Chapter 4

Early Rectal Cancer

Nidal Issa[1]*and Yaniv Fenig[2]

[1]Hasharon Hospital Rabin Medical Center, Sackler School of Medicine, Tel-Aviv University, Israel
[2]Monmouth Medical Center, Barnabas Health, Long Branch, USA

***Corresponding Author:** Nidal Issa, Hasharon Hospital Rabin Medical Center, Sackler School of Medicine, Tel-Aviv University, Israel, Tel: (+) 03-9372234/5; Fax: (+) 03-9372409; Email: nidaldrissa@hotmail.com , nidalissa@clalit.org.il

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Abstract

Colorectal cancer (CRC) is the 4th most frequently diagnosed cancer and the 2nd leading cause of cancer death in the US [1]. Although the incidence is increasing in individuals younger than 50 [2], in the overall population the incidence has been decreasing steadily since 2003 [1]. Contrary to the US trends, worldwide, CRC incidence has increased by more than 30% between 2008 and 2013 [3]. Rectal cancer has seen a steeper incidence rise in young adults as compared to colon cancer. Specifically in the US, rectal cancer incidence rates increased by 3.2% per year from 1974 to 2013 in adults age 20 to 29 years and since 1980 in adults age 30 to 39 years, and by 2.3% per year since beginning in the 1990s in adults age 40 to 49 years and 50 to 54 years [4].

In addition, recently, a trend in stage shifting towards early rectal cancer (T1-2N0M0) has been observed with the increasing utilization of screening colonoscopy [5].

This relative rise in early rectal cancer incidence along with the decrease in age of diagnosis, is challenging clinicians to veer from the standard of care, of total mesorectal excision (TME), due to its associated high morbidity of 33%, mortality of 2-3% [6,7], genitourinary dysfunction rates of 20-30% [8], bowel dysfunction and non-negligible rates of permanent stomas [9]. The impetus to utilize local excision (LE) methods is clearly present in the field of ear-

ly rectal cancer, with strong evidence to suggest comparable efficacy to TME in certain tumors, and superior safety with lower complication rates [10,11]. However, while LE is less invasive, it might be associated with poorer oncologic outcomes due to failure to remove occult lymph node metastases in the mesorectum. Debate is ongoing as to which tumors and which patients within the scope of early rectal cancer are best benefited from LE, rather than TME, as well as, what is the optimal LE technique. This chapter will provide the evidence to facilitate decision making in the treatment of early rectal cancer.

Pre-Operative Evaluation

Patients should always be evaluated with a history and physical examination. History should focus on changes in bowel habits, presence of incontinence to either stool or flatus, previous colonoscopies, and a detailed family history to assess for the possibility of a hereditary or familial syndrome. Approximately 20% of rectal cancers are familial [12]. Physical exam should include a digital rectal examination (DRE) to determine the distance of the lesion from the anal verge, its mobility and to assess its position in relation to the sphincter complex. The tumors can be classified as mobile, tethered or fixed on DRE [13]. Fixed tumors should not be treated by LE because these often ultimately show deep invasion on final pathology [14]. Complete colonoscopy should be part of the workup of rectal cancer as synchronous colon invasive carcinoma has been shown to occur in 2-7% of cases [15-18].

Imaging modalities used in the staging of rectal cancer include endorectal ultrasound (ERUS) and MRI. A large meta-analysis demonstrated the sensitivity of both ERUS and MRI for invasion of the submucosa, differentiating T1 from the more invasive tumors, is 94% [19]. This meta-analysis showed much lower sensitivities for CT in determining the T stage and therefore it is not routinely used in the staging of rectal cancer. In regards, to nodal involvement, this meta-analysis, showed the sensitivities and specificities of ERUS, MRI and CT were 67%/78%, 66%/76%, and 55%/74%, respectively. However, only CT and MRI can evaluate iliac and retroperitoneal lymph nodes and metastasis to the liver and lungs.

Lymph Nodes Involvement of Early Rectal Cancer

The frequency of localized rectal cancer (stage 1 and 2) is 43% [20] among all stages. Stage 1 rectal cancer is found in 20-34% of all newly diagnosed rectal cancer [21,22], which break down to 43% T1 and 57% T2 [23].

