Local Excision and Endoscopic Resections for Early Rectal Cancer

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Abstract

Keywords

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- local excision
- endoscopic resection
- transanal endoscopic microsurgery
- transanal endoscopic operation

Radical surgery is considered as the standard treatment for rectal cancer. Transanal local excision has been considered an interesting alternative for the management of selected patients with rectal cancers for many decades. Different approaches had been considered for local excision, from endoscopic submucosal dissection to resections using platforms, such as transanal endoscopic microsurgery or transanal minimally invasive surgery. Identifying the ideal candidate for this approach is crucial, as a local failure after local excision is associated with poor outcomes, even for an initial early rectal tumor. In this article, the diagnostic tools and criteria to select patients for local excision, the different modalities used, and the outcomes are discussed.

Transanal local excision has been considered an interesting alternative for the management of selected rectal cancers for many decades. The possibility of removing rectal tumors through the anus, by avoiding entry into the abdomen, and the complexity of working within the confines of the pelvis has always been an attractive alternative to transabdominal proctectomy. Transanal procedures have been performed with minimal morbidity and mortality rates. Also, early discharge of patients and no requirement for temporary or definitive stomas have been the advantages of this procedure.

However attractive the local excision of rectal tumors may be, the main drawback of the method is the lack of proper resection of regional lymph nodes. In this setting, oncological outcomes of local excision (without proper lymphadenectomy) are closely related to the risk of lymph node metastases (LNM). Therefore, recognition of risk factors for the presence of LNM by accurate staging is crucial for patient selection. Ideally, this procedure would be reserved for patients with small primary tumors, sufficiently low to be accessible through the anus (particularly before the development of transanal endoscopic microsurgical techniques) and with minimal or no risk for concomitant LNM.

Risk Factors for Lymph Node Metastases

Several studies have focused on clinical and pathological risk factors for LNM in rectal cancer, particularly for patients

considered for transanal local excision, including pT1 and pT2 rectal cancers.

One of the most important risk factors for N+ disease is pT classification. The risk of nodal metastases progressively increases with more advanced pT stage classification. Even for the earliest tumors invading the submucosa (pT1), the overall risk of LNM is around 12 to 13%. The subclassification of pT1 cancers into three levels of submucosal invasion has also been correlated with the risk of LNM, with a risk of 0 to 3, 8 to 11, and 11 to 25% for tumors invading sm1, sm2, and sm3, respectively.^{1,2} A large retrospective review of patients with pT1–pT2 rectal cancers reported a risk of LNM of 21% in pT2 rectal cancer.³

During the endoscopic examination of the primary rectal lesion, the level of invasion of the submucosa may be already estimated by the glandular crypt pattern. Identification of regular (and frequently small) pit patterns (I–III) often indicates the presence of lesions restricted to the mucosal layer. In contrast, the presence of irregular pit patterns with the architectural loss (IV) and amorphous structures (V) suggests an increased risk of deep submucosal invasion. Therefore, in the proper setting, endoscopic resection of types I to III may provide an alternative to local excision with submucosal dissection in very early lesions.⁴

In addition to pT classification, other pathological features have also been associated with an increased risk of LNM, including lymphovascular invasion and tumor grade.⁵ The presence of lymphovascular invasion and poor differentiation

significantly increases the risk of LNM. However, one study suggested that both pT1 and pT2 cancers would harbor a 100% risk of LNM in the coexistence of poor differentiation and lymphovascular invasion.³ Finally, distally located cancers were also found to be more likely to harbor LNM, and therefore constitute a high-risk factor.⁵ Therefore, a small ($\leq 2\text{--}3\text{ cm}$) pT1 rectal adenocarcinoma restricted to the sm1 level, well differentiated, and with no lymphovascular invasion would be the best candidate for a local treatment with nearly no risk for LNM.⁶

Local Staging

T-Stage Classification

Considering specific features of primary cancer (particularly pT status, lymphovascular invasion, and tumor grade) are directly associated with the risk of LNM, primary local staging of rectal cancer is of paramount importance for the selection of appropriate candidates for transanal local excision. Diagnostic biopsies may allow a proper determination of tumor grade. On the other hand, determination of intramural or microscopic lymphovascular invasion often requires excisional biopsy specimens and is therefore almost impossible to accurately assess preoperatively. Ultimately, clinical/radiological T and N classification (cT and cN) are frequently the only sources of information used for management decision of these patients.

