVOleucovorin (l-leucovorin).

◇ The dose of leucovorin in the two trials of modified FOLFOX6 was 350 mg/m^2. However, most clinicians use the standard 400 mg/m^2 dose as was used for original FOLFOX6.[7]

References:

1. *Cheeseman SL, et al. Br J Cancer 2002; 87:393.*
2. *Hochster HS, et al. J Clin Oncol 2008; 26:3523.*
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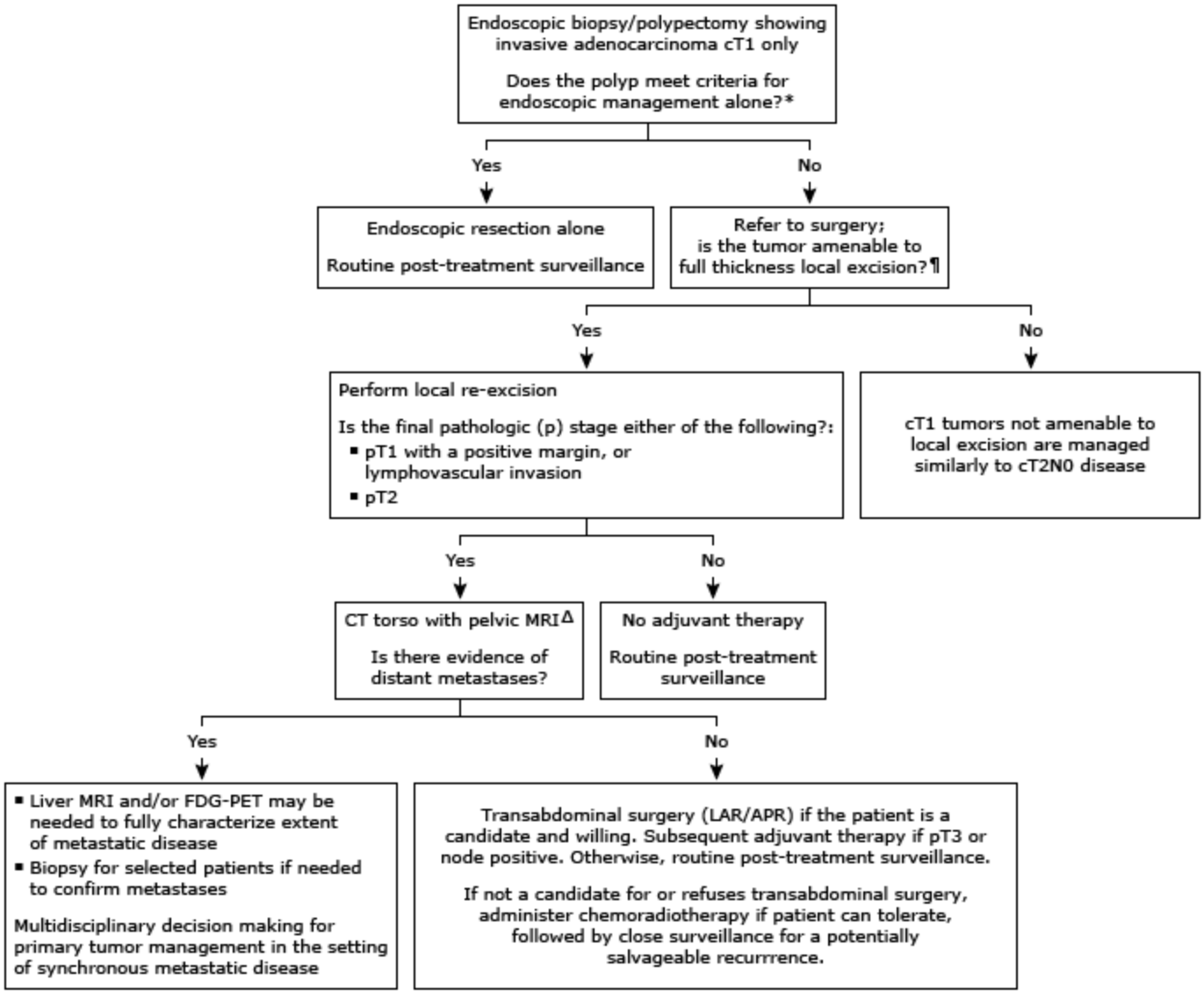
4. *Oxaliplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 13, 2015).*
5. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 13, 2011).*
6. *Leucovorin calcium injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 13, 2011).*
7. *Tournigand C, et al. J Clin Oncol 2004; 22:229.*

Graphic 50132 Version 43.0

Treatment for newly diagnosed cT1 rectal cancer



This is an overview of our approach to the management of newly diagnosed nonmetastatic rectal adenocarcinoma. It should be used in conjunction with other UpToDate content on rectal adenocarcinoma. T1 tumors invade through the muscularis mucosa but not into the muscularis propria.

