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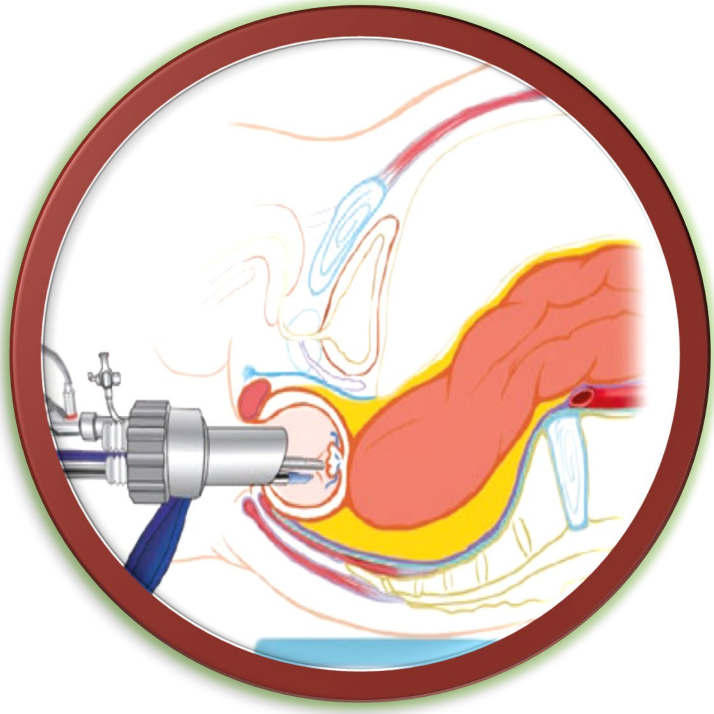
Optimizing rectal cancer surgery:

focus on Transanal Total Mesorectal Excision



PhD thesis

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PREFACE

This PhD thesis focuses on the optimization of rectal cancer surgery. I have been involved in management of rectal cancer ever since I finished my surgical training. It has been a privilege to work within this exciting field and being involved in management of patients suffering from this malignancy. I have spent a great deal of time involved in the clinical part of rectal cancer management. However, curiosity to improve the surgical technique and outcomes has always been the driving factor for me to contribute to the academic part of colorectal surgery and particularly the management of rectal cancer. While I believe that my academic work is by no means huge, I hope the results of my humble work can add a small portion of knowledge to the growing literature in the field of rectal cancer surgery, especially the transanal approach.

I would like to express my thanks to Professor Ismail Gögenur for his support and guidance so the thesis can be prepared and finished in its current way.

I would also like to thank all my Co-authors from the papers involved in this thesis for their valuable contribution. This work would not have been possible without their efforts. Special thanks to Dr Line Walker, who reviewed the final version of the thesis.

I dedicate this thesis to all included patients, who granted me the privilege to be part of management of their disease.

LIST OF THE ORIGINAL PAPERS

Study I

Perdawood SK, Lund T. Extralevator versus standard abdominoperineal excision for rectal cancer. Tech Coloproctol. 2015;19(3):145-52.[1]

Study II

Perdawood SK, Al Khefagie GA. Transanal vs laparoscopic total mesorectal excision for rectal cancer: initial experience from Denmark. Colorectal Dis. 2016; 18(1):51-8.[2]

Study III

Perdawood SK. A description of the learning curve for Transanal Total Mesorectal Excision using CUSUM analysis. [3]

Study IV

Perdawood SK, Thinggaard BS, Bjoern MX. Effect of transanal total mesorectal excision for rectal cancer: comparison of short-term outcomes with laparoscopic and open surgeries. Surg Endosc. 2018;32(5):2312-21.[4]

Study V

Witt I, Gögenur I, and Perdawood SK. A nationwide comparison of short-term outcomes after transanal, open, laparoscopic, and robot assisted Total Mesorectal Excision. [5]

Study VI

Perdawood SK, Kroeigaard J, Eriksen MH, Mortensen P. Transanal Total Mesorectal Excision: the Slagelse experience 2013 – 2019. [6]

INTRODUCTION

The prevalence of colorectal cancer globally is high, being the third most common cancer in women and the fourth in men [7]. The incidence of colorectal cancer increases worldwide, with an estimated 1.8 million new cases in 2018 [8]. In Denmark, 4.433 new cases of colorectal cancers were diagnosed in 2018, with almost similar numbers in the previous years [9], a third of these cases were rectal cancers.

While management of colon cancer is straight-forward in most cases, treatment of rectal cancer is challenging for several reasons; 1) anatomy of rectum and its relations in the lower pelvis, 2) impact of surgery on patients in terms of postoperative morbidity and functional results, and 3) the complexity of management algorithm, including the diagnostic work-up, neoadjuvant treatment, and availability of different surgical principles and approaches.

Surgery for rectal cancer remains a challenge in terms of the procedural details, especially surgery of the lower two-thirds of the rectum. Extent of resection, sphincter-saving, and the selected approach are the most frequent dilemmas. The principle of Total Mesorectal Excision (TME) is now a golden standard for mid and low rectal cancers [10]. Difficulty is usually encountered when the lowermost part is dissected; leading to high rates of intraoperative perforations, poor oncological outcomes [11], and high numbers of rescue Abdomino-Perineal Excisions (APE). The question is whether some of these cancers can be treated with less invasive methods leading to sphincter-saving.

While TME, by an open approach, following the principles described by Bill Heald [12-14], has shown a remarkable reduction in local recurrence rates, the "non-inferiority" of laparoscopic surgery was questioned recently, despite comparable long-term results to the open approach [15-18]. The authors of these randomized trials have concluded that, the application of laparoscopy to perform rectal resection cannot be recommended.

Transanal TME (TaTME) has been suggested as a "solution to some old problems" [19], which are experienced during standard laparoscopy. TaTME was introduced a decade ago [20], and literature is growing, with a focus on promising early outcomes [21, 22]. There are, however, few publications on long-term results, with different conclusions [23, 24]. It is currently not clear whether TaTME is going to be standard of care for mid and low rectal cancers.

BACKGROUND

A brief history of rectal cancer surgery

The English Surgeon John Arderne was the first to describe signs and symptoms of rectal cancer in 1376 [25]. A resection for rectal cancer was described for the first time in 1793 by the French surgeon Jean Faget for an extensive perianal abscess, which turned out to be cancer [26]. Jacques Lisfranc was the first to perform a planned rectal resection for cancer in 1826 [27]. These were primarily palliative perineal procedures. With the advent of anaesthesia, a more extensive resection that included removal of the coccyx was introduced, allowing resection to be curative. Pioneers of these resections were the French surgeon Aristide Verneuil and the Swiss surgeon Theodor Kocher in the 19th century [27].

The German surgeon Vincent Czerny performed the first APE in 1883. This happened while he could not complete rectal excision through a pure perineal approach, and thus he simply turned the patient to the supine position [28]. Rates of local recurrences after APE in these early days were very high, as shown in Table 1.

Surgeon	Number of patients	Recurrence rate
Allingham	18	100%
Cripps	85	67%
Vogel	1500	80%
Gant	?	84%
Edwards	50	86%
Miles	58	93%

Table 1. Local recurrence rates after rectal cancer surgery at the beginning of the 20th Century.

The English Surgeon Ernst Miles was one of the first to perform a more extensive "cylindrical excision" by perineal approach, known nowadays more commonly as Extralevator APE (ELAPE) [29] that involves a wide excision and removal of the coccyx. Although this has improved the oncological results, the procedure is mutilating. With the invention of staplers, an anterior resection for tumours in the upper part of the rectum has increasingly replaced ELAPE, especially with the rejection of downward lymphatic spread of cancer [30]. With time, standard anterior resection turned to almost the original limited resection of the rectal tube, leaving the mesorectal fat behind due to blind dissection of the rectum. It was probably for this reason, rates of local recurrence increased dramatically compared to Miles´ extensive excision. In late 1970s and early 1980s, Phil Quirke showed a correlation between involved radial resection margin and the rates of local recurrences [31].

In late 1970s and early 1980s, Bill Heald showed a dramatic improvement in local recurrence and 5-years survival rate by adopting a new TME technique that ensures complete removal of the mesorectum [10, 12, 13, 32, 33]. Bill Heald's TME is, nowadays the golden standard of surgical management of mid and low rectal cancers. Bill Heald's results have been reproduced multiple times and are well implemented worldwide, including in Scandinavia [34, 35].

Anatomy and embryology of the rectum

Understanding the anatomy of the rectum and its surrounding structures is essential to understand the basic principles of TME. Of importance is the different view of anatomy encountered during the transanal dissection that characterizes TaTME.

The distal portion of the colon and the rectum originate from the hindgut and shares the inferior mesenteric artery (the hindgut artery). Similarly, the venous and lymphatic drainage corresponds to this [36].

Rectum is the terminal portion of the bowel and located between the sigmoid colon and the anus. It occupies the sacral hollow from the level of S3 to the coccyx [37] and has a pelvic portion (the ampulla) and a perineal portion (the anal canal) [38]. A precise definition of the proximal and distal end of the rectum is debatable and often depends on whether it is an anatomic or a surgical definition. The proximal end is at the level of S3, defined by anatomists and at the sacral promontory by surgeons. In a recent Delphi consensus, most surgeons agreed on the point of "sigmoid take-of" as the proximal end of the rectum, which roughly corresponds to the sacral promontory [39]. Anatomists define the distal limit as the dentate line, while surgeons define it as the muscular anorectal ring [40]. The rectum has three parts; upper (10-15 cm), middle (5-10), and a lower part (0-5 cm) from the anal verge [38].

The rectum is retroperitoneal, apart from the anterior portion of the upper part, which is covered by the visceral peritoneum to the peritoneal reflection. The rectum has lateral curves, corresponding to the Houston valves, seen during endoscopy. These are usually three, two on the left and one on the right [40]. The dentate line is situated 1-2 cm from the anal verge. The surgical anal canal is the lowest 4 cm, which is the distance from the anal verge to the anorectal ring (level of levator ani). Together, the sphincteric muscles form an anteroposterior slit called the anal canal [41].

Mesorectum and fasciae

The endopelvic fascia is a vital structure that should be removed intact upon the performance of TME [42]. Visceral layer lines the rectum (the rectal visceral fascia). The parietal part covers the sacrum (presacral fascia) and the sidewall of the pelvis. Visceral rectal fascia forms an envelope that contains terminal branches of the inferior mesenteric artery, venous drainage, and lymphatics with a supporting fat pad, called "mesorectum" by colorectal surgeons. The following figures show these structures:

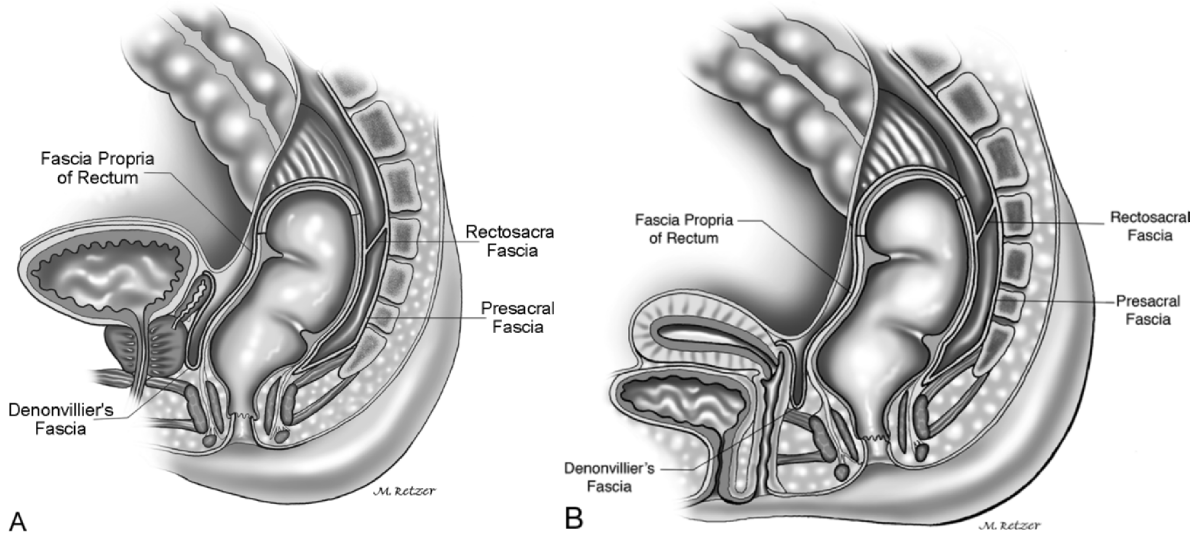

Figure 1. Fascial relationships of the rectum: A male, B female [40].

Mesorectum varies in thickness, usually depending on the BMI, and it is tapered in the distal end, so the most distal part of rectum is not covered by fat [43]. The avascular plane of loose areolar tissue between visceral rectal fascia and parietal fascia is commonly known as the "holy plane" described by Bill Heald [13]. The holy plane continues superiorly with the retroperitoneal space and inferiorly to the recto-sacral ligament, and a similar space is found below the recto-sacral ligament down to the anorectal junction.

Denonvilliers´ fascia

Also called recto-prostate septum in males and recto-vaginal septum in females. It lies anterior to the rectal visceral fascia and extends from the peritoneum of the recto-vesical pouch (pouch of Douglas) to the pelvic floor anteriorly and with clearly defined lateral edges [41, 44]. It has multiple connective tissue layers, which may contribute to mechanism of defecation. The significance of Denonvilliers´ fascia during TME relates to its proximity to the neurovascular bundles on one side and the rectal wall on the other.

For this reason, it is essential to consider the fascia as part of the specimen for anterior tumours and to leave the outer layer behind when it is oncologically safe. Dissection behind Denonvillier´s fascia is associated with a negligible risk of nerve injury, as the neurovascular bundles are located posterolateral to the prostate covered by the next layer of the fascia. On the other hand, risk of nerve injury is significant when dissection is anterior to the fascia [45]. When dissecting in front of the fascia, the part to be removed should be minimal and centred as risk is highest at the lateral edge, directed by the tumour location to avoid nerve injury [46].

Blood supply

The main artery of the rectum is the superior rectal artery, terminal branch of the inferior artery. The other arteries of the rectum are middle and lower rectal arteries.

The superior rectal artery continues to the back of rectum and divides at the upper third into two branches. Terminal branches of these vessels finally penetrate the submucosa and terminate as capillary plexus [47].

The middle rectal arteries are branches of internal iliac arteries. Their branches run anteromedially through the so-called "lateral ligaments" below the peritoneal reflection, but variations are common, and they may be absent [47-49]. The middle rectal artery does, however, not traverse them entirely, and only some branches are found within them in about 25% of cases, giving rise to some bleeding while dissecting distal part of the rectum [50]. On the one hand, there is a risk of bleeding and, on the other hand, risk of leaving mesorectal tissue behind [10, 31]. These *lateral ligaments (or stalks of the rectum)* are distal condensations of the pelvic fascia, forming a triangular structure. The base of this triangle is on the lateral pelvic wall and the apex attached to the sides of the rectum [51].

The inferior rectal arteries arise from the internal pudendal arteries, run medially, and terminate in the submucosa of the anal canal.

Besides, the aortic bifurcation gives rise to the medial sacral artery that runs posterior to the presacral fascia and, in some cases, terminates in the anal canal.

The venous drainage is mainly via the inferior mesenteric vein that joins the splenic vein and drains via the portal vein [52]. The lower third of rectum drains via internal iliac veins.

Sacral foraminal veins

Presacral veins form a venous plexus on the surface of the lower sacrum is connected to the intra-sacral canal venous plexus via sacral basivertebral veins at the level of the anterior sacral foramina [53]. Blunt dissection – which now belongs to the past – during rectal resection can lead to rupture of the basivertebral veins leading to massive haemorrhage.

Lymphatic drainage

The intramural lymphatic plexuses found in the submucosa and subserous layer of the rectal wall drains into the extramural lymphatics. These follow the supplying arteries, so lymphatics from the part of the rectum supplied by the superior rectal artery drain into the superior rectal nodes and then to the inferior mesenteric nodes. Up to 10% of lymphatics can pass directly through the rectal visceral fascia to the internal iliac veins. Lymphatics of the lower rectum drain either superiorly parallel to the middle rectal artery, or downwards parallel to the inferior rectal arteries leading to either internal iliac nodes, common iliac nodes, or the lumbar trunk. The lowermost part of the anal canal drains through the perineum to the superficial inguinal nodes.

Nerve supply

Damage to nerves during TME surgery can occur during ligation of the inferior mesenteric artery or at any of the following steps of abdominal or transanal/perineal dissection. The inferior mesenteric plexus lies on the anterior surface of the aorta at the origin of the inferior mesenteric artery. The right and the left *hypogastric nerves* arise from this plexus and run downwards slightly lateral to the midline and medial to ureters and the iliac arteries in a "wishbone" shaped fashion, and vary in thickness from under 1 mm to about 8 mm [54]. They run posterolaterally to the back of the rectum and give away some fibres to the rectal wall, urinary bladder, and the ureterovesical junction. At the lower pelvis, the hypogastric nerves lie on the anterolateral edge of the rectum and contribute to the formation of the *inferior hypogastric plexus*. The pelvic splanchnic nerves *(erectile nerves),* enter the pelvis through the sacral foramina and gives few branches that enter the mesorectum, mainly through the *lateral ligaments* [49, 55, 56]. During TaTME, the risk of nerve damage at the lowest part of the rectum below Waldeyer´s fascia, are those supplying the internal sphincter. Nerve damage at a higher level is minimal when approaching the field from below, as the hypogastric nerves are separated from the mesorectum at this level [45].

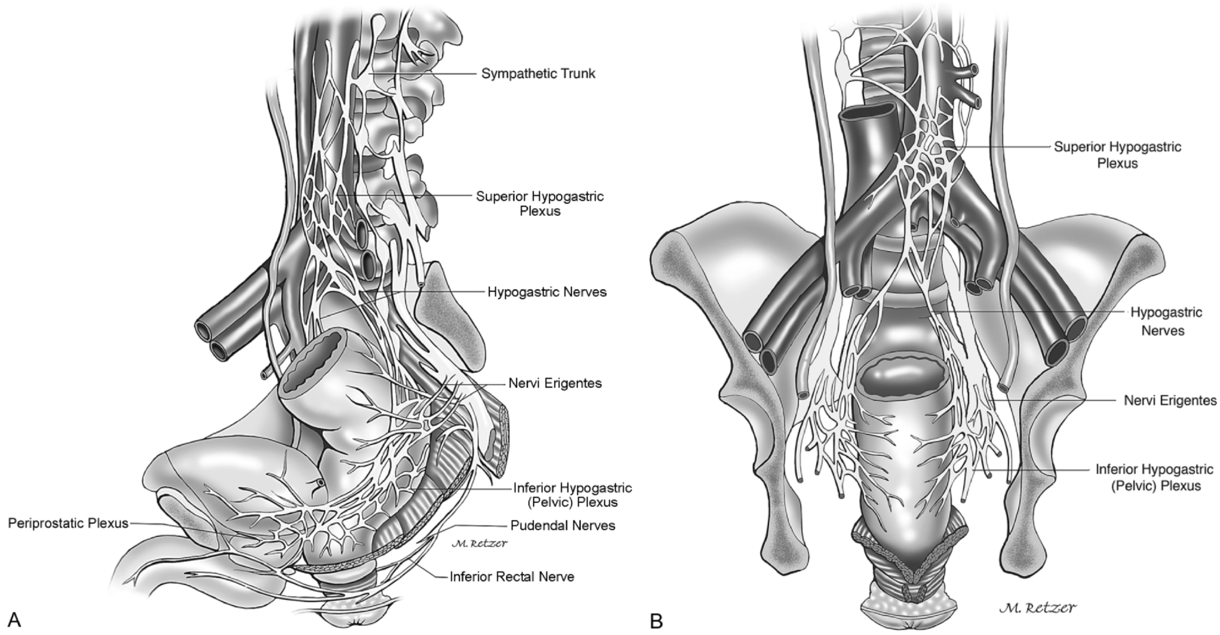

Figure 2. Innervation of the colon, rectum, and anal canal [40].

Total Mesorectal Excision

Bill Heald suggested transection of mesorectum at a distance of at least five centimetres below lower border of the tumour, to include draining lymph nodes and thus ensuring radical surgery [10, 57]. For tumours ≤10 cm from the anal verge, transection leads to the removal of all the mesorectum. Figure 3 demonstrates the optimal level of bowel transection.

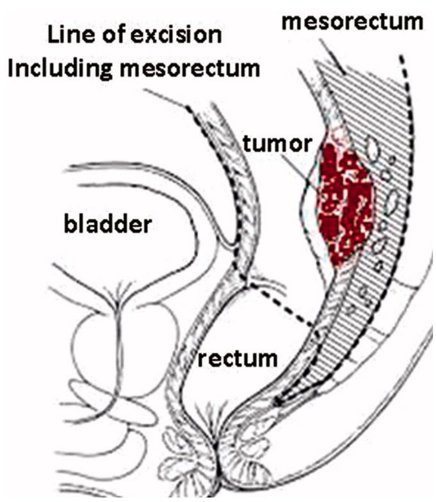

Figure 3. TME line. [10]

The optimal TME is one that involves; 1) a sharp dissection in the embryological plane, down to where the mesorectum tapers and leaves the rectal wall uncovered, 2) retrieval of an intact specimen without tears, 3) retrieval of as many as possible lymph nodes (at least 12 in nonradiated tumours), and 4) nerve-preserving dissection. The risky points during TME are well-defined, thanks to increasing knowledge of the anatomy of the rectum and its surrounding structures [58, 59]. Philip Quirke [60], has defined three grades of the rectal cancer specimen (mesorectum and sphincter complex) as follows:

Mesorectum

- *Mesorectal plane (complete):*
- *Intact mesorectum with only minor irregularities*
- *No defects deeper than 5 mm*
- *No coning toward the distal margin of the resection specimen*
- *Smooth CRM on transverse sections*

Intramesorectal plane (nearly complete):

- *Moderate bulk of the mesorectum*
- *One or more defects greater than 5 mm deep within the mesorectum*
- *Moderate coning*
- *No visible muscularis propria*
- *Irregular CRM on transverse sections*

Muscularis propria plane (incomplete):

- *Exposed muscularis propria*
- *Moderate to marked coning*
- *Irregular CRM on transverse sections*

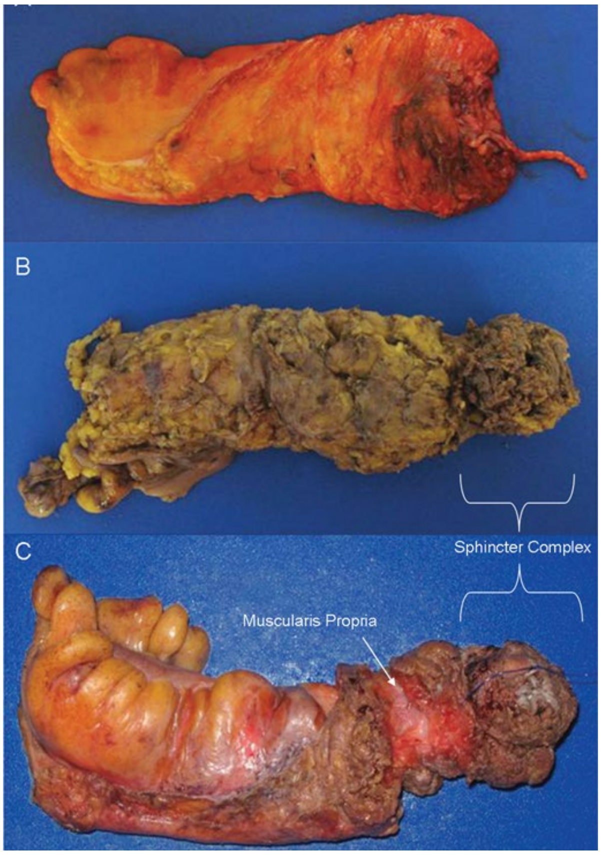

Figure 4. Mesorectal grading: (A) mesorectal plane; (B) intramesorectal plane; and (C) muscularis propria plane with arrow denoting the exposed muscularis propria.

Sphincteric complex

Extralevator:

- *Cylindrical specimen with no waist effect*
- *Levators removed en bloc*

Sphincteric plane:

- *Slight waist effect*
- *No significant defects or perforations*

Intrasphincteric/submucosal plane

- *Significant waist effect*
- *Perforation or missing areas of muscularis propria*

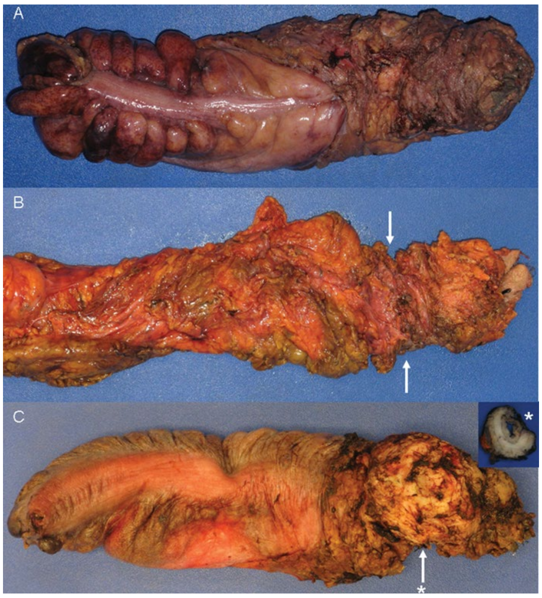

Figure 5. Sphincter grading: (A) extralevator; (B) sphincteric with arrows denoting "waist effect"; and (C) intrasphincteric with arrow denoting sphincteric defect and asterisk (*) indicating level of cross-section (inset).

According to Quirke, local recurrence rate increases when the specimen is less than "complete" [61, 62].

High ligation of the inferior mesenteric artery achieves a complete removal of the regional lymph nodes, but survival benefits are debatable [63-65]. The artery should be divided at least 1.5 cm from its origin to avoid injury to the inferior mesenteric plexus. During this step, care is taken not to injure the left ureter and gonadal vessels. After division of the artery, the retro-rectal space is entered just below the sacral promontory. Plane of dissection is between the prehypogastric plexus behind and the hypogastric nerves in the rectal visceral fascia in front, as shown in figure 6.

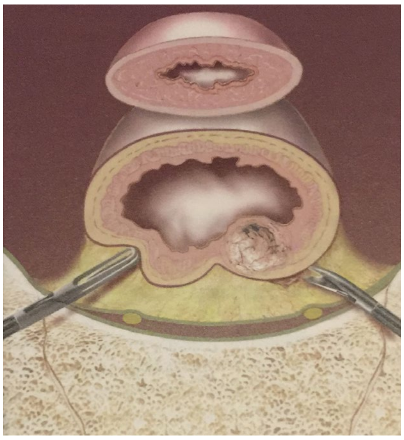

Figure 6. Retrorectal dissection. [58]

Posteriorly, the recto-sacral ligament should be sharply divided; revealing the distal part of rectal dissection with a similar areolar tissue as seen above the ligament, and the levators can be seen at this stage. It is important not to injure the hypogastric nerves and the foraminal sacral veins when performing this last part of the posterior rectal dissection. However, this part is the first part during TaTME, and the risk of vascular injury is minimal when dissection is kept in the "holly plane" [45]. The anterior dissection is done either by leaving the Denonvilliers´ fascia behind to preserve the nerves better, or removed as part of the specimen when the tumour is located anteriorly to avoid an involved radial resection margin [66].
The lateral dissection is completed by joining the anterior and posterior planes, as shown in figure 7.

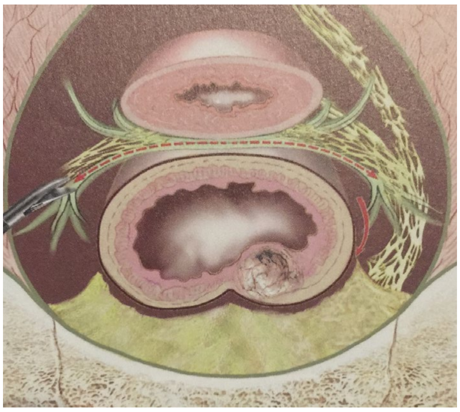

Figure 7. Anterolateral rectal dissection. [58]

Plane of dissection is at the rectal visceral fascia, and the only nerve division is of the distal branches of the inferior hypogastric plexus that form the *inferior rectal nerve plexus,* which runs to the posterolateral wall of the rectum and the internal anal sphincter. The middle rectal artery can be encountered and divided. This dissection must be kept directly on the rectal visceral fascia (*interfascial)*. Most nerve injuries during "top-down" TME, occur probably at this level [45].
The bowel is transected below the tumour, preferably after washout of the rectal lumen [67]. However, this is not done in APE, where the perineal procedure follows the abdominal dissection and proximal bowel transection. There are generally three strategies for the perineal approach, depending on the stage of the tumour:
1) Intersphincteric APE for cases where is the tumour is T2 or less in the lower rectum.
2) Extralevator APE for advanced tumours with threatened resection margins, or when there are signs of direct tumour invasion of the levator muscles.

"Conventional APE", involves removal of the external sphincter, continues straight upwards through the levator muscles close to the bowel wall. While it is less mutilating than ELAPE, it is associated with high recurrence rates, mainly due to bowel perforation and a positive radial margin [11, 68, 69]. In ELAPE, the dissection continues laterally under the levator muscles to the level of the bony boundaries, the levators divided, and the plane achieved from the abdominal side is entered. The procedure usually involves removal of the coccyx, to facilitate specimen removal. Construction of the perineal wound is needed, either with mesh or muscle flap.

3) Ischio-anal APE for tumours invading the ischio-anal fat. The ischio-anal APE is very similar to the ELAPE, except for the inclusion of a significant amount of skin and fatty tissue, needing wound reconstruction with a muscle flap.

Transanal TME

The essential part of the TME by whatever approach involves complete removal of the mesorectal package through dissection in the "holy plane" [13]. Denost et al. [70] found a reduced incidence of involved CRM by the perineal approach as opposed to the abdominal one, and they suggested a perineal approach as the new standard in rectal cancer surgery. One specific aspect of "bottom-up TME" is an enhanced vision, thanks to the proximity to the operative field. There is an anatomic distortion during TaTME, where the operative field is ever-changing and expanding progressively with the dissection [71]. It is therefore essential for TaTME surgeons to revisit the anatomy of the pelvis as seen from below [72]. The rules of "triangles" and "O"s known from Minimal Invasive Surgery (MIS) gain more importance during TaTME, probably due to the magnified field [73]. Accurate planning, preferably with a careful study of the rectal MRI, might facilitate different steps of TaTME [38, 74-77]. Furthermore, imaging technology can potentially aid dissection in real-time through the so-called "stereotactic navigation" [78, 79].

TaTME starts either with closure of the anus when the tumour is very low, followed by the fixation of a retractor and a transanal port, or with insertion of port for tumours above the anal sphincter complex. The most critical step is closure of the rectal lumen by a tight purse-string suture, followed by a rectal washout. The procedure then continues with a full-thickness incision of the rectal lumen below the purse-string suture, entering the "holy plane" of dissection from below. This technique is described in the literature, and most authors perform the procedure in a similar fashion, apart from variations in the starting point, the specimen extraction, and the anastomotic techniques, [80-83]. While most authors agree on the benefit of TaTME, questions remain on extent of reach from below and sequence of dissection [84-86].

Minimally Invasive Surgery (MIS)

The improvements in the rates of local recurrence and survival after TME occurred in the era of open surgery [32, 33]. Extensive excision by Ernst Miles [87] and TME by Bill Heald [88] focused on the pathological/oncological outcomes. Morbidity of laparotomy was not addressed until the 1990s, where MIS was introduced as an alternative to laparotomy in gallbladder surgery [89]. The advantages of MIS are convincing, less postoperative pain, faster recovery, reduced wound-related complications, and reduced rates of long-term consequences of laparotomy like hernias and adhesions [90]. The first MIS colonic resections were done in the early 1990s, and have shown the same advantages [91].

Laparoscopic surgery improved the outcomes of rectal cancer surgery regarding less blood loss, faster recovery, and less overall "late morbidity." The magnified view of anatomy and dissection plane in the pelvis results in a potentially improved specimen quality and better nerve preservation [92, 93].

Although the short-term pathologic outcomes are in favour of open approach, laparoscopic rectal resection has equivalent long-term outcomes to open surgery, based on several randomized studies [94-96]. A German national database study of more than 16000 patients has shown a better 5-year survival after laparoscopic, compared to open rectal cancer surgery [97]. However, traction and counter traction is limited in a narrow pelvis and can result in conversion to open surgery [98]. Robot-assisted surgery potentially overcomes these limitations through a better visual field and articulating instruments. Several case series have shown advantages of robotics, especially regarding the urogenital outcomes [99]. To date, the only randomized study comparing standard laparoscopy to robotic surgery (The ROLARR Randomized Clinical Trial) [100], has failed to show a significantly lower conversion to open surgery. In this study, risk of conversion was significantly increased in obese male patients, and when intended procedure was a low anterior resection.

Challenges in MIS for rectal cancer

The primary aim of surgery for rectal cancer is to cure the disease, achieved through improvements in rates of local recurrence and distant metastasis, which in turn translates to improved survival. Bill Heald has shown in his classical article, a low rate of local recurrence, achieved primarily through a change in the surgical technique of TME [10]. Quality of surgery is measured by surrogate pathological outcomes like achievement of free Circumferential Radial Margin (CRM) and Distal Resection Margin (DRM), retrieval of a specimen with an intact fascial covering, and an adequate number of draining lymph nodes [31, 101]. Secondary aims are preservation of neurovascular bundles in the lower pelvis (thus preservation of urogenital function), and ability to perform an anastomosis in patients with tumours localized in the lowest part of the rectum.

In recent years, MIS has set sights on next level ability to potentially achieve these aims with a minimal burden on the patient. The main advantages of standard laparoscopic or robot-assisted surgery are related to a faster recovery due to reduced surgical stress. However, MIS has provided another significant advantage related directly to dissection through a magnified view of the surgical field. It has enabled surgeons to see details of anatomy that were not possible to see previously during open surgery era. The numerous advantages of MIS were known from experience with gall bladder surgery and could be re-produced in colorectal surgery in an early phase of implementation.

As pathological outcomes remain the most critical quality parameters, MIS rectal cancer surgery is required to re-produce at least equal outcomes, compared to open surgery. Several randomized controlled trials have shown comparable pathological/oncological outcomes of laparoscopic to open surgery, with distinct advantages of laparoscopy over open approach regarding other short-term outcomes [98, 102-104].

The non-inferiority of laparoscopic surgery for rectal cancer has been questioned recently in two randomized clinical trials [16, 18]. Stevensen et al. [18] showed a conversion rate of 9%, while conversion to open surgery in the study by Fleshman et al. [16] occurred in 11.3% of patients. These studies have failed to show that standard laparoscopy is not “non-inferior” to open rectal resection, measured by a composite outcome calculated by a combination of specimen quality and free margins. The main reasons for conversion are difficulties encountered in the pelvic; thus, the challenges of pelvic dissection remain unsolved. These problems are primarily due to technical issues related to achievement of the most important goal, which is retrieval of an intact specimen, but also achievement of this goal through a minimally invasive approach.

Furthermore, limitations prevent reaching the outer limits of disease management, offering patients the opportunity to enjoy acceptable functional results, including stoma-free life (when desirable and technically possible), and a normal or near-normal urogenital and bowel functions.

Despite the introduction of robotics, dissection in the lower part of the pelvis remains a challenge, since conversion to open surgery is still necessary in difficult cases, as shown in the ROLLAR study [100]. These difficult cases are predominantly obese male patients, where the anatomy is particularly challenging.

Call for a change in low rectal cancer surgery

The oncological outcomes after surgery for low rectal cancer are probably inferior to those following surgery for middle and upper rectal cancers [68].

As mentioned above, there is a higher risk of conversion to open surgery from MIS, and probably a tremendous challenge in performing bowel transection and anastomosis, leading to an increased risk of anastomotic leakage [105]. Another risk is ending up performing a rescue APE, in cases where bowel continuity is planned.

Furthermore, cancers in the lowest 5 cm of the rectum often need an APE, which has been debated in the last two decades due to high recurrence rates. One reason for these results is a high risk of tumour perforation in standard APE [11], and failure to achieve a negative CRM [106, 107]. In a large study from the United States, Rickles et al. [108] have shown a positive CRM in 17.2% following rectal cancer surgery. Laparoscopic surgery was one predictor for this high recurrence rate, being negatively associated with involved margins, reflecting probably a variation in the experience, with more experienced surgeons being the ones who have adopted the new technology.

The question of optimal approach of the operative field has been explored as a possible way to solve these problems. Numerous animal and cadaveric studies have focussed primarily on surgery through Natural Orifice Transluminal Surgery (NOTES). Sigmoid and rectal resections were performed by platforms used for Transanal Endoscopic Microsurgery (TEM), developed in the early 1980s for the retrieval of the small rectal lesions by the German surgeon Gerard Buess [109].

Thanks to previous experiences with the transperineal approach (TATA) [110-113], hybrid TaTME is considered a further step towards NOTES. Denost et al. [70] explored the potential advantage of "bottom-up" dissection in a randomized study. The authors found an improvement in pathological outcomes when rectal dissection was performed from below, though not translated to long-term benefits [114]. An interesting finding by Denost et al. [70], was the ability to increase the distance of resection margin in the transanal approach, probably due to removal of more tissue.

Dissection from below provides clear visualization of the operative field by three-dimensional standard laparoscopic cameras, leading potentially to better nerve-preservation and a reduction in risk of tearing the specimen.

Thus, the potential benefits of TaTME are related to its ability to solve those issues encountered during a standard laparoscopic TME (LaTME).

These benefits include:

1. Easier access to the lowermost part of the operative field, and more straightforward navigation in the embryological plane, the so-called “innermost dissectible plane” of the mesorectum [13]. This part constitutes a significant challenge during LaTME, especially in obese male patients with a bulky mesorectum or large tumours.
2. Direct visualization of the tumour and a precise rectal wall transection below it. The risk of retrieving a specimen with a positive DRM should be negligible.
3. Potentially better anastomosis, for two main reasons; a) avoidance of an unnecessary low transection of the bowel, leading to potentially better bowel function, and b) avoidance of multiple firings of endo stapler (as it is often the case in LaTME), and cross-stapling.
4. Rectal washout is a routine step during TaTME. There is evidence of a reduced risk of local recurrence when rectal washout is done during rectal resection [115].
5. When the specimen is removed through the anus, risks of wound-related complications (infection and hernia) are reduced compared to LaTME.
6. Avoidance of unnecessary APE.

Safety of TaTME

Although transanal approach is not entirely new, the applied technology and extent of reach from below differ significantly from TATA and APE in combination with an open approach.

Several questions need answering before widespread adoption of TaTME:

1. Does TaTME cause a spread of cancer cells in the pelvis?
2. Does high CO2 pressure increase the risk of CO2 embolism?
3. Is there an increased risk of local recurrence by mechanisms like the abdominal port site metastasis seen in MIS?
4. Is there an increased risk of urethral injury?
5. Are the functional results worse after TaTME than the abdominal approaches?

Safety of TaTME has been of concern ever since its early adoption. Clinical application of the procedure was preceded by numerous feasibility animal and cadaveric studies. These studies have shown that TaTME is feasible [116, 117]. Since the first human case [20], several case series have demonstrated that the procedure is feasible and safe [21, 118].

However, Wasmuth et al. [24], have concluded, "Local recurrence rates and growth patterns were unfavourable" after TaTME, and have decided to stop performing the procedure in Norway. The authors found a multifocal pattern of local recurrence, a finding not yet confirmed in other studies. One possible mechanism of cancer spread is -in case the assumption of multifocal recurrence confirmed-, the seeding of cancer cells in the pelvis following the incision of the rectal wall. While the theory of TaTME-specific "multifocality" of local recurrence is not proved, caution is needed to perform a tight purse-string suture and a thorough lumen washout.

Another potential problem is risk of CO_2 embolism, a complication that rarely is reported in abdominal MIS [119]. Dickson et al. [120], have reported a 0.4% risk of CO_2 embolism after TaTME, and several recently published case reports have indicated a similarly low risk [121, 122]. Suggested mechanisms are bleeding from partially transected veins, high CO_2 pressure, and dissection out of plane. This complication requires caution when using high CO_2 pressure, avoidance of intraoperative bleeding, and following the correct dissection planes. Awareness of risk of CO_2 embolism is crucial, as it allows early recognition and management.

TaTME allows for transanal specimen extraction in the majority of cases [4]. Although some authors have reported use of wound protection devices during extraction, the specimen is extracted without wound protection in most cases. This practice, combined with inefficient purse-string suture, can lead to implantation of cancer cells in the small perineal wound or along the anastomotic line [123]. This could represent a form of "port site metastasis," known from early adoption era of laparoscopic surgery for cancer, a risk substantially decreased through wound protection measures [124-128]. However, currently, it remains a rare event in TaTME.

