Current Surgical Strategies for the Treatment of Rectal Adenocarcinoma and the Risk of Local Recurrence

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Keywords

Rectal cancer · Rectum · Recurrence · Surgery

Abstract

Background: Despite new medical and surgical strategies, 5-year local recurrence of rectal adenocarcinoma was reported in up to 25% of cases. Therefore, we aimed to review surgical strategies for the prevention of local recurrences in rectal cancer. **Summary:** After implementation of the total mesorectal excision (TME), surgical resection of rectal adenocarcinoma with anterior resection or abdominoperineal excision (APE) allowed decrease in local recurrence (3% at 5 years). More recently, extralevator APE was described as an alternative to APE, decreasing specimen perforation and recurrence rate. Moreover, technique modifications were developed to optimize rectal resection, such as the laparoscopic or robotic approach, and transanal TME. However, the technical advantages conferred by these techniques did not translate into a decreased recurrence rate. Lateral lymph node dissection is another technique, which aimed at improving the long-term outcomes; nevertheless, there is currently no evidence to recommend its routine use. Strategies to preserve the rectum are also emerging, such as local exci-

sion, and may be beneficial for subgroups of patients. **Key Messages:** Rectal cancer management requires a multidisciplinary approach, and surgical strategy should be tailored to patient factors: general health, previous perineal intervention, anatomy, preference, and tumor characteristics such as stage and localization.

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Introduction

Adenocarcinoma of the rectum, which arises from epithelial cells of the rectal mucosa, represents >90% of rectal cancers [1]. In the USA, the estimated incidence of rectal cancer was 43,340 cases in 2020 [2] and was responsible for 3.2% of all cancer deaths [3]. Moreover, its prevalence is increasing, especially in Western countries, with increased alcohol and meat consumption, tobacco, sedentary lifestyle, and obesity. Nonmodifiable risk factors for the development of rectal adenocarcinoma were also reported, such as male gender, age, genetic predisposition, inflammatory bowel disease, and radiation [3].

Surgery allows for the removal of the tumor and is a mainstay for the treatment of rectal cancer. Along with

preventive measures, treatments led to a reduction of 50% in the mortality rate from rectal cancer since 1976 [4]. As reported by 2 systematic reviews, the overall survival ranged from 74 to 78% at 2 years [5, 6]. However, overall recurrences, which are mainly represented by local recurrences [7], were reported in 10% of cases at a follow-up range between 4 and 7 years [5]. Local recurrences, defined as detectable disease inside the pelvis in patients who underwent resection [8], were associated with several risk factors including involvement of the circumferential resection margin (CRM), extent of the tumor, nodal status, size of the tumor, specimen perforation, R1-2 stages, and anastomotic leakage [9–13]. Incidences of local recurrences at 5 years were reported around 1% for T1-T2 tumors and 15% for T3-T4 tumors. These rates were even higher when the CRM was involved, with 12 and 24% of local recurrences, respectively [14].

Management of adenocarcinoma of the rectum is constantly developing and is based on a multimodal treatment approach. Improvements in surgical strategies, as well as neoadjuvant and adjuvant therapies, led to better oncological outcomes. Nevertheless, local recurrences of rectal adenocarcinoma lead to increased morbidity and mortality [15]. Therefore, we aimed to review the impact of current surgical strategies directed at reducing the occurrences of local recurrences.