CT: computed tomography; MRI: magnetic resonance imaging; FDG-PET: fluorodeoxyglucose positron emission tomography; LAR: low anterior resection; APR: abdominoperineal resection.

* Endoscopic excision alone is not appropriate for malignant polyps with any of the following:
  - For both pedunculated and nonpedunculated (sessile) polyps:
    - Piecemeal resection
    - Poorly differentiated histology
    - Lymphovascular or perineural invasion
    - Tumor budding (foci of isolated cancer cells or a cluster of five or fewer cancer cells at the invasive margin of the polyp)
    - Cancer at resection margin

- Submucosal invasion depth ≥1 mm

¶ Transabdominal surgery remains an option for patients with tumors amenable to local excision and may be preferred in some cases, especially in younger patients who are fit for surgery. Cases with all of the following features are amenable to local excision:

- Superficial T1 cancer, limited to the submucosa
- No radiographic evidence of metastatic disease to regional nodes
- Tumor <3 cm in diameter
- Low risk of developing positive regional nodes (well-differentiated, no lymphovascular or neural invasion)
- Involves <30% of the circumference of the lumen
- Mobile, nonfixed
- Margins clear (>3 mm)
- Compliance with appropriate postoperative surveillance

Δ Pelvic MRI recommended for rectal primaries. CT is appropriate for all except those with clinical T1N0 cancers with favorable histologic factors.

- If pelvic MRI has been done, we perform CT of the chest and abdomen
- If pelvic MRI has not been done, we perform CT of the chest, abdomen, and pelvis

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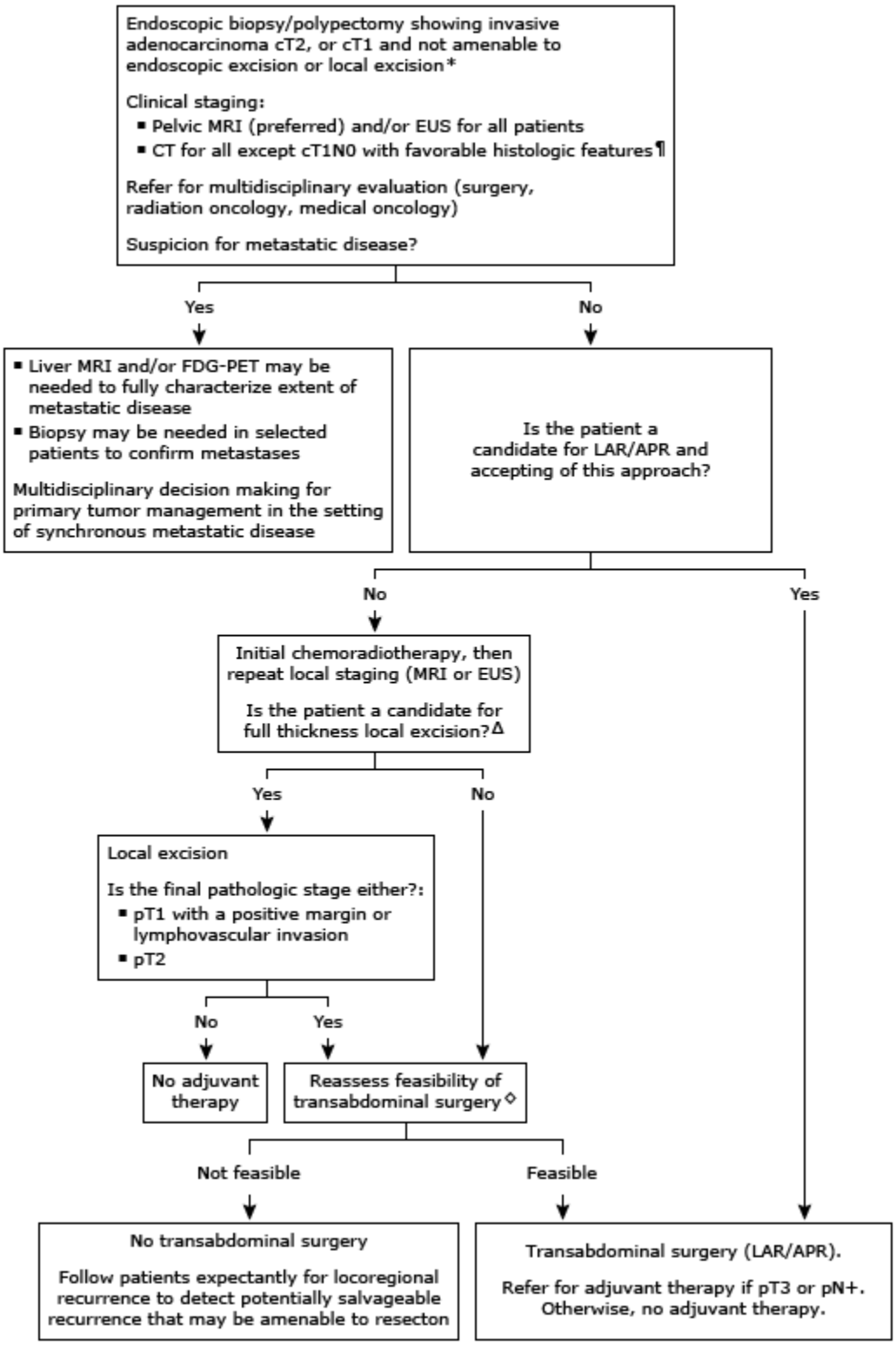
Graphic 131309 Version 2.0