Risk of urethral injury is thought to be higher during a TaTME than abdominal approaches [4, 129, 130], especially in the early phase of the learning curve. This can probably be reduced through a structured training program [131].

Potential trauma to the anal sphincter due to the transanal port can theoretically lead to worse functional results compared to abdominal approaches. However, this remains a theoretical risk. Koedam et al. [132], Bjoern et al. [133, 134], and Rubinkiewics et al. [135] have all reported similar functional results comparing TaTME and LaTME. Van der Heijden et al. [136], came to a similar conclusion.

Adoption of a new surgical method

The art of Surgery thrives best with innovations and adoption of new methods, usually less invasive than the previous ones. Ever since Lisfranc performed his first known planned operation for rectal cancer [137], through Mile´s [138] "cylindrical APE" and Henry Hartmann's [139] "excision and stoma procedure," to Bill Heald's [10] "TME" with its current status as standard of care for most rectal cancers, this continuous evolution has transformed a purely palliative limited tumour excision to a curative one. A change from standard rectal resection to TME is also feasible on a national level, with evidence of improved outcomes [140]. Adopting a new method needs to be planned well [141, 142], and it does involve some crucial steps.

First, a dedicated rectal cancer surgical team must be convinced of the need for a change in procedure. The challenge here is that new methods are rarely based on substantial evidence [68].

Second, the surgeon needs to train the team to be able to overcome barriers and execute the new method safely and effectively as a team.

Third, organizational changes leading to fewer surgeons performing the procedure, at least in the implementation phase.

Fourth, careful monitoring of outcomes is essential to ensure safety.

Fifth, publishing outcomes, either directly or as part of a collaborative effort through reporting to international registries [143].

AIM

To describe challenges associated with and analyse the outcomes of surgery for mid and low rectal cancer, with an emphasis on the TaTME.

The specific aims were to:

1. Describe outcomes of APE for low rectal cancer from a single centre.
2. Study the early outcomes of TaTME in a single centre.
3. Describe the learning curve of TaTME.
4. Report outcomes after TaTME beyond the learning curve from a single centre.
5. Compare outcomes of TaTME nationwide to other approaches for TME.
6. Report long-term oncological outcomes of TaTME in a single centre.

MATERIALS AND METHODS

Study population and data collection

Five studies are based on data from the Department of Gastrointestinal Surgery at Slagelse Hospital, a large-volume colorectal unit with a population base of around 450000 people from the Southern part of Zealand Region. Following the centralization of colorectal cancer surgery, our centre became one of the 12 centres allowed to perform rectal cancer surgery in Denmark [9].

In all studies, we have collected demographic data like age, sex, ASA (American Society of Anaesthesiologists) score, BMI (Body Mass Index), data on TNM (Tumour, Node, Metastasis) status, preoperative treatment, operative details, postoperative outcomes, and pathological outcomes.

For study I [1], we have retrospectively collected data and entered them into a local database for analysis. Data collection was done by both authors and was based on the electronic patient charts.

Following adoption of TaTME, we have established an electronic database, which included the variables mentioned above. We have chosen variables about patient demography and comorbidity with most relevance for the outcomes. Similarly, we have registered the most important variables related to operational performance like mobilization of the left flexure, anastomosis, operating time, and intraoperative complications. We also focused on the most critical pathological outcomes, like the specimen quality, CRM, and DRM involvements, plus distances, lymph node yield, as well as the postoperative complications. The operating surgeons and the author of this thesis collected data prospectively. Demographic and tumour data were collected upon the establishment of the final diagnosis and staging when the decision was made to operate the patient. Operative details were registered in the database immediately after surgery. We then registered the postoperative course following discharge and within 30 days, and occasionally while the patient was still in the hospital if complications occurred. Essential complications like anastomotic leakage were collected in more detail to describe the severity and management. We collected data on the outcomes related to the stoma, to determine the number of patients who had a permanent stoma, and to collect data on stoma closure. Postoperative complications were recorded according to Clavien and Dindo classification [144]. The pathological results were retrieved from the reports following surgery.

In study VI [6], all authors collected long-term oncological data, which were integrated into the TaTME database for analysis. The primary emphasis was on local and distant recurrences and survival. The authors have systematically reviewed the electronic patient charts, including CT and MRI scanning reports, to register any cases of recurrence, metastasis, or death. We registered time between the primary surgery and occurrence of any of these events.

We have used DCCG data for study V [5], without any additional data collection from patient charts. The DCCG database was established in 2001 and included demographic data and data on tumours, metastasis, operative details, pathological data, and the postoperative data up to 30 days. Reporting is mandatory by surgeons and pathologists. The database has a high completeness rate of > 95% [145], and there is an 86% agreement with the Danish Cancer Registry [146]. Registration of TaTME as a procedure in the DCCG database began in 2015, although we and some other centres have performed it since 2013.

We have applied the following inclusion criteria:

- Cancer type: Rectal cancer
- The operative principle: TME
- Procedure priority: Elective
- Period: 2014 - 2018.

We identified four groups of procedures for analysis and excluded patients who underwent extensive excisions (SAPE, ELAPE, Ischioanal APE). Register studies are limited by missing data and these missing data for each group and incorporated into the database for analysis.

Ethical considerations

The TaTME procedure was introduced as standard of care for mid and low rectum cancer at Slagelse hospital from December 2013. Other approaches for rectal cancer at our unit (open and laparoscopic) and on a national level (open, laparoscopic, and robot-assisted) and operative principles (anastomosis, Hartmann's operation, intersphincteric APE, SAPE, and ELAPE) were also routine procedures. Studies were conducted on the already treated population with procedures adopted as standard management and not as trial-based, and therefore did not need acceptance by the local ethics committee according to the Danish legislation. We have obtained approval from the Danish Data Protection Agency to develop and maintain our local TaTME database, and to store data from DCCG for statistical analysis. The scientific committee of the DCCG approves data retrieval from its database upon a study protocol-based request for data delivery.

Statistical Methods

Data presentation

In studies I [1] and II [2], we had two-group comparisons, while in study IV [4] and V [5], we had more than two groups. When making multiple-group comparisons, the probability values need to be adjusted, either by Bonferroni correction or through a calculation of an adjusted P-value from the so-called "z" scores.

Data analysis

Methods used were descriptive statistics and group comparisons. Categorical variables were analysed by Chi-Square test or Fisher´s exact test. For Numerical variables, we used the Mann-Whitney test or Student´s *t*-test.

In study IV [4], we had three groups and used the Chi Square test with correction of P value using Bonferroni correction for categorical variables, and used one-way analysis of variance (ANOVA) for numerical variables.

In study V [5], we had four groups and therefore chose to use the Chi Square test for categorical variables with a correction of the P value, using the adjusted residuals to detect inter-group differences. We used a one-way analysis of variance (ANOVA) for numerical variables. We used univariate and multivariate analyses to determine the predictors for anastomotic leakage and non-radical surgery.

In study VI [6], we used logistic regression analysis to determine the predictors of local recurrence and anastomotic leakage.

Cumulative Sum Analysis (CUSUM)

The CUSUM is a sequential-analysis technique used in statistical quality control. It was developed by ES Page in 1954 to monitor changes in the production process [147, 148]. This method involves a calculation of the cumulative sum; thus, it is sequential. CUSUM chart is used to monitor average of a process, and detection of any positive or negative deviations in process path. This makes it an attractive tool in medicine, to monitor clinical processes, and is especially useful in detecting rare events, for example, complications of a surgical procedure. The first published clinical use of CUSUM was in 1977 by Herbert Wohl [149], to monitor changes in the body temperature in septic patients. Leval [150] used CUSUM in neonatal surgery, including the surgeon, as a factor.

The process monitoring could be based on time (day 1, day 2, etc. of production) or case (patient 1, patient 2, etc.). The measurements of samples for each case (or for a given time) are a subgroup. The CUSUM chart shows the accumulated information of a given case and previous cases. For example, it can detect shifts from the mean of outcome(s). This means adding the difference observed in each case compared to a standard predetermined value. Target outcome(s) value(s) should be specified when applying the CUSUM chart, together with a reliable estimate of the standard deviation (for example the mean value for an outcome of a surgical procedure, whether from the literature or the mean value from the same sample). CUSUM chart detects any deviation through an *upward* or a *downward* drift of the cumulative sum. The process is out-of-control if the curve crosses the boundary, the moment a statistically significant deviation occurs from the mean. In CUSUM analysis, deviation (or the difference) occurs when it deviates from a reference value determined in advance.

CUSUM charts are simple and can visually show any undesirable changes in the process. For this reason, they are ideal when studying learning curves in surgery where rare events can occur, like complication [151, 152]. An essential advantage of CUSUM analysis is this ability for continuous monitoring of one or several outcomes at the same time. It can be beneficial in the introduction of new procedures or technologies, as well as measuring quality of treatment due to it is the ability to detect subtle results not measurable by other statistical methods [153, 154].

With worldwide introduction and gradual implementation of TaTME, achievement of competency in its critical steps was essential to perform the procedure safely. The essential first step of "*not harm*" highlights the importance of avoidance of complications during this initial phase. There is a need to determine the point where the "learning curve" stabilizes. Several studies have shown quite a high number needed to master the procedure [155-157].

Choice of the outcome of interest is debatable in studying learning curves; however, outcomes like operating time and occurrence of intraoperative complications indicate, to some extent, the procedural difficulty and competency. These measurable outcomes constituted the basis of the study of the learning curve included in this thesis [3]. Besides, it included anastomotic leakage (as it reflects a high degree of the competency in the purse-string suture), and the pathologic quality (as it is a surrogate marker of the oncologic quality).

Propensity Score Matching (PSM)

A propensity score is a probability of being assigned to treatment with a set of observed covariates. PSM is a statistical method to estimate effect of an intervention (for example, a surgical procedure) by accounting for covariates that predict being in the specific group (receiving the specific intervention). Its primary use is to reduce bias due to confounding variables in observational studies. In randomized studies, the process of randomization eliminates bias by accounting for covariates when allocating patients to the treatment group and balances the treatment groups on average.

Cohort studies like study IV [4] in this thesis carries the risk of bias due to the non-randomized design.

Paul Rosenbaum and Donald Rubin introduced PSM in 1983 [158]. The method reduces treatment assignment bias and mimics randomization.

PSM uses a predicted probability of group membership (treatment group vs control group), for example, TaTME vs LaTME vs OpTME, based on observed predictors obtained from a logistic regression analysis.

The method has the advantage of estimating an average treatment effect from observational data, and it balances groups on many covariates. One disadvantage of PSM is, it only accounts for observed covariates [159]; thus, it cannot be matched for the non-observed variables. Another disadvantage is that it demands large numbers of observations with considerable overlap between treatment group and control group. PSM is available in several statistical packages like R, SAS, Stata, and SPSS.

In study IV [4], we have matched cases 1:1, matching patients in the LaTME and OpTME groups 1:1, with TaTME as the treatment group. PSM models include only the preoperative variables and not post-treatment ones, due to the potential effect of treatment on these [160]. Variables included in the PSM model depend on the treatment groups and outcomes. In study IV [4], we have chosen the following variables as the basis for PSM:

- Demographic: gender, due to potentially more difficult dissection in the male pelvis, which might influence the outcomes.
- Co-morbidity: more challenging dissection in patients with high BMI.
- Macroscopic tumour pathology: tumour (T) status, and height of the tumour from the anal verge. TaTME has potentially more advantages in large-sized and low tumours.

PRESENTATION OF THE STUDIES

Study I

Perdawood SK, Lund T. Extralevator versus standard abdominoperineal excision for rectal cancer. Tech Coloproctol. 2015; 19(3):145-52. [1]

Aim

In this study, we wanted to answer this question: did the adoption of ELAPE improve pathological outcomes for patients with rectum cancer undergoing APE? We compared the pathological outcomes (rates of positive circumferential margin), postoperative course, complications, and length of stay of ELAPE versus SAPE.

Methods

A retrospective chart review of patients who underwent SAPE and ELAPE between 2006 and 2012 for rectal cancer (< 6 cm from the anal verge), in a single centre. Data collection included demographics, tumour status, operative details, pathological, and perioperative outcomes.

Results

We included 107 patients with a median age of 68 years (range 42-88), men=72 (SAPE= 39, ELAPE=68) patients. The groups were well balanced. However, a higher number of patients in the ELAPE group have received neoadjuvant chemoradiation. The rate of CRM + was higher in the ELAPE group (7.4 vs 2.6%, P=0.413). Seven patients (17.9%) in the SAPE group, versus nine patients in the ELAPE group (13.2%) developed local recurrence. ELAPE led to significantly lower rates of intraoperative bowel perforation (7.4% vs 20.5%, P=0.045). The overall rate of perineal wound infection was 42%, with no differences between the groups (SAPE= 38.5%, ELAPE=44.1%, P= 0.568). The median follow-up was 80 months after SAPE versus 50 months after ELAPE (P=0.001).

	SAPE (39)	ELAPE (68)	*p* value
pT stage			0.210
T0	2 (5.1)	8 (11.8)	
T1	0	2 (2.9)	
T2	17 (43.6)	29 (42.6)	
T3	20 (51.3)	25 (36.8)	
T4	0	4 (5.9)	
pN stage			0.596
N0	25 (64.1)	44 (64.7)	
N1	7 (17.9)	16 (23.5)	
N2	7 (17.9)	15 (14.0)	
Positive CRM	1 (2.6)	5 (7.4)	0.413
Positive CRM, tumour ≤4 cm from anal verge	1/36 (2.8)	3/52 (5.5)	1.000
Positive CRM; T3 and T4	1/30 (3.3)	5/60 (8.3)	0.659
Bowel perforation	8/39 (20.5)	5/68 (7.4)	0.045
Perforation, tumours ≤4 cm from anal verge	8/36 (22.2)	4/55 (7.3)	0.039
Operative time, median (range)	360 (240–520)	397 (240–630)	0.001
Hospital stay, median (range)	10 (5–92)	14 (7–62)	0.021
Wound infection	15/39 (38.5)	30/68 (44.1)	0.568
Wound infection, for patients not received chemoradiation	7/20 (35.0)	2/10 (48.3)	0.398
Local recurrence	7/39 (17.9)	9/68 (13.2)	0.513

Table 2. Postoperative and oncological outcomes

Conclusion

The main finding in this study was that ELAPE was associated with a lower rate of intraoperative bowel compared with SAPE group. ELAPE did not improve rates of involved CRM, although it improved rates of bowel perforation, which is a significant predictor of local recurrence [11]. Recurrence rates were high, though lower after ELAPE.

APE was performed for some relatively high tumours. The study indicated the need for a change in the approach towards a "tailored approach," where ELAPE is indicated for the more advanced tumours only. The question was: could a less mutilating procedure (and probably with anastomosis) be an alternative to APE for the less advanced tumours?

Strengths

The long follow-up time for both groups, and the relatively large sample size, considering the limited indications for APE and few cases operated annually at each colorectal unit.

Limitations

The most important limitation of this study is its retrospective nature, based on patient chart review. Data on postoperative complications are less precise when collected retrospectively. We introduced the ELAPE more recently than SAPE, and despite the overlap in a period, there is some comparison between two groups at different periods (a recent group of ELAPE with a historical group SAPE).

Study II

Perdawood SK, Al Khefagie GA. Transanal vs laparoscopic total mesorectal excision for rectal cancer: initial experience from Denmark. Colorectal Dis. 2016; 18(1):51-8. [2]

Aim

Can TaTME improve pathological outcomes in patients needing TME, compared to LaTME? We have adopted TaTME on the top of accumulating experience in laparoscopy. We aimed to compare its results to those after LaTME from our direct previous experience. The primary endpoints were short-term pathological results (involved margins and specimen quality), and secondary endpoints were operating time, perioperative complications, and hospital stay.

Methods

We included patients from our local TaTME database, operated from December 2013 to April 2015, and compared this cohort to a cohort of patients who underwent LaTME in the previous period. We selected 1:1 "nearest match," with gender as the only variable, to balance the groups. We ended up with the inclusion of LaTME for the period from February 2013 to November 2013.

Results

We had two well-balanced groups of 25 patients each. One patient in the TaTME group and four in the LaTME group had a specimen with an involved margin (P=0.349). None of the TaTME specimens was incomplete, while four in the LaTME was incomplete (P=0.113). Anastomotic level was significantly lower in the TaTME group (P=0.015). Conversion to open surgery occurred in zero patients in the TaTME group, while it occurred in four patients in the LaTME group (P=0.055). Intraoperative blood loss was less in the TaTME group (P=0.016). Length of stay was significantly shorter in the TaTME group (P=0.020).

	TaTME (25)	LaTME (25)	*P* value
Specimen quality (%)			
Complete	20 (80)	17 (68)	0.113
Nearly complete	5 (20)	4 (16)	
Incomplete	0	4 (16)	
Specimen quality for the LAR subgroup (%)			
Complete	15 (83.3)	12 (80)	0.214
Nearly complete	3 (16 7)	1 (6 7)	
Incomplete	0	2 (13.3)	
Specimen quality for the APE subgroup (%)			
Complete	5 (71.4)	5 (50)	0.422
Nearly complete	2 (28.6)	3 (30)	
Incomplete	0	2 (20)	
CRM involvement (%)	1 (4)	4 (16)	0.349
CRM distance, mm, median (range)	10 (1–20)	10 (0–32)	0.876
DRM distance, mm, median (range)	39 (4–95)	33 (5–97)	0.992
DRM distance, mm, median (range) for LAR subgroup	39.5 (20–95)	25 (14–97)	0.189
Number of retrieved lymph nodes	21 (9–42)	22 (7–45)	0.778
Tumour status			
T0	0	1	0.485
T1	0	1	
T2	8	4	
T3	16	18	
T4	1	1	
Lymph node status			
N0	14	14	0.429
N1	8	5	
N2	3	6	

Table 3. Pathological outcomes

	TaTME (25)	LaTME (25)	*P* value
Procedure			
Intersphincteric APE	7	10	0.551
LAR	18	15	
Reason for APE			
Planned	6	8	0.640
Rescue	1	2	
Splenic flexure mobilization	17	9	0.023
Splenic flexure mobilization in LAR	16	7	0.021
Anastomosis			
Side-to-end	9	12	0.077
End-to-end	9	3	
Anastomosis, height, cm, median (range)	4 (3–4)	4 (4–5)	0.015
Intra-operative complications, number			
Bleeding	2	1	0.286
Bowel perforation	0	2	
Conversion	0	4	0.055
Operating time, min, median (range)	300 (235–420)	351 (220–480)	0.002
Blood loss, ml, median (range)	50 (10–500)	100 (20–1000)	0.016
Anastomotic leakage, number	2	4	0.242
Urinary dysfunction on discharge	4	8	0.160
Readmission	4	4	1.000
Hospital stay, days (range)	5 (2–43)	14 (4–50)	0.020

Table 4. Intraoperative outcomes

Conclusion

TaTME has led to some improvement in specimen quality compared to LaTME and enabled a lower anastomosis, indicating significant potential of TaTME that could enable anastomosis in patients who might need an APE if operated by LaTME. The long operating time and the absence of significant improvement in the pathological outcomes in the TaTME group might be due to the learning curve. We wanted to investigate the volume needed to achieve proficiency in the procedure.

Strengths

The prospective data collection and comparison to a control group. It has a simple design, with well-known precise and commonly used endpoints.

Limitations

Retrospective data collection in control group. Patients were operated in two different periods, making it a comparison to a historical control group. Besides, the sample size was small, and we did not match the groups, apart from adjustment for gender.

Study III

Perdawood SK. A description of the learning curve for Transanal Total Mesorectal Excision using CUSUM analysis. [3]

Aim

To describe the learning curve of TaTME, defining the number of procedures needed to achieve proficiency.

Methods

Data were analysed from our local TaTME database, and we performed CUSUM analysis for four outcomes: 1) total and transanal operating times in minutes, 2) intraoperative blood loss in millilitres, 3) pathological outcomes: specimen grading (complete versus "incomplete or nearly complete") and CRM +.

The upper CUSUM describes deviations above the target, whereas lower CUSUM describes deviations below the target, which represents an average.

Results

The study included 125 patients who underwent TaTME between December 2013 and March 2017. Four surgeons did the procedures:

- Surgeon A: 75 procedures (60%).
- Surgeon B: 21 procedures (16.8%).
- Surgeon C: 20 procedures (16%).
- Surgeon D: nine procedures (7.2%).

Median operating time for the cohort was 280 minutes (range 180-480), and median transanal operating time was 80 minutes (range 30-180). Median blood loss was 50 ml (range 5-700). In 14 (11.2%) patients TME specimen was incomplete, and in eight (6.4%) patients, CRM was involved. In 106 (84.5%) patients, resection was successful, as defined by the combination of composite outcomes.

Learning curve analysis

Figures 8 and 9 show curves of operating times. For Surgeon A, the curves show "out-of-control" in the beginning, with stabilization around case 55 for both total and transanal parts. Overall, the results of CUSUM analysis have suggested two phases in the learning curve for one surgeon (Surgeon A), a learning phase up to case number 55, and a proficiency acquisition phase from case 56 to case 75. There were no significant differences in baseline characteristics and primary outcomes between the two phases.

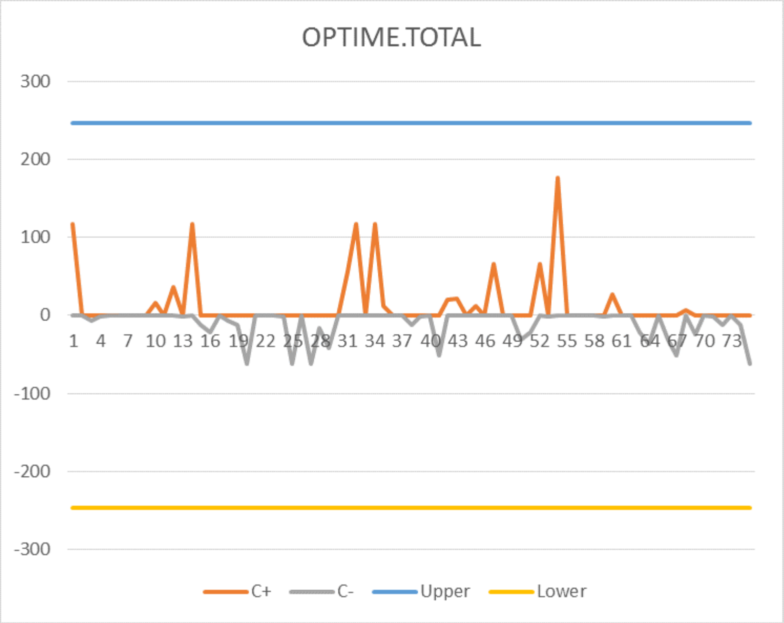

Figure 8. Total operation time for Surgeon A.

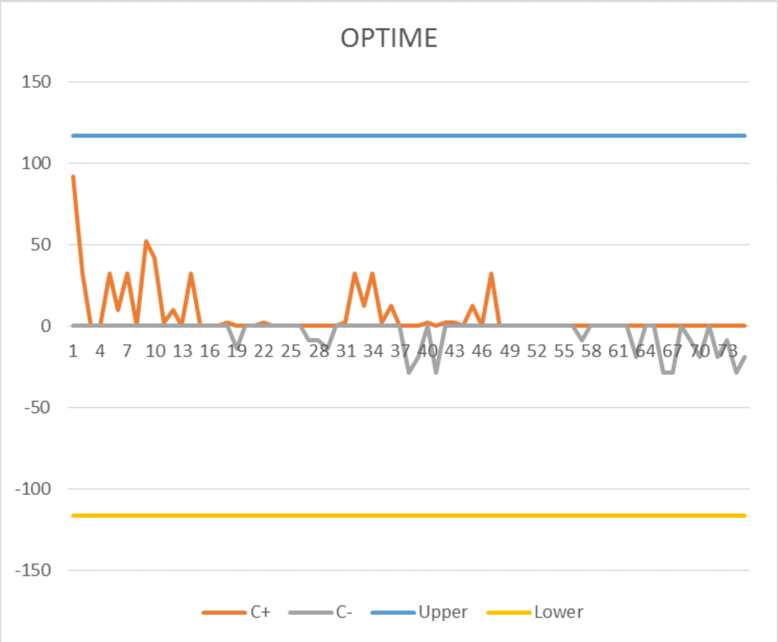

Figure 9. Transanal operation time for Surgeon A.

Conclusion

A case volume of at least 55 procedures was needed to achieve proficiency. The question was then: how we performed after the acquisition of proficiency in terms of short-term pathological outcomes and the intraoperative and postoperative outcomes? We needed to analyse our results after reaching proficiency, excluding those 25 cases published in study II.

Strengths

One strength of this analysis was to use CUSUM analysis, which is being increasingly used in medicine for quality control of interventions and reporting of various outcomes in colorectal surgery [153, 161]. In addition to a collective learning curve for all surgeons, we separately analysed data for the surgeon with the largest case-volume.

Limitations

Outcomes to be measured in learning curve analysis are not universal, and those that need to be included are debatable. A limitation of this study comes from several aspects. One is the accumulative nature of the learning process in MIS that could have influenced the learning process for TaTME. Second aspect is related to selection of outcomes to be analysed. One can discuss whether the operating time is a suitable outcome to measure the learning process. Another limitation is lack of complications as outcomes to be included in the CUSUM charts. Another limitation is the number of surgeons, which is relatively large (four surgeons) for a relatively small number of cases.

Study IV

Perdawood SK, Thinggaard BS, Bjoern MX. Effect of transanal total mesorectal excision for rectal cancer: comparison of short-term outcomes with laparoscopic and open surgeries. Surg Endosc. 2018; 32(5):2312-21. [4]

Aim

To determine the effect of TaTME on the primary outcomes after achieving experience compared to the previous approaches.

Methods

We included 100 patients who underwent TaTME and excluded the previously published 25 patients [2]. We matched patients 1:1 to patients who underwent LaTME and OpTME in the previous years. We first analysed baseline characteristics between TaTME and the whole cohort of 384 patients who underwent LaTME and OpTME and found no significant differences. We then performed case matching using PSM, based on the following criteria: sex, BMI, tumour status, and height of tumour from anal verge [162].

Primary endpoints were rates of involved CRM and DRM, as well as quality of the specimen. We calculated the successful resection based on a composite of the above two outcomes, as reported in the ACOSOG Z6051 randomized clinical trial [16]. Secondary endpoints were intraoperative outcomes and postoperative and complications.

Results

Table 1. Summarizes the pathological results. The TaTME group had the lowest rates of incomplete TME specimens and involved CRM. Overall rate of successful resection was comparable among the groups (P=0.174). TaTME led to the highest percentage of surgical success, and the lowest was in the LaTME group.

No conversion to open surgery occurred in the TaTME group, while 11 patients in the LaTME group were converted (P<0.001). Mean operation time was significantly shorter in the TaTME group (284.99±67.25, P<0.001). Rates of the intraoperative complications were comparable among the groups.

The number of planned anastomosis was highest in the OpTME (P=0.021); however, the number of performed anastomosis was comparable (P=0.876). Thus, TaTME allowed for higher rates of sphincter-saving procedures.

Rates of anastomotic leakage, wound infection, urinary complications, and 30-days mortality were comparable. Length of stay was shortest in the TaTME group (P=0.049).

	TaTME (100)	LaTME (100)	OpTME (100)	P value
Specimen quality, no.				0.041 (TaTME vs. LaTME, $P=0.016$; TaTME vs. OpTME, $P=0.082$; LaTME vs. OpTME, $P=0.750$)
Complete	58	68	68	
Nearly complete	28	12	15	
Incomplete	14	20	17	
CRM involvement	7	13	10	0.368 (TaTME vs. LaTME, $P=0.157$; TaTME vs. OpTME, $P=0.447$; LaTME vs. OpTME, $P=0.560$)
DRM involvement	0	1	1	0.604
CRM, mean ± SD, mm	8.99 ± 7.21	9.44 ± 7.86	9.57 ± 7.49	0.849
DRM, mean ± SD, mm	25.18 ± 14.34	24.95 ± 16.18	30.83 ± 21.91	0.052 (TaTME vs. LaTME, $P=0.995$; TaTME vs. OpTME, $P=0.065$; LaTME vs. OpTME, $P=0.052$)
DRM for LAR subgroup, mean ± SD, mm	22.22 ± 12.73	24.08 ± 15.136	34.76 ± 23.577	<0.001 (TaTME vs. LaTME, $P=0.826$; TaTME vs. OpTME, $P<0.001$; LaTME vs. OpTME, $P=0.002$)
Successful resection, no.	82	71	78	0.174
Retrieved LNs, mean ± SD, no.	22.32 ± 8.94	21.75 ± 10.98	17.92 ± 9.29	0.003 (TaTME vs. LaTME, $P=0.889$; TaTME vs. OpTME, $P=0.003$; LaTME vs. OpTME, $P=0.018$)
Number of positive LNs, mean ± SD	1.23 ± 2.78	1.46 ± 3.33	2.22 ± 4.57	0.134
Tumor status				0.004 (TaTME vs. LaTME, $P=0.355$; TaTME vs. OpTME, $P=0.004$; LaTME vs. OpTME, $P=0.298$)
T0[a]	4	4	3	
T1	8	2	2	
T2	36	33	19	
T3	48	54	67	
T4	4	7	9	
Lymph node status				0.213
N0	69	67	57	
N1	19	20	26	
N2	12	13	17	

Table 5. Pathological results

	TaTME (100)	LaTME (100)	OpTME (100)	P value
The performed procedure				0.876
LAR	63	66	66	
Intersphincteric APE	37	34	34	
Anastomotic method, no. (%)				0.044 (TaTME vs. LaTME, $P=0.890$; TaTME vs. OpTME, $P=0.022$; LaTME vs. OpTME, $P=0.015$)
Side-end	54 (85.7)	56 (84.8)	64 (97.0)	
End-end	9 (14.3)	10 (15.2)	2 (3.0)	
Splenic flexure mobilization	29	17	27	0.106
Splenic flexure mobilization in LAR, no.	24	17	26	0.192
Blood loss, mean ± SD, ml	82.10 ± 108.20	238.87 ± 355.15	704.50 ± 561.95	<0.001
Conversion to open procedure	0	11		<0.001
Intraoperative complications				0.693
Total, no.	13	12	16	
Bowel perforation	2	10	8	
Bleeding	8	2	6	
Urethral injury	1			
Urinary bladder injury	2		1	
Splenic injury			1	
Bowel perforation, tumors ≤ 6 cm from the anal verge, no.	1	3	4	0.304
Operation time, mean ± SD, min	284.99 ± 67.25	334.30 ± 84.31	325.25 ± 60.02	<0.001

Table 6. Intraoperative outcomes

Conclusion

TaTME resulted in higher rates of sphincter-saving procedures, shorter operation time, less blood loss, and shorter length of stay. Pathological results were not significantly superior to LaTME and OpTME. The procedure was safe and feasible beyond the learning curve.
The next question was to analyse the short-term results nationwide. At the time of this publication, several colorectal units have implemented TaTME.

Strengths

The prospective data collection for the TaTME group and most data for the other two groups through the DCCG database. Another strength is case matching.

Limitations

The retrospective data collection of some variables. Furthermore, the method of comparison with historical cohorts is another limitation. This study has compared three times periods, and the accumulated experience could have contributed to the learning curve of TaTME, especially laparoscopic surgery.

Study V

A nationwide comparison of short-term outcomes after transanal, open, laparoscopic, and robot assisted Total Mesorectal Excision. [5]

Aim

To determine the effect of TaTME on rates of non-radical surgery and perioperative complications compared to open (OpTME), laparoscopic (LaTME), and Robotic (RoTME) procedures in a nationwide cohort.

Methods

Data from patients who underwent curative OpTME, LaTME, RoTME, or TaTME between January 2014 and December 2018 were extracted from the national database DCCG. We have conducted multiple group-comparisons and uni- and multivariate analyses to determine predictors for non-radical surgery and anastomotic leakage.

Results

We included 2,393 patients (OpTME=205, LaTME=1163, RoTME=713, and TaTME=312). The rate of non-radical surgery was 5.7% after TaTME. The lowest rate of non-radical surgery was achieved after RoTME (2.52%, P<0.001). Predictors of non-radical surgery in univariate analysis were T4 tumours, preoperative radiotherapy, blood loss, perforation, APE, and OpTME. RoTME was associated with a higher rate of radical surgery (P=0.003). In multivariate analysis, T4 tumours, perforation, and RoTME were significant factors (P<0.001, P<0.001, P=0.003, respectively).

Predictors for anastomotic leakage in univariate analysis were male gender, high BMI, and intraoperative bowel perforation, and remained significant in the multivariate analysis (P<0.001, P=0.049, P=0.002 respectively). TaTME was associated with the highest rate of sphincter-saving procedures (79.8%, P<0.001), the lowest rate of bowel perforation (2.9%, P=0.028), and the lowest rate of conversion to open surgery (1.3%, P<0.001).

	OpTME	LaTME	RoTME	TaTME	*P*-value
T stage, n (%)					0.001
T 0	7 (3.4)	30 (2.5)	22 (3.0)	7 (2.2)	
T 1	12 (5.8)	167 (14.3)	103 (14.4)	42 (13.4)	
T 2	37 (18.0)	328 (28.2)	191 (26.7)	95 (30.4)	
T 3	137 (66.8)	595 (51.1)	375 (52.5)	162 (51.9)	
T 4	12 (5.8)	43 (3.6)	22 (3.0)	6 (1.9)	
N stage, n (%)					< 0.001
N 0	148 (72.1)	958 (82.3)	526 (73.7)	237 (75.9)	
N 1	26 (12.6)	124 (10.6)	105 (14.7)	45 (14.4)	
N 2	31 (15.1)	81 (6.9)	82 (11.5)	30 (9.6)	
Positive RM, n (%)	17 (8.2)	55 (4.7)	18 (2.5)	18 (5.7)	0.002
Intraoperative perforation, n (%)	3 (1.5)	12 (1.0)	7 (1.0)	4 (1.3)	0.922

Table 7. Pathological outcomes

	OpTME n=95	LaTME n=697	RoTME n=444	TaTME n=249	*P*-value
Anastomotic leakage, n (%)	11 (11.6)	79 (11.3)	54 (12.2)	24 (9.6)	0.790
Severity* of anastomotic leakage, n (%)					0.469
Grade A	0 (0.0)	9 (1.3)	11 (2.5)	5 (2.0)	
Grade B	5 (5.39	35 (5.0)	26 (5.9)	10 (4.0)	
Grade C	6 (6.3)	35 (5.0)	17 (3.8)	9 (3.6)	
Management of anastomotic leakage, n (%)					0.906
Anastomotic takedown	4 (4.2)	18 (2.6)	12 (2.7)	6 (2.4)	
No take down	7 (7.4)	61 (8.8)	42 (9.5)	18 (7.2)	

Table 8. Anastomotic leakage

Conclusion

In a nationwide audit of TME approaches, the rate of non-radical surgery was lowest with RoTME. TaTME was associated with the lowest rate of conversion and the highest rate of sphincter-saving. We found no differences in the other short-term outcomes.

We then wanted to study the long-term results after TaTME, in terms of local recurrence, metastatic disease, and survival, from our centre.

Strengths

Quality of data from the DCCG database and the large sample size.

Limitations

This study has several limitations. It is important to note that the TaTME procedure was introduced in Denmark in 2013, and some colorectal centres are still in the early phase of the learning curve, which might have caused some bias in the outcomes. Furthermore, the nationwide registry database may have natural sources of registration bias. Another limitation is lack of exact case matching.

Study VI

Perdawood SK, Kroeigaard J, Eriksen MH, Mortensen P. Transanal Total Mesorectal Excision: the Slagelse experience 2013 – 2019. [6]

Aim

To describe the long-term outcomes of local recurrence, distant metastasis, and survival after TaTME in a single centre.

Methods

We have updated our local TaTME database via a review of the electronic patient charts. We collected data on local recurrence, metastasis, and survival, and included all patients in the database since the implementation of the procedure. We retrieved long-term data from patient charts and radiology reports (CT and MR). Primary endpoints were local recurrence, distant metastasis, overall survival, disease-free survival, and pathological results. For the pathological results, we calculated the rate of successful resection based on the method described by Fleshman et al. [16].

We performed a logistic regression analysis to analyse the predictors of local recurrence and anastomotic leakage.

Results

We performed 200 TaTME procedures from December 2013 to July 2019. Following a mean follow-up of 29 months (range 1–61, ± SD 15.994), the number of surviving patients was 180 (90%), of whom 162 were disease-free (81%). LR occurred in seven patients (3.5%). All these occurred in patients with a minimum length of follow-up of 2 years (n = 150 patients, adjusted percentage of LR = 4.7%). Mean time to LR was 24 months (range 10–45, ± SD 12.632). Metachronous DM occurred in 24 patients (12%), and mean time to metastasis was 19 months (range 6–45, ± SD 10.185). In the logistic regression analysis, anastomotic leakage was a significant independent factor for the occurrence of LR (P = 0.019).

Outcome	Number (%)
Local recurrence	
Total	7 (3.5)
Extra luminal	2 (1)
Intra and extra luminal	2 (1)
Multifocal*	3 (1.5)
Distant metastasis	
Total	24 (12)
Liver	13 (6.5)
Lung	4 (2)
Multiple sites**	7 (3.5)
Local recurrence and distant metastasis	6 (4)
Local recurrence and liver metastasis	1 (0.6)
Local recurrence and lung metastasis	1 (0.6)
Local recurrence with both liver and lung metastasis	4 (2.8)
Total	25 (12.5)

Table 9. Oncological results.

Conclusion

Local recurrence rate was comparable after TaTME in a high-volume colorectal unit, compared to the literature.

Strengths

The prospective data collection through our local TaTME database.

Limitations

The study has several limitations. First, despite the prospective database as the primary source of data, we collected the oncological outcomes retrospectively. Second, the follow-up period for the whole cohort was not long enough, with only 150 patients had a follow-up of at least two years. Third, there was no control group.

DISCUSSION

Main findings

This thesis includes six studies on surgical management of mid and low rectal cancer and shows an advantage of standardization of the surgical technique. Studies focused on the effect of introducing new surgical procedures for rectal cancer.

A comparison of ELAPE to SAPE showed that ELAPE reduced the intraoperative perforation rate (study I) [1]. However, a tailored approach was not adopted, and ELAPE was performed for relatively high tumours, 5-6 cm from the anal verge. These tumours could potentially have been treated with sphincter-saving surgeries.

While laparoscopic surgery was a standard approach for mid and low rectal cancer treatment at Slagelse Hospital, TaTME was implemented due to limitations of laparoscopy in the pelvis. We have shown that TaTME is feasible, could overcome some limitations of LaTME, and allowed for a higher sphincter-saving rate (study II) [2]. We suggested the number of TaTME procedures needed to acquire proficiency. Through a CUSUM analysis, at least 55 procedures were shown to be associated with a stabilization in the primary outcomes like; pathological outcomes, operating time, and blood loss (study III) [3]. The transanal approach had, in our hands some advantages, compared to LaTME and OpTME in a cohort of patients operated following the standardization and full implementation, proving a positive effect of the procedure (study IV) [4]. We have explored the nationwide adoption of TaTME and compared its short-term results with OpTME, LaTME, and RoTME (study V) [5]. TaTME is implemented in several high-volume centres and –compared to other approaches- allowed for higher rates of sphincter-saving procedures, and lower rates of anastomotic leakage. In a nationwide cohort, TaTME was shown to be safe and feasible. Rates of radical surgery were, however, higher in the RoTME cohort. Long-term results after the TaTME in our centre were acceptable, with a local recurrence rate of 4.7% for patients with at least two years of follow-up (study VI) [6].

Clinical considerations

Optimizing APE

Surgery for rectal cancer has evolved from purely palliative with the relief of symptoms as the measure of success, through curable procedures with great mutilation, to minimally invasive techniques achieving a long-term cure. In early days of rectal cancer surgery, the procedure involved an abdominal approach in addition to a perineal approach that was limited to the removal of the rectal tube without the mesorectal fat [137]. The first documented attempt to do an extensive excision was made by Ernst Miles [69], through the “cylindrical APE” with an extensive excision of the rectum, the mesorectum, and the levators. Less extensive surgeries in the 1970s replaced the mutilating nature of the Miles´ procedure. However, Miles´ operation is still indicated in advanced low cancers, and the method was re-introduced again as ELAPE, a response to the inferior oncological results following APE [29, 68]. The ELAPE has been implemented in Denmark at an early phase, replacing the SAPE, probably without a clear-cut indication. According to the annual report of the DCCG in 2012, some 302 (26% of all rectal resections) patients underwent APE in the previous year. The distribution of ELAPE to SAPE was 129 and 173, respectively [163]. These numbers have declined to 75 and 61 for SAPE and ELAPE respectively in the 2018 DCCG annual report, with both procedures constituting 14.7% of the rectal excisions in the previous year [9]. This decline in the annual number of ELAPE procedures represents probably a better selection of patients.

