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ONCOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Oncology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in oncology. Each manual reviews a topic essential to the current practice of oncology.

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Management of Locally Advanced Rectal Adenocarcinoma

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INTRODUCTION

Colorectal cancers are among the most common cancers worldwide, and there is a high mortality rate for advanced-stage disease. Approximately 132,000 new cases of colorectal cancer will be diagnosed in the United States in 2015, and approximately 40,000 of these cases will be primary rectal cancers.[1] The incidence and mortality rates have been steadily declining over the past two decades, largely through advances in screening and improvements in treatment.[2,3] However, rectal cancer remains a significant cause of morbidity and mortality in the United States and worldwide.

The worldwide incidence rates of colorectal cancers are variable, with the highest rates of disease in North America, Europe, and Australia, and the lowest rates in Africa and parts of Asia.[4] Within a population, risk factors for the development of disease include lower socioeconomic status. This has been attributed to decreased physical activity, obesity, smoking, decreased dietary intake of fruits and vegetables, as well as decreased adherence to screening guidelines in persons of lower socioeconomic status.[5–8]

The majority of colorectal cancers occur sporadically and incidence increases with age, especially after the fourth decade of life. The incidence in the older population is decreasing while incidence rates in patients under 50 years of age have been increasing, but most new cases are still diagnosed in older patients.[9] Though relatively rare, hereditary cancer syndromes dramatically increase the risk of colorectal cancers in affected individuals. The most common inherited cause of colorectal cancer is the autosomal dominant hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndrome. Less common inherited colorectal cancer syndromes include familial adenomatous polyposis and its variants (Gardner and Turcot syndromes) and *MUTYH*-associated polyposis. A unique set of screening guidelines for both colorectal and noncolorectal cancers are warranted for patients identified with these syndromes.[10–12]

Inflammation has long been thought to play a role in colorectal carcinogenesis. Patients with chronic bowel inflammation from ulcerative colitis

and Crohn's disease have a higher risk of cancer development, as do patients with a history of radiation. These patients should also be screened more frequently than the general population.[13–15] Because they decrease inflammation, aspirin and nonsteroidal anti-inflammatory drugs have long been evaluated as a protective factor against colorectal cancer development. A significant number of observational and randomized trials have shown a reduction in both the incidence of colorectal adenomas and colorectal cancers.[16–18] However, because of their side effects these drugs are not yet recommended for the general population, although they are suggested for select high-risk patients, such as those with Lynch syndrome.[19]

This review focuses on the diagnosis, management, and surveillance of locally advanced rectal cancer. Although often grouped with colon cancers, rectal cancers differ from colon cancers in terms of diagnosis and management. Though early-stage disease can be cured with local excision, most cancers are more advanced at presentation in terms of depth of tumor invasion and adherence to local pelvic structures. Because of surgical challenges regarding tumor location, rectal cancers have historically been at higher risk for local recurrence than colon cancers. In addition, managing rectal tumors requires particular attention to quality of life issues, such as anal sphincter preservation and the bowel toxicity and sexual dysfunction that can arise from radiation. For the best outcome, these cancers require a multidisciplinary approach including chemotherapy, radiation, and surgery.

CLINICAL EVALUATION AND STAGING

CASE PATIENT

A 64-year-old woman without significant past medical or family history presents to her primary care physician after noting red blood in the toilet and pain with defecation for the last 3 weeks. She reports no abdominal or pelvic pain. Physical exam is notable for no palpable inguinal lymph nodes and no external anal lesions or hemorrhoids. Rectal exam reveals a palpable mass at 9 o'clock and stool guaiac test is positive. Laboratory evaluation is notable for hemoglobin of 10 mg/dL and a mean corpuscular volume of 75 fL. Rigid sigmoidoscopy reveals a nonobstructing ulcerated mass 4 cm from the anal verge. Biopsy is performed and findings are consistent with grade II adenocarcinoma.

- **How is rectal cancer defined?**

On average, the human rectum is 12 cm long. The sigmoid colon becomes the rectum at the fusion of the sigmoid colon tenia. The distal end of the rectum transitions to an ampulla with a circumference of 35 cm rather than the 15 cm of the rest of the rectum. The end of the rectum is considered to be the puborectalis ring or the dentate line, where the transitional mucosa of the anus begins.[20] The majority of the rectum (10 cm) lies outside the peritoneum, demarcated by the peritoneal reflection.

The significant majority of rectal cancers are carcinomas, which are primarily comprised of adenocarcinomas. Though squamous cell carcinomas, adenosquamous carcinomas, and undifferentiated carcinomas have been described, they are relatively unusual. Rarely, other tumors of the rectum, including neuroendocrine tumors, hamartomas, and lymphomas, have been described.[21] After establishing the histology of the tumor, the grade of differentiation is described. This is based on the degree of gland formation present, with well and moderately differentiated tumors exhibiting defined glandular structures and poorly differentiated tumors not exhibiting defined structures. The tumor

grade has been evaluated and is generally found to have prognostic significance.[22]