Treatment of newly diagnosed cT2N0 rectal adenocarcinoma or cT1 disease not amenable to local excision



This is an overview of our approach to the management of newly diagnosed locally advanced rectal adenocarcinoma. It should be used in conjunction with other UpToDate content on rectal adenocarcinoma.

MRI: magnetic resonance imaging; EUS: endoscopic ultrasound; CT: computed tomography; FDG-PET: fluorodeoxyglucose positron emission tomography; LAR: low anterior resection; APR: abdominoperineal resection.

* T1 tumors invade through the muscularis mucosa but not into the muscularis propria. T2 tumors invade the muscularis propria but not into the pericolorectal tissues.

cT1 tumors with all of the following features are amenable to local excision:

- Superficial T1 cancer, limited to the submucosa
- No radiographic evidence of metastatic disease to regional nodes
- Tumor <3 cm in diameter
- Low risk of developing positive regional nodes (well-differentiated, no lymphovascular or neural invasion)
- Involves <30% of the circumference of the lumen
- Mobile, nonfixed
- Margins clear (>3 mm)
- Compliance with appropriate postoperative surveillance

¶ CT is appropriate for all except those with clinical T1N0 cancers with favorable histologic factors.

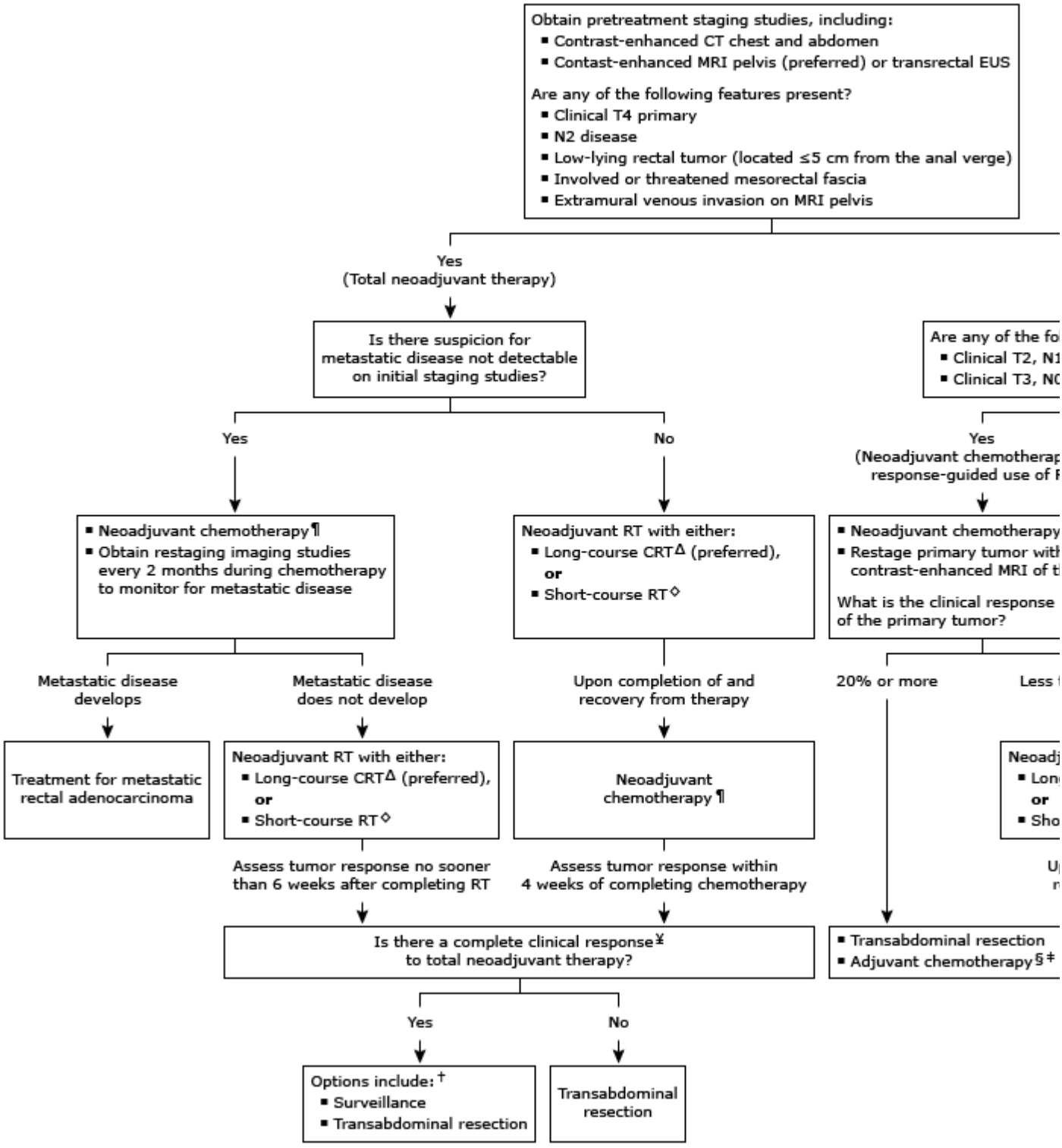
- If pelvic MRI has been done, we perform CT of the chest and abdomen
- If pelvic MRI has not been done, we perform CT of the chest, abdomen, and pelvis

Δ Patients who refuse surgery or are considered poor surgical candidates after chemoradiotherapy may be managed by full thickness local excision after chemoradiotherapy. Highly selected patients who appear to have a complete clinical response (scar only) may be considered for full thickness local excision or "watch and wait" but should understand that transabdominal surgery represents a standard approach in this setting. More extensive residual disease at the time of local excision should prompt reconsideration for transabdominal surgery.