The depth of the primary tumor may be accurately determined by the use of different radiological imaging modalities. Both endorectal ultrasound (ERUS) and high-resolution magnetic resonance (MR) imaging have been extensively studied for this particular purpose. Since the risk of LNM among T3 and T4 rectal cancers is exceedingly high, these patients are not even considered for local excision except in extreme palliative situations. The distinction between T2 and T3 rectal cancers would therefore possibly provide the first filter for patients potentially suitable for a local procedure. A meta-analysis of accuracy rates for local staging of rectal cancer has been performed comparing different staging modalities.⁷ Interestingly, ERUS was associated with higher sensitivity rates for the distinction between T2 and T3 cancers whereas specificity was nearly identical. In other words, MR may result in significantly more underestimation of T-stage of these patients, potentially leading to an inappropriate indication of local treatment for the unsuspected T3 disease.⁷

Distinguishing between cT1 and cT2 is perhaps the most relevant step in the assessment of these patients. A meta-analysis of the results of rectal cancer staging with MR and ERUS suggests that specificity for the distinction of pT1 from pT2 was best for ERUS, even though sensitivity was similar between both modalities. This means that MR overestimates more frequently between T1 and T2 rectal cancer when compared with ERUS.⁷ The ideal patient for a transanal local excision is the one with cT1 cancer, preferably restricted to sm1. This is because the risk of LNM may also be correlated with the level of submucosal involvement. However, partial thickness endoscopic resections may not provide the entire

submucosa for pathological review, and therefore subdivision into thirds may be impossible. In this setting, absolute measurement of the depth of tumor invasion (in specimens without entire submucosa available) may provide clinically relevant information as well. In nonpedunculated T1 cancers, invasion within the submucosa of $\leq 1,000\text{ }\mu\text{m}$ is associated with no risk of LNM even in the presence of lymphovascular invasion. Also, three-dimensional ERUS in experienced hands was able to identify the sm level of invasion with acceptable accuracy rates correctly.⁸ In one study, patients with pT0 and pT1 sm1 were correctly distinguished from pT1 with massive invasion or pT2 with excellent accuracy rates.⁸

N-Stage Classification

Another critical issue in local staging during preoperative assessment of these patients is accurate lymph node classification. Unfortunately, nodal assessment (cN) is considerably less accurate than the depth of invasion (cT). Overall, accuracy rates of MR and ERUS are in the range of 75 to 85% for correct nodal classification. On the contrary, in the meta-analysis comparing different imaging modalities, sensitivity and specificity rates were nearly identical between ERUS and MR.⁷ Still, the nodal assessment may be influenced by the depth of primary tumor invasion. In one retrospective study, the accuracy of nodal staging was significantly worse for pT1 and pT2 cancers. Considering these pT1 and pT2 cancers are those potential candidates for local excision, it is rather disappointing that nodal staging was less reliable. Ultimately, the authors suggest that these limitations in early cancer nodal staging may explain frequent failures after local excision alone.⁹

Defining High-Risk and Low-Risk Patients

Ultimately, surgeons should attempt to identify patients at high or low risk for development of LNM and local recurrence before offering local excision for rectal cancer (→Table 1). Histological and morphological features that define a higher risk of nodal spread in T1 tumors are poor differentiation, tumors larger than 3 cm or with more than 30% of the bowel lumen involved, the presence of lymphovascular or perineural invasion, margins less than 2 mm.^{3,10–14} pT2 tumors

Table 1 Criteria for definition of high-risk and low-risk tumors

High risk	Low risk
Poor differentiation	Well and moderate differentiation
Size $\geq 3\text{ cm}$	Size $< 3\text{ cm}$
Circumferential involvement $\geq 30\%$ of lumen	Circumferential involvement $< 30\%$ of lumen
Presence of lymphovascular invasion	
Presence of perineural invasion	
Margins $< 2\text{ mm}$	
pT2	

are also considered high-risk tumors. When such features are found in the preoperative assessment, local excision should be considered with caution and perhaps as an indication of palliative management (due to oncological reasons or significant medical comorbidities).

