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Current Surgical Methods in Local Rectal Excision

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Rectal cancer · Local excision · Surgical techniques · Transanal surgery · Organ preservation

Abstract
Background: The treatment of rectal cancer has evolved with the advancement of surgical techniques. Less invasive approaches are becoming more accepted as the primary treatment method. ***Summary:*** Such methods as transanal excision, transanal endoscopic microsurgery, and transanal minimally invasive surgery can reduce morbidity and mortality rates. However, not all patients are suitable candidates for these procedures, and proper diagnostics are necessary to establish indications. Compared to total mesorectal excision, transanal excision techniques have been shown to have fewer complications and comorbidities while still being able to remove cancerous tissue entirely. Transanal excision is the simplest method, where the operator removes visible rectal lesions. The basic principle of transanal endoscopic microsurgery is to dilate the rectum mechanically and by air insufflation and then use special surgical instruments to remove suspicious lesions under the vision of a telescope. Transanal minimally invasive surgery combines transanal endoscopic microsurgery and single-incision laparoscopic surgery, making the hard-to-reach proximal rectum accessible to classic laparoscopic instruments. ***Key Message:*** Local excision techniques, when used as a monotherapy for treating patients with rectal cancer, have established themselves as a curative and less radical treatment for strictly selected patients with early rectal carcinoma, leading to improved quality of life. When combined with other modalities such as neoadjuvant chemoradiotherapy, total neoadjuvant therapy, and immunotherapy, transanal surgery can be offered to patients with locally advanced rectal cancer as part of the organ preservation strategy. This review will discuss the patient selection and technical aspects of transanal surgery, showcasing its current role in treating rectal carcinoma.

Introduction

Although colon and rectal cancer incidence has been dropping since the mid-1980s, colorectal cancer (CRC) is still the third most diagnosed cancer worldwide [1]. Rectal carcinoma (colon cancer within 15 cm from the anal verge) affects approximately 737,000 new patients per year worldwide [2]. The incidence of CRC is highly associated with screening programs. Studies have shown that the incidence has been decreasing in countries with long-standing faecal testing and screening colonoscopy programs and increasing mainly in countries with no screening programs available [3, 4]. Also, because of screening and timely diagnosis, the percentage of early rectal carcinoma is increasing; another fact is that CRC is

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now more diagnosed in younger people, demanding the balance between good curative oncological outcomes and the bad functional outcomes caused by overtreatment.

Before and at the beginning of the 20th century, perineal excision was the standard surgical treatment for rectal cancers. However, high local recurrence rates and unsatisfactory surgical outcomes led to the search for alternative therapies. Miles was one of the authors who described abdominoperineal resection (APR) in 1908 [5]. The implementation of APR reduced local recurrence and improved long-term survival, but the downside was the need for permanent stoma formation. The introduction of circular staplers in the mid-1970s enabled surgeons to perform low anterior resection (LAR) [6]. Combined with standardisation and widespread implementation of total mesorectal excision (TME), as first described in 1982 by Heald et al. [7], LAR allowed survival and recurrence rates comparable to APR but without a permanent stoma [8, 9]. Unfortunately, TME performed either with proctectomy or with LAR is not devoid of significant morbidity, which includes anorectal, urinary, and sexual dysfunction [10].

The management of rectal cancer has transformed substantially over the last 3 decades and continues to evolve. Some of these changes parallel progress made with other cancers, but some improvements are specific to the rectal anatomic features and the possibility of a surgical approach that enables organ preservation [11]. Transanal or local excision (LE) was initially developed as an alternative to radical surgery for the management of rectal adenomas and other benign lesions. With the subsequent improvement of technology for transanal surgery by introducing transanal endoscopic microsurgery (TEM) in 1983 [12] and later transanal minimally invasive surgery (TAMIS) [13], its indications have progressively broadened to early rectal carcinoma [14].

With its primary curative intent, transanal surgery is becoming increasingly important in multimodal therapies. It is often used alongside neoadjuvant and adjuvant therapy as a part of individually tailored treatment. This review will discuss the technical aspects of transanal surgery and its place in modern rectal cancer treatment.

Indication for Transanal Surgery

The treatment of rectal cancer has become increasingly complex since the end of the 1990s due to the scientific and surgical upturns. Advances in preoperative staging and pathological assessment, neoadjuvant and adjuvant chemoradiotherapy (CRT) use, individual cancer DNA sequencing, and the development of surgical techniques have led to improved disease-free survival (DFS), lower recurrence rates, and better quality of life (QoL) for patients [9, 11, 15].

Surgical resection with TME is nowadays the primary treatment for rectal cancer, but it can come with significant morbidity and mortality. Therefore, organ-sparing treatments that include non-operative management or LE are becoming more important [16]. Organ preservation strategies have proven oncological safety with excellent long-term functional outcomes. However, strict selection criteria and frequent surveillance are essential [17].

One of the main indications for transanal surgery is early rectal cancer (ERC), which includes a variety of precancerous polyps and malignant lesions such as carcinoma in situ and T1 rectal carcinoma. The main characteristic of T1 lesions is that malignant cells spread into the submucosa (sm1) but not beyond it [18].

