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Non-operative management of locally advanced rectal cancer

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A B S T R A C T

A combination of chemoradiation therapy (CRT) and total mesorectal excision (TME) provides excellent locoregional control in locally advanced rectal cancer; however, this regimen may be associated with significant morbidity. Researchers have assessed the safety of omitting rectal resection in patients who achieve a clinical complete response to CRT. Preliminary results have been promising. However, the accurate identification of patients who have responded completely to CRT is a challenge to non-operative management. Other areas warranting further investigation include techniques to increase response rates and to identify upfront those patients who are most likely to respond to CRT.

1. Background

Surgery has been the mainstay of therapy for rectal cancer. Adjuvant 5-fluorouracil-based chemoradiation (CRT) was introduced to address the high local recurrence rates reported in the early surgical series using blunt dissection techniques.[1] Based on the results of several randomized trials of adjuvant 5-fluorouracil (5-FU)-based CRT,[2,3] the NCI issued a consensus statement in 1990, recommending adjuvant CRT for all patients with locally advanced (stage II–III) rectal cancer.[4] In 2004, the German Rectal Cancer Study Group published a seminal paper that established the superiority of preoperative versus postoperative administration of CRT. They reported that treatment of locally advanced rectal cancer with a sequence of neoadjuvant CRT, total mesorectal excision (TME), and adjuvant 5-FU resulted in an impressive 6% cumulative incidence of local relapse at 5 years.[5] It has been shown that both the TME and the CRT contribute to this excellent local control rate. As compared to rectal surgery using blunt dissection, radical resection using a TME technique, a sharp dissection to remove the rectal tumor and adjacent mesorectum *en bloc*, reduces the risk of local recurrence.[6,7] Despite better surgical technique, the Dutch TME study (CKVO 95-04) still showed a benefit in local control for preoperative radiotherapy versus surgery alone.[8]

Although a combination of CRT and TME provides excellent oncologic outcomes, this aggressive approach of radical surgery and pelvic radiotherapy can be associated with significant toxicity. Rates of perioperative mortality can be as high as 2.4%, and postoperative complications occur in over one-third of patients.[5,9] Patients may also develop delayed complications, such as bowel obstruction or incisional hernias, necessitating additional surgeries.[10] Furthermore, years after receiving CRT and TME, up to 39% of patients report urinary incontinence, 62% fecal incontinence, and 45% sexual dysfunction.[10–12] Patients with distal rectal tumors may require a permanent colostomy, often associated with poor body image.[11] Sphincter preservation for patients with low-lying rectal tumors can be achieved by performing a low anterior resection with a coloanal anastomosis; however, these procedures are associated with impaired bowel function.[13] Several prospective studies have evaluated patient-reported quality of life after treatment for rectal cancer and have demonstrated low scores, particularly in patients with stomas or low rectal anastomoses.[14–16] Thus, TME and CRT may have a permanent detrimental impact on patients' functioning.

Given the potential morbidity associated with this regimen, researchers have sought to identify patients who may safely forgo a component of standard management without sacrificing disease control. One example is omission of TME in patients who have achieved a clinical complete response (cCR) to CRT. Multiple groups have reported that approximately 20% of patients who receive neoadjuvant CRT experience a pathologic complete response (pCR), in which no residual tumor is appreciable in the surgical specimen.[17,18] These patients have particularly favorable outcomes, compared to those with residual cancer at the time of TME.[18,19] Intuitively, it seems that patients whose cancer has responded completely to neoadjuvant therapy may derive no benefit from radical surgery.

2. Reports of non-operative management

Long-term results of omitting TME in patients with a cCR to neoadjuvant therapy were initially described by Habr-Gama et al.[20] They reported on 265 patients with low rectal cancers, 71

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(27%) of whom demonstrated a cCR to CRT (50.4 Gy with concurrent 5-FU) at 8 weeks after treatment and did not undergo radical resection. These patients were closely monitored with a monthly serum carcinoembryonic antigen (CEA) level, digital rectal examination (DRE), proctoscopy, and biopsy of any suspicious lesion for 1 year, then continued under surveillance at 3-month intervals for an additional year and 6-month intervals thereafter. At a mean follow-up of 57.3 months, 2 patients (3%) experienced an endoluminal recurrence; both were effectively salvaged with a transanal excision or brachytherapy. There were no regional recurrences. Three patients developed distant metastases. Five-year disease-free survival was 92% and overall survival 100%. These results were not significantly different from those of a control group of 22 patients who underwent TME and were found to have a pCR. The authors concluded that a complete response to CRT is associated with excellent long-term results, regardless of whether surgical resection is included in the management.[20] Thus, in patients with a durable cCR, TME may not improve outcomes and may cause unnecessary morbidity.