However, sometimes these features are only confirmed after review of the pathological specimen following a local excision. In this case, additional treatment should be considered. One option includes completion of total mesorectal excision (TME) or salvage resection to provide radical lymphadenectomy. Alternatively, adjuvant radiation or chemoradiation (CRT) may be used for the management of these patients.¹⁵

Techniques of Local Excision

Traditional or Standard Transanal Local Excision

An anal retractor is used to dilate the anus and obtain an adequate exposure. A lone-star retractor may provide excellent access to the lower rectum for this purpose. Selectively, traction sutures may be placed laterally to the lesion to enhance exposure. A line of dissection with a margin of 1 cm is made with electrocautery circumferentially. The depth of resection should always reach the mesorectal fat to provide a maximal radial margin (►Figs. 1 and 2). The specimen should always be fixed to a cardboard for better assessment by the pathologist (►Fig. 3). The defect in the rectal wall is then closed transversely with a running suture, preferably with an absorbable material (PDS and/or Caprofil [Ethicon, Inc.]).

Minimally Invasive Options

Two relatively new techniques have been introduced to approach rectal tumors using the transanal approach with the use of rectal CO₂ distention (pneumorectum), endoscopic view, and minimally invasive instrumentation.^{16,17} These techniques may provide improved surgical field view and access to lesions in the middle and upper rectum. Implementation of these endoscopic microsurgical approaches has

Fig. 1 Standard local excision: the mesorectal fat can be seen after the excision of the surgical specimen.

Fig. 2 After fixation, a significant amount of the perirectal fat can be seen providing an appropriate radial margin.

resulted in significant improvements in quality of the resected specimen. In a review of 171 patients undergoing transanal endoscopic or standard local excision, margin clearance, specimen fragmentation, and local recurrence were all consistently higher among the patients operated by the traditional approach. Considering that the postoperative morbidity between the approaches is similar, the authors concluded that transanal endoscopic surgery is the procedure of choice for the local excision of rectal masses.¹⁸ In fact, recent meta-analyses suggest that the use of transanal endoscopic platforms resulted in less fragmentation of the specimen and lower risk for positive margins among these patients.¹⁹ Finally, this approach provides proper access to safe resection of upper rectal lesions and closure of peritoneal defects created by full-thickness excision in the

Fig. 3 The surgical specimen should be fixed to a surface to provide orientation for the pathologist.

anterior wall, particularly in males or posthysterectomy females.

Transanal Endoscopy Microsurgery

The procedure is performed using a special proctoscope of 4 cm in diameter available in lengths of 12 and 20 cm. The rectum is insufflated with CO₂ at 10 to 15 mm Hg. This can be achieved with the use of specific or usual laparoscopic CO₂ insufflators. The optical sixfold increase and the stability provided by the equipment, attached to the operating table, it allows an excellent view of the rectum and lesion. The proctoscope is frequently repositioned to allow the best visualization of the lesion during the procedure. Once the setup is complete, special endoscopic instruments are introduced through the proctoscope (usually four ports for entry) and resection is performed. In addition to the scope and two instruments manipulated by the surgeon, suction may be used through the fourth portal entry for aspiration of the smoke created by cautery (→Fig. 4). Marking of 1 cm circumferential margins around the primary lesion before resection is advised to avoid disorientation. Full-thickness resection is performed using electrocautery avoiding direct

manipulation of the tumor. Alternative energy sources may be utilized for this resection including harmonic or sealing devices. Once the specimen is removed, a final check for hemostasis is performed, and bleeds are carefully dealt with. In most cases, attempt to close the rectal defect is done with the use of an absorbable running suture.

The use of specific transanal endoscopic microsurgery (TEM) equipment requires a significant investment and cost-effectiveness becomes a relevant issue. In a recent retrospective case-control study, patients undergoing TEM were compared with standard rectal resection.²⁰ Even though the initial investment was significantly higher for TEM, decreased costs related to disposable instruments, hospital stay, and stoma takedown compensated differences. Ultimately, TEM resulted in a less expensive approach for the management of rectal lesions when compared with standard surgical resection despite the need for equipment purchase. In that study, the authors suggested that savings with TEM would provide compensation of the initial investment after 11 to 12 cases.

Transanal Minimally Invasive Surgery

More recently, a variation of the previous technique has been proposed to allow TEM with the use of standard laparoscopic equipment.¹⁷ This would potentially avoid the need for considerably expensive and exclusively dedicated TEM equipment. Instead, the use of simple and readily available laparoscopic equipment would allow similar efficacy with considerably lower associated costs. Also, the learning curve of the procedure could be minimized by the use of routinely used as opposed to specific TEM instruments.

