Management of Early Rectal T1 and T2 Cancers

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Abstract The treatment of rectal cancer has undergone a tremendous surgical evolution over the past century. Initially, in the 19th century, the only possible safe treatment was a diverting colostomy, which then evolved first to local treatment, primarily via the Lisfranc and Kraske procedures (posterior approach), and later, in the 20th century, to the abdominal-perineal resection popularized by Miles. Subsequently, anterior resection and low anterior resection gained a solid foothold as the most efficacious ways to treat most cancers of the rectum. In the past 3 decades, transanal excision has reemerged as a popular treatment option for T1 and selected T2 rectal adenocarcinomas, allowing less morbidity for early cancers. The selection criteria for this treatment have often included mobile tumor, size <4 cm, favorable histology without lymphovascular invasion, and anatomic accessibility with the ability to achieve 1-cm circumferential margins. Although the use of transanal excision for T1 rectal cancer increased from 26% to ~44% between 1989 and 2003, multiple recent retrospective studies have suggested that locoregional recurrence after this procedure is as high as 18% for T1 cancers and 47% for T2 cancers. Of interest, limited available prospective data reveal much better results (4-5% locoregional recurrence rate for T1 and 14-16% for T2). Much of the apparent discrepancy is due to patient selection, which is far more rigid in prospective trials. Conflicting data also exist as to how this outcome affects overall survival, although surgical salvage averages ~50% with close follow-up. The following topics will be discussed in this article: the surgical evolution of rectal cancer, best patient selection criteria for transanal excision versus more radical operation, utility and effect of adjuvant therapy in early-stage rectal cancer, current trends in the treatment of early-stage rectal cancer, and current early-stage rectal cancer trials.

Each year, more than 42,000 individuals in the United States are diagnosed with rectal cancer, and more than 8,500 die of the disease. Although surgery remains the cornerstone of therapy for rectal cancer, there has been a tremendous evolution in care, particularly over the past century. In 1826, Lisfranc was credited as the first person to remove the cancer-bearing segment of rectum; he did so using a transanal approach. In that era, the only feasible treatment of rectal cancer more commonly consisted of a colostomy to relieve obstruction, as first described by Amussat in 1839. In 1885, Kraske and colleagues approached rectal cancer using a transsacral approach (i.e., by removing the coccyx and distal sacrum, with preservation of the anus and its muscles). Development of the abdominoperineal resection (APR) followed and can be attributed largely to Ernest Miles, who, after observing a high incidence of cancer recurrence in patients undergoing local treatment for rectal cancer, developed the concept of radical rectal excision, APR, which he reported in 1908. Miles postulated that the lymphatic spread of rectal cancer was directed superiorly and that this surgery allowed complete resection of the anorectum and draining lymphatics. The procedure, which gained acceptance largely because it was oncologically sound and successful, has led to the cure of many patients with rectal tumors. Its feasibility was further enhanced by the availability of blood transfusion, allowing this radical surgery to become the most popular method of dealing with rectal cancer by 1947. The main disadvantages of this operation include associated morbidity and mortality as well as the necessity of a permanent stoma. Dixon established the safety of the anterior resection in the late 1940s, but this approach was mainly limited to the treatment of upper rectal cancer until the 1970s. At that time, the introduction of circular stapling devices facilitated the technical possibility of low rectal anastomosis and even coloanal anastomosis. This technological advance, along with the recognition that distal margins of <2 cm did not compromise outcome, dramatically changed the approach to many patients.

A further advance was the description of total mesorectal excision, which has been shown by Heald et al. (1) to minimize local recurrence, to allow even ultralow resections with coloanal anastomosis to be accepted as appropriate

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operations, and to result in survival rates comparable with APR without a permanent stoma. In dedicated specialty centers, these radical reconstructive operations have allowed APR to be relegated to use in a very small minority of patients (<10%), mainly those with direct sphincter invasion and/or preexisting incontinence (2).

Data from the National Cancer Data Bank reveal that APR use has declined nationwide, from 19.9% to 16.8% between 1998 and 2003. Nonetheless, these reconstructive operations are still associated with a relatively high rate of complications, including impotence, urinary dysfunction, anastomotic leak, and up to a 4% mortality (3).