Habr-Gama et al. updated their series in 2006 with the addition of 28 patients, for a total of 99 patients with a sustained cCR for $\geq$ 12 months who were managed non-operatively. At a mean follow-up of 60 months, this cohort experienced 13 (13%) recurrences. Of these, 5 (5%) were endorectal, 7 (7%) systemic, and 1 (1%) combined. The 5 isolated endorectal recurrences were effectively salvaged. The 5-year overall and disease-free survival rates were 93% and 85%, respectively.[21] These updated results corroborated the authors' initial report, supporting the hypothesis that patients who experience a cCR to CRT may safely be observed, with surgery reserved only for instances of disease recurrence.

Prompted by these promising results, Maas et al. conducted a prospective study of patients with a cCR after CRT who were managed with a non-operative "wait-and-see" approach. At 6–8 weeks after completion of CRT, patients were evaluated by MRI; if no residual tumor was apparent, an endoscopy was performed to further assess the endoluminal remnant. Patients were defined as having achieved a cCR if they had no residual tumor or suspicious lymph nodes on MRI, no residual tumor at endoscopy with negative biopsies from the former tumor location, and no palpable tumor by DRE. Follow-up consisted of an MRI, endoscopic examination with biopsy, computed tomography scan, and CEA level every 3–6 months. Among the 21 patients managed non-operatively, 1 developed a local recurrence and was salvaged surgically. The other 20 patients remained alive and without evidence of disease at a mean follow-up of 25 months. The cumulative probability of 2-year disease-free survival was 89% and overall survival 100%. These survival outcomes were not significantly different from those of a cohort of 20 patients who underwent TME and had a pCR. On the other hand, functional outcomes, as measured by the Memorial Sloan-Kettering Cancer Center (MSKCC) Bowel Function Index, were significantly better in patients who were managed non-operatively.[22] These results suggest that surgical resection in patients who have responded completely to CRT causes morbidity without providing benefit.

Other groups have retrospectively reviewed their institutional experiences with non-operative management. For example, at MSKCC, a total of 32 patients with a cCR to CRT were treated non-operatively from January 2006 to August 2010. A cCR was defined as no evidence of tumor by DRE or endoscopy. Patients were followed closely at the discretion of the treating physician, typically with a physical examination and flexible sigmoidoscopy every 3 months for the first year and every 4–6 months thereafter. Most patients were evaluated by cross-sectional imaging every 6 months for the first 2 years; however, neither endorectal ultrasound nor rectal MRI was used routinely. Outcomes of these patients were compared to those of 57 patients who underwent TME and had a pCR. Factors associated with selective non-operative management included lower pretreatment stage, older age, and distal tumor location. At a median follow-up of 28 months, 6 patients in the "non-operative" cohort developed a local recurrence and were salvaged surgically. Of these, 3 also developed distant metastases. These outcomes were not statistically different from those of the group that underwent rectal resection and had a pCR.[23]

Although the results of non-operative management in these series are impressive, some groups have reported significantly higher recurrence rates. The discrepant outcomes may be due to differences in neoadjuvant therapy, definition of pCR, or patient selection and follow-up. For example, in one series of 10 patients with a cCR who were treated non-operatively, 8 experienced a local recurrence within 3.7–8.8 months (mean 6 months). A cCR was defined as no evidence of tumor by a proctoscopy or biopsy performed at 3–4 weeks after the completion of CRT. No radiographic evaluation was performed.[24] The high rate of local failures soon after the completion of CRT suggests that proctoscopy and biopsy alone may be inadequate to identify patients who have responded completely (Table 1).

3. Challenges to non-operative management

A significant challenge to non-operative management is the accurate identification of patients who have experienced a complete response to neoadjuvant therapy. Physical examination alone is insufficient. In one prospective trial, 94 patients with locally advanced rectal cancer were examined by an experienced colorectal surgeon at diagnosis and pre-operatively. The extent of pathological downstaging was underestimated in 78% of cases, and only 21% of patients (3 of 14) with a pCR were correctly identified by preoperative DRE.[25] Endoscopy with biopsy or local excision of the residual scar may provide some reassurance about the presence or absence of residual tumor. However, a biopsy after

Table 1
Reports of non-operative management of rectal cancer.

Study	Number of patients managed non-operatively	Number of local recurrences	Follow-up	Evaluations used to define cCR
Habr-Gama et al.[20,21]	99	6 (6%)	Mean 60 ± 46 months	DRE, endoscopy, and biopsy
Maas et al.[22]	21	1 (5%)	Mean 25 ± 19 months	DRE, MRI, endoscopy, and biopsy
Smith et al.[23]	32	6 (19%)	Median 28 months (range 9–70)	DRE, endoscopy, and cross-sectional imaging in most patients
Dalton et al.[45]	6	0 (0%)	Mean 26 months (range 12–45)	MRI, examination under anesthesia, biopsy, and PET
Nakagawa et al.[24]	10	8 (80%)	Median 32.1 months (range 1.4–64)	Endoscopy and biopsy
Rossi et al.[46]	6	5 (83%)	Median 23 months (range 8–40)	Endoscopy and biopsy

cCR = clinical complete response; DRE = digital rectal examination.