Several transanal ports have been suggested for this approach including disposable or reusable single ports. After connection with the regular laparoscopic insufflator, a 5 mm laparoscopic scope is inserted to provide an endorectal view. In contrast to TEM, transanal minimally invasive surgery requires an assistant to control the camera and therefore, the stability of the image is lost. Once the additional instruments are inserted, the surgeon may perform the procedure very similar to the TEM technique. However, most single ports have only three portal entries, and therefore, smoke aspiration is not continuous. Finally, access to the lower rectum may be difficult due to a significant need for instrument angulation. On the other hand, access to the upper rectum may be limited by rectal folds in some patients. Middle rectal lesions are best suited for this technique.

Transcoccygeal Excision

The posterior approach via transsacral popularized by Kraske has been especially helpful for lesions on the posterior wall within the middle or distal thirds of the rectum.²¹ However, it also allows resection of lateral and anterior lesions. The advantage of this approach is that it provides exposure of the mesorectum. Therefore, perirectal nodes could potentially be removed for histopathological examination.

The patient should always be placed in jack-knife prone position. The coccyx is tackled by a longitudinal incision from the perineum to the second or third sacral vertebra. Gluteal

Fig. 4 (a) TEO/TEM equipment, with camera and insufflation in place. (b) The position of TEO/TEM equipment fixed to the surgical table and with instruments inserted. TEM, transanal endoscopic microsurgery; TEO, transanal endoscopic operation.

muscle insertions are released, and the anococcygeal ligament is transected. Removal of the coccyx is performed after total exposure. At this point, the middle sacral artery should be ligated. The rectum is approached through the perirectal fat, and through the levator ani, separated at midline. This provides a complete mobilization of the rectum within the intraperitoneal pelvis. For posterior lesions, it is useful to use the digital rectal examination to guide the resection. This gives the orientation of the lower edge of the tumor to achieve 1 cm circumferential margin. For anterior lesions, posterior proctectomy is required, allowing resection under direct vision of the primary tumor. All the defects in the rectal wall are closed transversely to prevent stenosis, using running absorbable suture. Finally, the levator ani is approximated at the midline, and the anococcygeal ligament is reattached to the sacrum. The subcutaneous tissue and the skin are closed. Morbidity rates for this procedure are higher than for transanal excision approaches. Development of rectocutaneous fistulae ranges from 15 to 25%, and sometimes a temporary diverting stoma is required. Other complications include urinary dysfunction, wound infection, and transient fecal incontinence. In this setting, the transsacral approach is being left as it is progressively less used. However, the procedure remains a viable option particularly to patients who are not amenable to a transanal approach.²²

Morbidity and Mortality

Mortality after local excision is very low, with most studies showing no mortality and others up to 2 to 3%.²³

The overall morbidity has been reported to range from 9 to 45%. Major complications are uncommon and occur in around 1.5% of cases. Bleeding is the most common major complication, eventually requiring reintervention. Infectious complications may rarely require a diverting stoma in around 1% of cases.²⁴

The single most relevant risk factor for postoperative complication is the use of neoadjuvant CRT. When preoperative CRT is delivered, TEM resection leads to a rectal wound that allows primary suturing without any technical difficulty, unless the proximal margin is very close to the anal canal/verge. In this situation, even though the upper border of the wound may retain its considerable elasticity, the lower border of the wound of the anal canal is rather fixed and with little mobility. If the resection is wide enough to result in significant separation of the proximal and distal borders, significant tension will be present, a known feature to contribute for wound dehiscence. Also, the anal canal has ectodermic nerve supply as opposed to endodermic nerve supply to the rectum. Therefore, wound separation and mucosal discontinuity in this area may be quite painful. Finally, regardless of the level of suturing (rectal or anal canal), the borders to be sutured after a TEM resection in previously irradiated rectum will necessarily put together two previously irradiated borders. This is quite different from a coloanal anastomosis following neoadjuvant CRT, where the proximal colon is never included in the radiation field, and therefore a normal colon is sutured to an abnormal

anal canal previously treated with a significant amount of radiotherapy (RT).²⁵ In fact, even after a coloanal anastomosis is constructed, the risk of dehiscence is so significant that a loop ileostomy is almost always recommended.²⁶ One can imagine the risk of wound dehiscence after suturing together two previously irradiated borders of rectum or anus, sometimes with significant tension depending on the level of the suture.