T1 rectal cancers, confined to the sub-mucosa, whether polypoid, flat or sessile, are sub-classified according to the depth of invasion into the sub-mucosa, which corresponds to the risk of local recurrence and lymph node involvement, according to Kikuchi and colleagues [23]. The levels of invasion are abbreviated sm (sub-mucosa), with sm1 representing the upper third of the submucosa, sm2-

the middle third and sm3 the lower third. The frequency of lymph node involvement and/or metastasis after radical resection (RR) for sm1 is 0-3.2%, 8-11% for sm2, and 12-25% for sm3 [16,25,26]. The local recurrence rates for T1 tumors treated with LE ranges from 0-24% in the literature, and for T1 tumors treated with RR ranges 0-9% [27-35]. Contrary, these studies showed local recurrence rates of T1 rectal cancer after RR to range from 0-4.4%.

T2 rectal cancer invades the muscularis propria. After RR 14.5%-25.7% of tumors found to be T2 on biopsy, showed nodal involvement [36-40]. A study evaluating risk factors for nodal involvement in T2 rectal tumors, found that poorly differentiated component, grade II/III, high-grade lymphovascular invasion, and a positive myxoid cancer stroma were independently predictive, and that the risk was cumulative. The local recurrence rates for T2 tumors treated with LE, range from 19% to 47 % in cases without adjuvant therapy and from 5 to 26 % in cases treated with adjuvant therapy [33]. T2 tumors treated with RR have been shown in the Dutch Colorectal trial to be associated with local recurrence rates of 1.1% when treated with pre-operative radiation therapy and 2.2% when treated without it[43].

Treatment of Early Rectal Cancer

The standard of care for rectal cancer has been RR by TME for stage 1 tumors for many years. The principles of

TME were described by Heald and are aimed to achieve complete removal of the lymph node bearing mesorectum along with its intact enveloping fascia [43]. TME comprises the following operative steps: (1) ligation of the inferior mesenteric artery (IMA) at its origin, (2) complete mobilization of the splenic flexure, (3) transection of the proximal left colon, (4) sharp dissection in the avascular plane into the pelvis—anterior to the presacral fascia—parietal fascia and outside the fascia propria or enveloping visceral fascia, (5) division of lymphatics and middle hemorrhoidal vessels anterolaterally at the level of the pelvic floor, and (6) inclusion of all pelvic fat and lymphatic material to the level of the anorectal ring or all fat and lymphatic material at least 2 cm below the level of the distal margin [44]. The actual resection of bowel is achieved by either low anterior resection or the abdominoperineal resection.

The morbidity associated with RR is very high. In the Dutch rectal cancer trial, mortality was 3.3%, anastomotic leakage was 16% (in the absence of protective stoma), and 30% of patients had a permanent stoma. Genitourinary complications were observed in 25% to 34% of participants, where-as incontinence to stool was observed in up to 60% of participants [45].

The first suggestion that LE may have comparable oncologic outcomes with lower morbidity was provided in the late 1970's by Morson and colleagues [46] and later in the late 1990's in the cancer and leukemia group B 8984

trial (CALGB) [47]. Recently, the treatment of early rectal cancer is seeing a shift from RR in the form of total mesorectal excision (TME) to less invasive procedures collectively termed local excision (LE). This shift is motivated by growing evidence that LE can provide comparable oncologic outcomes with superior safety and reduced morbidity, in select patients. LE methods include endoscopic mucosal resection (EMR), trans-anal excision (TAE), transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS).

The ideal candidate for LE is a patient who can undergo curative resection, meaning, they have no nodal involvement and a primary tumor can undergo R0 resection. Unfortunately, detecting lymph node involvement in early rectal cancer has not been very accurate. Therefore, it is hard to determine in advance whether a local excision procedure will also ultimately be the definitive treatment for the individual patient. LE should be discussed with the patient pre-operatively as the concept of "total biopsy" - a tool to gain additional information regarding tumor biology and risk of lymph node metastasis, with the ultimate goal to spare the patient RR. The patient should be aware that the method of "total biopsy" is inferior to RR in prognostication of the early rectal cancer, and that LE is still mostly adequate when the patient is unfit or unwilling to undergo RR.

