MINI-REVIEW

Treatment of locally advanced low rectal cancer

Po-Chuan Chen, Jenq-Chang Lee*

Division of Colorectal Surgery and General Surgery, Department of Surgery, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Received 19 November 2015; received in revised form 7 January 2016; accepted 23 February 2016

Available online 3 June 2016

KEYWORDS
neoadjuvant chemoradiation; rectal cancer; total mesorectal excision

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.

Copyright © 2016, Taiwan Surgical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Conflicts of interest: All contributing authors declare no conflicts of interest.

* Corresponding author. Division of Colorectal Surgery and General Surgery, Department of Surgery, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Number 138, Sheng Li Road, East District, Tainan 704, Taiwan.

E-mail address: leejc@mail.ncku.edu.tw (J.-C. Lee).

http://dx.doi.org/10.1016/j.fjs.2016.02.003

1682-606X/Copyright © 2016, Taiwan Surgical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
1. Introduction

Since total mesorectal excision (TME) was first described by Heald and Ryall in 1982, rectal cancer has become a potentially curable condition. Traditional abdominoperineal resection has gradually been replaced with TME and colorectal 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 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. 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. 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). 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. 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. 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. 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. The superior local control ability of neoadjuvant RT was confirmed by both the Dutch TME trial after 12 years of follow-up and the German Rectal Cancer Study Group trial after 11 years of follow-up.

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. 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. 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. 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. The addition of other chemotherapeutic or target therapy agents, including oxaliplatin, irinotecan, bev-acizumab, 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. 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. Because this large randomized controlled trial was performed by an...
acclaimed study group, we believe that more oxaliplatin-related neoadjuvant trials will be reported by surgical and oncological societies in the future. Accordingly, based on our personal series, the use of infusional 5-FU and a concomitant RT protocol can be expected to lower treatment toxicity without compromising the desirable treatment effects of neoadjuvant CRT in standard low rectal cancer patients. Finally, the choice of whether postoperative adjuvant CT should be given is controversial, particularly for ypT0-2N0 patients. A meta-analysis of the Cochrane review demonstrated that adjuvant CT after rectal cancer resection improved local control of the disease but not specifically under the premise of neoadjuvant CRT. To date, randomized trials targeting this issue do not support the use of postoperative CT after neoadjuvant CRT for operable rectal cancer. Additional appropriately designed studies are necessary to address this concern in the future.

6. Total mesorectal excision, minimally invasive surgery, and pelvic lymph node dissection

TME is the cornerstone of curative treatment for low rectal cancer patients. The natural barriers of the bony structure and pelvic organs render low pelvic dissection difficult, even in open surgery. With rapid advancements in technology, higher magnification and a clearer optic view can be obtained in minimally invasive surgery (MIS). In addition, faster tissue-dividing and safer vessel-sealing ability could be achieved with new ultrasonic or bipolar energy equipment. Thus, currently, TME with MIS in a narrow male pelvis can be performed safely with low risk of morbidity. Although relatively new, the prevalence of MIS in rectal cancer surgery has increased rapidly worldwide. Randomized controlled trials and many retrospective studies have confirmed that MIS, either laparoscopic or robotic, can achieve comparable surgical quality with similar morbidity and mortality to open surgery. Another aspect of surgery is about pelvic lateral lymph node dissection, which is an essential part of surgery for low rectal cancer in Japan, although it is not frequently performed in Taiwan. A noninferiority trial (JCOG0212) was conducted in Japan to examine the effectiveness of TME and lateral lymph node dissection compared with TME alone. The results of this study are expected to clarify the therapeutic benefits and long-term outcomes of this surgical procedure. By contrast, rectal cancer surgery has included the so-called “down-to-up” approach since the first report of transanal TME (or reverse TME) in 2010, which claimed it to be an easier surgical approach with shorter operation time for low rectal cancer. Increasingly more medical facilities have published reports of the short-term outcomes of this reversed procedure regarding specimen quality and operative