In fact, few studies compared the risk of wound separation and its consequences with or without previous exposure to CRT. Retrospective studies had suggested that the risk of wound dehiscence was significantly higher when CRT was delivered preoperatively. In one of these studies, diagnosis of wound dehiscence was made after more than 1 week following TEM and healing of the dehiscence took an average of more than 8 weeks to complete. In this situation, a surgery that otherwise would almost never require a stoma, occasionally required a diversion.²⁷ In another study, even though none of the dehiscences required stomas, pain management was quite significant requiring readmission for analgesia in a significant proportion of patients.²⁸ More recently, a prospective trial has been closed due to the increased morbidity associated with TEM following neoadjuvant short-course RT.²⁹

Ultimately, these findings raised the issue whether any attempt to close the wound defect created by TEM should even be performed. Leaving the wound open could potentially avoid the complication of wound dehiscence and minimize its consequences. However logical this may seem, there is no good evidence to support this idea from any study and the author's clinical experience with unclosed wounds showed no significant differences in pain control after TEM following neoadjuvant CRT for rectal cancers.²⁸

Outcomes

T1 Rectal Cancer—Local Excision Alone

Local excision alone was considered a valid treatment alternative for T1 rectal cancer for a long time. In the absence of prospectively randomized studies comparing full-thickness local excision to radical TME, most of the data arise from retrospective analysis and case series. Retrospective reviews of selected patients undergoing full-thickness local excision (FTLE), oncological outcomes (local recurrence, survival, and cancer-related death rates) were inferior to radical surgery for T1 disease, including a higher risk of cancer-related deaths.^{30,31} Even though transanal endoscopic techniques managed none of these patients and there was no distinction between favorable and unfavorable tumors, the authors suggested that local excision should be restricted to patients with prohibitive medical contraindications to major surgery.

The only prospective study on local excision alone for T1 rectal cancer was performed in the United States under Cancer and Leukemia Group B (CALGB).³² Between 1990 and 1995, 59 patients with T1 rectal cancer were managed by local excision alone. The 10-year local and distant recurrence rates were 8 and 5%, respectively. These encouraging results were followed by less successful outcomes in following

studies. Several studies with variable inclusion criteria, inconsistent pretreatment staging assessment, and no standard pathological reporting reported on a wide range of local recurrence rates (0–30%). The retrospective comparison of local excision to radical surgery for stage I rectal cancer consistently showed worse oncological outcomes after local excision, even though no randomization or case-matched study was ever possible.³⁰

A multicenter collaborative study performed in Europe included 21 centers performing TEM for nearly 500 early rectal cancers suggested that specific pathological features were associated with acceptable (<5%) 3-year local recurrence rates. Well-differentiated (≤ 3 cm) tumors restricted to sm1 and in the absence of lymphovascular invasion were considered to be appropriate candidates for this procedure.

Local recurrence for unselected pT1 rectal cancers, however, remains between 10 and 20%.³³ In addition to the considerably high local recurrence rates, salvage procedures after local recurrence offer poor oncological outcomes. A recent review of 88 patients with pT1 undergoing TEM, local recurrences were observed in 20% of the cases.³⁴ Of these recurrences, only a minority had unfavorable pathological features (sm3 invasion, lymphovascular invasion, and poor differentiation). More than 80% had advanced-stage disease at the time of recurrence, and even though R0 resection was possible in most cases, 3-year disease-free survival was disappointing (58%). Alternatively, immediate salvage resection following local excision seemed to have not compromised oncological outcomes of patients with early-stage rectal cancer. In a retrospective study of patients undergoing local excision followed by radical salvage resection within 30 days revealed that the results were similar to a matched control group of patients undergoing straight to radical surgery and comparable pathological staging.³⁵

Even though there is a suggestion that early or immediate salvage provides acceptable oncological outcomes for these patients, the procedure (radical TME) is not trivial. The quality of the resected mesorectum in this setting may be significantly compromised in a significant proportion of cases (moderate or poor in 36%). Also, some features of the original procedure such as the distal location of the tumor and long interval after local excision (≥ 7 weeks) were all associated with the risk of poor quality of the specimen.³⁶ Also, previous local excision has been shown to a significant and independent risk factor for subsequent abdominal perineal excision.³⁷

Distant metastases, when found after FTLE for T1 tumors, usually appear synchronically with local recurrence. Although salvage surgery after local excision is feasible in most patients with T1 tumors, survival might be limited, mainly because of distant metastases.³⁴

Transanal Endoscopic Microsurgery versus Endoscopic Submucosal Dissection

An alternative treatment strategy to surgical transanal local excision is endoscopic resection of early rectal cancers. The endoscopic approach of early rectal lesions allows for a

“surgical-like” en bloc resection with negative margins, with no need for general anesthesia (most centers in eastern countries use no anesthesia or sedation at all), minimal invasiveness and shorter hospital stay. The procedure is, however, technically demanding with currently available equipment using a single working channel. This significantly limits the effect of traction and constitutes a significant challenge in tissue manipulation during the procedure, particularly relevant during resection of larger lesions. Ultimately, these limitations may lead to longer operative times.³⁸

Very few studies have compared head-to-head these two different alternatives for the management of early rectal cancers. Therefore, the best evidence is derived from systematic reviews and meta-analysis including case series of either technical approach with its inherent selection biases.

