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MINI-REVIEW

Treatment of locally advanced low rectal cancer

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Abstract Rectal cancer is a formidable disease with high recurrence and metastasis rates, particularly before total mesorectal excision (TME) was first described by Heald and Ryall in 1982. Through this ground-breaking operative procedure, rectal cancer has become a potentially curable condition. Traditional abdominoperineal resection has gradually been replaced with TME and coloanal anastomosis for resectable low rectal cancer. In addition, improved overall survival and decreased local recurrence rates have been achieved. For locally advanced (cT3/4, cN1/2) low rectal cancer (lower tumor margin $<$ 6 cm above the anal verge), sphincter preservation is a major concern in cancer treatment. Randomized controlled trials have shown that neoadjuvant chemoradiation therapy (CRT) leads to a decrease in tumor size and enhances the likelihood of tumor resectability and sphincter preservation with low local recurrence rates. Therefore, neoadjuvant CRT followed by TME is the standard treatment guideline used worldwide for patients with low rectal cancer. However, one must understand the basic principles of TME to know why this procedure should be employed to treat locally advanced low rectal cancer. We therefore performed a minireview to explore how surgeons address this problem, how to help patients live longer, and how to reduce the occurrence of perioperative morbidities.

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1. Introduction

Since total mesorectal excision (TME) was first described by Heald and Ryall[1] in 1982, rectal cancer has become a potentially curable condition. Traditional abdominoperineal resection has gradually been replaced with TME and coloanal anastomosis for resectable low rectal cancer. In addition, improved overall survival and decreased local recurrence rates have been achieved. Furthermore, for locally advanced (cT3/4, cN1/2) low rectal cancer (lower tumor margin < 6 cm above the anal verge), sphincter preservation is a major concern in cancer treatment. Randomized controlled trials have shown that neoadjuvant chemoradiation therapy (CRT) leads to a decrease in tumor size and increases the likelihood of tumor resectability and sphincter preservation[2,3] with low local recurrence rates. Therefore, neoadjuvant CRT followed by TME is the standard treatment guideline used worldwide for patients with low rectal cancer.

2. Clinical staging evaluation

Computed tomography, which determines the clinical staging of low rectal cancer, is widely used worldwide because of easy accrual, short execution time, and relatively low costs. Rectal tumor shrinkage after neoadjuvant CRT correlates positively with clinical and pathologic changes.[4–6] However, until now, magnetic resonance imaging (MRI) for selecting node-positive patients, and transrectal ultrasound (TRUS) for determining tumor invasion depth have been the gold standards for clinical staging. Similar to other types of ultrasound, TRUS is operator dependent. However, with an experienced operator, TRUS can be as effective as MRI in detecting perirectal lymphadenopathy.[7] Nevertheless, using MRI to determine whether the circumferential resection margin (CRM) is compromised during TME is another major benefit of using this approach to determine whether patients require neoadjuvant radiotherapy (RT).[8–10] Finally, before we depend totally on modern technology, a digital examination should always be performed, which can be as accurate as TRUS or MRI in tumor staging when performed by an experienced surgeon.

3. Evolutionary process of chemotherapy, radiotherapy, and chemoradiation therapy

Prior to the widespread acceptance of TME, randomized controlled trials had confirmed that using adjuvant chemotherapy (CT) and RT could significantly reduce local recurrence rates and improve overall survival rates for rectal cancer patients.[11–13] In addition, general consensus indicates that neoadjuvant RT has the effects of *sterilization* of the mesorectal lymphatic channels, tumor bulk reduction in improving resectability and increasing sphincter preservation, exclusion of the small bowel from the radiation field, improved response in untreated tumors, and superior function of nonirradiated neorectum.[14] TME and RT have merged gradually, such that both CT and RT, which are used prior to surgery, enable superior local control and higher overall survival, setting the foundation for subsequent randomized controlled trials in validating their effects.[15–18] After TME became the dominant surgical procedure for low rectal cancer, more randomized controlled trials were executed, revealing a phenomenon that neoadjuvant RT could reduce local recurrence rates, even after TME surgery.[19–21] The superior local control ability of neoadjuvant RT was confirmed by both the Dutch TME trial after 12 years of follow-up[22] and the German Rectal Cancer Study Group trial after 11 years of follow-up.[2]

4. Short- versus long-course radiotherapy

The choice of long- or short-course RT has long been an active debate; each choice has its own proponents. However, in improving the tumor *downsizing* effect, long-course RT is superior to short-course RT, although short-course RT with a longer waiting period can still achieve the same effect, as reported by the Stockholm III trial.[23] Regarding local control, the effectiveness of short-course RT is at least comparable with that of long-course RT.

Table 1 summarizes crucial randomized controlled trials about neoadjuvant and adjuvant RT, CT, and CRT with long-term follow-up results.

5. Neoadjuvant chemotherapy regimens (infusional 5-fluorouracil, oral 5-fluorouracil, and other agents)

Adding 5-fluorouracil (5-FU) CT to RT in gastrointestinal cancer treatment to improve overall survival (compared with RT alone) was approved in 1969.[24] To determine the effect of neoadjuvant CT, the European Organization for Research and Treatment of Cancer 22921 randomized controlled trial reported that combining CT with RT preoperatively could improve pathologic response rates and the *downsizing* effects.[25] Therefore, to decrease the tumor bulk to improve the likelihood of sphincter preservation, using long-course instead of short-course CRT is a more rational choice, which is similar to a finding reported in the German Rectal Cancer Study trial. Regarding the choice of CT, infusional 5-FU/leucovorin with RT is currently the gold standard. Oral 5-FU (uracil, tegafur, and capecitabine) with RT has been proven to have therapeutic effects similar to those of infusional 5-FU.[26–28] The addition of other chemotherapeutic or target therapy agents, including oxaliplatin, irinotecan, bevacizumab, and cetuximab, is currently being investigated in randomized controlled trials, but it is not considered in standard treatment plans because of higher toxicities, despite similar pathologic complete response (PCR) rates.[29] Notably, in 2015, the German Rectal Cancer Study Group published remarkable results for a randomized controlled trial, stating that if oxaliplatin were incorporated into both neoadjuvant 5-FU-based CRT and adjuvant CT for patients with locally advanced rectal cancer, better disease-free survival could be achieved with acceptable treatment-related toxicity and death.[30] Because this large randomized controlled trial was performed by an