Transanal total mesorectal excision for rectal cancer

Francisco de Borja de Lacy Oliver

DOCTORAL THESIS

TRANSANAL
TOTAL MESORECTAL EXCISION
FOR RECTAL CANCER

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Dr. Antoni Castells Garangou, Director and Tutor of the Doctoral Thesis
"Transanal total mesorectal excision for rectal cancer,"

CERTIFIES:

That this work has been carried out under his direction in the Doctorate Program in Medicine and Surgery by the Ph.D. candidate Francisco de Borja de Lacy Oliver.

That the studies included meet the conditions required by the University of Barcelona for submission of a compendium of articles.

Finally, this Doctoral Thesis meets the conditions for its defense according to regulations of the University of Barcelona.

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Para Catalina, mi madre

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List of Abbreviations

TNM	Tumour-node-metastasis
TME	Total mesorectal excision
RCT	Randomized controlled trial
APC	Adenomatous polypsis coli
MSI	Microsatellite instability
EGFR	Epidermal growth factor receptor
MDT	Multidisciplinary team
TaTME	Transanal total mesorectal excision
DRM	Distal resection margin
CRM	Circumferential resection margin
LapTME	Laparoscopic total mesorectal excision
QoL	Quality of life
TEM	Transanal endoscopic microsurgery
TAMIS	Transanal minimally invasive surgery
NOTES	Natural orifice transluminal endoscopic surgery
TATA	Transanal abdominal transanal proctosigmoidectomy
AIS Channel	Advances in Surgery Channel
MCBF	Microcirculation blood flow
IAP	Intraabdominal pressure
ASM-Evac	AirSeal Mode Evacuation
$PetCO_2$	End-tidal CO_2
MAC	Minimum alveolar concentration
CM	Colon mucosa
CS	Colon serosa
MC	Mesentery of the colon
JM	Jejunum mucosa

JS	Jejunum serosa
M	Mesentery
RC	Renal cortex
RM	Renal medulla
CI	Cardiac index
HR	Heart rate
MAP	Mean arterial pressure
GEDI	Global end-diastolic index
SVRI	Systemic vascular resistance index
NO	Nitric oxide
NO_2-	Nitrite
NO_3-	Nitrate
PRA	Plasma renin activity
95% CI	95% confidence interval
IQR	Interquartile range
SD	Standard deviation
OR	Odds ratio
HR	Hazard ratio
RR	Risk ratio
GEE	Generalized estimating equations
CEM	Coarsened exact matching
CEA	Carcinoembryonic antigen
CT	Computed tomography
MRI	Magnetic resonance imaging
R-TME	Robotic total mesorectal excision
MRF	Mesorectal fascia
BMI	Body mass index
ASA	American Society of Anaesthesiologists
AV	Anal verge
ARJ	Anorectal junction
EMVI	Extramural venous invasion

cCR	Clinical complete response
pCR	Pathological complete response
ROC	Receiver operator characteristic
AUC	Area under the curve
TRG	Tumour regression grade
APR	Abdominoperineal resection
SCRT	Short course radiotherapy
SCRT-IS	Short course radiotherapy with immediate surgery
LCRT	Long course radiotherapy
LCCRT	Long course chemoradiotherapy
CT	Chemotherapy
LARS	Low anterior resection syndrome
IIEF-5	International Index of Erectile Function
FSFI	Female Sexual Function Index
ICIQ	International Consultation on Incontinence Questionnaire
EORTC	European Organization for Research and Treatment of Cancer
MID	Minimally important difference

CHAPTER 1

INTRODUCTION

INTRODUCTION

Colorectal cancer

Colorectal cancer is a major global public health issue. According to the 2018 Global Cancer Statistics, 1.8 million new cases of colorectal cancer are diagnosed worldwide, with almost 900,000 deaths per year (Figures 1-2) (1). It is the 2nd most common malignancy worldwide in women and the 3rd in men, and the most frequent tumour-node-metastasis (TNM) stages at diagnosis are II (T3-4 node-negative disease) and III (node-positive disease) (2). The implementation of screening programs, especially with colonoscopy, has been shown to reduce colorectal cancer incidence and mortality (3-5). However, incidence in young adults in developed countries seems to be increasing, which might be related to hereditary contribution but especially to lifestyle habits and the obesity epidemic (6, 7).

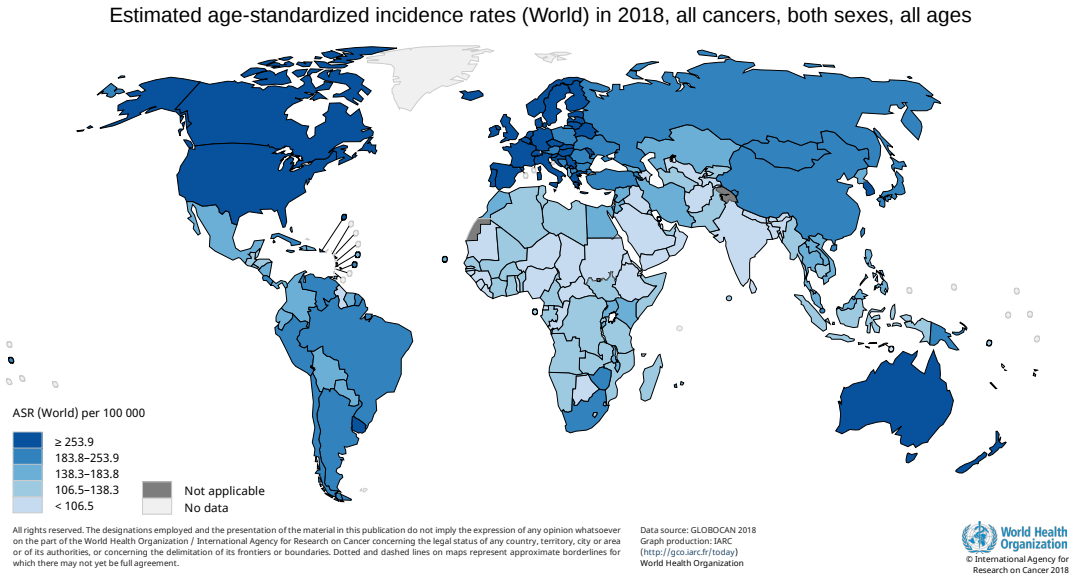


Figure 1: *Estimated age-standardized worldwide colorectal cancer incidence rates according to the latest WHO International Agency for Research on Cancer Figures (1, (8)*

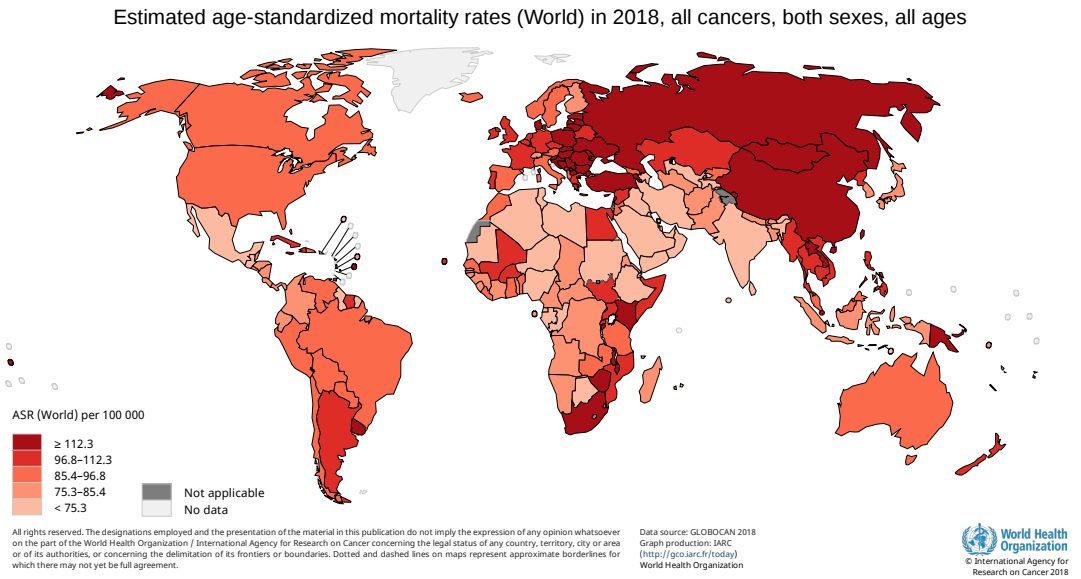


Figure 2: *Estimated age-standardized worldwide colorectal cancer mortality rates according to the latest WHO International Agency for Research on Cancer Figures (1, (8)*

Rectal cancer

The reported anatomical, molecular, pathophysiological, clinical and therapeutic differences between colon and rectal cancers have popularized the study of these diseases as two different entities. Approximately 30 to 35% of all colorectal cancers arise in the rectum (1, 9). Considering the difference in length between the colon (approx. 150 cm) and the rectum (15-16 cm), it has been suggested that rectal mucosa has a relative risk of malignant transformation four times greater than colonic mucosa (10). Nevertheless, determining rectal cancer specific mortality is challenging, since a significant number of deaths are still misclassified as due to colon cancer.

Primary rectal cancer evaluation

While rectal cancer progresses without any symptoms in the early stages, its clinical presentation usually includes a wide range of signs and symptoms, such as rectal bleeding, anaemia, tenesmus, and changes in bowel habits. Late symptomatic presentation in patients with metastatic disease will depend on the spread route of the tumour cells: hematogenous, where the lungs are the main target through the rectal veins draining to the inferior vena cava; lymphatic, where the supraclavicular lymph nodes can be palpated; peritoneal, where peritoneal implants develop; or contiguous invasion to neighbour structures. Thus, the clinical history must be complemented with a complete physical examination that includes exploration of signs of ascites, hepatomegaly, increased lymph nodes, and a digital rectal examination.

The diagnosis of rectal cancer is usually made by colonoscopy, identifying the lower border of the tumour less than 15 cm from the anal verge (AV). Colonoscopy makes it possible to establish tumour location, carry out biopsies, and exclude the presence of synchronous neoplasms. Given the considerable risk of synchronicity, in patients that are unable to undergo complete diagnostic colonoscopy, as with occlusive tumours, CT colonography is recommended. In patients with acute presentation, with symptoms of bowel obstruction, perforation or uncontrollable bleeding, the diagnosis of rectal cancer can also be made by means of imaging techniques or surgical intervention.

Consensus guidelines recommend the use of magnetic resonance imaging (MRI) for the locoregional staging of rectal cancer. MRI allows detailed planning prior to surgery, together with the addition of preoperative radiotherapy in selected cases, and guides further treatment pronouncements (11, 12). An accepted exception is in non-stenotic cT1N0M0 rectal cancer, where a transrectal ultrasound alone might be sufficient for local staging. Distant staging is routinely performed by thoracic and abdominopelvic CT scan. Although there is a lack of consensus from current practice guidelines, the role of PET-CT scan is increasing, especially

in those patients with resectable metastatic disease or with known allergy to iodine. Optimal determination of liver lesions usually requires an MRI.

A full blood count and determination of the carcinoembryonic antigen level (CEA) are recommended at the time of diagnosis. The baseline CEA value is a known prognostic survival indicator and enhances postoperative surveillance.

For pathological staging, the preferred system is he American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM. There are also several recognised poor prognostic factors, such as poor differentiation, lymphovascular invasion, perineural invasion, deficient tumour regression, and extramural deposits (13). In recent years, the molecular biology of (colo) rectal cancer is being increasingly recognised through several improvements and discoveries (14, 15). Chromosomal instability is the basis for mutations in the tumour suppressor gene adenomatous polypsis coli (APC). DNA mismatch repair genes, such as MLH1 and MSH2, are critical for preserving genomic integrity, and the loss of their activity results in the microsatellite instability (MSI) characteristic of Lynch syndrome. Furthermore, for (colo)rectal cancers with high MSI, immunotherapy is being currently considered as an effective therapy (16). Finally, mutations along the RAS/BRAF signalling pathway are predictive biomarkers for the response to antibodies against the epidermal growth factor receptor (EGFR). Therefore, the role of histology in (colo)rectal cancer staging, in addition to guiding further surgical and systemic therapeutic decisions, is still noteworthy.

Rectal cancer management

Rectal cancer modern therapy is eminently multidisciplinary. The discussion of the imaging, oncological, surgical, and pathological data in a multidisciplinary team (MDT) has led to improved cancer care, and these tumour boards are considered as mandatory in national treatment guidelines for meeting quality standards (12, 17-19). MDT decisions should guide the management of all rectal

tumours, including indications for neoadjuvant therapy, the precision surgery, the non-operative management, and the optimal indications for adjuvant or systemic therapy. From now on we will refer to the standard curative treatment of primary rectal cancer, since a detailed discussion of other techniques and options for metastatic disease is beyond the scope of this thesis.

Despite the new advances that allow local therapies for selected early cancers and even non-interventional settings, the gold-standard curative treatment for rectal cancer is the total mesorectal excision (TME) (20). This technique consists in the radical resection of the rectum, tumour, and locoregional lymph nodes included in the mesorectal envelope. The pathologist acts as an auditor of the rectal cancer specimen, since the main factors when evaluating TME quality are the integrity of the mesorectum, the status of the resection margins, and the number of resected lymph nodes:

Integrity of the mesorectum (Figures 3-4): the integrity of the mesorectum is directly related to the plane at which the surgeon performs dissection of the rectum and the perirectal soft tissue from the pelvis. Thus, the plane of surgery can be mesorectal, intramesorectal, or muscularis propria, as delineated by Quirke and colleagues (21).

Resection margins: the concept of distal tumour spread is presence of tumour cells within the mesorectum or rectum, distal to the level of the tumour. Several studies demonstrated that the presence of tumour distal spread beyond 2 cm is exceedingly rare (22, 23). As a result of this discovery, distal margins of 2 cm became generally accepted. More recently, with the introduction of surgical techniques such as double stapling as well as neoadjuvant chemoradiotherapy and the widespread use of TME, 1 cm or sub-centimetre distal resection margins (DRM) have gained greater approval. The importance of the circumferential resection margin (CRM) has been demonstrated by Quirke in a landmark study published in 1986, where the high incidence of local recurrence in patients with rectal cancer was directly related to the involvement of the CRM rather than

the distal margin (24). Numerous subsequent studies have confirmed that the presence of tumour ≤1 mm from the CRM adversely affects outcomes both at the local and systemic levels. There are three basic mechanisms for CRM involvement: 1) direct tumour extension; 2) foci of vascular / perineural invasion or tumour deposit; and 3) positive lymph node. Although there are currently no published series addressing the prognostic significance of each of these events, it appears that direct extension of the tumour into the CRM would carry a more ominous prognosis. Several factors have been associated with a positive CRM. including large and deep tumours, vascular and perineural invasion, poor tumour differentiation, advanced age, and mesorectal quality based on the quality of the surgical resection. The latter in particular has significant influence on the status of the CRM, which is only logical, as specimens with incomplete peritumoral mesorectums have a higher risk of a positive CRM.