At the time of reporting the results after ELAPE from our unit, several efforts were already made to optimize the outcomes after rectal cancer management; MRI had become an integrated part of rectal cancer care, surgery was centralized, pathology reports were standardized, and the management was discussed at multidisciplinary team meetings. All these efforts had led to an improved survival for rectal cancer patients in Denmark [164]. One example of these changes is the higher number of patients in the ELAPE group who have received neoadjuvant chemoradiation [1]. In our study, ELAPE did not have an oncological superiority over SAPE. However, the overall rate of involved CRM of 5.6% was lower than those in the literature [165, 166], which have shown the superiority of ELAPE over SAPE. Asplund et al. [167] did not find an oncological superiority of ELAPE over SAPE, similar to our results. In their study, the perforation rate was higher than the perforation rate in our study [1]. In a recent meta-analysis of 17 studies that included more than 4000 patients, where half of them underwent ELAPE, authors found that ELAPE has reduced intraoperative bowel perforation and had lower local recurrence rates than SAPE [168]. In a systematic review, De Nardi et al. [169], found that ELAPE led to less intraoperative bowel perforations and superior oncological outcomes compared to SAPE. Intraoperative bowel perforation is associated with poorer oncological outcomes [11]. In APE, one challenge is to avoid bowel perforation, especially at the surgical waist at about 3.5-4.2 cm from the anal verge, which is the part dissected from below [107]. The lowermost part of the APE procedure is crucial, and probably explains the lower rate of perforation in ELAPE, which leads to the removal of more tissue and a higher distance from the muscularis layer to the resection margin, as shown by How et al. [170]. The authors found a more significant benefit of ELAPE for tumours located laterally at or below 5 cm from the anal verge.

Indications for an APE do still exist, though probably less than previously practised. A “tailored approach” seems to be essential to achieve the balance between superior oncological results by ELAPE, and a less invasive approach when ELAPE is unlikely to benefit. The nationwide decline in the type of APE in Denmark could be explained by the adoption of a "tailored approach" following accumulating evidence for its benefits.

Low cancers where no ELAPE is needed

The locally advanced tumours in the lower third of the rectum must be removed by ELAPE, while the unsolved issues are the mid and low rectal tumours, where less invasive resection can provide a cure. Proper surgery alone can cure most of these cancers [57]. In our first study [1], we performed APE for tumours as high as 6 cm from the anal verge, and the annual DCCG report includes a considerable number of patients with relatively high tumour levels treated with APE [9, 163]. APE is sometimes preferable for mid rectal tumours where the patient's condition does not allow for anastomosis. In these cases, APE can be a better alternative to a low Hartmann´s operation to prevent pelvic sepsis [171]. Besides, the technical difficulty can probably lead to rescue APE in some cases of the otherwise planned anastomosis. Wang et al. [172] found superior oncological outcome after low anterior resection (LAR) compared to APE. As a change in the operative strategy, we have shown in study II [2], that TaTME can ensure sphincter-saving for low tumours as well.

Short-term outcomes

Sphincter preservation

The historical dogma was that the distal resection margin should be 5 cm below the tumour, leading to an APE for most mid rectal tumours [173]. This strategy has been challenged in recent years to consider 2 cm or even 1 cm as sufficient distance [30, 174], allowing for sphincter-saving in mid rectal tumours without jeopardizing the oncological safety. Apart from challenges related to dissection in the pelvis (in abdominal approaches), an anastomosis carries an extra challenge. Bowel transection often needs two or more stapler firings, which increases the risk of anastomotic leakage [175]. However, sphincter preservation remains an essential aim in rectal cancer surgery [176, 177], and a transanal approach seems to achieve this aim [70]. We demonstrated a higher rate of sphincter-saving procedures and lower rescue APEs by TaTME, compared to LaTME in study II [2], and study IV [4] showed a similar tendency.

Pathological results (and Specimen grading)

The essential aim of rectal cancer surgery is to achieve a radical tumour resection. The potential advantages of TaTME would thus be evident in the lowermost part of the rectum. This "*TaTME* *effect*" can potentially improve the quality of the specimen [178]. The existence of residual mesorectum is not uncommon after rectal cancer surgery, even following TME [179]. Veltcamp et al. [180], showed in their study, based on MRI evaluation of the pelvis that TaTME has significantly improved the specimen quality. An improved specimen grading would, in turn, positively affect the overall pathological success rate of surgery [4, 181]. An involved CRM or DRM carries a significant risk of local recurrence [31, 61, 182]. Rickles et al. [108] reported in a large register-based study, including over 16000 patients, 17.2% involved CRM. Stevenson et al. [18], have shown an involved CRM of 7% in the LaTME group of the randomized clinical trial (AlaCaRT study) comparing LaTME to OpTME. Fleshman et al. [16] showed an involved rate of CRM of 12.1% in the laparoscopic group of the ACOSOG randomized trial, and an involved CRM of 10%. In a meta-analysis by Ke Chen et al. [104], the involved CRM rate was 6.25% after laparoscopic surgery, and 5.14% after open surgery. In study VI [6], we have shown an involved CRM in 5.5% of cases, and in our previous publications (study II and study IV) [2, 4], the rate of involved margins was comparable to other approaches (LaTME and OpTME), with comparable rates of successful resection, according to Fleshman et al. [16]. Simillis et al. [21] have shown in a systematic review, an involved CRM rate after TaTME of 5%, while Penna et al. [143], have shown an involved CRM in 2.7% from the international TaTME registry. The registry data can, however, be subject to reporting bias.

Safety (minimal invasiveness)

Minimally invasive surgery has well documented intraoperative safety. We have shown in a systematic review that complications probably occur at the same rate after all approaches [183]. In the COLOR II study, the authors reported comparable complication rates after laparoscopic and open surgeries, with less blood loss in the laparoscopic group [184]. The same conclusion was drawn by Ke Chen et al. [104] in their meta-analysis, which showed that laparoscopic surgery was associated with fewer complications than open. The superiority of MIS over open approach has been reported repeatedly in numerous other studies.

The intraoperative blood loss in our studies (II and IV) was significantly less in the TaTME group than the LaTME group [2, 4], and negligibly low in study VI [6], and study V [5], which is in accordance with the literature [21, 143, 181, 185-187], and might reflect a further improvement in the MIS outcomes in terms of less intraoperative blood loss [188].

Urethral injury carries substantial morbidity, and proper training is necessary to avoid it. It has been reported during APE but is unusual during low anterior resection; however, it seems that

TaTME carries a risk of urethral injury. Rouanet et al. [129] reported two cases of urethral injury among 34 TaTME procedures for advanced rectal cancer. In a recent international collaborative paper, Sylla et al. [131] have reported 34 urethral injuries during TaTME, the majority of which occurred during the early period of adoption. The authors suggested structured training to avoid this complication. We experienced one case of urethral injury [4], which corresponds to 0.5% of our cases. In our nationwide study V [5], we found three cases of urethral injury among 312 TaTME procedures; all occurred during LAR.
Carbon dioxide embolism is rare, though potentially dangerous complication of MIS. There are some reported cases in TaTME literature [120-122, 189]. The suggested mechanisms are intraoperative bleeding, high CO2 flow by AirSeal™ CO2 pressure insufflator (Surgiquest Inc., Milford, USA), and it seems to correlate with the level of rectal transection with a low start being a risk factor. We did not experience any case of CO2 embolism.
Conversion from MIS to open surgery carries a risk of complications, and the literature shows a conversion rate of up to 17% [184]. The robotic-assisted approach [190] was not associated with a reduction in conversion rate compared to standard laparoscopy in a randomized trial [100]. TaTME seems to have solved this problem, as literature shows low conversion rates [21, 143, 185, 191]. In our studies II, IV, and VI [2, 4, 6], we showed low conversion rates, and in study V [5], conversion was lowest in the TaTME group.

Postoperative outcomes

Anastomotic leakage is a severe complication after sphincter-saving surgery for rectal cancer and carries considerable morbidity. Potential advantages of TaTME regarding anastomosis are two-fold; an increased number of sphincter-saving procedures and a reduction in the number of anastomotic leakages, through a novel technique that differs from the standard cross stapling. Penna et al. [192], reported an anastomotic leakage rate of 17.5% from the international TaTME registry. The authors identified the following risk factors of anastomotic leakage after TaTME; male sex, obesity, smoking, diabetes mellitus, tumour size >25 mm, excessive intraoperative blood loss, manual anastomosis, and prolonged perineal operative time. We had an anastomotic failure rate of 9.3% [6], which is lower than the registry and the randomized trial by Van der Pas (13% in the laparoscopic group and 10% after the open group) [184]. In our nationwide study (study V) [5], the leakage rate was 9.6%. From the literature, it is not evident whether TaTME has led to a reduced leakage rate, and this is probably related to learning curve issues and a tendency towards performing very low anastomosis in TaTME, compared to abdominal approaches, were performing a low anastomosis can be challenging. In our experience, the leakage rate was stabile during our learning curve and beyond [2, 4, 6], and was lower than leakage rates after TaTME in a nationwide study in Holland by Detering et al. [193]. In their study, the leakage rate was 16.5% after TaTME, and the authors attributed this high leakage rate to the learning curve.

There is probably an underreporting of anastomotic leakage in the literature. Borstlap et al. [194] reported in a Dutch cross-sectional study after TME surgery in Holland, a leakage rate of 13.4%, which increased to 20% beyond 30 days. One reason for underreporting of anastomotic leakage is that most studies report leaks within 30 days postoperatively.

In study VI [6], the leakage rate of 9.3% is based on a re-evaluation of patient charts, meaning that any long-term anastomotic failures would have been found at the time of this study.

One advantage of MIS is a shorter length of stay compared to open surgery. In a meta-analysis by Zhang et al. [191], hospital stay was comparable between TaTME and LaTME. Detering et al. [193] also reported a comparable length of stay in the two approaches. Roodbeen et al. [195], showed similar results. Wu et al. [196], found a significantly shorter length of stay after TaTME, compared to LaTME. In our experience (study II and study IV) [2, 4], we demonstrated a significant reduction in the length of hospital stay following TaTME adoption. One explanation is that TaTME is a more recent method, adopted at a time where enhanced recovery programs are well established in most colorectal units. Another reason is a reduction of severe complications following TME surgery, a tendency seen in recent years due to various efforts aiming at the optimization of patient´s physiological condition in the perioperative period.

The wound-related complications are directly related to the number of wounds. It is a logical consequence of TaTME to decrease these complications, compared to LaTME or RoTME. These were, however, comparable in our experience and the literature [2, 4, 5, 183, 191].

Long-term outcomes

There is a limited number of publications about long-term outcomes after TaTME, and the follow-up time for the published reports is not long enough to make reliable conclusions. To date, the driving factor behind the enthusiasm to implement TaTME is the promising pathological outcomes as surrogate markers of the oncological results [118, 197]. We have reported in study VI [6], seven cases of local recurrence, and 24 cases of distant metastases. However, the study has a significant limitation due to the relatively short follow-up time, although recurrences occurred among those 150 patients who had a follow-up time of at least two years, with a recurrence rate of 4.7%. The Norwegian report of 11.6% local recurrence rate occurred within a mean follow-up of 2.4 years [24]. The authors found that the recurrences were multifocal and occurred shortly after surgery. The study from Holland [23] showed a local recurrence rate of 5% at 5-years follow-up, and the time to recurrence was 19 months. Roodbeen et al. [198] reported local recurrence in 24 (3%) patients in their multicentre study of 767 patients and observed no multifocal pattern of LR. The authors concluded, "*The local recurrence is low after TaTME in selected cases from tertiary referral centres and does not indicate an inherent oncological risk of the surgical technique*." Future reports from expert centres with longer follow-up can probably answer the question of oncological safety.

Learning and implementing TaTME

Although TaTME is potentially a solution for difficulties encountered during standard laparoscopy, the procedure itself is not easy to master. In study III [3], we needed some 55 cases to achieve competency similar to what others have found [155, 157, 199]. Implementing a new surgical method is a complex process that involves several factors: experience of the surgeon, support from colleagues, economy, instrumentation, and training. A structured training pathway seems to be essential [200], and efforts are needed to introduce the procedure for appropriate indications safely [201-203]. The individual surgeon needs to be familiar with the specific anatomical, physiological, and procedural aspects of TaTME [71, 120, 131, 201-205].

CONCLUSIONS

Surgery is one element in the sophisticated algorithm of management of rectal cancer and has evolved from pure palliation to MIS procedures with curative intent. However, there are unresolved issues related to the surgical technique. Improvements in surgical principles and approaches can potentially increase the chances of achieving free resection margins. Studies presented in this thesis have focused on auditing APE procedures for low rectal cancer and explored the potential advantages of ELAPE [1]. The treatment of less advanced cancers, where ELAPE is unlikely to provide benefits, is probably underestimated with a tendency towards over-treatment, as some cancers might benefit from sphincter-saving and less mutilating procedures [206].

The bulk of this thesis has, however, focused on the transanal approach as a potentially better alternative to abdominal approaches. The standard laparoscopic approach has limitations that probably lead - in some cases - to suboptimal outcomes. These problems [19, 92], can potentially be solved by a change in approach and adoption of a “bottom-up” dissection. There is evidence of improved short-term outcomes, when lower part of rectum is approached from below, even without MIS instruments [70, 207, 208], although this was not translated to better long-term outcomes [114].

Pushing the limits of the transanal approach needs, however, a higher reach from below. A higher reach has been proven possible in cadaveric studies [117], and in 2010 the first human case was published [20].

From studies in this thesis, we conclude that TaTME has some advantages:

- Reduced conversion to open surgery.
- Intraoperative outcomes were comparable to LaTME.
- A relatively higher rate of sphincter-saving procedures.
- Relative reduction in the rate of anastomotic leakage.
- Comparable pathological and oncological results to other approaches.

TaTME is a challenging procedure, and we needed at least 55 procedures to achieve stability in the primary outcomes [3]. Several colorectal units in Denmark have now implemented the procedure, with evidence of its feasibility and pathological safety [5]. However, there is a risk of severe complications like urethral injury, and a widespread adoption needs structured training. The long-term oncological superiority of TaTME is not yet evident, although the risk of local recurrence in our experience was comparable with the literature [6, 198].

PERSPECTIVE AND FUTURE STUDIES

Tailored ELAPE

The number of ELAPE procedures in Denmark has decreased over the last few years [9]. Studies based on the nationwide DCCG database are needed to analyse the results after ELAPE in the last ten years in terms of outcomes and indications. The database is validated for studies on long-term results [209]. Of specific interest is the precise indication for ELAPE, which has similar short-term outcomes to SAPE nationwide [210], indicating the lack of precise practice regarding these low tumours. To date, the question of a tailored approach is not studied nationwide in Denmark.

Safety of TaTME and oncological outcomes

The body of literature, mostly from early adopters, shows that TaTME is feasible and safe. However, severe complications like urethral injury, ureteric injury, and CO2 embolism need further observation. We need to determine the technical aspects of the procedure that can prevent tissue injury and CO2 embolism. Furthermore, the rectal washout during TaTME can be one essential aspect to prevent local recurrence and must be studied to determine the type and volume of fluid needed.

Studies on long-term results are scarce to date, and no definite conclusions can be made on the oncological safety of TaTME [6, 23, 24, 198]. A nationwide audit on all TaTME procedures in Denmark to date could contribute to the accumulating evidence in the upcoming years.

Functional outcomes

Bowel function

Faecal continence is an essential aim after sphincter-saving surgery for rectal cancer, the severity of which is related to anastomotic height [211], and it improves over time [212]. No reliable conclusions on the potential benefits of TaTME on bowel function are possible, due to the limited number of studies to date [132, 133]. There is a need for prospective studies to evaluate the sphincter function, before and after a sphincter-saving TaTME.

Urinary and sexual function

The TME technique has improved the urogenital function, compared to non-TME surgery [213]. One potential advantage of TaTME is nerve-sparing, translated potentially to better urogenital functions [133, 214]. Studies focused on the assessment of urogenital function could add to the available evidence.

Training and implementation

Since the introduction of TaTME, considerable efforts were made to standardize the procedure to aid the structured learning and implementation. The focus was on indications, procedural details, and the optimal way to incorporate TaTME into the daily practice [71, 200, 203, 215, 216]. To date, there are only a few studies on the learning curve of TaTME [155, 156, 199, 217]. Most studies have focused on primary outcomes and do not describe the learning process of the individual steps of the procedure. It would be of interest to analyse the crucial steps during TaTME, for example, purse-string suture, different steps of the dissection, and anastomotic technique. These steps would probably improve the outcomes through a definition of procedural details.

Future technology

One of the critical steps during TaTME is the airtight closure of the rectal lumen by a purse-string suture to prevent spillage of cancer cells and bowel content. The reported recurrences in the literature might be due to the failure of the purse-string suture [23, 24, 123]. Technological advances can refine the technique for a higher reach from below, a precise dissection, and the performance of a perfect purse-string suture. The single-port DaVinci robot (Intuitive Surgical, USA), can potentially achieve these goals. It has been used in cadaveric models [218] to perform colonic resection [86].

ENGLISH SUMMARY

The TME is considered the standard surgical principle in management of mid and low rectal cancer and has proved to improve the long-term oncological outcomes [32]. Besides oncological outcomes, surgery aims at sphincter-preservation and minimal invasiveness.

The primary purpose of this thesis was to study outcomes of surgery for mid and low rectal cancers and to investigate the possibility of implementation of the relatively new surgical approach of TaTME. Furthermore, the thesis focused on the learning curve and the status of nationwide implementation.

This thesis includes six studies. Study I [1] is based on historical data of patients operated at Slagelse Hospital, retrieved from electronic patient charts. We have based studies II-IV and VI [2-4, 6] on the local TaTME database at our centre. The database includes all TaTME procedures from case one in 2013. The database is maintained, and the data collected prospectively. We have based study V [5] on the nationwide DCCG database.

Study I [1] focused on the outcomes of the APE for low rectal cancer (< 6 cm from the anal verge). In this study, the APE was performed for relatively high tumours (up to 6 cm from the

anal verge). The main finding was that ELAPE had reduced intraoperative bowel perforation rate, compared to SAPE. However, ELAPE might be an over-treatment for the less advanced and relatively high tumours, where a sphincter-saving procedure is usually a preferable option.
In study II [2], we studied the initial results of TaTME for our first 25 procedures. We compared the short-term results of TaTME to those after LaTME in the previous period before the adoption of TaTME. The study showed that TaTME is feasible and had comparable short-term pathological results without serious complications.
In study III [3], we investigated the learning curve to determine the number of procedures needed to achieve procedural proficiency. Several outcomes of interest were selected, like total operation time, transanal operation time, blood loss, and pathological results. The study showed that at least 55 procedures were needed to achieve stability in performance.
In study IV [4], we compared the outcomes of TaTME beyond the learning curve to those of open and standard laparoscopic approaches. The TaTME was standardized, and the level of competency was comparable at this time to the other approaches at our unit previously. The main finding was that TaTME could be performed safely and in a shorter time. An interesting finding was a higher rate of sphincter-saving procedures compared to the other approaches.
We wanted in study V [5] to audit the short-term pathological and perioperative outcomes of TaTME nationwide, compared to outcomes after the other approaches (OpTME, LaTME, RoTME). The study showed that TaTME is implemented in several centres with acceptable safety, apart from a few cases of urethral injury. The rates of sphincter-saving procedures were higher in the TaTME group. The short-term outcomes did not differ among the groups, with significantly favourable rates of involved CRM in the RoTME group.
In study VI [6], the long-term oncological outcomes at our centre were analysed. Following 200 procedures, seven cases of local recurrence occurred, 4.7% for the 150 cases with a follow-up period of at least two years. The oncological results are thus comparable to the literature, yet follow-up was not long enough.
More research is needed to investigate several aspects of surgery for mid and low rectal cancer like indications for ELAPE, safety, procedural details, and further studies of the long-term outcomes of TaTME.

DANSK RESUMÉ

TME betragtes er den standard kirurgiske princip i behandling af midt- og lav rectum cancer, med evidens for forbedret langtids onkologiske resultater [32]. Ud over de onkologiske resultater, sigter kirurgi mod en mere sfinkterbevarende og minimal invasiv tilgang. Hovedformålet med denne PhD afhandling var at undersøge resultater af kirurgi for rectum cancer og implementering, læringskurven, og status af landsdækkende implementering af TaTME.

Afhandlingen inkluderer seks studier. Studie I [1] er baseret på retrospektive journal gennemgang af patienter opereret på Slagelse Sygehus. Studierne II-IV, og VI [2-4, 6] er baseret på den lokale TaTME-database, der indeholder alle TaTME-procedurer siden 2013, med prospektivt dataindsamling. Der er løbende dataindsamling og opdatering. Studie V [5] er baseret på den landsdækkende DCCG database.

Studie I [1] fokuserede på resultaterne af APE for lav rectum cancer, og det viste at APE blev udført for relativt høje tumorer (op til 6 cm fra anal åbning). ELAPE var associeret med lav intraoperativ tarmperforation, sammenlignet med SAPE. Imidlertid, er ELAPE muligvis ikke altid indiceret til mindre avancerede og relativt høje tumorer, som kan behandles med en sfinkterbevarende procedure.

I studie II [2], rapporterede vi resultaterne efter vores initiale TaTME procedurer. Vi sammenlignede de kortvarige resultater af TaTME med dem efter LaTME i den umiddelbare periode inden implementering af TaTME. Studiet viste at TaTME er gennemførlig og har sammenlignelige kortvarige patologiske resultater, uden risiko for alvorlige intraoperative komplikationer.

I studie III [3], blev læringskurven undersøgt for at beregne antallet af procedurer, der er nødvendige for at opnå kompetence. Flere outcomes blev valgte; total operationstid, transanal operationstid, blodtab og patologiske resultater. Studiet viste, at mindst 55 procedurer er nødvendige for at opnå kompetence i TaTME.

I studie IV [4], blev resultaterne af TaTME efter indlæringskurven sammenlignet med resultaterne efter åben og laparoskopisk kirurgi. Baggrunden for studiet var, at vores kompetenceniveau for TaTME var sammenligneligt på dette tidspunkt med åben og laparoskopisk kirurgi. TaTME kunne udføres sikkert og på kortere tid end de øvrige procedurer. Et interessant fund er en højere rate af sfinkterbevarende procedurer ved TaTME.

I studie V [5] auditerede vi de landsdækkende kort-tids patologiske og perioperative resultater af TaTME, sammenlignet med resultater efter OpTME, LaTME, og RoTME. Studiet viste, at TaTME er implementeret i flere centre i Danmark, med acceptable resultater, bortset fra få tilfælde af intraoperativ skade på urinrør. Antallet af sfinkterbevarende procedurer var højere i TaTME-gruppen. De kort-tidsresultater var sammenlignelige blandt grupperne med en signifikant høj radikalitetsrate efter RoTME.

I studie VI [6], blev de langtids onkologiske resultater i vores center analyseret. Efter 200 procedurer, forekom der syv tilfælde af lokalt recidiv, svarende til 4,7% for de 150 patienter med en opfølgningstid på mindst to år. De hidtil onkologiske resultater er således sammenlignelige med litteraturen [198].

Der er behov for mere forskning for at undersøge flere aspekter af kirurgi ved midt- og lav rectum cancer, herunder indikation for ELAPE, sikkerhed, proceduremæssige detaljer, lang-tids onkologiske, og funktionelle resultater.

ABBREVIATIONS

ASA score	Physical status score of American Society of Anaesthesiologists
APE	Abdomino Perineal Excision
BMI	Body Mass Index (kg/m²)
DCCG	Danish Colorectal Cancer Group
CD	Clavien Dindo Classification of Surgical Complications
CRM	Circumferential Resection Margin
DRM	Distal Resection Margin
LAR	Low Anterior Resection
LaTME	Laparoscopic Total Mesorectal Excision
NOTES	Natural Orifice Transluminal Surgery
OpTME	Open Total Mesorectal Excision
PSM	Propensity Score Matching
RoTME	Robotic Total Mesorectal Excision
SD	Standard Deviation
TaTME	Transanal Total Mesorectal Excision
TME	Total Mesorectal Excision
TNM	Tumour Node Metastasis system

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ORIGINAL ARTICLE

Extralevator versus standard abdominoperineal excision for rectal cancer

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Abstract
Background Extralevator abdominoperineal excision (ELAPE) probably improves the oncological quality of low rectal cancer surgery, as compared to standard abdominoperineal excision (SAPE), possibly due to lower rates of accidental perioperative bowel perforations and lower rates of circumferential resection margin (CRM) positivity. The procedure may however, increase post-operative morbidity. The aim of this paper was to compare outcomes of SAPE and ELAPE for carcinoma of the lower rectum.
Methods This is a retrospective study of patients operated on at a single colorectal unit, in a provincial hospital in Denmark. Consecutive patients undergoing abdominoperineal excision (APE) between 2006 and 2012 were included. During this period, a gradual paradigm shift occurred towards adopting ELAPE, although both procedures were performed without a clear selection strategy. We reviewed medical records, including the pathological and radiological data. Patients were divided into two groups, SAPE and ELAPE. Main endpoints were rates of positive CRM, intraoperative bowel perforations, local recurrence rate, length of hospital stay, operative time, and perineal wound-related complications.
Results One hundred and seven patients were included (median age 68 years, range 42–88 years; men = 72). The SAPE group included 39 patients and the ELAPE group 68 patients. Intraoperative bowel perforation was significantly lower in the ELAPE group (20.5 % SAPE vs 7.4 % ELAPE, $p = 0.045$). The rate of positive CRM was not significantly different (2.6 % SAPE vs 7.4 % ELAPE, $p = 0.413$). The local recurrence rate was not statistically significant (17.9 % SAPE vs 13.2 % ELAPE, $p = 0.513$). In the ELAPE group, operative time and hospital stay were significantly longer than the SAPE group ($p = 0.001$ and $p = 0.021$, respectively).
Conclusions We found low rates of positive CRM after APE compared with the literature. ELAPE did not reduce these rates, and although the local recurrence rate was lower, this did not reach statistical significance. ELAPE has significantly reduced the rate of intraoperative bowel perforation and can optimize low rectal cancer surgery in selected patients. We found no significant differences between the two procedures regarding wound-related complications. A tailored approach and a larger trial with longer follow-up are needed to evaluate long-term results.

Keywords Rectal cancer · ELAPE · Abdominoperineal excision · Extralevator

Introduction

Since the introduction of total mesorectal excision (TME) [1, 2], local recurrence after rectal cancer surgery is less frequent and survival has improved [3, 4]. Surgery for very low cancers necessitating abdominoperineal excision (APE) has been shown to have poorer oncological results compared with anterior resection (AR) [5, 6]. Standard abdominoperineal excision (SAPE) may have contributed to these results, as it involves dissection close to the rectal wall, creating a specimen with a "waist". For tumours in the lower 4 cm of the rectum, there is a great risk of endangering the circumferential resection margin (CRM) [7]. Involvement of CRM and inadvertent intraoperative bowel perforation are important predictive factors of local

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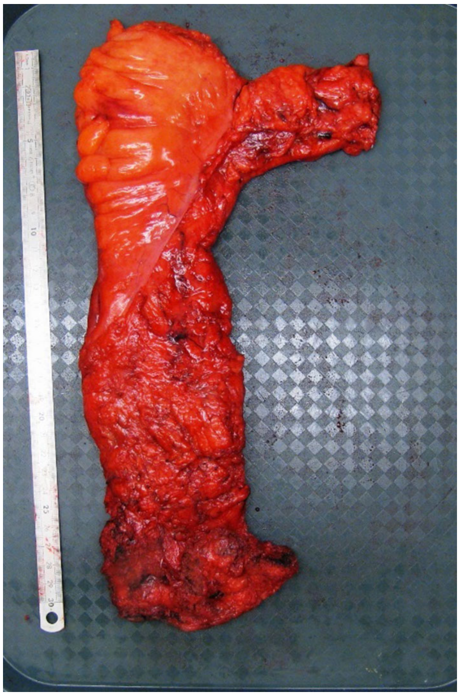

Fig. 1 Extralevator APE specimen

recurrence [8, 9]. To overcome these issues, a more extensive excision that yields a "cylindrical" specimen has been proposed [10], which involves en bloc excision of levator muscles and the rectum (extralevator abdominoperineal excision; ELAPE) (Fig. 1). Initial results were encouraging, and a multicentre study conducted by West et al. [11] demonstrated a significant reduction in the rates of positive CRM and intraoperative perforation. Although no large randomized controlled trials exist comparing the techniques, ELAPE has gained some acceptance. The concept of ELAPE is, however, controversial and some authors questioned its oncological benefits [12]. The controversy especially concerns the amount of tissue removed and patient position during the perineal part of the procedure (supine or prone position). Wide excision can increase morbidity and wound complications [11]. Furthermore, a larger perineal defect due to removal of the levator muscles requires some form of reconstruction.

Our aim in this study was to audit our results over the last 7-year period when both procedures were practised. Main outcome measures in this study were rates of positive CRM, intraoperative bowel perforations, local recurrence rate, operative time, wound complications, and length of hospital stay.

Materials and methods

Patients with primary adenocarcinoma of the lower rectum, who underwent APE between 2006 and 2012, were included. We excluded patients undergoing intersphincteric rectal resection and patients in whom multi-visceral resection was performed. Patients were identified through our hospital's electronic chart system and double-checked with the national database of Danish Colorectal Cancer Group, in which data were collected prospectively. Data collection included age, sex, and data on the primary tumour, American Society of Anesthesiologists (ASA) classification, and preoperative radiological investigations. Further data collection included neoadjuvant chemoradiation, details of the surgical procedure, hospital stay, the presence or absence of perineal wound complication, follow-up, and outpatient visits.

The preoperative diagnostic workup included full colonoscopy for non-obstructing tumours, radiological staging done by thoraco-abdominal computerized tomography (CT) scanning, and local tumour staging by magnetic resonance imaging (MRI). Tumours staged T3 or T4 were managed by preoperative long-course neoadjuvant chemoradiation (radiation dosage of 50.4 Gy, 28 fractions, in combination with 5-fluorouracil chemotherapy), according to the Danish guidelines [13]. CT and MRI were repeated 6 weeks following the completion of chemoradiation to assess response to neoadjuvant treatment and distant metastasis. Surgery was performed 7–8 weeks after completion of chemoradiation. During the study period, multidisciplinary team meetings were implemented and all patients with rectal cancer discussed prior to surgery [14]. Patients in this study were not in an enhanced recovery programme.

Tumour height was defined as the distance in centimetres from the anal verge to the lower margin of the tumour measured by rigid proctoscope. We used initial MRI reports for information on tumour staging and localization in relation to bowel wall quadrants. Based on clinical and MRI evaluations, tumours were classified as anterior, posterior, lateral (right and left), or circumferential.

All APE specimens underwent standardized pathological processing as recommended by Quirke [15]. The quality of the specimen was assessed to identify any signs of incompleteness. Intraoperative bowel perforation was defined as any perforation of the rectum reported by either the surgeon or the pathologist. The exact location of perforations in relation to the tumour-bearing quadrant was not specified. A positive CRM was defined as a distance of 1 mm or less from the tumour, or from a malignant-involved lymph node to the lateral resection margin, in accordance with the literature [16]. A local recurrence was defined as any cancer recurrence in the pelvis, verified either histologically or by MRI.

Operative time was extracted from an electronic booking system, and length of hospital stay calculated in days from the date of operation to the date of discharge. A perineal wound infection was defined as any signs of secretion, or delayed healing described by a surgeon, after removal of the wound stitches 12–14 days post-operatively, which necessitates frequent dressings, wound revision, or mesh removal. We could not calculate the exact length of time required for wound healing, because patients were not routinely followed up until healing through outpatient visits, but rather by their family physician.

Experienced colorectal surgeons performed all procedures in this study. However, none was trained in national or international ELAPE-specific programs. Learning was based on experience gained from leading international colorectal surgeons who pioneered ELAPE. This included visiting hospital and participating in workshops.

SAPE was performed with the patient in the supine position. The abdominal phase involved colonic and mesocolic dissection from retroperitoneal space, ligation of the inferior mesenteric artery proximal or distal to the origin of the left colic artery, and selective mobilization of the splenic flexure. Rectal dissection followed TME principles [1], and the dissection was continued as far down as possible in the pelvis. Thus, a complete TME was performed during the abdominal phase of the procedure. The colon was divided, a colostomy fashioned, and the abdomen closed. The perineal phase involved incision around the anus excising some ischioanal fat and dissection done sharply up towards the levator muscles, which then divided close to the bowel, leaving most of the levator tissue. Dissection continued until the plane achieved in the abdominal phase was reached, and the specimen removed, followed by primary closure of the perineal wound. In some cases, simultaneous abdominal and perineal dissections were performed.

ELAPE was performed as described by Holm [10]. The abdominal phase of the procedure differed from SAPE, in which dissection stopped at the level of the inferior hypogastric plexus laterally and just below the seminal vesicles anteriorly, to achieve en bloc resection of the mesorectum and levator muscles. For the perineal phase, the patient was in the prone jack-knife position and this part differed from SAPE, in which dissection continued laterally along the levator muscles, which were then divided close to the pelvic sidewalls. The coccyx was removed, as is routinely done to facilitate specimen retrieval, and the anterior dissection continued after reflecting the specimen. Perineal wound closure was performed in two different ways; gluteus maximus myocutaneous flap reconstruction was used in the beginning of the study period. A strict post-operative regime followed flap reconstruction [17]. Later, in the study period, biologic meshes were used for the reconstruction and the procedure involved fixation of the mesh to the cut edges of the levators by non-absorbable 2–0 sutures. An abdominal and a perineal drain were used, and each was removed when drainage was minimal. Antibiotic prophylaxis involved a single dose at the beginning of the study period and later a continued antibiotic treatment until drain removal for patients undergoing mesh closure. Patients were discharged after removal of both drains and if no serious complication occurred. Follow-up included a visit to the outpatient department to remove wound stitches at around post-operative day 14, a thoraco-abdominal CT scan after 1 and 3 years from surgery and a colonoscopy every 5 years until the age of 5 years post-operatively. In addition, follow-up data were collected from the electronic patient data system that covers the whole country. Patients were contacted by phone in some cases to complete follow-up data.

Statistical analysis

Results are presented as median with ranges, percentages given in parentheses. The Chi-square test was used for comparison of categorical variables and the non-parametric Mann–Whitney *U* test was used to compare ordinal variables. A p value of ≤ 0.05 considered statistically significant. Statistics package program SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) used for all calculations.

Results

One hundred and seven consecutive patients, operated on between 2006 and 2012, fulfilled the inclusion criteria (39 SAPE vs 68 ELAPE). Demographic data were similar between groups (Table 1). Four patients had resectable distant metastasis in ELAPE group versus none in SAPE group (Table 2).

The median tumour height from the anal verge was not significantly different between groups [3 cm (range 1–6 cm) SAPE vs 4 cm (range 1–6 cm) ELAPE, $p = 0.068$] (Table 3). There were no significant

Table 1 Patient characteristics

	SAPE (39)	ELAPE (68)	*p* value
Gender			0.746
Male	27 (69)	45 (66)	
Female	12 (31)	23 (34)	
Age (years), median (range)	69 (58–88)	68 (42–85)	0.193
ASA classification			0.339
ASA I	5 (12.8)	15 (22.1)	
ASA II	20 (51.3)	36 (52.9)	
ASA III	14 (35.9)	17 (25.0)	

ASA American Society of Anesthesiologists

Table 2 Perioperative data

	SAPE (39)	ELAPE (68)	*p* value
M stage			0.294
M0	39 (100)	64 (94)	
M1	0	4 (6)	
Tumour height, median (range)	3 (1–6)	4 (1–6)	0.068
Tumour stage			0.225
T2	9 (23.1)	8 (11.8)	
T3	22 (56.4)	39 (57.4)	
T4	8 (20.5)	21 (30.9)	
Tumour localization			0.173
Anterior	2 (5.1)	10 (14.7)	
Posterior	11 (28.2)	10 (14.7)	
Lateral	10 (25.6)	23 (33.8)	
Circumferential	16 (41)	25 (36.8)	
Preoperative chemoradiation	19 (48.7)	58 (85.3)	<0.001
Operative method			0.784
Open	20 (51.3)	33 (48.5)	
Laparoscopic	19 (48.7)	35 (51.5)	
Perineal reconstruction			<0.001
Primary suture	39 (100)	1 (1.5)	
Myocutaneous flap	0	20 (29.4)	
Permacol	0	16 (23.5)	
Strattice	0	31 (45.6)	

Table 3 Oncological and post-operative outcomes

	SAPE (39)	ELAPE (68)	*p* value
pT stage			0.210
T0	2 (5.1)	8 (11.8)	
T1	0	2 (2.9)	
T2	17 (43.6)	29 (42.6)	
T3	20 (51.3)	25 (36.8)	
T4	0	4 (5.9)	
pN stage			0.596
N0	25 (64.1)	44 (64.7)	
N1	7 (17.9)	16 (23.5)	
N2	7 (17.9)	15 (14.0)	
Positive CRM	1 (2.6)	5 (7.4)	0.413
Positive CRM, tumour ≤4 cm from anal verge	1/36 (2.8)	3/52 (5.5)	1.000
Positive CRM; T3 and T4	1/30 (3.3)	5/60 (8.3)	0.659
Bowel perforation	8/39 (20.5)	5/68 (7.4)	0.045
Perforation, tumours ≤4 cm from anal verge	8/36 (22.2)	4/55 (7.3)	0.039
Operative time, median (range)	360 (240–520)	397 (240–630)	0.001
Hospital stay, median (range)	10 (5–92)	14 (7–62)	0.021
Wound infection	15/39 (38.5)	30/68 (44.1)	0.568
Wound infection, for patients not received chemoradiation	7/20 (35.0)	2/10 (48.3)	0.398
Local recurrence	7/39 (17.9)	9/68 (13.2)	0.513

differences in tumour stage and tumour localization in relation to bowel quadrants ($p = 0.139$ and $p = 0.173$, respectively).

A significantly higher number of patients in the ELAPE group received preoperative neoadjuvant chemoradiation [19 patients (48.7 %) SAPE vs 58 (85.3 %) ELAPE, $p < 0.001$] (Table 2).

The number of laparoscopic procedures was not significantly different [19 (48.7 %) SAPE vs 35 (51.5 %) ELAPE, $p = 0.784$] (Table 2).

Perineal wounds were closed primarily in the SAPE group, while some form of reconstruction were used in the ELAPE group as follows: primary closure in one patient, gluteus maximus myocutaneous flap in 20 patients, and biologic mesh, Permacol™ (Tissue Science Laboratory, Covington, USA) and Strattice™ (LifeCell, Branchburg, NJ, USA) in 16 and 31 patients, respectively (Table 2).

Histopathological examination revealed no differences in the pT and pN stages ($p = 0.210$ and $p = 0.596$, respectively) (Table 3).

The assessment of the APE specimen's quality revealed a "complete" specimen in 29 patients in the SAPE group (74.4 %) and in 53 patients in the ELAPE group (77.9 %). The difference was not statistically significant ($p = 0.673$).

The overall rate of CRM involvement was 5.6 % (6/107), with no significant difference according to tumour localization in relation to bowel quadrant (one posterior, one lateral, one anterior, three circumferential), ($p = 0.841$). The rate was lower in the SAPE group (2.6 %) than in the ELAPE group (7.4), and the difference was not statistically significant ($p = 0.413$). Differences were still non-significant when data on CRM positivity were analysed for T3 and T4 tumours alone, or for tumours located 4 cm or less from the anal verge (Table 2).

The overall rate of intraoperative bowel perforation was 12 % (13/107), with no significant difference according to tumour localization in relation to bowel quadrant (three posterior, five lateral, one anterior, and four circumferential), $p = 0.861$. The perforation rate was significantly higher in SAPE [8 patients (20.5 %) SAPE vs 5 patients (7.4 %) ELAPE, $p = 0.045$]. The significance level increased when tumours located higher than 4 cm from the anal verge were excluded from the analysis ($p = 0.039$). In the SAPE group, all intraoperative bowel perforations occurred in the perineal phase of the procedure. In the ELAPE group, four perforations occurred in the perineal phase and one in the abdominal phase (Table 3).

There was no statistically significant difference in the local recurrence rate [7/39 (17.9 %) SAPE vs 9/68 (13.2 %) ELAPE, $p = 0.513$] (Table 3).

Median operative time was significantly longer in the ELAPE group [360 min (240–520) SAPE vs 397 min (240–630) ELAPE, $p < 0.001$]. The difference remained significant after excluding patients where perineal reconstruction was done by myocutaneous flap [360 min (240–520) SAPE vs 410 min ELAPE (240–630), $p < 0.001$ (Table 3)].