If there is suspicion of a rectal lesion, a colonoscopy is performed to rule out any synchronous lesions, followed by a rectal lesion biopsy. After endoscopic biopsy, the depth of rectal wall penetration by malignant cells is determined histologically [19]. Pedunculated malignant colorectal polyps are classified according to the Haggitt criteria 1-4. Haggitt level 1 describes carcinoma invasion into the sm1, which is restricted to the head of the polyp. In level 2, invasion extends into the neck of the polyp; level 3 includes carcinoma invasion of the stalk of the polyp; and level 4 describes invasion below the stalk but is still limited to the sm1 with no extension into the muscularis propria [20]. The Kikuchi classification is used to describe sessile and flat malignant colorectal lesions. sm1 describes invasion of carcinoma in the upper third of the sm1, sm2 describes invasion into the middle third, and sm3 is defined as invasion in the lower third of the sm1 close to the muscularis propria [21]. The ability of these classification systems to delineate high-risk polyps (Haggitt stage 3/4 and sm2/3) from low-risk polyps (Haggitt stage 1/2 and sm1) can provide estimates of the risk of concurrent lymphatic spread with malignant polyps, thus guiding the appropriate surgical therapy. Risks of lymphatic spread in sm2/3 sessile polyps and Haggitt 3/4 pedunculated polyps range from 5.8% to 13.0%, representing an unacceptable risk for patients [22].

Further testing is necessary for accurate staging if the biopsy returns a malignant lesion. Rectal cancer is staged preoperatively using the TNM classifications to predict the likelihood of a curative resection based on the depth of penetration to the rectal wall and the presence of

lymphatic and distant metastases [8]. Physical examination should include a digital rectal exam, and in some cases, preoperative rigid proctoscopy performed by the surgeon to assess the characteristics of the tumour: size, mobility, location, circumferential involvement, and distance from the anal verge [23]. Imaging methods significantly impact decisions on the intended operative approach in their ability to differentiate between T1 and T2 carcinoma. The current Guidelines for Rectal cancer recommend MRI as the preferred modality, and endorectal ultrasound is suggested as a complementary study [24, 25]. Computed tomography scans of the thorax, abdomen, and pelvis should be performed to exclude metastasis [23]. Routine laboratory bloodwork is included as part of the preoperative evaluation. The baseline CEA level, measured before any treatment, is one of the prognostic factors of long-term survival and is used as a reference during follow-up [26].

Local methods or TME resection are recommended upon accurately determining the tumour stage and the nature of the tumour (size, grade, possible invasion of lymphatic and/or blood vessels, invasion of sm1 according to Haggitt/Kikuchi classification). The indication for the utilisation of transanal surgery relies on a discussion with a multidisciplinary team and a detailed discussion with the patient regarding the risks and benefits of offering LE without lymphadenectomy [18, 27]. According to the ESMO and ASCRS Clinical Practice Guidelines, transanal LE is indicated for early stage, low-risk cT1N0 rectal cancer, offering curative resection with good oncological outcomes while avoiding morbidity and poor functional outcomes of the TME. Patients considered to be the best candidates for LE in terms of oncologic safety and cure have tumours up to 3 cm occupying less than 30% of the rectal lumen circumference, within 8 cm from the anal verge, with invasion limited to superficial sm1 and containing histological features of lower risk such as well to moderate differentiation, no lymphovascular or perineural invasion, and low tumour budding [28, 29]. Tumour budding (bd1–bd3) is becoming an increasingly important feature, as studies have found a positive correlation between the severity of the tumour budding and positive lymph nodes, and this factor should be considered in future treatment decisions [30]. If poor histological features are present on preoperative staging (lymphatic/vascular/perineural invasion, poor differentiation, tumour budding) or deeper invasion (sm2 or sm3), the patient should be managed as having a T2 lesion [18, 24].

As endoscopic biopsies provide preliminary histology and often are unreliable in determining submucosal depth penetration, the LE specimens must be correctly taken – excision of the tumour with a full-thickness excision containing the mucosa, sm1, and muscularis propria down to the mesorectal fat. Ideally, 1 cm radial margins on the oncologic sample and a deep margin of 2 mm are recommended. Maximum attention should be taken to avoid specimen fragmentation. Upon final histological examination, additional treatments can be carried out if needed [18, 24].

Methods of LE

Transanal Excision

Until the broad implementation of TME and the development of rigid platforms for transanal surgery in the late 1980s and early 1990s, transanal excision (TAE) was considered adequate for removing ERC [31]. Among the modalities of transanal surgery, TAE is the most straightforward and simple. Simplicity refers to the surgical principle in which the operator removes visible rectal lesions. However, the surgical technique is quite complex and demanding.

Bowel preparation and preoperative antibiotics are given to all patients. Anaesthesia may be general or regional. The patient positioning is highly dependent on the location of the lesion: a lithotomy position could be appropriate for the posterior lesions and a prone position for the anteriorly localised tumours. After positioning, anal retractors are used to create space and enable visualisation of the lesion. A direct light source is needed due to low visibility and can be introduced either by a headlamp or by special retractors with a light source. The resection begins by placing traction sutures around the lesion for easier specimen manipulation during resection. Next, the resection margin is marked using electrocautery and is usually 1–2 cm from the edge of the lesion. After marking, the lesion is resected with standard surgical instruments while coagulation is performed simultaneously.