In a recent 2013 systematic meta-analysis review of these techniques (TEM or endoscopic submucosal dissection [ESD]) for the treatment of early rectal tumors, specific surgical outcomes were compared. Rates of en bloc resection (absence of fragmentation of the specimen) and negative margins (R0 resection) were shown to be superior for TEM (en bloc 98.7 vs. 87.8%; $p < 0.001$ and R0 88.5 vs. 74.6%; $p < 0.001$). Overall postoperative complication rates (8.4 vs. 8%; $p = 0.874$) were similar between both techniques and the need for subsequent abdominal surgery for the management of complications was also similar (1.6 vs. 1.3%; $p = 0.665$).

Both rates of invasive cancer in the resected specimen and disease recurrence was similar between patients undergoing TEM or ESD (5.2 vs. 2.6%; $p = 0.068$). However, provided patients undergoing ESD were less likely to undergo R0 resection, completion abdominal surgery was more often required among this subgroup of patients (2.9 vs. 8.4%; $p = 0.011$).

Altogether, the study concluded that patients undergoing TEM were more likely to have en bloc resection with a negative margin (R0) specimen and less likely to require completion abdominal surgery (for oncological reasons) when compared with ESD.³⁹

Local Excision and Adjuvant Therapy

In the presence of high-risk pathological features seen in the surgical specimen following local excision, an alternative to complete TME is the use of adjuvant RT or CRT. Most studies have considered the presence of T2 tumors, close or positive resection margins, lymphovascular invasion, and poor differentiation for such purposes. In the CALGB study, negative margins pT2 cancer patients were offered adjuvant 5-fluorouracil (5FU)-based CRT (54 Gy). In that study, 10-year local and systemic recurrence rates were 18 and 12%, respectively. However, the median time to recurrence for pT2 cancers was nearly 2 years, significantly shorter than for pT1 cancers (approximately 4 years) in the same study (treated by local excision alone).

The RTOG study showed slightly better results for local excision. CRT was given when local excision specimens showed unfavorable histopathological features in T1 tumors

or T2 tumors and a higher dose of CRT when margins were involved. Low-risk T1 tumors were only observed without further surgery. The overall local recurrence rate was 16%, and local recurrence-free survival was 86% for patients treated with adjuvant therapy in 5 years. These rates are similar to the ones seen for TME in the literature. There was no difference in disease-free survival or overall survival between patients who received adjuvant CRT and those who did not. The local recurrence rates were 1/14 (7.1%) in patients who were only followed up and 2/51 (3.9%) in those who received CRT.⁴⁰

A retrospective cohort of T1/T2 rectal tumors with adjuvant radiation following FTLE or FTLE alone has shown interesting findings. In the irradiation group, local control rates for high-risk T1 tumors were 100%, while 85% for T2 tumors. In the FTLE alone group, local control rates were 89 and 33% for T1 and T2 tumors, respectively. The addition of systemic chemotherapy with 5FU did not significantly improve local control or recurrence-free survival in the irradiation group. With these results, they recommended only adjuvant CRT for high-risk tumors after local excision.⁴¹ In another recent study, local excision alone for pT1/2 with favorable features and local excision + adjuvant CRT for pT1/2 with unfavorable features resulted in 0% local recurrence. Local recurrences were exclusively observed after the presence of adverse features and failure to undergo adjuvant CRT.⁴²

Main limitations of studies focused on local excision followed by adjuvant RT include variable RT regimens and technique, variable surgical techniques, and absence of information regarding unfavorable pathological features.