The overall rate of post-operative perineal wound infection was 42 %, with no significant differences between the groups [15 patients (38.5 %) SAPE vs 30 patients (44.1 %) ELAPE, $p = 0.568$]. The difference remained non-significant when patients who received neoadjuvant chemoradiation were excluded from analysis ($p = 0.398$) (Table 3).

Hospital stay was significantly longer in the ELAPE group [10 days (range 5–92 days) SAPE vs 14 days (range 7–62 days) ELAPE, $p = 0.021$]. The difference was, however, not significant when patients with perineal reconstruction by myocutaneous flap were excluded from analysis [10 days (range 5–92 days) SAPE vs 12 days (range 7–62), $p = 0.296$,]. No deaths occurred within the first 30 post-operative days in either group (Table 3).

Median length of follow-up was longer in SAPE group [80 months (range 47–103 months) SAPE vs 50 months (range 15–102 months) ELAPE, $p < 0.001$].

Discussion

We aimed in this study to evaluate the short-term outcomes of SAPE and ELAPE at a single colorectal unit, where all procedures were performed by the same group of experienced colorectal surgeons. The study shows that ELAPE has an advantage over SAPE in terms of lower rates of intraoperative bowel perforation. The operative time and hospital stay were longer in ELAPE, although the difference was not significant after excluding patients with pelvic reconstruction with a myocutaneous flap. Rates of positive CRM were higher in the ELAPE group. Local recurrence rate was lower in ELAPE, although the difference does not reach statistical significance.

Since the re-introduction of Miles' original extended APE operation [18] by the Swedish surgeon Torbjön Holm [10], ELAPE has gained popularity among colorectal surgeons. SAPE is, however, the procedure of choice to date. According to a recent annual report of the Danish Colorectal Cancer Group, of the 1128 patients operated on for rectal cancer in Denmark in the year 2012 [19], 302 (26 %) underwent APE, (129 SAPE vs 173 ELAPE). The majority of colorectal units in the country performed both procedures during that year, with a large regional variation in the relative numbers of each procedure. The reason for this practice variation is not yet clear, and explanations could be the absence of well-defined selection criteria in choosing the appropriate procedure, as well as differences in personal preferences and experience among colorectal surgeons.

Our institution was one of the first colorectal units in Denmark to adopt ELAPE for very low rectal cancer, with procedures performed back in the year 2004. This paradigm shift occurred gradually, and ELAPE has largely replaced SAPE in the last few years in our unit. The same group of experienced colorectal surgeons, who performed SAPE, performed ELAPE. To eliminate the effect of a "learning curve" and "implementing phase", only patients operated from 2006 on were included, although our experience with ELAPE started a few years prior to that.

Management of rectal cancer has changed during the study period; Multidisciplinary team meetings to plan management of colorectal cancer were introduced [20], radiological staging improved and was standardized with the use of CT scanning (instead of abdominal ultrasound and chest X-ray) to detect distant metastasis and MRI for local tumour staging. Neoadjuvant chemoradiation was given to an increasingly larger number of patients [21].

Histopathological reports became more structured and up to date, following international guidelines [22], with more focus on CRM [7]. These factors could have influenced the results of this study, especially at the end of the study period, where ELAPE comprised the majority of APEs. Description of specimen completeness, with focus on the quality of TME, was missing in about 25 % of patients in this study; results were, however, non-significant for the remaining patients.

In this study, a significantly higher number of patients in the ELAPE group had received chemoradiation. This may reflect improved radiological tumour staging and standardized national guidelines, rather than a real difference between groups.

In rectal cancer surgery, CRM involvement is a predictor of local recurrence and long-term survival [16, 23, 24]. We have shown in this study that ELAPE has no statistically significant oncological advantage over SAPE, using a positive CRM as a surrogate marker. The overall rate of positive CRM of 5.6 % in this study is lower than the reported rates in the literature [11], and both groups had low rates of positive CRM, lower in the SAPE group than in the ELAPE group, although this was not statistically significant. It was, however, surprising, since the aim of doing a wider excision was a reduction in rates of positive

CRM. An explanation could be improved and standardized histopathological assessment. A recent meta-analysis by Huang et al. [25] of 6 comparative studies (881 patients) showed that ELAPE had a significantly lower CRM involvement than SAPE, and the total positive CRM rate was 22.1 % (30.3 % SAPE vs 14.6 % ELAPE). Asplund et al. [26, 27] had shown that ELAPE did not provide any advantages over SAPE, with a positive CRM of 20 %. The study is similar to ours, as both procedures were done in one centre and by the same colorectal surgeons, although higher recurrence rates in both groups were found in our study. To our knowledge, West et al. [11] has reported the highest rates of positive CRM in the literature, with significantly lower rates in the ELAPE group (49.6 % SAPE vs 20.3 % ELAPE, $p < 0.001$). Data were from 9 centres in Europe and procedures done by 11 different surgeons, with a median number of 11 cases per surgeon (range 5–19 procedures). A recent meta-analysis of 8 studies (949 patients) came up with the same conclusion that ELAPE is oncologically superior to SAPE [28]. Both meta-analyses included retrospective studies and one randomized study [29] from major institutions, in contrary to our study that is from a community hospital. One common limitation of all included studies in these meta-analyses is their focus on the oncological superiority measured by CRM involvement and intraoperative perforation, without necessarily having sufficient data on long-term survival and comparison of complication rates. Anteriorly located tumours have been associated with higher rates of positive CRM [30]. We could not find similar results in this study, where positive CRM rates were independent of tumour localization.

Intraoperative bowel perforation has a negative effect on local recurrence and long-term survival [31]. We have shown in this study, a significant reduction in perforation rates in accordance with those reported after ELAPE in the literature [11, 26]. The perforation rate of 20.5 % in SAPE is higher than in other reports [29, 30, 32]. In the ELAPE group, the rate of 7.4 % is comparable to what others have reported [26]. The overall perforation rate of 12 % in this study is in accordance with rates from a national cohort study by Bulow et al. [33], who showed a perforation rate of 10 %. However, their study showed results primarily of SAPE, before the year 2006. Higher rates of perforation occur in APE than in AR, especially during the perineal part of the procedure [34], and as is the case for perforations in our study. The perineal dissection in the lowest part of the rectum endangers the surgical “waist”, which is shown to be 3.5–4.2 cm from the anal verge [35]. All but one intraoperative bowel perforation occurred during the perineal phase of the procedure in our study. This highlights the importance of this part of the operation and possibly the importance of patient positioning. Removal of more tissue combined with an easier view of the operation field could be reasons for the lower perforation rate in the ELAPE group. How et al. [36] have demonstrated that more tissue is removed in ELAPE than in SAPE, with a higher “muscularis to margin” distance. They have examined 20 APE specimens, with pathological slices matched to MRI images, and have shown greater benefit of ELAPE for tumours at the level of the puborectalis sling, which corresponds to where the “waist” is located. Benefits seem to be lower for anteriorly located tumours or tumours higher, or lower than this surgical “waist”. These findings are interesting; in that, a “tailored approach” suggested by the authors will ensure better selection, with ELAPE offered to patients with advanced tumours, located laterally and in the lower 5 cm of the rectum.

Performing the extralevator procedure in the prone jack-knife position is time consuming. Turning the patient, inability to perform both abdominal and perineal procedures simultaneously (as it is sometimes the case in SAPE), and time taken to reconstruct the perineal defect, all these factors may explain the significantly longer operative time in the ELAPE group in our study. On the other hand, a shorter operative time is to be expected in the abdominal phase of ELAPE, as it is not necessary to dissect the mesorectum completely from the pelvic floor. It is our belief that with accumulating experience in performing procedures in the jack-knife position a shorter time for turning the patient is to be expected.

Comparing the two procedures depends on the pattern and amount of tissue removed in the perineal phase and not on patient position; for this reason, we have precisely defined the way by which each procedure is performed, and the amount of tissue removed, to allow for comparisons. There is some confusion in the literature dealing with the terminology of these two procedures and the way in which each one is actually performed [37]. The perineal part of ELAPE is usually done in prone jack-knife position [10] although comparable oncological outcomes are reported with APE done in supine position [38, 39]. Turning the patient to prone jack-knife position greatly facilitates the procedure, especially anteriorly which is the most challenging part. The focus needs to be on the pattern of tissue removal to create an intact specimen rather than patient position [40].

Post-operative perineal wound infection rates were high in our study, but comparable to what others have reported [26, 41]. Both groups had similar high infection rates, even after excluding patients who received chemoradiation. Our definition of wound infection could explain this outcome.

Perineal wound closure differed between the groups; reconstruction was used in ELAPE, with either tissue flap or mesh, and primary closure in SAPE. There is no evidence of superiority of flap or mesh repair, regarding complication rates [42]. However, mesh repair allows for a less restrictive post-operative regimen and has shortened hospital stay in this study, as differences in hospital stay turned non-significant after excluding patients with flap reconstruction.

Patients undergoing ELAPE had a long hospital stay (median 14 days in the whole ELAPE cohort and median 12 days in patients with pelvic reconstruction with mesh), and this is partly due to our standardized post-operative regimen, which included delayed drain removal that postponed discharge. Kipling et al. [43] have reported a shorter hospital stay (7 days) than our study. Patients in their study followed an enhanced recovery programme and they included only laparoscopic procedures. Thus, short-term benefits could probably be achieved in addition to oncological benefits in our study, by adopting minimally invasive surgery combined with an enhanced recovery programme.

The longer follow-up in the SAPE group can be explained by the gradual introduction of ELAPE procedure in our institution, which was the result of a higher number of patients undergoing SAPE in the beginning of the study period.

Limitations of our study include: retrospective data collection that negatively affected the precision of data, especially the nature of wound complications and lack of evaluation of long-term complications, especially perineal hernia and chronic pain. A follow-up study would be valuable to assess long-term results and quality of life after APE.

Conclusions

In our institution, APE resulted in a low CRM involvement, without a statistically significant difference between SAPE and ELAPE. Perforation rates were higher than in the literature, and occurred mainly in the surgical "waist". ELAPE resulted in significantly lower perforation rates. The local recurrence rate was lower in ELAPE, although not statistically significant. Findings suggest that ELAPE can optimize low rectal cancer surgery in selected patients. A tailored approach should be adopted to select patients who benefit most from ELAPE. The wound-related outcomes do not seem to be different from SAPE. A tailored approach and larger trials with longer follow-up are needed to evaluate long-term results.

Conflict of interest None.

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Original article

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Transanal *vs* laparoscopic total mesorectal excision for rectal cancer: initial experience from Denmark

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Abstract

Aim Laparoscopic total mesorectal excision (LaTME) has improved short-term outcomes of rectal cancer surgery with comparable oncological results to open approach. LaTME can be difficult in the lowermost part of the rectum, leading potentially to higher rates of complications, conversion to open surgery and probably suboptimal oncological quality. Transanal TME (TaTME) can potentially solve these problems. The aim of this study was to compare the short-term results after TaTME with those after LaTME.

Method A prospectively collected database of consecutive patients who underwent TaTME was maintained. Results were compared with those who underwent LaTME in the preceding period. Patients who underwent low anterior resection or intersphincteric abdominoperineal excision were included. Primary end-points were radical resection and specimen quality. Secondary end-points were complications, rates of conversion, operating time and hospital stay.

Results In total, 50 patients were included (TaTME = 25, LaTME = 25). The groups were comparative in demographic data and tumour characteristics. Circumferential resection margin was positive in one patient in the TaTME group *vs* four patients in the LaTME group ($P = 0.349$). All patients in the TaTME group had either complete or nearly complete specimen quality, while four patients in the LaTME group had incomplete specimen quality ($P = 0.113$). Less blood loss, shorter operating time and shorter hospital stay were found in the TaTME group (P values 0.016, 0.002 and 0.020 respectively). Intra-operative complications were comparable ($P = 0.286$).

Conclusion The TaTME procedure had comparable pathological results and acceptable short-term postoperative outcomes compared to LaTME.

Keywords Transanal TME, TaTME, rectal cancer, surgery

What does this paper add to the literature?
This paper shows acceptable short-term and pathological results after TaTME compared to those after LaTME. It adds to the accumulating evidence for the feasibility and safety of TaTME.

Introduction

Total mesorectal excision (TME) is widely accepted as the standard surgical treatment for mid and low rectal cancer. It has led to reduced local recurrence and improved survival [1–3]. Laparoscopy has improved short-term outcomes of the procedure [4,5]. The laparoscopic approach is challenging in the lowermost part of the rectum, however, especially in male patients with high body mass index and narrow pelvis [6–8]. A transanal assistance to complete TME in the lowest part of the pelvis aims to overcome these limitations. The initial results after transanal TME (TaTME) are encouraging, with several large series published [9–16]. This study represents the initial results from a high-volume colorectal unit in Denmark and adds to the growing literature on TaTME. We have compared short-term outcomes after this new approach with those obtained with well-established laparoscopic TME (LaTME) in our department.

Methods

Data were collected prospectively on all consecutive patients who underwent TaTME from December 2013 to April 2015. The cohort was 1:1 matched with consecutive patients who underwent LaTME in the period

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prior to the introduction of the TaTME procedure at our unit. Patients included in this study had rectal adenocarcinoma located at or below 10 cm from the anal verge. TaTME was applied to all patients who were candidates for TME. Patients who underwent intersphincteric abdominoperineal excision (APE) were included, while patients who underwent standard or extralevator APE were excluded. Patients with T4 tumours were included if a radical resection was thought to be achieved after chemoradiation. Selection of the control group included also the inclusion of the same number of female patients in the LaTME group. Based on the above criteria, patients were included for LaTME from February 2013 to November 2013.

Preoperatively, a rigid proctoscopy was performed to precisely measure the distance from the tumour to the anal verge. A full colonoscopy if possible, thoracoabdominal CT scanning to detect possible metastatic disease, and MRI of the pelvis for tumour staging. Patients with advanced T3 (a distance of ≤ 5 mm from the tumour to the mesorectal fascia) or T4 tumours were given preoperative long-course neoadjuvant chemoradiation (radiation dosage of 50.4 Gy, 28 fractions, in combination with 5-fluorouracil chemotherapy), according to the Danish Colorectal Cancer Group guidelines [17]. In this case, a new set of CT and MRI were obtained 6 weeks following the completion of chemoradiation, to assess the tumour regression and possible metastatic disease. Tumour response to chemoradiation was graded according to a standardized method. Lymph node status on MRI was not part of the evaluation for neoadjuvant chemoradiation. All patients were discussed at a multidisciplinary team meeting before and after surgery. Surgery was performed 8 weeks after completion of chemoradiation. Oral mechanical bowel preparation with Moviprep (Norgine Danmark A/S Stamholmen, 2650 Hvidovre, Denmark) Swas used routinely in all patients undergoing TME with intended anastomosis; otherwise an enema preparation was utilized. Two colorectal surgeons (the authors) performed all TaTME procedures, while four colorectal surgeons including the authors performed the LaTME procedures. The colorectal unit is one of the largest in Denmark [18], where minimal invasive laparoscopic surgery is well established and performed on all colorectal operations if no contraindications exist. Training in TaTME included two workshops and cadaver dissection.

LaTME was performed in the lithotomy position using four ports (two 12 mm and two 5 mm), or in two cases through a single port device at the planned ileostomy site. The procedure followed a standardized method, described in the literature [19]. It included a medial to lateral dissection, central ligation of the inferior mesenteric artery, splenic flexure mobilization in selected cases, division of the bowel with endostapler after complete TME, specimen retrieval through a Pfannenstiel incision (or through the perineum following APE procedures), end-to-end or side-to-end colorectal anastomosis, and loop ileostomy (or permanent colostomy and anal canal excision in APE). Conversion was defined as conversion to any incision other than the Pfannenstiel incision.

TaTME was performed in the lithotomy position. The procedure followed the same principles described in the literature [20] and started always with a transabdominal dissection, as described for LaTME. One surgical team performed the procedures. An experienced colorectal surgeon always assisted the operating surgeon. The abdominal dissection in TaTME was continued down to the inferior hypogastric plexus laterally. The peritoneal reflection was not opened. Dissection had to stop earlier than mentioned if a narrow pelvis did not allow that. For the transanal part, a retractor (Retractor; Lone Star Medical Products, Houston, Texas, USA) was fixed and a GelPoint Path Transanal Access Platform (GelPoint Path Transanal Access Platform; Applied Medical, Rancho Santa Margarita, California, USA) was inserted. Carbon dioxide insufflation started with an intraluminal pressure of 8–15 mmHg. A 5 mm camera was used. After thorough assessment of the tumour, a purse string suture using 2-0 prolene was inserted 2 cm below the tumour (this was done under direct vision for very low tumours). The lumen was then rinsed with an antiseptic solution. A full thickness bowel transection 1 cm below the purse string suture was performed with diathermy. Transanal dissection was continued either with hook diathermy or with a sealing device. Dissection then proceeded in the avascular plane between the mesorectum and presacral fascia, first posteriorly, then anteriorly, and then laterally in a cephalic dissection. The peritoneal cavity was entered anteriorly, the specimen was then pushed upwards and the last adhesions were dissected free. A purse string suture was placed on the rectal/anal stump, and the specimen was then retrieved transanally. In the case of a bulky specimen, this was retrieved through a Pfannenstiel incision. Following division of the bowel, a colorectal anastomosis was fashioned by EEA Haemorrhoid stapler (EEA Haemorrhoid stapler; Covidien, Mansfield, Massachusetts, USA). The procedure was finished by creation of a loop ileostomy, insertion of a suction drain to the pelvis just above the anastomosis, and a suprapubic urinary catheter was inserted.

When a permanent colostomy was planned, the procedure was finished by colostomy creation and anal canal excision in the intersphincteric plane. We defined conversion as an abdominal assistance when the planned dissection from below was not completed transanally.

Patients in this study were not in an enhanced recovery programme. This was similar for both groups. Patients were discharged when oral diet was tolerated, they had no signs of complications and had learned stoma care.

Histopathological examination of the specimens followed a standardized method described by Quirke *et al.* [21]. The pathologist's report included information about the specimen quality (complete, nearly complete, not complete), circumferential resection margin (CRM), distal resection margin (DRM), lymph node yield and involvement, tumour deposits and neurovascular invasion. Resection margin was considered involved if this was < 1 mm from the tumour or from a lymph node with metastatic deposits. For patients in the TaTME group who had their ileostomy closed by the end of this study, an assessment of the anal sphincter function was conducted using the Cleveland (Wexner) incontinence score [22].

Statistical method

The statistical software package SPSS 20.0 (SPSS 20.0; SPSS Inc., Chicago, Illinois, USA) was used for all calculations. Data are presented as median with range. Continuous variables were compared by the non-parametric Mann–Whitney *U* test. Categorical variables were compared by the Pearson's chi-squared test or Fisher's exact test when appropriate. A *P* value < 0.05 was considered statistically significant.

Results

From December 2013 through April 2015, a total number of 85 patients with rectum cancer were operated on. Procedures included local resection (eight), partial mesorectal excision (32), extralevator APE (10) and TME (35). Among 35 patients who were candidates for TaTME, 25 underwent the procedure. The remaining 10 patients underwent LaTME as it was in the implementing period. Thus, 50 patients were included in this study (TaTME = 25, LaTME = 25). Patient and tumour characteristics were similar between the groups and are summarized in Table 1. Groups were also comparable in the percentage of patients who had received neoadjuvant chemoradiation therapy. One patient in the LaTME group and three patients in the TaTME group had metastasis to the liver at the time of diagnosis; all underwent radical surgery prior to rectum resection. Table 2 summarizes the operative and postoperative data.

Table 1 Patient and tumour characteristics.

	TaTME (25)	LaTME (25)	*P* value
Gender, female:male	6:19	6:19	1.000
Age, median (range)	70 (54–76)	70 (49–84)	0.361
BMI, median (range)	28 (18–46)	26 (19–38)	0.070
ASA classification			
ASA 1	5	8	0.429
ASA 2	14	14	
ASA 3	6	3	
WHO performance status			
0	13	9	0.376
1	10	14	
2	2	2	
Previous abdominal surgery	6	5	0.733
Tumour height, cm, median (range)	8 (4–10)	8 (5–10)	0.773
Tumour size, mm, median (range)	50 (20–70)	50 (20–80)	0.359
MRI/CT, TNM classification			
T			
T2	4	7	0.241
T3	19	18	
T4	2	0	
N			
N0	18	11	0.091
N1	4	5	
N2	3	9	
M			
M0	22	24	0.609
M1	3	1	
MRI, tumour site			
Circumferential	13	12	0.270
Anterior	4	1	
Posterior	2	4	
Right	4	2	
Left	2	6	
Preoperative chemoradiation, number received	7	4	0.306

BMI, body mass index; ASA, American Society of Anesthesiologists.

Two patients in the TaTME group had a T4 rectal cancer on MR scanning with signs of invasion to the uterus. Both received neoadjuvant chemoradiation and in one patient an *en bloc* resection of the adherent uterus was performed during rectum resection. Both patients had a radical resection with a negative CRM.

The procedures performed in this study included low anterior resection with colorectal anastomosis and inter-

Table 2 Operative data and postoperative results.

	TaTME (25)	LaTME (25)	*P* value
Procedure			
Intersphincteric APE	7	10	0.551
LAR	18	15	
Reason for APE			
Planned	6	8	0.640
Rescue	1	2	
Splenic flexure mobilization	17	9	0.023
Splenic flexure mobilization in LAR	16	7	0.021
Anastomosis			
Side-to-end	9	12	0.077
End-to-end	9	3	
Anastomosis, height, cm, median (range)	4 (3–4)	4 (4–5)	0.015
Intra-operative complications, number			
Bleeding	2	1	0.286
Bowel perforation	0	2	
Conversion	0	4	0.055
Operating time, min, median (range)	300 (235–420)	351 (220–480)	0.002
Blood loss, ml, median (range)	50 (10–500)	100 (20–1000)	0.016
Anastomotic leakage, number	2	4	0.242
Urinary dysfunction on discharge	4	8	0.160
Readmission	4	4	1.000
Hospital stay, days (range)	5 (2–43)	14 (4–50)	0.020

APE, abdominoperineal excision; LAR, low anterior resection.

sphincteric APE, with no significant differences in their proportions between groups ($P = 0.551$). APE procedures were done in 17 patients (TaTME = 7, LaTME = 10). In three patients, APE was a rescue procedure; one patient with a history of cardiovascular disease in the TaTME group underwent APE due to unsatisfactory circulation in the distal part of the colon. Two patients in the LaTME group underwent APE due to difficult dissection in the lower pelvis, with inability to perform bowel transection under the tumour.

Splenic flexure mobilization was completed in a significantly higher number of patients in the TaTME group, and the difference remained statistically significant when patients with APE were excluded. A larger number of patients had an end-to-end anastomosis in the TaTME group; the difference was not statistically significant, however. The height of anastomosis from the anal verge was significantly lower in the TaTME group. The specimen was extracted transanally in 10 low anterior resection (LAR) patients (56%) in the TaTME group.

Intra-operative bleeding occurred in two patients in the TaTME group. In both patients, bleeding occurred during the abdominal part of the dissection, one from presacral veins and the other in the left side of the mesorectum. Bleeding was controlled in both patients without the need for conversion. Blood losses were approximately 500 ml in each patient and both patients were men.

Intra-operative complications occurred in three patients in the LaTME group, one bleeding and two bowel perforations. The bleeding occurred in a female patient in the lateral pelvic sidewall and necessitated conversion to open surgery. Perforation occurred in one female patient where the procedure was converted to open surgery, and in a male patient who underwent APE and the perforation occurred during the perineal part of the procedure.

None of the TaTME procedures needed conversion, while four patients in the LaTME group underwent conversion from laparoscopic to open procedure. Apart from the two mentioned conversions, the two other conversions were due to difficult dissection in one female patient due to previous surgery and to dilated small and large bowel in one male patient. Blood loss was significantly lower in the TaTME group ($P = 0.016$). Anastomotic leakage occurred in two patients in the TaTME group, both managed successfully with endosponge (B. Braun Medical B.V., Melsungen, Germany) as described in the literature [23]. The diverting stoma is scheduled for closure in one of these two patients, while closure is awaiting adjuvant chemotherapy in the other patient. Anastomotic leakage occurred in four patients in the LaTME group. Leakage occurred in one female patient after ileostomy closure. The patient had a new ileostomy fashioned and the leakage was treated conservatively. In the second patient, leakage was managed by endosponge and the stoma was closed later. The last two patients with leakage were men; both were operated as emergencies, the anastomoses were taken down, and permanent colostomies were fashioned. Splenic flexure was mobilized in five out of six cases of anastomotic leakage.

Urinary dysfunction occurred in four patients in the TaTME group (three men) and in eight male patients in the LaTME group. All were patients who developed postoperative complications.

Four patients in the TaTME group were readmitted; two were patients with anastomotic leakage, two patients due to dehydration caused by excessive ileostomy output. In the LaTME group, four patients were readmitted due to anastomotic leakage (one), stoma complication (one) and dehydration (two).

Other postoperative complications included stoma complication in two patients in the TaTME group. One patient underwent a rescue APE as mentioned above. The patient developed stoma necrosis and was reoperated, and after resection of 40 cm colon a new colostomy was fashioned. The other patient had a mechanical obstruction at the ileostomy site and underwent an early stoma closure after 2 weeks.

Stoma complications occurred in four patients in the LaTME group: excessive output in three patients with ileostomy (one patient underwent early stoma closure and two were managed conservatively), and necrosis of the colostomy in one patient that was treated surgically.

Mechanical bowel obstruction occurred in two patients in the TaTME group (both APE); both were reoperated and adhesions were the reason for obstruction. Prolonged paralytic ileus occurred in two patients in the LaTME group, one after APE and one after LAR. Both were treated conservatively. Minor surgical wound complications occurred in one patient from each group.

In LAR patients, eight patients in the TaTME group (32%) had their diverting ileostomy closed at the end of this study period. The median Wexner incontinence score for these eight patients was 4.5 (range 0–7). Stoma closure rate in the LaTME group was 48% (12 patients). The total number of patients with postoperative morbidity was 34 (TaTME = 13, LaTME = 21). Table 3 summarizes the main complications.

Median hospital stay was shorter in the TaTME group and the result was statistically significant [TaTME 5 days (range 2–43) and LaTME 14 days (range 4–50), $P = 0.020$]. Table 4 summarizes the pathological results. No statistically significant difference was found in the response grade after neoadjuvant chemoradiation. All specimens in the TaTME group were either complete (80%) or nearly complete (20%), while four patients (16%) had an incomplete specimen in the LaTME group (LAR = 2, APE = 2); the difference was not statistically significant, however ($P = 0.113$).

Table 3 Postoperative complications.

Complications	TaTME	LaTME
Anastomotic leakage		
Grade 3a	2	2
Grade 3b	0	2
Urinary dysfunction on discharge		
Grade 2	4	8
Dehydration		
Grade 2	2	2
Stoma complications		
Grade 3a	0	2
Grade 3b	1	2
Grade 4a	1	0
Mechanical bowel obstruction		
Grade 3a	2	0
Prolonged paralytic ileus		
Grade 2	0	2
Wound infection		
Grade 1	1	1

Complications are graded according to the classification system suggested by Dindo *et al.* [38].

One patient (4%) in the TaTME group and four patients (16%) in the LaTME group had an involved CRM. The patient in the TaTME group had a T3N1 cancer and did not receive preoperative chemoradiation as the CRM was not threatened on MRI. The specimen was nearly complete and the CRM was considered involved due to a distance of less than 1 mm to an involved lymph node. The final pathology was T4N2 (11 out of 33 lymph nodes were involved). Patients with involved CRM in the LaTME had T3 tumours on MRI as well as in the pathologist's report. Only one patient had received preoperative chemoradiation and had an involved CRM due to tumour distance to CRM. The other three all had involved CRM due to the short distance to an involved lymph node. All four patients had complete specimens.

No statistically significant differences were found in the median CRM or DRM between groups ($P = 0.876$ and $P = 0.189$ respectively). However, median DRM was higher in the TaTME group. With regard to the median number of retrieved lymph nodes, tumour status and lymph node status there

Table 4 Pathological results.

	TaTME (25)	LaTME (25)	*P* value
Specimen quality (%)			
Complete	20 (80)	17 (68)	0.113
Nearly complete	5 (20)	4 (16)	
Incomplete	0	4 (16)	
Specimen quality for the LAR subgroup (%)			
Complete	15 (83.3)	12 (80)	0.214
Nearly complete	3 (16 7)	1 (6 7)	
Incomplete	0	2 (13.3)	
Specimen quality for the APE subgroup (%)			
Complete	5 (71.4)	5 (50)	0.422
Nearly complete	2 (28.6)	3 (30)	
Incomplete	0	2 (20)	
CRM involvement (%)	1 (4)	4 (16)	0.349
CRM distance, mm, median (range)	10 (1–20)	10 (0–32)	0.876
DRM distance, mm, median (range)	39 (4–95)	33 (5–97)	0.992
DRM distance, mm, median (range) for LAR subgroup	39.5 (20–95)	25 (14–97)	0.189
Number of retrieved lymph nodes	21 (9–42)	22 (7–45)	0.778
Tumour status			
T0	0	1	0.485
T1	0	1	
T2	8	4	
T3	16	18	
T4	1	1	
Lymph node status			
N0	14	14	0.429
N1	8	5	
N2	3	6	
Response in patients who received chemoradiation			
TRG 1	0	0	0.307
TRG 2	3	0	
TRG 3	4	2	
TRG 4	0	2	
TRG 5	0	0	

Values are median and numbers in parentheses are percentages, unless otherwise mentioned. APE, abdominoperineal excision; CRM, circumferential resection margin; DRM, distal resection margin; LAR, low anterior resection; TRG, tumour regression grade.

was no statistically significant difference between the groups ($P = 0.778$).

Discussion

Since the major revolution in rectal cancer surgery through TME [3], significant improvements in the oncological [1] and short-term outcomes have been seen [24]. Laparoscopic surgery is associated with favourable short-term outcomes compared to open surgery [6,25]. However, difficult dissection in obese patients can necessitate conversion to open surgery [26]. Perineal dissection has been shown to decrease the risk of involved CRM compared to abdominal dissection during LAR [27]. A recent evolution in laparoscopic rectal cancer surgery is TaTME. Several cadaveric and human series have been published in the last few years, with encouraging short-term results [28–33].

This study represents the initial experience with TaTME from a Danish colorectal unit, compared with historical material of well-established laparoscopic rectal cancer surgery. We have shown that TaTME yields acceptable short-term results without increasing the rates of intra-operative and postoperative complications. The overall morbidity was lower in TaTME than LaTME. Our study is biased in that we compared results after TaTME during a period with a learning curve with the well-established LaTME.

The rates of neoadjuvant chemoradiation were low in this study and no differences in tumour response were found. The high number of early T3 tumours could explain this. Furthermore, lymph node status on MRI was not part of decision making for neoadjuvant chemoradiation.

The quality of the specimen obtained after TME is an important parameter [21,34,35], as well as the rates of involved CRM [36]. Our study shows that rates of involved CRM and the median number of lymph nodes retrieved are comparable with those reported by other authors [9,14,16,20]. Compared with LaTME, acceptable results were achieved. Fernández-Hevia *et al.* [9] have shown in their comparative study of 37 TaTME *vs* 37 TaTME similar oncological outcomes between the groups. Velthuis *et al.* [10] reported a higher rate of specimen completeness in 25 patients after TaTME compared with results after LaTME. Results in this study are in accordance with what these studies have found.

The median CRM distance was comparable in our study between the groups. These results are similar to those reported by others [9,10]. DRM was higher, however, in the TaTME group, although not statistically significant. After excluding APE patients from the analysis, the difference remained non-significant. This is reflected in a statistically significant lower anastomotic height in the TaTME group. An explanation could be a tendency towards removal of more tissue in the TaTME procedure due to purse string suturing and the following steps.

We have shown that TaTME is feasible and safe with a minimal risk of conversion to open surgery. Despite the stepwise transabdominal-transanal approach in the majority of patients, the median operating time was significantly shorter in the TaTME group. We believe that two consultants operating together has made the procedure faster by having an experienced assistant. This is contrary to LaTME where the assistant was usually a younger colleague. Although no change in the patient management pathway was done between the two periods of the study, hospital stay was shorter after TaTME than after LaTME, and was comparable with other reports [9,33,37]. The significant difference in hospital stay in favour of TaTME is probably due to a higher complication rate in LaTME. Rates of anastomotic leakage and urinary dysfunction were also favourable in the TaTME group and in accordance with those reported by other authors [11]. We have performed TaTME in two patients with T4 tumours on preoperative MRI, with a multi-visceral resection in one patient. Radical surgery could be performed without serious intra-operative complications. There is some reluctance among colorectal surgeons to perform TaTME in patients with T4 tumours with risk of serious complications [15]. However, with careful selection a safe oncological procedure can be performed.

The long-term oncological results are awaited, as it is unclear whether TaTME jeopardizes the oncological safety through bowel transection. Furthermore, the long-term sphincter functional outcomes after TaTME are unknown, the latter due primarily to the stretched sphincter during the transanal part of the procedure. Larger studies with long follow-up, preferably through randomization, are needed to clarify all aspects of TaTME before it can be recommended as an alternative to LaTME.

Conclusions

This study showed, in accordance with the literature, that TaTME is safe, feasible and with comparable pathological results and acceptable short-term postoperative outcomes compared to LaTME.

Author contributions

Sharaf Karim Perdawood has contributed to the design, data acquisition, analysis, interpretation of data, and furthermore to writing the manuscript, final approval; he agrees to be responsible for all aspects of the work. Ghalib Ali Abod Al Khefagie has contributed to design, data acquisition, interpretation and writing the manuscript; he agrees to take full responsibility for the work.

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A description of the learning curve for Transanal Total Mesorectal Excision using CUSUM analysis

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Abstract

Background: There is a growing number of publications describing the TaTME procedure for rectal adenocarcinoma. The procedure is shown to be feasible and safe, though technically demanding. A safe and effective performance of the procedure require a great deal of caution and proper training. The learning curve is not well defined.
Objective: To describe the learning pathway during implementation phase of Transanal Total Mesorectal Excision (TaTME) for rectal adenocarcinoma.
Methods: Since 2013, four colorectal surgeons with expertise in minimal invasive laparoscopic rectal cancer surgery have performed the procedures. Their initial experiences were analyzed to determine the number of procedures needed to achieve proficiency. Different learning curve aspects studied, using the cumulative curve summation (CUSUM) analysis.
Results: A 125 TaTME procedures were performed since 2013. The number of procedures performed by four surgeons was as follows: 75 (60%), 21 (16.8%), 20 (16%), nine (7.2%). The procedures included 81 low anterior resections (64.8%) and 44 intersphincteric resections (35.2%). The median total operation time was 280 minutes (range 180-480) and the median operation time for the transanal part was 80 minutes (range 30-180). The median estimated intraoperative blood loss was 50 milliliters (range 5-700). Some degree of stability was observed after performing 55 cases.
Conclusions: To master TaTME, a case volume of consequently performed at least 55 cases is required.

Keywords: Rectal cancer surgery, Total Mesorectal Excision, Laparoscopy, TaTME

Introduction

Learning curve can be defined as learning over time, of a body of knowledge or the acquisition of acceptable competency in a new procedure or activity (1). In surgery, the learning curve of the surgeon represents the acquisition of proficiency in a surgical procedure and its subsequent modifications. One method of assessing the learning curve is the so-called cumulative sum (CUSUM) method. The method was originally developed by E.S. Page (2). The technique is used to detect changes in mean over time, thus monitoring performance in each procedure or production. The method has been adopted latter on to analyze the learning curve in medicine (3). Through a simple method of transforming data into a running total of deviations from the

mean, CUSUM charts enable the reader to detect trends in the process of learning.
The surgical treatment of mid and low rectal cancer has evolved from the original open surgery method (4), to minimal invasive methods aiming at the achievement of the same outcomes through laparoscopic (5) and robot-assisted procedures (6). The most recent evolution in the surgical treatment of mid and low rectal cancer is TaTME. While the initial reports have shown promising short-term results (7-9), the number of procedures needed to achieve proficiency in TaTME is unknown, though some evidence exist showing favorable results related directly to the sum of the procedures performed by a given colorectal unit (10). While it is acknowledged that measurement of learning curve can be uncertain and parameters measured are debatable, one way to assess proficiency and monitor the progress in learning is through plotting CUSUM charts. We aimed in the present analysis to assess the learning curve of TaTME, for four colorectal surgeons applying CUSUM method.

Method

Slagelse Hospital in Denmark is a large-volume center where minimal invasive laparoscopic surgery is well implemented (11). We have adopted TaTME since 2013. The procedure was implemented gradually, shifting from standard laparoscopic TME to TaTME. Two colorectal surgeons have performed the initial cases, followed by supervision of another two colorectal surgeons. All four were certified colorectal surgeons with experience in at least 100 laparoscopic rectal resections prior to their engagement in TaTME procedure. We have previously published our initial experience with TaTME (12), where details of the surgical procedure are described. This present study includes those initial cases as well. From our prospectively maintained database, we have collected relevant data for the purpose of this analysis. We have calculated the rate of successful resection from a composite of clear radial and distal resection margins and complete or nearly complete TME specimen. Fleshman et al. suggested this method, in a recent randomized controlled trial comparing laparoscopic and open rectal resections (13). We have decided to choose four separate outcomes as indicators of proficiency acquisition (total and transanal operation time, blood loss, pathological TME specimen quality and the number of non-radical surgeries as defined by involved resection margins). In addition, CUSUM charts were plotted for the composite successful outcome mentioned above. Each outcome was plotted as chart for the whole cohort, as well as for each individual surgeon separately. In case CUSUM charting suggested a significant shift in the curve, the cohort was divided into groups to compare between different phases of procedure implementation.

CUSUM charting

CUSUM charts are essential parts of the quality control toolbox. They have traditionally seen application as stochastic control measures in production environments (14). The present paper introduces upper and lower CUSUM plots as assessment tool for operational procedures, without making strict assumption on limits for success or failure on measures such as operation time, total operation time and blood loss. The applicability is just as diverse as failure CUSUM graphs and moving average plots since it is possible to adopt predefined measures of target and acceptable deviations.
The upper CUSUM describes deviations above target, whereas lower CUSUM describes deviations below target. Let ***m*** denote mean and ***s*** denote standard deviation of a continuous

measure of interest, e.g. raw values of operation time. These empirical measures may be replaced by theoretical or formal reference values describing a target and its variation. An allowance measure ***k*** is introduced with a value dependent on the context of the observed process (ranging from 0.2 to 1.0) (15).

In our case set at a value of 0.5 to match risks of a stable process:

$C_i^+ = \max\{0, x_i-(m+ks)+C_{(i-1)}^+\}$,

$C_i^- = \min\{0, x_i-(m-ks)+C_{(i-1)}^-\}$

The control limits for the graphs are +/- hs, where the usual value of h is 4 depending on context (15). Points beyond the control limits mark special cases, whereas the slope may indicate shifts in the process.

Statistical analysis

Data are presented as medians with range. Categorical variables were compared by Chi square test or Fishers exact test as appropriate. Numerical variables were compared by Students *t* test. Calculations were performed using the statistical software package SPSS version 24.0 (SPSS 24.0; SPSS Inc., Chicago, Illinois, USA).

Results

Outcomes

Between December 2013 and March 2017, 125 patients with mid and low rectal cancer underwent TaTME at our unit. Patient and tumour characteristics are shown in Table 1. The number of procedures performed by the four surgeons was as follows: 75 (60%), 21 (16.8%), 20 (16%), nine (7.2%) for surgeons A, B, C and D, respectively. The procedures included 81 low anterior resections (64.8%) and 44 intersphincteric resections (35.2%). The median total operation time was 280 minutes (range 180-480) and the median operation time for the transanal part was 80 minutes (range 30-180). The median estimated intraoperative blood loss was 50 milliliters (range 5-700). The TME specimens were graded as incomplete as suggested by Quirke et al (16), in 14 patients (11.2%). The CRM was involved in eight patients (6.4%) and the number of successful resections, based on composite outcomes accounted for 106 patients (84.5%). These outcomes are shown in Table 2.

Learning curve analysis

Total operation time and time spent to perform the transanal part are shown in Figures 1a-j. For the whole cohort, there is a peak at case number 66; afterwards, the curve shows descend and acceptable variation. However, for the transanal part, the curve exceeds the upper limit and the process is out of control from case 12 to case 31 after which there is a steady fall, and the curve stabilizes. For surgeon A, both curves become stable after case 35 for total operation time and for the transanal part with only one peak at case 55. Thus, it seems that surgeon A has achieved a certain level of proficiency around case 55, where both curves are stable. The following 20 cases were performed in a stable speed. For surgeon B, stable operation time with peak at the end of the curve, which could be due to cases performed without supervision/assistant. For surgeon C, the curve is almost flat with a single peak around case 13, probably due to constant proctoring. The case volume for surgeon D includes only nine proctored cases and no conclusion can be made.