The development of better staging modalities has led to a resurgence in the local treatment of early-stage rectal cancer via local (primarily transanal) excision with curative intent. Controversy exists, however, on the use of local treatment for rectal cancers and has been fueled by conflicting data from both retrospective and prospective studies, which are discussed in detail in this article.

Treatment Options for Early-Stage Rectal Cancer

Radical resection. As stated above, APR and anterior resection have become the mainstay of therapy for rectal cancer. These operations allow the surgeon to remove not only the primary tumor but also the draining lymph nodes, which may serve to further stage the patient and to decrease both distant and local recurrence. In a retrospective study, Bentrem et al. (4) evaluated 168 patients with T1-stage rectal cancer who were treated with radical surgery; of these, 31 patients (18%) had lymph node metastasis. The investigators reported local recurrence, distant recurrence, and estimated 5-year overall recurrence of 3%, 3%, and 6%, respectively. The incidence of recurrence was low, although 18% of tumors showed lymphovascular invasion and 6% of the tumors were poorly differentiated; of note, 10% of the overall group received radiation therapy (primarily for involved nodes) and 17% received adjuvant chemotherapy.

In a retrospective study comparing transanal excision with radical surgery for rectal cancer, Mellgren et al. (5) reviewed 153 patients who underwent radical resection. The investigators noted a 9% overall recurrence for T1N0 tumors and 16% for T2N0 tumors, with no local recurrence in the former group and 6% local recurrence in the latter group. The results of this study agree with many others, confirming the possibility of achieving a low recurrence rate in early-stage cancer without using adjuvant therapy.

In a prospective study, Endreseth et al. (6) compared major surgery with transanal excision in T1 tumors. In the group of patients treated with radical surgery (n = 256), 63% of patients underwent anterior resection, 34% underwent APR, and 3% had a Hartmann's procedure. Local recurrence and distant metastasis rates were low (6% and 7%, respectively). This article also adds to the body of literature proving that radical resection is effective in minimizing cancer recurrence. Nevertheless, as noted above, these operations are accompanied by significant site-specific complications and other concurrent risks of major abdominal surgery, which has led surgeons to search for less invasive, safer alternatives that yield similar results.

Transanal excision. Over the past 3 decades, transanal excision has become a popular treatment option for T1 and selected T2 rectal adenocarcinomas. Between 1989 and 2003, there has been an increase in this approach for both T1 and T2 cancers (26.6-43.7% and 5.8-16.8%, respectively; ref. 7). Preoperative staging is very important when determining whether transanal excision is an appropriate option for treating rectal cancer. It is generally agreed that tumors treated in this manner should be mobile, UT1 or UT2 and node negative on ultrasound, and <10 cm from the anal verge; comprise <40% of the circumference; and have favorable histology on biopsy without lymphovascular invasion. Transanal excisions should be done as a full thickness resection down to perirectal fat, along with a 1-cm radial margin. The specimen should be pinned and oriented before submitting it to the pathologist.

Several recent retrospective and prospective studies have compared local excision with more radical operations; the findings have varied. Garcia-Aguilar et al. (8) retrospectively reviewed 82 patients (T1, n = 55; T2, n = 27) treated for rectal cancer with local excision. Patients' tumors were excised with negative margins and were moderately or well differentiated and without lymphovascular invasion. Despite these favorable characteristics, local recurrence for T1 and T2 cancers was 18% and 37%, respectively. Although this study was retrospective and included patients who had been operated on by several surgeons over a 10-year period, the investigators concluded that local excision has a much higher recurrence rate than previously reported. Mellgren et. al (5) followed-up on this study by evaluating the same group of patients but also including patients with unfavorable histology. In this retrospective study, 108 patients with T1 and T2 rectal cancers treated by local excision were compared with 153 patients with T1N0 and T2N0 cancers treated with radical surgery. Sixty-nine patients with T1 tumors and 39 patients with T2 tumors were treated with local excision, and 19 additional patients were excluded due to positive margins. Of patients evaluated, 17% had poorly differentiated tumors, and lymphovascular invasion was not mentioned. Five-year local recurrence was estimated to be 18% and 47%, respectively, for T1 and T2 rectal cancers treated with local excision alone compared with 9% and 16%, respectively, for T1 and T2 tumors treated with radical surgery. It is important to note that poorly differentiated tumors are not considered to be ideal candidates for local excision in most centers. Additionally, the inclusion of only known node-negative patients in the radical surgery group would seem to unfairly bias the results in favor of this group.

