Is Surgery Always Necessary in Rectal Cancer?

In this article, we review risks and benefits of the standard treatment approach for rectal cancer and compare standard treatment with alternative methods aimed at rectal preservation.

Introduction

Anatomically, the rectum begins above the dentate line, which marks the cephalic extent of the anal canal, and extends above the peritoneal reflection to the sigmoid colon.[1] Although didactically divided into lower rectum, mid rectum, and upper rectum, the most valuable information one can obtain from the localization of a rectal tumor is whether or not it is surrounded by peritoneum. Generally, peritonealized tumors can be surgically and clinically managed as colon tumors. On the other hand, the lack of a peritoneal covering confers a higher risk of local recurrence (LR) of the rectal tumor, and different medical approaches, often including more radical surgical procedures, may be required.[2]

In the latter scenario, total mesorectal excision (TME) and neoadjuvant chemoradiotherapy (CRT) have been proven to effectively treat the disease.[3-5] (See Table 1 for selected LR and overall survival (OS) rates reported with this approach.) Multidisciplinary treatment with neoadjuvant therapy followed by surgery with TME is now the standard of care for patients with deperitonealized T3 or N1 distal rectal tumors (DRTs).

In spite of progress in preventing LR, treatment of DRTs remains very aggressive. Very-low-lying rectal tumors usually require an abdominoperineal resection (APR), a procedure that completely removes the distal colon, rectum, and anal sphincter complex, resulting in a permanent colostomy.[6,7] This is the only way to assure the necessary surgical margins, free of neoplastic cells. APR is the standard of care even for patients with early-stage (T2N0) DRTs that may not require multimodality treatment.[8]

Besides the need for a permanent colostomy, the sequelae of APR may manifest in a variety of ways. Perineal wound complications are not rare, and they may cause pain and pressure and lead to skin breaks and evisceration.[9] Permanent sexual or urinary dysfunction occurs in about 60% of patients treated by APR.[10,11] Sphincter-sparing resections (SSRs) can be an alternative approach for low rectal tumors localized at least 3–4 cm above the anal verge.[12] However, difficulties with evacuation and incontinence in patients with very low SSRs can cause an equal detriment to the quality of life.[13-15] For these reasons, the possibility of avoiding permanent stoma and even eliminating surgery without compromising the curability rate is one of the most important unmet needs of patients suffering from a DRT.

The Paradox of a Pathologic Complete Response After Neoadjuvant Treatment

With routine use of neoadjuvant CRT, it was possible to observe that some tumors are downstaged markedly at the time of surgery.[16] Complete tumor response (indicated by a specimen without any residual tumor cells) and near-complete response (single cells or small groups of cancer cells) can be observed in approximately 15% to 30% of rectal cancer tumors managed with neoadjuvant CRT.[17,18] Interestingly, therapy-induced downsizing effects have widely been described as important prognostic factors, and these major responses to neoadjuvant treatment have been associated with a strongly favorable prognosis.[19-22] Indeed, it seems that response of the primary rectal cancer serves as a marker of effectiveness of systemic control and long-term oncological outcome. Local and distant failures are virtually absent in patients who achieved a pathologic complete response (pCR) after neoadjuvant CRT.[23,24] Based on these data, one can argue that the...
information that a particular patient has achieved a complete response (CR) postoperatively, without viable tumor cells in the rectum, is desirable and very welcome. Indeed, these selected patients with rectal cancer who obtained a pCR after preoperative CRT could, at least theoretically, be spared from APR and permanent colostomy with little risk of compromising their prognoses. If there were really no cancer cells remaining in the rectum, then surgery would be unnecessary.

The obvious problem with this argument is that pathological responses can only be categorized based on findings extracted from the assessment of the entire resected specimen and therefore, after the radical surgery. The double-edged sword is that a patient can have had a very good oncological outcome but also have been subjected to unnecessary mutilation, with these conclusions drawn from the same pathological findings.

The Difficulty of Predicting a CR

The ideal solution to avoid the paradox described above would be to have clinical surrogates could anticipate the pathological response. The majority of patients with an apparent pCR postoperatively have residual microscopic extraluminal disease.[25] In this regard, the value of several post-treatment predictors of pCR has been extensively studied.