◇ Transabdominal surgery may not be feasible for patients with more advanced tumors (eg, T2N0 or higher stage) if they have significant medical comorbidities, refuse transabdominal surgery, or have an estimated short life expectancy for whatever reason.

Graphic 131310 Version 1.0

Initial management of locally advanced rectal adenocarcinoma (cT3-4, Nx, M0 c



The initial management of locally advanced (clinical T3-4 or node-positive) pMMR/MSS rectal adenocarcinom
The diagnosis must be pathologically confirmed on biopsy, and imaging and clinical studies should show no
metastatic disease. Multidisciplinary treatment input is necessary from surgical oncology, radiation oncolog
oncology. For further details and evidence, refer to UpToDate content on the management of rectal adenoca

CAPOX: capecitabine and oxaliplatin; CT: computed tomography; CRT: chemoradiation; EUS: endoscopic ultr
fluouracil, leucovorin, and oxaliplatin; FOLFIRINOX: fluouracil, leucovorin, irinotecan, and oxaliplatin; FU: fluo
metastasis; MRI: magnetic resonance imaging; MSS: microsatellite stable; MRI: magnetic resonance imaging
proficient mismatch repair; RT: radiation therapy; T: tumor.

* Neoadjuvant chemotherapy plus response-guided use of RT allows most patients to omit RT and avoid its

¶ For total neoadjuvant therapy, chemotherapy is administered for 12 to 16 weeks with either FOLFOX, CAPO

Δ Long-course CRT is administered at 45 to 54 Gy in 25 to 30 fractions. Chemotherapy is concurrently admin
either capecitabine or infusional FU. For patients with any of the following high-risk features, we suggest lor
than short-course RT due to lower locoregional recurrence rates:

- Clinical T4a/b primary tumor
- Clinical N2 disease
- Extramural venous invasion
- Involved mesorectal fascia
- Enlarged lateral lymph nodes

◇ Short-course RT is administered at 25 Gy in 5 fractions.