Local Extension of Rectal Adenocarcinoma at Diagnosis

Local Extent of Resection

Total Mesorectal Excision or No Total Mesorectal Excision

With the aim of improving oncological outcomes along with good quality of life, various surgical techniques were developed for the treatment of rectal adenocarcinoma. Abdominoperineal excision (APE), first described by Miles [16], was associated with a high recurrence rate of up to 30% and a definitive colostomy. In addition to complications related to oostomy, postoperative complications related to APE include perineal wound dehiscence, hernia, persistent pain, or infection. The latter was reported in 14–85% of patients and may be avoided by filling the defect in the pelvis and by postoperative closed suction drain placement [17]. Subsequently, sphincter-preserving procedures were developed, with anterior resection first described by Balfour in 1910 [18] being the procedure of choice for upper and midrectal cancer. Specific anterior resection complications com-

prise anastomotic leakage in the early postoperative course (incidence 5.5–8%) and low anterior resection syndrome in the long-term postoperative course (incidence 55.2–58%) [19]. Nowadays, the choice of the technique relies on the size and the localization of the tumor [20]. APE is mandatory when the anorectal junction or anal sphincter is invaded, while anterior resection may be otherwise satisfactory [21]. These techniques initially performed with a blunt dissection without direct vision of the mesorectal fascia led to a high rate of CRM involvement. Therefore, the mesorectum was incompletely removed and resulted in local recurrence rate up to 40% [22]. Consequently, Heald et al. [23] introduced total mesorectal excision (TME) in 1982. This technique completely excises the mesorectum which may contain cancer deposits and lymph nodes, leading to decreased recurrences [24]. As showed by the long-term results of curative resections with TME published in 1998 by Heald et al. [25], 5- and 10-year local recurrence rates were 3 and 4%, respectively. Maurer et al. [26] compared surgical resection (APE or anterior resection) for rectal adenocarcinoma after implementation of TME, with a cohort composed of 118 TME, versus 53 resections before the implementation of TME. After a follow-up of 7 years, TME was associated with decreased local recurrences: 5.9% with TME versus 20.8% without TME ($p = 0.003$). TME is now considered as the gold standard procedure for middle and lower third rectal cancers [20]. For upper third rectal adenocarcinoma, partial mesorectal resection with a distal margin of at least 5 cm of mesorectum may be sufficient, as stated by the European Society for Medical Oncology (ESMO) guidelines [21, 27]. Complete TME with an intact mesorectal fascia envelope and negative CRM are keys to minimize recurrence rate. The Quirke classification [28] of the mesorectum specimen quality entailed complete, nearly complete, or incomplete (Table 1). Moreover, CRM is considered negative if the distance between the tumor and the margin is >1 mm [28]. Based on an observational cohort of 130 patients [29], the Quirke classification was shown to be an independent predictor for local recurrences (1.6% with complete, 5.7% with nearly complete, and 41% with incomplete, $p = 0.0001$, median follow-up of 26 months).

Extra-TME Resection

Nagtegaal et al. [30] compared 846 anterior resections to 373 APE for rectal cancer. Unsurprisingly, the rate of low rectal tumor was increased in the APE group; however, tumor stages were similar between the 2 groups (T1–T4 and N0–N2 included). Moreover, APE was asso-

Table 1. Quality of the mesorectum adapted from the Quirke classification

Mesorectum	Complete	Nearly complete	Incomplete
Surface	Intact with only minor irregularities	Moderate bulk	Little bulk
Defects	No defect >5 mm	One or more defects >5-mm deep, without visualization of the muscularis propria	Exposed muscularis propria
Distal coning	None	Moderate	Moderate to marked
CRM	Smooth	Irregular	Irregular

CRM, circumferential resection margin.

ciated with increased specimen perforation and CRM involvement, leading to increased local recurrences after a median follow-up of 60 months (30.4% in APE with positive CRM vs. 8.6% in APE with negative CRM, $p = 0.0002$) [30]. This led to technique modifications: the extralevator APE (ELAPE). Initially described in 2007 by Holm et al. [31], ELAPE was performed for T3 and T4 low adenocarcinoma of the rectum. It involved an extended perianal resection with the patient in a prone position, resecting the levator ani en bloc with the rectum and mesorectum. The latter avoided coning of the distal part of the specimen at the level of the levator ani typically seen with conventional APE and resulted in a cylindrical resection. Seventeen studies were included in a recent meta-analysis [32], totalizing 2,248 ELAPE and 1,801 APE. The CRM involvement rate was similar; however, ELAPE led to decreased perforation rate (6.6 vs. 11.3%, $p < 0.001$, respectively) and local recurrence (8.8 vs. 20.5%, $p < 0.001$, at a mean follow-up of 41 months, respectively). Postoperative complications were more frequent after ELAPE, when compared to APE, for perineal wound infection or dehiscence (44 vs. 25%, $p < 0.001$, respectively) and perineal pain (38 vs. 22%, $p < 0.001$, respectively), but were similar for perineal hernia [33].