- **What pretreatment staging evaluation is recommended?**

Even though screening for colorectal cancer is increasingly utilized, the majority of patients are still diagnosed after presenting due to symptoms. Careful medical history should include information about constitutional symptoms like weight loss and fatigue as well as local issues such as pain or changes in urinary and bowel habits. Particular attention should be paid to symptoms of potential obstruction, which might warrant urgent surgical intervention. Physical exam should include rectal exam and stool guaiac assessment. Basic blood testing should be performed to evaluate for significant anemia and abnormal liver function tests and generally includes a complete blood count, chemistry panel, liver function tests, and measurement of carcinoembryonic antigen (CEA). Though CEA is not indicated for screening or diagnosis of colorectal cancer, it does have value in prognosis (a level greater than 5 ng/mL is associated with poorer prognosis) and surveillance after surgical resection.[23]

Appropriate staging workup is particularly important in rectal cancers as it helps define the sequence of treatments, including which surgical approach is appropriate. Full colonoscopy is indicated to evaluate for synchronous cancers prior to further management. Synchronous second primary cancers are found in up to 5% of patients.[24] Rigid sigmoidoscopy is used to determine the distance between the distal tumor margin and the top of the anorectal ring as well as the orientation of the tumor.

Computed tomography (CT) scans of the thorax, abdomen, and pelvis are routinely performed to evaluate for metastatic disease.[25] In general, positron emission tomography (PET) scans are not routinely indicated in the staging of rectal cancer.[26] Similarly, liver magnetic resonance imaging (MRI) can be used if there are equivocal results on CT scan.

Despite their use for distant disease, CT scans are not optimal for local evaluation of tumor depth, nodal invasion, and circumferential resection margin (CRM). The CRM is an important prognostic factor in rectal cancer as patients with a threatened CRM (tumor within 1 to 2 mm of the mesorectal fascia) are more likely to have local recurrence and should be considered for neoadjuvant chemoradiation, regardless of stage.[27]

For local disease evaluation and TNM staging (**Table**), transrectal ultrasound (TRUS) and rectal MRI are preferred over CT scan. TRUS helps distinguish cancers that penetrate the muscularis propria from those that involve only the mucosa or submucosa.[28] It has been shown to be overall more accurate with regards to T staging, with sensitivity and specificity ranging from 88% to 98% for all T stages.[29] However, TRUS has more interoperator variability.[30,31] With regards to N staging accuracy, TRUS is similar to both CT and MRI.[32]

Rectal MRI can be performed with or without an endorectal coil. Some studies suggest that MRI has higher sensitivity for nodal staging than TRUS because MRI uses more than just size to determine if lymph nodes are involved (border irregularity, mixed signal).[33] For predicting T stage, a meta-analysis showed that MRI has sensitivity and specificity of 87% and 75%, respectively.[34] In a large meta-analysis of 90 studies comparing the 2 modalities, it was found that TRUS has higher specificity for T1 and T2 disease as well as higher sensitivity for T3 disease.[32] However, another meta-analysis concluded that MRI was the best

Table. TNM Staging for Locally Advanced Adenocarcinoma

Primary Tumor (T)		
T1	Tumor invades submucosa	
T2	Tumor invades muscularis propria	
T3	Tumor invades through muscularis propria into perirectal tissue	
T4a	Tumor penetrates visceral peritoneum	
T4b	Tumor directly invades or is adherent to other organs or structures	
Regional lymph node (N)		
N0	No regional lymph node metastasis	
N1	Metastasis in 1–3 regional lymph nodes	
	N1a	Metastasis in 1 regional lymph node
	N1b	Metastasis in 2–3 regional lymph nodes
	N1c	Tumor deposit(s) in the subserosa, mesentery, or perirectal tissue without regional node metastasis
N2	Metastasis in 4 or more regional lymph nodes	
	N2a	Metastasis in 4–6 regional lymph nodes
	N2b	Metastasis in ≥7 regional lymph nodes
Stage	**T**	**N**
I	T1	N0
	T2	N0
IIA	T3	N0
IIB	T4a	N0
IIC	T4b	N0
IIIA	T1-T2	N1/N1c
	T1	N2a
IIIB	T3-T4a	N1/N1c
	T2-T3	N2a
	T1-T2	N2b
IIIC	T4a	N2a
	T3-T4a	N2b
	T4b	N1-N2
	T4b	N1-N2

Adapted with permission from Edge SB, Byrd DR, Compton CC, et al, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.

modality for evaluating CRM.[35] At present, either modality is acceptable for routine use.

MANAGEMENT

CASE PATIENT CONTINUED

The patient undergoes colonoscopy, which shows no evidence of synchronous cancers. CT scans of the thorax, abdomen, and pelvis as well as PET scan show no evidence of metastatic disease (**Figure 1**). TRUS confirms T3N1 disease (**Figure 2**).