§ For neoadjuvant chemotherapy followed by the response-guided use of CRT, we administer 6 cycles (3 mo
FOLFOX and 6 cycles (3 months) of adjuvant FOLFOX.

¥ A complete clinical response is scar only with no clinical evidence of residual tumor on digital rectal exam,
direct endoscopic evaluation.

‡ In most centers, all patients who undergo neoadjuvant CRT are offered adjuvant chemotherapy due to diff
nodal status in the treated surgical specimen.

† Surveillance is an option for patients with a complete clinical response.* Surveillance should be performed
excellence in the multidisciplinary management of rectal cancer. In observational studies, although surveilla
with higher rates of rectal preservation, local regrowth can occur in up to one-third of patients. Randomized
surveillance with resection are necessary to accurately assess long-term rates of local and distant failure and

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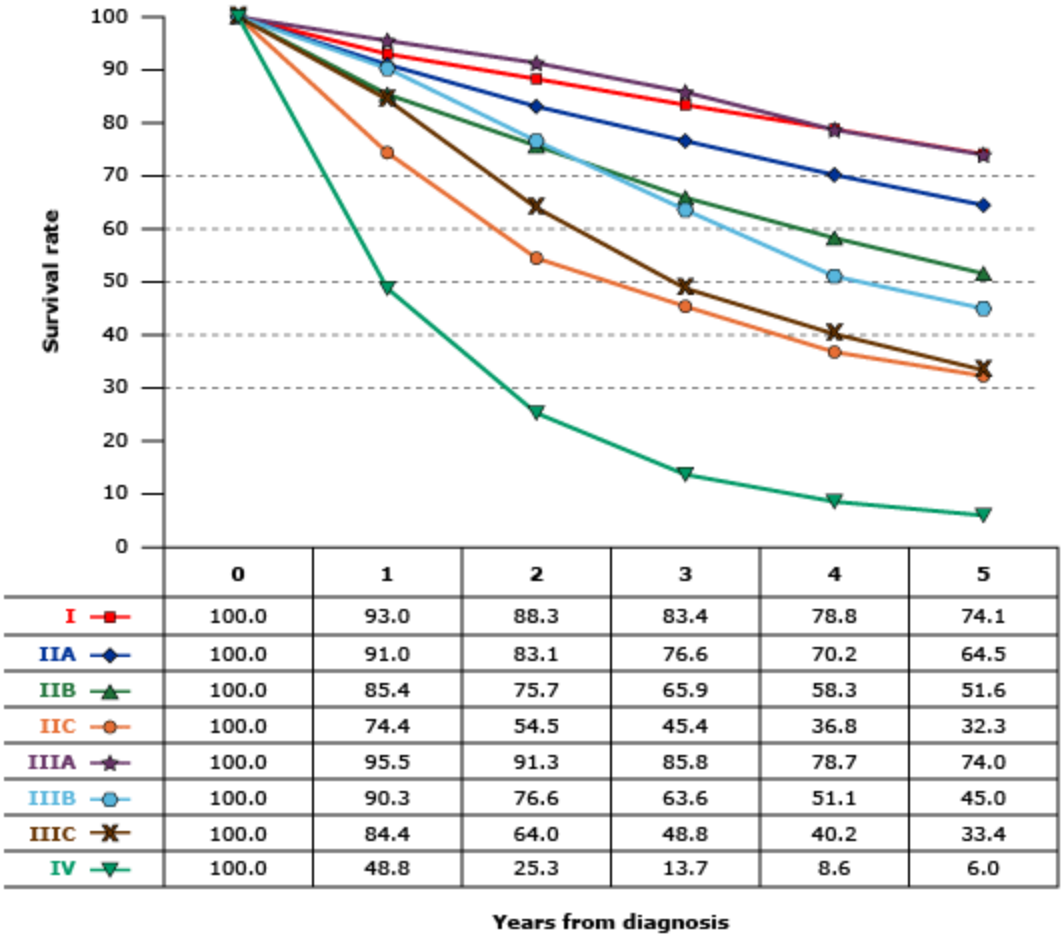
Graphic 131311 Version 3.0