Overall, TME is the gold standard for resection of rectal adenocarcinoma. Anterior resection was associated with better oncological outcomes than APE, but the latter is still mandatory for some cases. Moreover, modifications of conventional techniques with ELAPE yielded encouraging oncological outcomes, at the expense of an increased morbidity.

Surgical Approach

Open, Laparoscopic, or Robotic Approach

To achieve a complete resection, distinct approaches are available. Initially, open resection was described.

Then, with the implementation of minimal invasive surgery, laparoscopic and robotic techniques have been developed. The Cochrane review published in 2014 by Vennix et al. [34] included 14 randomized controlled trials (RCTs) to compare laparoscopic TME versus open TME and found similar 3-year local recurrence rate (4.8 vs. 5.4%, $p = 0.6$, respectively) and similar 5-year overall survival (70.9 vs. 67.9%, $p = 0.32$, respectively). Moreover, laparoscopic TME was associated with a shorter hospital stay, fewer wound infections, and less postoperative bleeding [34]. These results were supported by a more recent meta-analysis published in 2017 [35–38] and another by Nienhüser et al. published in 2018 [39]. The latter included 14 RCTs totalizing 3,528 patients. Compared to the review by Vennix et al. [34], they provided the long-term outcomes of COREAN [40] and COLOR II [41] trials and added new data from ALaCaRT [42] and ACOSOG [43] trials published in 2015. Nienhüser et al. [39] reported similar local recurrence rates at 3 and 5 years ($p = 0.91$ and $p = 0.89$, respectively). They ranged from 3.6 to 9.9 and 2.8–9.3% in the laparoscopic group versus 4.7–10.2 and 8.3–8.6% in the open group (at 3 and 5 years, respectively) [39]. Nevertheless, laparoscopic surgery is associated with some limitations. This technique is based on a 2-dimensional view and is technically demanding, especially in narrow pelvis as seen with males. Moreover, manipulation and instrumentation are limited and require an extended learning curve estimated between 50 and 150 procedures [44].

Robotic surgery was developed as another minimal invasive technique capable to overcome these limitations. This approach offers a 3-dimensional view, superior dexterity and ergonomics, and a better identification of anatomical structures in the confined pelvis [45]. Another advantage may be a shorter learning curve (estimated 15–44 procedures) [46]. Compared to laparoscopy, 3 meta-

analyses [47–49] showed similar oncological outcomes and postoperative morbidity associated with the robotic approach. Among them, the meta-analysis by Xiong et al. [47] included 8 studies to compare 554 robotic TME versus 675 laparoscopic TME for upper, middle, or low rectal cancer stages T0–T4. They reported a decreased positive CRM rate associated with the robotic TME (OR = 0.4, 95% CI: 0.2–1.0, $p = 0.04$). However, this did not translate in different oncological outcomes, as showed by similar local recurrence up to 29 months of follow-up and similar 2-year overall survival. Moreover, the complication rate and operation time were similar, but robotic TME resulted in lower conversion rate (OR = 0.2, 95% CI: 0.1–0.5, $p = 0.0004$). Nevertheless, the quality of these results was low, with majority of included studies being retrospective cohorts. Only one RCT was identified [50], which was based on a small sample of 29 robotic versus 37 laparoscopic rectal resections for rectal cancer stages I–IV, with a mean distance from the anal verge of 11 cm in the laparoscopic group versus 6 cm in the robotic group ($p < 0.01$). Local recurrences were increased in the laparoscopic group versus robotic group (5.4% at a mean of 19 months vs. 0% at a mean of 29 months, respectively). However, the statistical value of the latter result cannot be interpreted, as no p value was reported.