Full-thickness excision is performed, taking care to protect the vagina or prostate. Finally, depending on the operator's preference, the defect can be sutured using absorbable stitches or left open to heal secondarily. Postoperative analgesia requirements are minimal, and antibiotics may be continued for 24 h. Patients can eat normally immediately after surgery and generally leave the hospital within 48 h. The complication rate is very low (0–22%), with the most commonly occurring bleeding (less than 5%), local sepsis, urinary infection or retention and faecal incontinence. More severe complications, such as rectovaginal fistula, may occasionally occur. TAE is not usually performed for lesions beyond 10 cm from the dentate line due to technical difficulties accessing the lesion with standard instrumentation [8, 32, 33].

Transanal Endoscopic Surgery

TAE's lack of space and visibility has made surgeons seek ways to improve LE techniques. Two rigid platforms that overcome these limitations are used to perform transanal endoscopic surgery (TES): Transanal Endoscopic Microsurgery (TEM) and Transanal Endoscopic Operation (TEO) [34].

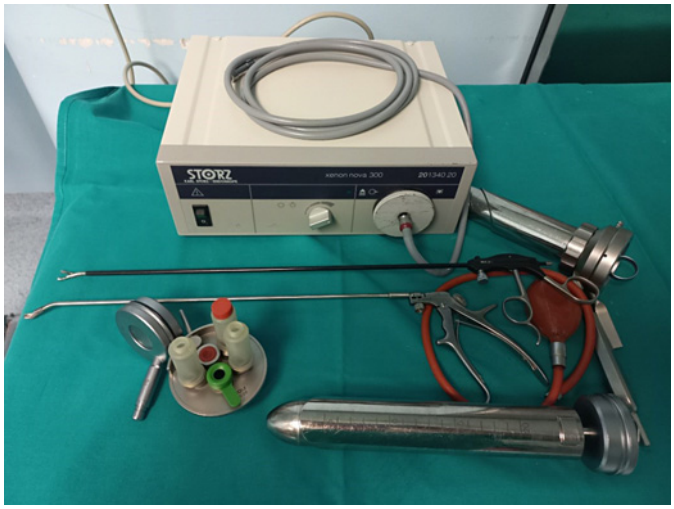

Fig. 1. TME platform.

TEM was introduced in 1983 by Buess et al. [12] and it has become one of the valuable procedures in treating rectal lesions. At first, TEM was intended to remove benign polyps in the rectal canal, but with time, it became clear that it could also be a method for treating precancerous and early cancerous lesions [35].

TEM uses the standard transanal approach as in TAE but with a new technique to dilate the rectum by air insufflation and superb vision under the stereoscopic angled telescope [36]. The TEM platform consists of a single rectal tube (4 cm in diameter), length depending on the tumour location (12 or 20 cm long) and several channels for working instruments. Instruments are usually designed explicitly for TEM operation, although some standard laparoscopic devices are at the operator's disposal (Fig. 1). The rectoscope is connected to the operating table by Martin's arm and fixed in position depending on the location of the lesion. The telescope provides a 3D visualisation, and the image may be projected via a connected endoscopic surgery tower, like in any other laparoscopic procedure [37, 38].

The TEO platform is similar to that for TEM but is manufactured by Karl Storz (Fig. 2). The rectoscope is also 4 cm in diameter and can be 7, 5, 15, and 20 cm long. The rectoscope is placed in the anus and held in place by a multijoined clamp. It has three working ports for the instruments, and a 30° telescope is used. In opposition to TEM, two main differences of TEO are standard laparoscopic instruments and telescopic camera that display images on the laparoscopic monitor; hence, binocular visualisation is unnecessary [36].

The preparation and positioning of the patient for TEM/TEO are the same as for TAE. The procedure starts with setting up and fixing the platform, followed by the insufflation of carbon dioxide gas inside the rectum until reaching an adequate and stable pneumorectum. Aimed pressure should be lower than in standard pneumoperitoneum procedures. Using a closed endoscopic system, TEM allows constant carbon dioxide pressure, creating stable distension of the rectum and a satisfactory operating field. One of the essential parts of the TEM/TEO systems is the suction and irrigation unit, which needs to be used constantly to allow adequate visualisation of the lesion (Fig. 3). After visualisation, the

Fig. 2. TEO platform (Courtesy of KARL STORZ SE & Co. KG).