Neoadjuvant Chemoradiation Followed by Local Excision

Even though postoperative (adjuvant) therapy would have the benefit of offering patients treatment after confirmation of the presence of “unfavorable” pathological findings, the observation of decreased toxicity and improved local disease control in prospective randomized trials of rectal cancer in the setting of radical surgery led to the utilization of radiation and chemotherapy in the preoperative period (neoadjuvant).^{43–45} Also, the exposure of healthy and well-oxygenated tissue, as opposed to postoperative fibrotic tissue, to radiation would theoretically improve its antineoplastic effects. Finally, perhaps one of the most beneficial aspects of offering patients preoperative neoadjuvant therapy would be the effect on tumor shrinkage. The decrease in tumor size (downsizing) and shifts in tumor stage (downstaging) have been well documented after neoadjuvant therapies with radiation and CRT.^{46–49} In fact, the addition of chemotherapy to radiation has been shown to significantly increase the effects on tumor size and stage when delivered preoperatively.⁴⁶ Also, this downsizing and downstaging seem to be time-dependent and therefore, at least 6, 8, or even 12 weeks may be required to obtain maximal results tumor regression.^{50–52}

It appeared that neoadjuvant therapy, particularly CRT, was the answer to all prayers for TEM in rectal cancer:

improved local disease control, minimized toxicity, decreased tumor size, downstaged cancers, and a minimally invasive approach without all of the downsides of radical TME.

However, the expected benefits of this strategy came at a significant cost in terms of wound healing (as mentioned previously) and salvage possibilities. Also, local recurrences may still be a concern depending on the baseline and post-treatment characteristics.

Local Recurrence

As mentioned earlier, local recurrence rates have historically paralleled the risk of LNM in patients treated by FTLE for rectal cancer. pT status is one of the most relevant determinants of the risk of perirectal nodal metastases both with or without CRT.^{53–56} In fact, studies have suggested that the risk of LNM is < 5 to 10% for ypT0, 10 to 15% for ypT1, and nearly 20% for ypT2.⁵⁷ Therefore, one could expect these rates of local recurrence after treatment with CRT followed by local excision regardless of the original baseline staging.

However, radiological imaging has evolved significantly over the years, and nodal staging has improved. Even though accuracy is still far from 100%, MR and endorectal ultrasound have been studied extensively to improve detection of LNM. It has been suggested that MR could safely assign patients after CRT that would be appropriate candidates for FTLE by correctly identifying ycT0–2N0 (accuracy ≥ 90%).⁵⁸ This suggests that ypT0, ypT1, and ypT2 would all be suitable candidates for FTLE or TEM, once nodal metastases have been ruled out.

Bonnen et al, in 2004, published their results comparing 26 patients with T3 tumors submitted to neoadjuvant CRT followed by local excision and 405 patients submitted to neoadjuvant CRT followed by TME. In the local excision group, the pCR was 54%. The 5-year local recurrence rate was 6% in this group while 8% in the TME group, and 6% in the subgroup of complete responders in the TME group. Overall survival was 86 and 81% in the local excision and TME groups, respectively. An update on their data⁵⁹ showed that results were maintained after a longer follow-up of 63 months. They suggest that highly selected patients who respond well to CRT might be submitted to FTLE.⁶⁰

A retrospective study of patients with locally advanced rectal cancer following long-course CRT with near-complete response (≤3 cm, ycT0–2N0) managed by TEM has been reported. In this study, the overall local recurrence rate was nearly 15%.⁶¹ In this study, most patients had ypT1/ypT2 whereas ypT0 were very few.

In a recent report from a multicenter study in Italy (phase II), 63 patients underwent CRT for cT2–3N0–1 disease at baseline.⁶² Of these, 42 had ypT0 and were treated by FTLE alone with no recurrence. Also, one patient with ypT1 and TRG2 did not have any recurrence. However, of the nine patients with ypT2 who refused radical TME, two developed local recurrences after FTLE alone (22%). Similar results have been reported by the CARTS study, where patients with ypT2 following TEM that refused completion TME developed local recurrence in nearly 30% of cases.⁶³

Other authors have suggested that baseline staging is also important and only small and cT2N0 followed by neoadjuvant CRT would be appropriate candidates for FTLE or TEM.⁶⁴

In fact, the single randomized study that compared cT2N0 followed by neoadjuvant CRT and TEM or TME found in its first report advantages in early/immediate outcomes favoring TEM (less transfusion and stoma requirements, less hospital stay and less need for intensive care unit). Local recurrence rates were similar between groups.⁶⁵ In a more recent update, local recurrence rates were still similar between groups. However, TEM resulted in more early recurrences when compared with TME. Also, TEM was considered to be an independent risk factor for the development of recurrent disease (metastatic or local recurrence) after multivariate analysis.⁶⁶ Ultimately, local recurrence rates were all < 10% in both groups. Still, it should be noted that nearly one-third of the patients in each group (total of 50 patients in each group) had a complete pathological response (ypT0), a known predictor of low risk for LNM. Also, all of the local recurrences were among patients with ypT2 residual cancers.