The uncertainty in determining lymph node involvement using only imaging modalities as described above, led researches to identify various histopathologic characteristics that pertain high-risk. Currently, there is no single predictive histopathologic, genetic or molecular factor of lymph node involvement, and a combination of factors is used to evaluate the risk. Colonoscopy provides a sample of only a small portion of the tumor, whereas an excisional full-thickness biopsy allows a more comprehensive examination of depth of invasion, tumor histology and margin status.

The first and strongest predictor of lymph node involvement is depth of invasion, as described above. Another strong predictor is Lymphovascular invasion (LVI), which is found in 12–32% of T1 rectal cancers [48]. The level of differentiation is also predictive, with poor differentiation associated with higher rates of lymph node involvement, although not a common occurrence in early rectal cancer [49,50].

Endoscopic Mucosal Resection (EMR)

EMR can achieve removal of diseased mucosal tissue or at most, the superficial submucosa instead of a full-thickness excision [51]. When used for tumors greater than 2 cm in diameter, a piecemeal resection is often re-

quired, which has been shown to result in higher recurrence rates when compared to other LE methods [52-54]. Bleeding after EMR has been shown to be a common complication occurring in up to 45% of cases [55]. EMR of high-risk T1 colorectal cancer was reported to have a recurrence rate of 20.1% compared with 3.7% following RR [56], and is therefore only acceptable for low-risk T1 colorectal cancer. Higher recurrence rates were also observed when compared with TEM, however with lower post-operative complication rates [57].

Transanal Excision (TAE), Transanal Endoscopic Microsurgery (TEM), Transanal Minimally Invasive Surgery (TAMIS)

TAE is a very widely used technique for full thickness excision of a lesion in the anal canal and distal rectum. It is performed with the patient in the prone jackknife position or the modified lithotomy, under local, regional or general anesthesia. The buttocks are taped apart, and a Lone Star retractor (Lone Star Inc., Dallas, Texas) is used to efface the anus and facilitate exposure of the distal rectum. The lesion is examined with direct vision using a Hill Ferguson, Park, or a Barr retractor. The lesion is excised with a 1 cm margin using electrocautery. If posterior and above the puborectalis muscle, the defect in the rectal wall is closed with absorbable suture. If the tumor is anterior,

the defect is left open due to concern for injury to the vagina, prostate or urethra with closure.

First described in the 1980's by Buess, TEM is a minimally invasive endoscopic technique that improves the quality of the local excision by excellent access and 3D visualization of the surgical field and by precise full-thickness excision of rectal lesions [58]. TEM can facilitate lesion much farther from the anal verge up to 20 cm.

TAMIS, introduced in 2009, is also a minimally invasive approach, but uses a transanal port and the standard laparoscopic instruments. This makes it a cheaper option, but is only optimal for tumors 8-12 cm from the anal verge, because tumors more distal will be covered by the port and tumors more proximal involve a high risk of peritoneal entry [59].

T1N0M0

The NCCN guidelines note that use of TAE in select patients with low-risk histopathologic findings, in a tumor that is less than 3 cm in diameter, within 8 centimeters of the anal verge and occupies less than 30% of the bowel circumference may result in acceptable oncologic outcomes [60]. However, a recent meta-analysis shows that TEM may achieve superior oncologic outcomes to TAE [61]. When compared to TAE, both TEM and TAMIS have been shown to result in less specimen fragmentation with a higher rate of completely intact, margin-negative excision [58,62,63].

The first randomized controlled trial by Winde and colleagues [64], demonstrated that patients with T1 rectal cancer who underwent TEM versus RR had no difference in survival and cure. These results were replicated 2 years later in another trial [65].