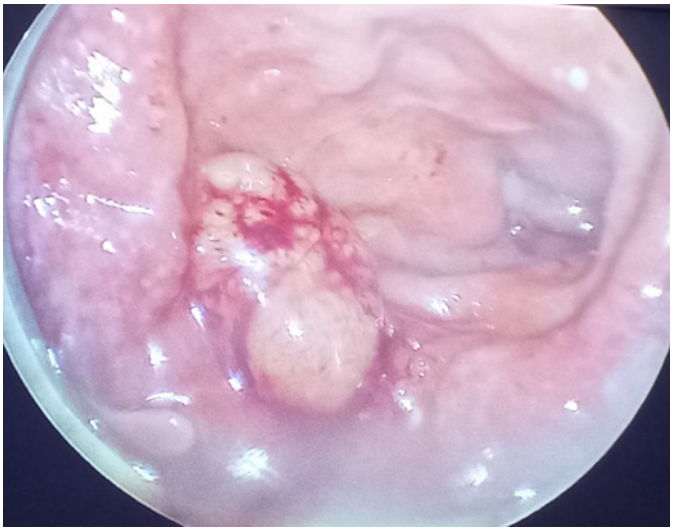

Fig. 3. Rectal lesion, view from TEO platform (Courtesy of Prof. Alberto Arezzo, Ospedale Molinette, Torino).

operator marks and dissects the lesion using electrocautery devices (Fig. 4). The lesion is completely removed in the desired plane and sent for further pathohistological analysis (Fig. 5). The rectal wall

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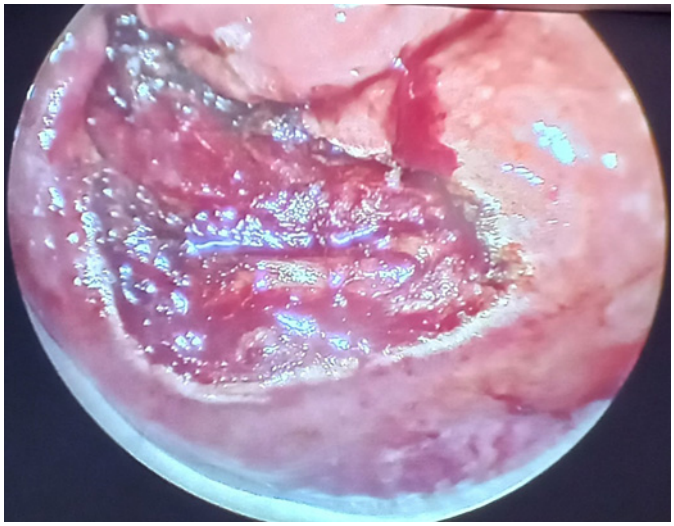

Fig. 4. Defect of the rectal wall after the excision of the lesion (Courtesy of Prof. Alberto Arezzo, Ospedale Molinette, Torino).

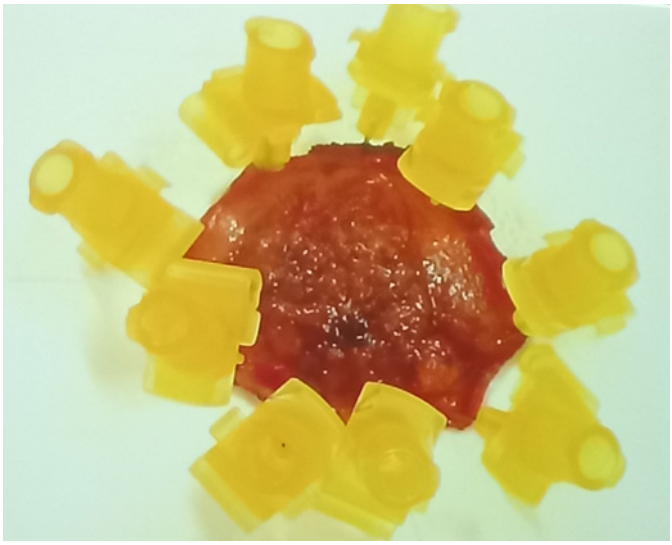

Fig. 5. Specimen after local resection (Courtesy of Prof. Alberto Arezzo, Ospedale Molinette, Torino).

defect is closed with a continuous absorbable suture or secured by silver clips. It may be left open if it is below the peritoneal reflection [37, 39].

Although, in theory, lesions up to 25 cm from the anal verge may be excised by TEM, the procedure is usually reserved for tumours in the extraperitoneal rectum due to the risk of perforation and creation of pneumoperitoneum, as well as technical difficulties. These factors limit the technique to lesions up to 20 cm on the posterior wall, 15 cm laterally, and 12 cm on the anterior wall. Also, the most distal lesions, within 4 cm of the anal verge, are often unsuitable for TEM excision as it is difficult to maintain a seal around the rectoscope and adequate pneumorectum [8, 40]. In these patients, TAE could be considered the preferred procedure [32, 33].

Disadvantages of TEM include an initially high equipment cost (somewhat lower for TEO, as conventional laparoscopic instruments and column is used), a long learning curve similar to that of laparoscopic surgery and difficulty in haemostasis of large vessels. However, TEM provides a magnified view of the operative field and accurate, oncologically correct excision of the tumours [8, 41]. Complications of TES are rare, occurring in only 2–15% of cases. The most common complications include bleeding, suture dehiscence, and temporary faecal incontinence, while more severe complications, such as intraperitoneal perforation and fistula formation, are infrequent [42, 43]. So far, no technical or clinical differences have been observed between TEM and TEO, except for the lower cost of TEO [44].