- **What is the current approach to treatment of locally advanced rectal cancer?**

NEOADJUVANT CHEMORADIOTHERAPY

The standard treatment for locally advanced rectal cancer is neoadjuvant chemoradiation with an infusional 5-fluorouracil backbone followed by surgical resection and adjuvant chemotherapy. Historically, the standard of care was adjuvant chemoradiotherapy until a randomized trial from Germany that assigned patients with T3/T4 or node-positive disease to neoadjuvant 5-fluorouracil with radiation versus adjuvant chemoradiotherapy showed improvement in the rate of sphincter-sparing surgery, local relapse, and toxicity.[36] There was no difference in overall survival, however. This trial established a new standard of care that has subsequently been used throughout the United States and Europe. A similar trial, National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03, randomly assigned T3/T4 or node-positive patients to preoperative 5-fluorouracil with radiation versus adjuvant chemoradiotherapy. Though this trial closed early due to poor accrual, a statistically significant improvement in disease-free survival was seen in the neoadjuvant group and a trend towards improvement in overall survival

was observed as well.[37] Interestingly, there was no difference in locoregional control between the groups. A Korean phase 3 trial randomly assigned the same population of patients (T3/T4 or node-positive) to preoperative capecitabine with radiation versus postoperative chemoradiation.[38] However, all patients received an additional 4 cycles of postoperative capecitabine. There was no benefit with regards to survival or rate of local recurrence, but the preoperative group patients with low lying tumors did have an increase in sphincter-sparing operations. In this trial, preoperative chemoradiotherapy did not appear to increase the perioperative complication rate from surgical resection.

The large European Organisation for Research and Treatment of Cancer (EORTC) 22921 study evaluated both the role of preoperative chemotherapy with radiation as well as the role for adjuvant treatment. Patients with T3 or T4 disease were randomly assigned to preoperative radiation alone versus 5-fluorouracil with radiation and then to 4 cycles of postoperative 5-fluorouracil, using a 2 x 2 factorial design.[39,40] Improvement in disease-free survival was found if chemotherapy was given at some point during treatment, but there was no improvement in overall survival. In another study of patients with unresectable T4 or recurrent tumors, the combination of chemotherapy and radiation together was shown to improve overall survival compared to radiation alone.[41] However, a meta-analysis of several studies comparing radiation alone to chemoradiotherapy demonstrated improvement in local control but no improvement in overall survival.[42] Though no sustained benefit in overall survival has been established, neoadjuvant chemoradiotherapy remains the standard of care for T3, T4, and node-positive disease.

In the past, chemotherapy options were limited and infusional 5-fluorouracil has been the standard of care because of its tolerability. Bolus 5-fluorouracil with leucovorin has been evaluated,[43] but is not routinely utilized given the additional toxicities associated with this regimen. Data from the adjuvant setting suggests that infusional 5-fluorouracil might be more effective with regards to local relapse and overall survival compared to the bolus regimen.[44] Capecitabine has been shown to be noninferior to infusional 5-fluorouracil in this setting.[45,46] A retrospective trial has even shown improvement in pathologic complete response rate with capecitabine.[45,47] This has led to capecitabine being used interchangeably with infusional 5-fluorouracil. However, more toxicity with capecitabine has been described as compared to 5-fluorouracil, including more hand/foot skin reaction, fatigue, and radiation dermatitis.[48]

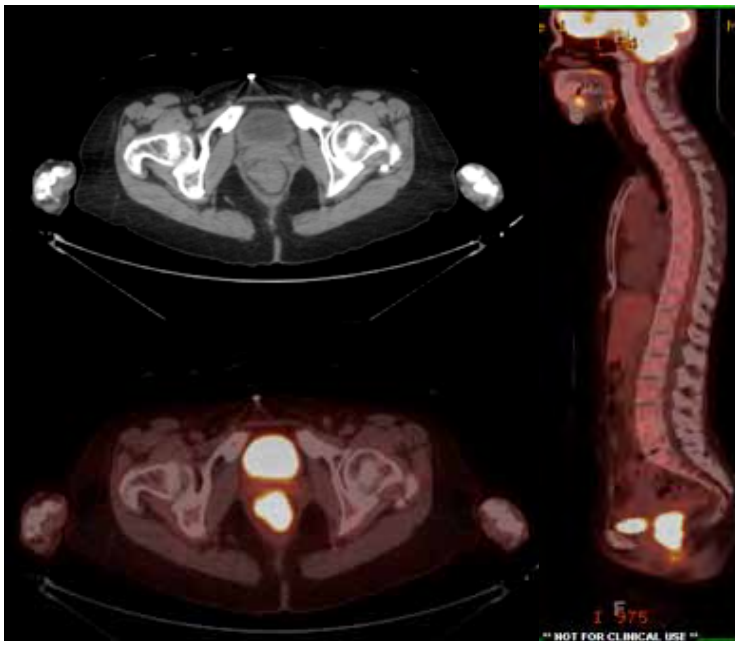

Figure 1. Computed tomography and positron emission tomography scans showing rectal lesion.