Overall, laparoscopic TME showed advantages for the short-term postoperative recovery, but did not confer oncological benefit over open TME. The robotic approach could be an alternative to laparoscopy yielding similar oncological outcomes, but larger prospective and randomized trials (i.e., long-term results of the ROLARR trial [51]) are required to strengthen the evidence base.

Abdominal Only versus Mixed Approach

From the abdomen, dissection of the lower rectum in the distal pelvis is anatomically challenging, particularly in males, obese, or irradiated pelvis. These difficulties may result in incomplete resection and subsequent increased recurrences. To improve accessibility and quality of the specimen resection, another approach to perform TME was described, with a retrograde dissection from below. Initially described in 1984 by Marks et al. [52] as an open approach, the transabdominal transanal (TATA) technique started mobilizing the rectum transanally with an open perineal approach. The procedure was followed with an abdominal approach for mobilization of the left colon. The initial results [52] for low rectal cancer reported a 5-year local recurrence rate of 9%. Following the development of minimal invasive surgery, Sylla described in 2010 [53] the transanal TME (TaTME) using endoscopic

and laparoscopic instruments through the natural orifice of the anus. Transabdominal laparoscopic assistance can be performed, helping dissection of the proximal colon. TaTME allows magnified visualization and accessibility of the tumor, which help optimal oncological distal margin during the resection [54]. Moreover, TaTME achieved better mesorectal resection than laparoscopic TME, as demonstrated by the lower rate of inadvertent residual mesorectum detected on postoperative magnetic resonance imaging (MRI) (OR 0.1, 95% CI: 0.0–0.4, $p = 0.005$) [55]. Another advantage of TaTME is a better view of the anatomical plane, which facilitates dissection and avoids coning of the mesorectum that typically occurs with an abdominal approach [56]. International guidelines [57, 58] advocated TaTME for large tumors located in the distal rectum, for narrow pelvis (i.e., male gender) or visceral obesity. The main issue with the TaTME is the risk of injury to the prostatic urethra or to the vagina [57], but observational studies [54, 59, 60] showed the TaTME to be safe and feasible. Other specific intraoperative complications include rectal perforation (0.5%), which may require conversion to laparotomy [61]. A systematic review [62] demonstrated superiority when >30 TaTME were performed compared to low-volume centers (≤ 30 TaTME). In this study, high-volume centers were associated with lower major complications (10.5 vs. 12.2%, respectively), higher rate of complete mesorectum resection (89.7 vs. 80.5%, respectively), and lower local recurrence rate (2.8 vs. 8.9% with an overall follow-up time of 19 months, respectively). Compared to laparoscopic TME, a meta-analysis by Zhang et al. [63] showed similar overall recurrence rate associated with TaTME ($p = 0.573$, mean follow-up up to 63 months), and similar 2-year overall and disease-free survivals ($p = 0.241$ and $p = 0.505$, respectively). Benefits of TaTME are conflictual, and this technique was suspended in Norway due to a high rate of local recurrence, as demonstrated by Wasmuth et al. [64]. The latter compared 152 patients undergoing TaTME versus 1,118 low anterior resections from a national cohort. Local recurrences at 2.4 years were increased in the TaTME group (11.6 vs. 2.4%, $p < 0.001$, respectively). They hypothesized that spillage of tumor cells in the pelvis and rectal stump during transanal dissection could be responsible for the increased recurrence rate. Moreover, TaTME is technically demanding, as showed by the increased anastomotic leak rate (8.4 vs. 4.5%, $p = 0.047$, respectively).