CUSUM charts for the estimated intra-operative blood loss are shown in Figure 2a-e. For the whole cohort, the largest peaks occur in cases 81 and 90, after which the curve descends and stabilizes. The same peak is seen for surgeon A, where the curve is out of control at case 80, representing this surgeon's case 43. The curves for surgeons B-D are almost flat with no "out of control" events. Thus, blood loss seems to have been larger in the beginning of the learning curve with tendency towards a stable low blood loss after case 43 for surgeon A. This is almost like the number of cases needed to reach stable operation time.

The curves for the quality of the TME specimen are shown in Figure 3a-e. The number of retrieved specimens with suboptimal quality "incomplete" is small, though the highest number is seen from cases 81-90 (Figure 3a). This is also reflected in the curve for surgeon A (Figure3b) where the concentration of incomplete specimens is around cases 43-55, which represent the same period for the whole cohort (cases 81-90). No incomplete specimens were found for surgeon B and few sporadic cases for surgeons C and D. Thus, for this pathological outcome, surgeon A has demonstrated stable low percentage of suboptimal quality in the beginning of the adoption period, with a peak after performing more than half of the procedures and regain of a somewhat stable period afterwards around case 55. Although several suboptimal results are seen towards the last cases.

Almost an identical tendency is seen for involved CRM outcome as for specimen quality (Figure 4a-e). While sporadic cases are seen throughout the curve, half of the eight cases with involved CRM were between case 85 and 100 that represent cases 43-55 for surgeon A. Surgeons B-D had no cases with involved CRM.

CUSUM charting of the combined composite outcome is shown in Figure 5a-e). Like curves for composite outcome´s two components, more unsuccessful surgeries were performed around cases 81 and 97. For surgeon A, this represents the period from case 42-58. Curves for surgeons B-D, show either no or very few sporadic cases and cannot be used to make conclusions.
The results of the above CUSUM charting suggested two phases in the learning process of the TaTME procedure for a single surgeon (surgeon A). The optimal outcome to predict proficiency acquisition is difficult to define. However, the above findings suggest that case 55 for surgeon A marks the beginning of a new phase. Thus, we have divided the cohort operated by surgeon A into two phases, Phase Ⅰ: cases 1-55 and Phase Ⅱ: cases 56-75. Differences in the baseline characteristics and main outcomes were not statistically significant. Table 3 shows these comparisons.

Discussion

Although the interpretation of the results of the present study is difficult, they suggest some degree of proficiency acquisition with TaTME around case 55 for a single surgeon. This has allowed for a somewhat stable performance, measured by almost all outcomes. However, the study of learning curve for a procedure like TaTME is a complex one. One reason is that TaTME is merely a modification of laparoscopic surgery, which is already "learned" by the surgeon who adopts TaTME. Another reason is the difficulty to define the outcome that would predict

learning.
We have used the CUSUM method to study the ongoing process of TaTME adoption at our unit and used several outcomes separately. Curves for the whole cohort showed that most difficulty was encountered in the transanal part at the beginning of the implementation phase. While total operation time demonstrated variations almost throughout the curve, the transanal part took longest recorded time in the beginning. This is expected for a new procedure, especially a challenging one like TaTME. In contrary, the peak in the suboptimal pathological outcomes after around 80 cases could be explained by the inclusion of more difficult cases as the team gained confidence. By analyzing curves for the surgeon with the largest volume (surgeon A), similar findings to the whole cohort could be demonstrated. One interesting finding is the earlier flattening of the curve for the total operation time, than that of transanal operation time. This can be due to the inclusion of difficult cases at that period, where the abdominal part takes longer time.
It is difficult to suggest an exact number at which TaTME can be mastered. Learning is a continuous process and without doubt, more cases add to one surgeon´s experience. From this study, it is safest to consider the period after at least case 55 as where stability is seen when all chosen outcomes are taken into consideration. It is also at this period where all newcomers with mid and low rectal cancer were included, which means difficult cases are also included in the analysis. With a careful interpretation and understanding of all dynamics in the process of implementing TaTME, it is probably reasonable to consider a volume of at least 50-60 cases as where a single surgeon (who performs TaTME consequently) can be confident in his/her performance.

One strength of the method used in this study is the utilization of CUSUM analysis. It has been increasingly used in medicine in the recent years for quality control of interventions and reporting of various outcomes in colorectal surgery (17, 18). In rectal cancer surgery, the method has been used to assess learning curve for robotic resection with suggestion of 25 procedures required to achieve proficiency, as reported by Yamaguchi et al (19) and Foo et al (20). The analysis was, however based on operating time in these studies as the only outcome. In another study of a relatively large number of patients, Sng et al (21) found an initial learning phase of 35 cases, based on operation time. For single incision laparoscopic rectal resection, Kim et al (22) suggested a volume of at least 61 cases to achieve competency. Park et al (23) have compared learning curves for robotic and laparoscopic rectal resections, based on pathological outcomes. They suggested a needed number of 44 and 41 cases for robotic and laparoscopic resections, respectively. What is probably more interesting is the accumulative nature of the learning process in rectal cancer surgery. In a study of robotic rectal cancer resection, Odermatt et al (6) have reported a shorter learning process of robotic resection for a surgeon with prior laparoscopic experience. Likewise, a prior experience in laparoscopic rectal resection is a determinant of learning curve for TaTME.

Conclusion

The learning curve of TaTME is complex and depends probably on previous experience in minimal invasive surgery. Our experience suggests that a case volume of at least 55 procedures is needed to achieve proficiency, taking into consideration several important outcomes.

Conflicts of interest
Dr. Sharaf Karim Perdawood has no conflicts of interest or financial ties to disclose.

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Tables and figures

Sex, No. (%)	
Female	34 (27.2)
Male	91 (72.8)
Age, years, median (range)	69 (40-90)
BMI, kg/m2, median (range)	26 (17-46)
ASA classification, No. (%)	
ASA 1	46 (36.8)
ASA 2	53 (42.4)
ASA 3	26 (20.8)
WHO performance status, No. (%)	
0	84 (67.2)
1	33 (26.4)
2	8 (6.4)
Previous abdominal surgery, No. (%)	29 (23.2)
Tumour height, cm, median (range)	8 (4-11)
TNM, T status, No. (%)	
T1	4 (3.2)
T2	56 (44.8)
T3	61 (48.8)
T4	4 (3.2)
Preoperative chemoradiation, No. (%)	25 (20)

Table 1. Patient and tumour characteristics

The performed Procedure, No. (%) LAR Intersphincteric APE	 81 (64.8) 44 (35.2)
Anastomotic method, No. (%) Side - end End - end	 63 (77.8) 18 (22.2)
Splenic flexure mobilization, No. (%)	44 (35.2)
Blood loss, ml, median (range)	50 (5-700)
Conversion to open procedure	0
Intraoperative complications, No. (%) Bowel perforation Bleeding Urethral injury Urinary bladder injury	 2 (1.6) 10 (8) 1 (0.8) 2 (1.6)
Total operation time, min, median (range)	280 (180-480)
Transanal part operation time, min, median (range)	80 (30-180)
Specimen quality, No. (%) Complete/Nearly complete Incomplete	 111 (88.8) 14 (11.2)
CRM involvement, No. (%)	8 (6.4)
DRM involvement, No. (%)	0
CRM, mm, median (range)	8 (0-35)
DRM, mm, median (range)	25 (1-95)
Successful resection, No. (%)	106 (84.5)
Retrieved LNs, No., median (range)	22 (1-45)
Pathological Tumour status, No. (%) T0 * T1 T2 T3 T4	 4 (3.2) 8 (6.4) 44 (35.2) 64 (51.2) 5 (4)

Table 2. Perioperative and pathological results

	Phase Ⅰ: cases 1-55	Phase Ⅱ: cases 56-75	P value
Sex, No. (%)			1.000
Female	10 (18.2)	3 (15)	
Male	45 (81.8)	17 (85)	
Age, years, median (range)	69 (47-90)	63 (42-85)	0.154
BMI, kg/m2, median (range)	28 (21-35)	25 (17-46)	0.212
ASA classification, No. (%)			0.716
ASA 1	19 (34.6)	8 (40)	
ASA 2	23 (41.8)	9 (45)	
ASA 3	13 (23.6)	3 (15)	
Previous abdominal surgery, No. (%)	11 (20)	5 (25)	0.751
Tumour height, cm, median (range)	8 (4-11)	7 (4-11)	0.209
TNM, T status, No. (%)			0.085
T1	2 (3.6)	0	
T2	21 (38.2)	14 (70)	
T3	29 (52.7)	6 (30)	
T4	3 (5.5)	0	
The performed Procedure, No. (%)			0.061
LAR	31 (56.4)	16 (80)	
Intersphincteric APE	24 (43.6)	4 (20)	
Blood loss, ml, median (range)	50 (20-700)	30 (5-150)	0.163
Total operation time, min, median (range)	270 (180-480)	245 (180-330)	0.704
Transanal part operation time, min, median (range)	80 (30-180)	55 (30-80)	0.067
Specimen quality, No. (%)			0.431
Complete/Nearly complete	48 (87.3)	16 (80)	
Incomplete	7 (12.7)	4 (20)	
CRM involvement, No. (%)	5 (9.1)	3 (15)	0.463
Successful resection, No. (%)	45 (81.8)	14 (70)	0.341

Table 3. Baseline characteristics and outcomes in the two phases

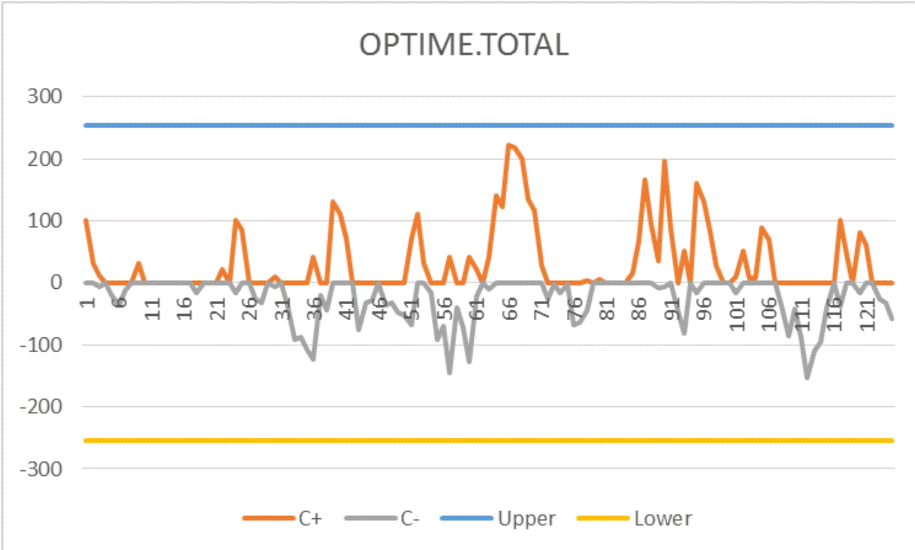

Figure 1. CUSUM charts for the total (TOT) and transanal operation time (OPT). a) TOT, whole cohort.

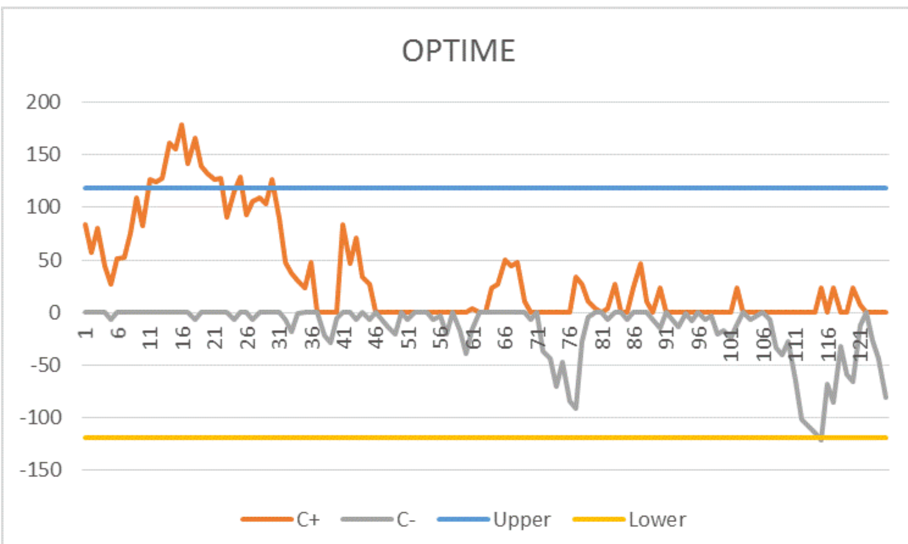

Figure 1. CUSUM charts for the total (TOT) and transanal operation time (OPT). b) OPT, whole cohort.

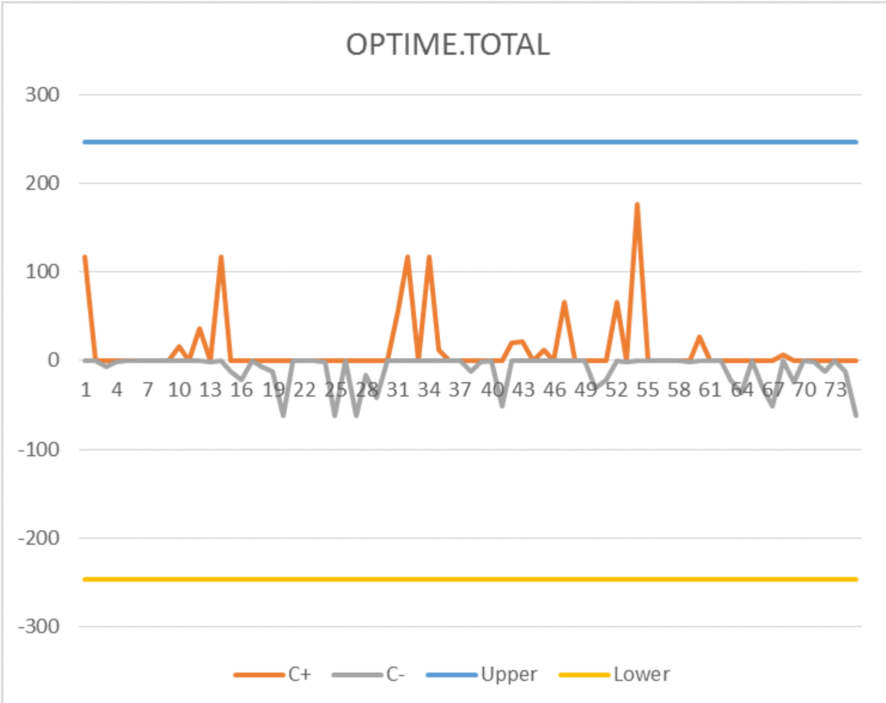

Figure 1. CUSUM charts for the total (TOT) and transanal operation time (OPT).c) TOT, surgeon A.

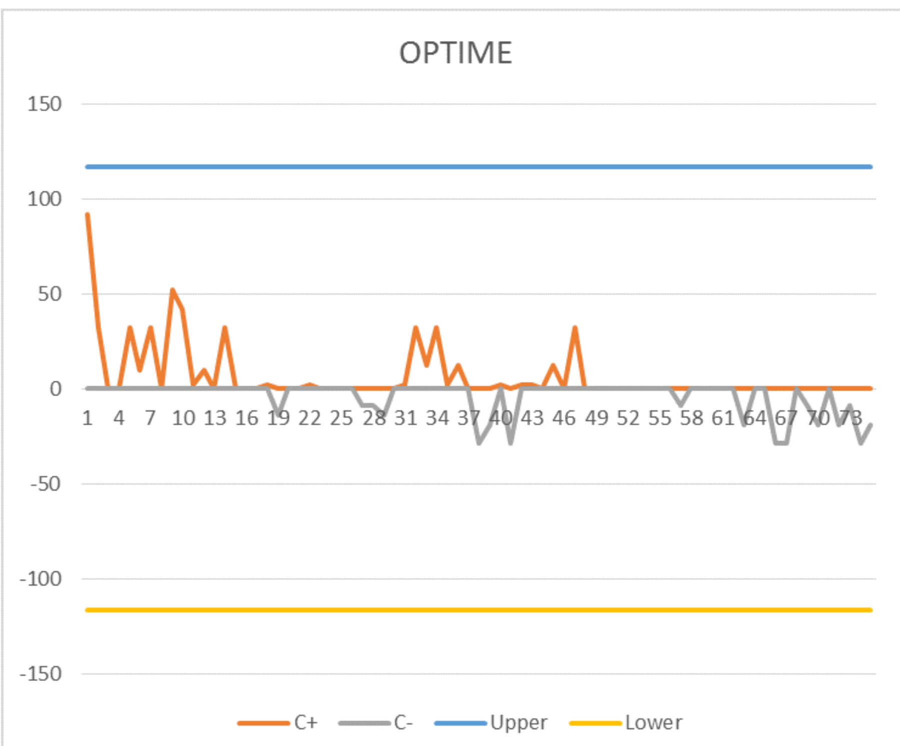

Figure 1. CUSUM charts for the total (TOT) and transanal op. time (OPT). d) OPT, surgeon A.

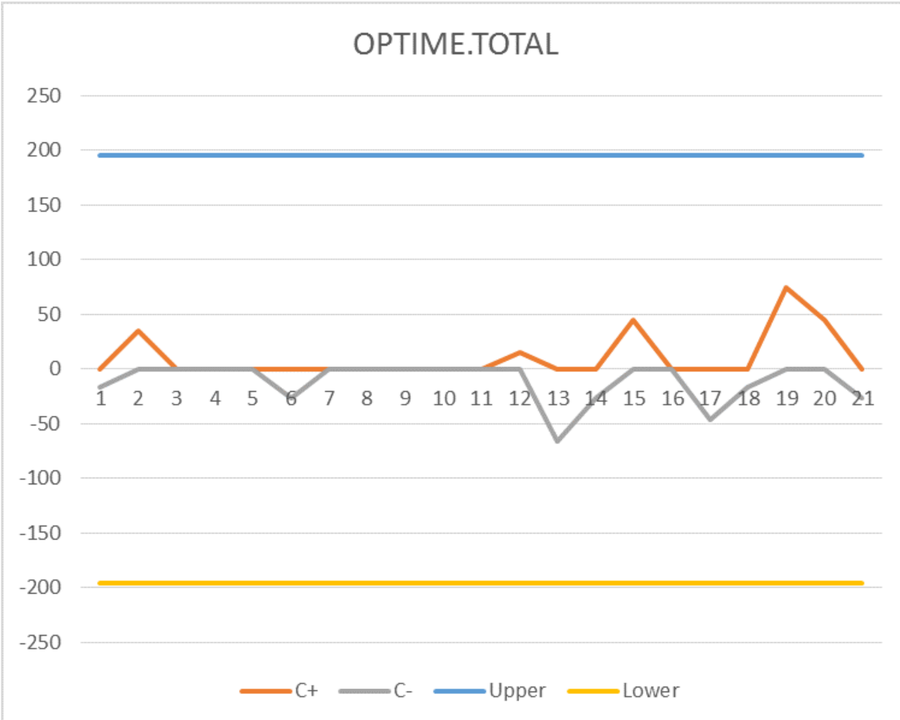

Figure 1. CUSUM charts for the total (TOT) and transanal operation time (OPT). e) TOT, surgeon B.

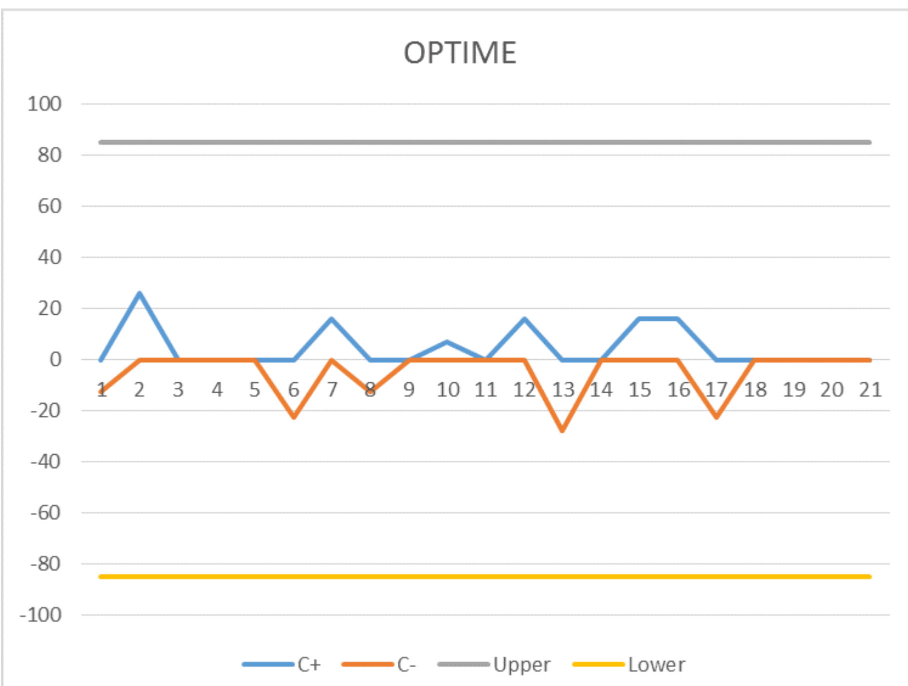

Figure 1. CUSUM charts for the total (TOT) and transanal operation time (OPT). f) OPT, surgeon B.

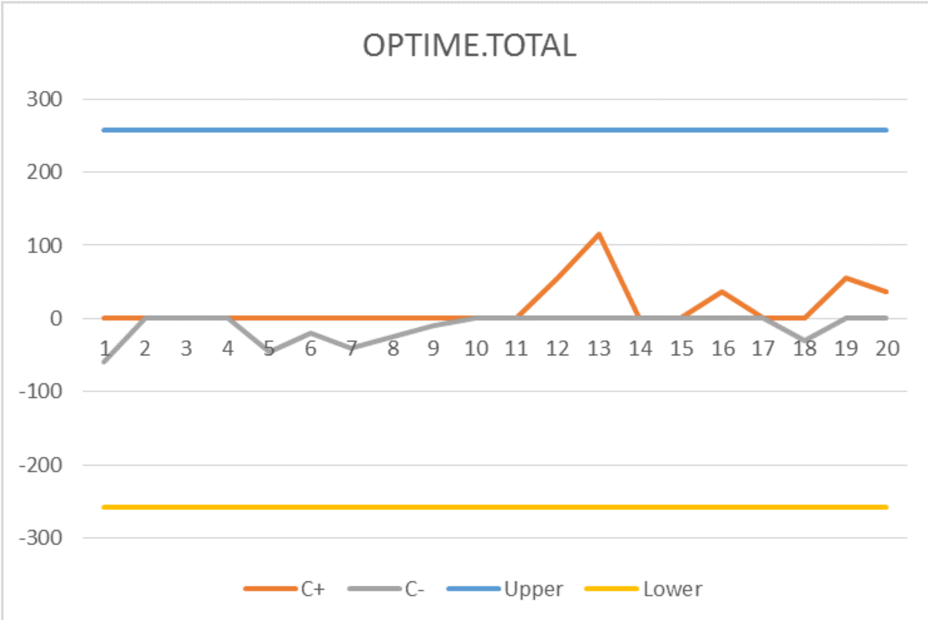

Figure 1. CUSUM charts for the total (TOT) and transanal operation time (OPT). g) TOT, surgeon C.

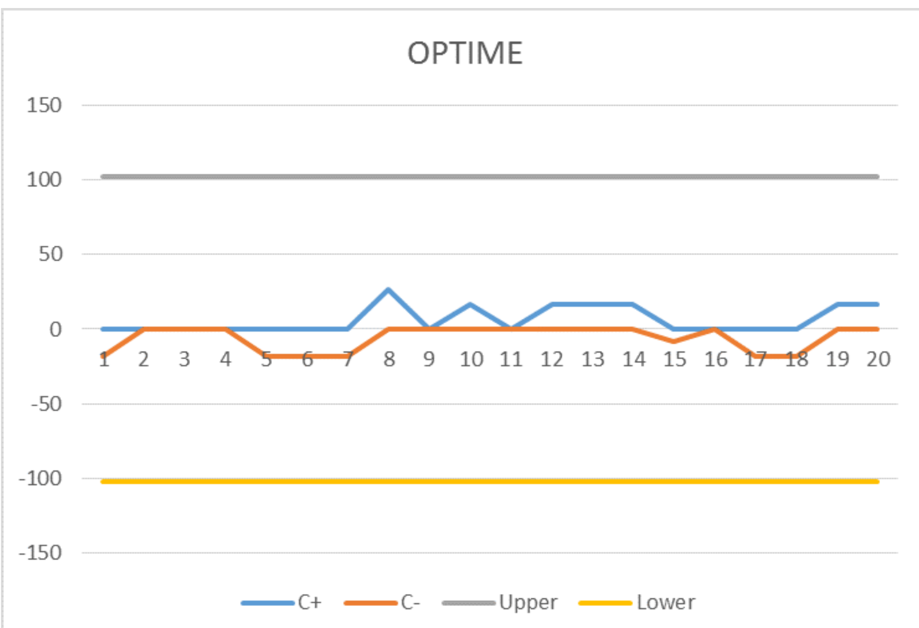

Figure 1. CUSUM charts for the total (TOT) and transanal operation time (OPT). h) OPT, surgeon C.

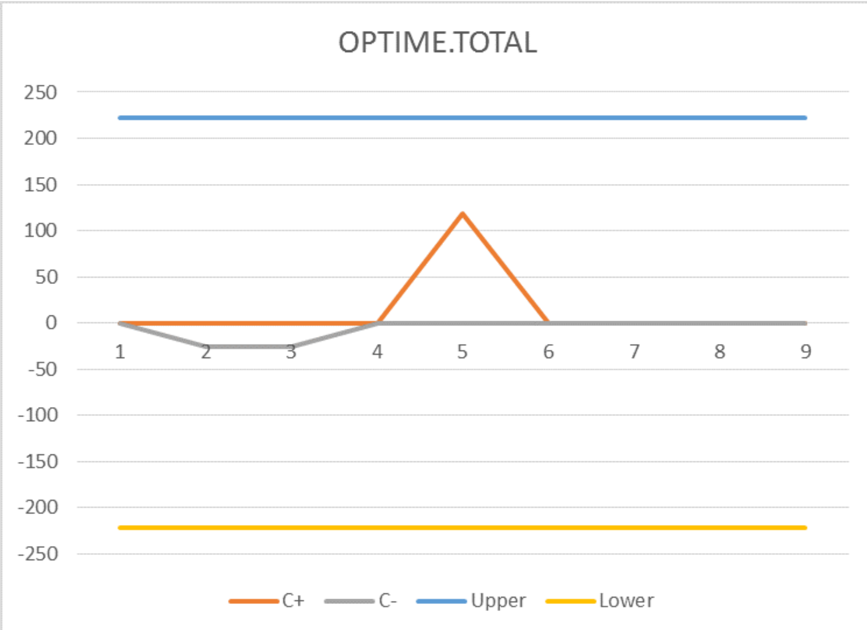

Figure 1. CUSUM charts for the total (TOT) and transanal operation time (OPT).
i) TOT, surgeon D.

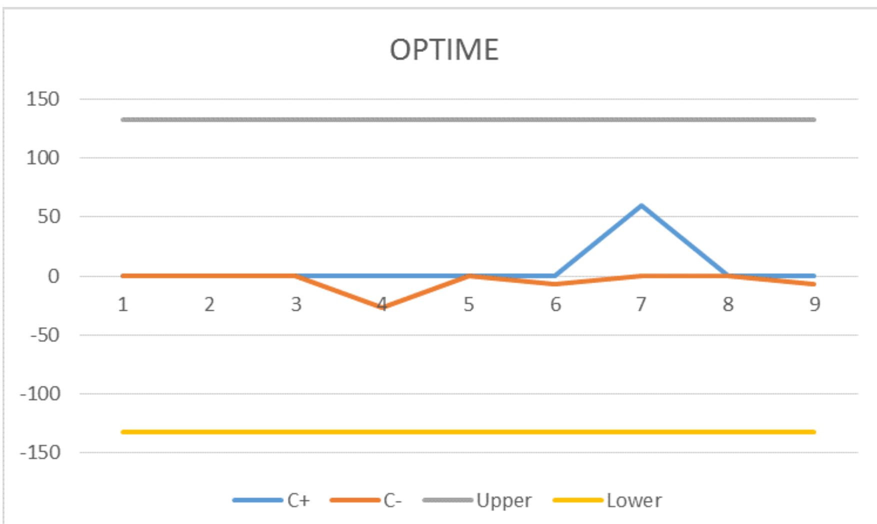

Figure 1. CUSUM charts for the total (TOT) and transanal operation time (OPT).
j)TOT, surgeon D.

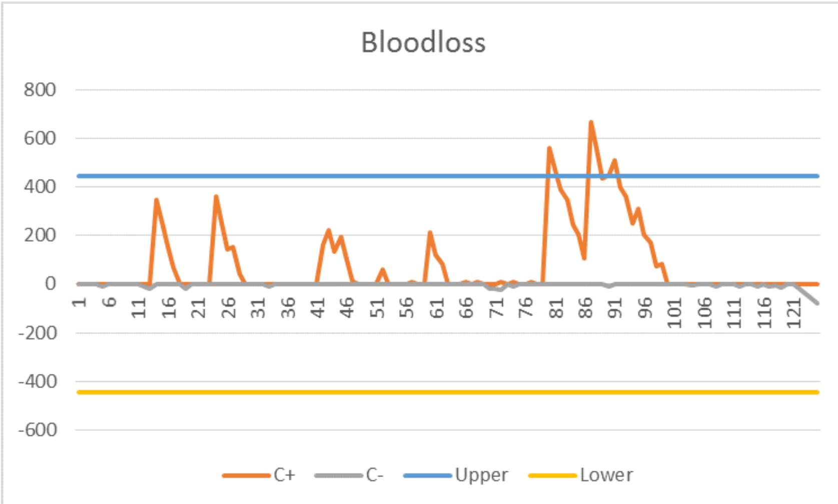

Figure 2. Estimated intraoperative blood loss. a) All patients

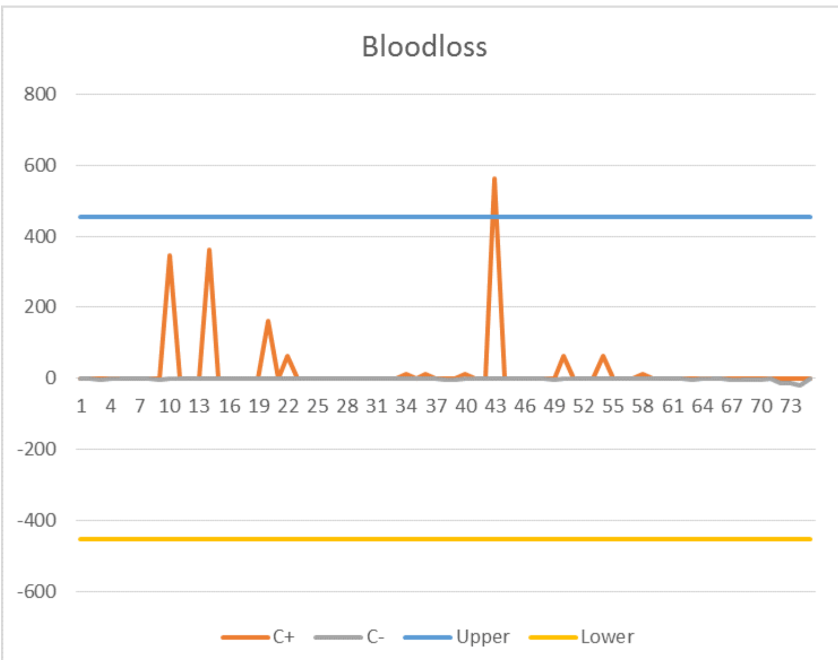

Figure 2. Estimated intraoperative blood loss. b) Surgeon A.

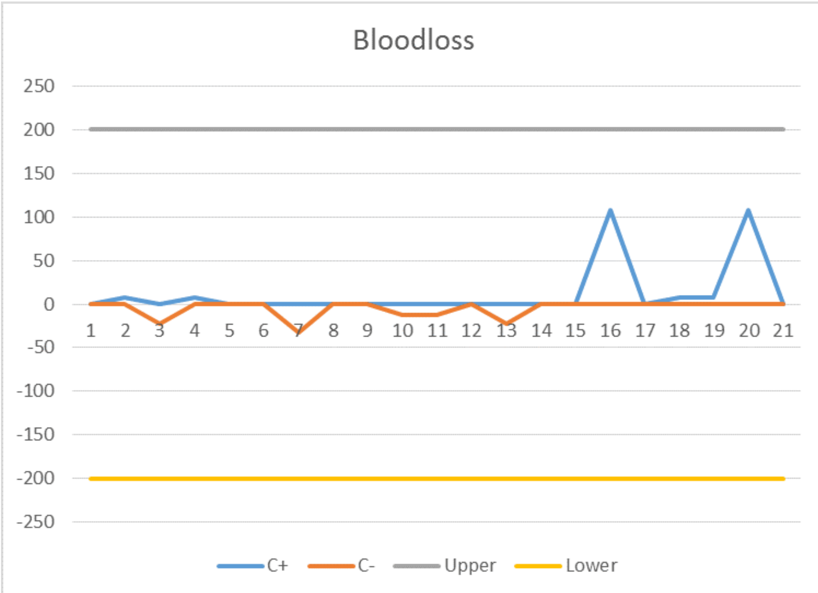

Figure 2. Estimated intraoperative blood loss. c) Surgeon B.

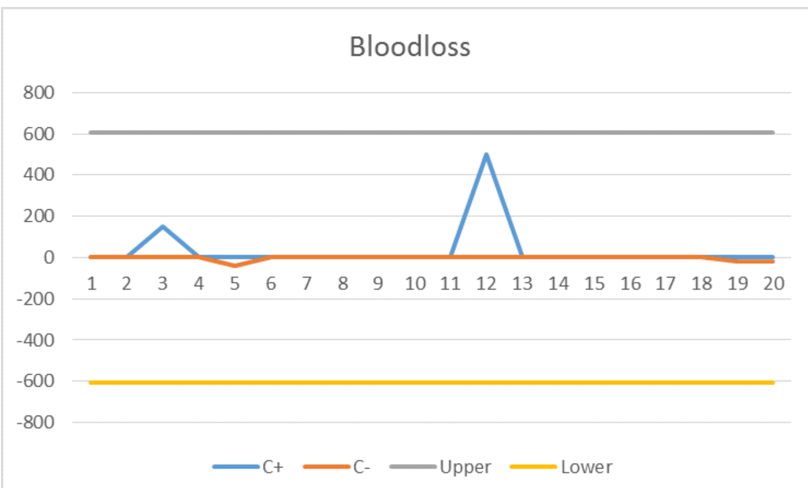

Figure 2. Estimated intraoperative blood loss. d) Surgeon C.

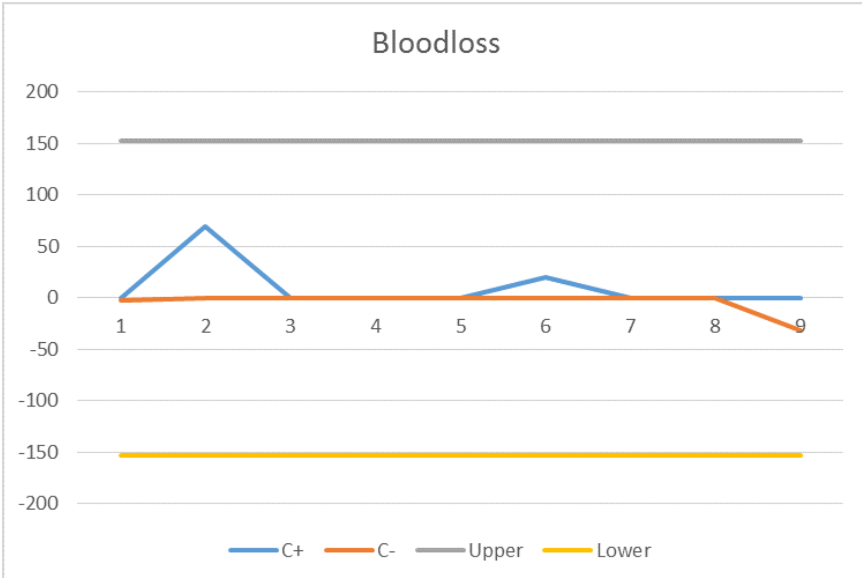

Figure 2. Estimated intraoperative blood loss. e) Surgeon D

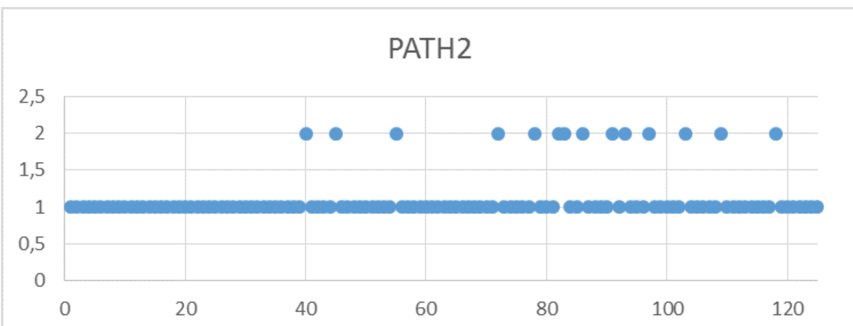

Figure 3. TME specimen quality. a) All patients.

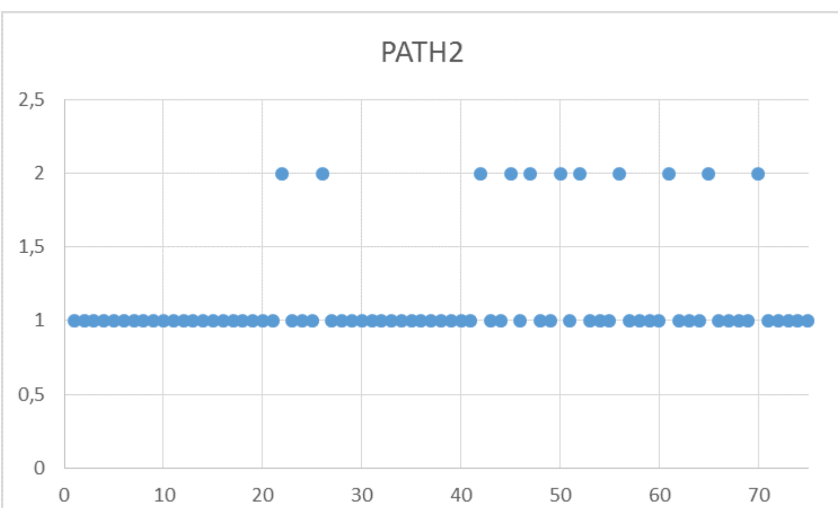

Figure 3. TME specimen quality. b) Surgeon A.

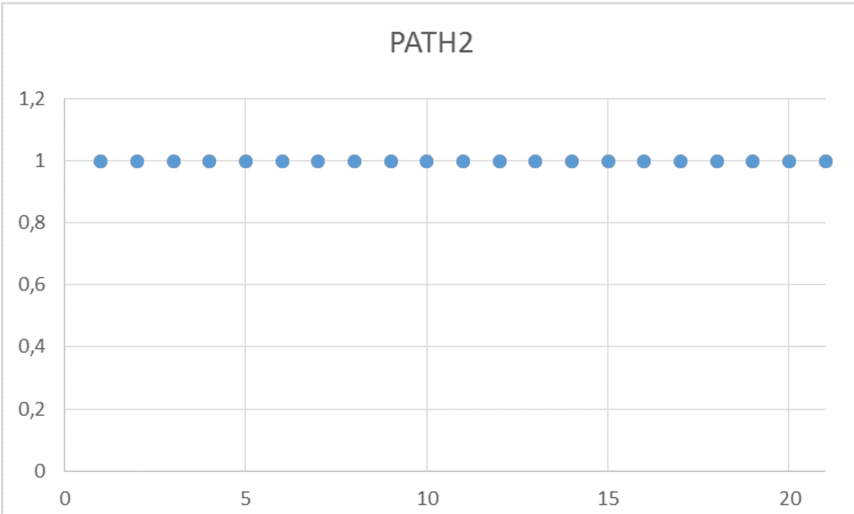

Figure 3. TME specimen quality. c) Surgeon B.