In an effort to improve local control, response rate, and overall survival, novel agents have been added to a 5-fluorouracil backbone. Because of its role in potentiating 5-fluorouracil in the metastatic

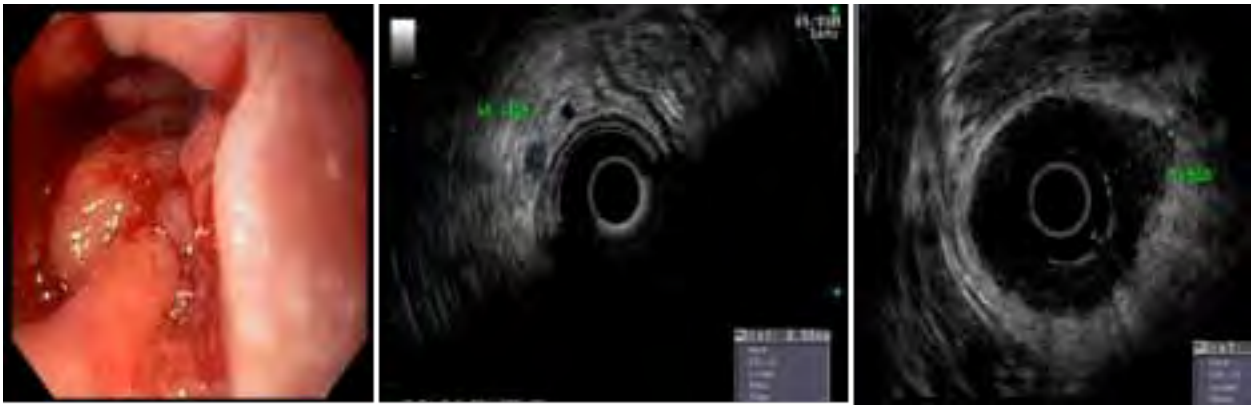

Figure 2. Endoscopy and transrectal ultrasound images of rectal lesion.

setting, leucovorin has been added to the chemoradiotherapy regimen.[37] As there are no prospective, randomized trials, the benefit of adding leucovorin is unclear and it is not recommended as part of routine practice. Similarly, the addition of irinotecan in a phase 2 study did not show any significant benefit.[49] Phase 2 trials have shown tolerability of bevacizumab, cetuximab, and panitumumab added to neoadjuvant chemoradiotherapy in locally advanced rectal cancer, but these results have not been validated in phase 3 trials and these agents are not part of current practice.[50–53] The addition of oxaliplatin has been evaluated in several trials and has generally shown increased toxicity but no significant benefit.[46,54–56] However, the German AIO randomly assigned patients with T3, T4, or node-positive rectal cancer to 5-fluorouracil with radiation with or without the addition of oxaliplatin, both as part of neoadjuvant treatment and as part of the adjuvant chemotherapy-alone regimen.[57] The patients who received oxaliplatin had improvement in disease-free survival though the data are not yet mature regarding overall survival.[58]

In addition to optimal selection of a chemotherapy backbone, another effort to tailor treatment regimens to specific patients has been underway. Pelvic radiation has long been part of the standard of care of locally advanced rectal cancer to decrease the risk of local recurrence. However, given the high rate of distant metastatic disease after treatment as well as toxicities from radiation, there has been interest in the earlier introduction of more intense systemic neoadjuvant chemotherapy without radiation in selected patients. In a pilot study, patients with T3 node-negative or node-positive rectal cancer were treated with 6 cycles of FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin). Adjuvant radiation was planned if there was stable or progressive disease seen during surgery, but all the patients had a response and did not require radiation.[59] They had similar outcomes to historical controls. A multicenter phase 3 study is underway to further evaluate these promising results. However, this approach cannot yet be recommended in routine practice.[60]

The type of radiation delivered has been studied in various trials. The established standard is to treat patients to 50.4 centigray (cGy) using 3-dimensional conformal radiation therapy. A boost to the tumor bed brings the radiation dose to 54 cGy. Short-course radiotherapy (5 days of 5 cGy) has been evaluated in T3 node-negative and node-positive rectal cancer. Patients were randomly assigned to standard chemoradiotherapy versus

short-course radiation followed by surgery and adjuvant chemotherapy. There was no significant difference between groups, though there was a trend towards increased local recurrence in the short-course radiotherapy group. In a similar study of T3 or T4 lesions, no significant difference was found between groups.[61] In clinical practice, long-course radiotherapy remains the standard treatment.

Despite many trials to delineate an improved outcome with decreased toxicity, for now the standard of care for T3/T4 or node-positive rectal cancers remains chemoradiotherapy with an infusional 5-fluorouracil backbone.

CASE CONTINUED

The patient receives neoadjuvant chemoradiation with infusional 5-fluorouracil and 54 cGy but is hesitant about proceeding with surgery because of the risk of complications and the possibility of a permanent colostomy.

SURGICAL RESECTION

The types of surgical resection for rectal cancer include the low anterior resection and the abdominoperineal resection. The former is sphincter sparing and is generally used for cancers in the middle to upper third of the rectum. Abdominoperineal resection are generally reserved for lower lying cancers and those in whom negative margins cannot be achieved with a sphincter-sparing procedure. In either case, a total mesorectal excision (excising a larger plane past the mesorectum) has been associated with significantly improved outcomes and is the preferred approach.[62]

In general, it is advisable to wait between 4 and 6 weeks after the completion of chemoradiation to proceed with surgery to allow for maximum shrinkage of the tumor. Studies have been performed to evaluate longer and shorter wait times, but the optimal interval between completion of neoadjuvant conventional fractionated radiation therapy and surgery in rectal adenocarcinoma remains unknown.[63]

CASE CONTINUED

The patient agrees to undergo surgery and has a low anterior resection, which she tolerates well. Pathology shows that her disease is down staged from a T3N1 to T2N1, with 1 lymph node positive out of 18 nodes examined. Tumor regression grade (TRG) is 1, indicating a moderate response.