Lymph node evaluation: although the adverse impact of lymph node metastasis is well known, the total number of dissected lymph nodes, regardless of status (positive or negative), also influences the outcome of patients with (colo) rectal cancer. It is important to point out that the rectum inherently contains fewer and smaller lymph nodes compared to other segments of the intestinal tract. In addition, factors including obesity, male gender, advanced age, and neoadjuvant radiation have all been associated with a lower number of lymph nodes (25). Conversely, tumour features such as depth of invasion into the rectal wall and poor differentiation have been found to correlate with a higher node yield. Certainly, the number of lymph nodes evaluated also reflects the quality of the surgery performed by the surgeon. as well as the diligence and effort of the dissecting pathologist. In cases of an optimal TME, the lymph node harvest depends entirely on meticulous work by the pathologist. Although lymph node dissection from rectal cancer specimens is traditionally carried out through a combination of palpation and visualization of the mesorectal tissue, several auxiliary techniques have been developed to further increase nodal yields.

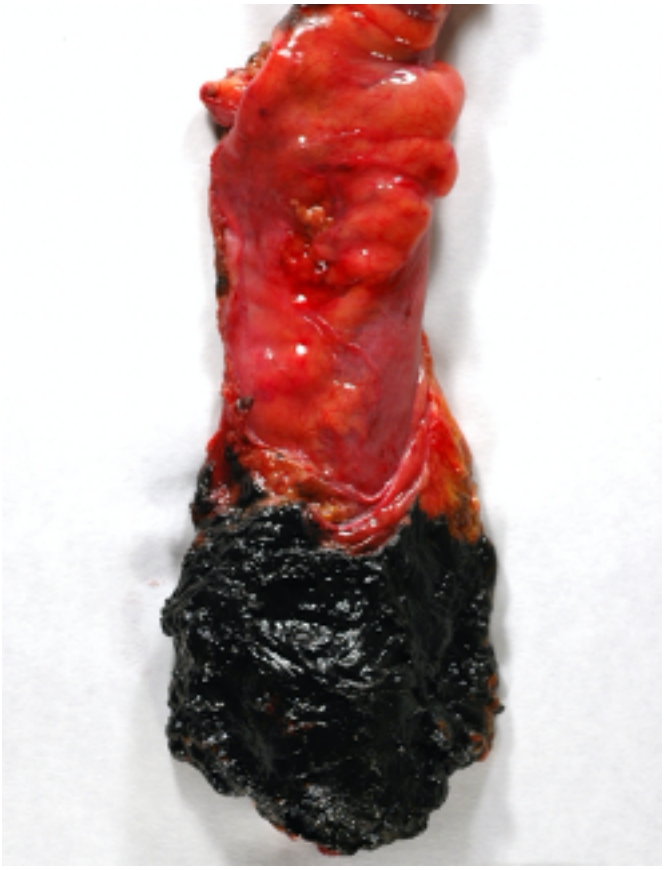


Figure 3: *Macroscopic evaluation of a complete mesorectum (mesorectal plane) from an anterior view. Photos courtesy of Dr. M Cuatrecasas, Hospital Clínic of Barcelona, Spain*

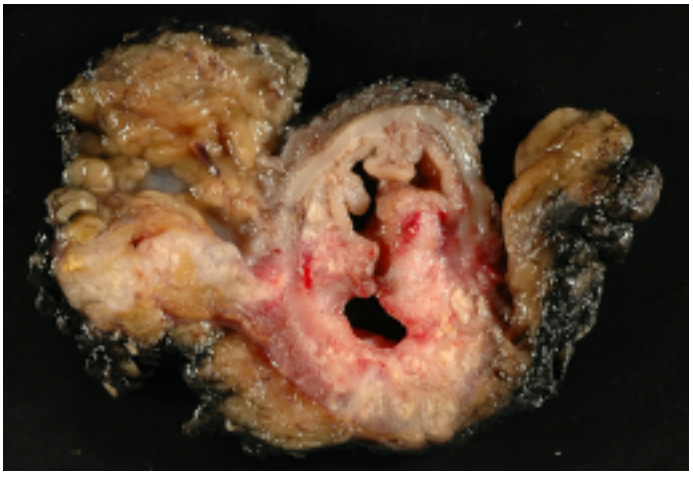


Figure 4: *Macroscopic evaluation an incomplete mesorectum (muscularis propria in contact with the resection plane) from a coronal view*

Besides the quality of surgery, there is evidence that supports the indication of neoadjuvant therapy in selected cases, based on a lower risk of locoregional recurrence (26). Traditionally, rectal cancer neoadjuvancy has been based on two schemes: a) long-course chemoradiotherapy administered by continuous 5-fluorouracil infusion (225 mg/m^2 for five days per week) or capecitabine (825 mg/m^2 twice daily for five days per week), and a total dosage of 45 Gy, by means of a weekly dose of 9 Gy divided into five days each week, for a total of five weeks; b) short-course one-week radiotherapy administered as 25 Gy in five daily fractions. However, other approaches, such as induction chemotherapy followed by long-course chemoradiotherapy, and consolidation chemotherapy after long-course chemoradiotherapy but before surgery, seem to be evidence-based (12). The classical indication for neodjuvant therapy was T3-4 or node-positive tumours below the peritoneal reflection. Nevertheless, research has focused on new target biomarkers such as extramural venous invasion (EMVI) and threatened CRM on baseline MRI.

The main objective of neoadjuvant therapy is to reduce tumour burden and facilitate downstaging, thus increasing the likelihood of obtaining higher rates of R0 resections (27, 28). However, pathological complete response (pCR) is observed in 10-25% of rectal cancers following neoadjuvant therapy, and is currently considered as one of the main predictive factors affecting long-term survival and recurrence (29, 30). The role of organ-preserving strategies and the appropriate interval between neoadjuvant radiotherapy completion and surgery, seeking the highest pCR rates, are currently promising research areas.

Adjuvant therapy is usually considered for fit patients with pathological-confirmed node-positive disease for which R0 resection has been performed. In the case of node-negative disease, adjuvant therapy is discussed by the MDT, considering the remaining risk factors for recurrence and the predicted toxicity. The most widely accepted adjuvant therapy is an oxaliplatin-regimen associated with a fluoropyrimidine (fluorouracil or capecitabine). However,

whether adjuvant chemotherapy improves outcomes in patients who have received neoadjuvant chemoradiotherapy is currently under debate.

Until the 1980s, rectal cancer surgery was associated with locoregional recurrence rates as high as 30%. However, significant improvements in recurrence and overall survival rates have been achieved over the past three decades. Centralization in high-volume centres and the use of neoadjuvant therapy in selected patients resulted in improved survival outcomes. Still, for cancer of the mid and distal rectum, TME has been the main single prognostic factor influencing long-term outcome (24, 31). Dissection along embryological-specific planes has decreased locoregional recurrence risk to less than 10% and increased five-year overall survival to about 75% (20, 32).

Surgical therapy in rectal cancer

The classical TME surgery was performed by laparotomy. However, in the 1990s, the introduction of laparoscopy for the management of multiple abdominal diseases was associated with an enhanced recovery, with less postoperative pain and shorter hospital stay (33-36). Nevertheless, evaluation of the safety of minimally invasive techniques in oncological diseases was mandatory. In rectal cancer, several randomized controlled trials (RCT) showed that laparoscopic TME was associated with short-term benefits and similar disease-free and overall survival compared to open surgery (37, 38). Currently, laparoscopic primary TME represents roughly 90% of all rectal operations in specialized centres (39).

However, the technical challenges of working in the low pelvis with laparoscopic instruments, and especially the recent concerns about its oncological safety reported in the two RCTs, have arisen as arguments against its routine use (40-42). These two studies, namely ALaCaRT (Australasian Laparoscopic Cancer of the Rectum) and ACOSOG (American College of Surgeons Oncology Groups) Z6051,

were similarly designed non-inferiority trials that utilized a new trichotomous composite outcome based on the completeness of the mesorectal excision as well as the negativity of the circumferential and distal resection margins. Both trials failed to demonstrate a non-inferiority of the laparoscopic approach relative to the traditional open approach, although the lack of validation, and therefore the unestablished clinical and oncologic significance of the primary composite outcome, made the oncology community somewhat hesitant to accept these trials results.

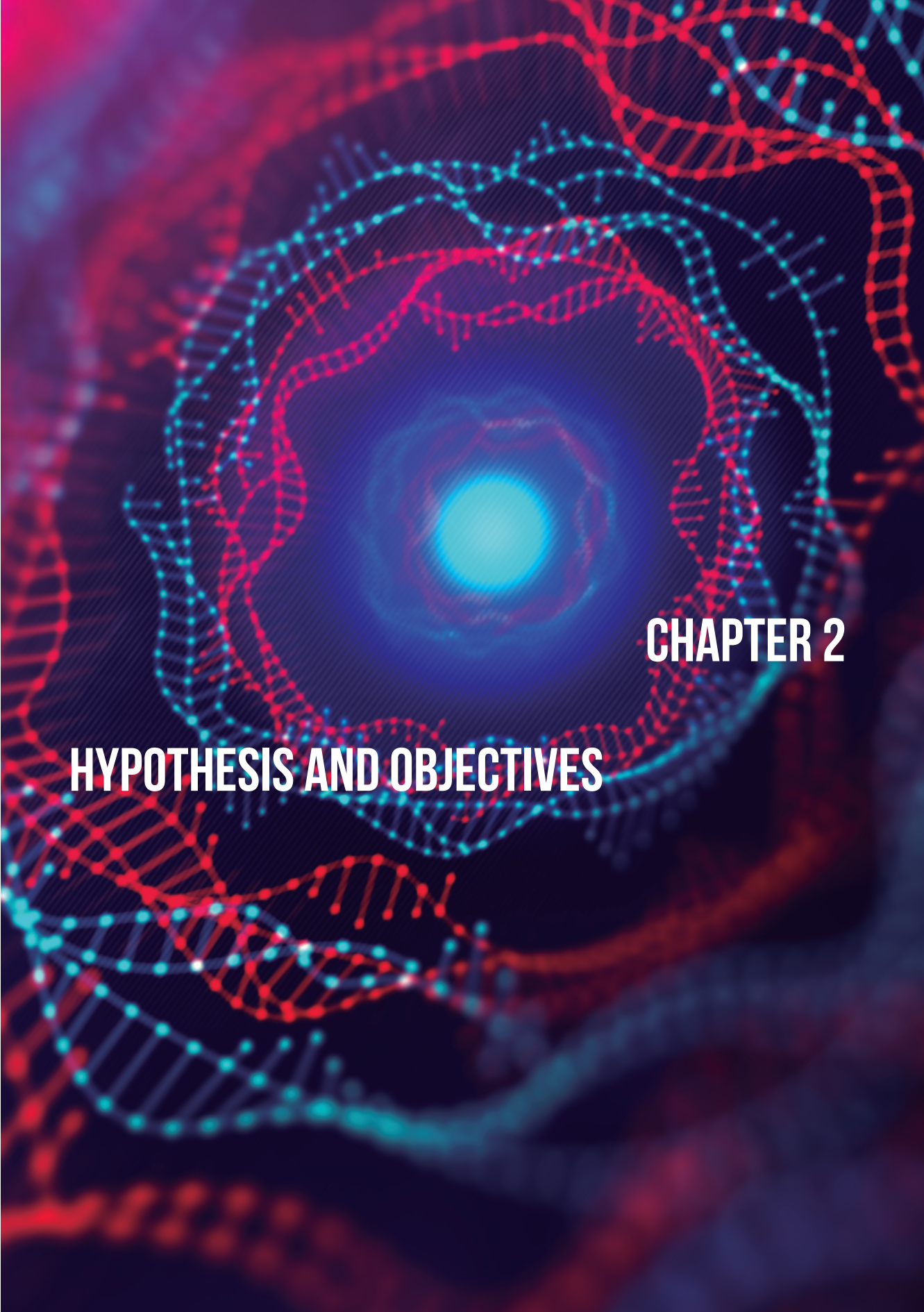
Recently, the mid-term outcomes of the ACOSOG Z6051 found similar survival between laparoscopic and open TME within two years after surgery (43). Still, the study was not designed as an equivalence trial for survival and recurrence, and the absence of numerical distinctions might not be indicative of any dissimilarity. Thus, waiting for further evidence, the doubts over the oncological safety of the laparoscopic approach for rectal cancer surgery persist.

Two technical innovations have been proposed to address this issue. The first innovation is robotic surgery, which provides a valuable three-dimensional view, endowristed instrumentation, and a stable camera platform (44). Robotic-assisted laparoscopic TME might potentially achieve acceptable outcomes, although this is yet to be confirmed (45). Moreover, it requires an in-depth cost-effectiveness analysis. The second innovation is Transanal Total Mesorectal Excision (TaTME), a minimally invasive transanal approach to conventional transabdominal laparoscopy. TaTME was first performed in Barcelona in 2009 and has become an acceptable alternative to open and purely laparoscopic surgery (46). The value of TaTME lies in easier dissection of the distal rectum and direct control of the DRM. TaTME is said to improve resection quality, especially in obese, male patients, with narrow pelvis and mid-low tumours (47, 48).

In 2016, the results of the TaTME International Registry were published, bringing together the data collected in 66 units from 23 countries to evaluate the short-term results of the first 720 patients (48). The anastomotic leak rate was 6.7%,

96% of mesorectal specimens were considered complete or almost complete, and the CRM was positive in 2.4% of cases. The investigators concluded that TaTME seemed an effective technique for dissection of the distal mesorectum, with acceptable short-term outcomes and excellent specimen quality. Veltcamp Helbach et al. reported that TaTME was associated with significant decrease in the prevalence of residual mesorectal tissue on postoperative imaging compared to standard laparoscopic TME (LapTME) (3.1% vs. 46.9%) (49). Besides, two meta-analyses have showed a significant benefit of TaTME for the integrity of the mesorectum and the status of the CRM compared to LapTME (50, 51). And a recent single-arm study including 767 patients from six high-volume rectal units with more than two years follow-up has shown a two-year local relapse rate of 3% (52). In the absence of randomized data, the outstanding results from observational studies and international prospective registries have led to the global expansion of TaTME (53).

Bearing this background in mind, there are good reasons to believe that TaTME may play a substantial role in the treatment of rectal cancer. However, a comprehensive approach is required to accept a new technique, and several issues need a more in-depth analysis. Moreover, TaTME can be technically challenging, and formal research and structured training are highly recommended for safe implementation (54, 55). Otherwise, patient experience and safety will not be optimized. For example, recent studies have shown an unexpected pattern of early and aggressive locoregional recurrence after TaTME (56, 57). These unfavourable oncological outcomes may result from a lack of experience during the initial phase of the learning curve. Thus, in-depth research is required to avoid risks that may discredit a surgery that seems to bring benefits to selected patients.