Since then, the evidence have been growing and two meta-analysis, both published in 2015, drew very similar conclusions. The first [11], a comprehensive meta-analysis of all three local excision techniques, TAE, TEM and TAMIS compared to RR in the treatment of T1N0M0 rectal cancer concluded that LE with TEM offers "oncologic control similar to RR," but that LE with TAE does not, with a significantly lower 5-year survival rate. The second [66], also comprehensive but focusing on TEM, included no additional trial, and came to the same conclusion that TEM, although associated with significant higher recurrence rates than RR, is comparable in terms of overall survival and is associated with lower perioperative morbidity and mortality.

In terms of oncologic outcomes, no head-to-head trials exist comparing TEM to TAMIS by use of randomization. However, an ex-vivo trial requiring 10 surgeons to perform the same task of excising a 3 cm lesion in a trainer box, found no difference in accuracy of dissection, but TEM was significantly quicker in both dissection and suturing of the rectal wall [67]. The quick reply from Atallah and colleagues [68] shed light on the fact that the

former study did not utilize the various types of TAMIS platforms available or the accessory devices commonly used by TAMIS surgeons, such as automated suturing and knot-forming devices, and that in-fact, suturing the rectal wall defect with these additional tools is very timely and comparable to TEM. They also noted the significantly longer preparation time required to perform TEM, compared with TAMIS, on the individual case, as well as, the temporary impairment of sphincter function for up to 6 weeks postoperatively, including a decrease in anal sphincter tone and a significant reduction in maximum contraction and resting contraction pressures with TEM.

T2N0M0

It is a bit like comparing apples to oranges, when comparing LE to RR in the sub-group of T2N0 tumors, because of an inherent unavoidable selection bias that exists in the LE group. The pT2 group treated with LE, does not undergo microscopic evaluation of the mesorectum lymph node basin, and hence, may in-fact contain tumors with occult lymph node involvement that are by definition stage 3 rectal cancers and associated with poorer oncologic outcomes. Given the inaccuracy of pre-operative imaging and histopathologic determinants to predict lymph node invovlvement, and the innate higher lymph node involvement rates of T2 versus T1 tumors, heterogeneity of the clinical T2N0M0 is a real concern.

The surveillance epidemiology and end results (SEER) trial has demonstrated that T2N0M0 rectal cancer is not adequately treated with LE, when compared to RR, due to unacceptable local recurrence rates and decreased disease-specific survival rates [69], however this trial included in its LE group also polypectomy and the rates of full thickness excision was not specified. It is not reported what percentage of the T2 group treated with LE received adjuvant or neo-adjuvant radiation therapy.

The NCCN practice guidelines in oncology no longer propose local excision with adjuvant therapy for the treatment of T2N0M0 rectal cancer, as they did in 2008 [70]. The local recurrence rates for the LE group with this approach ranges from 16% to 25% [47,71].The findings have been disappointing with local recurrence rates of 16-25%.

The ACOSOG Z6041 trial [72] was a multicenter, single-arm study that evaluated the outcomes of neoadjuvant CRT with subsequent local excision of the tumor by either TAE or TEM. It found local recurrence rates of 4%. Overall survival was in the range of the results for stage 1 rectal cancer in the TME trial COLOR II [73], although the latter did not stratify stage 1 according to T class.

Another trial by Lezoche and colleagues [74] randomized this patient population to either neoadjuvant CRT and TEM or to neoadjuvant CRT and laparoscopic TME in patients with ultrasound-staged T2N0M0 rectal cancers. After 5 years of follow-up, 8% of patients in the local

excision group and 6% in the TME group had developed local recurrence, rates not very different from the results of the ACOSOG Z6041 trial.

A systematic review and meta-analysis comparing the outcome of LE versus RR after CRT has been published recently, which found that there were no differences in oncologic outcomes [75]. However, most of the studies were underpowered, the median follow-up varied significantly between studies, there was significant methodologic heterogeneity between the included non-randomized studies with different T staging in each study. We therefore, interpret these findings with caution.

Currently, there is an ongoing phase II multicenter randomized controlled trial called the transanal endoscopic microsurgery and radiotherapy in early rectal cancer (TREC). This trial will be conducted to compare between TME and short-course radiation therapy followed by TEM 8–10 weeks later in early rectal cancer [76].

At present, we believe, this combination therapy should be reserved for patients who are unfit or unwilling to undergo the accepted standard of care of RR.

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