Observed survival rates for 9,860 cases with adenocarcinoma of the rectum



	0	1	2	3	4	5
I	100.0	93.0	88.3	83.4	78.8	74.1
IIA	100.0	91.0	83.1	76.6	70.2	64.5
IIB	100.0	85.4	75.7	65.9	58.3	51.6
IIC	100.0	74.4	54.5	45.4	36.8	32.3
IIIA	100.0	95.5	91.3	85.8	78.7	74.0
IIIB	100.0	90.3	76.6	63.6	51.1	45.0
IIIC	100.0	84.4	64.0	48.8	40.2	33.4
IV	100.0	48.8	25.3	13.7	8.6	6.0

Data from the SEER 1973-2005 Public Use File diagnosed in years 1998-2000. Stage I includes 3470; Stage IIA, 2752; Stage IIB, 165; Stage IIC, 268; Stage IIIA, 595; Stage IIIB, 615; Stage IIIC, 761; and Stage IV, 1234.

Graphic 60598 Version 12.0

5- and 10-year disease-free survival (DFS) according to posttreatment pathologic (yp) stage and tumor regression grade (TRG) at resection after neoadjuvant chemoradiotherapy in the German Rectal Cancer Study Group (CAO/ARO/AIO-94) trial

yp category	5-year DFS (%)	10-year DFS (%)
ypT		
T0	86	90
T1	95	95
T2	81	78
T3	65	66
T4	42	40
ypN		
N0	85	84
N1	65	59
N2	18	28
TRG	**5-year DFS (%)**	**10-year DFS (%)**
4	86	90
2-3	75	74
0-1	63	63

Five-tier system for TRG. Complete regression = TRG 4; intermediate regression = TRG 2-3; poor or no regression = TRG 0-1.

Data from: Rödel C, Martus P, Papadoupolos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005; 23:8688 and Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. J Clin Oncol 2014; 32:1554.

Graphic 111443 Version 2.0

The revised Bethesda guidelines for testing colorectal tumors for microsatellite instability (MSI)

Tumors from individuals should be tested for MSI in the following situations:
1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors*, regardless of age.
3. Colorectal cancer with the MSI-H¶-like histologyΔ diagnosed in a patient who is less than 60 years of age◇.
4. Colorectal cancer diagnosed in a patient with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

HNPCC: hereditary nonpolyposis colorectal cancer; MSI-H: microsatellite instability-high.

* HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratocanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

¶ MSI-H in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.

Δ Presence of tumor infiltrating lymphocytes. Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

◇ There was no consensus among the Workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines.

Graphic 72965 Version 5.0

Approach to screening for Lynch syndrome in individuals with colorectal and/o

CRC: colorectal cancer; IHC: immunohistochemistry; MSI: microsatellite instability; MMR: mismatch repair.

* Germline genetic evaluation may be appropriate in individuals with any one of the following: 1) Family can Bethesda guidelines; 2) >2.5% chance of an MMR gene mutation by prediction models; 3) First-degree relati

¶ Normal IHC is only approximately 85% sensitive for Lynch syndrome. Consider MSI testing to confirm or ru

Δ The presence of MLH1 promoter methylation or BRAF V600E mutation is suggestive of sporadic CRC.

◇ Endometrial tumors are not eligible for BRAF V600E testing, so those with loss of MLH1/PMS2 on IHC shou

§ Lynch syndrome should be suspected in individuals with synchronous or metachronous CRC, CRC prior to CRC and endometrial, ovarian, stomach, small intestine, or renal pelvis/ureter), and in cases of familial cluste

¥ Other important considerations include ethnicity, the prevalence of particular genetic founder mutations i

‡ Refer to UpToDate content on genetic evaluation for Lynch syndrome.

† Individuals with bi-allelic somatic inactivation (by mutation and/or loss of heterozygosity) of MMR genes d

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Graphic 130015 Version 1.0

Summary of professional guidelines regarding posttreatment surveillance for resected colon and rectal cancer