CHAPTER 2

HYPOTHESIS AND OBJECTIVES

HYPOTHESIS AND OBJECTIVES

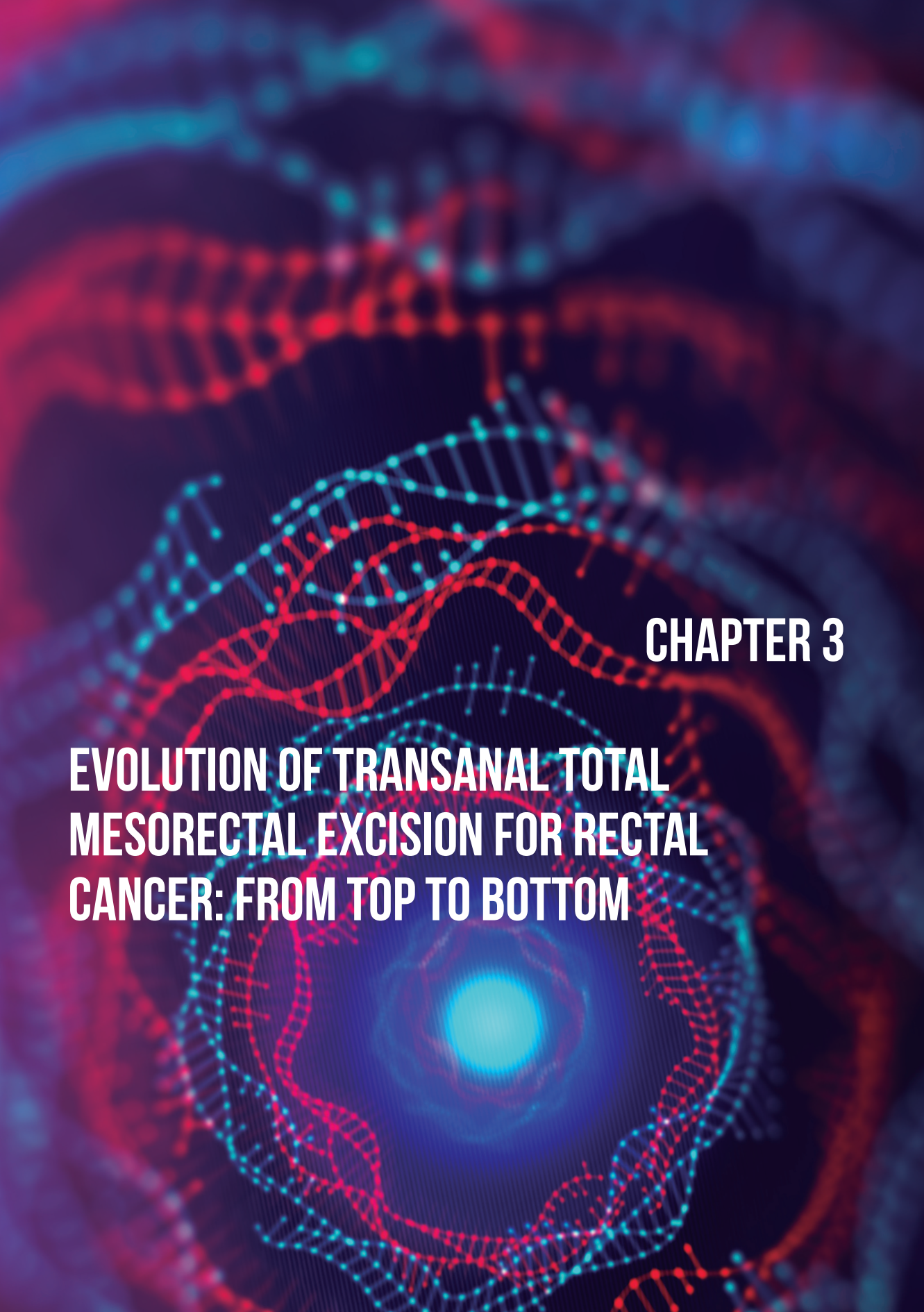
HYPOTHESIS

The oncological outcomes of TaTME are, at least, similar to those of the established conventional TME techniques for rectal cancer, without a worsening of the functionalism and the patient's health-related quality of life.

OBJECTIVES

- To evaluate the impact of TaTME on the short- (histopathological) and mid-term (survival and recurrence) outcomes in patients with rectal cancer (**Chapters 4, 5, and 6**).
- To evaluate the impact of TaTME on the function and health-related quality of life among patients with rectal cancer (**Chapter 7**).
- To compare the quality of the resection in the two proposed solutions for the dilemma of minimally invasive TME: TaTME *versus* robotics (**Chapter 8**).
- To evaluate the effects on tissue microcirculation and surgical stress of a new CO2 insufflation system specially designed for TaTME (**Chapter 9**).


TaTME
for rectal cancer
Histopathological outcomes
Funtional outcomes and quality of life
Predictive factors for CRM+ and risk model
TaTME vs Robotics
Survival and recurrence
Experimental study



CHAPTER 3

EVOLUTION OF TRANSANAL TOTAL MESORECTAL EXCISION FOR RECTAL CANCER: FROM TOP TO BOTTOM

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REVIEW

Evolution of transanal total mesorectal excision for rectal cancer: From top to bottom

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Conflict-of-interest statement: Professor Lacy is the founder and director of Advances in Surgery (AIS) channel, Dr. Lacy and Dr. Martin-Perez are members of the team operating the AIS channel, and Mr. Chand is the AIS Country Coordinator in United States. There was no association between the present work and the AIS channel. Dr. Emile and Dr. Keller have no potential conflicts of interest.

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Abstract

The gold standard for curative treatment of locally advanced rectal cancer involves radical resection with a total mesorectal excision (TME). TME is the most effective treatment strategy to reduce local recurrence and improve survival outcomes regardless of the surgical platform used. However, there are associated morbidities, functional consequences, and quality of life (QoL) issues associated with TME; these risks must be considered during the modern-day multidisciplinary treatment for rectal cancer. This has led to the development of new surgical techniques to improve patient, oncologic, and QoL outcomes. In this work, we review the evolution of TME to the transanal total mesorectal excision (TaTME) through more

traditional minimally invasive platforms. The review the development, safety and feasibility, proposed benefits and risks of the procedure, implementation and education models, and future direction for research and implementation of the TaTME in colorectal surgery. While satisfactory short-term results have been reported, the procedure is in its infancy, and long term outcomes and definitive results from controlled trials are pending. As evidence for safety and feasibility accumulates, structured training programs to standardize teaching, training, and safe expansion will aid the safe spread of the TaTME.

Key words: Rectal cancer; Total mesorectal excision; Transanal total mesorectal excision; Transanal total mesorectal excision; Sphincter sparing surgery; Colorectal surgery

Core tip: The evaluation and management of rectal cancer have evolved remarkably over the last few decades. Total mesorectal excision (TME) has been recognized as the standard surgical management for curative radical treatment of rectal cancer. While abdominal procedures, whether by the open or minimally invasive approaches, apply the classical concept of "top-to-bottom" dissection, the transanal TME (TaTME) uses the opposite approach of "bottom-to-top" dissection. In this review we discuss the evolution of TME for rectal cancer to the TaTME, its technical aspects, advantages, shortcomings, and current needs. The research and education initiatives as well as future directions of TaTME were also highlighted.

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INTRODUCTION

Despite the current multidisciplinary modern management, rectal cancer remains a formidable challenge for the colorectal surgeon. Surgical therapy for rectal cancer has evolved since Dr. Ernest Miles described the abdominoperineal resection in 1908. With this radical resection and the realization that rectal cancer must be tackled from the both abdomen and perineum, Miles reduced the local recurrence rate from nearly 100% to 30%[1]. Defining the "zone of upward spread" he introduced the concept of surgical oncology whereby the tumor, blood supply and nodal tissue needed to be excised.

With better surgical tools enabling a low anastomosis, a shift toward sphincter-saving approaches began, with the anterior resection replacing abdominoperineal resection as the standard curative resection, when possible. These approaches resulted in poor oncologic outcomes for recurrence and overall survival. Technical advancement came to light in 1982, when Heald *et al*[2] published the total mesorectal excision (TME) technique. The TME entails sharp, nerve-sparing dissection in the avascular plane between the mesorectum and surrounding structures circumferentially. A complete TME with intact fascia and no invasion into the muscular coat or mucosa is an important, positive prognosticator against locoregional tumor recurrence[3].

TME became the gold standard for curative resection from proven better local control and survival[4]. Neoadjuvant and adjuvant chemotherapy and radiotherapy serve as adjuvants to improve the outcome after surgery; the dose and timing of these adjuncts are variable based on the disease stage and patient-related factors[5-14]. However, these adjuncts are not a substitute for a proper TME, with poor surgery yielding an inadequate surgical specimen invariably leading to local recurrence[15]. Additional evidence from the Medical Research Council of United Kingdom CR07 and National Cancer Institute of Canada-CTG CO16 (CR07) trial highlighted the importance of good quality surgery, and how inadequate surgery can be only minimally compensated for by chemoradiotherapy[3,16]. In the early 1990's, laparoscopic surgery was introduced, and gradually become applied to colon and rectal cancer. While there were initial concerns about the oncological safety of laparoscopy, the Clinical Outcomes of Surgical Therapy (COST) Trial demonstrated the safety, oncologic equivalency, and clinical benefits over open surgery[17]. Abundant support has reported comparable oncologic outcomes and improves short-term benefits of laparoscopic over open surgery for rectal cancer[3,18-21]. The safety of laparoscopy for rectal cancer was less clearly defined initially, as early controlled trials concentrated on the oncologic safety of colon cancer[17,20]. While skepticism remained, the improved outcomes with TME were shown to be generalizable in both open and minimally invasive approaches[3,6,22-28]. Then recent studies further questioned the oncologic equivalence of the laparoscopic approach for rectal cancer. The ALaCaRT and ACOSOG Z6051 trials failed to establish the non-inferiority of laparoscopy compared to open rectal cancer surgery[29,30]. The authors of ALaCaRT recommended using a different platform in low rectal cancers than pure abdominal laparoscopy, as working in the deep pelvis with rigid, straight laparoscopic instruments from difficult angles was challenging and required complex maneuvers[29]. Technical limitations exist with the laparoscopic approach, especially during the distal transection of the rectum, due to limited visualization and restriction working in the confined, bony pelvis[31]. These limitations highlighted the need for other approaches to

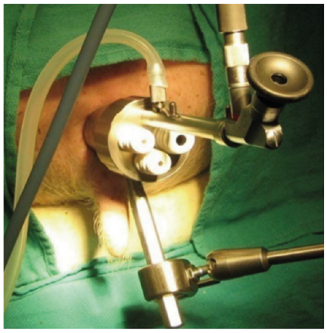

Figure 1 Transanal endoscopic microsurgeryplatform.

rectal cancer. Robotic assisted surgery was introduced to address the limitations of laparoscopy, and gained acceptance from the improved visualization, lower conversion rates, better TME quality lower positive CRM rate, and earlier recovery of genitourinary functions[32-34]. Studies reported equivalent oncologic and functional outcomes of both approaches, which raise the issue about the cost-effectiveness of the robotic platform, and the need for more effective and cost-efficient platforms[35-37].

Literature search

For this review, three of the authors reviewed published data regarding rectal cancer surgery, with attention to surgical techniques over the last several decades leading to the transanal TME. With the defined focus, PubMed and MEDLINE databases and the #colorectal research hashtag on Twitter were searched from database inception through September 15, 2017 for articles and data published with relevant evidence regarding the evolution of surgery for rectal cancer. The following search terms were used: "total mesorectal excision", "transanal excision", "local excision", "laparoscopic colorectal surgery", and "transanal total mesorectal excision", "TaTME", "rectal carcinoma" and "rectal cancer". Reference lists were manually searched and relevant articles were added if pertinent to the scope of the study. Articles were included if in English and the full content was available. Conference proceedings and videos were not included.

Evolution of surgical approaches in rectal cancer towards the TaTME

Despite significant advances in technology and use of minimally invasive approaches in many other surgical disciplines, open surgery remains the gold standard for rectal cancer. Technical challenges and subsequent low uptake of laparoscopy in low rectal cancer surgery and contention on the value of robotic platforms have left the door open for a new approach. An ideal approach would involve a short learning curve, low relative cost, reproducibility and clear evidence of patient safety.

Local excision

To leverage the benefits of a minimally invasive approach, intraluminal, endoscopic, transanal, and hybrid techniques have been expanded in recent years. Additional desire to improve not only oncological outcomes but also function and quality of life outcomes led to investigation of local excision techniques[38,39]. While local excision has improved functional outcomes compared with radical resection, the lack of lymphadenectomy and higher rates of positive resection margins, locoregional recurrence, and lower overall survival means that it may not be directly comparable to TME in terms of oncological outcomes[38-45]. Therefore, it is currently recommended for benign and early (T1) rectal lesions, unless on clinical trial[46,47]. With these outcomes, it was necessary to develop more precise methods for local excision[48].

Transanal endoscopic surgery

Advanced endoscopic platforms, combining the transanal and minimally invasive approaches addressed the limitations of conventional transanal resections, and allowed precise dissection of low and mid rectal tumors, a limitation of other platforms to date.

Transanal endoscopic microsurgery

In 1983, Dr. Gerhard Buess developed Transanal Endoscopic Microsurgery (TEM), (Figure 1), offering improved visualization from a stereoscopic magnified view in the gas-dilated rectum for precise excision in an operative space that would be otherwise difficult to reach, as well as significantly lower morbidity, lower local recurrence rates, with a higher rate of negative resection margins than traditional TAE[49-52]. Widespread adoption was limited due to the cost of the specialized instrumentation, additional learning curve, and limited indications for the technique[53-56].

Transanal minimally invasive surgery

Dr. Sam Atallah introduced Transanal Minimally Invasive Surgery (TAMIS), (Figure 2) as an alternate advanced videoscopic transanal platform that also combines minimally invasive benefits with transanal resection, but addresses some limitations of TEM[55]. The same superior visualization and reach of TEM is offered but using standard laparoscopic equipment reduces the cost and learning curve[55,57,58]. The TAMIS platform may also be less traumatic to the anal sphincter than TEM[57]. A recent systematic review described low conversion rate of 2.3%, and low rates of positive margins, tumor fragmentation, and overall complications of 4.36%, 4.1% and 7.4%, respectively[54]. Both TEM and TAMIS have limitations in patient selection, lack of adequate lymphadenectomy inability to adequately stage the pelvis, and prohibitively high recurrence rates with

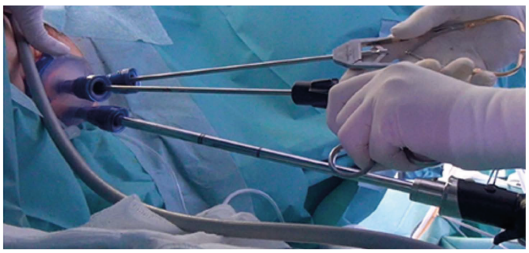

Figure 2 Transanal minimally invasive surgery platform. Photo courtesy of Antonio Lacy, Hospital Clinic and AIS Channel.

