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Current Developments in the Management of Colorectal Cancer

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Treatment Deintensification in Locally Advanced Rectal Cancer: When Less Is More

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H&O Why is it so important to determine which components of treatment can be omitted in patients with locally advanced rectal cancer?

AC The treatment modalities for patients with locally advanced rectal cancer include chemotherapy, radiation or chemoradiation, and then surgery. This approach is very successful in terms of cure, but the treatments can cause a lot of toxicity. The radiation field includes the ovaries and the uterus in women, which means that younger women go into immediate menopause and become infertile. Sexual dysfunction in both men and women, bowel dysfunction, and bladder dysfunction are all potential concerns. Approximately 30% of patients need a permanent colostomy because of the location of the tumor. Cure is important, of course, but we also have to think about patient quality of life. Numerous studies are looking at possible ways to omit one of these modalities—surgery, radiation, or chemotherapy—while improving survival because the effects on our patients are so important.

H&O What are some of the most important studies that have looked at nonoperative management in these patients?

AC Nonoperative management, or organ preservation, was pioneered by Dr Angelita Habr-Gama and her group in Brazil.[1] These researchers noticed that a proportion of patients had a pathologic complete response to chemoradiation alone that was seen at the time of surgical resection. This finding led to several observational studies and eventually a large, multicenter phase 2 study called OPRA, which definitively showed that certain patients with rectal cancer are eligible for nonoperative management with total neoadjuvant therapy.[2] In this study, 324 patients with stage II or III rectal cancer received neoadjuvant therapy and were then randomly assigned to receive either chemoradiation followed by consolidation chemotherapy (the consolidation group) or induction chemotherapy followed by chemoradiation (the induction group). Chemotherapy consisted of either 5-fluorouracil (5-FU)/leucovorin/oxaliplatin (FOLFOX) or capecitabine/oxaliplatin (CAPOX), and long-course chemoradiation consisted of 5 1/2 weeks of radiation plus either capecitabine or 5-FU. We found that surgery could be avoided in approximately 40% of patients with this approach without affecting overall survival or the rate of metastases. Overall, the rates of organ preservation were higher in the patients in the consolidation group than in those in the induction group (53% vs 41%; P=.01). The ability to preserve the rectum without compromising survival in a large proportion of patients is very important.

We have learned from this study and earlier studies that local tumor recurrence is most common during the first 2 years after treatment, so careful follow-up is important. If local regrowth is detected, we can use the same surgery for salvage that we would have offered earlier. The need for surveillance has been incorporated into the National Comprehensive Cancer Network (NCCN) guidelines for rectal cancer.[3]

Several ongoing studies are now examining nonoperative management following the intensification of neoadjuvant therapy. The ongoing, multicenter phase 2 JANUS study, which is sponsored by the National Cancer Institute, is looking at the intensification of chemotherapy to increase the number of patients who achieve a clinical complete response and become eligible for nonoperative management, which is a very exciting prospect (NCT05610163). Approximately 312 patients are being randomly assigned to standard neoadjuvant chemotherapy with FOLFOX or CAPOX or intensified neoadjuvant chemotherapy with modified 5-FU, irinotecan, leucovorin, and oxaliplatin (mFOLFIRINOX). Likewise, the ongoing German ACO/ARO/AIO-18.1 trial is investigating long-course radiation therapy vs chemoradiotherapy (NCT04246684), and the ongoing Japanese ENSEMBLE trial is investigating neoadjuvant intensification of chemotherapy following short-course radiation therapy with selective organ preservation (NCT05646511/jRCTs031220342).

> Just 3 months of FOLFOX would have allowed more than 1 in 5 patients to avoid surgery.

H&O What are some of the most important studies that have looked at omitting radiation in these patients?

AC Although radiation has never been shown to improve overall survival, it is an important part of treatment because it does a very good job of controlling disease in the pelvis. At the same time, the effects of radiation are important in all patients and are of special concern in younger patients because radiation affects fertility and sexual function. Younger patients also have more years ahead of them to deal with side effects. Unfortunately, we are seeing more and more young patients worldwide with colorectal cancer. Most of these cancers are left-sided, and the large majority are rectal tumors. We know that a patient whose tumor is very low in the rectum and who does not achieve a clinical complete response with neoadjuvant therapy will need surgery leading to a permanent colostomy.