ADJUVANT TREATMENT

TRG describes the degree of tumor regression after treatment. A 3-point TRG has been shown to be the most reproducible and to have prognostic value.[64] At present, the post-surgical management strategy is not altered by factors like TRG.

In the United States, adjuvant chemotherapy is the standard of care for all patients with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy.[25] This standard has been extrapolated from studies showing the benefit of adjuvant therapy that were performed prior to the era of regular use of neoadjuvant therapy. However, trials have not definitively shown benefit of adjuvant therapy in patients who received neoadjuvant chemotherapy.

Prospective randomized studies have evaluated the role for adjuvant chemotherapy in patients who received neoadjuvant chemotherapy but have had conflicting results regarding which patients are likely to benefit. In the EORTC 22921 trial, patients who had received either radiation alone or neoadjuvant chemoradiation were randomly assigned to postoperative 5-fluorouracil with leucovorin or no adjuvant therapy.[39] The initial results showed an improvement in local control with the addition of chemotherapy

given before or after surgery. However, a recent update of EORTC 22921 suggests that there is no significant disease-free or overall survival benefit of adjuvant chemotherapy in patients who received preoperative radiotherapy or chemoradiotherapy.[40] This finding has not yet changed clinical practice, likely because there was a significant lack of adherence to postoperative therapy; over half of the patients in the adjuvant chemotherapy groups did not receive the intended 4 cycles of treatment and 25% did not receive any adjuvant therapy.

Another prospective study from Italy randomly assigned patients who had received preoperative chemoradiotherapy to adjuvant bolus 5-fluorouracil and leucovorin versus observation and showed no advantage in disease-free or overall survival.[65] Similarly, the Dutch PROCTOR/SCRIPT trials randomly assigned patients with stage II and III rectal cancers to postoperative 5-fluorouracil and leucovorin or capecitabine versus observation after having received neoadjuvant chemoradiotherapy. There was no difference in overall survival between groups.[66] The UK Chronicle trial randomly assigned patients who had received neoadjuvant fluoropyrimidine therapy to adjuvant capecitabine with oxaliplatin versus observation. Though the trial was closed early secondary to poor accrual, there was a suggestion of improvement in disease-free survival for the treatment arm, but this was not statistically significant. There was no difference in overall survival.

Meta-analyses of the individual patients in these studies have concluded that fluoropyrimidine-based adjuvant therapy has not yet been shown to improve disease-free or overall survival.[67,68] However, this treatment remains the standard of care and ongoing trials might definitively answer this question.[66,69,70] At present, physicians should discuss the risks and benefits of adjuvant treatment with individual patients.

The choice of adjuvant regimen has also been evaluated. The phase 2 ADORE study randomly assigned rectal cancer patients with pathologic T3/T4 or node-positive disease to FOLFOX versus 5-fluorouracil and leucovorin and showed a benefit of FOLFOX with regards to disease-free survival.[71] The overall survival data is still premature, but there is a suggestion of overall survival benefit with FOLFOX as well. Another study, the German AIO trial, randomly assigned patients with T3/T4 or node-positive disease at diagnosis to oxaliplatin as part of both neoadjuvant and adjuvant treatment, regardless of pathologic response. They found a disease-free survival benefit compared to 5-fluorouracil alone but no improvement in overall survival.[39,58]

SURVEILLANCE AND LONG-TERM EFFECTS

CASE CONTINUED

The patient receives adjuvant chemotherapy with FOLFOX for a total of 8 cycles. Though she has few symptoms during treatment, she develops numbness and tingling in her feet bilaterally after completion of chemotherapy.

- **What are the current recommendations regarding surveillance following treatment for locally advanced rectal cancer?**

In current standard practice, after the completion of treatment for locally advanced rectal cancer, patients should have a clinical encounter, including a careful history and physical exam, with their physician every 3 to 6 months for the first 3 years and every 6 months during years 4 and 5. A serum CEA level should be measured at each follow-up visit for the first 3 years. In addition, annual CT scans of the chest, abdomen, and pelvis for at

least 3 years should be obtained.[72] In addition to the perioperative full colonoscopy to detect synchronous lesions, a repeat colonoscopy should be performed 1 year later to exclude new lesions. If this is normal, subsequent studies should be performed at intervals of 3 to 5 years depending on the results of the prior colonoscopy.[25,73,74]

The purpose of intensive surveillance is to identify asymptomatic recurrence in patients who could then receive curative intent surgery. The recurrence risk is highest within 2 to 3 years after surgery and drops significantly after 5 years.[75] The components of surveillance have been individually evaluated. History and physical examination have not been shown to contribute to early detection.[76,77] Serial CEA measurements and routine CT were compared to minimal follow up in a large UK study and found to detect recurrent disease earlier and allow patients to go for curative surgery more often. However, there was no statistically significant difference in survival.[78] The role of CEA monitoring is controversial. Though it is not sensitive or specific as a screening test, it can be correlated to disease burden and has prognostic value. CEA has been shown to detect disease earlier than other modalities, although it is questionable if that results in improved overall survival.[79] A newly elevated CEA should be confirmed by retesting, as false positives are common.[80] Though caution should be used with CEA testing, it is still recommended as part of routine practice.