Bentrem et al. (4) retrospectively evaluated transanal excision (n = 151) versus radical surgery (n = 168) in patients with T1 adenocarcinoma of the rectum over a 17-year period; of note, the latter group included all T1 patients, even those with positive nodes. Eleven percent of patients who underwent transanal excision had lymphovascular invasion, 6% had poorly differentiated cancers, and margins were not specifically mentioned (although 11 patients received adjuvant radiation for a "close margin"). Estimated overall 5-year recurrence was 23% and 6% in the local excision and radical surgery groups, respectively. Estimated local and distant recurrence was 15% and 12%, respectively, in the local excision group compared with 3% and 3%, respectively, in the radical surgery group. The investigators also concluded that risk of tumor recurrence was higher with transanal excision than radical surgery, although

both groups did well, as evidenced by 5-year disease-specific survival (89% in the local excision group and 93% in the radical treatment group; P = not significant). The favorable survival rates in both groups may have been partly due to an aggressive approach to recurrence (see discussion of salvage below).

Madbouly et al. (9) also retrospectively evaluated recurrence after transanal excision of T1 rectal cancers in 52 patients over an 18-year period. Preoperative ultrasound was done on 31 of the patients, and tumors that were poorly differentiated or had lymphovascular invasion were excluded. Two patients were reexcised within 2 weeks to obtain clear margins. Local recurrence was 17%; distant recurrence, 4%; and combined local and distant recurrence, 6%. Average time to recurrence was 32 months. Although this study included patients who were seemingly ideal candidates for transanal excision, its retrospective nature, combined with the 18-year accrual period, raises questions about the results.

Three significant prospective trials have examined outcome of transanal excision. Steele et al. (10) reported the results of the Cancer and Leukemia Group B study, which prospectively evaluated 59 patients with T1 disease who received only local excision and 51 patients with T2 disease who received local excision followed by chemoradiation. Tumor excision specimens in both groups had negative margins and no lymphovascular invasion; information was not provided on the differentiation status of lesions. Average follow-up was 48 months. Local and distant recurrence for T1 cancers was 3.4% and 1.7%, respectively; one patient (1.7%) had combined local and distant recurrence. Recurrence for T2 cancers after local excision and chemoradiation was 10% local, 6% distant, and 4% both. This prospective trial seems to show that local excision, if done using strict criteria, is a safe option for early-stage rectal cancer.

Russell et al. (11) reported the results of a Radiation Therapy Oncology Group prospective study evaluating patients with low rectal cancers who underwent local excision, selecting only those who would otherwise have required APR as conventional therapy. This trial was conducted over a 3-year period and included 65 patients (T1, n = 27; T2, n = 25; and T3, n = 13). All patients had local excision using either a transanal, transcoccygeal, or transsacral approach. If the tumor was T1 and low grade, and margins were >3 mm, without lymphovascular invasion, patients received no further treatment (n = 14). Patients with clear margins, but a higher tumor grade or deeper invasion, received chemoradiation (n = 18). Patients with margins <3 mm underwent a higher dose of chemoradiation (n = 33). Locoregional recurrence for T1, T2, and T3 tumors was 4%, 16%, and 23%, respectively. The investigators also concluded that, in appropriately selected patients with early rectal cancer, local therapy is appropriate.

As part of the Norway Rectal Cancer Study Group, Endreseth et al. (6) prospectively followed patients with T1 cancer treated with radical surgery (n = 256) or transanal excision (n = 35) over a 6-year period. Local recurrence was 12% with local excision compared with 6% with radical surgery. The investigators concluded that patients who underwent transanal excision had a significantly increased risk of local recurrence. This conclusion was made in spite of the fact that 17% of patients who underwent local treatment had macroscopically positive margins (R2), another 17% had margins <1 mm (R1), and 20% of patients had indeterminant margins (Rx). Thus, more than one third of patients had what could be considered positive margins and less than one half of patients had documented clear margins.

