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The Role of Local Excision after Neoadjuvant Therapy for Locally Advanced Rectal Cancer: A Different Perspective

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The concept of using preoperative radiation to downstage locally advanced rectal cancer (LARC) before limiting surgical resection to only local excision (LE) was introduced more than 30 years ago.[1,2] Initially, this strategy was reserved for patients not suitable for total mesorectal excision (TME). However, the clinical indications for this approach have been refined and it is applied now as a method of organ preservation, even for patients who are fit to undergo radical resection, to avoid the long-term sequelae of TME.[3–6] In addition, concurrent chemotherapy, usually 5-fluorouracil (5-FU) or capecitabine, is now added to radiation therapy to improve the response rate. In some circumstances, LE is performed as an alternative to TME, even when significant residual disease persists after neoadjuvant therapy. This is often either due to patients' refusal of TME or patients' frailty. A discussion of the role of LE under these circumstances is beyond the scope of this commentary and we will consider only the role of LE when it is reserved for patients with complete clinical response (CCR) or near CCR (nCCR) following neoadjuvant treatment. Several prospective, retrospective, and one randomized studies confirmed the safety of this approach when compared with TME. When LE is performed for patients with CCR or nCCR and subsequent histological examination confirms the ypT0 status, the expected local control rate is approximately 95%.[7,8] Completion TME is recommended when histological examination reveals more extensive disease than ypT1-R0. Eradication of the residual cancer is accomplished within a few weeks following LE, through completion TME, thus avoiding the potential risk of undetected malignancy for a prolonged period, which may increase the risk of distant metastasis.[9] The recently published OPRA trial indicated high regrowth rates in both the induction and consolidation arms (40 and 27.5%). In addition, a high rate of pelvic failure (24%) was reported following salvage TME in cases of regrowth.[10] These results reflect the difficulty of post-neoadjuvant therapy clinical restaging, even when patients are managed in large centers with a clear interest in the conservative management of rectal cancer, and under strict protocol guidelines and quality assurance procedures. The high regrowth rate necessitates close follow-up and the availability of experienced physicians and high-quality imaging capabilities.

These requirements can be particularly challenging in a high mobility society as in the U.S. or in the current health care environment where physicians have to struggle frequently to secure preauthorization for patients' imaging studies and also when institutions' and physicians' "participation" in various health insurance programs are changing continuously.

Despite these clear advantages, LE is currently not included in either the National Comprehensive Cancer Network or American Society of Colon and Rectal Surgeons guidelines as an acceptable organ preservation strategy for patients diagnosed with LARC.[11,12] In addition, there are no U.S.-based

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active trials currently listed on the Clinicaltrials.gov Web site that is conducted by a cooperative group or major institutions aiming to define and further refine the role of LE in the management of LARC. We will attempt to address the perceived shortcomings of LE commonly cited in the literature and are probably the cause of its underutilization.[13–18]

Fragmentation Pattern of Residual Disease after Neoadjuvant Therapy

Some studies of the microscopic pattern of distribution of residual cancer after neoadjuvant therapy describe a nonuniform tumor fragmentation.[19,20] Islands of residual cancer are scattered around the main residual bulk and are separated by benign tissue, thus creating the potential for an incorrect assumption of R0 resection when LE is performed. We do not think that this observation is relevant when the purpose of LE is to confirm the pathological absence of cancer cells rather than to play any therapeutic role. In addition, the only prospective trial that studied the pattern of residual microscopic disease after neoadjuvant therapy, using whole organ examination, reported a very low incidence (1.8%) of extension of microscopic disease outside the mucosal abnormality to a distance less than 1 cm.[21] This finding is similar to that of our previous work.[22] We are not aware of any study reporting the presence of microscopic scattered cancer cells in the absence of detectable tumor in the bowel wall directly underneath the residual mucosal abnormality. Therefore, we believe that excising only the bowel wall directly underneath the mucosal abnormality with no margin, regardless of the initial size or circumferential involvement of the rectal wall at diagnosis, will suffice for accurate determination of the ypT status. Removing extra margin around the residual mucosal abnormality or extending the dissection into the mesorectal fascia will not increase the accuracy of detecting subclinical microscopic cancer and may only result in increased postoperative complications.