Transanal Minimally Invasive Surgery

In 2010, Atallah et al. [13] pioneered the use of TAMIS, which combines the transanal approach of TEM with the port for single-incision laparoscopic surgery (SILS). The SILS port consists of a large port and multiple integrated cannulas for inserting operating instruments. The most common ports are the SILS™ Port (Covidien, Mansfield, MA, USA) and GelPOINT Path Transanal Access Platform (Applied Medical, Rancho Santa Margarita, California, CA, USA). These devices are flexible and easy to place transanally. Gas insufflation through a designated channel is used to establish pneumorectum. Stable gas pressure between 10 and 20 mm Hg is essential for all transanal rectal procedures as it helps with good visualisation and prevents movement inside the rectum [23, 45].

TAMIS differs from rigid platforms because it is not fixed in position with a clamp. Because of its movements within the rectum, an assistant is required to stabilise it and hold the camera, which is not integrated into the platform [36]. Usually, a 30- or 45-degree angled 5 mm laparoscope is used for better visualisation due to limited operating space. Another benefit of an angled laparoscope is that the patient's position does not depend on the tumour's location [46]. The use of the classical laparoscopic instrument is a significant benefit in TAMIS surgery since it does not require expensive equipment or devices used in TEM. Like with standard cutting and cautery instruments, smoke evacuation is essential for a clear line of sight and precise recognition of the edges of the lesion. With cautery, the edges around the tumour are marked, and the full-thickness excision is performed. Depending on the defect size and the surgeon's preference, the defect in the wall of the rectum is closed. Closure is generally performed with absorbable interrupted sutures. Closure can also be accomplished with sutures and knot-tying facilitated by disposable-suture devices such as the Cor-Knot® System (LSI Solutions) or laparoscopic knot pushers. Alternatively, continuous V-Loc™ suture (Covidien) can also provide closure of the defect, avoiding knot-tying [23].

Kim et al. [23], in a systematic review of the literature on TAMIS, found a rate of complication of 18.4%. The postoperative complications that mainly occur include bleeding, postoperative urinary retention, fever, and penetration into the peritoneal cavity. Most of these are resolved with conservative treatments such as

antibiotics and blood transfusions, but surgical reintervention is required in 9.9% of the cases [23]. The patients are usually released home after a short period of hospitalisation.

Preoperative Preparation for Transanal Surgery

In all transanal procedures, bowel preparation is necessary. The most commonly performed is complete mechanical bowel preparation. However, oral laxatives and enemas could also be an option for distal bowel preparation [47]. A widely used perioperative antibiotic for prophylaxis is intravenous cephalosporin, although surgeons in some institutions administer cephalosporin and oral or intravenous metronidazole [48]. Low-molecular-weight heparin is the most commonly used anticoagulant for the prevention of deep vein thrombosis. β-Blockers are used to decrease bowel motility, although some surgeons use hyoscine butylbromide (Buscopan), which has a similar effect. The positioning of the patient on the operating table in TEM/TEO is highly dependent on a preoperative assessment of the tumour's location. The ideal position for the lesion is between 3 and 7 o'clock. Hence, if the lesion is located anteriorly, the optimal position of the patient is a prone jack-knife position. For the posterior lesions, a lithotomy position is required. A lateral position on the right or left can be used if the lesion is on the side or a prone position poses a high risk for anaesthesia. The advantage of TAMIS is that the patient could be put in a lithotomy position, regardless of the location of the lesion, which enables faster set-up in the operating room and better airway control by the anaesthesiologists [23, 49]. Surgery is usually performed under general anaesthesia; spinal anaesthesia may also be considered, especially in high-risk patients [50].

Several studies have compared the oncological outcomes of patients with T1N0 rectal cancer who were subjected either to TAE or TEM. The studies show significantly higher rates of tumour fragmentation and positive resection margins after TAE than TEM [51]. In patients with early rectal carcinoma who undergo LE, a minimally invasive approach by TEM or TAMIS is associated with a decreased rate of recurrence and improved relapse-free survival (RFS) and local RFS compared to conventional TAE, with no significant difference in perioperative complication rate [52]. Although available data are limited because of a lack of randomised control trials, a systematic review and meta-analysis demonstrated that TEM is oncologically superior to TAE regarding R0 resection, specimen fragmentation, and local recurrence [53].

When comparing rigid and flexible platforms, all studies show that both techniques produce almost similar results. TAMIS, conceived more than 20 years after TEM and rapidly and widely accepted, appears to have equivalent indications and outcomes compared with TEM/TEO [54, 55]. No significant differences were found between the TEO and TAMIS techniques in complication rate, recurrence, visual analogue scale, or Faecal Incontinence Severity Index [55]. Another study comparing TEO and TAMIS found similar surgical results, but the TEO platform seems superior in obtaining full-thickness specimens and R0 resection [56]. A more recent study by Stipa et al. [57] shows that TEM and TAMIS are equally effective in the quality of LE and perioperative complications. TAMIS was associated with less set-up and operative time than TEM. High-quality LE for rectal tumours can be equally achieved using any of the TES techniques: TEM, TEO, or TAMIS. The choice of operating platform depends on surgeon preference, availability, and cost [58].