After examining both retrospective and prospective trials, it remains difficult to determine whether transanal excision of early-stage rectal cancer offers the same oncologic benefit as a more traditional radical operation; however, if ideal criteria (i.e., clear margins, well-differentiated/moderately well-differentiated tumor, and no lymphovascular invasion) are not satisfied, recurrence seems to be higher. This finding is not really surprising, as local excision does not adequately stage or remove mesorectal lymph nodes, which will be positive in as many as 20% of unselected stage I rectal cancers (4, 12–14).

As noted above, one of the most significant problems with local excision is the difficulty in obtaining clear margins. Transanal endoscopic microsurgery (TEM) has sought to solve this problem. Stipa et al. (15) studied 69 patients who underwent TEM for Tis, T1, and T2 cancers; all of the patients had full thickness excision, with 1-cm margins. Local recurrence was 8.7%. Of note, 30% of the patients received adjuvant radiation therapy, whereas 21% received preoperative chemoradiation. Of the patients who received neoadjuvant therapy, no local recurrence and only one distant recurrence was reported. From the data presented here, it seems that TEM may allow the surgeon to more easily obtain clear margins, but it is unclear if the procedure itself or the chemoradiation led to the low rates of local recurrence.

Maslekar et al. (16) prospectively studied 52 patients (T1, n = 27; T2, n = 22; and T3, n = 3) who underwent TEM for rectal cancer. All of the T1 lesions were completely excised, with clear margins. After a median follow-up of 40 months, no recurrence was found in the T1 group despite the fact that adjuvant or neoadjuvant therapy was not used and that four of the patients had poorly differentiated tumors. Nineteen of the 22 patients with T2 lesions had clear margins, and 4 patients had recurrence; 3 of the patients with recurrence were salvaged by a radical procedure. The investigators concluded that, when local excision is an appropriate treatment option, TEM should be the treatment of choice. If appropriate selection criteria are applied, TEM seems to be an appropriate treatment alternative in patients with T1 cancers, but prospective studies comparing TEM with more traditional transanal excision are needed.

Local Resection plus Adjuvant Therapy

Patients treated for T2 rectal cancer by local excision often receive adjuvant radiation therapy, the primary focus of which is treatment of the mesorectum to decrease local recurrence. Prospective data are limited, but in the Radiation Therapy Oncology Group study reported by Russell et al. (11), 25 patients with T2 cancer were divided into two investigative groups. The first group consisted of 8 patients who were treated with adjuvant radiotherapy (50-56 Gy) and two cycles of 5-fluorouracil; the second group included 17 patients who received a higher dose of radiation (59.4-65 Gy) and the same chemotherapy. The investigators noted a 16% locoregional recurrence rate, and 12% of patients developed distant recurrent disease. This study also included 13 patients with T3 tumors; of these, 3 patients received the lower-dose chemoradiation regimen and 10 patients received the higher

dose. In this group, locoregional recurrence and distant dissemination were 23% and 31%, respectively.

The Cancer and Leukemia Group B study, reported by Steele et. al (10) and discussed above, investigated 51 patients with T2 tumors treated with local excision and adjuvant therapy (external beam radiation and 5-fluorouracil). At 48 months, the failure rate was 20% (10 of 51 patients), of which 50% was local, 30% was distant, and 20% was local and distant.

Taken together, the above-mentioned prospective studies suggest that, despite adjuvant therapy, transanal excision for T2 and T3 tumors is associated with a significant rate of recurrence. However, when comparing these results with those following radical surgery for T2N0 tumors, as reported by Mellgren et al. (local recurrence, 6% and overall recurrence, 16%; ref. 5), the differences are not striking. This is particularly true when considering the preferential bias afforded by the radical surgery group because of consideration of only node-negative tumors.

