



Current Trends in the Rate of Rectal Cancer Restorative Operations in the Era of Neoadjuvant Chemoradiation

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Abstract

Purpose of Review The following review addresses the relationship between neoadjuvant chemoradiotherapy and the rate of restorative operations in patients with rectal cancer.

Recent Findings The rate of restorative operations performed for rectal cancer has improved over the past several decades. The relationship between this increase and the addition of neoadjuvant chemoradiotherapy to the treatment regimen for locally advanced rectal cancer is still being defined. Improved rates of sphincter-sparing procedures between patients who receive preoperative chemoradiation compared to those who receive treatment postoperatively have not been supported in the literature. The patients who seem to benefit from neoadjuvant therapy in terms of sphincter preservation are those with distal tumors. Better tumor response to neoadjuvant chemotherapy and longer interval to surgical intervention appear to have little if any benefit to preserving the sphincter.

Summary Increased rates of restorative operations for rectal cancer seem to be most significant among distal tumors. The reasons for the increase are likely multifactorial and include improvements in patient selection, surgical technique, imaging modalities, and patient care. The role of neoadjuvant chemoradiotherapy in this setting remains equivocal.

Keywords Rectal cancer · Rectal adenocarcinoma · Neoadjuvant chemoradiotherapy · Restorative operations · Sphincter-sparing operations · Sphincter preservation

Abbreviations

NCRT	Neoadjuvant chemoradiotherapy
CRT	Chemoradiotherapy
APR	Abdominoperineal resection
LAR	Low anterior resection
TME	Total mesorectal excision
SSS	Sphincter-sparing surgery
LARC	Locally advanced rectal cancer
cCR	Clinical complete response
pCR	Pathologic complete response
CR	Complete response

Introduction

Rectal cancer management has significantly evolved since William Ernest Miles published a Lancet article establishing abdominoperineal resection (APR) as the gold standard procedure in patients with rectal cancer in 1908. This novel approach decreased Miles' recurrence rate from 95% in perineal resections to 29.5%. By World War II, improvements in care including anesthesia, patient selection, and other areas resulted in an associated mortality of just 10% [1]; however, the creation of a permanent colostomy was an obvious disadvantage of the operation, and the total mesorectal excision (TME) technique was introduced by Heald in 1982 as a sphincter-sparing option for the treatment of rectal cancer [1]. With similar mortality, morbidity, and local recurrence rates between the two, restorative TME became the treatment of choice when technically possible [2]. Unfortunately, locoregional recurrence rates continued to be unacceptably high with surgery alone (18%). The Dutch Colorectal Cancer Group examined the efficacy of preoperative radiotherapy in combination with TME in patients with rectal cancer versus surgery alone and discovered a significant

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reduction in locoregional recurrence at 2 years (2.4 vs 8.2%) [3]. Over the next few years, guided by the results of the Swedish Rectal Cancer Trial [4] and the German Rectal Cancer Study Group study [5] among others, neoadjuvant chemoradiotherapy (NCRT) became standard of care for locally advanced rectal cancer (LARC) [6].

Over the past several decades, several factors including the acceptance of narrower distal margins [7], increased use of neoadjuvant chemoradiotherapy (NCRT) [8], development of the circular stapler, and advancements in patient care are thought to have resulted in increased numbers of restorative operations offered to rectal cancer patients. This paper aims to review the most current literature on the topic and explore the factors which may contribute to a higher rate of sphincter preservation.

Has NCRT Increased Rates of Restorative Operations?

The operative planning process for rectal cancer patients begins prior to administration of NCRT after initial staging is complete; however, once patients finish their course of NCRT, they are re-staged, and accordingly, the surgical options are revisited with particular consideration of tumor shrinkage and response to therapy, achievable margins, body habitus and pelvic anatomy, and anorectal function [9]. While those patients with LARC who receive NCRT can have rates of pathologic complete response (pCR) between 10 and 27% [10, 11], studies have conflicting findings on whether pCR is associated with improved outcomes with or without surgery [12, 13]. Furthermore, the ability to predict pCR preoperatively is limited at this time, and a significant percentage of patients with clinical complete response (cCR) have persistent disease on pathologic exam [11]. Therefore, surgeons will often recommend surgical intervention in the setting of cCR if comorbidities do not preclude an operation. In the case of persistent yet small tumor near or involving the sphincter after NCRT, distal margins and sphincter function play an important role in decision-making.