T2 and more advanced rectal tumors[55,59-62]. TEM and TAMIS remain important in the evolution of the TaTME platform.

Natural orifice transluminal endoscopic surgery

Natural orifice transluminal endoscopic surgery (NOTES) further pushed the boundaries of minimally invasive surgery, eliminating the extraction wound, associated pain, risk of wound infection and incisional hernia. The per-oral transgastric approach was first developed in animal models, and then intensely explored across transoral, transanal, transurethral, and transvaginal routes, before being cautiously tested in clinical practice[63,64]. Dr. Mark Whiteford reported a successful NOTES transanal sigmoid colectomy cadaver series in 2007[65], while Dr. Patricia Sylla combined the transgastric endoscopic and TEM platform in a swine rectosigmoid resection series[66].

Dr. Antonio Lacy was instrumental in moving the concept of NOTES out of the "lab" and into potential practise, reporting a sigmoid resection using transvaginal mini-laparoscopic-assisted natural orifice surgery for sigmoid adenocarcinoma[67]. Using the TEM platform in a human rectal cancer series, there seemed to now be a safe alternative to open and laparoscopic TME[68]. Several colorectal series followed, affirming the feasibility of NOTES[69-76]. However for the majority NOTES remains experimental, with concerns over the operative platform, accidental organ injury and viscerotomy closure[64,73]. The potential of performing complex colorectal dissection using existing transanal endoscopic platforms fueled the movement towards the TaTME.

Trans abdominal trans anal proctosigmoidectomy

Hybrid approaches to rectal cancer were occurring long before NOTES. For sphincter preservation and conservation of adequate function in very distal lesions, Dr. Gerald Marks developed the TransAnal Abdominal TransAnal Proctosigmoidectomy with colo-anal anastomosis (TATA) technique in 1984, a transanally initiated TME dissection that offers a direct, precise distal dissection, assuring adequate distal margins[77,78]. Dr. John Marks routinely integrated laparoscopic and robotic approaches with TATA, adding the advantages of minimally invasive surgery to this groundbreaking procedure. The TATA introduced the concept of "bottom-up" technique, in contrast to the "top-down" traditional technique followed in the abdominal procedures.

Transanal TME

TaTME extends the TATA's principle of initiating the TME dissection transanally (bottom-up) and accomplishes the most difficult part of the dissection from the caudal side[77]. Sylla and Lacy first described the TaTME in 2010[79] followed by an early case series of 20 patients[68], and a further validated series in 140 patients[80]. Since these early reports, numerous series have described the safety and feasibility of taTME even in challenging patients. The theoretical advantages of access and visualization have established this technique as not only a credible alternative to more traditional approaches which has the potential to provide optimal outcomes for oncologic resection of low rectal cancers[81-91].

Indications for TaTME: TaTME is mainly indicated for treatment of malignant tumors affecting the middle and lower third of the rectum. Moreover, it can be applied in benign conditions affecting the rectum such as Crohn's disease and ulcerative colitis. Benign indications for TaTME may include reversal of Hartmann's procedure, restorative proctocolectomy or completion proctectomy and ileal-pouch anal anastomosis[92].

Technical points of the TaTME: Briefly, the procedure is performed in the modified lithotomy (Lloyd-Davies) position. It can be performed by a single team or, as originally described by Lacy, two-team ("Cecil Approach"), which allows for shorter operative times, improved visualization, and better traction and counter-traction to facilitate the resection (Figure 3). The abdominal approach is determined by surgeon preference, and entails full left colon and splenic flexure mobilization, high ligation of the inferior mesenteric artery (with identification and preservation of the pelvic nerve plexuses), and division of the inferior mesenteric vein was divided at the inferior pancreas border, and a TME performed.

For TaTME, the rectum is irrigated, a purse-string suture placed to occlude the rectum, then the Transanal Access Platform inserted as shown in Figure 4, and pneumorectum established. Performing a tight purse-string suture is imperative to prevent translocation of liquid stool and cancer cells while the dissection is being carried out. Adequate rectal irrigation and the purse-string suture may help reduce the potential for implantation of cancer cells and/or bacteria inherent in the transanal dissection plane that could result in abscesses or local recurrence. While long-term outcomes will need to be assessed for these risks, measures to prevent the risk include standard manipulations and appropriate case selection as well as rectal irrigation with a cytocidal solution[93]. Under endoscopic visualization, the rectum is circumferentially

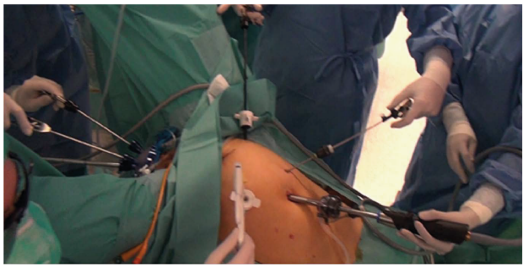

Figure 3 Two-teams working simultaneously for transanal total mesorectal excision ("Cecil Approach"). Photo courtesy of Antonio Lacy, Hospital Clinic and AIS Channel.

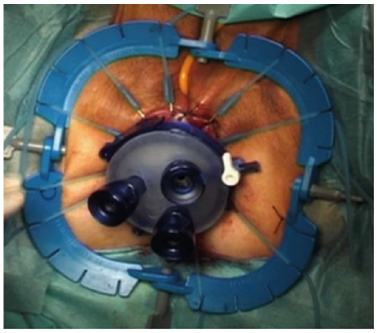

Figure 4 Transanal access platform with trocar insertion in an inverted triangle shape. Photo courtesy of Antonio Lacy, Hospital Clinic and AIS Channel.

mobilized, and the dissection continued proximally in the avascular TME plane towards the peritoneal reflection to meet the abdominal mobilization (Figure 5)[82,92]. The extraction can be performed transanally, or though a Pfannenstiel or stoma-site incision, depending on the abdominal approach used and the bulk of the specimen.

Safe implementation of TaTME: TaTME may enhance distal rectal access and visualization, allowing optimal margins, adequate lymph node yield, and high quality resection, even in the most difficult patients[94-96]. Denost *et al*[97] showed that the perineal approach reduces the risk of positive CRM compared to an abdominal approach, and may be an oncologically superior approach for low rectal cancer. Report from the International TaTME Registry suggests the procedure is oncologically safe and effective[83]. Since TaTME is in its infancy, longer follow-up and controlled trials needed. It is important to note that the TaTME is technically challenging, and formal training through a hands-on course is recommended, with active proctoring during the first year and ongoing participation within multicenter registries, for quality improvement and long term follow up[98]. Consensus for standardization of the technique and structured training are ongoing, to facilitate safe, appropriate implementation into clinical practice[92,98-101].

Advantages of TaTME: In general, transanal approaches allow better visualization of the distal rectum and clearly demonstrates the distal resection margin. The TaTME furthers these benefits, uniquely allowing deep pelvic dissection without the need for traction on the rectum. The plane of resection is clearly identified, even in obese and male patients with narrow pelvis, which were considered unfavorable conditions for laparoscopic TME[102].

Oncological benefits: The major potential benefit of TaTME is its theoretical ability to obtain a higher quality TME specimen. Results from the international TaTME registry showed complete or almost complete mesorectal excision rate of 96%, CRM positive rate of 2.4% and DRM positive rate of 0.3%[83]. Similarly, Xu *et al*[103] and colleagues concluded that TaTME provided lower rate of positive CRM compared to laparoscopic TME (OR: 0.34, 95%CI: 0.12-0.93; I^2 = 0%). A recent meta-analysis reinforced the previous results, demonstrating that TaTME attained significantly higher rate of complete and near complete mesorectal excision than laparoscopic TME[104]. Additionally, TaTME had wider CRM with a significantly lower number of patients with positive CRM (OR: 0.39, P = 0.02). However, more controlled trials including larger number of patients are required to validate the oncologic and pathologic outcomes with TaTME.

Functional benefits: Bowel, bladder, and sexual dysfunctions are among the most common and devastating complications of rectal cancer surgery. TaTME decreases the number of permanent stomas, but at the cost of increasing the rate of coloanal anastomoses. With this, there is the theoretical risk of impaired continence and functional outcomes. Few studies have addressed long-term functional outcomes to date. Preliminary results demonstrate similar postoperative sphincter function when compared with laparoscopic or open TME[105-107]. A recent review of 30 patients evaluating functional outcomes 6 mo after TaTME showed acceptable quality of life and functional outcomes, comparable to published results after conventional laparoscopic low anterior resection[108]. In this study, deterioration for all domains was observed at one month after surgery compared to baseline, but returned to baseline at 6 mo for all areas except social function and anal pain. More studies with larger sample sizes and longer follow up are needed. A lower rate of urinary dysfunction has been observed after TaTME, which can be attributable to the enhanced visualization that improves definition of anatomic landmarks and allows nerve-sparing dissection in the presacral plane[109].

The risk of urethral injury is a real concern, and a unique complication of the procedure; Studies have shown an incidence of more than 10%, in addition, injury of the urethral sphincter can lead to urinary

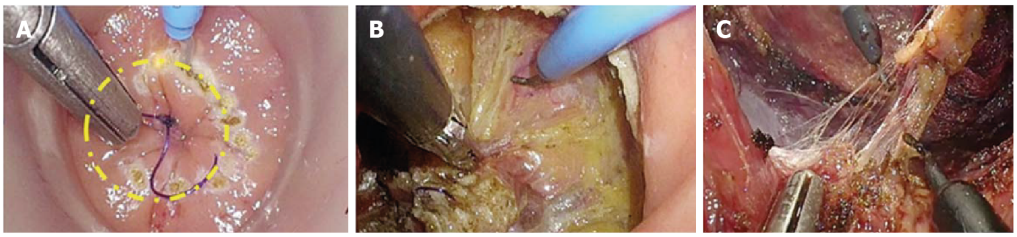

Figure 5 Transanal total mesorectal excision. A: Circumferential mucosal tattoo after pure-string placement; B: Bottom-up dissection; C: "Rendez-vouz" with the abdominal team. Photo courtesy of Antonio Lacy, Hospital Clinic and AIS Channel.

incontinence and dysfunction[83]. The membranous urethra is put at risk if the posterior prostatic lobe is deflected downwards inadvertently, or during the perineal phase of an abdominoperineal resection. Urethral injury may be prevented with adequate training and mentoring of the technique and following a meticulous technique of dissection in the anterior plane[110]. Methods to better identify the urethra intraoperatively and reduce injury rates, such as with fluorescence imaging, have been described and may also be beneficial with this new technique[111,112].

Perioperative benefits

Technical benefits of TaTME include having significantly shorter operation time than laparoscopic TME[103]. A plausible explanation is that the bottom-up approach overcomes the technical limitations associated with laparoscopic TME, enabling surgeons to proceed more easily and efficiently. Also, the simultaneous two-team technique can help reducing the operation time significantly[25]. Another technical advantage of TaTME is having lower rates of conversion to open surgery compared to laparoscopic TME (OR: 0.29, P = 0.02)[104]. The overall conversion rate of laparoscopic TME was almost four-times that of TaTME (8.6% *vs* 2.6%). On analysis of the reasons for conversion, technical difficulties accounted for 25% of conversions in the TaTME group *vs* 47% in the laparoscopic TME group. Technical difficulties necessitating conversion in the laparoscopic group were related to high BMI and narrow pelvis as previously implied. TaTME also allows for transanal specimen extraction, thus decreasing the need for an abdominal assist incision.

Safety: The safety and feasibility of TaTME for short and midterm outcomes has been extensively described[80,89,91,113-115]. A report from the TaTME International Registry reported postoperative morbidity, anastomotic leakage and mortality rates of 32.6%, 6.7% and 2.6%, respectively[83]. A pooled analysis in a recent systematic review had similar rates of intraoperative complications and lower rate of postoperative morbidity compared to laparoscopic TME, with no significant difference between the TaTME and laparoscopic TME in regards to anastomotic leak[104]. However, there remain some concerns about the rapid development of this new technique and critics would point to the more catastrophic complications including prostate and urethral injuries. But this had led to design and implementation of detailed national training programs which have been initiated in the United States and Europe. This may help safe expansion of the technique and mitigate the safety issues.

Other side of the coin: Shortcomings of TaTME

Although TaTME has achieved promising oncological and functional results in treatment of rectal cancer as reported in several studies, the technique does have certain limitations that need to be addressed. Firstly, the bottom-to-up dissection approach followed in TaTME can be quite difficult since the majority of surgeons are not familiar with such different anatomical perspective for dissection, therefore adequate training under expert supervision is imperative before employing the technique in practice. Secondly, with new techniques new complications may arise, this is true with TaTME as a number of complications were recognized after the procedure. Complications specific to TaTME include formation of local collection or abscess secondary to bacterial contamination due to transection of the rectum at the start of the procedure. In one report[116], TaTME was found to be associated with positive cultures in more than one-third of the patient, with development of pre-sacral abscess in 17% of the patients.

As aforementioned, the risk of injury of the urethra and urethral sphincter, which can occur in up to 10% of patients, is a unique complication of TaTME compared to the abdominal approaches for rectal cancer[84]. The risk of urinary retention and transient urinary dysfunction was previously reported and minimal detrusor activity was documented in urodynamic studies implying neurogenic bladder dysfunction[82]. It is also worthy to note that the CO_2 insufflation used to aid dissection might expose planes beyond the scope for dissection particularly during lateral and posterior dissection of the mid rectum which can lead to extending the dissection too deep into the pre-sacral space which carries a significant risk of injuring the autonomic nerves and venous plexus in this plane[96,117].

TaTME: Research and education initiatives

In order to establish the efficacy of a new surgical treatment, well-designed controlled experiments must be performed. Trials such as the COLOR III[118] and the TaTME trial in United States are currently recruiting, with the primary outcome of non-inferiority for local recurrence. While we wait for the definitive outcomes from large-scale controlled trials, multicentre registries are valuable for quality assurance and audits to optimize and standardize outcomes. The international TaTME registry, in which worldwide surgeons performing TaTME are invited to join, is a secure online database funded by the Pelican Cancer Foundation (https://tatme.medicaldata.eu). The analysis of this large population-based cohort is a joint of effort with the objective of improving research and care of the patients with rectal cancer treated with TaTME.