Local Excision after Neoadjuvant Therapy

Although local excision for rectal cancer is commonly done in selected T1 and T2 patients, the procedure is rarely advocated in patients with T3 rectal cancers, except in those unable to tolerate major surgery due to comorbidities. Bonnen et al. (17) retrospectively reviewed 26 patients with T3 cancer, who, over the course of 12 years, were treated with local excision after receiving neoadjuvant therapy. Median initial tumor size was 3.5 cm, and 23 patients had well-differentiated or moderately differentiated tumors. Seventy-three percent of the patients had only a residual scar after neoadjuvant therapy. Fifty-four percent of patients had a complete histologic response to neoadjuvant therapy, with no residual cancer. Furthermore, 35% of the patients had only microscopic residual disease, whereas only 12% had gross residual disease. Pelvic recurrence was 6%. In a comparison group of patients treated with radical surgery with mesorectal excision, pelvic recurrence was 8%. Although these results are intriguing, longer follow-up and prospective trials are needed. A current American College of Surgeons Oncology Group trial is evaluating the outcome of local excision following preoperative chemoradiation in ultrasound-staged T2N0 rectal cancers.

Survival after Salvage Surgery for Recurrence of Locally Excised Rectal Cancer

Prospective data are lacking on survival after salvage surgery in recurrent rectal cancer previously treated by local excision. Madbouly et al. (9) retrospectively evaluated 52 patients who underwent transanal excision. Fourteen of the 15 patients who had recurrence underwent salvage surgery, with a 56.2% salvage rate. In the previously discussed Radiation Therapy Oncology Group trial (11), salvage surgery was attempted in five patients with initial local failure; four of the five patients developed distant metastasis. Mellgren et al. (5) treated 24 of 25 patients with local recurrence with radical salvage surgery and reported a 5-year disease-free survival rate of 50%.

Friel et al. (18) retrospectively reviewed 29 patients who underwent salvage radical surgery for local recurrence after transanal excision. Ninety percent of patients had rectal wall recurrence; 10% of patients had extrarectal recurrence. Seventy-nine percent of patients were thought to be cured by the salvage procedure. Disease-free survival was 68% in patients with tumors of favorable histology versus 29% in those with tumors of unfavorable histology. The investigators noted that outcome of salvage surgery for recurrence after failed local excision was not equivalent to patients who were first treated by the more radical procedure. Weiser et al. (19) reached a similar conclusion in a retrospective study of 50 patients who underwent surgical salvage after transanal excision for T1 and T2 cancers. Forty-nine patients had a successful salvage surgery, and 47 patients had complete pathologic resection. Disease-specific survival was 53%, lower than what would be expected for an original early-stage cancer.

To attempt to answer a slightly different (but relevant) question—whether immediate radical surgery after local excision in the setting of unfavorable characteristics would be successful—Hahnloser et al. (20) reviewed 52 patients with locally excised rectal adenocarcinomas followed by radical surgery (APR, 24; low anterior resection, 28) within a 30-day period. Radical surgery was done because of a cancerous polyp (n = 42), positive margins (n = 5), lymphovascular invasion (n = 3), and T3 cancer (n = 2). Overall, 23% of patients were found to have nodal involvement, and 29% had residual cancer in the specimen. Nodal involvement was 21% in patients with T1 cancer. The investigators found no significant difference in local recurrence in patients in the study group (3%) versus matched patients who underwent primary radical surgery (5%) versus patients who underwent local excision alone (8%). In addition, no significant difference in 5-year overall survival was noted. The investigators concluded that local excision followed by radical resection within 30 days does not compromise outcome. Thus, from the limited data available, it seems that, although salvage surgery does not offer the same disease-free survival as initial radical surgery, 50% of patients will be salvaged. Additionally, if done "immediately" for adverse features, the procedure seems to have success comparable with that of initial radical surgery.

Conclusions

Data on the role of local excision in early-stage rectal cancer are conflicting primarily because of the inability to achieve ideal characteristics in all patients. In particular, the relatively high degree of failure in achieving appropriate clear margins is disappointing and probably accounts for a significant number of local failures. Nonetheless, local excision seems to be a viable option in well-selected patients (i.e., those with well-differentiated or moderately well-differentiated T1 cancers involving <40% of the circumference, without lymphovascular invasion), particularly when the only other option is APR. Three key factors should be noted. First, good preoperative staging, which would include the use of a physician highly skilled in endorectal ultrasound to ensure optimal patient selection, is critical. Second, clear margins must be obtained by the surgeon, which from a review of the literature is easier said than done. Third, on determination of the final pathology, additional therapy (either radical surgery or perhaps chemoradiation) should be considered if any unfavorable characteristics are present.

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