The transanal TME (TaTME) method is worth mentioning. This type of surgery combines two approaches: transabdominal, which includes laparoscopic TME, and transanal approach, which uses one of the platforms for transanal surgery (TEM, TEO, or TAMIS). TaTME was first published in 2010 by Sylla et al. [59] It is designed to overcome some of the limitations of laparoscopic TME, which may be caused by the unfavourable patient and tumour characteristics such as low and bulky rectal cancer with the need for ultra-low sphincter-saving laparoscopic surgery and a high risk of leaving a positive circumferential resection margin, narrow pelvis, male sex, high BMI [60]. TaTME will not be discussed further here as the subject of this review is the LE of rectal lesions.

Discussion

Transanal surgery can be used as a curative or palliative therapy or as a part of multimodal therapy in an organ preservation approach.

Curative Therapy

While TME remains the gold standard for the surgical treatment of most rectal cancers, for highly selected patients with early rectal carcinoma (cT1N0), LE may be the preferred surgical option, reaching good oncological outcomes and avoiding the substantial morbidity of TME.

Most outcome data supporting LE in early rectal carcinoma came from observational, non-randomised, single-institutional experiences [61]. Only RCT comparing outcomes was published by Winde et al. [62] in 50 patients with T1N0 rectal tumours who were assigned to either transabdominal resection or TEM. This study found equivalent 5-year local recurrence rates (4%) and overall survival (96%). Also, the TEM group had decreased morbidity, blood loss, length of hospitalisation, and operative time. Additional data supporting the use of LE for early rectal carcinoma have come from a meta-analysis that included this study and 12 observational studies comparing LE with radical surgical resection (RSR). While the combined LE group (TAE + TEM) had higher local recurrence rates than RS, this difference was not seen in the TEM subgroup [63]. Similar results came from a meta-analysis done by Lu et al. [64] The distant metastasis, overall survival, and DFS rates did not differ between the TEM and TME groups for the patients with T1 rectal carcinoma. However, the local recurrence rate after TEM was higher than that after TME. A recent meta-analysis comparing TEM and RSR in patients with ERC found that there was no difference in overall survival (OR: 0.93; 95% CI) in rectal cancer-specific survival (OR: 1.08; 95% CI) or for distant metastasis (OR: 0.86; 95% CI) between the two groups. The TEM group had shorter

hospital stay and operating time, less blood loss, and fewer post-operative complications. However, the local recurrence rate was higher in the TEM group than in RSR, which warrants further study and confirms the necessity of proper patient selection criteria [65].

Palliative Therapy

LE can be used as a palliative treatment option for patients who are not fit or not willing to undergo a more extensive resection or those who do not accept the possibility of permanent stoma [66, 67]. This treatment can be combined with radiotherapy for patients with locally advanced rectal tumours who are at high risk and cannot undergo major surgery [68]. In elderly patients aged between 75 and 84 years and very elderly patients aged 85 years or above, TEM provides a safe and feasible alternative to radical resection with a very low mortality rate and minimal complications [69]. Studies suggest that transanal surgery can be safely performed under spinal anaesthesia, providing an added benefit for patients in poor clinical conditions and unfit for general anaesthesia. TEM under spinal anaesthesia is a short procedure with no increase in intraoperative and postoperative complications or hospital stay [70, 71].

Part of Multimodal Therapy in the Organ Preservation Approach

Patients with more advanced rectal tumours (T2N0) treated with LE alone had a higher local and overall recurrence rate and shorter overall survival than TME [72]. More recently, several prospective trials have been conducted to determine if the transanal approaches can be combined with neoadjuvant radiation and/or chemotherapy (NA-CRT) to allow for organ preservation for patients with more advanced rectal cancer. In the URBINO study, patients with T2N0 rectal cancer who received a long-course NA-CRT were randomised in the TEM group and laparoscopic resection group. Results showed no significant difference between the two groups in the local recurrence, DFS, or distant relapse at 5 years; hence, in selected patients, TEM combined with NA-CRT had similar oncological results to TME [73].

Further randomised clinical trials evaluated the outcomes of LE versus TME after NA-CRT for patients with more advanced rectal cancers (T1-T3N+). GRECCAR 2 was the first multicentre, randomised trial to compare LE with TME in downstaged low rectal cancer. Patients with T2T3 low rectal cancer of maximum size 4 cm, who had a clinically good response after CRT (residual tumour ≤2 cm), were randomly assigned to either the LE or TME group. The 5-year results of this multicentre randomised trial corroborate the 3-year results, providing no evidence of a difference in oncological outcomes (5-year local recurrence, metastatic disease, overall survival, DFS, or cancer-specific mortality) between LE and TME. In conclusion, LE can be offered to selected patients having a small T2T3 rectal cancer with a good clinical response after CRT [74, 75].

CARTS study aimed to explore long-term oncological outcomes and health-related QoL in patients with cT1-3N0M0 rectal cancer who underwent NA-CRT, followed by TEM in good clinical responders. Results showed that CRT with additional TEM surgery enables organ preservation in approximately two-thirds of patients with good long-term oncological outcomes comparable to TME and good QoL. However, this multimodality treatment triggers a certain degree of bowel dysfunction; LAR syndrome still occurs in 50% of patients with preserved rectum and one-third of patients were referred to radical surgery and could have been spared NA-CRT [76].