Overall, TaTME could be an alternative to laparoscopic TME, but it is nowadays difficult to draw conclusions on long-term oncological outcomes. However, this com-

plex procedure should be performed in expert centers, and multidisciplinary team assessment is mandatory for case selection [58]. Multicentric RCTs are needed, such as the ongoing COLOR III [65] and GRECCAR 11 [66] trials.

As described above, laparoscopic surgery is associated with some limitations which can be dealt with a robotic platform. Transition from the laparoscopic to the robotic TaTME has been proposed by Atallah et al. [67] in 2013. They started the abdominal approach with laparoscopic instruments to mobilize the colon and ligate the inferior mesenteric vessels. The procedure was followed by a perianal approach using a robotic Si system, to perform the proctectomy. The largest cohort was reported by Hu et al. in 2019 [68], with 20 middle and low adenocarcinoma of the rectum. They reported 90% of complete mesorectal resection (according to the M.E.R.C.U.R.Y. criteria [69]) and 85% of negative CRM. Moreover, only 1 patient (5%) developed local recurrence at 1.5 years. Overall, this technique seems to be safe and feasible, but nowadays only case series are reported with a short-term follow-up, precluding any strong recommendations. As shown by a pre-clinical study on human cadavers [70], perspective for the robot is to use a single-port robotic SP system to perform abdominal and perianal parts of the TaTME.

Lymphatic Spread of Rectal Adenocarcinoma

Lateral Lymph Node Dissection

Rectal adenocarcinoma may spread through the lymphatic drainage upward to the lateral lymph nodes located along iliac and obturator arteries. Therefore, metastasis to the lateral lymph nodes occurs in 25% of low rectal cancer [71]. Involvement of lateral lymph nodes was associated with increased 10-year local recurrence rate (45.5% with positive nodes vs. 23.4% with negative nodes, $p = 0.048$) and decreased 10-year overall survival (54.5% with positive nodes vs. 80.4% with negative nodes, $p = 0.01$) [72]. Management of these metastases is controversial and differs among countries. Asian guidelines recommended lateral lymph node dissection (LLND) associated with TME for rectal cancer with lower border distal to the peritoneal reflection and invasion beyond the muscularis propria [73], considering lateral lymph node spread as local disease. On the contrary, they are considered as advanced disease in Western countries; therefore, neoadjuvant radiochemotherapy is associated with surgical resection [74]. Comparison of TME with LLND versus TME without LLND was reported in 2 meta-analyses, includ-

ing rectal cancer stages T1–4 and N0–2 [75, 76]. However, they failed to find oncological benefit from the LLND, as showed by similar 5-year local recurrence rate (10.5% with LLND vs. 11.6% without LLND, $p = 0.27$ [75]; and 12.6% with LLND vs. 14.2% without LLND, $p = 0.23$ [76]). Moreover, 5-year survival rate was also similar between the 2 groups ($p = 0.48$ [75] and $p = 0.62$ [76]). Since then, several studies [77–80] added new information to these meta-analyses. Among them, a noninferiority RCT (JCOG0212) [77] assigned 701 patients with rectal adenocarcinoma stage II or III located below the peritoneal reflection to TME with LLND or TME alone. They did not report difference in their primary outcome, defined as the relapse-free survival at 5 years ($p = 0.0547$). However, 5-year local recurrence rate was significantly increased in the TME alone group (12.5% for TME alone vs. 7.4% for TME + LLND, $p = 0.024$).

Overall, as showed by a recent systematic review [81], benefits of LLND for overall and disease-free survivals are conflictual. However, it is necessary to pay more attention on the preoperative findings in order to better identify lateral lymph node involvement. Afterward, a tailored approach, that is, for cases with enlarged lymph nodes on preoperative MRI ≥ 7 mm [82], could be offered with LLND to the most appropriate selected group of patients.