The phase 2/3 PROSPECT study asked the very important question of whether a patient who has experienced a response of 20% or higher to neoadjuvant therapy can skip radiation and go straight to surgery.[4] The study was designed to include patients whose tumors were in the mid to high rectum and exclude patients whose tumors were lower in the rectum and were at risk of needing a permanent colostomy. More than 1000 patients who were eligible for surgery were randomly assigned to chemotherapy plus chemoradiation (the control arm) or to chemotherapy with the addition of chemoradiation only if needed (the experimental arm). The patients in this study received FOLFOX chemotherapy because the study opened in 2012; today we would substitute CAPOX.

We learned 2 important lessons from this trial. First, 5-year disease-free survival was not compromised by the omission of radiation. Second, 22% of patients in the experimental arm had a pathologic complete response and did not need surgery. In other words, just 3 months of FOLFOX would have allowed more than 1 in 5 patients to avoid surgery.

H&O Can you describe your recent trial?

AC When we have a very good treatment for a specific biomarker, another way to improve our results with neoadjuvant therapy is to use biomarkers. If effective, this approach gives us the potential to omit other components of standard care. In our phase 2 study at Memorial Sloan Kettering Cancer Center, which I presented at the 2024 American Society of Clinical Oncology Annual Meeting, we enrolled 48 patients with stage II or III mismatch repair–deficient (MMRd) rectal cancer.[5] Patients received 6 months of the programmed death 1 (PD-1)–blocking monoclonal antibody dostarlimab (Jemperli, GSK). When we designed the study, we already knew that patients who had MMRd tumors had excellent responses to PD-1 blockade in the metastatic setting. Now we know that dostarlimab is also effective in eligible patients with stage II or III disease, as all 41 of the patients who completed treatment achieved a clinical complete response. On the basis of this response, all 41 patients were able to avoid chemotherapy, radiation, and surgery. Checking MMR status early in the treatment of locally advanced rectal cancer has now been incorporated into the NCCN guidelines, which recommend immunohistochemistry testing for MMR proteins before treatment is started. Patients with MMRd tumors are eligible for upfront induction treatment with PD-1 blockade, and patients with MMR-proficient (MMRp) tumors are eligible for neoadjuvant therapy with chemotherapy and chemoradiation.

MMR deficiency plus PD-1 blockade represents an

excellent match between biomarker and biomarker-selected therapy, which raises the question of what other matches might be available. We currently have a study looking at the use of human epidermal growth factor 2 (HER2)–targeted therapy in patients with *HER2*-amplified, *RAS* wild-type colorectal cancer (NCT05672524).

H&O What else should physicians consider when determining the best approach to treatment in locally advanced rectal cancer?

AC The goal is always cure, but we should be tailoring the treatment to the individual patient. This means that we should factor in the tumor stage, tumor location, patient age, and patient preferences regarding survivorship when we decide on a treatment approach. We also need to be able to pivot and omit components of treatment that are no longer required.

We also are enrolling patients in a study that is looking at combination immunotherapy with botensilimab and balstilimab in locally advanced MMRp rectal tumors (NCT06843434). Data from small trials in patients with colon cancer treated with this combination followed by surgery suggest that some patients with MMRp tumors can have significant pathological responses. Many additional trials are looking at the use of immunotherapy combination as part of a totally neoadjuvant approach.

H&O What questions remain to be answered?

AC We have many questions to answer. For example, how can we identify upfront those patients for whom nonoperative management will be appropriate or who can avoid radiation? It would be useful in our decision making to have this information earlier. We hope to learn which patients are sensitive to and can benefit from immunotherapy, and how to improve upon and extend that treatment to more patients with MMRp tumors.

Disclosures

Dr Cercek has served on advisory boards for Amgen, AbbVie, Agenus, Daiichi Sankyo, Merck, GSK, Pfizer, Roche, Janssen, Summit Therapeutics, 3T Biosciences, UroGen Pharma, and Regeneron, and holds research funding from GSK and Pfizer. She holds a pending patent on neoadjuvant PD-1 for mismatch repair–deficient rectal cancer.

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