The absence of visible (by proctoscopy) or touchable (by digital rectal examination [DRE]) mucosal abnormalities is highly associated with ypT0 status ($P < .0001$), but approximately 25% of patients with mucosal CR still have residual disease.[25-27] So, although essential, a normal examination is not sufficient for predicting a pCR. Furthermore, distinguishing between residual tumor and actinic ulcers or intramural fibrosis following CRT is not an easy task. Histopathologic assessment by rectal biopsy is far less precise than histopathologic examination of the entire resection specimen, because not all parts of the tumor show regressive changes in a similar manner. After CRT, tumor normally follows a centrifugal pattern of regression. Residual neoplastic cells are usually still found in deeper areas of the tumor, when superficial tumor has completely disappeared.[28] A positive biopsy is proof of residual tumor but a negative biopsy may be a false negative and cannot be relied on to exclude persistent disease.[29] Also, approximately 15% of patients with ypT0 status have lymph node metastases, an occurrence that may have an important prognostic impact.[30]

Radiological restaging after CRT has proven difficult. No staging method has been found that can accurately determine pT and pN categories after CRT. Magnetic resonance imaging (MRI) is currently the imaging modality of choice for detection, characterization, and staging of rectal cancer.[31,32] It is clearly superior to tomography for assessing T and N status. However, the accuracy of MRI in predicting response post-CRT remains elusive, mainly because of the difficulty in determining whether residual lymph nodes are still malignant.[33] High-resolution MRI has been tested to assess tumor response before surgical resection and showed encouraging results in predicting survival outcomes after surgical resection.[34] Measurement of tumor replacement by fibrosis can be done reliably with this technique, allowing identification of good and poor response groups. In spite of the strong correlation with histopathologic grading of response, MRI is still insufficient for diagnosing a status of pCR. The value of 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)-CT for evaluation of treatment response to CRT in rectal tumors is controversial. Changes in the levels of 18F-FDG uptake before and after CRT could theoretically be used to differentiate between responders and nonresponders,[35,36] but use of this method to identify patients who achieve a pCR has been somewhat disappointing. Moreover, radiation-induced inflammation in rectal cancers post-CRT may cause nonspecific 18F-FDG uptake and produce false-positive results.[37]

The ‘Watch-and-Wait Protocol’ as a Strategy for Predicting pCR and Avoiding Unnecessary Surgery

An interesting strategy to predict a pCR or near pCR, known as the “watch-and-wait protocol” (W&W), was developed by a Brazilian group.[38-40] This strategy defines a different category of response called “sustained clinical complete response” (SCCR). According to this approach, patients who have obtained a clinical and radiologic CR 10 weeks after completion of CRT are clinically and radiologically examined bimonthly for 1 year. Patients are considered to have an SCCR if at 12 months from CRT completion they still maintain a clinical CR. Clinical CR is defined as absence of residual rectal wall irregularity by DRE and proctoscopy,[26] and includes radiological features of a CR, such as the presence of residual low-signal-intensity areas with absence of restriction to diffusion at MRI, or absence of residual FDG uptake within the rectal wall at PET-CT. Patients with any clinical or radiologic findings suspicious for residual cancer or relapse at any time during this 12-month
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Follow-up are managed by full-thickness transanal excision and are maintained in the W&W protocol only if a ypT0 status is found. Patients who, after 12 months, are maintained without any evidence of relapse are considered to have an SCCR and are followed, without surgery, in the same way as if they had had surgery immediately after CRT completion.

In a seminal study from the Brazilian group, 71 patients who had complete clinical response following CRT were treated by observation alone.[41] Just two patients developed pelvic (endorectal) recurrences, which were successfully treated by full-thickness transanal excision or brachytherapy. OS and disease-free survival (DFS) were very similar between these patients and the surgically managed ypT0 status patients. Recently these authors reported an even more impressive result: Using a slightly different neoadjuvant CRT protocol[42] and applying the same concept of SCCR, they avoided surgery in 50% of highly selected patients initially considered for APR.[43]

This kind of approach is now under investigation at multiple international sites, and three other groups have already described similar results with comparable strategies. Table 2 highlights selected studies investigating the W&W approach. A recently published article by investigators from Memorial Sloan Kettering Cancer Center reviewed the outcome of 32 patients with distal rectal cancer managed without surgery after a clinical CR to neoadjuvant therapy.[44] Patients were counseled that the approach was not standard and that it could compromise their oncologic outcomes. Rectal resection was successfully avoided in 81% of these patients. Salvage surgeries were able to control LR, and OS was similar to that of the patients with pCR treated by rectal resection.