TREC trial showed that short-course radiotherapy (SCRT) followed by TAMIS achieves high levels of organ preservation, with relatively low morbidity and improved QoL. Participants with rectal adenocarcinoma, staged T2 or lower, with a maximum diameter of 30 mm, were randomly allocated to undergo either organ preservation with SCRT followed by TAMIS after 8–10 weeks or TME. If the specimen attained by LE showed higher risk histopathological features, patients were considered for planned completion TME (cTME) surgery. A non-randomised prospective registry included patients for whom randomisation was considered inappropriate because of a strong clinical inclination for one of the treatment groups. Organ preservation was achieved in 70% of randomised and 92% of non-randomised patients. These data support a multimodal organ preservation approach for patients considered unsuitable or unfit for primary TME (pTME) and support further evaluation of SCRT to achieve organ preservation [77].

Phase II of the NEO trial aimed to determine the outcomes and organ-sparing rate of patients with early stage (T1-T3abN0) low- or mid-rectal adenocarcinoma treated with 3 months of NA-CRT. Those with evidence of good clinical response proceeded to transanal surgery 2–6 weeks later. Thirty-three of fifty-eight patients had tumour downstaging to ypT0/1N0 on the surgery specimen, resulting in an intention-to-treat protocol-specified organ preservation rate of 57%. The remaining patients were recommended for TME surgery based on protocol requirements. Thirteen declined and opted for observation, resulting in 79% achieving organ preservation. The

remaining patients proceeded to TME, seven of whom had no histopathologic residual disease. The 1-year and 2-year locoregional RFS was 98% (95% CI: 86–100) and 90% (95% CI: 58–98), respectively, with no distant relapses or deaths. Minimal changes in QoL and rectal function scores were observed. The trial showed that 3 months of induction chemotherapy may successfully downstage a significant proportion of early stage rectal cancer, allowing organ-preserving surgery [78].

In conclusion, for T1 rectal cancer with favourable histopathologic characteristics, studies demonstrate no difference in recurrence or 5-year survival rate between the LE and TME groups. As a single therapy, LE of T2 tumours is associated with poor oncological outcomes and a high local recurrence rate compared to TME [35]. However, for selected patients, if a complete or near complete pathological response occurs after neoadjuvant treatment, LE may achieve equivalent oncological outcomes as TME, proving that LE combined with NA-CRT may be a feasible and safe organ preservative approach for patients with clinical T2 low rectal cancer [79–81].

Total Neoadjuvant Therapy

Locally advanced rectal cancers (LARCs), stage II and III, were traditionally treated with NA-CRT, followed by TME and postoperative adjuvant chemotherapy. This multimodal approach improved local control, but distant metastases remained a significant problem. In clinical trials of patients with stage II and III disease, distant relapse occurs in 25–30%, notwithstanding the treatment approach [82]. The probable reasons for this were the spread of micrometastasis during the waiting period from NA-CRT to surgery and poor compliance with postoperative adjuvant chemotherapy [83]. In various attempts to improve the survival of patients with LARC, a new treatment strategy called total neoadjuvant therapy (TNT) emerged. It consists of the delivery of CRT or SCRT and chemotherapy before surgery. TNT has several advantages compared with standard treatment: earlier administration of effective systemic chemotherapy enables better compliance and less toxicity, reducing the likelihood of distant metastasis and improving DFS.

Moreover, TNT and the longer interval from the beginning of treatment to surgery enhance local tumour regression, pathological complete response (pCR), and complete R0 resection rates and may ultimately enable the possibility of organ preservation via LE or non-operative management. Results from two randomised phase III trials, RAPIDO and PRODIGE 23, confirmed the validity of this approach [84, 85]. Both trials consistently showed better short- and long-term outcomes with TNT compared to standard neoadjuvant long-course CRT or SCRT. They provided high-level evidence to endorse TNT as a new management option in the stage II-III rectal cancer treatment algorithm [86].

Two TNT sequences have emerged: induction chemotherapy followed by CRT/SCRT and CRT/SCRT followed by consolidation chemotherapy. Two randomised control trials, CAO/ARO/AIO-12 and OPRA, were published comparing the induction and consolidation chemotherapy as a TNT [87–89]. The secondary analysis of CAO/ARO/AIO-12 showed that CRT followed by chemotherapy resulted in a higher pCR without compromising DFS, toxicity, QoL, or stool incontinence and is thus proposed as the preferred TNT sequence if organ preservation is a priority [88]. The conclusion of the OPRA trial is that organ preservation is achievable in half of the patients with rectal cancer treated with TNT, without an apparent detriment in survival, compared with earlier standard treatment (NA-CRT, TME, adjuvant CTH) [89]. The 2022 version of the National Comprehensive Cancer Network (NCCN) Guidelines for Rectal Cancer adjusted the algorithms for stage II and III disease to reflect new data demonstrating the prominent role of TNT and new recommendations for a "watch-and-wait" non-operative management (NOM) for patients that show a complete response to neoadjuvant therapy [90].