Frequent and Severe Postoperative Complications

The perceived high incidence of severe postoperative complications after LE is perhaps the most important factor that causes its underutilization. The following three studies are often cited to illustrate this perception:

Marks et al[23] examined postoperative complications after neoadjuvant radiotherapy and LE. At the time of the study, LE was generally recommended for patients with tumors < 3 cm and stage cyT2 or lower. However, patients with tumors not meeting these criteria were also included if they were not fit for or refused TME. Twenty-three percent of patients presented with stage T3, and 58% had tumors within 3 cm of the anus. At the time of LE, only 33% of patients had achieved CCR. The overall observed morbidity rate was 33%. The mean radiation dose was 5175 (4000–5580). The initial goal was to deliver 55.8 Gy, but because of intolerance, some patients got lower doses. A relatively large amount of tissue was excised with 40% of patients undergoing hemicircumferential excision.

Perez et al[13] reported a retrospective review of a prospectively maintained database for 23 patients undergoing LE after neoadjuvant therapy. The department policy was to consider LE for patients with small residual disease, and it was used primarily as a diagnostic approach. Patients were also eligible if they refused TME. All patients received preoperative chemoradiotherapy (CRT) to the pelvis at a radiation dose of 50.4 to 54 Gy. All patients had locally advanced low (7 cm from the anus) rectal cancer with cT3-cT4 and cN1-cN2 stages. The extent of surgical resection, as described in another publication from the same group,[15] extended to the mesorectal fascia to provide maximal radial margins. The rate of immediate postoperative complications was quite high (56%), with wound dehiscence being the most common; other complications included severe pain and rectal bleeding. Wound dehiscence occurred in 1 of 5 patients with preoperative stage ycT0 and 13 of 18 (72%) patients with stage ycT+, raising the question of a possible correlation between the occurrence of complications and the extent of resection, as the surgeons may have performed more extensive resection in cases of known residual disease. Most of LE procedures in this series were therapeutic and not to confirm the ypT0 status.

Garcia-Aguilar et al[24] conducted a prospective trial to investigate the management of ycT2 tumors by preoperative CRT and LE. All patients underwent LE regardless of the response to treatment, and no restaging determination was required. Concurrent doublet chemotherapy of 5-FU and oxaliplatin was administered. A radiation dose of 54 Gy was used initially, and it was lowered to 50 to 50.4 Gy when high morbidity rate was realized. Decreased toxicity was noticed with lowering of the radiation dose. LE was performed therapeutically and not to confirm the presumed complete eradication of the tumor. The study protocol mandated excision of the tumor site with 1 cm of normal surrounding tissues and that all participating surgeons had to have performed at least three LE procedures with negative margins before participating. The published report did not indicate the size of the resected specimens, and it is plausible that a wider margin than 1 cm was excised in some cases, as the rate of positive surgical margin was quite low. High toxicity rates resulted in early termination of the trial.

These studies suggest that when LE is done with a therapeutic intention, it is often performed with wide surgical resection and deep dissection into the perirectal fat. This aggressive resection likely contributed to the observed high complication rate. The distance of the tumor from the anus can also affect the incidence postoperative complications as more significant postoperative toxicity is expected when the surgery involves part of the lower anal canal. Habr-Gama et al[14] proposed a reasonable theory to explain this finding related to lack of tissue elasticity and different innervation in these tissues. The exact distance of individual tumors from the anus was not reported in any of these studies, but the average reported distances indicate that many tumors likely extended through the lower anal canal. In all these studies, a radiation dose above 50.4 Gy was administered to some patients, and this slight dose escalation may have

contributed to the postoperative morbidity, as in Garcia-Aguilar et al's study. The radiation volume was specified only in this study where the radiation fields were routinely extended for adequate coverage of the common iliac lymph node chains. In many early tumors typically selected for organ preservation strategy, extending the radiation coverage to the common iliac chain may be unnecessary as illustrated by the recommendations of Valentini et al.[25] The contribution of this large radiation volume, if any, to the development of subsequent complications is not known but cannot be excluded.