A more recent prospective study specifically dealing with cT2N0 rectal cancer patients managed by long-course CRT followed by FTLE (including but not necessarily TEM) has been recently reported.⁶⁷ The 3-year local recurrence rates seem acceptable ($\leq 5\%$) and encouraging. However, similar findings were obtained. First, a high percentage of complete pathological responses (nearly 50%) was observed. These patients are excellent responders and may not even require surgical resection. Second, all local recurrences were observed among noncomplete responders.

Altogether, the available data suggest that one could expect that local recurrence rates will ultimately depend on the effectiveness of CRT. If CRT was highly effective, with many ypT0, local recurrences would probably be low. However, if ypT2 were frequent, one could expect higher local recurrence rates.

Tumor Fragmentation, Tumor Scatter, and Local Excision after Chemoradiation

In addition to the risk of LNM inherent to ypT2 cancers despite proper staging and restaging suggesting N0 disease, there are other risk factors for the development of local recurrence. The lymphatic or lymphovascular invasion has been considered a risk factor in these patients and should prompt or at least consider additional therapy in these patients as previously mentioned. However, another feature may play a role in local recurrence among these patients with residual cancer following CRT.⁶⁸

In a recent report after pathological measuring of residual cancer after proctectomy identified invisible nests of tumor cells away from the residual mucosal abnormality in up to 3 cm (**Fig. 5**).⁶⁹ This intriguing finding of tumor fragmentation after neoadjuvant CRT is now being examined in different series of patients undergoing proctectomy and TEM. These nests of tumor cells separated from the primary residual ulcer may be a result of tumor fragmentation due to irregular response to CRT. CRT-sensitive areas may sur-

Fig. 5 Fragmented pattern of tumor regression showing discontinued foci of cancer cells ≥ 1 mm away from each other.

round areas of the tumor that are resistant to CRT. CRT may lead to complete regression of the sensitive areas leaving discontinuous “nests” of tumor cells viable.

In this setting, excision of the visible residual mucosal abnormality may not allow excision of the entire residual cancer as invisible residual cancer cells away from the ulcer may still be present.⁶⁸

Ultimately, unless there is a significant regression of the primary tumor ypT1 and/or $\leq 10\%$ of residual cancer cells, rectal cancers may not be suitable for local excision despite significant downsizing if tumor fragmentation is present leaving viable cancer cells away from the visible residual mucosal abnormality.

ypT0: TEM or Watch and Wait?

Ultimately, the conclusion of this review could be that TEM would perfectly fit patients with the complete pathological response after CRT due to the minimal risk of local recurrence and proper avoidance of radical surgery with its intrinsic morbidity and functional consequences. In fact, resection by TEM in these patients would merely serve as a confirmation of the excellent effects of CRT and no actual cancer cells would be removed. Postoperative complications related to wound healing would still be an issue (as discussed previously) and even though the risk of nodal metastases is low, it seems that it may reach up to 5 to 10%, meaning that ultimately a radical TME is still a possibility in the case of local recurrence.⁶⁸

No immediate surgery and observation alone have been proposed for these patients with clinical and radiological evidence of a complete response to CRT (complete clinical response—cCR).^{70,71} The absence of any residual ulceration, mass, irregularity or stenosis, in the presence of standard radiological imaging studies (including preferably MR with diffusion-weighted series or positron emission tomography/computed tomography) have been considered key findings for the diagnosis of a cCR.^{72–74} With this nonoperative approach (at least immediately after 8–12 weeks from CRT completion), patients could avoid any of the difficulties in wound healing associated with TEM after CRT. Also,

surveillance of the rectal wall would be facilitated by the absence of a scar, granulation tissue, and other fibrotic changes. Finally, in the event of a local recurrence, salvage with TME and sphincter preservation (when appropriate) would also be facilitated by no previous scarring and/or violation of the mesorectal fascia.

Ultimately, TEM may be perfect for those patients with suspicious residual cancers by clinical and radiological studies that pathology reveals complete pathological response. This may, in fact, represent a significant proportion of patients.⁷⁵

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