In the last few years, there has been an increase in availability, quality, and utilization of online and social media resources for surgery. These platforms best feature offer instant and unlimited medical knowledge. Tools such as the online Advances in Surgery (AIS) Channel (https://aischannel.com) or iLappSurgery Foundation app (www.ilappsurgery.com) have gained favour in the surgical community. They have taken the next step by providing high-quality surgical education, which is clearly one of the keys to raise the standards of training. These two platforms are focused specifically on laparoscopic surgery and colorectal procedures, with TaTME being one of its cornerstones.

All these initiatives for TaTME research, training and education have experienced a great acceptance. This is based on the obvious theoretical benefits that can overcome problems such as the risk for increased non-complete specimens obtained by laparoscopy and the longer operative times and higher costs associated with robotics. The international TaTME registry, AIS Channel and iLappSurgery Foundation have been developed for being guidance not only for trainees but also for experienced surgeons. TaTME is a complex procedure to learn, so continuous quality improvement from data analysis as well as high-quality training programs are needed for correct standardization and safe implementation of the technique[98,100,101].

Future direction for TaTME

The survival outcomes with respect to disease recurrence in rectal cancer surgery are directly related to the quality of resection[3], and thus the success of TaTME must be held against this quality assurance measure to ensure oncological parity and perhaps superiority. This new technique is complex and requires exceptional anatomical knowledge to perform an unfamiliar dissection. Previous laparoscopic colorectal experience and a high case volume are essential to reach a standard in an acceptable amount of time. Nursing/operating room staff and anaesthesiology also require specific training to become familiar with the new set up, particularly when performing a two-team approach, where the coordination among all operating room staff is crucial to avoid a potentially dangerous situation.

The learning curve of TaTME is yet to be established; however, according to estimation by expert groups approximately 20 consecutive cases are sufficient to develop an adequate learning curve for a surgeon proficient in laparoscopic and transanal surgery. In accordance with this appraisal, a minimum of five proctored cases is recommended in order to achieve an optimal level for the TaTME performance. However, establishing centres of excellence would allow surgeons to increase volume of cases and allow training of more junior surgeons in a safe manner. Different training courses taught by expert groups are available, which generally include didactic lessons, live cases, and hands-on cadaver labs. After completion of the courses, proctoring in the origin institutions should be the next step in the adoption process. Mentors should travel and proctor cases along with the trainees, to show on the spot the tips and tricks as well as adjusting the technique to the site´s intrinsic characteristics. Validation and accreditation of the technique are also under development and a matter of discussion in the international surgical societies[98,100].

CONCLUSION

The TaTME was developed from existing platforms and as an attempt to resolve the challenges of minimally invasive low rectal cancer surgery. As evidence for safety and feasibility accumulates, and with the implantation of structured training programs in order to standardize training, teaching, and safe expansion, TaTME seems on course for further uptake. The improved visibility of the pelvic structures and better accessibility for ultralow anastomoses may render the transanal approach ideal for a wide variety of cases. The indications for TaTME are currently expanding beyond mid and low rectal cancers, and open up new possibilities to use the approach for different diseases. Although the initial results of TaTME are promising and encouraging, further controlled clinical trials including larger number of patients with long-term follow-up are required to validate the oncologic and pathologic outcomes of TaTME. With the international registry and ongoing controlled trials, we look forward to long-term outcomes with this innovative approach.

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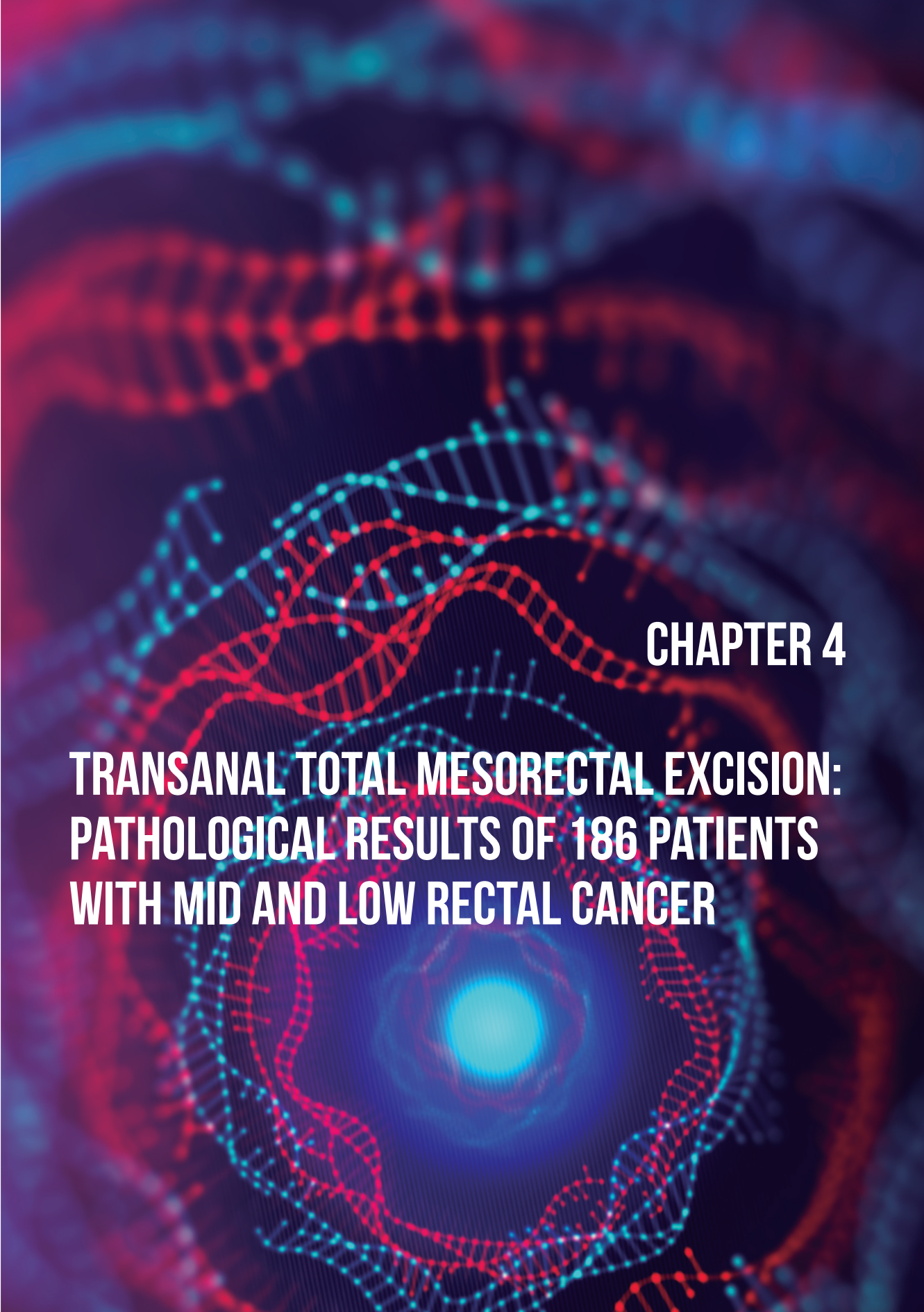

CHAPTER 4

TRANSANAL TOTAL MESORECTAL EXCISION: PATHOLOGICAL RESULTS OF 186 PATIENTS WITH MID AND LOW RECTAL CANCER

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Transanal total mesorectal excision: pathological results of 186 patients with mid and low rectal cancer

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Abstract

Background Transanal total mesorectal excision (TaTME) seems to be a valid alternative to the open or laparoscopic TME. Quality of the TME specimen is the most important prognostic factor in rectal cancer. This study shows the pathological results of the largest single-institution series published on TaTME in patients with mid and low rectal cancer.

Methods We conducted a retrospective cohort study of all consecutive patients with rectal cancer, treated by TaTME between November 2011 and June 2016. Patient data were prospectively included in a standardized database. Patients with all TNM stages of mid (5–10 cm from the anal verge) and low (0–5 cm from the anal verge) rectal cancer were included.

Results A total of 186 patients were included. Tumor was in the mid and low rectum in, respectively, 62.9 and 37.1%. Neoadjuvant chemoradiotherapy was given in 62.4%, only radiotherapy in 3.2%, and only chemotherapy in 2.2%. Preoperative staging showed T1 in 3.2%, T2 in 20.4%, T3 in 67.7%, and T4 in 7.5%. Mesorectal resection quality was complete in 95.7% ($n=178$), almost complete in 1.6% ($n=3$), and incomplete in 1.1% ($n=2$). Overall positive CRM (≤ 1 mm) and DRM (≤ 1 mm) were 8.1% ($n=15$) and 3.2% ($n=6$), respectively. The composite of complete mesorectal excision, negative CRM, and negative DRM was achieved in 88.1% ($n=155$) of the patients. The median number of lymph nodes found per specimen was 14.0 (IQR 11–18).

Conclusions The present study showed good rates regarding total mesorectal excision, negative circumferential, and distal resection margins. As the specimen quality is a surrogate marker for survival, TaTME can be regarded as a safe method to treat patients with rectal cancer, from an oncological point of view.

Keywords Rectal cancer · Total mesorectal excision · Transanal TME · Circumferential resection margin · Mesorectal resection quality

Total mesorectal excision (TME) has been the standard surgical treatment for rectal cancer since its introduction by Heald et al. [1] The quality of the TME specimen is a prognostic factor on both locoregional recurrence rate and long-term survival [2, 3]. Optimal pathological results can reduce locoregional recurrence rates by approximately 60–70% and increase 5-year survival by approximately 20% [4]. Additionally, adjuvant therapy further improves these figures [4, 5].

An increasing number of rectal surgeons worldwide are incorporating transanal TME (TaTME) in the treatment of patients with rectal cancer [6, 7]. However, published results of large series of patients treated by this technique

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on pathological, oncological, and functional outcomes are scarce [7, 8].

It has been shown that the most important features for the evaluation of the quality of the specimen are the integrity of the mesorectum, the status of the resected margins, and the number of dissected lymph nodes. TaTME provides a better view of the plane of surgery and direct sight of the tumor, improving control over circumferential and distal resection margins. Our hypothesis is that the transanal approach may therefore provide improved pathological outcomes. In 2015, our research group published the initial results on operative and postoperative outcomes of patients with (high, mid, and low) rectal cancer treated by TaTME. The present analysis focuses on the pathological results of resection specimens retrieved by TaTME in a relatively large series of patients with mid and low rectal cancer, over a 5-year period.

Materials and methods

We conducted a retrospective cohort study of all consecutive patients with rectal cancer treated by TaTME between November 2011 and June 2016. Patient data were prospectively included in a standardized database. Patients with all TNM stages of mid (5–10 cm from the anal verge) and low (0–5 cm from the anal verge) rectal cancer were included. Patients with T4 tumors and/or threatened circumferential resection margin (CRM) on preoperative imaging were also included. Exclusion criteria for this analysis were patients requiring abdominoperineal resection or pelvic exenteration.

Tumors were staged using the 7th edition TNM classification [9]. The pretreatment work-up included blood analysis of carcinoembryonic antigen (CEA) and a total colonoscopy in which biopsies of the tumor were obtained. Oncological staging was done by transanal ultrasonography, thoracic and abdominal computed tomography (CT), and magnetic resonance imaging (MRI) of the pelvis. In patients in whom the tumor was not palpable by digital rectal examination, a rigid rectoscopy was also performed. All patients were discussed in a multidisciplinary oncological board which provided advice on further treatment. Patients were eligible for neoadjuvant chemoradiotherapy in the case of T3–T4/N0 or T1–T4/N1-2 tumors [10]. The same dedicated surgical team treated all patients. Patients were either operated on by one surgical team or by two surgical teams (the hybrid Cecil procedure) [11]. In the one-team procedure, the abdominal part was performed first because of the pneumoretroperitoneum that could develop after creating the pneumorectum in the transanal phase. This could result in difficult visualization of the dissection plane [11]. In the two-team hybrid procedure, the abdominal and the transanal dissections were performed simultaneously. The two-team hybrid procedure is a standardized procedure performed by two experienced oncologic gastroenterology surgeons and has been described elsewhere [11–13].

The same pathological team processed all the specimens [13]. The quality of the specimen was defined by the composite endpoint of (1) mesorectal quality and (2) status of the resected margins. The quality of the mesorectum was graded as described by Nagtegaal et al. [14]: (1) complete, in which the mesorectum is intact with only minor irregularities of a smooth mesorectal surface. No defect is deeper than 5 mm and there is no coning toward the distal margin of the specimen. There is a smooth circumferential resection margin on slicing. (2) Nearly complete, in which there is irregularity of the mesorectal surface. Moderate coning of the specimen is allowed. At no site, the muscularis propria is visible with exception of the insertion of the levator muscles. (3) Incomplete, little bulk to the mesorectum with defects down onto muscularis propria and/or very irregular circumferential resection margin. The CRM was considered positive in case of tumor growth ≤ 1 mm (continuous or discontinuous) and in case of a positive lymph node at ≤ 1 mm of the radical (non-peritoneal) dissection plane [3, 9]. The distal resection margin (DRM) was considered positive if microscopically involved by or ≤ 1 mm from the tumor margins. Tumor response to chemoradiotherapy was scored by a modification of the Ryan tumor regression grade, based on the volume of residual primary tumor cells: Grade 0: complete response (no viable cancer cells), Grade 1: moderate response (single cells or small groups of cancer cells), Grade 2: minimal response (residual cancer outgrown by fibrosis), and Grade 3: poor response (minimal or no tumor response; extensive residual cancer) [15].

Statistical analysis

Parametric data were reported as means with standard deviation (SD), and non-parametric data were reported as medians with the corresponding interquartile range (IQR). Data were analyzed with IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA).