Importantly, other authors have published favorable postoperative toxicity profiles. The TAUTEM trial[26] reported postoperative complications grade > III in only 8.5% of patients. In that study, LE dissection did not extend into the perirectal fat. In another series of 425 patients treated by LE alone (120 patients) or after neoadjuvant radiation (350 patients), only 10% of the entire cohort experienced minor complications, with major complications affecting only 1.4% of patients.[27] Similarly, in a study of 43 patients treated by neoadjuvant therapy followed by LE, only 1 patient experienced grade III complications, and 5 experienced grade I or II adverse effects.[28] Our group has also published a small study with a favorable postoperative toxicity profile.[29]

Posttreatment Anorectal Function

There is a paucity of data of sufficient strength to describe the anorectal function after preoperative treatment and LE, particularly compared with the watch-and-wait (WW) approach. The study by Habr-Gama et al[30] is commonly cited to indicate a significantly inferior anorectal function after LE when compared with that after WW. In this report, the anorectal function was measured by anorectal manometry, fecal incontinence index, and quality of life assessment. The LE arm included 46 patients who received neoadjuvant CRT, with some patients receiving a radiation dose of 54 Gy. Although the treatment policy was to offer LE only to patients with residual small tumors < 3 cm with good response to preoperative CRT resulting in ycT1-T2-yN0, 37% of patients had ycT3 and an average residual tumor size of 5.1 cm. Of course, all patients in the WW group achieved CCR. Average distance between the tumor and the anal verge in the LE arm was 2.6 cm, and all tumors were resected with at least a 1-cm margin and the dissection extended to the mesorectal fascia. All patients treated by LE developed significant postoperative pain.

It appears that the anorectal function following LE is superior to that after TME if clinical staging before surgery is reasonably accurate to avoid, as much as possible, the necessity of completion TME, which is associated with poor anorectal function.[31–33] We are not aware of any studies describing the rectal function following "limited LE"[29] and completion TME. There is insufficient data to compare the posttreatment function between carefully selected patients for LE and patients managed by WW. To this end, it is important to note that major low anterior resection syndrome symptoms were reported in 36% of patients in one WW series.[34]

Difficulty of Follow-Up

Another argument against LE is the potential challenge in interpreting clinical and imaging surveillance findings because postoperative changes in the surgical bed cloud the distinction between recurrent disease and normal posttreatment fibrotic changes, particularly in the setting of development of postsurgical complications.[14] When LE is performed solely to document the ypT0 status, the probability of local recurrence is small (in the range of 5%), as has been shown in multiple studies and the postoperative complication rate is expected to be low. While close follow-up is still required, this theoretical difficulty in interpreting imaging and clinical surveys becomes less important.

Lack of Randomized Trials Comparing the Safety of LE to WW

As discussed above, the safety of LE when compared with the standard of care approach with TME was shown in a randomized trial with relatively long follow-up and in several prospective and retrospective series. We are not aware of any published randomized trial results comparing WW and TME, but WW is recognized as a possible strategy, with some restrictions, by the national guidelines. We do not agree that an investigational procedure such as LE should have to prove its equivalency to another investigational procedure (WW) in a randomized trial before it receives the same degree of recognition.

Suggested Approach

The goal of this commentary is not to promote LE over WW but to identify the benefits and limitations of each approach and dispel the perception of frequent and severe complications resulting from LE after neoadjuvant therapy. We believe that each approach has a place in specific clinical scenarios. Tumors in the very distal rectum are better managed by WW than LE to avoid the postoperative morbidity associated with LE for tumors in these locations. The difficulty of performing sphincter preserving completion TME (if needed) should be considered, as well as the reported poor rectal function associated with the excision of tumors a very short distance from the anus.[28,29] Limited LE can be a viable option for higher tumors, even when CCR is achieved, particularly if the treating physicians are concerned about the feasibility of regular and close follow-up or the availability of high-quality imaging facilities.

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Conflict of Interest
The authors have no conflicts to declare.

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