Since the 1980s, there has been a marked increase in the rate of restorative operations from 14% [14] to as high as 77% [15]. However, the relationship between this increase and NCRT is unclear. A 2003 study retrospectively reviewed the records of 238 patients with distal LARC who received NCRT followed by mesorectal or local excision to evaluate tumor response and sphincter preservation rates. The authors found an increase in the percentage of sphincter-sparing surgeries (SSS) performed at their institution from 28 to 67% over the course of a decade with no change in the rate of recurrence. This difference was most significant in tumors 3 cm or less from the anal verge [16]. Accordingly, the German Rectal

Cancer Study Group study also showed a statistically significant increase in sphincter preservation among patients that received NCRT [5]. In subsequent studies, however, this trend has not been supported. Roh et al. compared NCRT to postoperative chemoradiotherapy in patients with cT3, T4, or node-positive rectal cancer and reported similar rates of sphincter-sparing operations between groups (47.8 vs 39.2%) [17]. These rates continued to be equivalent when followed out to 5 years.

Multiple systematic reviews of evidence have been conducted aimed at defining the influence of NCRT on sphincter-sparing surgery numbers. A 2006 review investigated randomized trials of patients who experienced tumor shrinkage after NCRT and those who did not and found no difference in rates of sphincter preservation [18]. Another article published in 2012 reviewed data from 17 randomized trials and noted that while the rate of restorative operations has improved over time, aggregate data failed to demonstrate significant benefit related to the administration of NCRT for sphincter preservation [19]. In 2017, a meta-analysis of 3 randomized phase III trials compared outcomes for NCRT and postoperative CRT in patients with stages II–III resectable rectal cancer. Overall, there were 637 patients analyzed. In accordance with prior literature, locoregional recurrence was lower in the NCRT group (6.6 vs 11.3%), and there was no difference regarding overall survival which was attributed to the equivalent late failure rates. In total, 68.7% (436) of NCRT patients and 64.7% (412) of postoperative CRT patients underwent sphincter-sparing procedures ($p = 0.24$) which were not statistically significant; however, when interrogating patients in each group with low rectal tumors (<5 cm from anal verge) who were preoperatively planned for APR but who ultimately underwent an LAR, the conversion rate was significantly different in favor of NCRT (HR 1.78, $p < 0.001$) [20••].

Do Distal or Low Rectal Cancers Treated With NCRT Have Higher Rates of Restorative Operations?

Initially, the primary oncologic advantage of NCRT was improvement in locoregional recurrence, although more recent data has demonstrated increased disease-free survival in patients with pCR [12]. Additionally, many providers opt for preoperative administration of chemoradiotherapy due to a theoretical associated tumor shrinkage which ideally allows for a sphincter-sparing operation with R0 resection. When assessing outcomes in rectal cancer patients grouped by distance from the anal verge, patients with low rectal tumors (<5 cm from the anal verge) were more likely to receive NCRT (75.2 vs 38%) but were less likely to undergo restorative

surgery (15.4 vs 79%) when compared to patients with tumors in the mid or upper rectum. They were also more likely to have positive resection margins with no difference in recurrence or survival [21•].

In a cohort of 238 T3/T4 low rectal cancer patients (< 6 cm from anal verge) treated with NCRT, increased tumor distance from the anal verge was an independent predictor of sphincter-sparing surgical intervention as expected. When analyzing rates of sphincter preservation over time, the reported increase was most marked in the very low rectal tumors (< 3 cm from the anal verge). The rate of sphincter preservation was 49% overall, 53% for T3 tumors and 20% for T4 tumors overall. Of note, additional factors found to be predictive of sphincter-sparing procedures included increased distance of tumor from the anal verge, clinical T3 disease, lack of obstruction, lack of circumferential tumor involvement of the rectal lumen, tumor mobility on clinical exam, more recent year of treatment, and complete clinical response of the tumor [16].