Immunotherapy for Microsatellite Instability-High Rectal Cancer

Immunotherapy, which uses immune checkpoint inhibitors (ICIs) to modulate the response of the immune system to tumour cells, has become a recognised treatment for several types of cancer, including microsatellite instability-high (MSI-H) or deficiency in mismatch repair (dMMR) CRC. Providing that the MSI status and tumour mutation burden are clarified before starting treatment, this subgroup of patients responds exceptionally well to ICIs such as anti-PD-1 antibodies pembrolizumab and nivolumab and anti-CTLA-4 antibody ipilimumab [91, 92].

ICIs have shown therapeutic efficacy in patients who have failed to respond to standard therapy, and pembrolizumab is recommended as first-line therapy for dMMR/MSI-H metastatic CRC [93]. Recent studies have shown that ICIs can also be effective in earlier stages of LARC treatment, with breakthrough efficacy and an organ preservation rate of mono-immunotherapy in dMMR/MSI-H patients [94]. For instance, neoadjuvant dostarlimab monotherapy for non-operative management of dMMR/MSI-H rectal cancer reported a 100% remission rate [95].

The results of clinical trials have shown that ICIs are more active in treatment-naïve patients than in those with refractory MSI-H/dMMR metastatic CRC and even more active in patients with locally advanced tumours [96]. Impressive results of ICIs in clinical stage 2 and 3 microsatellite instable rectal cancer have been published, with a series of patients with dMMR/MSI-H rectal adenocarcinoma who had a clinical complete response after receiving anti-PD-1 immunotherapy. The 2-year local recurrence-free survival, distant metastasis-free survival, DFS, and overall survival for the whole cohort were 100%, 100%, 100%, and 100%, respectively [97].

Multiple clinical trials are ongoing to assess the efficacy of combining NA-CRT (chemotherapy, radiotherapy, or molecularly targeted agents) and immunotherapy in microsatellite stable (MSI-L/pMMR) rectal carcinoma. The results of these trials have demonstrated good short-term efficacy, which could further improve the clinical and pCR rate [92, 98]. Although longer follow-ups and larger cohorts are needed to verify this innovative treatment, the results obtained so far are promising and offer the possibility of expanding the field for organ preservation with LE or even non-operative "watch and wait" management.

Completion and Salvage Surgery after LE

LE of low-risk ERC aims to be curative while maintaining QoL through organ preservation. However, some patients treated with LE will require radical resection surgery prompted by unexpected poor pathology upon histopathological evaluation of the resected specimen or local recurrence. In a systematic review by Jones et al. [99], the authors propose the term "salvage surgery" for recurrence after LE and "completion surgery" for poor pathology. Most completion surgical operations were done within 4 weeks; the local recurrence rate was 5%, and the overall disease recurrence rate was 14%. The majority of salvage operations for local recurrence were within 15 months of local excision, often following adjuvant treatment. Re-do LE was done in 15%; APR was the most common radical procedure. Secondary local recurrence was rare (3%), but the overall disease recurrence rate was 13%. The estimated 5-year survival after salvage or completion surgery (CS) was in the order of 50% [99].

In the literature, we found numerous studies that aimed to clarify clinical and long-term oncological outcomes of completion and salvage surgery and whether a LE could compromise the results of radical surgery. Junginger et al. [100] demonstrated that LE followed by early radical surgery did not appear to compromise outcomes compared to patients with primary surgery for pT1/2 rectal cancer. As expected, rectal wall perforation at the site of LE and residual cancer were the main risks for poor oncological outcomes associated with CS [100].

Completion TME (cTME) surgery after TAMIS is not associated with increased peri- or post-operative morbidity or mortality compared with primary TME (pTME). After cTME surgery, patients have similar disease-free and overall survival rates compared to patients undergoing pTME [101]. Compared with pTME, CS requires a higher rate of APR but has similar post-operative morbidity, TME quality, and oncological results [102]. A recent study showed that oncological results were similar between CS and TME. However, there may be an increased risk of a permanent stoma in the CS group [103].

Similarly, salvage TME is not associated with increased post-operative morbidity, mortality, or local recurrence compared to pTME. However, the operative times are longer than in pTME, and specimen quality could be of lower quality [104].

Conclusion

Rectal cancer is one of the most common types of cancer and a leading cause of death worldwide. It poses a significant challenge in the diagnostic and therapeutic fields of medicine. To treat the cancer, patients often undergo radical treatments that can result in temporary or permanent stomas, as well as significant comorbidities such as anorectal, urinary, or sexual dysfunction. LE techniques have been successful in reducing complications and comorbidities while still achieving the proper removal of cancerous tissue. With available screening and diagnostic tests, more tumours are being detected in the early stage, allowing for local treatment, good oncological outcomes, and improved QoL. Therefore, LE techniques have established themselves as a curative treatment for favourable patients with ERC. Recent advancements in combining these techniques with NA-CRT and TNT, as well as immunotherapy, have shown promising results and could achieve organ preservation even in more advanced stages of rectal cancer.

Conflict of Interest Statement

The authors have no relevant financial or non-financial conflicts of interest to declare.

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Author Contributions

Kristina Šemanjski: conceived and designed the study; collected the data; performed the analysis and interpretation of data; wrote the paper; approved of the version of the manuscript to be published; and other contributions: supervision, resources, and project administration. Karla Lužaić and Jure Brkić: collected the data; contributed interpretation of data; wrote the paper; and approved the version of the manuscript to be published.

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