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Current Developments in the Management of Colorectal Cancer

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Who Is a Candidate for Nonoperative Management of Early-Stage Rectal Cancer?



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H&O What is standard treatment for early-stage rectal cancer?

CH Surgery is the standard treatment for early-stage rectal cancer. In patients with T1N0 disease, the standard treatment is typically a minimally invasive transanal resection of the affected part of the rectal wall. In patients with T2N0 or larger tumors that are not amenable to a transanal excision, the standard is total mesorectal excision (TME), in which the rectum and the surrounding mesorectal lymph nodes are removed. The procedure involves either a permanent colostomy if the tumor is very low in the rectum, or reconstruction with a colorectal anastomosis if the tumor is higher up in the rectum.

H&O What are the disadvantages of surgical treatment?

CH Surgery always carries risks, which include bleeding, infection, and other postoperative complications. Although the morbidity associated with transanal excision is relatively limited, the morbidity associated with TME tends to be more pronounced. Even when patients are eligible for rectal reconstruction, removal of most of the rectum may lead to long-term changes in bowel function. Patients may experience low anterior resection syndrome (LARS), a constellation of changes in lower gastrointestinal function that include looser or more frequent bowel movements. Although LARS can be relatively mild in

some patients, it can be severe enough to affect quality of life in others. TME also carries a small risk for urinary or sexual dysfunction.

H&O What are the goals of the nonoperative management of early-stage rectal cancer?

CH The primary goal is to avoid the types of morbidity that are associated with surgery—especially for patients who have very distal tumors and whose only surgical option includes a permanent colostomy—without a reduction in tumor control.

H&O What are the options for nonoperative management in early-stage rectal cancer?

CH Chemotherapy and radiation therapy can be used in an effort to eradicate the tumor, negating the need for surgery, or to shrink the tumor, permitting the surgeon to perform less-extensive surgery. However, it should be noted that chemotherapy and radiation therapy also can have a significant effect on bowel function.

H&O Do you consider the use of immunotherapy agents in patients with mismatch repair-deficient (MMR-d) early-stage rectal cancer?

CH Immunotherapy is an established standard of care for patients with metastatic MMR-d or microsatellite

instability–high colorectal cancer. Very recently, data were presented on the use of immunotherapy in patients with earlier disease. At the 2022 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, Dr Melissa Lumish presented some very preliminary data on patients with locally advanced MMR-d rectal cancer. All of the first 11 patients in the study experienced a complete response to single-agent treatment with the anti–programmed death 1 (PD-1) agent dostarlimab (Jemperli, GlaxoSmithKline) and did not require chemotherapy or surgery. This was a small cohort of patients with a very limited follow-up, but the data seemed to suggest that PD-1 blockade might be an option for achieving a complete response in patients with locally advanced, nonmetastatic rectal cancer. The phase 2 EA2201 trial from the ECOG-ACRIN Cancer Research Group, which is currently recruiting patients, is trying to better assess this treatment approach (NCT04751370).

H&O How are patients selected for nonoperative management?

CH Patients typically undergo an assessment of response approximately 6 to 12 weeks after the completion of chemotherapy and radiotherapy. The assessment typically includes a digital rectal examination, flexible sigmoidoscopy, and high-quality pelvic or rectal magnetic resonance imaging (MRI). In general, if the response of the tumor in the rectum is good, then the response of any cancer in the lymph nodes will also be good.

H&O Are any biomarkers being used to predict or assess response?

CH We do not currently have any proven biomarkers in this context, but ongoing research is trying to identify molecular biomarkers that will help identify up front whether a tumor will respond to treatment, or imaging biomarkers that will allow us to assess response. In radiomics, computed tomography or MRI is used to conduct a more advanced assessment of the tumor before and after treatment. The use of circulating tumor DNA to assess response to treatment is also being evaluated. In addition, blood biomarkers such as circulating tumor DNA could be used for surveillance, which would be extremely helpful because flexible sigmoidoscopy and pelvic MRI are invasive and somewhat expensive, and they need to be repeated every 3 to 6 months for the first couple of years of surveillance. The phase 2 NOM-ERA trial, which is evaluating short-course radiation therapy followed by chemotherapy in nonmetastatic rectal cancer, is also assessing the role of circulating tumor DNA in response assessment and surveillance (NCT03904043).