Other tumor markers such as cancer antigen (CA) 19-9 and DR-70 have been evaluated but are not recommended for routine use in surveillance of colorectal cancers.[81,82] Liver function tests and complete blood counts are also not routinely recommended as they are unlikely to help predict recurrence. Routine CT scans have been found to detect recurrent disease, especially in the liver, earlier than CT evaluation once symptoms arise and CT scan is therefore recommended annually.[83] Several meta-analyses have shown a small overall survival benefit from intensive surveillance but have been limited by variation in the type of follow up utilized as well as the inclusion of stage I patients who likely do not need intensive follow up.[84–86] Regular surveillance of patients with locally advanced rectal cancer after curative therapy is warranted.

In addition to surveillance for recurrent disease, patients should engage in a healthy lifestyle with regards to diet and exercise. Though this recommendation is based on observational studies, it has been adopted in the American Society of Clinical Oncology guidelines as part of secondary prevention of disease.[73] Patients should be monitored for long-term toxicities of treatment. Quality of life often returns to normal about a year after treatment,[87] but psychosocial issues stemming from treatment should be considered. Patients with a permanent ostomy can have issues with social relationships, sexual function, and depression.[88,89] Medical problems after radiation and chemotherapy can include bowel and bladder dysfunction and neuropathy.[90,91]

Though genetic syndromes have been established, the majority of colorectal cancers are sporadic. Careful family history should be updated regularly in order to evaluate for disorders like Lynch syndrome and familial adenomatous polyposis. Testing for microsatellite instability can be performed in at-risk patients, usually those younger than age 50 at diagnosis or who meet the Bethesda criteria, though some centers endorse universal testing.[92]

CONCLUSION

The management of locally advanced rectal cancer continues to evolve. Careful staging helps

define those patients who will benefit from neoadjuvant therapy. This might continue to consist of chemoradiotherapy with a 5-fluorouracil backbone or may progress to exclude radiation for selected patients in the future based on the results of currently accruing studies. Surgical resection is the mainstay of therapy and should include attention to the CRM. Adjuvant therapy remains the established standard, although its utility is being evaluated in several ongoing trials. Finally, intense surveillance is appropriate for rectal cancer survivors, and particular attention should be paid to the unique set of psychosocial issues that arise from treatment.

BOARD REVIEW QUESTIONS

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
2. Siegel R, Ward E, Brawley O, Jemal A. The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212–36.
3. Jemal A, Simard EP, Dorell C, et al. Annual report to the nation on the status of cancer, 1975–2009, featuring the burden and trends in human papillomavirus (HPV)–associated cancers and HPV vaccination coverage levels. J Natl Cancer Inst 20136;105:175–201.
4. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
5. Doubeni CA, Laiyemo AO, Major JM, et al. Socioeconomic status and the risk of colorectal cancer. Cancer 2012;118:3636–44.
6. Klabunde CN, Cronin KA, Breen N, et al. Trends in colorectal cancer test use among vulnerable populations in the United States. Cancer Epidemiol Biomarkers Prev 2011;20:1611–21.
7. Cokkinides VE, Chao A, Smith RA, Vernon SW, Thun MJ. Correlates of underutilization of colorectal cancer screening among US adults, age 50 years and older. Prev Med 2003;36:85–91.
8. Koushik A, Hunter DJ, Spiegelman D, et al. Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. J Natl Cancer Inst 2007;99:1471–83.
9. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.
10. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 2006;296:1507–17.
11. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol 2006;101:385–98.
12. Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS. Clinical implications of the colorectal cancer risk associated with MUTYH mutation. J Clin Oncol 2009;27:3975–80.
13. Eaden J, Abrams K, Mayberry J. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526–35.
14. Gillen C, Andrews H, Prior P, Allan R. Crohn's disease and colorectal cancer. Gut 1994;35:651–5.
15. Nottage K, McFarlane J, Krasin MJ, et al. Secondary colorectal carcinoma after childhood cancer. J Clin Oncol 2012;30:2552–8.
16. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 2010;376:1741–50.
17. Rodríguez LAG, Huerta-Alvarez C. Reduced risk of colorectal cancer among long-term users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs. Epidemiology 2001;12:88–93.
18. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2012;378:2081–7.
19. Cuzick J, Otto F, Baron JA, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol 2009;10:501–7.
20. Edge SB, Byrd DR, Compton CC, et al, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
21. Kang H, O'Connell JB, Leonardi MJ, et al. Rare tumors of the colon and rectum: a national review. Int J Colorectal Dis 2007;22:183–9.
22. Compton CC, Fielding LP, Burgart LJ, et al. Prognostic factors in colorectal cancer. Arch Pathol Lab Med 2000;124:979–94.
23. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol 2006;24:5313–27.
24. Mulder SA, Kranse R, Damhuis RA, et al. Prevalence and prognosis of synchronous colorectal cancer: a Dutch population-based study. Cancer Epidemiol 2011;35:442–7.