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years</th>
<th>Protocol</th>
<th>Long-term results</th>
<th>Follow-up (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish Rectal Cancer Trial</td>
<td>1987–1990</td>
<td>25-Gy neoadjuvant RT vs. surgery</td>
<td>Neoadjuvant RT decreased local recurrence rates &amp; is beneficial for overall &amp; cancer-specific survival</td>
<td>13</td>
</tr>
<tr>
<td>Dutch TME Trial</td>
<td>1996–1999</td>
<td>25-Gy neoadjuvant RT vs. surgery</td>
<td>Neoadjuvant RT reduced local recurrence by 50% with improved cancer-specific survival but equal overall survival</td>
<td>12</td>
</tr>
<tr>
<td>German Rectal Cancer Study Group</td>
<td>1995–2002</td>
<td>5040-cGy neoadjuvant CRT plus adjuvant C/T vs. 5580 cGY adjuvant CRT</td>
<td>Persistent better local control for neoadjuvant CRT</td>
<td>11</td>
</tr>
<tr>
<td>Polish Rectal Cancer Trial</td>
<td>1999–2002</td>
<td>25-Gy neoadjuvant RT vs. 5040 cGY adjuvant CRT</td>
<td>Comparable survival, local recurrence, &amp; distant metastasis rates; comparable late toxicity</td>
<td>3</td>
</tr>
<tr>
<td>EORTC 22921</td>
<td>1993–2003</td>
<td>45-Gy neoadjuvant RT vs. 45-Gy neoadjuvant CRT vs. 45-Gy neoadjuvant RT plus adjuvant C/T vs. 45-Gy neoadjuvant CRT plus adjuvant C/T</td>
<td>Adjuvant fluorouracil-based chemotherapy does not affect disease-free or overall survival after neoadjuvant RT or CRT</td>
<td>11</td>
</tr>
<tr>
<td>Stockholm III</td>
<td>1998–2010</td>
<td>25-Gy neoadjuvant RT vs. 25-Gy neoadjuvant RT plus delayed surgery</td>
<td>Increased tumor downstaging if surgery after 4–8 wks</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

CRT = chemoradiation therapy; CT = chemotherapy; EORTC = European Organisation for Research and Treatment of Cancer; RT = radiotherapy; TME = total mesorectal excision.
morbidity; basically, perioperative outcomes are comparable with those of traditional laparoscopic surgery.\textsuperscript{41,42} More studies are currently underway to confirm the safety and feasibility of this procedure.

7. Timing of surgery after neoadjuvant chemoradiation therapy

The optimal timing of interval surgery remains unclear. When a surgeon chooses either short- or long-course RT, surgery should be undertaken within 2 weeks or after 6 weeks, respectively, to avoid severe tissue edema and postoperative morbidity. However, to gain the benefit of tumor downsizing and sphincter preservation, long-course RT is the more rational choice. According to a German rectal cancer study, a duration of 6–8 weeks post-RT can avoid severe surgical morbidities and significantly raise the likelihood of sphincter preservation.\textsuperscript{65} Currently, longer waiting times are supported by evidence from retrospective studies, showing that a higher PCR rate can be expected for longer waiting times without causing greater surgical morbidity. On the basis of a retrospective analysis of a Dutch surgical colorectal audit database, the highest PCR rates occurred when operations were postponed for 10–11 weeks.\textsuperscript{55} However, the only randomized controlled trial addressing this issue to date is the Lyon R90-01 trial in 1999,\textsuperscript{44} in which patients were randomized into short (<2 weeks) and long (6–8 weeks) course groups, and 6–8-week intervals became the current standard practice. Hence, additional prospective studies are necessary to address this issue.