Organization	History and physical examination	CEA testing	CT scanning	Endoscopic surveillance	C
ASCO[1] and CCO[2]	Every 3 to 6 months for 5 years.	Every 3 to 6 months for 5 years.	Abdomen and chest annually for 3 years; pelvis: rectal cancer only, annually for 3 to 5 years.	Colonoscopy at 1 year*; subsequent studies dictated by prior findings. If negative, every 5 years. Proctosigmoidoscopy every 6 months for 2 to 5 years if rectal cancer and no pelvic RT.	Posttre surveill guided risk of functio recomr for rese III colo cancer. Recom provide stage I to lack recomr
American Cancer Society[3]	Every 3 to 6 months for the first 2 years, then every 6 months to 5 years.	Every 3 to 6 months for the first 2 years, then every 6 months to 5 years if the patient is a potential candidate for further intervention.	Abdomen/pelvis and chest every 12 months for 5 years for stage III and high-risk stage I/II disease.	Colonoscopy in year 1; if advanced adenoma, repeat in 1 year; otherwise, repeat in 3 years. If no advanced adenoma in year 4, repeat every 5 years.	High-ri disease
NCCN[4]	Every 3 to 6 months for 2 years, then every 6 months for 3 years.	Every 3 to 6 months for 2 years for ≥T2 disease, then every 6 months for 3 years. For resected metastatic disease, every 3 to 6	Colon: Abdomen/pelvis and chest every 6 to 12 months for up to 5 years for those at high risk of recurrence¶. For rectal cancer, CT chest/abdomen	Colonoscopy at 1 yearΔ; subsequent studies dictated by prior findings. If no advanced adenoma, repeat at 3 years, then every 5 years; if advanced adenoma at 1 year, repeat at 1 year.	Recom to stag resecte cancer, II, III, o IV recta

		months for 2 years, then every 6 months for 3 to 5 years.	and pelvis every 3 to 6 months for 2 years, then every 6 to 12 months for up to 5 years for those at high risk of recurrence¶. For resected metastatic disease, CT abdomen/pelvis and chest every 3 to 6 months for 2 years, then every 6 to 12 months up to a total of 5 years.	Flexible sigmoidoscopy with EUS or MRI every 3 to 6 months for 2 years, then every 6 months to complete 5 years for patients with rectal cancer undergoing transanal excision only.	
ESMO colon cancer[5]	Every 3 to 6 months for 3 years, then every 6 to 12 months for 2 more years.	Every 3 to 6 months for 3 years, then every 6 to 12 months for 2 years.	Abdomen, chest, and pelvis every 6 to 12 months for 3 years, then every 12 months for 2 more years.	Colonoscopy at 1 year; every 3 to 5 years thereafter.	Guideli localize do not applica stage I More ir surveill years f metast Refer t on "Sur colorec resecti
ESMO rectal cancer[7]	Every 6 months for 2 years◇.	Every 6 months for the first 3 years.	A minimum of 2 CT scans of the chest, abdomen, and pelvis in the first 3 years.	Colonoscopy every 5 years up to age 75.	High-ri circum resecti positive more p surveill recurre

					More ir surveill years f metast Refer t on "Sur colorec resecti
New Zealand[8]	Clinical assessment§ stratified according to risk of recurrence: ▪ *High-risk cancer (stage IIB, III):* Every 6 to 12 months for 3 years, then annually for 2 years. ▪ *Lower risk (stage I, IIA), or with comorbidities restricting future surgery:* Annual review for 5 years or when symptoms occur.	*For high-risk cancer (stage IIB, III):* Every 6 to 12 months for 3 years, then annually for 2 years. *For lower risk (stage I, IIA), or with comorbidities restricting future surgery:* Annually for 5 years.	All individuals with stages I to III colorectal cancer should have liver imaging between years 1 and 3.	Colonoscopy at 1 year¥; colonoscopy every 6 to 12 months for 3 years for high-risk patients (stages IIB, III), then annually for at least 5 years. For low-risk patients, colonoscopy every 3 to 5 years. For rectal cancer, proctoscopy or sigmoidoscopy at 3, 6, 12, and 24 months postsurgery; colonoscopy at 3- to 5-year intervals thereafter.	Recom stages colorec
US Multi-Society Task Force on Colorectal Cancer[9]				Colonoscopy 1 year after surgery (or 1 year after the clearing perioperative colonoscopy). The interval to the next colonoscopy should be 3 years and then 5 years. If neoplastic polyps are	

				detected, the intervals between colonoscopies should be shorter and in accordance with published guidelines for polyp surveillance intervals[10]. These intervals do not apply to patients with Lynch syndrome. For rectal cancer, flexible sigmoidoscopy or EUS every 3 to 6 months for the first 2 to 3 years after surgery for patients at high risk for local recurrence. Refer to UpToDate topic on "Surveillance after colorectal cancer resection."	
British Columbia Medical Association[11]	Every 3 to 6 months for 2 years, then every 6 months for 3 years.	Every 3 months for 3 years, then every 6 months for 2 years.	Liver ultrasound or CT scans (preferred) every 6 months for 3 years, then annually for 2 years. Annual chest CT for 3 years.	Colonoscopy at 1 year; if normal, repeat 3 years later and, if normal, every 5 years thereafter.	These g resecte colon a Patient comorb advanc 5-year are not surveill
American Society of Colon and Rectal Surgeons[12]	Every 3 to 12 months for 2 years, then every 6 to 12 months for 3 years.	Every 3 to 12 months for 2 years, then every 6 to 12 months for 3 years.	Twice in 5 years or up to annually for 5 years.	Colonoscopy at 1 year (or 1 to 6 months after surgery if inadequate colonoscopy preoperatively, and depending on findings, repeat at 3 years, then every 5 years or more	Recom to high (eg, rec posttra colorec endosc only, or based t stage I disease