25. National Comprehensive Cancer Network. NCCN Guidelines: Colon/Rectal Cancer. 2015.
26. Furukawa H, Ikuma H, Seki A, et al. Positron emission tomography scanning is not superior to whole body multidetector helical computed tomography in the preoperative staging of colorectal cancer. Gut 2006;55:1007–11.
27. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol 2008;26:303–12.
28. Beynon J, Foy D, Roe AM, Temple L, Mortensen N. Endoluminal ultrasound in the assessment of local invasion in rectal cancer. Br J Surg 1986;73:474–7.
29. Puli SR, Bechtold ML, Reddy JB, et al. How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review. Ann Surg Oncol 2009;16:254–65.
30. Herzog U, Von Fluee M, Tondelli P, Schuppisser J. How accurate is endorectal ultrasound in the preoperative staging of rectal cancer? Dis Colon Rectum 1993;36:127–34.
31. Rafaelsen SR, Sørensen T, Jakobsen A, Bisgaard C, Lindebjerg J. Transrectal ultrasonography and magnetic resonance imaging in the staging of rectal cancer. Effect of experience. Scand J Gastroenterol 2008;43:440–6.
32. Bipat S, Glas AS, Slors FJ, et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. Radiology 2004;232:773–83.
33. Brown G, Richards CJ, Bourne MW, et al. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology 2003;227:371–7.
34. Al-Sukhni E, Milot L, Fruitman M, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol 2012;19:2212–23.
35. Lahaye M, Engelen S, Nelemans P, et al. Imaging for predicting the risk factors—the circumferential resection margin and nodal disease—of local recurrence in rectal cancer: a meta-analysis. Semin Ultrasound CT MR 2005; 26:259–68.
36. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–40.
37. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 2009;27:5124–30.
38. Park JH, Yoon SM, Yu CS, et al. Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. Cancer 2011;117:3703–12.
39. Bosset J-F, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114–23.
40. Bosset J-F, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014;15:184–90.
41. Brændengen M, Tveit KM, Berglund Å, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 2008;26:3687–94.
42. McCarthy K, Pearson K, Fulton R, Hewitt J. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. Cochrane Database Syst Rev 2012;12:CD008368.
43. Grann A, Minsky BD, Cohen AM, et al. Preliminary results of preoperative 5-fluorouracil, low-dose leucovorin, and concurrent radiation therapy for clinically resectable T3 rectal cancer. Dis Colon Rectum 1997;40:515–22.
44. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 1994;331:502–7.
45. Hofheinz R-D, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579–88.
46. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant therapy for rectal cancer: Mature results from NSABP protocol R-04. ASCO GI 2014; Abstract 390.
47. Saif M, Hashmi S, Zelterman D, Almhanna K, Kim R. Capecitabine vs continuous infusion 5-FU in neoadjuvant treatment of rectal cancer. A retrospective review. Int J Colorectal Dis 2008;23:139–45.
48. Kim JS, Kim JS, Cho MJ, et al. Preoperative chemoradiation using oral capecitabine in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2002;54:403–8.
49. Mohiuddin M, Paulus R, Mitchell E, et al. Neoadjuvant chemoradiation for distal rectal cancer: 5-year updated results of a randomized phase 2 study of neoadjuvant combined modality chemoradiation for distal rectal cancer. Int J Radiat Oncol Biol Phys 2013;86:523–8.
50. Crane CH, Eng C, Feig BW, et al. Phase II trial of neoadjuvant bevacizumab, capecitabine, and radiotherapy for locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2010;76:824–30.
51. Willett CG, Duda DG, di Tomaso E, et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. J Clin Oncol 2009;27:3020–6.
52. Velenik V, Ocvirk J, Oblak I, Anderluh F. A phase II study of