8. Prognostic factors of surgical specimen (distal resection margin, circumferential resection margin, and tumor regression grade)

Regarding the surgical quality affecting both local and distant metastasis, three factors have been identified to be of crucial prognostic value: the distal resection margin (DRM), circumferential resection margin (CRM), and lymph node yield. The DRM and CRM are associated with local control of a disease, disease-free survival, and overall survival.\textsuperscript{45–47} Traditionally, 2 cm of the distal margin is considered adequate. However, increasingly more retrospective series have demonstrated that 1 cm appears to be a sufficient DRM in low rectal cancer patients who received neoadjuvant CRT.\textsuperscript{48} In addition, tumor involvement over the CRM has a negative effect on the 5-year local recurrence, distant metastasis, and overall survival rates in patients with low rectal cancer. Frequently, fewer than 12 lymph nodes can be harvested despite maintaining vigorous surgical standards in low rectal cancer patients if neoadjuvant CRT was performed.\textsuperscript{49,50} However, the persistence of lymph node metastasis after a patient undergoes neoadjuvant RT is associated with a poor prognosis and survival, and may serve as a marker of aggressive tumor behavior.\textsuperscript{51,52} Another crucial concern about the treatment response is the pathologic tumor regression grade, which is graded 1–5, according to the Mandard score. A PCR, which is Grade 1, is a major prognostic factor in rectal cancer patients who receive neoadjuvant CRT.\textsuperscript{53–55} A rectal cancer specimen with a PCR is an excellent marker for both exceptional local control and disease-free survival. The PCR can be affected by various factors including CT regimen, RT dosage, and surgical interval. Large-scale retrospective studies have demonstrated that PCR rates could be increased if the surgical interval was prolonged up to 12 weeks. However, whether higher PCR rates from longer waiting times translate into improved local and systemic control is unknown.

9. Stool diversion after total mesorectal excision and postoperative anal function

Routine temporary defunctioning stoma construction after TME was previously considered controversial.\textsuperscript{56} However, current opinions have gradually shifted to support the routine construction of defunctioning stoma to minimize postoperative complications.\textsuperscript{57–59} A meta-analysis demonstrated that anastomotic leakage can have a negative effect on local recurrence and cancer-specific survival in patients with colorectal cancer.\textsuperscript{60} In our personal series, a defunctioning loop stoma was created for every low rectal cancer patient treated with neoadjuvant CRT and a sphincter-saving procedure, achieving extremely low rates of early and late surgical complications. Based on our experience and that of other researchers, we believe that routine defunctioning stoma construction prevents significant postoperative complications, including fistula formation from anastomotic leakage and subsequent permanent colostomy, and guarantees a smooth and safe treatment course.\textsuperscript{21}

For patients undergoing TME and coloanal anastomosis, postoperative anal function recovery is crucial. In addition, neoadjuvant RT was reported to delay postoperative anorectal function recovery.\textsuperscript{61} In our personal series, with the use of the Memorial Sloan-Kettering Cancer Center anal function score, approximately 50% of the patients reported poor–fair anal function 1 month after surgery, but this could be improved to fair–good 2 years after a straight coloanal anastomosis procedure.\textsuperscript{31} The benefit of a straight coloanal anastomosis is that the splenic flexure does not need to be taken down routinely during surgery, reducing the likelihood of operative morbidity. A previous report and our experience have shown that 2 years after a straight coloanal anastomosis, anal function would be comparable with that of patients who underwent J-pouch coloanal anastomosis or T-coloplasty.\textsuperscript{62}

10. Now and the future

To date, treatment of locally advanced low rectal cancer patients through neoadjuvant CRT with infusional 5-FU can minimize associated morbidities and achieve a comparable pathologic response. TME at 6–11 weeks after RT with routine defunctioning stoma construction can achieve excellent local control and guarantee a smooth and safe treatment course. After 30 years of evolution, these procedures are the gold-standard treatment options. However, additional paradigm-shifting ideas are continually proposed. More individually tailored approaches, including the choice of radiation for individual patients, a nonoperative organ-preserving approach for selected patients, or...
Locally advanced rectal cancer

precise treatment regimens based on the treatment response for every patient and tumor, are gaining increasingly more attention from surgical societies worldwide.63 Thus, the future of treating low rectal cancer is expected to remain exciting and challenging.

References

31. Lin SC, Chen PC, Lee CT, et al. Routine defunctioning stoma after chemoradiation and total mesorectal excision: a single-