H&O How effective is nonoperative management in selected patients?

CH Approximately 20% to 50% of patients have a complete response to radiation and chemotherapy, depending on the study. Among those who have a complete clinical response and undergo surveillance instead of surgery, approximately 20% to 30% experience a recurrence, most commonly in the wall of the rectum. That rate is higher than the local recurrence rate seen after TME, which is less than 10%, so the trade-off for preserving the rectum is a modestly elevated risk for local recurrence. The greater risk for local recurrence is generally considered acceptable because most patients with local recurrence can undergo salvage TME, which has a relatively high cure rate, and because the risk of developing distant metastases is fairly low in these patients.

A team-based approach is the best way to identify patients who are eligible for nonoperative treatment, provide treatment, and monitor patients after treatment.

H&O What are the most important studies to look at nonoperative management?

CH Two important studies are the International Watch & Wait Database (IWWD) and the OPRA study. IWWD is a large registry of patients with rectal cancer who were managed with a watch-and-wait strategy after a clinical complete response to radiotherapy with or without chemotherapy. Outcomes from this series have been published several times over the past few years, starting with nearly 900 patients and now including more than 1500 patients. Early and continued follow-up has shown that the risk for recurrence is in the range of 25% to 30%, with most recurrences happening in the first 2 to 3 years.

OPRA is a multicenter prospective study from the Memorial Sloan Kettering Cancer Center. Nearly 300 patients with stage II or III rectal cancer were enrolled, who received total neoadjuvant therapy (chemotherapy followed by chemoradiotherapy, or chemoradiotherapy

followed by chemotherapy). Depending on the response to treatment, patients were recommended for TME or watch-and-wait. The researchers found that 79% of patients who had a complete clinical response to total neoadjuvant therapy were able to avoid TME, and 52% of patients who had a near clinical response were able to avoid TME. The 3-year overall survival rate was high: 97% among those with a complete clinical response, 93% among those with a near clinical response, and 90% among those with an incomplete clinical response. These data are some of the strongest we have regarding watch-and-wait, and we consider this approach to be a viable option for well-informed eligible patients.

H&O What ongoing studies are assessing nonoperative management?

CH Several studies around the world are further assessing nonoperative management. A few studies are randomly assigning patients to either standard surgery or nonoperative management. These are challenging studies to perform because many patients are unwilling to undergo this type of randomization. For example, the international STAR-TREC trial from the United Kingdom, the Netherlands, and Denmark is randomly assigning patients to either standard TME surgery, organ-preserving treatment with long-course concurrent chemoradiation, or organ-preserving treatment with short-course radiotherapy (NCT02945566).

Other ongoing studies are looking at ways to optimize the use of chemotherapy, radiation, and nonchemotherapy systemic treatments. The National Cancer Institute is also developing a cooperative group trial that is expected to open in the next couple of years.

H&O What should the next step in research be?

CH We want to be able to identify before treatment who is most likely to respond to chemotherapy and radiation on the basis of factors such as the molecular features of the tumor. We want to identify optimal regimens for radiation and systemic therapy, including targeted therapy such as immunotherapy. We want to make surveillance less cumbersome and invasive for patients by using markers such

as circulating tumor DNA to evaluate those who have had a complete response.

H&O What advice do you have for oncologists who want to provide nonoperative management of early-stage rectal cancer?

CH Ideally, nonoperative management should be done at high-volume centers where experienced medical oncologists, radiation oncologists, colorectal surgeons, gastroenterologists, radiologists, and pathologists have expertise in the diagnosis and treatment of rectal cancers. A team-based approach is the best way to identify patients who are eligible for nonoperative treatment, provide treatment, and monitor patients after treatment. If a patient has a recurrence, we want to find it early enough that the patient is still a candidate for salvage treatment.

Second, I would emphasize that this approach is not for all patients. Patients who choose this approach must accept a somewhat higher risk for recurrence and adhere to a rigorous follow-up schedule that includes some invasive studies; many patients will be uncomfortable with these realities.

Disclosure

Dr Hallemeier has no relevant disclosures.

Suggested Readings

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