cetuximab, capecitabine and radiotherapy in neoadjuvant treatment of patients with locally advanced resectable rectal cancer. Eur J Surg Oncol 2010;36:244–50.
53. Helbling D, Bodoky G, Gautschi O, et al. Neoadjuvant chemoradiotherapy with or without panitumumab in patients with wild-type KRAS, locally advanced rectal cancer (LARC): a randomized, multicenter, phase II trial SAKK 41/07. Ann Oncol 2012;24:718–25.
54. Gérard J-P, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012;30:4558–65.
55. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011;29:2773–80.
56. Schmoll H-J, Haustermans K, Price TJ, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: disease-free survival results at interim analysis. ASCO Annual Meeting 2014; Chicago; May 30–June 3, 2014. Abstract 3501.
57. Rödel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012;13:679–87.
58. Rodel C, Liersch T, Fietkau R, et al: Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: Results of the German CAO/ARO/AIO-04 randomized phase III trial. ASCO Annual Meeting 2014; Chicago; May 30–June 3, 2014. Abstract 3500.
59. Schrag D, Weiser MR, Goodman KA, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 2014;32:513–8.
60. Palta M, Willett C, Czito B. Neoadjuvant chemotherapy alone in locally advanced rectal cancer: an interesting PROSPECT but not ready for primetime. 2014 Gastrointestinal Cancer Symposium Daily News. January 17, 2014.
61. Bujko K, Nowacki M, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215–23.
62. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638–46.
63. Stein DE, Mahmoud NN, Anné PR, et al. Longer time interval between completion of neoadjuvant chemoradiation and surgical resection does not improve downstaging of rectal carcinoma. Dis Colon Rectum 2003;46:448–53.
64. 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;32:1554–62.
65. Sainato A, Nunzia VCL, Valentini V, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). Radiother Oncol 2014;113:223–9.
66. Breugom A, van Gijn W, Muller E, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo) radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomised phase III trial. Ann Oncol 2015;26:696–701.
67. Breugom AJ, Swets M, Bosset J-F, et al. Adjuvant chemotherapy after preoperative (chemo) radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16:200–7.
68. Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. Ann Oncol 2010;21:1743–50.
69. Wales Cancer Trials Unit. Oxaliplatin, Leucovorin, and Fluorouracil Before and After Radiation Therapy and Surgery in Treating Patients With Rectal Cancer That Can Be Removed by Surgery (COPERNICUS). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT01263171. Accessed August 6, 2015.
70. Oncology AfCTi. PROSPECT: Chemotherapy Alone or Chemotherapy Plus Radiation Therapy in Treating Patients With Locally Advanced Rectal Cancer Undergoing Surgery. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT01515787. Accessed August 6, 2015.
71. Hong YS, Nam BH, Kim KP, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. Lancet Oncol 2014;15:1245–53.
72. Benson AB, Venook AP, Bekaii-Saab T, et al. Rectal Cancer, Version 2.2015. J Natl Compr Canc Netw 2015;13:719–28.
73. Meyerhardt JA, Mangu PB, Flynn PJ, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol 2013;31:4465–70.

74. Glimelius B, Tiret E, Cervantes A, Arnold D. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi81–vi8.
75. Sargent D, Sobrero A, Grothey A, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2009;27:872–7.
76. Graham RA, Wang S, Catalano PJ, Haller DG. Postsurgical surveillance of colon cancer: preliminary cost analysis of physician examination, carcinoembryonic antigen testing, chest x-ray, and colonoscopy. Ann Surg 1998;228:59.
77. Castells A, Bessa X, Daniels M, et al. Value of postoperative surveillance after radical surgery for colorectal cancer. Dis Colon Rectum 1998;41:714–23.
78. Primrose JN, Perera R, Gray A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. JAMA 2014;311:263–70.
79. Bruinvels DJ, Stiggelbout AM, Kievit J, et al. Follow-up of patients with colorectal cancer. A meta-analysis. Ann Surg 1994;219:174.
80. Litvak A, Cercek A, Segal N, et al. False-positive elevations of carcinoembryonic antigen in patients with a history of resected colorectal cancer. J Natl Compr Canc Netw 2014;12:907–13.
81. Shimwell NJ, Wei W, Wilson S, et al. Assessment of novel combinations of biomarkers for the detection of colorectal cancer. Cancer Biomarkers 2010;7:123–32.
82. Carpelan-Holmström M, Louhimo J, Stenman U-H, et al. Estimating the probability of cancer with several tumor markers in patients with colorectal disease. Oncology 2003;66:296–302.
83. Chau I, Allen MJ, Cunningham D, et al. The value of routine serum carcino-embryonic antigen measurement and computed tomography in the surveillance of patients after adjuvant chemotherapy for colorectal cancer. J Clin Oncol 2004;22:1420–9.
84. Pita-Fernández S, Alhayek-Aí M, González-Martín C, et al. Intensive follow-up strategies improve outcomes in non-metastatic colorectal cancer patients after curative surgery. A systematic review and meta-analysis. Ann Oncol 2015;26:644–56.
85. Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for no-metastatic colorectal cancer. Cochrane Database Syst Rev. 2007;(1):CD002200.
86. Baca B, Beart Jr RW, Etzioni DA. Surveillance after colorectal cancer resection: a systematic review. Dis Colon Rectum 2011;54:1036–48.
87. Gall CA, Weller D, Esterman A, et al. Patient satisfaction and health-related quality of life after treatment for colon cancer. Dis Colon Rectum 2007;50:801–9.
88. Traa MJ, Orsini RG, Oudsten BLD, et al. Measuring the health-related quality of life and sexual functioning of patients with rectal cancer: Does type of treatment matter? Int J Cancer 2014;134:979–87.
89. McMullen CK, Hornbrook MC, Grant M, et al. The greatest challenges reported by long-term colorectal cancer survivors with stomas. J Support Oncol 2008;6:175–82.
90. Emmertsen KJ, Laurberg S. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. Br J Surg 2013;100:1377–87.
91. Mols F, Beijers T, Lemmens V, et al. Chemotherapy-induced neuropathy and its association with quality of life among 2-to 11-year colorectal cancer survivors: results from the population-based PROFILES registry. J Clin Oncol 2013;31:2699–707.
92. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the Familial Risk–Colorectal Cancer: European Society for Medical Oncology Clinical Practice Guidelines. J Clin Oncol 2015;33:209–17.