Does Tumor Response After Neoadjuvant Therapy Affect Rates of Restorative Operations?

We are now in an age where clinical and even pCR to NCRT in rectal cancer are possible, and the rate of the clinical downstaging of tumors can be significant. The clinical implications of these findings in terms of oncologic outcomes and surgical decision-making are still debated. A 2005 study examined tumor regression outcomes in distal (0–7 cm from anal verge) rectal cancer patients managed with NCRT. cCR was observed in 28% of patients, and these patients were treated with observation alone. Those patients which had a clinically incomplete tumor response (72%) underwent surgical excision. Interestingly, no difference in survival was shown between those patients with incomplete tumor response who underwent surgery and were found to have pCR and those patients with cCR who were observed. Of note, within the cCR group, 19.7% initially had a T2 lesion, 69% had T3 lesions, and 11.3% had T4 lesions. Mean follow-up was 57 months and 2.8% of patients developed locoregional recurrence while 4.2% developed systemic unresectable metastatic disease [22].

There is some evidence that higher doses of radiation may improve tumor shrinkage and rates of sphincter preservation. In a prospective study of 88 patients with locally advanced (T2, T3, Nx, M0) low rectal cancer (< 6 cm from anal verge) treated with either standard or high-dose preoperative radiotherapy, improvements in cCR (2 vs 24%) and sphincter preservation (44 vs 76%) were observed with no significant differences in toxicity or 2-year survival [23].

The literature is mixed with regard to the effect that tumor response to NCRT has on rates of restorative operations. A

prospective study of 86 patients with distal rectal cancer (< 5 cm from the anal verge) who underwent NCRT at a single institution was conducted in 2015. These patients underwent surgical intervention 6–8 weeks after completion of NCRT. Sphincter-preserving surgery was performed in 81.9% of patients. Clinical and pathologic down-staging was seen in 45.7 and 61% of cases, respectively. The authors used pelvic MRI to assess tumor height as a marker of tumor response to NCRT and found no change in the rate of restorative operations between those that experienced a significant change in tumor height on MRI and those that did not [24]. Crane et al. reported a complete response (CR) rate of 47% for all patients (T3 49%, T4 32%) in their cohort of low rectal cancer patients with a sphincter-preserving rate of 49%. CR was defined as no residual or only microscopic disease in the resected specimen. The authors found CR to be predictive of the use of a restorative operation, and this effect was most noticeable in the very low tumor group (< 3 cm from anal verge) [16].

A systematic review which examined 10 randomized trials including just over 4500 patients sought to define the effect of tumor response on the rate of sphincter-saving procedures. The combinations of chemotherapy and radiation studied in these randomized trials were variable, but none of the trials reported a difference in sphincter preservation. In terms of conversion from APR to anterior resection after NCRT, three studies described their findings. Only one of these studies demonstrated an increased conversion rate to a restorative operation in the experimental group compared to controls; however, sphincter preservation was not a primary endpoint, and the experimental group included a disproportionate number of distal tumors which may explain the higher conversion rate seen in this study [18]. The lack of data supporting increased restorative operations in patients with responsive rectal tumors could be related to the widely held belief in the surgical community that in patients with cCR, a significant percentage will continue to have nodal micrometastatic disease. In fact, one study examining patients with LARC who underwent NCRT followed by surgical resection found that in those patients with pathologic T0 tumors, 13% had lymph node metastatic disease which is best treated by total mesorectal excision [25]. A retrospective review of 488 patients who underwent NCRT followed by resection for T3 or T4 tumors or node-positive disease found that just 25% of patients with cCR to NCRT went on to have CR on pathologic exam [11].

Does the Timing of Surgery After NCRT Matter?