				frequently as indicated). Proctoscopy ±endoscopic ultrasound every 6 to 12 months after rectal cancer resection with anastomosis (no RT), or every 6 months following local excision for 3 to 5 years.	curativ UpToD "Survei colorec resecti

CEA: carcinoembryonic antigen; CT: computed tomography; ASCO: American Society of Clinical Oncology; CCO: Cancer Care Ontario; RT: radiation therapy; NCCN: National Comprehensive Cancer Network; EUS: endoscopic ultrasound; MRI: magnetic resonance imaging; ESMO: European Society for Medical Oncology.

* Except if no preoperative colonoscopy because of obstructing lesion; do as soon as possible after completion of adjuvant chemotherapy rather than waiting until 1 year.

¶ Features suggesting a high risk of recurrence: poorly differentiated histology, lymphatic or venous invasion.

Δ Except if no preoperative colonoscopy because of obstructing lesion; recommend at 3 to 6 months rather than waiting until 1 year.

◇ Minimum provisional recommendation.

§ Clinical assessment for patients with colon cancer includes physical examination, CEA, chest/abdominal and pelvic CT scans, colonoscopy, and liver ultrasound. Clinical assessment for rectal cancer patients includes physical examination, CEA, chest/abdominal and pelvic CT scans, colonoscopy, and proctoscopy or sigmoidoscopy.

¥ If no complete colonoscopy before surgery, perform colonoscopy within 6 months.

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Graphic 91618 Version 21.0

American Society of Clinical Oncology (ASCO) framework of resource stratification[1,2]

Setting	Description
Basic	Core resources or fundamental services are absolutely necessary for any public health/primary health care system to function; basic-level services typically are applied in a single clinical interaction.
Limited	Second-tier resources or services are intended to produce major improvements in outcome, such as incidence and cost effectiveness, and are attainable with limited financial means and modest infrastructure; limited-level services may involve single or multiple interactions. Universal public health interventions are feasible for a greater percentage of the population than the primary target group.
Enhanced	Third-tier resources or services are optional but important; enhanced-level resources should produce further improvements in outcome and increase the number and quality of options and individual choice (perhaps ability to track patients and links to registries).
Maximal*	May use high-resource-setting guidelines.
	High-level/state-of-the-art resources or services may be used or are available in some high-resource countries and/or may be recommended by high-resource-setting guidelines that do not adapt to resource constraints, but that nonetheless should be considered a lower priority than those resources or services listed in the other categories on the basis of extreme cost and/or impracticality for broad use in a resource-limited environment.

* To be useful, maximal-level resources typically depend on the existence and functionality of all lower-level resources.

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Graphic 120538 Version 1.0

Contributor Disclosures

Richard M Goldberg, MD Equity Ownership/Stock Options: Advanced Chemotec Inc [Pancreatic cancer]; Compass Therapeutics [Biliary tract and colorectal cancer]. Consultant/Advisory Boards: AbbVie [GI cancers]; Advanced Chemotherapy Technologies [GI cancer]; AstraZeneca [GI cancer]; Bayer [GI cancer]; Compass Therapeutics [GI cancer]; Eisai [GI cancer]; G1 Therapeutics [GI cancer]; GSK [Colorectal cancer]; Innovative Cellular Therapeutics [Colorectal cancer]; Inspirna [Colorectal cancer]; Merck [GI cancer]; Modulation Therapeutics [Lymphoma]; Novartis [GI cancer]; Sorrento Therapeutics [GI cancer]; Taiho [GI cancer]. Other Financial Interest: Taiho [Expert testimony GI cancer]. All of the relevant financial relationships listed have been mitigated. **Christopher G Willett, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Martin Weiser, MD** Consultant/Advisory Boards: PrecisCa [Gastrointestinal surgical oncology]. All of the relevant financial relationships listed have been mitigated. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Wenliang Chen, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose.

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