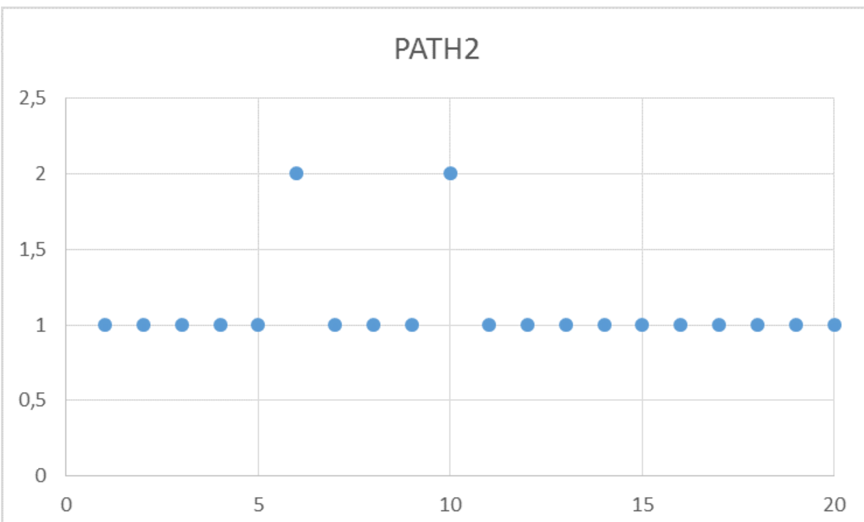

Figure 3. TME specimen quality. d) Surgeon C

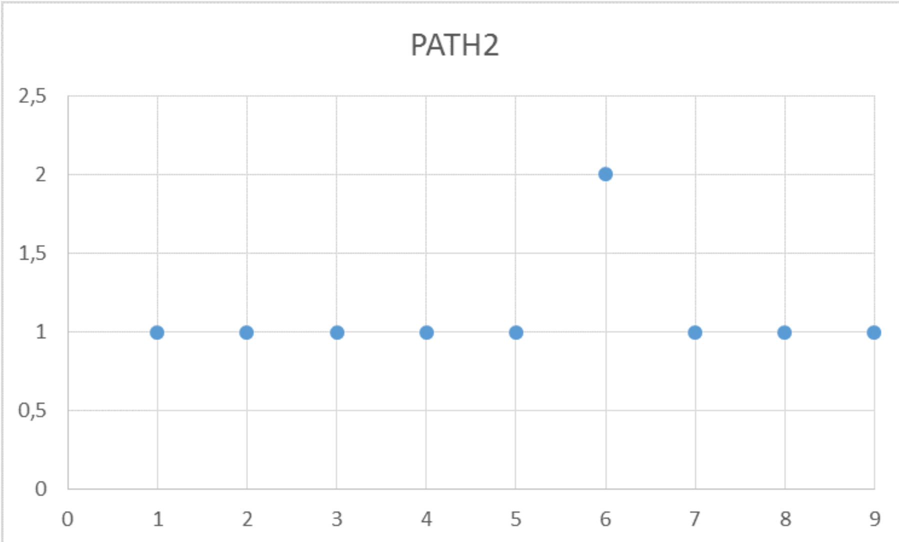

Figure 3. TME specimen quality. e) Surgeon D

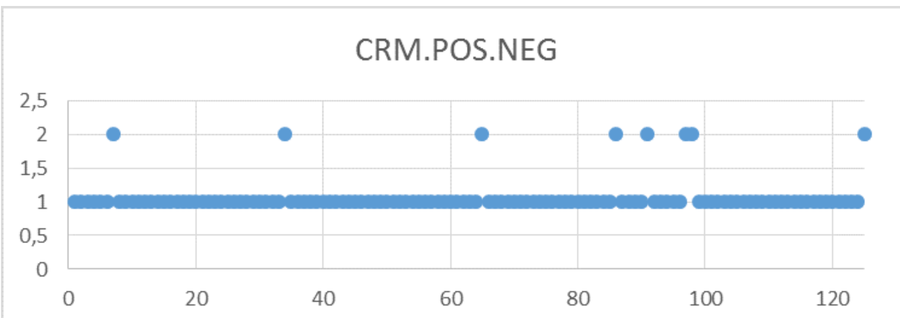

Figure 4. Circumferential resection margin. a) All patients.

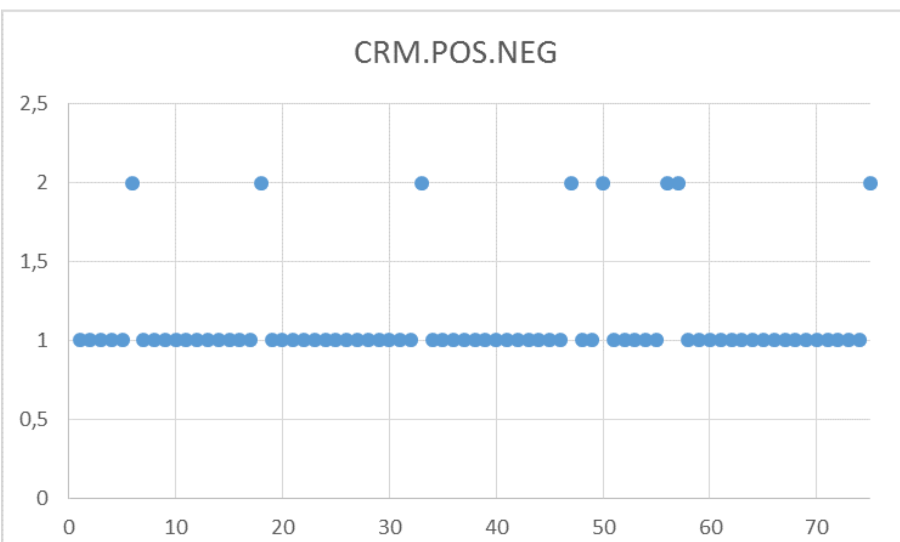

Figure 4. Circumferential resection margin. b) Surgeon A

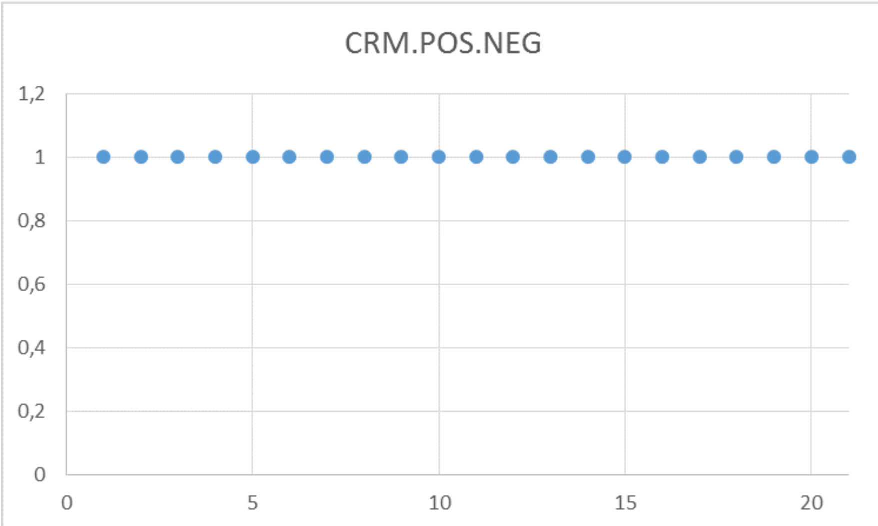

Figure 4. Circumferential resection margin. c) Surgeon B

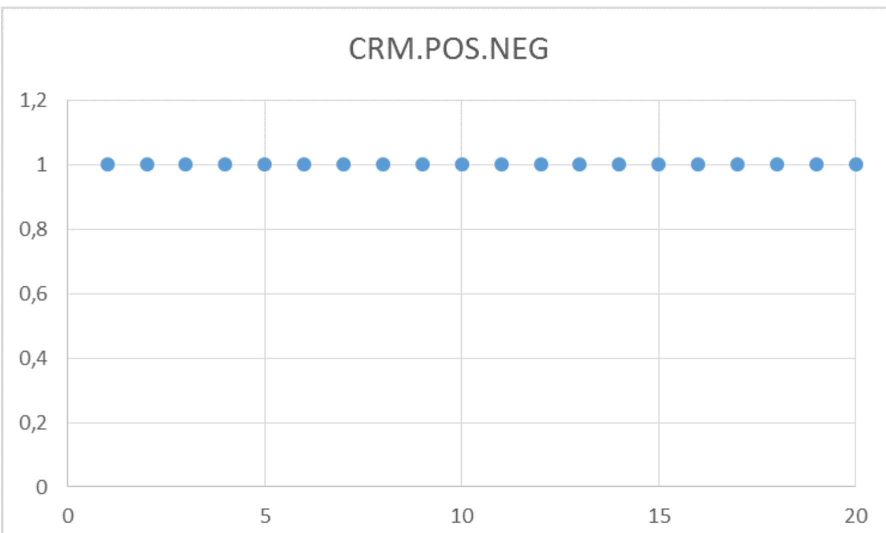

Figure 4. Circumferential resection margin. d) Surgeon C.

Figure 4. Circumferential resection margin. e) Surgeon D

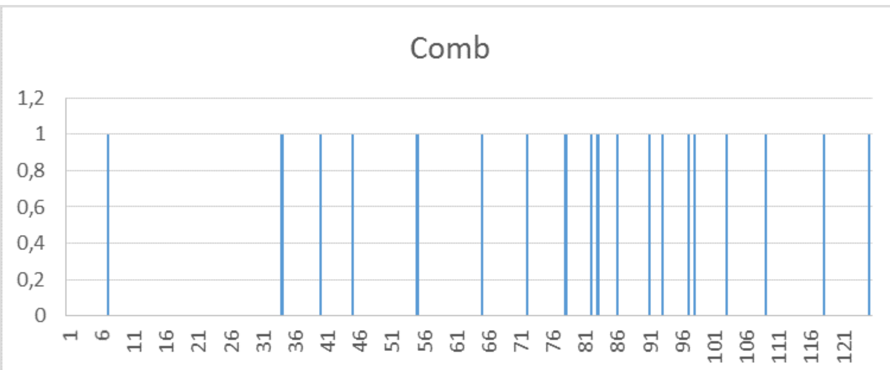

Figure 5. Composite outcome, All patients

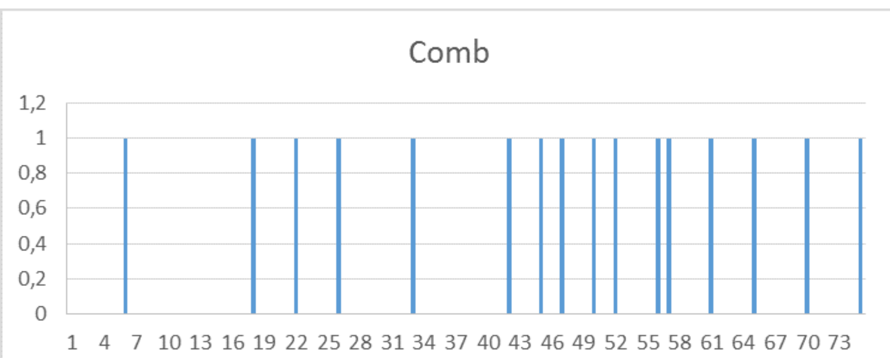

Figure 5. Composite outcome b) Surgeon A

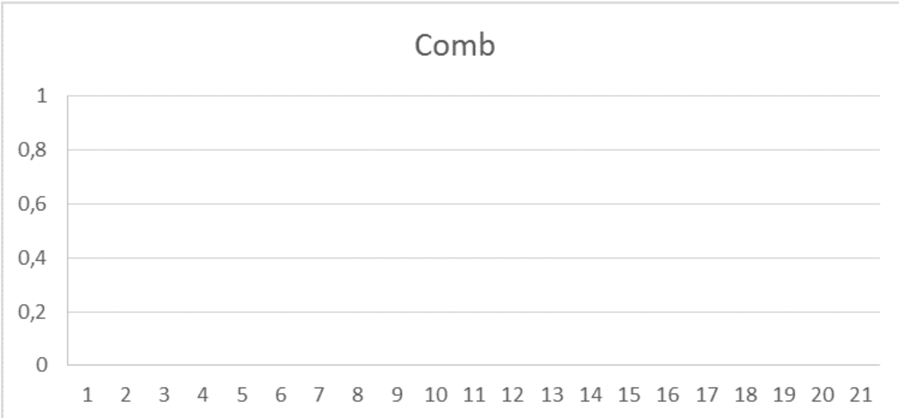

Figure 5. Composite outcome. c) Surgeon B

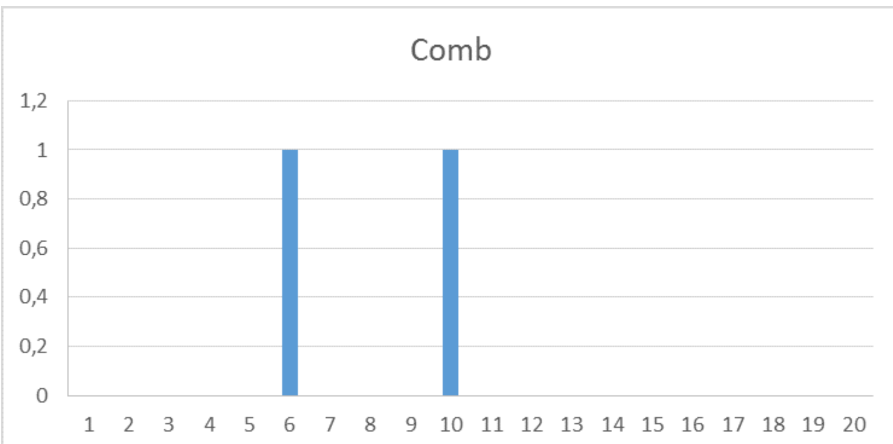

Figure 5. Composite outcome. d) Surgeon C.

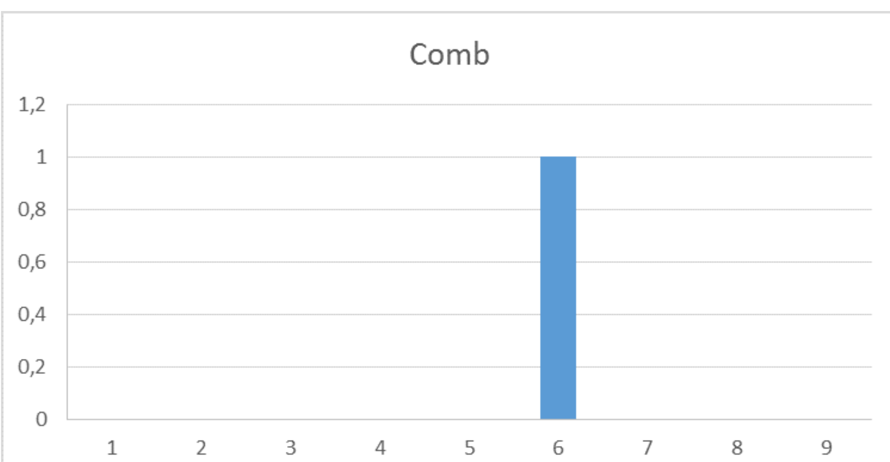

Figure 5. Composite outcome. e) Surgeon D

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Effect of transanal total mesorectal excision for rectal cancer: comparison of short-term outcomes with laparoscopic and open surgeries

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Abstract

Objective To compare short-term results of total mesorectal excision (TME) for mid and low rectal cancer, achieved by transanal (TaTME), laparoscopic (LaTME), and open (OpTME) approaches.

Background The impact of TaTME on the surgical treatment of mid and low rectal cancer has yet to be clarified.

Methods This is a case-matched study, based on data from a prospectively maintained database of patients who underwent TaTME from May 2015 to March 2017, and a retrospective chart review of patients who underwent LaTME and OpTME in the previous period. Each patient in the TaTME group was matched to one LaTME and one OpTME based on sex, BMI, tumor status, and the height of the tumor from the anal verge. Primary end-points were rates of positive circumferential resection margin (CRM), distal resection margin, and the macroscopic quality of the surgical specimen. Composite of these outcomes was compared as an indication for successful surgery. Secondary end-points included intraoperative data and postoperative course and complications.

Results Three hundred patients were included (TaTME = 100, LaTME = 100, OpTME = 100). The three groups were comparable in the baseline characteristics. TaTME resulted in lower rates of incomplete TME specimens than LaTME, but not OpTME ($P = 0.016$, $P = 0.750$, respectively). The rates of CRM involvement, mean CRM distance, and the percentages of successful surgery were comparable among the three groups ($P = 0.368$). The conversion to open surgery occurred only in the LaTME group. TaTME resulted in shorter operation time and less blood loss than the other two groups ($P < 0.001$ and $P < 0.001$). Hospital stay was shorter in the TaTME group ($P = 0.002$); complication rate and mortality were comparable among the groups.

Conclusions TaTME had, in our hands, some obvious benefits over other approaches. The pathological results were not significantly superior to LaTME and OpTME. The procedure is however feasible and safe. Further studies are needed to evaluate the long-term oncological and quality of life outcomes.

Keywords Rectal cancer surgery · Total mesorectal excision · Laparoscopy · TaTME

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While total mesorectal excision (TME) has improved the outcomes of rectal cancer surgery [1–3], the impact of minimally invasive surgery on treatment outcomes and the choice of the optimal approach to treat this common form of cancer needs to be clarified. Contradicting results have been found in different controlled randomized studies, comparing the outcomes after open vs. laparoscopic surgery [4–7]. While LaTME has apparent advantages in the form of shorter recovery, its impact on the pathological results is debatable. The main challenges facing LaTME are related to the dissection and bowel transection in the deeper part of the pelvis. Conversion rates during LaTME are still significantly high [4]. Even more concerning are the high rates of involved radial margins of the removed mesorectal specimens [8, 9], rendering rectal cancer surgery one of the most challenging procedures in colorectal surgery. The emergence of TaTME as an evolution to the standard laparoscopic approach could probably solve some of the technical challenges of LaTME

[10–12]. We aimed through this study to compare our own results after TaTME with those after LaTME and OpTME in the previous years. All three surgical procedures were routinely performed for all incomers with mid and low rectal cancer during the specific periods. To our knowledge, well-implemented rectal cancer surgery procedures at a large-volume colorectal center reflect the standard state of care in most colorectal units around the world.

Methods

We have implemented the TaTME procedure in our unit since 2013 and have published our early short-term results of the first 25 cases [13]. A prospective database is maintained to continuously audit results of all performed TaTME surgeries at Slagelse Hospital. The database has been approved by the Danish Data Protection Agency. The project was approved as a quality insurance project by the institutional board. Informed consent was obtained from all patients prior to surgery and data collection. For the purpose of this present analysis, we have chosen to include consecutive patients who underwent TaTME following our initial 25 cases. These initial cases were not included as these were during learning curve for TaTME, and to avoid repeat publication of the same cohort. Thus, we have included the further 100 cases of TaTME procedures who were operated from May 2015 to March 2017. These 100 patients were matched to patients who underwent LaTME and OpTME in the previous years, excluding patients who underwent LaTME already described in our previous publication [13]. Data from these patients were prospectively registered as part of the clinical quality surveillance, in the database of the Danish Colorectal Cancer Group (DCCG). Data collection to this national clinical database includes baseline demographic data, preoperative data, and limited information about the surgical procedures and the postoperative course [14]. Patients were included when TME was the operative principle, regardless of whether sphincter-saving procedure or resection and colostomy were planned. Exclusion criteria included extralevator abdominoperineal excision and standard abdominoperineal excision. Only patients with tumors 4–11 cm from the anal verge were included. Patients with T4 tumors were included if radical surgery was found to be achievable following preoperative neoadjuvant chemoradiation.

Thus, we matched 100 patients who underwent TaTME to 200 patients who underwent LaTME and OpTME, from a cohort of 384 patients (LaTME = 100, OpTME = 100). We have first analyzed the baseline characteristics between the whole cohort and patients who underwent TaTME, and found no significant difference. We then performed case matching using propensity score matching [15] based on the following criteria: sex, BMI, tumor status, and height of the tumor from the anal verge. Each patient in the TaTME group was matched to one patient who underwent LaTME and one who underwent OpTME (matching: TaTME: LaTME = 1:1, TaTME: OpTME = 1:1). The following data were collected from patient charts: operative data, postoperative course, and pathological data.

Our method of preoperative diagnostic work-up and details of the surgical steps for TaTME and LaTME procedures, as well as details about the postoperative care regime, are described in detail in our previous publication [13]. OpTME procedure is also well described in the literature [1–3]. Patients were offered the standard surgical care of the particular study period (open, laparoscopic, or transanal). Patients were offered TME surgery for tumors at or below 10 cm from the anal verge, and occasionally for tumors located higher up (11–12 cm from the anal verge). Patients with advanced T3 tumors (distance of < 5 mm from the deepest tumor invasion in the mesorectum to the mesorectal fascia and located 5–10 cm from the anal verge as well as all T3 tumors below 5 cm from the anal verge) and those with T4 tumors were treated with preoperative long-course neoadjuvant chemoradiation. The radiation dosage was 50.4 Gy, 28 fractions in combination with 5-fluorouracil or equivalent chemotherapy, according to the DCCG guidelines [16]. At approximately 6 weeks following the end of chemoradiation, new CT and MRI scans were obtained to reassess the tumor and to exclude metastatic disease. Surgery was performed 8–12 weeks after the completion of chemoradiation. Patients planned for sphincter-saving procedure received oral mechanical bowel preparation with Moviprep (Norgine Danmark A/S Stamholmen, 2650 Hvidovre, Denmark); otherwise, they received only enema preparation.

Histopathological examination of the specimens followed a standardized method as described by Quirke et al. [17, 18]. The quality of the removed TME specimen was graded as complete, nearly complete, or incomplete. The CRM, DRM, lymph node yield, and involvement were reported systematically. An involved CRM or DRM was defined as the distance of < 1 mm from the tumor to the inked surface of the fixed specimen or from the tumor to the distal cut edge of the tissue, respectively.

Primary end-points were the rates of involved CRM and DRM, as well as the quality of the removed TME specimen. In addition, we have calculated the surgical success based on a composite of the above outcomes as reported in the recent ACOSOG Z6051 randomized clinical trial [5]. Accordingly, we considered the TME surgery as successful when all of the following criteria were fulfilled: (1) clear CRM (defined as a distance ≥ 1 mm between the deepest extent of tumor invasion into the mesorectum and the inked surface on the fixed specimen); (2) clear DRM (defined as the distance ≥ 1 mm between the tumors to the distal cut edge of the tissue); and (3) a TME specimen quality graded as complete (the entire specimen is smooth with no defects) or nearly complete (minor defects accepted up to 5 mm, and minor conning accepted) as suggested by Quirke et al. [18].

Secondary end-points included intraoperative outcomes and postoperative course and complications. Operation time was defined as the time from the skin incision/insertion of the first laparoscopic port to the last stich for skin closure or stoma creation. For TaTME, this included the time spent to prepare for the transanal part of the procedure. Conversion was defined as any skin incision used to perform dissection in the LaTME or TaTME group, other than a Pfannenstiel incision to perform specimen extraction. Bowel perforation was defined as the perforation of the rectum during the dissection. The decision to plan for sphincter-saving surgery was always taken at the outpatient clinic, based on tumor height, sphincter function, and patient wish. Whether or not the planned anastomosis could be performed during the operation depended on the technical difficulties and intraoperative complications, for example major bleeding.

The postoperative complications were defined as any adverse event within 30 days after surgery. Complications were graded according to the classification system described by Dindo et al. [19]. Anastomotic leakage was defined as clinically suspected and radiologically proven, and in which active therapeutic intervention was performed. Urinary dysfunction was defined as the inability of spontaneous voiding at discharge. Stoma complication was defined as any complication related directly to the stoma itself (ileostomy or colostomy). Hospital stay was calculated from the day of the surgery to discharge. Enhanced recovery program was not the standard of postoperative care for patients in this study. Discharge from the hospital was considered when patients did not show signs of complications, tolerated oral diet, and when capable of independent stoma care or home-nurse help could be arranged.

Statistical analysis

The statistical analyses were performed using the software package SPSS version 24.0 (SPSS 24.0; SPSS Inc., Chicago, Illinois, USA). Data are presented as mean with standard deviation. Categorical variables were compared by Pearson's χ^2 test or Fisher's exact test when appropriate. Continuous variables were compared by Student's *t* test. Quantitative differences between the three groups were analyzed using one-way analysis of variance to perform multiple comparisons. Probability adjustments were performed by Bonferroni correction and two-sided Dunnett's test for the post hoc between-group comparisons, comparing each of the LaTME and OpTME groups to the TaTME group separately. A *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline patient and tumor characteristics are summarized in Table 1. No statistically significant differences were found among the three groups, regarding these characteristics. A larger number of patients in the LaTME group have received preoperative neoadjuvant chemoradiation, although the difference did not reach statistical significance. Tumor site ratio was comparable among the groups ($P=0.490$), as well as tumor (T) and metastasis (M) status ($P=0.096$ and $P=0.719$, respectively). Lymph node (N) status was significantly different among the groups ($P<0.001$). However, N status had no influence on the choice of the operative strategy or the choice of preoperative neoadjuvant chemoradiation according to our guidelines. A comparable number of patients have had a previous abdominal operation ($P=0.422$).

Pathological results

Pathological results are summarized in Table 2. Quality of the TME specimen in all 300 patients in this study was complete (64.7%) and nearly complete (18.3%) in 83% of cases. Multiple comparisons revealed a statistically significant difference among the groups ($P=0.041$). Paired group comparisons showed that the difference was significant only between the TaTME and LaTME groups. The TaTME group had the lowest rates of incomplete specimens (TaTME vs. LaTME, $P=0.016$; TaTME vs. OpTME, $P=0.082$; LaTME vs. OpTME, $P=0.750$). A larger number of patients in the LaTME group had involved CRM margins than the other two groups and the rates were the lowest in the TaTME group. However, differences did not reach statistical significance ($P=0.368$). Paired group comparisons were not significantly different either (TaTME vs. LaTME, $P=0.157$; TaTME vs. OpTME, $P=0.447$; LaTME vs. OpTME, $P=0.560$). The mean CRM distance was also comparable among the groups ($P=0.849$), likewise after paired comparisons (TaTME vs. LaTME, $P=0.906$; TaTME vs. OpTME, $P=0.849$; LaTME vs. OpTME, $P=0.992$). The DRM was involved in two patients (OpTME = 1; LaTME = 1). The mean DRM distance was longer in the OpTME group compared to the other two groups, although the difference did not reach statistical significance ($P=0.052$). Paired comparisons showed comparable results as well (TaTME vs. LaTME, $P=0.995$; TaTME vs. OpTME, $P=0.065$; LaTME vs. OpTME, $P=0.052$). Subgroup analysis of patients undergoing sphincter-saving surgery showed a significantly longer DRM distance in the OpTME group compared to the other two groups (TaTME vs. LaTME, $P=0.826$; TaTME vs. OpTME, $P<0.001$; LaTME vs. OpTME, $P=0.002$).

Table 1 Patient and tumor characteristics

	TaTME (100)	LaTME (100)	OpTME (100)	*P* value
Sex				0.864
Female	28	31	28	
Male	72	69	72	
Age, mean ± SD, year	67.33 ± 10.807	66.86 ± 10.733	68.19 ± 8.910	0.646
BMI, mean ± SD, kg/m^2	25.65 ± 3.924	25.43 ± 4.437	26.75 ± 4.833	0.074
ASA classification				0.086
ASA 1	41	36	29	
ASA 2	39	53	49	
ASA 3	20	11	22	
WHO performance status				0.879
0	71	68	74	
1	23	24	21	
2	6	8	5	
Previous abdominal surgery, no.	23	23	30	0.422
Tumor height, mean ± SD, cm	7.53 ± 1.972	7.83 ± 1.781	7,92 ± 1.779	0.296
Tumor height, cm				0.564
≤ 6 cm	35	28	31	
> 6 cm	65	72	69	
Tumor site				0.490
Circumferential	40	47	52	
Anterior	18	12	13	
Posterior	14	19	11	
Right	16	14	11	
Left	12	8	13	
TNM classification				0.096
T				
T2	56	45	37	
T3	43	53	62	
T4	1	2	1	
N				< 0.001
N0	81	34	27	
N1	8	23	26	
N2	11	43	47	
M				0.719
M0	94	91	92	
M1	6	9	8	
Preoperative chemoradiation	18	27	21	0.470
Planned surgical procedure				0.021 (TaTME vs. LaTME, *P* = 0.067; TaTME vs. OpTME, *P* = 0.008; LaTME vs. OpTME, *P* = 0.397)
LAR	63	75	80	
APE or Hartmann	37	25	20	

LAR low anterior resection, *APE* abdominoperineal excision

Overall surgical success, based on a composite of negative CRM and DRM plus complete or nearly complete TME specimen, was comparable among the groups ($P = 0.174$). The highest percentage of surgical success was achieved in the TaTME group and the lowest percentage in the LaTME group (TaTME = 82%; LaTME = 71%; OpTME = 78%).

The difference in the number of retrieved lymph nodes was statistically significant among the groups ($P = 0.003$). A fewer number of lymph nodes were retrieved in the OpTME than the other two groups (TaTME vs. LaTME, $P = 0.889$; TaTME vs. OpTME, $P = 0.003$; LaTME vs. OpTME, $P = 0.018$). Pathological T status was significantly different among the groups ($P = 0.004$). Paired analysis showed a

Table 2 Pathological results

	TaTME (100)	LaTME (100)	OpTME (100)	*P* value
Specimen quality, no.				0.041 (TaTME vs. LaTME, $P=0.016$; TaTME vs. OpTME, $P=0.082$; LaTME vs. OpTME, $P=0.750$)
Complete	58	68	68	
Nearly complete	28	12	15	
Incomplete	14	20	17	
CRM involvement	7	13	10	0.368 (TaTME vs. LaTME, $P=0.157$; TaTME vs. OpTME, $P=0.447$; LaTME vs. OpTME, $P=0.560$)
DRM involvement	0	1	1	0.604
CRM, mean ± SD, mm	8.99 ± 7.21	9.44 ± 7.86	9.57 ± 7.49	0.849
DRM, mean ± SD, mm	25.18 ± 14.34	24.95 ± 16.18	30.83 ± 21.91	0.052 (TaTME vs. LaTME, $P=0.995$; TaTME vs. OpTME, $P=0.065$; LaTME vs. OpTME, $P=0.052$)
DRM for LAR subgroup, mean ± SD, mm	22.22 ± 12.73	24.08 ± 15.136	34.76 ± 23.577	< 0.001 (TaTME vs. LaTME, $P=0.826$; TaTME vs. OpTME, $P<0.001$; LaTME vs. OpTME, $P=0.002$)
Successful resection, no.	82	71	78	0.174
Retrieved LNs, mean ± SD, no.	22.32 ± 8.94	21.75 ± 10.98	17.92 ± 9.29	0.003 (TaTME vs. LaTME, $P=0.889$; TaTME vs. OpTME, $P=0.003$; LaTME vs. OpTME, $P=0.018$)
Number of positive LNs, mean ± SD	1.23 ± 2.78	1.46 ± 3.33	2.22 ± 4.57	0.134
Tumor status				0.004 (TaTME vs. LaTME, $P=0.355$; TaTME vs. OpTME, $P=0.004$; LaTME vs. OpTME, $P=0.298$)
T0[a]	4	4	3	
T1	8	2	2	
T2	36	33	19	
T3	48	54	67	
T4	4	7	9	
Lymph node status				0.213
N0	69	67	57	
N1	19	20	26	
N2	12	13	17	

CRM circumferential resection margin, *DRM* distal resection margin, *LAR* low anterior resection, *LNs* lymph nodes

[a]Either complete pathological response or no tumor found after salvage surgery

significant difference only in the OpTME group compared to the TaTME group (TaTME vs. LaTME, $P=0.355$; TaTME vs. OpTME, $P=0.004$; LaTME vs. OpTME, $P=0.298$). A larger number of T3 tumors were found in the OpTME group. Pathological lymph node status was comparable among the groups ($P=0.213$).

Intraoperative results

Intraoperative outcomes are summarized in Table 3. The number of sphincter-saving procedures was comparable among the groups ($P=0.876$). However, the number of planned anastomoses was higher in the OpTME group than in the TaTME group, and the difference was statistically significant ($P=0.008$), as shown in Table 1. A number of APE procedures in the LaTME and OpTME groups were rescue procedures at the rates of 0, 9, and 14% in the TaTME, LaTME, and OpTME groups, respectively. The method of performing the anastomosis was significantly different among the groups ($P=0.044$), with higher rates of side-end anastomosis observed in the OpTME group (TaTME vs. LaTME, $P=0.890$; TaTME vs. OpTME, $P=0.022$; LaTME vs. OpTME, $P=0.015$).

The number of procedures that required mobilization of the splenic flexure of the colon was comparable among the groups ($P=0.106$). Intraoperative blood loss was significantly larger in the OpTME group than the other two groups, and was least in the TaTME group (TaTME vs. LaTME, $P=0.014$; TaTME vs. OpTME, $P<0.001$; LaTME vs. OpTME, $P<0.001$). None of the TaTME procedures were converted to open surgery, while 11 patients in the LaTME group underwent conversion ($P<0.001$), and the reason for conversion was mentioned to be difficult dissection in the lower pelvis. The operation time differed among the groups, and the difference was statistically significant ($P<0.001$), with TaTME being the fastest. The difference was not

Table 3 Intraoperative results

	TaTME (100)	LaTME (100)	OpTME (100)	*P* value
The performed procedure				0.876
LAR	63	66	66	
Intersphincteric APE	37	34	34	
Anastomotic method, no. (%)				0.044 (TaTME vs. LaTME, $P=0.890$; TaTME vs. OpTME, $P=0.022$; LaTME vs. OpTME, $P=0.015$)
Side-end	54 (85.7)	56 (84.8)	64 (97.0)	
End-end	9 (14.3)	10 (15.2)	2 (3.0)	
Splenic flexure mobilization	29	17	27	0.106
Splenic flexure mobilization in LAR, no.	24	17	26	0.192
Blood loss, mean ± SD, ml	82.10 ± 108.20	238.87 ± 355.15	704.50 ± 561.95	< 0.001
Conversion to open procedure	0	11		< 0.001
Intraoperative complications				0.693
Total, no.	13	12	16	
Bowel perforation	2	10	8	
Bleeding	8	2	6	
Urethral injury	1			
Urinary bladder injury	2		1	
Splenic injury			1	
Bowel perforation, tumors ≤ 6 cm from the anal verge, no.	1	3	4	0.304
Operation time, mean ± SD, min	284.99 ± 67.25	334.30 ± 84.31	325.25 ± 60.02	< 0.001

APE abdominoperineal excision, *LAR* low anterior resection

statistically significant between the LaTME and OpTME groups (TaTME vs. LaTME, $P<0.001$; TaTME vs. OpTME, $P<0.001$; LaTME vs. OpTME, $P=1.000$).

Intraoperative complications occurred in 41 patients (13.7%), and the rates of significant complications did not differ significantly among the groups ($P=0.693$). A larger number of intraoperative bowel perforations occurred in the LaTME and OpTME groups, though the difference of perforation rate did not reach statistical significance ($P=0.062$). Perforation rates in patients with tumors ≤ 6 cm from the anal verge were also comparable ($P=0.304$). Urethral injury, which is probably the only TaTME-specific complication, occurred in one patient (1%).

Postoperative course and complications

The postoperative outcomes are listed in Table 4. Complications are graded according to the Clavien–Dindo classification [19].The difference in 30-day mortality was not statistically significant among the three groups ($P=0.407$). The rate of anastomotic leakage was the highest in the OpTME group and the lowest in the TaTME group ($P=0.051$). The difference reached statistical significance when the TaTME group was compared to the OpTME group (TaTME vs. LaTME, $P=0.231$; TaTME vs. OpTME, $P=0.016$; LaTME vs. OpTME, $P=0.201$). Anastomotic leakages that necessitated colostomy occurred in two patients in the TaTME group (3.2%). This was lower than the leakage rates in the other two groups [three patients in the LaTME group (4.5%) and four patients in the OpTME group (6.0%)]. Groups were comparable regarding this outcome ($P=0.737$). A larger number of patients in the LaTME group suffered from urinary dysfunction, though the difference between the three groups was not statistically significant ($P=0.179$). Groups were comparable regarding the rates of stoma complications, postoperative bowel obstruction, and wound infection ($P=0.709$, $P=0.063$, and $P=0.244$, respectively). Hospital stay was the longest in the OpTME group and the shortest in the TaTME group, and the difference was statistically significant ($P=0.002$). Between-group comparisons showed a statistically significantly shorter hospital stay in the TaTME group when compared with the other two groups. The difference was not significant between the LaTME and OpTME groups (TaTME vs. LaTME, $P=0.002$; TaTME vs. OpTME, $P<0.001$; LaTME vs. OpTME, $P=0.719$). Readmission rate was significantly higher in the LaTME group ($P=0.049$), and paired comparisons showed a significant difference only between the LaTME and TaTME groups (TaTME vs. LaTME, $P=0.044$; TaTME vs. OpTME, $P=0.879$; LaTME vs. OpTME, $P=0.484$). Causes for readmission related in all groups mainly to postoperative complications and in some cases to dehydration due to high stoma production. Postoperative mortality did not differ among the groups and deaths were not related to surgery.

Table 4 Postoperative course and complications

	TaTME (100)	LaTME (100)	OpTME (100)	*P* value
Anastomotic leakage, no./no. of anastomoses (%)	6/63 (9.5)	11/66 (16.7)	17/66 (25.8)	0.051 (TaTME vs. LaTME, $P = 0.231$; TaTME vs. OpTME, $P = 0.016$; LaTME vs. OpTME, $P = 0.201$)
Grade 3a	4	8	8	
Grade 3b	2	2	7	
Grade 4a		1	2	
Urinary dysfunction on discharge, no.	19	27	22	0.179 (TaTME vs. LaTME, $P = 0.179$; TaTME vs. OpTME, $P = 0.517$; LaTME vs. OpTME, $P = 0.446$)
Stoma complications				0.709
Total no.	4	2	3	
Grade 1				
Grade 2	2	1		
Grade 3a	2			
Grade 3b		1	3	
Mechanical bowel obstruction				0.063
Total no.	1	8	5	
Grade 2		1	1	
Grade 3b		7	4	
Grade 4a	1			
Wound infection				0.244
Total no.	6	13	10	
Grade 1	2	4	2	
Grade 2	1	4	2	
Grade 3a	3	2		
Grade 3b		3	6	
Hospital stay, mean ± SD, days	8.63 ± 6.20	14.23 ± 15.67	15.51 ± 11.14	0.002 (TaTME vs. LaTME, $P < 0.001$; TaTME vs. OpTME, $P < 0.001$; LaTME vs. OpTME, $P = 0.719$)
Readmission, no.	14	28	20	0.049 (TaTME vs. LaTME, $P = 0.044$; TaTME vs. OpTME, $P = 0.879$; LaTME vs. OpTME, $P = 0.484$)
30-days mortality, no.	2	4	2	0.407

Discussion

Results of the present case-matched comparative study of three surgical procedures for the treatment of mid and low rectal cancer suggest that TaTME has some advantages. The procedure showed some superiority over LaTME and OpTME in terms of favorable specimen quality and lower rates of involved resection margins, and provided a higher rate of successful TME surgery. Furthermore, TaTME offered the highest chance of performing anastomosis when this was planned and it abolished the need for conversion to open surgery, without increasing rates of overall intraoperative complications. Despite being performed as one-team approach, the mean operation time was shorter for TaTME and the procedure resulted in comparable rates of postoperative complications and significantly shorter duration of hospital stay.

Although this study was not randomized, it represents experience from a large-volume colorectal center where TaTME is standardized. Dedicated, highly skilled, experienced, and certified colorectal surgeons performed the surgeries. The risk of selection bias was minimized through a case-matched study design. The risk of surgeon's preference for a particular procedure was eliminated in our study, as all three procedures were performed in periods where the particular type of surgery was the standard of care. At our unit, TME surgery for rectal cancer was adopted in the last two decades, and was performed as OpTME, followed by the gradual adoption of LaTME around the year 2005. TaTME is also well implemented at this time, and all the new comers with mid and low rectal cancer undergo TaTME if the tumor is assessed to be surgically removable. We have published our initial results of 25 cases [13]. The quality of data collection for this analysis was satisfactory, as most were collected prospectively in the form of a maintained database of patients undergoing TaTME, and the prospectively reported data to the clinical database of the DCCG. Intraoperative and postoperative outcomes, as well as pathological outcomes were collected from the review of electronic patient charts.