Organ Preservation Therapy

Local Excision

Transanal endoscopic microsurgery (TEM) is a minimal invasive approach derived from the technique described in 1984 by Buess et al. [83], allowing intraluminal excision of rectal cancer with its underlying muscularis propria. TEM alone reduced postoperative morbidity in comparison with excision of the rectum. Most of the postoperative complications are minor (95%) and mainly represented by bleeding (3.5%) or urinary complications (i.e., infection in 1.3% and acute urinary retention in 2.8% of cases). Compared to TME, 3 meta-analyses [84–86] reported higher local recurrence rate for tumors staged T1–2N0M0, but similar distant metastasis and overall and disease-free survivals. Among them, Kidane et al. [85] pooled 2,855 patients from one RCT and twelve observational studies and showed an increased 5-year local recurrence rate (8.8% after TEM vs. 3.2% after TME, $p < 0.00001$). More recently, the GRECCAR 2 trial included 145 cases of low rectal cancer T2–3N0–1 undergoing preoperative radiochemotherapy with good clinical response, defined as a residual tumor of ≤ 2 cm on MRI. The

randomization yielded 81 local excisions and 61 TME, which showed similar primary composite outcomes of death, recurrence, morbidity, and complications. Moreover, 2-year local recurrence rate was similar (6% for local excision vs. 3% for TME, $p = 0.63$) [87]. Several risk factors for recurrences after TEM were reported, such as the submucosal infiltration (pT1 sm2-3: HR = 1.3–2.7), pT stage (pT2: HR = 1.6–2.5; pT3: HR = 2.2–4.1), tumor grading (G3: HR = 1.9–3.3), and lymphovascular invasion (HR = 1.8–1.9) [88, 89]. Furthermore, if histopathological analysis after TEM showed involved margins, stage sm3, lymphovascular/perineural invasion, and high grade, they should undergo completion TME [20, 21]. For these “high-risk” cases, adjuvant chemoradiotherapy was proposed as an alternative to completion TME. However, this led to increased local recurrence rate: 14% with TEM + adjuvant therapy versus 7% in TEM + completion TME (follow-up range: 3–10 years) [90]. However, these results should be cautiously interpreted due to the heterogeneity of cohorts. Moreover, no RCT was reported and the results of the TRESAR trial [91] are awaited (participants: pT1-2 mid or low rectal cancer after local excision; intervention: adjuvant chemoradiotherapy; comparison: completion TME; primary outcome: 3-year local recurrence).

Overall, the European Society of Coloproctology (ESCP) recommended TEM for rectal cancer <3 cm in diameter, limited to the mucosa (T1sm1), and without lymphovascular or nodal invasion [20]. Other indication is rectal cancer stage ypT0–1 (T2–T3N0M0 stage with good response to preoperative RT with or without chemotherapy) [92–94]. However, the latter would lead to high rate of completion TME (35%) and subsequently increased morbidity and complications [87]. Therefore, this indication is debated and need to be confirmed with ongoing trials (STAR-TREC [95] and TAU-TEM [96]).

Conclusion

Different strategies are available, which are mainly reported with heterogeneous indications in the literature. The laparoscopic or robotic approach and ELAPE may be alternatives to conventional surgeries, although no evidence of decreased local recurrence rate from these techniques were reported. On the other hand, oncological benefits of LLND are still controversial and LLND is not routinely performed in Western countries. Strategies to preserve the rectum are also emerging, such as local excision, and may be beneficial for subgroups of patients. Moreover, trials are ongoing and will give more information about the role of these strategies. Nevertheless, management of adenocarcinoma of the rectum requires a multidisciplinary approach and surgical strategy should be tailored to patient factors: general health, previous perineal intervention, anatomy, preference, and tumor characteristics such as stage and localization.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

G.L. and J.M. conceived the review. G.L., J.M., M.S., Z.A., C.T., F.R., and N.C.B. interpreted the data. G.L., J.M., M.S., Z.A., C.T., F.R., and N.C.B. contributed to the writing of the manuscript and to its critical revision. G.L., J.M., M.S., Z.A., C.T., F.R., and N.C.B. approved the final version of the manuscript.

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