Results

A total of 186 patients were included in this analysis. Demographics are stated in Table 1. Surgery was performed by the one-team approach in 21.0% ($n = 39$) of the patients and by the two-team approach in 79.0% ($n = 147$) of the patients. Mean operative time was 147.8 min (SD 51.2), and anastomosis was performed in 98.3% ($n = 183$) of the patients. There were two intraoperative perforations of the rectum: one patient had a cT3N1 tumor, neoadjuvant treatment included only radiotherapy, and intraoperatively the tumor was found to infiltrate the pelvis. The

Table 1 Baseline characteristics of patients with mid or low rectal cancer treated by TaTME at Hospital Clinic Barcelona

		Transanal TME ($n=186$)
Age (years)	Median (IQR)	65.0 (56.0–75.0)
Gender	M/F (%)	118/68 (63.4/36.6)
BMI (kg/m^2)	Mean (±SD, range)	25.1 (±3.9, 17.7–36.2)
≥ 25	*N* (%)	71 (38.2)
≥ 30	*N* (%)	22 (11.8)
ASA classification[a]		
1	*N* (%)	7 (3.8)
2	*N* (%)	150 (80.6)
3	*N* (%)	25 (13.4)
4	*N* (%)	1 (0.5)
Unknown	*N* (%)	3 (1.6)
Tumor location		
Mid rectum	*N* (%)	117 (62.9)
Low rectum	*N* (%)	69 (37.1)
Tumor height[b]		
Mid rectum	Mean (±SD)	7.9 (±1.5)
Low rectum	Mean (±SD)	3.5 (±1.3)
Distance to MRF (mm)	Mean (±SD)	7.39 (9.0)
>1 mm	*N* (%)	118 (63.4)
≤1 mm	*N* (%)	45 (24.2)
Unknown	*N* (%)	23 (12.4)
≤1 mm excl. T4	*N* (%)	35 (20.8)
Neoadjuvant chemoradiation		
Yes	*N* (%)	116 (62.4)
No	*N* (%)	58 (31.2)
Only radiotherapy	*N* (%)	6 (3.2)
Only chemotherapy	*N* (%)	4 (2.2)
Unknown	*N* (%)	2 (1.1)
T stage		
T1	*N* (%)	6 (3.2)
T2	*N* (%)	38 (20.4)
T3	*N* (%)	126 (67.7)
T4	*N* (%)	14 (7.5)
N stage[c]		
N0	*N* (%)	102 (54.8)
N1	*N* (%)	63 (33.9)
N2	*N* (%)	19 (10.2)
Nx	*N* (%)	1 (0.5)
N-location		
Mesorectal	*N* (%)	77 (96.3)
Extramesorectal	*N* (%)	3 (3.8)
M stage		
M0	*N* (%)	167 (89.8)
M1	*N* (%)	19 (10.2)

[a]American Society of Anaesthesiologists classification: (1) healthy, (2) mild systemic disease, (3) severe systemic disease, (4) severe life-threatening systemic disease

Table 1 (continued)

[b]Height of distal edge of the tumor (cm) from the anal verge

[c]Assessed by magnetic resonance imaging

mesorectum was incomplete and with a positive CRM. The other patient had a rectal perforation at the anterior side, with a past medical history of radiotherapy and prostatectomy, and was staged as pT4.

As stated in Table 2, the overall mesorectal quality was complete in 95.7% ($n=178$) of the patients, almost complete in 1.6% ($n=3$), and incomplete in 1.1% ($n=2$). Both patients with an incomplete mesorectal resection had a mid rectal (cT3) tumor in which the pathologist reported a pT4 tumor, both patients were male and had a BMI > 25 kg/m2 (one of the patients was treated with radiotherapy before because of another malignancy). In the patients with a low rectal tumor, the mesorectal specimen was complete in 95.6% ($n=66$), almost complete in 2.8% ($n=2$), and unknown in 1.4% ($n=1$).

Overall positive CRM (≤ 1 mm) ratio (including T4 tumors) was 8.1% ($n=15$). Of the 15 patients with positive CRM: four patients (25%) had a T4 tumor, of whom one patient had tumor growth in the surrounding organs (vagina); in three patients (all with a low T3 rectal tumor), the specimen showed focal tumor contact at the CRM in the distal part of the specimen but had a complete mesorectal resection. Of these 15 patients with positive CRM, 10 patients received neoadjuvant chemoradiotherapy (80.0% had minimal or poor response) and five patients did not receive neoadjuvant chemoradiotherapy (previous radiotherapy, advanced age, and chronic renal failure).

The DRM was positive in six patients (3.2%), five of whom were treated with neoadjuvant chemoradiotherapy and three of whom had a tumor within 3 cm from the anal verge (type II according to Rullier classification [16]) and required partial intersphincteric resection. The tumor stage in patients with a positive DRM was T2 in one patient, T3 in four patients, and Tis in one patient (giant 8-cm circumferential polyp for which the pathology report confirmed a positive DRM with low-grade dysplasia). In patients with mid rectal cancer, the mean distal margin in cm was 2.7 (SD 1.6), with a positive DRM rate of 0.9% ($n=1$). In patients with low rectal cancer, the mean distal margin in cm was 1.1 (SD 1.0), with a positive DRM rate of 7.8% ($n=5$). From the five patients with low rectal cancer and a positive DRM, three patients had a positive CRM.

Complete mesorectal excision, negative CRM, and negative DRM were achieved in 91.1% ($n=102$) of the patients with mid rectal cancer and in 82.8% ($n=53$) of the patients with low rectal cancer.

Table 2 Tumor characteristics and pathological results of patients with mid or low rectal cancer treated by TaTME at Hospital Clinic Barcelona

		Transanal TME ($n=186$)
Tumor size (cm)	Mean (±SD)	2.9 (±4.1)
CRM < 1 mm		15 (8.1)
CRM < 1 mm excl. T4 tumor		11 (6.4)
CRM mid rectal tumor		
≤1mm[a]	*N* (%)	8 (6.8)
≤1 mm excl. T4	*N* (%)	6 (5.5)
Unknown[b]	*N* (%)	2 (1.7)
CRM low rectal tumor		
≤1mm[a]	*N* (%)	7 (10.1)
≤1 mm excl. T4	*N* (%)	5 (8.1)
Unknown[b]	*N* (%)	1 (1.4)
CRM (mm)	Mean (±SD)	15.4 (15.5)
Mesorectal resection quality		
Complete	*N* (%)	178 (95.7)
Almost complete	*N* (%)	3 (1.6)
Incomplete	*N* (%)	2 (1.1)
Unknown[b]	*N* (%)	3 (1.6)
Evaluated lymph nodes		
Overall	Median (IQR)	14.0 (11–18)
Non-irradiated patients	Median (IQR)	15.0 (14–22)
Distal resection margin (cm)	Mean (±SD)	2.1 (1.6)
Mid rectal tumor	Mean (±SD)	2.7 (1.6)
Low rectal tumor	Mean (±SD)	1.1 (1.0)
Distal resection margin affected		
Mid rectal tumor	*N* (%)	1 (0.9)
Low rectal tumor	*N* (%)	5 (7.8)
Proximal margin (cm)	Mean (±SD)	13.9 (4.9)
Perineural invasion	*N* (%)	15 (8.1)
Vascular invasion	*N* (%)	31 (16.7)
Perforation	*N* (%)	2 (1.1)
Differentiation grade		
Good	*N* (%)	7 (4.5)
Moderate	*N* (%)	117 (75.5)
Poor	*N* (%)	11 (7.1)
Budding		
No	*N* (%)	150 (91.5)
Low grade	*N* (%)	12 (7.3)
Moderate grade	*N* (%)	1 (0.6)
High grade	*N* (%)	1 (0.6)
Histological subtype		
High-grade dysplasia	*N* (%)	1 (0.5)
Adenocarcinoma	*N* (%)	173 (93.5)
Mucinous adenocarcinoma	*N* (%)	11 (5.9)
Regression grade[c]		
Grade 0	*N* (%)	24 (12.9)
Grade 1	*N* (%)	35 (18.8)
Grade 2	*N* (%)	29 (15.6)
Grade 3	*N* (%)	12 (6.5)
Unknown	*N* (%)	33 (17.8)
No neoadjuvancy	*N* (%)	53 (28.5)
pT stage		
T0	*N* (%)	30 (16.1)
Tis	*N* (%)	3 (1.6)
T1	*N* (%)	12 (6.5)
T2	*N* (%)	55 (29.6)
T3	*N* (%)	78 (41.9)
T4	*N* (%)	5 (2.7)
Unknown	*N* (%)	3 (1.6)
pN stage		
N0	*N* (%)	121 (65.1)
N1	*N* (%)	39 (21.0)
N1c	*N* (%)	3 (1.6)
N2	*N* (%)	13 (7.0)
Nx	*N* (%)	7 (3.8)
Unknown	*N* (%)	3 (1.6)
Stage		
Complete pathological response	*N* (%)	21 (11.5)
Stage I	*N* (%)	37 (20.3)
Stage II	*N* (%)	54 (29.7)
Stage III	*N* (%)	50 (27.5)
Stage IV	*N* (%)	19 (10.4)

[a]CRM involvement: circumferential resection involvement margin ≤ 1 mm

[b]Patients treated at Hospital Clinic of Barcelona, referred from other hospitals and follow-up was done elsewhere

[c]Regression grade modified from Ryan

Discussion

This study presents the largest single-center cohort on pathological results of patients with mid and low rectal cancer treated with TaTME. Mesorectal quality was complete or nearly complete in 97.3% of the patients. Negative CRM was obtained in 91.9% of the patients—including T4 tumors—and negative DRM was obtained in 96.8% of the patients. A median of 14.0 lymph nodes was harvested per specimen.

The transanal technique could offer advantages in obtaining optimal pathological outcomes compared to open approach or laparoscopy. Various randomized controlled trials have been performed trying to establish which technique is superior in the treatment of patients with rectal cancer, comparing laparoscopy and open approach in TME [17–20]. Complete TME ranged between 74.7 and 95.1% for open surgery and between 72.4 and 92.1% for laparoscopic

surgery. Negative CRM ranged between 87.9 and 97.0% for open surgery and between 90.5 and 97.1% for laparoscopic surgery.

The transanal technique provides a clear view of the plane of surgery, which could lead to easier deep pelvic dissection and a higher percentage of complete mesorectal specimens [21]. The most challenging patients (male, obese, and with narrow pelvis) could be the patients who benefit the most. The advantages of this technique allow even the patients with ultra-low rectal tumors to be treated by sphincter-saving surgery. Another possible advantage of TaTME is that during dissection there is no traction on the rectum and thereby no traction on the tumor [11]. Hypothetically, as the rectum is pushed forward, there is less risk of rupturing the tumor or damaging the mesorectal circumferential fascia.

TaTME provides a direct sight of the tumor and thus determination of the pure string placement, hypothetically improving the control of the DRM [11]. In the present cohort of patients, however, six patients had a positive DRM, which was remarkable. The DRM is decided just below the tumor to preserve as much length of the rectum as possible. One hypothesis for the positive DRM is the presence of tumor cells beyond the distal resection from the residual tumor after neoadjuvant therapy [22]. Another hypothesis is that the positive DRM is caused by the presence of occult tumor beneath the mucosal edge, although this is a rare event [23].

A total of 97.3% of the patients had a complete or nearly complete mesorectal resection quality. In contrast, 8.1% of the patients had a positive CRM. In the evaluation of the CRM, there is no difference in the definition of CRM involvement due to continuous tumorous tissue, discontinuous tumor "nests," or due to an invasion of lymph nodes aligned at the CRM [9]. In the case of advanced tumor growth, obtaining a negative CRM is not always possible. The risk of involved CRM is highest in stage T4 tumors, in T3 tumors with risk of an involved CRM on preoperative imaging, and when stage N2 is suspected. Furthermore, the mesorectum becomes thinner and less voluminous toward the pelvic floor, with tumor growth through the mesorectal fascia (MRF) occurring sooner in comparison to tumors in the mid or high rectum [24]. As a result, negative CRM is much harder to obtain in the low rectum, despite complete mesorectal excision. This was supported by the results of this study, in which a negative CRM was obtained in 93.2% of the patients with mid rectal tumors and in 89.9% of the patients with low rectal tumors. To clarify, 7.5% of the patients had a T4 tumor and 24.2% had a distance of less than 1 mm to the MRF, based on preoperative imaging.

Recently, outcomes from the international TaTME registry have been published [6]. A total of 66 units from 23 countries pooled their data, accounting for 720 patients. In 96.0% of the patients, a complete or nearly complete mesorectal quality was obtained, and positive CRM and DRM ratios were 2.4 and 0.3%, respectively. The mean number of lymph nodes harvested was 16.5 compared to 14.0 in this study. In both studies, the benchmark for lymph node yield of 12 lymph nodes was achieved. The international TaTME registry showed high-quality pathological results. Nevertheless, starting in November 2011, all consecutive patients with rectal cancer not requiring APR or pelvic exenteration were intended to treat by TaTME and included in the present analysis, limiting the inclusion bias.

At the Hospital Clínic of Barcelona, the experience with TaTME is extensive. This study evaluates a cohort of patients treated by TaTME in this single institution, which might be a limitation for the generalizability of our results. Much progress has been made since our first description of TaTME in 2010 [25]. Potential pitfalls are based on the differences in anatomy, especially in patients with previous pelvic surgery or radiotherapy. Although mid- and long-term oncological outcomes need to be evaluated, these outcomes suggest that the potential of TaTME is enormous. However, performance of an optimal TaTME requires training [7].

Conclusions

This study shows good rates regarding total mesorectal excision, negative circumferential, and distal resection margins. As the specimen quality is a surrogate marker for survival, TaTME can be regarded as a safe method to treat patients with rectal cancer, from an oncological point of view. Clinical oncological outcomes for this cohort of patients treated by TaTME will follow in the future.

Compliance with ethical standards

Disclosure Dr Antonio M. Lacy reports personal fees from Medtronic, Olympus, Applied Medical, and Conmed, outside the submitted work. Drs F. Borja de Lacy, Dr Jacqueline JEM van Laarhoven, Drs María Clara Arroyave, Drs Raquel Bravo, and Dr Miriam Cuatrecasas have no conflict of interest or financial ties to disclose.