In this study, we have focused on the surrogates of the oncological quality, in the form of involved CRM and DRM, as well as the macroscopic quality of the TME specimen. The pathologist's assessment of these parameters is well standardized and its outcomes are a direct result of the quality of surgery. Poor pathological outcomes are associated with higher chances of local recurrence and metastatic disease [18]. We have calculated the percentage of successful surgery, based on a novel composite measure [5], to allow some form of comparison with the available literature. We have chosen to include "nearly complete" specimen quality combined with "complete specimen," as suggested by Fleshman et al. [5]. In another randomized trial that compared laparoscopic rectal cancer surgery with open surgery by Stevenson et al. [6] with a similar protocol, the composite outcome did not count "nearly complete" specimen as surgical success. Both randomized trials have concluded that laparoscopic surgery for rectal cancer failed to meet the "non-inferiority" criterion for successful resection, compared to open approach. Thus, the routine use of laparoscopy to treat rectal cancer could not be recommended based on results from these two recent randomized clinical non-inferiority trials. In both trials, the quality of surgery was rather satisfactory. The successful surgery was, in one study [5], accomplished in 81.7 and 86.9% of patients in the laparoscopic and open resection groups, and in the second trial [6] 82 and 89% in the laparoscopic and open resection groups, respectively. In the present study, TaTME resulted in a higher percentage of successful TME surgery, although the difference was not statistically significant. However, the quality of surgery in our study was not as high as in the above trials. A significantly lower percentage of TME specimens were incomplete in the TaTME group than in the LaTME and OpTME groups, although a higher percentage of TME specimens were nearly complete. Our results are in accordance with findings from several randomized trials, which have shown comparable rates of specimen incompleteness between laparoscopic and open surgeries [5–7, 20]. According to a study by Bulow et al. [21], CRM involvement was found in 18% of patients treated for low rectal cancer. The study was based on the DCCG database. We found lower rates of CRM involvement in the TaTME group, though the difference did not reach statistical significance. Several randomized trials have shown that laparoscopic and open surgeries for rectal cancer had similar rates of involved margins [4–7, 22, 23]. Compared to laparoscopic surgery, results of these two parameters (specimen quality and involved margins rates) have been shown to be comparable in some initial series [13, 24–27]. In the present study, rates of TME completeness were lower than those reported in the literature after TaTME. One explanation could be related to the standard method of transanal specimen extraction in our unit, which could result in minor defects rendering TME specimens "nearly complete," The 7% rate of involved CRM is also higher than the rates of involved margins reported after TaTME, including our own initial experience [13, 28]. The rate of CRM involvement in our present study is however comparable to that of laparoscopic surgery, reported in the literature [5, 6, 28].

One important advantage of TaTME is the precise selection of the distal margin, which is reflected in this study. The DRM was free in all patients in the TaTME group, while one patient in each of the other two groups had involved DRM. Another potential advantage is related directly to the ability to dissect in the deep pelvis. This can explain the absence of rescue APE procedures in the TaTME group in our study, while a significant number of patients in the other two groups had rescue APEs.

The shorter operation time in the TaTME group is in accordance with our own previous publication [13]. In earlier studies, the shorter operation time correlated with TaTME was a direct consequence of the two-team operation technique consisting of a simultaneous laparoscopic and transanal dissection (push me-pull you principle), which has the advantage of being efficient and quick. The improved operation time reflects probably the increasing expertise of the colorectal surgeons in our unit during the last few years. In our study, none of the TaTME procedures were converted to open surgery, while 11 patients in the LaTME group underwent conversion. This significant difference substantiates the theory of TaTME easing the technical difficulties in the dissection in the narrow pelvis. Rates of intraoperative complications were comparable among the groups. However, serious complications like urethral injury call for caution when TaTME is adopted. We had one case of urethral injury during the transanal part of a TaTME procedure. The complication occurred in a male patient with an advanced low rectal cancer. The patient was treated by preoperative neoadjuvant chemoradiation. Urethral injury is reported in the literature during the early years of TaTME adoption [29]. Bowel perforation rate was lower in the TaTME group. One reason could be the difficulty in dissection and instrumentation during the last part of the procedure in the LaTME and OpTME approaches. While this difficult part is performed from below in TaTME, this ensures probably a better view that improves the dissection technique. Intraoperative perforation rate in low rectal cancer surgery was reported to be 10% in a Danish study based on DCCG data [30].

Anastomotic leakage is a serious complication and occurred in rates of up to 26.7% after rectal cancer surgery, according to the latest annual report of the DCCG [31] and

12% according to a study based on DCCG database [14]. Compared to reports in the literature, anastomotic leakage rate in the TaTME in this study can be considered acceptable [32]. Leakage rates are however higher than those reported in the most recent studies that include laparoscopic and open approaches [5, 6]. One explanation for the falling leakage rates in our unit could be the improved anastomotic technique itself in TaTME procedure. We did not study the sexual and urinary functions systematically. However, urinary function based on whether patients were discharged with catheter or not was comparable among the groups.

Limitations of our study are mainly related to non-randomization and the retrospective data collection for some variables in the control groups. With the OpTME as the procedure considered the gold standard that improved the quality of rectal cancer surgery [1–3], pathological outcomes of minimally invasive surgery should be evaluated against OpTME. Indeed, minimally invasive colorectal surgery has proven short-term benefits in terms of earlier recovery and long-term benefits in terms of lower hernia and adhesion formation; hence, the shift towards OpTME does not seem to be an option. Furthermore, short-term benefits and pathological outcomes have been shown to be similar to OpTME [4]. However, rectal cancer surgery is challenging, especially the lowermost part of the pelvis where, despite improved visualization in laparoscopic surgery, colorectal surgeons still encounter difficulties due to the use of rigid instruments with limited ability to maneuver and perform precise dissection and bowel transection. Robotic surgery could solve some of these problems and the evidence supporting its safety and feasibility in rectal cancer surgery is growing, with proven lower conversion rates and similar pathological results to laparoscopic rectal cancer surgery [33, 34]. Results of the clinical randomized trial Robotic OR Laparoscopic Anterior Rectal Resection (ROLARR) [35] are to be awaited. TaTME emergence in the last few years can probably solve some of the problems encountered during standard laparoscopy [10]. The publication list is growing and the results show consistently favorable short-term results, though full implementation of TaTME needs caution due to possibly higher morbidity during the initial phase of adoption [12, 28, 36, 37]. Although designed as a non-inferiority trial, the ongoing COLOR III [38] comparing TaTME to LaTME is expected to provide the evaluation of the new approach to rectal cancer. While the results of these trials evaluating transanal and robotic approaches are awaited, we believe that our study provides evidence from the daily clinical practice.

Conclusion

In conclusion, some of the limitations of laparoscopic rectal cancer surgery seem to be overcome through the adoption of the transanal approach. TaTME had, in our hands, some obvious benefits over other approaches in terms of the operation time, blood loss, and higher rates of sphincter-saving procedures. However, the pathological results were not significantly superior to LaTME and OpTME. The procedure is, however, feasible and safe. Further studies are needed to evaluate the quality of life, genitourinary function, fecal incontinence, and the evaluation of low anterior resection syndrome in patients undergoing TaTME. In addition, research-based modifications of the instrumentation used in TaTME are warranted to reduce pitfalls and complications.

Compliance with ethical standards

Conflicts of interest Drs. Sharaf Karim Perdawood, Benjamin Sejr Thinggaard, and Maya Xania Bjoern have no conflicts of interest or financial ties to disclose.

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A nationwide comparison of short-term outcomes after transanal, open, laparoscopic, and robot assisted Total Mesorectal Excision

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ABSTRACT

Background Laparoscopic rectal cancer surgery has several limitations. The Transanal Total Mesorectal Excision (TaTME) can potentially overcome these limitations.

Objective To compare the pathological and short-term outcomes after TaTME, open TME (OpTME), laparoscopic TME (LaTME), and robotic TME (RoTME) procedures in a nationwide cohort.

Method We extracted the demographic, perioperative, and pathological data of patients who underwent a curative OpTME, LaTME, RoTME, or TaTME procedure between January 2014 and December 2018 from the national database of the Danish Colorectal Cancer Group (DCCG). We have conducted multiple group-comparisons and uni- and multivariate analyses to determine the factors associated with non-radical surgery and anastomotic leakage.

Results We included 2,393 patients (OpTME=205, LaTME=1163, RoTME=713, and TaTME=312). The rate of non-radical surgery was 5.7% after TaTME. The lowest rate of non-radical surgery was achieved after RoTME compared to the other procedures (8.2%, 4.7, 2.52%, and 5.7%, after OpTME, LaTME, RoTME, and TaTME respectively, $P<0.001$). In multivariate analysis, having a T4 tumour, intraoperative bowel perforation, and RoTME were significantly associated with the risk of non-radical surgery ($P<0.001$, $P<0.001$, $P=0.003$ respectively). The factors associated with anastomotic leakage in multivariate analysis were male gender, high BMI, and intraoperative bowel perforation, ($P<0.001$, $P=0.049$, $P=0.002$ respectively). TaTME was associated with the highest rate of sphincter-saving procedures (79.8%, $P<0.001$), the lowest rate of bowel perforation (2.9%, $P=0.028$), and the lowest rate of conversion to open surgery (1.3%, $P<0.001$).

Conclusion In a nationwide audit of TME approaches, the rate of non-radical surgery was lowest after RoTME, and no differences were found between the four approaches regarding the risk of anastomotic leakage. TaTME offered advantages related to sphincter-saving, perforation, and conversion.

Keywords: rectal cancer surgery, TME, TaTME, robotics, laparoscopy

INTRODUCTION

While laparoscopic TME (LaTME) is a standard approach for TME worldwide, data on the potential advantages of the Transanal approach (TaTME) and robot-assisted TME (RoTME) are increasingly being reported [1–4]. Recently, two major multicenter randomized trials compared laparoscopic to open rectal resection, and failed to demonstrate the "non-inferiority" of laparoscopy regarding the short-term pathological results, compared to open resection [5,6]. Nationwide studies and randomized clinical trials are needed to evaluate the outcomes after TaTME, especially compared to other minimally invasive procedures.

The challenges encountered during LaTME are related to the pelvic dissection, especially in obese male patients with a narrow pelvis [7,8]. In these cases, TaTME can potentially be useful, enabling an improved dissection and performance of anastomosis. The procedure was adopted in Denmark in 2013, and an increasing number of centers have since adopted it [9], and the short-term outcomes seem to be acceptable. On the other hand, long-term functional and oncological outcomes need to be clarified. Few studies exist have reported these outcomes with different conclusions [10–12].

We aimed in this study to audit the nationwide short-term results of the TaTME, compared to OpTME, LaTME, and RoTME during a five-year period. The primary aim was to investigate the rates of non-radical resection (defined as an involved resection margin), and the secondary aim was to investigate the effects TaTME on the rate of the anastomotic leakage within 30 days after surgery.

METHODS

Patients who underwent a curative OpTME, LaTME, RoTME, or TaTME procedures between January 2014 and December 2018 were identified from the nationwide DCCG Database, which is a population-based clinical colorectal cancer database with a 95% rate of data-completeness [13]. The database includes data on patient demographics, preoperative cancer staging, intraoperative findings, postoperative outcomes (up to 30 days from the primary surgery), and the initial pathology results. Reporting to the database is mandatory and constitutes a quality parameter for the colorectal units in Denmark; the operating surgeons do it prospectively, while pathologists report the pathological outcomes. The surgical procedures in this study have followed the same operative principles described previously for the particular approach. These procedures are well-described in the literature [14–19]. We selected cases for the analysis based on the following criteria: rectum cancer, TME as the operation performed, curative procedure, and the 2014-2018 time interval. The procedures included: low anterior resection, Hartmann's procedure, intersphincteric abdominoperineal excision (APE). We excluded patients who underwent extralevator APE and pelvic excenteration. Data collection included: gender, body mass index (BMI), American Society of Anaesthesiologists (ASA) physical status, performance status according to Zubroed/WHO classification [20,21], tumour distance from the anal verge, tumour stage according to TNM classification, and preoperative oncological treatment, intraoperative data, anastomotic techniques, blood loss, conversion rates, and intraoperative complications such as bowel perforation, blood loss, and iatrogenic intraabdominal lesions. Postoperative complications were defined as any adverse event within 30 days of the primary surgery. Postoperative complications were classified according to the Clavien-Dindo (CD) classification [22]. The severity of anastomotic leakage was graded according to the system proposed by the International Study Group of Rectal Cancer (ISGRC) [23]. Rectal cancer was defined as an adenocarcinoma located at, or below 15 cm from the anal verge. A macroscopic curative resection was determined by the operating surgeon following the procedure and recorded as a variable in the database. Conversion to open surgery was defined as any abdominal incision done for purposes other than specimen extraction.

An involved resection margin (RM) was defined according to Danish Guidelines, as either an involved Circumferential Resection Margin (CRM) or Distal Resection Margin (DRM). That is to say, a distance of ≤ 1 mm from the tumour to the inked surface of the fixed specimen, or the distal cut edge of the tissue. An involved margin was, however, not explicitly defined in the database version that was available for this study, as to whether it was an involved CRM or DRM. Instead, the existence of an involved CRM or DRM was merely reported as "radical resection: yes/no" variable, and thus constituted a non-macro radical resection (pathologic R1 resection). An involved CRM or DRM was registered as a non-radical surgery and, therefore defined in this paper as the presence of microscopic evidence of an involved RM.

Statistical Analysis

The categorical variables are presented as numbers with percentages and the numerical variables as means with standard deviation. The Chi-squared test was used to compare the categorical variables, with Bonferroni correction and Dunnett's Multiple Comparison test to adjust the *P*-value between the groups when appropriate for multiple comparisons. A P-value < 0.05 was considered statistically significant in pair-wise comparisons. The significance level of the P-value was adjusted according to the calculated significance level for multiple post hoc comparisons by calculating the Chi-squared value from the adjusted Z scores. Thus, for the multiple comparisons, the P-value was lower than 0.05 and differed according to the number of analyses. For the continuous variables, a one-way Analysis of Variance (one-way ANOVA) analysis with post hoc statistics with Bonferroni correction for multiple groups to allow for pair-wise comparisons was used.

We conducted a Forward Stepwise (Wald) logistic regression analysis to determine the associated factors with a non-radical surgery and anastomotic leakage (in the 1485 patients who underwent low anterior resection among the whole cohort). The univariate model for anastomotic leakage included the covariates age, gender, ASA score, BMI, tumour status, tumour height, preoperative radiotherapy, blood loss, procedure, approach, and an intraoperative bowel perforation. The univariate model for non-radical surgery included the covariates age, gender, ASA score, BMI, tumour status, tumour height, preoperative radiotherapy, blood loss, intraoperative bowel perforation, procedure, approach, and anastomotic leakage. The multivariate analysis was conducted for covariates that had a significant predictive value for anastomotic leakage and non-radical surgery in the univariate model. Odds ratios were obtained with a 95% Confidence Interval, and a *P*-value of <0.05 was considered statistically significant. The Data Protection Agency approved the study (ID-nr REG-002-2018).

Registration with the Ethical Committee was not required, as this study did not involve any intervention. The statistical software package SPSS version 24 was used for calculations (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.).

RESULTS

Between January 2014 and December 2018, a total of 5174 patients were operated on for rectal cancer in Denmark, of whom 3032 patients underwent TME. In 12 of those 3032 patients, the procedure was registered as an emergency. Of the remaining 3020 patients who underwent an elective TME, the procedures included: low anterior resection (1485), Hartmann's procedure (237), Ischioanal APE (15), ELAPE (381), standard APE (231), and intersphincteric APE (671). A total number of 2393 patients were included for analysis (OpTME=205, LaTME=1163, RoTME=713, and TaTME=312).

The mean tumour distance from the anal verge in the TaTME group was 7.85 cm and was significantly lower compared to tumour height in the LaTME (8.67 cm) and the RoTME (8.70 cm) groups (TaTME vs LaTME, P<0.001 and TaTME vs RoTME, P<0.001). A larger number of patients in the OpTME group received preoperative neoadjuvant radiotherapy (5.36%, 1.71%, 3.08%, and 0.96% for OpTME, LaTME, RoTME, and TaTME groups respectively), chemoradiation (29.7%, 13.92%, 17.25%, and 16.34% for OpTME, LaTME, RoTME, and TaTME groups respectively), and chemotherapy (6.34%, 1.97%, 1.82%, and 2.24% for OpTME, LaTME, RoTME, and TaTME groups respectively). The number of patients who received preoperative neoadjuvant oncologic treatment, in general, were significantly fewer in the LaTME group. Table 1 shows the baseline characteristics.

Pathology Results

The rate of non-radical surgery (+RM) was significantly lower in the RoTME group (2.5%, P=0.002). The highest percentage of +RM was seen in the OpTME group (8.2%), followed by TaTME (5.7%), and LaTME (4.7%), as shown in Table 2. Factors associated with non-radical surgery in the univariate analysis were: T4 tumors (odds ratio 4.1; 95% CI 2.5-0.9; P<0.001), preoperative radiotherapy (odds ratio 1.7; 95% CI 1.1-2.6; P=0.016), blood loss (odds ratio 2.26; 95% CI 1.3-3.9; P=0.004), intraoperative bowel perforation (odds ratio 4.8; 95% CI 2.7-8.4; P<0.001), and APE (odds ratio 1.67; 95% CI 1.1-2.4; P=0.009). The multivariate analysis showed that T4 tumors (odds ratio 3.67; 95% CI 2.17-6.19; P<0.001) and perforation (odds ratio 4.16; 95% CI 2.3-7.4; P<0.001) were significantly associated with a non-radical surgery. The RoTME was significantly associated with radical surgery (odds ratio 0.450; 95% CI 0.267-0.758; P=0.003) in both univariate and multivariate analyses.

Short-term outcomes

Anastomotic leakage occurred in 11.6%, 11.5%, 12.2%, and 9.6% following OpTME, LaTME, RoTME, and TaTME respectively (P=0.698). There was no difference in the severity and the management of the anastomotic Leakage (P=0.469 and P=0.906, respectively). The mean timeline from the primary surgery to the diagnosis of anastomotic leakage was comparable between the groups (7.36, 7.20, 7.80, and 9.17 days following OpTME, LaTME, RoTME, and TaTME respectively, P=0.360). s

The univariate analysis showed that male gender (odds ratio 2.27; 95% CI 1.5-3.2; P<0.001), high BMI (odds ratio 1.58; 95% CI 1.0-2.4; P=0.037), high ASA score (odds ratio 1.7; 95% CI 1.08-2.8; P=0.022), and intraoperative bowel perforation (odds ratio 2.8; 95% CI 1.17-6.7; P=0.020) were independent associated factors with anastomotic leakage. In the multivariate model, gender (odds ratio 2.27; 95% CI 1.5-3.3; P<0.001), perforation (odds ratio 2.8; 95% CI 1.16-6.8; P=0.022) and BMI (odds ratio 1.48; 95% CI 0.9-2.3; P=0.049) were associated factors with anastomotic leakage. Tables 3 summarizes the results of univariate and multivariate analyses for non-radical surgery and anastomotic leakage.

The number of sphincter-saving procedures was highest in the TaTME group (79.8%), and lowest (46.3%) in the OpTME group (P<0.001). Hartmann's procedure was more often performed in the LaTME group (13.9%, P<0.001), and least in the TaTME and RoTME groups (4.2% and 4.8% respectively, P<0.001 and P<0.001, respectively). The intersphincteric APE was more frequently performed in the OpTME group (40%, P<0.001), and less in the TaTME and the RoTME groups (16% and 33% respectively, P<0.001 and P<0.001).

Urethral injury occurred in eight patients (OpTME=1, LaTME=4, RoTME=0, TaTME=3), and were not significantly different between the groups (P=0.101). However, urethral injuries occurred during low anterior resection procedures in the TaTME group, while in the LaTME group, they occurred during intersphincteric APE procedures. Conversion to open surgery occurred significantly less in the TaTME group (10.9%, 5.6%, and 1.3% in LaTME, RoTME, and TaTME respectively, P<0.001). Intraoperative bowel perforation occurred significantly less in the TaTME group (7.8%, 3.7%, 4.8%, and 3.8% in the OpTME, LaTME, RoTME, and TaTME respectively, P=0.028). The rate of sphincter-saving surgery was significantly higher in the TaTME group (46.3%, 59.9%, 62.3%, and 79.8% in OpTME, LaTME, RoTME, and TaTME respectively, P<0.001). Table 4 summarizes the intraoperative results.

Postoperative surgical complications rates were similar between the groups. The 30-day mortality rates were low and did not differ significantly among the groups. Table 5 and the Supplementary Table a show the postoperative complications.

The Implementation of TaTME in Denmark

The minimally invasive rectal cancer surgery was done in 91.4% of cases during the study's time period (LaTME=48.6%, RoTME=29.8%, and TaTME=13%). Supplementary Figures 1 and 2 show the distribution of TaTME and RoTME procedures in the five regions in Denmark from 2014-2018.

DISCUSSION

We found that RoTME was associated with a lower rate of R0 resection, and no significant differences were found in the risk of anastomotic leakage between the groups. The TaTME was used predominantly for cancers in the lowest part of the rectum, in male patients, as there were significantly more male patients in the TaTME group in this study.

Different aspects of the Danish experience with TaTME were published previously [9,12,24]. This study showed a significantly lower conversion rate in the TaTME group, followed by the RoTME group (1.3% and 5.6% respectively). Intraoperative blood loss was significantly less in the TaTME group compared to the LaTME and the OpTME groups. However, it did not reach a statistically significant difference compared to the RoTME group. Previous studies have shown similar results, proving that TaTME can overcome the technical difficulties seen in LaTME [25–27]. Our study confirms the technical benefits of TaTME in patients with low and mid rectal cancer. It highlights the potential of better visibility of the operative field in the TaTME approach. A low anterior resection was more frequently performed in the TaTME group, suggesting that the transanal approach offers the best possibility for performing an anastomosis, even in very low tumours.

The rate of non-radical surgery was significantly lower in the RoTME group (2.5%, P=0.002), followed by LaTME and the TaTME groups (4.7% and 5.7%, respectively). The ROLARR study showed no oncological advantage of robot-assisted surgery over standard laparoscopy, [28]. The COLOR II randomized clinical trial study showed positive margins in 7% of the laparoscopic group and 9% in the open [29]. Detering et al. presented a similar CRM involvement rate in the TaTME and the LaTME procedures (4.3% vs 4.0%, respectively) [25].

In our study, the TaTME group had a 9.6% rate of anastomotic leakage and did not differ significantly from the other groups. Data from the international TaTME registry reported a 6.7% leakage rate, while in a recent national cohort study from the Netherlands, Detering et al.[25], reported a leakage rate of 16.5%. The rate of the anastomotic leakage in the current study is comparable with the results reported elsewhere [10,27,29].

Urethral injury is described in the literature as a significant complication during TaTME [26,31]. In this study, eight cases of urethral injury were found, three were in the TaTME group, with no significant difference in the number of intraoperative urethral lesions between the groups. Urethral injury is a severe complication [24,32], and is almost specific for TaTME, being rare during an abdominal approach. This was observed in this study, as all urethral lesions in other groups occurred during intersphincteric APE, suggesting that the perineal dissection is in itself a risk factor. No intraoperative lesions were reported in the RoTME group, in accordance with the literature [28,30].

We found no significant difference regarding postoperative surgical and medical complications. The 30-day mortality rates were comparable, and in the TaTME group, this was 1% in accordance with the literature [10].

This study has several limitations. It is important to note that the TaTME procedure was introduced in Denmark in 2013, and some colorectal centers are still in the early phase of the learning curve, which may explain some outcomes, for example, the rate of non-radical surgery. The current study also carries potential selection bias, regarding the approach used, especially the RoTME and TaTME by the operating surgeons. Furthermore, the study is based on a nationwide registry database, which may have inherent sources of registration bias. Another limitation is the lack of exact case-matching. Nonetheless, it does represent a realistic picture of the state of rectal cancer surgery in Denmark at this time.

CONCLUSIONS

In a nationwide audit of four different approaches for TME, the rate of non-radical surgery was lowest in RoTME, and there were no significant differences in anastomotic leak rate between the four approaches. The TaTME procedure was associated with the lowest rate of conversion and bowel perforation, and the highest rate of sphincter-saving surgery. Further studies are needed to evaluate the long-term results, quality of life, and cost-effectiveness. Of particular importance would be a national audit of TaTME to analyze the long-term oncological results and factors associated with local recurrence.

Compliance with ethical standards

Dr Ilze Witt declares that she does not have any conflicts of interest.

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TABLES AND FIGURES

Table 1. baseline characteristics

	OpTME n=205	LaTME n=1163	RoTME n=713	TaTME n=312	*P*-value
Gender, n (%)					0.001
Female	73 (35.6)	449 (38.6)	240 (33.7)	85 (27.2)	
Male	132 (64.4)	714 (61.4)	473 (66.3)	227 (72.8)	
Age, mean ±SD, years	66.96±10.246	67.61±10.254	67.28±10.074	65.65±10.038	0.026 (TaTME vs. OpTME P=0.981; TaTME vs. LaTME P=0.015; TaTME vs. RoTME P=0.113; OpTME vs. LaTME P=0.771; OpTME vs. RoTME P=1.000; LaTME vs. RoTME P=1.000)
BMI, mean ±SD, kg/m²	26.67±9.244	26.52±7.199	26.15±4.405	26.08±4.419	0.471
ASA classification, n (%)					< 0.001
ASA 1	34 (16.6)	343 (29.5)	223 (31.3)	108 (34.6)	
ASA 2	126 (61.5)	627 (53.9)	407 (57.1)	168 (53.8)	
ASA 3	43 (21.0)	180 (15.5)	78 (10.9)	36 (11.5)	
ASA 4	0 (0.0)	8 (0.7)	1 (0.1)	0 (0.0)	
Missing, n	2	5	4	-	
WHO-performance status, n (%)					< 0.001
0	119 (58.0)	816 (70.2)	546 (76.6)	244 (78.2)	
1	55 (26.8)	234 (20.1)	126 (17.7)	57 (18.3)	
3	22 (10.7)	55 (4.7)	26 (3.6)	7 (2.2)	
4	5 (2.4)	7 (0.6)	4 (0.6)	1 (0.3)	
Missing, n	4	51	11	3	
Distance from the anal verge, mean ±SD, cm	8.5±2.621	8.7±2.803	8.7±2.714	7.8±2.179	< 0.001 (TaTME vs. OpTME P=0.048; TaTME vs. LaTME P<0.001; TaTME vs. RoTME P<0.001; OpTME vs. LaTME P=1.000; OpTME vs.RoTME P=1.000; LaTME vs. RoTME P=1.000)
TNM classification					

T, n (%)					< 0.001
T0	1 (0.5)	12 (1.0)	11 (1.5)	6 (1.9)	
T1/T2	35 (17.1)	405 (34.8)	189 (26.5)	120 (38.5)	
T3	103 (50.2)	516 (44.4)	376 (52.7)	157 (50.3)	
T4	43 (21.0)	54 (4.6)	37 (5.2)	12 (3.8)	
Tx	23 (11.2)	176 (15.1)	100 (14.0)	17 (5.4)	
N, n (%)					< 0.001
N0	124 (60.5)	794 (68.3)	431 (60.4)	190 (60.9)	
N1	27 (13.2)	149 (12.8)	129 (18.1)	40 (12.8)	
N2	42 (20.5)	121 (10.4)	84 (11.8)	34 (10.9)	
Nx	12 (5.9)	99 (8.5)	69 (9.7)	48 (15.4)	
M, n (%)					< 0.001
M0	174 (84.9)	1069 (91.9)	658 (92.3)	287 (92.0)	
M1	31 (15.1)	77 (6.6)	48 (6.7)	20 (6.4)	
Mx	0 (0.0)	17 (1.5)	7 (1.0)	5 (1.6)	
Preoperative oncologic treatment, n (%)					< 0.001
Radiotherapy	11 (5.36)	20 (1.71)	22 (3.08)	3 (0.96)	
Chemoradiation	59 (29.7)	162 (13.92)	123 (17.25)	51 (16.34)	
Chemotherapy	13 (6.34)	23 (1.97)	13 (1.82)	7 (2.24)	

ASA, American Society of Anesthesiologists-Classification [21].

Table 2. Pathology results

	OpTME n=205	LaTME n=1163	RoTME n=713	TaTME n=312	*P*-value
T stage, n (%)					0.001
T 0	7 (3.4)	30 (2.5)	22 (3.0)	7 (2.2)	
T 1	12 (5.8)	167 (14.3)	103 (14.4)	42 (13.4)	
T 2	37 (18.0)	328 (28.2)	191 (26.7)	95 (30.4)	
T 3	137 (66.8)	595 (51.1)	375 (52.5)	162 (51.9)	
T 4	12 (5.8)	43 (3.6)	22 (3.0)	6 (1.9)	
N stage, n (%)					< 0.001
N 0	148 (72.1)	958 (82.3)	526 (73.7)	237 (75.9)	
N 1	26 (12.6)	124 (10.6)	105 (14.7)	45 (14.4)	
N 2	31 (15.1)	81 (6.9)	82 (11.5)	30 (9.6)	
Positive RM, n (%)	17 (8.2)	55 (4.7)	18 (2.5)	18 (5.7)	0.002

RM. Resection Margin; TME, total mesorectal excision

Table 3. Univariate and Multivariate analyses of associated factors for radical surgery and anastomotic leakage

Covariate	Univariate				Multivariate			
	Non radical surgery		Anastomotic leakage		Non radical surgery		Anastomotic leakage	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age: < 80 vs ≥ 80 y	1.311 (0.671-2.561)	0.428	0.535 (0.127-2.263)	0.395		0.490		0.388
Gender: F vs M	0.928 (0.622-.385)	0.715	2.274 (1.541-3.254)	<0.001		0.914	2.274 (1.541-3.357)	<0.001
ASA score: <III vs ≥ III	1.400 (0.857-2.86)	0.179	1.758 (1.086-2.845)	0.022		0.475		0.156
BMI: <30 vs ≥ 30 kg/m²	0.586 (0.293-1.171)	0.130	1.587 (1.028-2.450)	0.037		0.185	1.488 (0.947-2.338)	0.049
T status: <T4 vs ≥ T4	4.171 (2.5086-.943)	<0.001	1.799 (0.942-3.437)	0.075	3.671 (2.177-6.192)	<0.001	1.556 (1.002-2.416)	0.099
Tumor height: ≥6 vs <6 cm	1.380 (0.899-.118)	0.140	0.803 (0.474-1.361)	0.414		0.126		0.637
Preop. radiotherapy: no vs yes	1.703 (1.103-2.629)	0.016	0.857 (0.534-1.375)	0.522		0.348		0.437
Blood loss: < 500 vs ≥ 500 ml	2.264 (1.301-3.941)	0.004	1.452 (0.726-2.906)	0.292		0.07		0.918
Perforation: no vs yes	4.835 (2.758-8.476)	<0.001	2.820 (1.174-6.772)	0.020	4.162 (2.337-7.413	<0.001	2.824 (1.164-6.855)	0.022
Procedure: LAR vs APE	1.676 (1.138-2.466)	0.009				0.155		
Anastomotic leakage: no vs yes	0.628 (0.252-1.562)	0.317				0.267		
TaTME vs no TaTME	1.354 (0.805-2.280)	0.253	1.113 (0.710-1.744)	0.614		0.391		0.665
OpTME vs no OpTME	2.084 (1.216-3.572)	0.008	0.729 (0.389-1.366)	0.323		0.101		0.321
LaTME vs no LaTME	1.102 (0.749-1.622)	0.621	0.947 (0.692-1.295)	0.733		0.776		0.916
RoTME vs no RoTME	0.458 (0.274-0.765)	0.003	1.115 (0.797-1.560)	0.525	0.450 (0.267-0.758)	0.003		0.637

Table 4. Intraoperative results

	OpTME n=205	LaTME n=1163	RoTME n=713	TaTME n=312	*P* value
The performed procedure, n (%)					< 0.001
LAR	95 (46.3)	697 (59.9)	444 (62.3)	249 (79.8)	
Intersphincteric APE	82 (40.0)	304 (26.1)	235 (33.0)	50 (16.0)	
Hartmann	28 (13.7)	162 (13.9)	34 (4.8)	13 (4.2)	
Anastomotic method, n (%)					< 0.001
Hand-sewn anastomosis	1 (1.1)	9 (1.3)	3 (0.7)	1 (0.4)	
Stapled anastomosis	78 (82.1)	555 (79.6)	333 (75.0)	157 (63.1)	
Missing	16 (16.8)	133 (19.1)	108 (24.3)	91 (36.5)	
Anastomotic technique, n (%)					< 0.001
End-end	57 (60.0)	372 (53.4)	220 (49.5)	113 (45.4)	
Side-end	19 (20.0)	170 (24.4)	111 (25.0)	42 (16.9)	
Pouch	3 (3.2)	22 (3.2)	5 (1.1)	3 (1.2)	
Unknown	16 (16.8)	133 (19.1)	108 (24.3)	91 (36.5)	
Conversion to open procedure, n (%)	0 (0.0)	127 (10.9)	40 (5.6)	4 (1.3)	< 0.001
Multiorgan resection, n (%)	67 (32.7)	54 (4.6)	34 (4.8)	12 (3.8)	< 0.001
Intraoperative complications					
Bowel perforation, n (%)	16 (7.8)	43 (3.7)	34 (4.8)	9 (2.9)	0.028
Intraoperative lesions					
Vagina, n (%)	2 (1.0)	(0.00)	0 (0.00)	4 (1.3)	< 0.001
Bladder, n (%)	0 (0.00)	8 (0.7)	0 (0.00)	2 (0.60)	0.100
Urethral, n (%)	1 (0.5)	4 (0.34)	0 (0.00)	3 (1.0)	0.101
Ureteric, n (%)	2 (0.97)	4 (0.34)	0 (0.00)	3 (1.0)	0.056
Presacral veins, n (%)	0 (0.00)	7 (0.60)	0 (0.00)	1 (0.32)	<0.001
Blood loss, mean ±SD, ml	526.63±796.864	168.89±356.592	128.75±180.793	101.44±236.20	< 0.001 (TaTME vs. OpTME *P*<0.001; TaTME vs. LaTME *P*=0.023; TaTME vs. RoTME *P*=1.000; OpTME vs. LaTME *P*= *P*<0.001; OpTME vs. RoTME *P*<0.001; LaTME vs. RoTME *P*=0.125)

LAR low anterior resection; APE abdominoperineal excision

Table 5. Postoperative surgical complications

	OpTME	LaTME	RoTME	TaTME	*P*-value
Surgical complications, n (%)	55 (26.8)	300 (25.8)	192 (26.9)	77 (24.7)	0.875
Bleeding, n (%)					0.165
CD I-II	2 (1.0)	7 (0.6)	10 (1.4)	0 (0.0)	
CD III	0 (0.0)	14 (1.2)	8 (1.1)	2 (0.6)	
CD IV	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.3)	
CD V	0 (0.0)	4 (0.4)	0 (0.0)	0 (0.0)	
Wound dehiscence, n (%)					0.129
CD I-II	1 (0.5)	1 (0.1)	1 (0.1)	0 (0.0)	
CD III	7 (3.4)	14 (1.2)	8 (1.1)	0 (0.0)	
CD IV	1 (0.5)	2 (0.2)	0 (0.0)	0 (0.0)	
CD V	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	
Bowel obstruction, n (%)					0.125
CD I-II	10 (4.9)	37 (3.2)	24 (3.3)	9 (2.9)	
CD III	4 (2.0)	29 (2.5)	17 (2.4)	12 (3.8)	
CD IV	0 (0.0)	3 (0.3)	2 (0.2)	0 (0.0)	
CD V	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	
Wound infection, n (%)					0.429
CD I-II	4 (2.0)	15 (1.3)	8 (1.1)	5 (1.6)	
CD III	8 (3.9)	23 (2.0)	12 (1.7)	7 (2.3)	
CD V	0 (0.0)	4 (0.4)	0 (0.0)	0 (0.0)	
Intra-abdominal abscess, n (%)					0.086
CD I-II	1 (0.5)	7 (0.6)	3 (0.4)	0 (0.0)	
CD III	10 (4.9)	22 (1.8)	20 (2.8)	6 (2.0)	
CD IV	1 (0.5)	2 (0.2)	3 (0.4)	0 (0.0)	
CD V	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	
Stoma complications, n (%)					0.074
CD I-II	2 (1.0)	12 (1.0)	14 (2.0)	11 (3.6)	

CD III	3 (1.5)	35 (3.0)	22 (3.1)	10 (3.2)	
CD IV	1 (0.5)	3 (0.3)	2 (0.3)	0 (0.0)	
CD V	0 (0.0)	1 (0.1)	2 (0.3)	0 (0.0)	
Anastomotic leakage, n (%)*	11 (11.6)	80 (11.5)	54 (12.2)	24 (9.6)	0.698
Severity** of anastomotic leakage, n (%)					0.469
Grade A	0 (0.0)	10 (1.3)	11 (2.5)	5 (2.0)	
Grade B	5 (5.39)	35 (5.0)	26 (5.9)	10 (4.0)	
Grade C	6 (6.3)	35 (5.0)	17 (3.8)	9 (3.6)	
CD I-II	0 (0.0)	9 (1.1)	3 (0.7)	4 (1.6)	
CD III	9 (9.5)	62 (8.9)	50 (11.3)	19 (7.6)	
CD IV	1 (1.1)	7 (1.0)	1 (0.2)	1 (0.4)	
CD V	1 (1.1)	2 (0.3)	0 (0.0)	0 (0.0)	
Management of anastomotic leakage, n (%)					0.906
Anastomotic takedown	4 (4.2)	18 (2.6)	12 (2.7)	6 (2.4)	
No take down	7 (7.4)	62 (8.9)	42 (9.5)	18 (7.2)	
Timeline of anastomotic leaks, mean ±SD, days	7.36 (±3.042)	7.20 (±4.941)	7.80 (±4.553)	9.17 (±5.181)	0.360
30-days mortality, n (%)	0 (0.0)	21 (1.8)	6 (0.8)	3 (1.0)	0.029

CD, The Clavien-Dindo classification of surgical complications [22]. * In patients with anastomosis (OpTME=95, LaTME=697, RoTME=444, TaTME=249.
**Severity of anastomosis leak according to the grading system proposed by International Study Group of Rectal Cancer (ISGRC) [23].

Supplementary Table a. Postoperative medical complications

	OpTME	LaTME	RoTME	TaTME	*P*-value
Total, n (%)	29 (14.1)	115 (9.9)	75 (10.5)	25 (8.0)	0.150
Apoplexy, n (%)					0.010
CD I-II	26 (12.7)	112 (9.6)	74 (10.4)	25 (8.0)	
CD III	3 (1.5)	1 (0.1)	1 (0.1)	0 (0.0)	
CD IV	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	
Acute myocardial infarction, n (%)					0.395
CD I-II	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	
CD III	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	
CD IV	1 (0.5)	1 (0.1)	0 (0.0)	0 (0.0)	
Aspiration, n (%)					0.531
CD I-II	1 (0.5)	2 (0.2)	0 (0.0)	1 (0.3)	
CD III	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	
CD IV	0 (0.0)	2 (0.2)	1 (0.1)	1 (0.3)	
CD V	0 (0.0)	6 (0.5)	1 (0.1)	0 (0.0)	
Pneumonia, n (%)					0.338
CD I-II	6 (2.9)	25 (2.1)	21 (2.9)	4 (1.3)	
CD III	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	
CD IV	0 (0.0)	9 (0.8)	1 (0.1)	0 (0.0)	
CD V	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	
Cardiac insufficiency, n (%)					0.308
CD I-II	1 (0.5)	5 (0.4)	3 (0.4)	3 (1.0)	
CD III	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	
CD IV	1 (0.5)	12 (1.0)	1 (0.1)	1 (0.3)	
CD V	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	
Pulmonary embolism, n (%)					0.282
CD I-II	0 (0.0)	1 (0.1)	3 (0.4)	1 (0.3)	
CD III	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	
CD IV	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	
CD V	0 (0.0)	1 (0.1)	2 (0.3)	0 (0.0)	
Pulmonary insufficiency, n (%)					0.027
CD I-II	0 (0.0)	9 (0.8)	0 (0.0)	2 (0.6)	

CD III	1 (0.5)	2 (0.2)	2 (0.2)	0 (0.0)	
CD IV	1 (0.5)	17 (1.5)	3 (0.4)	0 (0.0)	
CD V	0 (0.0)	5 (0.4)	1 (0.1)	1 (0.3)	
Renal insufficiency, n (%)					0.059
CD I-II	4 (2.0)	6 (0.6)	4 (0.5)	2 (0.6)	
CD III	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	
CD IV	1 (0.5)	5 (0.4)	0 (0.0)	1 (0.3)	
CD V	0 (0.0)	3 (0.3)	2 (0.3)	0 (0.0)	
Sepsis, n (%)					0.095
CD I-II	1 (0.5)	11 (1.0)	10 (1.4)	1 (0.3)	
CD III	0 (0.0)	2 (0.2)	1 (0.1)	1 (0.3)	
CD IV	1 (0.5)	20 (1.7)	1 (0.1)	2 (0.6)	
CD V	0 (0.0)	3 (0.3)	2 (0.3)	0 (0.0)	
Deep vein thrombosis, n (%)					0.363
CD I-II	0 (0.0)	4 (0.3)	1 (0.1)	0 (0.0)	
Arterial embolism, n (%)					0.042
CD I-II	1 (0.5)	0 (0.0)	1 (0.1)	0 (0.0)	

CD, The Clavien-Dindo classification of surgical complications [18].

