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EDITORIAL – COLORECTAL CANCER

Assessment of Clinical Complete Response After Chemoradiation for Rectal Cancer with Digital Rectal Examination, Endoscopy, and MRI

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Over the past 30 years, multimodal therapy has emerged as the treatment of choice for rectal cancer. Standard management includes neoadjuvant chemoradiation with capecitabine or 5-fluorouracil and total mesorectal excision (TME), with adjuvant chemotherapy, including a fluoropyrimidine and oxaliplatin. A recent trend has emerged in which adjuvant chemotherapy is delivered as an induction before chemoradiation.[1–3] In spite of achieving impressive local control, this trimodal therapy is arduous, and many patients do not complete it, especially when chemotherapy is planned for postoperative administration. It is associated with short-term toxicity and long-term complications, and accompanied by significant alterations in quality of life. Strategies are emerging to lessen the intensity of treatment by either modifying the treatment schedule or removing either radiotherapy or surgery, thereby reducing morbidity and deleterious changes in patients' quality of life while maintaining or even improving oncologic outcomes.

One such strategy involves the elimination of the routine use of radiotherapy. After encouraging results in a small pilot trial, a large cooperative group trial, PROSPECT (Preoperative Radiation Or Selective Preoperative Radiation and Evaluation before Chemotherapy and Total Mesorectal Excision) (NCCTG-N1048; N1048; NCT01515787), is attempting to individualize treatment by selectively using radiotherapy in patients whose disease does not regress as a result of initial FOLFOX chemotherapy, rather than providing it to all patients.[4] By randomizing patients to standard preoperative chemoradiation followed by TME or to preoperative chemotherapy and selective use of radiotherapy before TME, PROSPECT may provide an opportunity to reduce the use of pelvic radiation in patients who might not benefit from it. With a goal of accruing 1000 patients, and with over 350 currently randomized, the trial is well on its way to answering the question of whether radiotherapy can be selectively used in the treatment of rectal cancer.

Another effort to individualize rectal cancer treatment is the watch-and-wait approach. This approach, which is synonymous with deferred surgery, nonoperative management, and rectal preservation, treats rectal cancer patients with chemotherapy and radiation, attempting to avoid surgery in the approximately 15–20 % of patients who experience a complete response (CR). Habr-Gama and colleagues in Sao Paulo, Brazil, published the first organized report of a nonoperative approach more than 10 years ago. After chemoradiation, rectal cancer patients were evaluated; those with residual disease underwent rectal resection, while those with a complete clinical response were closely observed with digital rectal examination, proctoscopy, serum carcinoembryonic antigen measurement, and biopsy of suspicious lesions. Patients with evidence of tumor proceeded to rectal resection, while patients with a sustained complete clinical response after 1 year continued surveillance every 3 months for an additional year, then every 6 months thereafter. Twenty-seven percent of rectal cancer patients treated according to this protocol experienced a sustained complete clinical response and were spared TME. It is important to note that patients with local relapse identified during follow-up

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underwent curative TME as salvage therapy. Outcome analysis indicated that those with sustained clinical response and no surgery had similar survival to those with pathologic CR and surgical resection.[5–7]

The group from Maastricht University in the Netherlands added to the nonoperative management literature with their report of 192 rectal cancer patients treated from 2004 to 2010.[8] Twenty-one patients with complete clinical response, as determined by clinical examination, MRI, and endoscopic biopsy, were treated expectantly without rectal resection. After a mean follow-up of 25 months, one patient developed local tumor regrowth but was able to undergo curative salvage surgery; the other 20 patients remained without disease. Outcomes in patients with clinical CR, treated with initial nonoperative management, were similar to those with pathologic CR after TME.

The experience from Memorial Sloan Kettering Cancer Center was first published in 2012 and was updated at the Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology (GI-ASCO) in 2015.[9] In total, 73 patients were treated nonoperatively between 2006 and 2010. Tumor regrowth occurred locally in 19 patients (26 %), who were treated with subsequent resection. Similar to the experiences from Sao Paulo and Maastricht, 70 % of tumor regrowth occurred within 13 months of completing chemoradiation. The cohort treated with the nonoperative approach was compared to 72 patients who underwent resection with pathologic CR. In this retrospective study, disease-free and overall survival were similar, indicating that tumor regrowth could be salvaged and did not appear to lead to distant metastases.

The Achilles' heel of nonoperative management lies in identifying those who will experience CR. Studies that use clinical examination and standard imaging, including PET imaging, have proven neither sensitive nor specific.[10,11] Our colleagues from Maastricht report an impressive series utilizing a combination of physical examination, proctoscopy, and diffusion-weighted MRI (DWI) to accurately identify those patients who are likely to experience CR.[12] Six to eight weeks after long-course chemoradiation, patients were assessed by clinical examination, consisting of digital rectal examination and proctoscopy, and by MRI. The authors utilized T2-weighted MRI (T2W-MRI) with DWI. CR was defined as either no residual tumor after rectal resection or sustained clinical CR for 12 months in those who did not undergo surgery. Using these definitions, CR was noted in 17 (34 %) of 50 patients. Diagnostic performance, as calculated by area under the receiver operator characteristics curve, was 0.79 for T2W-MRI and DWI, 0.88 for physical examination and 0.89 when both modalities were utilized. When the MRI or physical examination criteria were met, 75 and 90 % of patients experienced a CR, respectively. However, the combination of physical examination, proctoscopy, and T2 W-MRI and DWI identified 98 % of those with CR, missing residual disease in only 2 %. Nevertheless, the criteria could not identify all those who would experience CR because even when all modalities indicated the presence of residual tumor, 15 % of patients still experienced a CR.

The advantage of T2W-MRI and DWI is that it capitalizes on the tumor biology rather than relying on only morphologic appearance. DWI utilizes special pulse sequence design and motion-probing magnetic gradients in combination with fat-saturated T2W sequences. Protons/water molecules in normal tissue, which are moving freely after excitation with the radiofrequency pulse, will move away from their original location when the listening coil is turned on; therefore, the signal returned will be weak. In contrast, in pathologic tissue with tightly packed tumor cells, water movement is restricted, leading to high signal as the excited protons are trapped in place when the listening coil is turned on. As treatment succeeds in reducing tumor cell density and lysing membranes, the motion of protons increases and the signal decreases. Tumor is likely to be present when the signal is high, the result of restricted proton motion, while in a CR or nearly CR protons are moving with no or little restriction in the restored normal tissue, and signal is no longer produced.

This report by the Maastricht group has added significantly to the field of nonoperative management of rectal cancer by describing a systemic grading scheme and categorization of clinical and radiographic response of rectal cancer to neoadjuvant therapy. If the nonoperative approach is to reach its potential, it must be generalizable and capable of being performed not only in expert tertiary-care centers. The findings outlined by Maas and colleagues are an important preliminary step in that direction, but they must be validated in a larger series and in a multi-institutional setting.

DISCLOSURE None.

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