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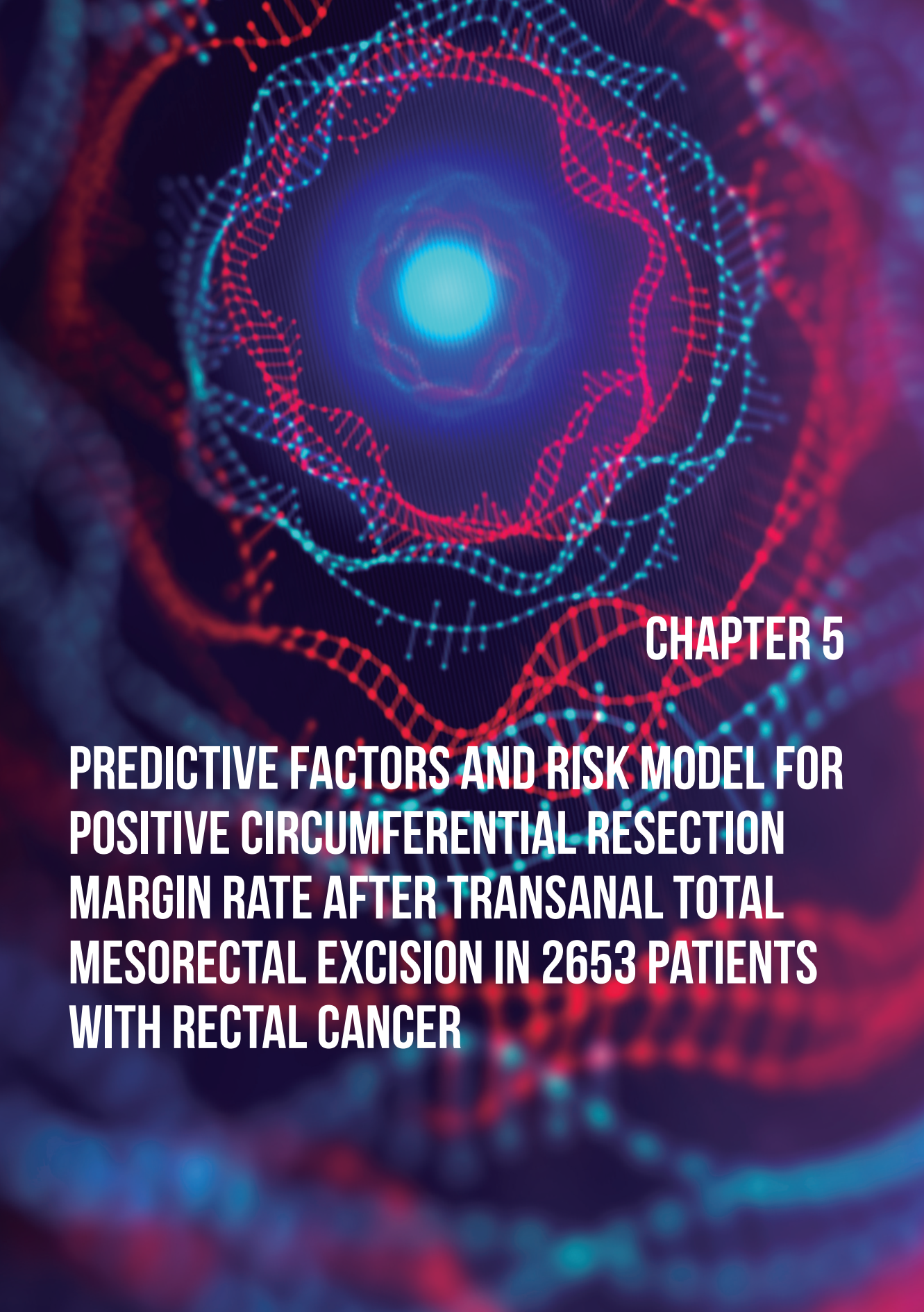

CHAPTER 5

PREDICTIVE FACTORS AND RISK MODEL FOR POSITIVE CIRCUMFERENTIAL RESECTION MARGIN RATE AFTER TRANSANAL TOTAL MESORECTAL EXCISION IN 2653 PATIENTS WITH RECTAL CANCER

Predictive Factors and Risk Model for Positive Circumferential Resection Margin Rate After Transanal Total Mesorectal Excision in 2653 Patients With Rectal Cancer

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Objective: The aim of this study was to determine the incidence of, and preoperative risk factors for, positive circumferential resection margin (CRM) after transanal total mesorectal excision (TaTME).

Background: TaTME has the potential to further reduce the rate of positive CRM for patients with low rectal cancer, thereby improving oncological outcome.

Methods: A prospective registry-based study including all cases recorded on the international TaTME registry between July 2014 and January 2018 was performed. Endpoints were the incidence of, and predictive factors for, positive CRM. Univariate and multivariate logistic regressions were performed, and factors for positive CRM were then assessed by formulating a predictive model.

Results: In total, 2653 patients undergoing TaTME for rectal cancer were included. The incidence of positive CRM was 107 (4.0%). In multivariate logistic regression analysis, a positive CRM after TaTME was significantly associated with tumors located up to 1 cm from the anorectal junction, anterior tumors, cT4 tumors, extra-mural venous invasion (EMVI), and threatened or involved CRM on baseline MRI (odds ratios 2.09, 1.66, 1.93, 1.94, and 1.72, respectively). The predictive model showed adequate discrimination (area under the receiver-operating characteristic curve >0.70), and predicted a 28% risk of positive CRM if all risk factors were present.

Conclusion: Five preoperative tumor-related characteristics had an adverse effect on CRM involvement after TaTME. The predicted risk of positive CRM after TaTME for a specific patient can be calculated preoperatively with the proposed model and may help guide patient selection for optimal treatment and enhance a tailored treatment approach to further optimize oncological outcomes.

Keywords: circumferential resection margin, rectal cancer, registry, risk factors, transanal total mesorectal excision

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Total mesorectal excision (TME), as first described by Heald in 1982, established what is now considered optimal surgical treatment for patients with resectable rectal cancer.[1] Subsequently the treatment of rectal cancer has changed, with use of neoadjuvant therapy (NAT) in patients with advanced cancers, and a move toward minimal access techniques in selected cases.[2] More recently, transanal total mesorectal excision (TaTME) has been developed aiming to increase the quality of surgical resection and improve oncological outcomes, particularly in patients with low rectal cancers.

One of the fundamental principles of TME, and indeed all rectal cancer surgery, is to remove the tumor with a clear circumferential resection margin (CRM). Quirke et al have repeatedly shown that a positive CRM is associated with a significant increase in both local and systemic recurrence.[3,4] Despite some reported benefits from laparoscopic rectal resection, CRM positivity rates have not diminished over time.[5–8] Several tumor-related factors (anterior location, cT4-status) and patient-related factors (male sex, obesity),[9–13] are known to increase the technical difficulty in conventioneal laparoscopic TME, and therefore associated with a positive CRM.[14–17] However, there is little information on predictive factors for positive CRM after TaTME. Predictive factors might differ from the well-known risk factors after conventional laparoscopic resection, considering the different approach from below.

The present study aimed to determine the incidence of positive CRM after TaTME surgery for rectal cancer, for patients recorded on an international TaTME registry. Moreover, formulating a predictive model, preoperative predictive factors for positive CRM will be studied.

METHODS

Patient Selection

This was an analysis of prospective registry-based data. The study population comprised patients recorded on the international TaTME registry between July 2014 and January 2018.[18] Exclusion criteria were benign indications for TaTME, previous local excision, and cases in which CRM status was not known. The registry is a secure online voluntary database where surgeons worldwide are invited to record their TaTME cases, with an extensive collaboration among 172 centers worldwide.[19] Ethical approval for the registry was granted by the UK Health Research Authority (REC reference 15/LO/0499, IRAS project ID 156930). Before data analysis, registered surgeons were invited via email to update their patients'

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records, with multiple reminders to minimize missing data. Surgeons were individually contacted to clarify unexpected or possibly erroneously entered results.

Data Extraction and Outcome Parameters

The registry is designed to prospectively collect data on patient demographics, tumor staging and neoadjuvant treatment (NAT), operative details, postoperative clinical and histological outcomes, readmission details, late morbidity, and long-term oncologic follow-up. The main endpoints of this study were the incidence of, and predictive factors for, positive CRM, defined as the presence of tumor or a malignant lymph node 1 mm, or less, from the CRM. The TME specimen quality was categorized using the principles described by Nagtegaal et al.[20] The MRI response to NAT was scored by the tumor regression grade (TRG) classification, which was subgrouped into ''good response'' (mrTRG 1 and 2) and ''bad response'' (mrTRG 3, 4 and 5) as defined in the TRIGGER trial.[21] Patients treated with short-course radiotherapy and immediate surgery were included in the ''no-neoadjuvant group'' for the analysis of mrTRG, as this is not associated with significant tumor downstaging.

Statistical Analysis

Statistical analyses were performed in the Statistical Package for Social Sciences (SPSS) of IBM Statistics, version 24. Missing data for variables included in the model were imputed using single imputation with predictive mean. For the other variables presented that were not included in the predictive model, missing data did not exceed 15%. Percentages shown represent actual data available, excluding missing values.

Categorical variables were defined as absolute numbers of cases and percentages. Continuous data were reported as mean with standard deviation (SD). Continuous variables such as BMI and tumor height from anorectal junction (ARJ) were categorized into clinically relevant subgroups. For intergroup variation, the chi-square test was used, whereas the Mann–Whitney *U* test was used for continuous variables. Variables to be included in the multivariate analysis were chosen based on a priori known risk factors for positive CRM from the literature. Variables reaching a $P < 0.05$ using backward step selection in the multivariate regression analysis were deemed significant and included as a predictive factor for positive CRM in the predictive model. The coefficients derived from the multivariate analysis were multiplied by 10 and used as weights in the nomogram for predicting the risk of positive CRM after TaTME for rectal cancer.

Model Validation

An interval validation was performed by drawing a random sample of 150 patients from the original study population. The so-called ''bootstrap'' technique is thought to be the optimum technique of internal validation.[22] Calibration, or goodness-of-fit, refers to the ability of the model to assign the correct probabilities of outcome to individual patients. This was checked by plotting the observed number of positive CRM to the expected number of positive CRM. Discrimination refers to the ability of the model to assign higher probabilities of positive CRM to patients who actually have a positive CRM compared with patients who do not. This was tested using the area under the receiver-operating characteristic (ROC) curve with 95% confidence intervals (CIs). The performance of the prediction model was analyzed using RStudio (version 1.1.453).

RESULTS

Patient Characteristics and Pathologic Outcomes

All cases recorded on the international TaTME registry between July 2014 and January 2018 were reviewed (n = 3240).

TABLE 1. Patient and Tumor Characteristics and Pathological Outcome

Factor	TaTME Registry Data Results Total = 2653
Patient characteristics	
Mean age, yrs (SD)	64.4 (11.7)
Male sex	1827 (68.9%)
Mean BMI, kg/m^2 (SD)	26.3 (4.5)
BMI >30 kg/m^2	507 (19.1%)
ASA classification	
I	597 (22.5%)
II	1418 (53.4%)
III	507 (19.1%)
IV	62 (2.3%)
Previous pelvic therapies	
Hysterectomy	72 (2.7%)
Prostatectomy	66 (2.5%)
Radiotherapy	33 (1.2%)
Tumor characteristics	
Mean distance from ARJ, c, (SD)	3.8 (2.6)
Within 1 cm	523 (19.7%)
Anterior tumor	1181 (44.5%)
Clinical T-stage	
cT0	16 (0.7%)
cT1	78 (3.3%)
cT2	615 (25.6%)
cT3	1534 (63.9%)
cT4	157 (6.5%)
Clinical N-stage	
cN0	1187 (44.7%)
cN1	1015 (38.3%)
cN2	451 (17.0%)
EMVI positive on baseline MRI	895 (33.7%)
Pretreatment threatened/involved CRM	674 (25.4%)
Neoadjuvant therapy	1569 (59.1%)
Short course radiotherapy immediate surgery	150/1569 (9.6%)
Long course radiotherapy delayed surgery	175/1569 (11.2%)
Long course chemoradiotherapy	1027/1569 (65.5%)
Chemotherapy alone	180/1569 (11.5%)
Contact radiotherapy	2/1569 (0.1%)
Unknown/other	35/1569 (2.2%)
TRG response post downsizing therapy*	
''Good response''	612/1419 (43%)
''Bad response''	810/1419 (57%)
Sphincter saving surgery	2442 (92.0%)
Pathological outcome	
T-stage	
pT0	293 (11.0%)
pT1	298 (11.2%)
pT2	834 (31.4%)
pT3	1126 (42.4%)
pT4	66 (2.5%)
N-stage	
pN0	1865 (70.3%)
pN1	532 (20.1%)
pN2	256 (9.6%)
Mean number of lymph node harvested (SD)	17.7 (10.3)
Mean tumor size, mm (SD)	26.1 (19.3)
Size >20 mm	1745 (65.8%)
Size >30 mm	1159 (43.7%)
CRM involvement	107 (4.0%)
DRM involvement	26 (1.0%)
TME specimen grade	
Complete	2145 (80.9%)
Near-complete	274 (10.3%)
Incomplete	89 (3.4%)
Rectal perforation	47 (1.8%)
Composite poor pathological outcome	224 (8.4%)

ARJ indicates anorectal junction junction; ASA, American Society of Anaesthesiologists-Classification; bad response, mrTRG 3, 4 and 5; BMI, body mass index; cN-stage, clinical nodal stage; CRM, circumferential resection margin, defined as involved if the distance of tumor or malignant lymph node to the mesorectal fascia was 1 mm or less; CT, chemotherapy; cT-stage, clinical tumor stage; DRM, distal resection margin; Composite poor pathology, CRM+ and/or DRM+ and/or incomplete TME specimen and/or perforations; EMVI: extramural venous invasion; good response, mrTRG 1 and 2; IQR, interquartile range; LCCRT, long course chemoradiotherapy; LCRT, long course radiotherapy; MRI, magnetic resonance imaging; pN-stage, pathological nodal stage; pT-stage, pathological tumor stage; R1, tumor or malignant node 1 mm or less from the resection margin; SCRT, short course radiotherapy (including contact radiotherapy and short course radiotherapy with delayed surgery); TME, total mesorectal excision; TRG, tumor regression grading on MRI.

*Downsizing therapy was considered as all neo-adjuvant treatment, with exclusion of patients receiving short course radiotherapy and immediate surgery (1569–150 = 1419).

TABLE 2. Multivariable Analysis of Preoperative Risk Factors for CRM Positivity in All Patients (n = 2653)

		Multivariate Analysis		
Factor	**Event Rate (%)**	**Odds Ratio**	**95% CI**	***P***
Up to 1 cm from ARJ				
Yes	38/523 (7.3%)	2.09	1.368–3.194	0.001
No	69/2130 (3.2%)	Ref.		
Anterior tumor				
Yes	62/1181 (5.2%)	1.66	1.118–2.485	0.012
No	45/1472 (3.1%)	Ref.		
cT4 tumor				
Yes	19/157 (12.1%)	1.93	1.074–3.479	0.028
No	88/2496 (3.5%)	Ref.		
EMVI on MRI				
Yes	56/895 (6.3%)	1.94	1.297–2.930	0.001
No	51/1758 (2.9%)	Ref.		
Threatened CRM on baseline MRI				
Yes	49/674 (7.3%)	1.72	1.116–2.679	0.014
No	58/1979 (2.9%)	Ref.		
Sphincter-saving surgery				
Yes	90/2442 (3.7%)	Ref.		
No	17/211 (8.1%)	1.75	0.998–3.009	0.051

ARJ indicates anorectal junction; CRM, circumferential resection margin; EMVI, extramural venous invasion; MRI, magnetic resonance imaging.

A total of 2653 TaTME cases met the eligibility criteria and were included in this analysis.

Table 1 presents patient and tumor characteristics and pathological outcome. Of the included patients, 1827 (68.9%) were male and 507 (19.1%) had a BMI of >30 kg/m^2. Tumor height was within 1 cm from the ARJ in 523 (19.7%) and anteriorly located in 1181 (44.5%). Preoperative staging was reported as cT1 in 78 (3.3%), cT2 in 615 (25.6%), cT3 in 1534 (63.9%), and cT4 in 157 (6.5%). Overall, extramural venous invasion on MRI (mrEMVI), was reported in 895 (33.7%) of the cases. Threatened CRM on baseline MRI was reported in 674 (25.4%). Neoadjuvant treatment (NAT) was given in 1569 (59.1%). Patients receiving NAT to induce tumor downsizing (this excludes short-course radiotherapy with immediate surgery) obtained a ''good response'' (mrTRG 1 or2) in 612 (43%) and a ''bad response'' (mrTRG 3, 4 and 5) in 810 (57%).