Figure 1. Performed TaTME procedures (%) by region

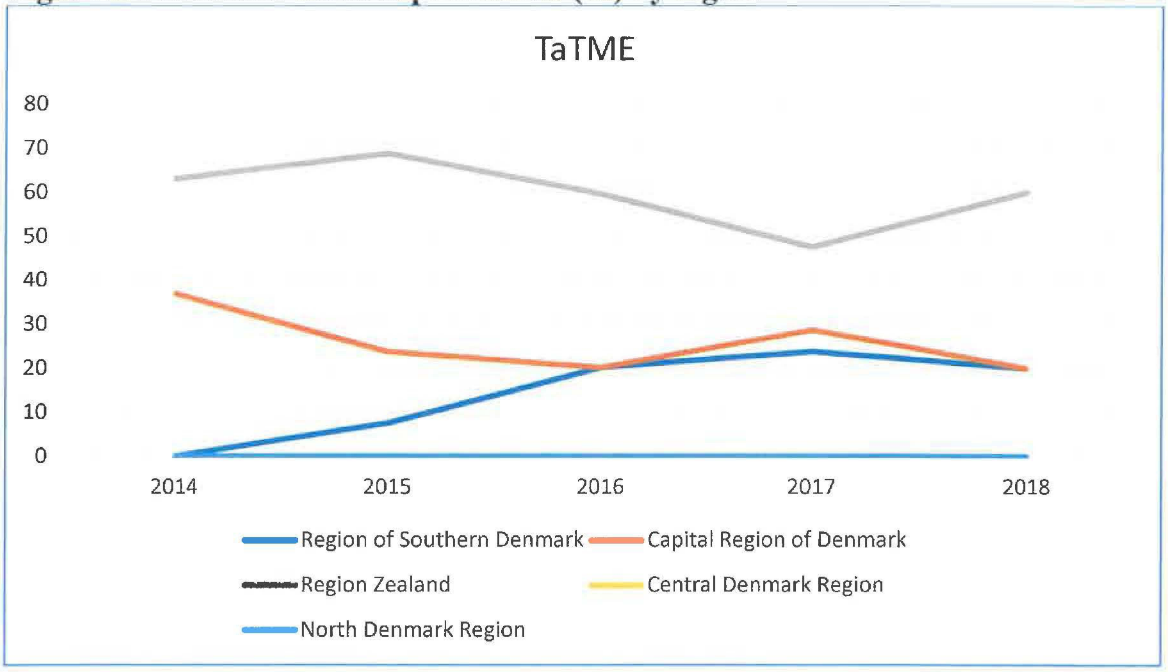
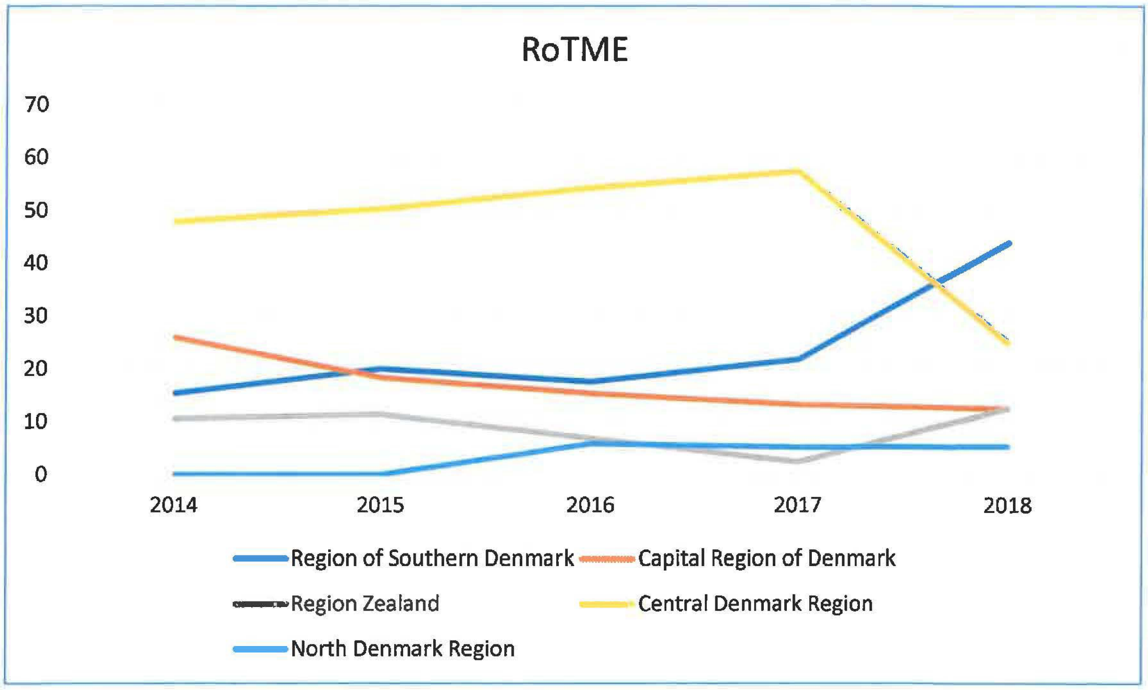


Figure 2. Performed RoTME procedures (%) by region



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Transanal total mesorectal excision: the Slagelse experience 2013–2019

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Abstract

Objective To describe outcomes after transanal total mesorectal excision (TaTME) 5 years from implementation at a large-volume colorectal unit, including local recurrence, distant metastasis, and survival.

Background Transanal total mesorectal excision (TaTME) is a relatively new procedure for mid- and low-rectal cancer, with well-documented safety and feasibility. However, data on long-term results are limited.

Methods This study was based on a prospective data collection via a maintained database in a large colorectal unit. The database included patients who underwent TaTME from December 2013 through July 2019. We have updated the database through a review of patient charts, including radiology and pathology reports. Data collection included operative details, intraoperative findings, postoperative complications, pathologic results, and oncologic results.

Results During the study period, two hundred patients underwent TaTME in the study period (men = 147). The mean BMI was 26.7%, and the mean tumor height from the anal verge was 7.86 cm. Neoadjuvant treatment was given to 22% of patients. Anastomotic leakage occurred in 9.3% of patients, and the overall rate of postoperative complications was 24.5%. The TME specimen was incomplete in 11% of patients, and the CRM was positive in 5.5% of patients. Local recurrence (LR) occurred in seven patients with a follow-up of at least 2 years (4.7%). Distant metastasis (DM) occurred in 12% of patients. The overall survival was 90% and disease-free survival was 81%. The operating time was reduced in the later period of our experience.

Conclusions This study showed that TaTME is feasible, safe, and had acceptable short-term outcomes and an acceptable rate of LR. The study included, however, one group that was non-randomized, and the follow-up was not long enough for most patients. Studies with longer follow-up data are awaited.

Keywords Total mesorectal excision · TaTME · Rectal cancer surgery · Oncologic results

The most recently introduced approach in the treatment of rectal cancer is TaTME, being at this time practiced over a decade. As a "solution to some old problems" [1], it has gained enormous focus, with considerable interest from colorectal surgeons. Most studies have focused on technical tips, risks, safe introduction, complications, and short-term outcomes. The long-term oncologic safety needs, however, to be established before we can consider it as a gold standard.

As a large-volume colorectal unit, we have adopted TaTME as a standard of care for patients with mid- and low-rectal cancer since 2013 [2]. With our growing experience, we aimed in this report to audit our results so far, focusing on long-term outcomes and including all patients operated since 2013.

Methods

We have maintained a prospective TaTME database that includes all patients operated since December 2013. All patients have provided informed written consent for the surgical procedure and the research related to different aspects of their treatment. The institutional review board approved this study and the database. The Danish Data Protection Agency has approved the database, which includes demographics, tumor characteristics, operative details, postoperative results, pathological results, and long-term oncologic results. We have published several papers on different

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aspects of TaTME [2–5]. These papers focused on short-term outcomes of our first 150 cases. We have since updated the database regularly to audit the results and detect any tendencies of complications or poor oncologic results. We have reviewed the database recently and present our findings in this study, including data on local recurrence (LR), distant metastasis (DM) and survival. Thus, the present study includes data on cases already published, and an additional 75 patients operated on afterward. The standard variables in the database constituted the source of data collection, in addition to a careful review of patient charts for the period that followed the index operation to the present date. The chart review included all radiological investigations including computerized tomography (CT) and magnetic resonance imaging (MRI) scans, pathology reports from biopsies or specimens (if any), endoscopic procedures and any clinical chart notes indicating the probability of the existence of LR or DM. Our electronic patient chart system is linked to the Central Person Register, allowing the calculation of the date of death for deceased patients. The diagnosis of LR and MD was thus based on either pathology (for patients who underwent surgery for LR or MD), radiologic evidence, or clinical suspicion. We have adopted this method because in some cases, no further diagnostic workup is necessary when it is evident that the patient has LR or MD and radical surgery is not an option. In these cases, we offer palliative chemotherapy based on the radiological evidence and the background of the patient's history of colorectal cancer.

We have previously published our protocol for the diagnostic workup and details of surgery according to our standardized routine at Slagelse Hospital [2, 3]. Besides, the procedure is well described in the literature [6–8]. We apply TaTME for all newcomers with rectal cancer at or below 10 cm from the anal verge, including patients where intersphincteric APE would be performed. Indications for TME are tumors at or below the distance of 10 cm, and exceptionally in some cases for a slightly higher tumor up to 12 cm from the anal verge. According to the national guidelines from the Danish Colorectal Cancer Group (DCCG), patients with advanced mid- and low-rectal tumors are offered neoadjuvant chemoradiation [9]. Advanced tumors are defined according to our national guidelines as all T4 tumors and T3 tumors in the lowest five cm of the rectum. In patients with advanced mid-rectal T3 tumors (distance 5–10 cm from the anal verge), the indications for neoadjuvant treatment are a distance of less than five mm from the most profound invasion of the tumor into the mesorectal fat to the mesorectal fascia. This guideline was revised recently, and the most crucial change is the definition of an advanced mid-rectal T3 tumor, which is defined as one with a distance from the most profound invasion in the mesorectal fat to the mesorectal fascia of two mm or depth of invasion into the mesorectal fat of ≥ 5 mm. The radiation dosage is 50.4 Gy, 28 fractions in combination with 5-fluorouracil or equivalent chemotherapy. Patients who receive neoadjuvant chemoradiation undergo surgery after 8–12 weeks from the date of the last radiation dose, preceded by a new radiologic evaluation with CT and MR scans.

We have introduced an enhanced recovery program (ERAS) since 2017. Patients planned for sphincter-saving surgery have received oral mechanical bowel preparation with Moviprep (Norgine Denmark A/S Stamholmen, 2650 Hvidovre, Denmark) plus enema in the morning of surgery.

The usual method of TaTME in our unit is a hybrid method, where TME starts through the abdominal approach, and the transanal part follows. The extent of the abdominal part depended in some cases on the feasibility of dissection from above. We have adopted a routine splenic flexure mobilization in every case of low anterior resection. Splenic flexure was not always mobilized at the beginning of our experience. Our routine for anastomotic technique is a stapled side-end or in some cases end-end. Where possible, we have extracted specimens through the transanal route. A standard laparoscopic or a single port procedure was performed for the abdominal part. A diverting loop ileostomy was performed in all patients who had a colorectal anastomosis (low anterior resection).

Histopathological examination was performed on freshly extracted specimens, based on a standard protocol following the method described by Phil Quirke and colleagues [10–12]. The quality of the resected TME specimen was graded as complete, nearly complete or incomplete. The standard pathology report included information about the number of retrieved lymph nodes and the number of nodes involved by cancer, as well as information on the Circumferential and Distal Resection Margins (CRM and DRM). An involved CRM or DRM was defined as a distance of ≤ 1 mm from the tumor to the inked surface of the fixed specimen or from cancer to the distal cut edge of the tissue, respectively.

The primary outcomes in this study were the long-term oncologic results (LR, DM, OS, and DFS), pathologic results (CRM, DRM, quality of TME specimen). As in our previous paper [3], we calculated the surgical success based on a composite based on the quality of TME specimen, CRM, and DRM as described by Fleshman et al. [13]. A successful resection fulfilled the following criteria: (1) clear CRM (defined as a distance >1 mm between the most profound extent of tumor invasion into the mesorectum and the inked surface on the fixed specimen), (2) clear DRM (defined as the distance >1 mm between the tumor to the distal cut edge of the tissue), and (3) a TME specimen graded as complete or nearly complete as defined above.

The secondary outcomes included intraoperative details and postoperative complications. Operating time was calculated in minutes from skin incision/insertion of the first laparoscopic port to the last stitch for either skin closure or stoma creation—this included time spent in preparation for the transanal part. The operating time for the transanal part was calculated from the fixation of the Lone Star retractor to the creation of the anastomosis of the last stitch on perineal skin in abdominoperineal excision (APE) procedures. Conversion to open procedure was defined as any skin incision done for purposes other than specimen retrieval. Bowel perforation was defined as any perforation during either the abdominal or the transanal part. Rescue APE was defined as one done in a patient for whom anastomosis was otherwise planned. The decision to perform anastomosis was taken at the outpatient clinic depending on the tumor height, intraoperative complications, patient wishes, and comorbidities. We have a systematic approach in patients who undergo low anterior resection, to inform about low anterior resection syndrome (LARS), followed by information on stomas by a stoma nurse.

Postoperative complications were defined as any complication within 30 days after surgery. Complications were graded as described by Clavien et al. [14]. Anastomotic leakage was defined as one that was clinically suspected, radiologically, or endoscopically proved and actively treated. Urinary dysfunction was defined as an inability of spontaneous voiding at discharge. Stoma complication was defined as any complication related directly to the stoma. The hospital stay was calculated from the day of surgery to discharge. The criteria for discharge were the absence of signs of complications tolerated oral diet and when capable of independent stoma care or help arranged by a home-nurse.

Long-term outcomes were registered in our database according to predefined variables based on chart review. LR was defined as the recurrence of malignancy in the pelvis or perirectally, whether histologically proven (biopsy, surgery or autopsy), radiologically diagnosed or clinically suspected. DM was defined as any histological or radiological sign of metachronous tumor growth outside the pelvis. Time to LR or DM was calculated from the date of surgery to the date of diagnosis of LR or DM. Overall Survival (OS) was defined as the number of patients alive at the end of this study. Disease-free survival (DFS) was defined as the number of patients alive and without signs of LR or DM at the end of this study.

The following variables were analyzed as predictors for anastomotic leakage: gender (female/male), BMI (>30 vs. <30 kg/m^2), preoperative chemoradiation (yes/no), anastomotic orientation (side-end/end-end), and the size of the circular stapler (32/33 mm). The following variables were analyzed as predictors for incomplete TME specimen, positive CRM and a successful resection: gender (female/male), BMI (>30 vs. <30 kg/m^2), T4 tumor (T4/not T4), the performed procedure (anastomosis/APE), and intraoperative bowel perforation (yes/no).

The following variables were analyzed as predictors for LR: Gender (female/male), BMI (>30 vs. <30 kg/m^2), T4 tumor (T4/not T4), tumor height (>5/<5 cm from anal verge), preoperative chemoradiation (yes/no), anastomotic leakage (leak/no leak), quality of TME specimen (incomplete/complete or nearly complete), CRM (±), rates of retrieved positive lymph nodes (pN0/pN1 or pN2), extraction site (transanal or perineal/transabdominal), and the performed procedure (anastomosis/APE).

We have compared the main characteristics and short-term outcomes between two subgroups, representing our first 100 cases versus the last 100 cases. We have chosen this method as a pragmatic and simple way to explore the potential advances, which might have been achieved with time. The first 100 cases were operated on between December 2013 and June 2016; the second 100 cases were operated on between July 2016 and July 2019.

Statistical analysis

Numerical data are presented as means with standard deviation where relevant and categorical data are presented as numbers with percentages. A χ^2 test was used to compare nominal categorical variables, and Student's *t*-test was used to compare quantitative variables. We conducted a binary logistic regression analysis to define predictors of anastomotic leakage, incomplete TME specimens, CRM positivity, and local recurrence. We have plotted the cumulative sum (CUSUM) charts to determine the learning curve. A P value of <0.05 for variables in the equation of the analysis was considered statistically significant. We used the statistical software package SPSS version 24 for calculations (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.).

Results

We have performed 200 hybrid TaTME procedures from December 2013 through July 2019. Table 1 shows patient and tumor characteristics. Among 60 APE procedures, five were as rescue procedures in the otherwise planned anastomosis; of these, two were due to intraoperative bleeding and three were due to technical difficulty in the lower part of the pelvis. One urethral injury occurred during the transanal part in a patient who had received neoadjuvant chemoradiation. Transabdominal specimen extraction was done in 38 (19%) patients, of whom five had APE procedures. We performed a side-end anastomosis in 80% of cases. Tables 2 and 3 show the operative details.

Postoperative surgical complications occurred in 49 (24.5%) patients. Among 140 patients with an anastomosis, leakage occurred in 13 (9.3%) patients. Management of

Table 1 Patient and tumor characteristics

Gender, number (%)	
Female	53 (26.5)
Male	147 (73.5)
Age, years, years (± SD)	67 (10.212)
BMI, mean (± SD)	26.7 (4.341)
ASA score, number (%)	
ASA 1	72 (36)
ASA 2	97 (48.5)
ASA 3	31 (15.5)
WHO performance status, number (%)	
PS 0	149 (74.5)
PS 1	43 (21.5)
PS 2	8 (4)
Previous abdominal surgery, number (%)	
Yes	42 (21)
No	158 (79)
Tumor height from anal verge, cm, mean (± SD)	7.86 (1.859)
Tumor localization in the lumen, number (%)	
Anterior	35 (17.5)
Posterior	29 (14.5)
Left	22 (11)
Right	28 (14)
Circumferential	86 (43)
Tumor size, mm, mean (± SD)	38.64 (15.087)
Clinical TNM status, T, number (%)	
T1	9 (4.5)
T2	77 (38.5)
T3	105 (52.5)
T4	9 (4.5)
Clinical TNM status, N, number (%)	
N0	142 (71)
N1	24 (12)
N2	34 (17)
Clinical TNM status, M, number (%)	
M0	187 (93.5)
M1	13 (6.5)
Preoperative neoadjuvant treatment, number (%)	
Short course radiotherapy	4 (2)
Long course chemoradiation	36 (18)
Chemotherapy alone	4 (2)

ASA American Society of Anaesthesiologists, *BMI* body mass index, *T* tumor, *N* node, *M* metastasis

Table 2 Operative details

Procedure performed, number (%)	
Low anterior resection	140 (70)
Intersphincteric APE	60 (30)
Splenic flexure mobilization, number (%)	
Yes	93 (46.5)
No	107 (53.5)
Operating time, minutes, mean (± SD)	
Total	285.55 (63.334)
Transanal part	69.66 (30.852)
Blood loss, milliliters, mean (± SD)	79 (125.05)
Intraoperative complications, number (%)	
Total	18 (9)
Bleeding	12 (6)
Bowel perforation (abdominal part)	2 (1)
Bowel perforation (transanal part)	2 (1)
Bladder injury	2 (1)
Urethral injury	1 (0.5)
Extraction site, number (%)	
Transanal/through perineal wound	162 (81)
Suprapubic incision	38 (19)
Conversion to open surgery, number (%)	1 (0.5)
The sequence of the procedure, number (%)	
Abdominal–transanal	189 (94.5)
Transanal–abdominal	1 (0.5)
Synchronous	10 (5)

APE abdominoperineal excision, *SD* standard deviation

anastomotic leakage was as follows: repeated rectal washout (2), endosponge [15] no treatment (10), and colostomy (1). Five patients who had anastomotic leakage ended up having a permanent colostomy. Table 4 shows the postoperative surgical complications, and Table 5 shows the postoperative medical complications, which occurred in 14 (7%) patients.

In the logistic analysis, none of the following variables was significantly associated with anastomotic leakage: gender ($P = 086$), BMI ($P = 0.984$), preoperative neoadjuvant treatment (0.664), anastomotic orientation ($P = 0.664$) ,or the size of the circular stapler ($P = 0.586$).

Among 140 patients with anastomosis and diverting ileostomy, 113 underwent stoma closure. However, only 104 patients were stoma-free at the end of the follow-up period; eight patients had a permanent colostomy, and one patient underwent a new loop ileostomy formation. Thus, the number of patients with a stoma was 36 (colostomy = 8, ileostomy = 28).

Pathologic outcomes

The TME specimen was incomplete in 22 (11%) patients, and the CRM was positive in 11 patients (5.5), and the DRM was positive in one patient (0.5%). In the logistic regression analysis, the only significant independent factor for incomplete TME specimen was a T4 tumor ($P = 0.004$). Gender ($P = 0264$), BMI ($P = 0.438$), tumor height from the anal verge ($P = 0.804$), intraoperative bowel perforation ($P = 0.055$), and the performed procedure ($P = 0.824$) were not significant predictive factors for incomplete TME

Table 3 Operative details of the low anterior resection subgroup

	Number = 140
Tumor height from anal verge in cm, mean (± SD)	8.26 (1.682)
Splenic flexure mobilization, number (%)	
Yes	85 (60.7)
No	55 (39.3)
Type of anastomosis, number (%)	
Side-end	112 (80)
End-end	28 (20)
Size (mm) of the circular stapler, number (%)	
33	63 (45)
32	72 (51.5)
31	3 (2.1)
28	2 (1.4)
Height of anastomosis from anal verge in cm, number (%)	
3	25 (17.9)
4	45 (32.1)
5	50 (35.7)
6	19 (13.6)
7	1 (0.7)
Extraction site, number (%)	
Transanal	107 (76.4)
Suprapubic incision	33 (23.6)

SD standard deviation

specimen. Intraoperative bowel perforation was the only significant positive predictive factor for positive CRM ($P < 0.001$). A T4 tumor was the only significant independent predictive factor for a non-successful resection ($P = 0.003$) (Table 6).

Oncologic results and survival

Following a mean follow-up of 29 months (range 1–61, ± SD 15.994), the number of survived patients was 180 (90%), of whom 162 were disease-free (81%). LR occurred in seven patients (3.5%). All these occurred in patients with a minimum length of follow-up of 2 years ($n = 150$ patients, adjusted percentage of LR = 4.7%). The mean time to LR was 24 months (range 10–45, ± SD 12.632). Metachronous DM occurred in 24 patients (12%), and the mean time to metastasis was 19 months (range 6–45, ± SD 10.185). Four patients who developed distant metastasis had metastatic disease at diagnosis and underwent radical liver surgery before rectal resection. Patients who developed LR had no metastasis at diagnosis.

In the logistic regression analysis, anastomotic leakage was a significant independent factor for the occurrence of LR, among 140 patients who had an anastomosis at the primary surgery ($P = 0.019$). Gender ($P = 0.945$),

Table 4 Postoperative surgical complications

Complication	Number (%)
Anastomotic leakage (among 140 patients)	
Total	13 (9.3)
CD 2	4 (2.9)
CD 3a	7 (5)
CD 3b	2 (1.4)
Mechanical bowel obstruction	
Total	4 (2)
CD 3b	3 (1.5)
CD 4a	1 (0.5)
Paralytic ileus	
Total	13 (6.5)
CD 1	2 (1)
CD 2	9 (4.5)
CD 3b	2 (1)
Intraabdominal abscess	
CD 3b	3 (1.5)
Bleeding	
Total	2 (1)
CD 2	1 (0.5)
CD 4b	1 (0.5)
Wound infection	
Total	12 (6)
CD 1	3 (1.5)
CD 2	3 (1.5)
CD 3a	5 (2.5)
CD 3b	1 (0.5)
Stoma necrosis	
CD 3b	2 (1)
Total	49 (24.5)

CD Clavien Dindo classification of surgical complications

Table 5 Postoperative medical complications

Complication	Number (%)
Myocardial infarction, total	1 (0.5)
CD 3a	1 (0.5)
Aspiration, total	1 (0.5)
CD 3b	1 (0.5)
Pneumonia, total	9 (4.5)
CD 2	8 (4)
CD 4a	1 (0.5)
Respiratory failure, total	2 (1)
CD 4a	1 (0.5)
CD 5	1 (0.5)
Renal failure, total	1 (0.5)
CD 2	1 (0.5)
Total	14 (7)

CD Clavien Dindo classification of surgical complications

Table 6 Pathologic results

TME specimen grade[a], number (%)	
Complete	133 (66.5)
Nearly complete	45 (22.5)
Incomplete	22 (11)
CRM, number (%)	
CRM negative	189 (94.5)
CRM positive	11 (5.5)
DRM, number (%)	
DRM negative	199 (99.5)
DRM positive	1 (0.5)
CRM in mm, mean (range, ± SD)	9.06 (0–50, 7.413)
DRM in mm, mean (range, ± SD)	26.27 (0–95, 16.157)
Successful resection rate, number (%)	
Resection successful	172 (86)
Resection not successful	28 (14)
Pathology staging, T, number (%)	
T0	7 (3.5)
T1	16 (8)
T2	65 (32.5)
T3	105 (52.5)
T4	7 (3.5)
Pathologic staging, N, number (%)	
N0	130 (65)
N1	44 (22)
N2	26 (13)

[a]According to Quirke et al.: *TME* total mesorectal excision, *CRM* circumferential resection margin, *DRM* distal resection margin, *T* tumor, *N* node

BMI ($P = 0.632$), preoperative neoadjuvant therapy ($P = 0.997$), quality of TME specimen ($P = 0.820$), rates of positive CRM ($P = 0.208$), T4 tumor ($P = 0.999$), rates of retrieved positive lymph nodes ($P = 0.073$), tumor height ($P = 0.315$), extraction site ($P = 0.516$), and the performed procedure ($P = 0.183$) were not positive predictive factors for LR (Table 7).

Comparison of the early versus late period

During the second period of our experience, we performed a low anterior resection in 81% of patients. This was significantly higher than 59% in the first period ($P = 0.001$). The operating time for the transanal part was significantly shorter in the second period ($P < 0.001$). We found no statistically significant differences between the two periods for the other main short-term outcomes. Table 8 shows these comparisons.

Table 7 Local recurrence and distant metastasis

Outcome	Number (%)
Local recurrence	
Total	7 (3.5)
Extra luminal	2 (1)
Intra and extra luminal	2 (1)
Multifocal[a]	3 (1.5)
Distant metastasis	
Total	24 (12)
Liver	13 (6.5)
Lung	4 (2)
Multiple sites[b]	7 (3.5)
Local recurrence and distant metastasis	6 (4)
Local recurrence and liver metastasis	1 (0.6)
Local recurrence and lung metastasis	1 (0.6)
Local recurrence with both liver and lung metastasis	4 (2.8)
Total	25 (12.5)

[a]Multiple foci in the pelvis

[b]Lung, liver, and carcinomatosis

Learning curve

Figure 1 shows the CUSUM chart for the total operating time. The chart shows a decrease in the total operating time in case 140. Prior to that, the operating time tends to lie in the upper limits, with an "out of control" pike at case 133 and 134. Figure 2 shows the CUSUM chart for the transanal part of the procedure, which decreases significantly in case 151 and afterward and falls below the average. The chart shows a steady decrease in the operating time for the transanal part from case 96. The intraoperative blood loss is shown in Fig. 3, where the blood loss was "out of control" on several occasions, the last of which at case 139, after which the blood loss was generally less than that in the previous period. In accordance with findings in Table 8, these results indicate proficiency acquisition in the second half of our experience, translated into stability in some important outcomes.

Discussion

This was an audit of a single-center experience with a consecutive large number of TaTME procedures. We have shown that the procedure is feasible and safe in accordance with the literature and our own previous experience [2, 3, 16]. The application of such a demanding approach for patients with mid- and low-rectal cancer was in accordance with expert recommendations [17]. The rates of intraoperative complications were in accordance with the literature [16, 18], especially severe complications like urethral

Table 8 The main characteristics and primary short-term outcomes compared between first and second periods

Variable/outcome	Cases 1–100	Cases 101–200	*P* value
Gender, number			0.873
Female	27	26	
Male	73	74	
BMI, mean (± SD)	26 (± 4.359)	27 (± 4.244)	0.793
Tumor height from anal verge, cm, mean (± SD)	7.6 (± 1.917)	8.12 (± 1.771)	0.219
Procedure performed, number (%)			0.001
Low anterior resection	59	81	
Intersphincteric APE	41	19	
Operating time, minutes, mean (± SD)			
Total	289.39 (± 63.514)	281.70 (± 63.237)	0.392
Transanal part	85.41 (± 28.771)	53.90 (± 24.169)	< 0.001
Blood loss, ml, mean (± SD)	95.85 (± 120.958)	63.24 (± 127.599)	0.069
Intraoperative complications, number	13	5	0.048
Anastomotic leakage (among 140 patients), number (%)	4/59 (6.8)	9/81 (11)	0.383
TME specimen grade[a], number			0.900
Complete	67	66	
Nearly complete	23	22	
Incomplete	10	12	
CRM, number			1.000
CRM negative	94	95	
CRM positive	6	5	
Successful resection rate, number			0.419
Resection successful	87	85	
Resection not successful	13	15	

SD standard deviation, *BMI* body mass index, *CRM* circumferential margin

Fig. 1 CUSUM chart for total operating time

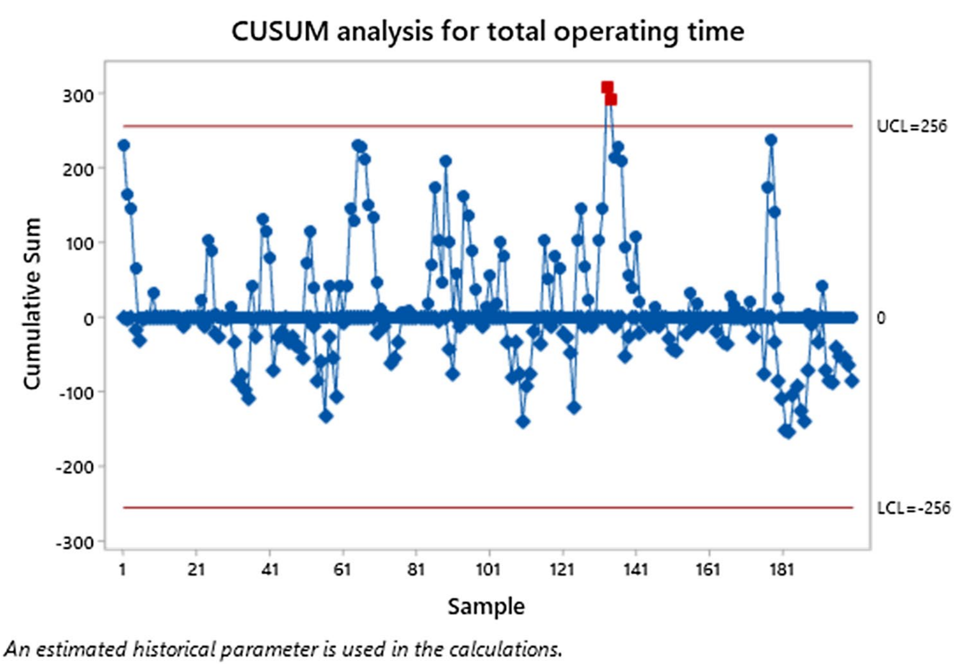


Fig. 2 CUSUM chart for transanal operating time

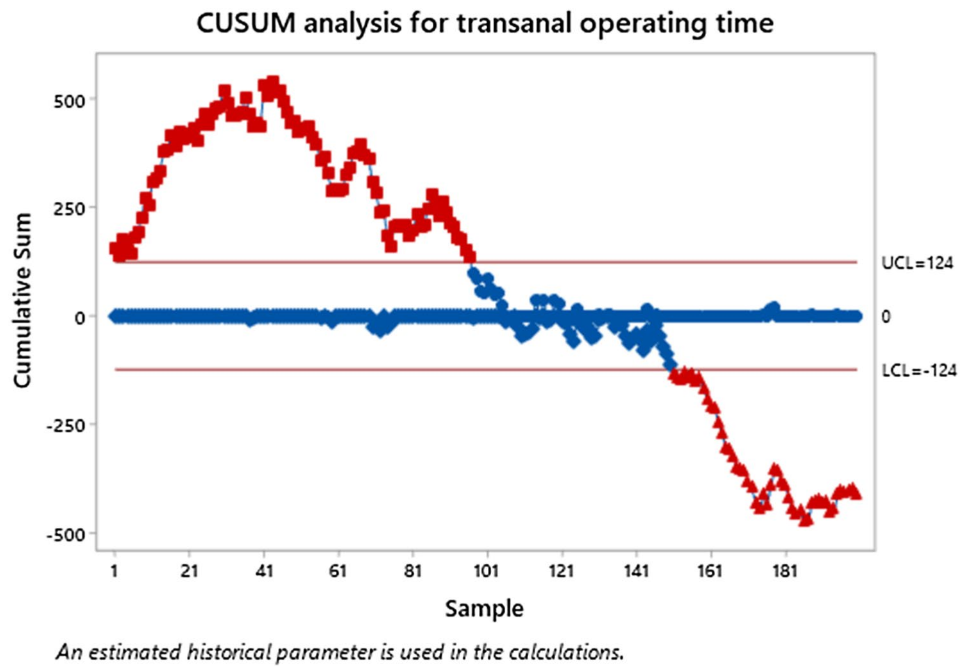
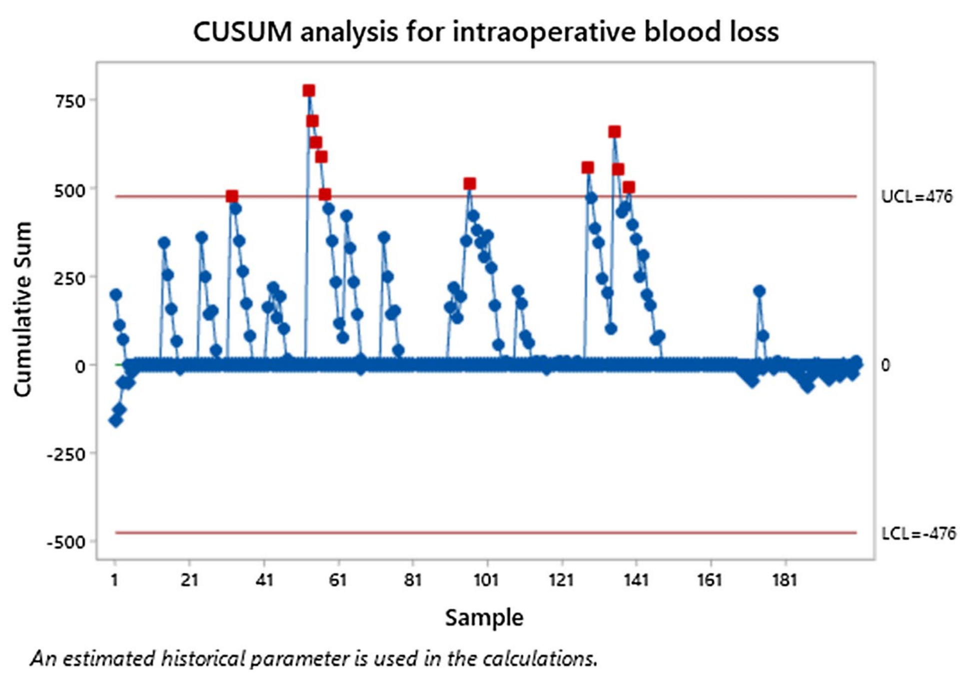


Fig. 3 CUSUM chart for intraoperative blood loss



injury, which occurred in one patient. No incidence of Carbon Dioxide (CO_2) embolism occurred, a complication that was previously reported in association with TaTME [19]. The conversion rate was almost negligible (0.5%). Four patients had an intraoperative bowel perforation. In two cases, the perforation occurred during the transanal phase of the procedure. Perforation is a severe complication and had a predictive effect on the rate of non-radical surgery in this study, but not on LR, and has been identified as a significant risk factor for LR [20].

The rates of postoperative surgical and medical complications were in accordance with the literature [21]. The rate of anastomotic leakage was likewise within the known range in the literature and lower than anastomotic leak rate reported by Penna et al. from the international TaTME registry [22]. Most leaks were mild and treated without the need for anastomosis takedown. Our rate of complete specimens was not very high. However, the rate of complete and nearly complete specimens was 89%. One explanation is our routine transanal extraction whenever this is possible, which could tear the specimens leading to a higher rate of incomplete and nearly complete TME specimens. The rate of positive CRM of 5.5% is to be considered acceptable and in accordance with the literature, and probably slightly higher than selected cases in the international registry [16, 23]. The rate of successful resection was lower in open and laparoscopic rectal surgery, in accordance with our own previous results [3, 13, 24]. One explanation is the relatively high rate of incomplete specimens in this study.

Seven patients in this study had LR, which, for patients with a follow-up length of at least 2 years, is equal to 4.7%. Anastomotic leakage had a predictive effect on LR. This rate is in accordance with the literature. One of these cases was published earlier [25]. There have been improvements in rates of LR and survival. Bill Heald, who introduced TME in the late 1970s and early 1980s, made the most critical change and could show dramatic improvements [26–28].

While the minimally invasive approach is the standard way to perform TME in large parts of the globe, the very same original TME principles are applied at this time. It is the oncologic safety of Bill Herald's TME, which remains the primary outcome to be valued highest when a new procedure is introduced. Minimal invasive laparoscopic and robot-assisted laparoscopic surgery are well established, mainly due to the reproducible results and robust evidence [29–32]. However, the "non-inferiority" of laparoscopic surgery has been questioned in two recent randomized trials [13, 24, 33]. The main challenges in rectal cancer surgery remain the lowermost part of the operative field, leading to conversion and inferior oncological outcomes [20, 34, 35]. Robot-assisted laparoscopic surgery probably overcomes some of the difficulties and yet to be proved [36]. The critical point is perhaps the direction of dissection and not the way of it, in other words, "from where" and not "by what" we perform the dissection. A very old method that was practiced in over a 100 years that is "dissection from below" is now being explored, utilizing a new technology. Funahashi et al. [37] reported a new procedure in 2009, where some dissection was done through the transanal route, followed by laparoscopic dissection, thus allowing for the most difficult lower part to be done from below where the surgeon is closest to the operative field. The results were quite acceptable. Denost et al. [38] have randomized 100 patients to either transanal or abdominal dissection of the lowermost part of the rectum and found improved short-term pathological outcomes, although this could not be translated to an improvement in local recurrence rate [39].

Since Buess developed his transanal endoscopic microsurgery (TEM) procedure for small rectal lesions in the early 1980s [40], several experimental studies explored the possibility of utilities beyond local excision [41, 42]. These and several other studies showed promising results in terms of feasibility in dissecting through a transanal platform using standard laparoscopic instruments. In the last decade, flexible transanal platforms are used to perform local excisions, and parts of TME procedures, the so-called hybrid procedure TaTME. With hundreds of reports on its feasibility in clinical practice [2, 3, 21, 43, 44] and thousands of patients treated this way [16, 22], the safety and effectivity regarding short-term outcomes are well established.

The oncologic safety of TaTME is, on the other hand, not established yet. Concerns about early recurrence have led to the abandonment of TaTME in at least one country [45]. Hol et al. [46] have reported quite acceptable long-term results. Roodbeen et al. [47] have reported a low recurrence rate after TaTME from expert centers. Thus, no definite alarming data are yet available, and long-term results from centers with the most extensive experience would add more evidence, and clarify whether TaTME is the new gold standard [48]

This study had several limitations. Although it is a prospective study in the sense of data collection and a systematically maintained database, it is not a randomized study. We believe, however, that we had no missing data due to a quite well-established electronic chart system, regular multidisciplinary meetings, and a systematic method of clinical, radiological, and endoscopic controls for patients with rectal cancer. Another limitation is the absence of a control group, though this was done in our previous publication [3]. The follow-up period was probably not long enough, although 150 patients had at least 2 years of follow-up. This is essential as most recurrences occur during the first 2 years after rectal cancer surgery, and even earlier after TaTME [45].

Conclusion

This study showed that TaTME is feasible, safe, and had acceptable short-term outcomes and an acceptable rate of LR. Studies with longer follow-up are to be awaited.

Compliance with ethical standards

Disclosure Drs. Sharaf Karim Perdawood, Jens Krøigaard, Marianne Eriksen, and Pauli Mortensen have no conflicts of interest or financial ties to declare.

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