The optimal time to wait between NCRT and surgery is unclear. The traditionally utilized waiting period is based on the Lyon R90-01 randomized trial which compared a short

interval (<2 weeks) group to a long interval (6–8 weeks) group. The study found that the long interval group had improved clinical response rates and pathologic down-staging with no differences in morbidity, local recurrence, and short-term survival. Sphincter preservation was similar between groups (2 weeks 76%, 6–8 weeks 68%) [26]. Since this study was published, there has been continued discussion about the potential benefit of longer wait intervals on rates of pathologic responses and possibly lower rates of APR.

In 2016, the *Journal of Clinical Oncology* published a multicenter, randomized, controlled trial (GRECCAR-6) which sought to define the effect of the time from NCRT to surgical intervention. The study compared 265 patients who underwent surgery at either 7 or 11 weeks after NCRT. Patients with cT3/T4 or TxN+ tumors of the mid or lower rectum who underwent NCRT were included. The primary outcome was pCR, and this was found to be statistically similar between groups (7 weeks 15% vs 11 weeks 17.4%); however, postoperative medical complications were noted to be increased in the 11-week group. Additionally, the rate of sphincter preservation was equivalent between groups (7 weeks 90.4% vs 11 weeks 89.1%).

A systematic review published in 2017 evaluated the effect of the time interval between NCRT and surgical intervention on outcomes of locally advanced rectal cancer patients. The primary outcome of the study was pCR rates. Rate of restorative procedures was a secondary outcome measure. The paper reviewed 13 studies totaling almost 20,000 patients and found that patients that waited > 8 weeks for surgical intervention had a statistically significant improvement in pCR when compared to those who waited < 8 weeks. However, these patients did not experience benefit in terms of local recurrence, overall survival, or rates of sphincter-sparing surgeries. Of note, there was also no increase in operative time [27]. These results are similar to another meta-analysis from 2016 which also showed an increase in pCR among patients who waited greater than the traditional 6–8 weeks with no associated change in rate of sphincter-sparing surgeries or outcomes [28].

Conclusions

Avoidance of a colostomy has long been among the goals of rectal cancer management due in part to the worsened social well-being compared with controls [29]; however, interest in functional outcomes with regard to sphincter preservation is growing, especially in the context of NCRT. A 2015 study investigating 29 patients treated with NCRT followed by low anterior resection revealed significant bowel dysfunction impacting patient quality-of-life scores [30]. Bowel-related quality-of-life impairment was reported in 85% of patients after curative restorative surgery for rectal cancer in one study with the highest proportion of major impairments (60%)

observed in patients with low rectal cancer who had undergone NRT [31]. These considerations make patient selection for and counseling about sphincter-sparing operations a particularly important aspect of care.

NCRT is often discussed as having potential benefit with regard to conversion to a sphincter-sparing operation; however, the data is mixed, and it is difficult to discern whether NCRT-related tumor shrinkage is the reason for improved numbers of restorative operations for rectal cancer. A major issue to address is micrometastatic disease in lymph nodes even if clear margins are achieved intraluminally. In the current review, the data does not clearly support NCRT, interval from NCRT to surgery, or tumor response to NCRT as associated with improved rates of sphincter-sparing operations. There is evidence to suggest that distal tumors, while subject to APR more frequently than mid or upper tumors, may benefit the most from NCRT and tumor response with regard to conversion to a restorative operation. Interestingly, Kahn et al. found that a substantial proportion of patients with low rectal cancer who were deemed technically able to undergo a restorative operation instead underwent non-restorative operations. Reasons for this included patient comorbidities, anastomotic leak risk, sphincter dysfunction, and patient preference [21] supporting the idea that decisions about sphincter preservation are complex and multifactorial in nature. Ultimately, better patient selection, improved surgical technique and instruments, advancement in imaging modalities, and more well-rounded patient care developed over the last several decades likely significantly contribute to the overall increase in restorative operations but also result in a mixed picture in the literature with regard to the role that NCRT has played in this trend.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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