Another single-institution study from the United Kingdom reported that after neoadjuvant CRT, 50% of the patients with no evidence of residual disease detected on examination under anesthesia and biopsy (about 25% of all patients studied) could be managed without surgery. At the time of publication, these patients were disease-free 25 months after finishing CRT.[45] These results are similar to results initially described by the Brazilian group.

An interesting article from Maastricht University Medical Center, in the Netherlands, reported the clinical experience with the W&W approach that had been offered since 2004 as an experimental option for patients with clinical CR after CRT. The majority of patients expressed a strong preference for not undergoing surgery, mostly because of the possibility of avoiding a permanent colostomy. After giving their informed consent, patients with a clinical CR were included in the study and monitored by an intensive follow-up protocol. Cumulative probabilities for DFS and OS were not significantly different between patients managed with the W&W approach and those who had surgery.[46]

Local Excision as a Surgical Option After CRT

Many clinicians argue that local excision (LE) of a residual tumor after CRT is a much safer approach than the W&W policy, because it provides reassurance about the presence or absence of residual tumor. LE of distal rectal cancer is associated with a much lower rate of complications than APR. LE can avoid postoperative urinary and sexual dysfunction and can preserve the anal sphincter, but it is considered a curative surgical approach only for very early rectal cancers (T1sm1N0) with favorable histology.[47,48] LE is also acceptable for patients who are unfit for major surgery because of medical comorbidities.[49] Introduction of the transanal endoscopic microsurgery (TEM) procedure was an important technical advance for LE of rectal cancer.[50] Compared with the traditional transanal approach, TEM permits a complete full-thickness excision to be performed with an appropriate surgical margin (1 cm), and with the largest amount of adjacent perirectal fat. However, it is important to note that it does not allow for lymph node analysis.

With the oncologic benefits of neoadjuvant CRT in patients with locally advanced rectal cancer, several retrospective case series[51-57] and some prospective studies[58-60] suggest that CRT before LE reduces recurrence to a level comparable to that associated with TME. The rationale for this approach is that there is a correlation between chemoradiosensitivity and the intrinsic aggressiveness of rectal cancer.[61] A good CRT response (without necessarily achieving a CR) would allow for choosing appropriate candidates who could avoid aggressive treatments. Furthermore, aggressive tumors not responding to CRT would have great risk of local and distant recurrence even if they were managed with TME. Several studies have reported the feasibility of performing local excision for T2-3 rectal cancer following preoperative CRT; most of them show favorable long-term outcomes for selected cases of T2–3 rectal cancer that has downstaged to ypT0–1 post-CRT. LR after failed LE is usually amenable to radical salvage surgery, with acceptable long-term survival rates.[62,63] A multi-institutional series of 487 patients undergoing TEM for rectal cancer reported 63 patients (23 with T1 tumors, 31 with T2 tumors, and 9 with T3 tumors) who...
underwent radical surgery within 3 months of TEM, for different reasons. Only one of 63 patients had recurrent disease.[64]

Because only a minority of patients obtain the clinical CR necessary to be included in a W&W program, the alternative of offering an initial treatment with LE to patients who respond well to CRT seems attractive. The weakness of this strategy, however, is the absence of large trials assessing W&W in this setting; the imprecise definition of good response to CRT; and, most important, the lack of lymph node analysis.[65]

Conclusions

Several studies suggest that nonoperative strategies for management of distal rectal cancers are feasible for some patients. The actual benefit of aggressive surgery with TME in patients with very good response to CRT is not clear. These data are, however, generally viewed with caution, and many physicians, understandably, are still reluctant to treat patients without surgery. A recent survey of surgeon members of the Association of Coloproctology of Great Britain and Ireland showed that the majority (69%) will never consider nonoperative management in patients fit for curative surgery.[66] The reason for this skepticism may reflect some degree of prejudice but is based mainly on the absence of prospective studies with long-term follow-up.[67-69]

Omission of surgery in selected patients identified in these trials will limit the toxicities associated with standard therapy but without compromising disease control, in a manner very similar to the optimization of outcomes obtained in certain patients with breast cancer. Defining strategies that would enable organ preservation while achieving survival rates comparable to those associated with standard treatments is, undoubtedly, one of the most important goals in the care of patients with rectal cancer.

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Table 1: Studies Evaluating Preoperative Chemoradiotherapy Followed by TME

Table 2: Studies Investigating the Watch-and-Wait Approach in Rectal Cancer

References:


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