Pathological complete tumor response (pT0) was found in 293 (11.0%). Pathological T-stage was ≥T3 in 1192 (44.9%). Positive lymph nodes were detected (pN ≥ 1) in 788 (29.7%). In total, the CRM was positive in 107 (4.0%). TME specimen quality was defined as complete or near-complete in 2419 (91.2%). The composite rate for poor pathological outcome [positive resection margin, either CRM or distal resection margin (DRM), incomplete TME specimen or rectal perforation] was 224 (8.4%).

TABLE 3. Preoperative Risk Scoring for a Positive CRM Based on Prediction Model

Preoperative Risk Scoring	
Risk Factor	**Weight**
Tumor height from AJR 0 to 1 cm	1.5
Anterior tumor location	1
cT4 tumor	1.4
EMVI on baseline MRI	1.2
CRM+ on baseline MRI	1.1
Cumulative points	6.2

Note: The coefficients derived from the multivariate analysis were multiplied by 10 and used as weights in the nomogram for predicting the risk of positive CRM after TaTME for rectal cancer.

Development of the Predictive Risk Model

Table 2 shows the multivariable analysis of risk factors for positive CRM. A positive CRM after TaTME was independently associated with low tumors located within 1 cm from the ARJ, anterior tumors, cT4 tumors, EMVI on MRI and involved or threatened CRM on baseline MRI [odds ratios (ORs) 2.09, 1.66, 1.93, 1.94, and 1.72, respectively]. Resecting the sphincter by abdomino-perineal excision was just not significantly associated with CRM involvement ($P = 0.051$). No patient-related factors, such as male sex, obesity (BMI > 30 kg/m^2), or previous prostatectomy, were associated with a positive CRM (Supplemental Table 1, http://links.lww.com/SLA/B727).

The weights of the individual risk factors represent the log of the odds ratios, and are shown in Table 3. The weights for the 5 risk factors were 1.5 for tumors within 1 cm from the ARJ, 1 for anterior tumors, 1.4 for cT4 tumors, 1.2 for mrEMVI positive, and 1.1 for involved or threatened CRM on baseline MRI. The nomogram, resulting from the cumulative weights, is displayed in Figure 1. When no risk factors are present (cumulative score of 0), the predicted risk of positive CRM is 1.5%. A cumulative score of 1, 2, 3, 4, 5, 6, or the maximum score of 6.2 points is correlated with a predicted positive CRM risk of 2.5%, 2.9%, 5%, 8.9%, 15.5%, 18.5%, or 27.9%, respectively.

The ROC curve was 0.715 (CI 0.669–0.703) and after correcting for optimism, the c-statistic was 0.703. The curves are shown in Supplemental Figure 1, http://links.lww.com/SLA/B727.

The model-predicted risk of a positive CRM compared with the actually observed risk of positive CRM in this cohort is displayed in Figure 2. Table 4 shows the predicted risk (and cumulative score) for pCRM involvement according to the 5 independent risk factors.

DISCUSSION

Involvement of the CRM is considered as one of the most important causes of preventable locoregional recurrence in patients undergoing surgery for rectal cancer.[4] The consequences of a locoregional relapse are significant, with a direct impact on morbidity, mortality, quality of life, and treatment costs. Therefore, given the increase in popularity and prevalence of the transanal approach in

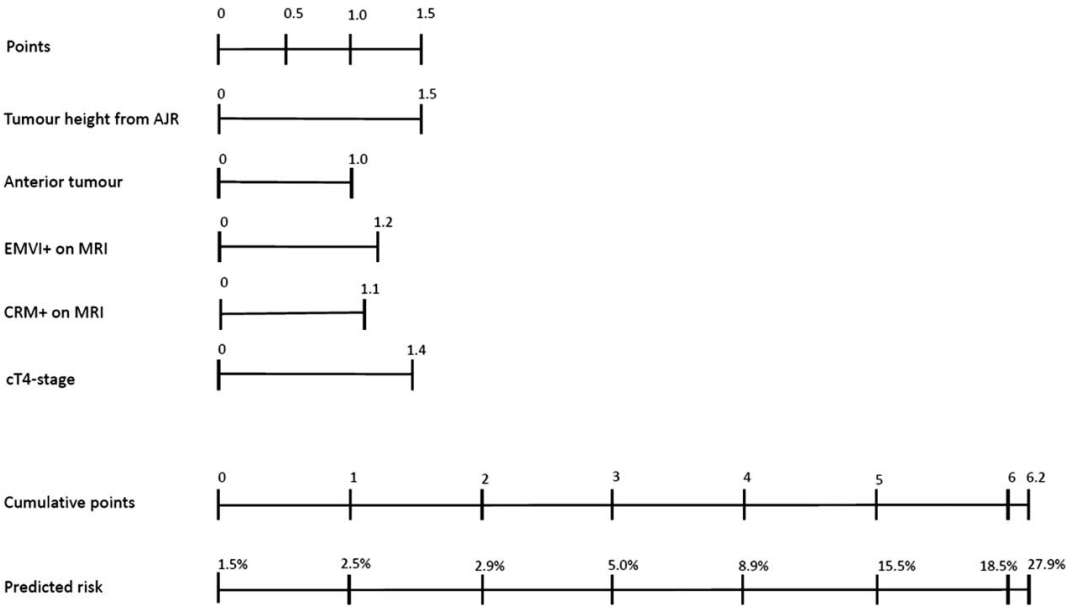

FIGURE 1. Nomogram for predicting positive CRM rate after TaTME. Note: Instructions for use: Sum the points achieved for each preoperative predictor and locate this sum on the ''cumulative points axis.'' Draw a line straight down to find the patient's probability of attaining a positive CRM.

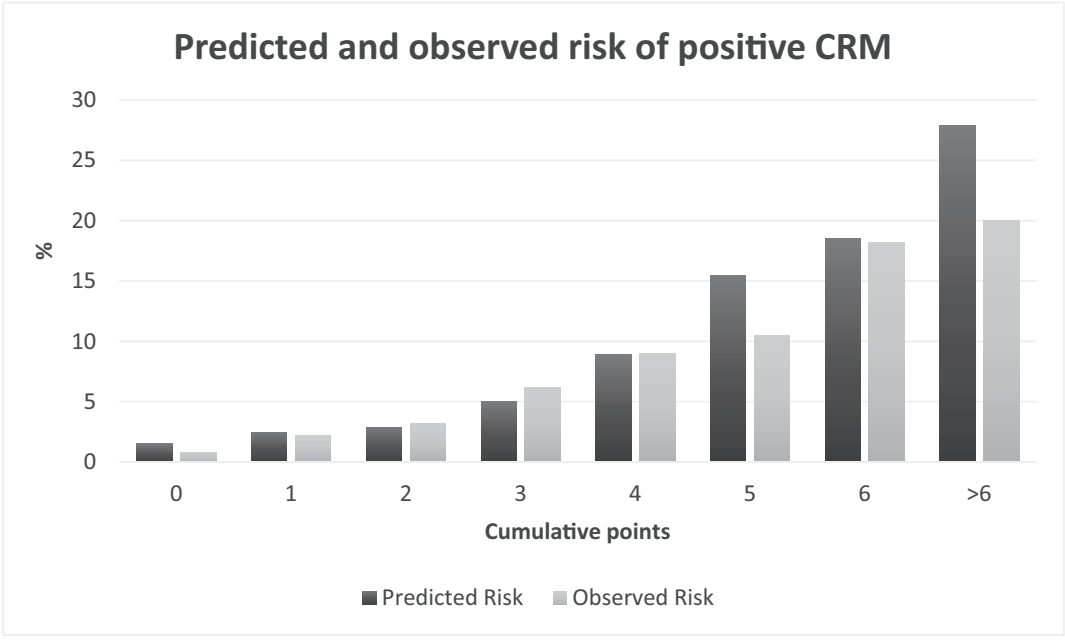

FIGURE 2. Comparison of observed and model-predicted risk of positive CRM.

TABLE 4. The Predicted Risk (and Cumulative Score) for pCRM Involvement According to the Five Independent Risk Factors

Predicted risk % of pCRM incolvement (cumulative score)									
		cT1-3-stage				cT4-stage			
EMVI on MRI	CRM on MRI	Tumor height >1cm ARJ		Tumor height ≤1cm ARJ		Tumor height >1cm ARJ		Tumor height ≤1cm ARJ	
⊖	⊖	**1.5%** (0.0)	**2.5%** (1.0)	**3.2%** (1.5)	**5.4%** (2.5)	**3.0%** (1.4)	**5.0%** (2.4)	**6.4%** (2.9)	**10.4%** (3.9)
⊖	⊕	**2.6%** (1.1)	**4.3%** (2.1)	**5.5%** (2.6)	**9.0%** (3.6)	**5.2%** (2.5)	**8.5%** (3.5)	**10.7%** (4.0)	**16.9%** (4.1)
⊕	⊖	**2.8%** (1.2)	**4.7%** (2.2)	**6.0%** (2.7)	**9.7%** (3.7)	**5.6%** (2.6)	**9.1%** (3.6)	**11.5%** (4.1)	**18.1% (5.1)**
⊕	⊕	**4.8%** (2.3)	**7.9%** (3.3)	**10.0%** (3.8)	**15.9%** (4.8)	**9.4%** (3.7)	**15.0%** (4.7)	**18.6%** (5.2)	**27.9%** (6.2)
		not Anterior	**Anterior**	**not Anterior**	**Anterior**	**not Anterior**	**Anterior**	**not Anterior**	**Anterior**

Green, low (<5%) predicted risk of pCRM positivity; Amber, intermediate (5%–15%) predicted risk of pCRM positivity; Red, high (>15%) predicted risk of pCRM positivity.

rectal cancer surgery, it was important to investigate the incidence of positive CRM and preoperative risk factors for a positive CRM after TaTME surgery. In the present study, the positive CRM rate in a large number of patients treated by TaTME was 4.0%, which can be considered as an indirect marker of good surgical oncological performance. In this study we analyzed the predictive factors for CRM involvement and noted that these were solely tumor characteristics, specifically tumors up to 1 cm from the ARJ, anterior position, cT4, and baseline MRI findings of mrEMVI positive and threatened CRM. Patient-related factors, such as male sex and BMI, which are known to pose greater technical difficulty in a conventional approach from the abdomen, did not influence CRM outcome after TaTME.

The transanal approach has been reported to enhance access to, and better visualization of, the distal part of the rectum. Thus, allowing for a more accurate oncologic dissection and increase the quality of the TME. In a randomized trial, Denost et al reported that the perineal dissection was associated with a decreased risk of CRM involvement, compared with a purely abdominal TME (18% vs 4%; $P = 0.025$).[23] The oncological superiority of the transanal approach, and more specifically TaTME, was reinforced by a recent meta-analysis that showed a higher rate of complete mesorectal resection (OR 1.75; 95% CI, 1.02–3.01; $P = 0.04$), together with a lower rate of positive CRM (OR 0.39; 95% CI, 0.17 to 0.86; $P = 0.02$).[24] In the conventional laparoscopic TME, working in the low pelvis with straight instruments may be extremely challenging, even for experienced colorectal surgeons, especially in patients with challenging anatomy. Moreover, parameters such as male sex and obesity have been associated with rates of positive CRM up to 18% to 21%.[16]

In the first report from the international TaTME registry, Penna et al reported that low tumors, positive CRM on staging MRI, and extensive abdominal dissection were independent risk factors for a poor pathological specimen.[19] The results of the present study concur with those findings, reinforcing the authors' suggestion that adverse patient characteristics, traditionally increasing the difficulty of rectal resection, are less problematic in TaTME. The MERCURY II study also reported on the predicted risk of pathological positive CRM, based on MRI findings,[25] and found the same risk factors as this study, with exclusion of cT4 tumors. These high-risk tumor features are difficult to modify, and more evidence is needed to guide the surgeon in deciding the optimal technique for each case in this high-risk group. However, TaTME seems to mitigate the effect of adverse patient-related factors, potentially improving oncological outcomes in a high-risk group.

In Table 4, the predicted risk of pCRM involvement for individual patients with different combinations of risk factors can be seen. This model provides a framework for surgeons to identify the high-risk patients (>15%) and decide preoperatively on the best surgical technique for each patient. In those cases, nonrestorative procedures or beyond TME approaches should always be considered, of course, in discussion with the patient.

In this study, the strongest predictor for CRM positivity was a tumor <1 cm from the ARJ. The ARJ in adults is located approximately 2.1 cm from the anal verge.[26] In the Mercury II study, similar analyses among patients with low rectal cancer (≤6 cm from the anal verge) identified tumor height <4 cm from the anal verge as one of the main risk factors for pathological CRM involvement (OR 3.39; 95% CI, 1.3–8.8; $P = 0.012$).[25] The association between low tumors and a higher risk of circumferential margin involvement can be explained by the tapering of the mesorectum toward the anus, thereby reducing the range for obtaining clear margins.

EMVI was also found as a prognostic factor for obtaining a positive CRM in this risk model. A systematic review by Chand et al[27] found that the presence of EMVI clearly leads to worse survival outcomes; however, there has been huge variation in the prevalence of EMVI through inconsistent reporting. They propose that as detection rates become more consistent, by standardizing histopathological definitions and the increased use of MRI, EMVI may be considered as part of risk-stratification in rectal cancer.

Although a good correlation between mrTRG status and the final histopathology has been shown,[28] we did not find mrTRG response to be significant associated with CRM status in multivariate regression analysis.[15] MRI is increasingly playing an important role in restaging rectal cancer patients after neoadjuvant treatment. However, it can be challenging to differentiate between residual tumor and fibrosis, leading to a moderate degree of heterogeneity among radiologists, which may have influenced the findings in the present study.[29]

Statistical predictive risk models and nomograms can be used to forecast oncological patient outcomes.[30] In the present study, a dataset of 2653 rectal cancer patients treated with TaTME was used to develop a model that preoperatively identifies patients at high-risk of a positive circumferential margin resection. This high-risk group

may benefit from different treatment modalities, such as prolonged neoadjuvant therapy, additional boost doses of radiotherapy, or even extended surgical resection. This predictive model may improve outcomes of TaTME, by guiding professionals in identifying high-risk patients and selecting the optimal treatment plan, reducing the chance of noncurative surgery.

This study has some limitations. First, the results are based on registry information, introducing the potential for selection bias, as well as relying on accurate recording of data. Recording cases on the registry is not obligatory, and can be very time consuming, which is why not all practicing surgeons contribute cases to the registry and it might be that some "bad" cases were not recorded on the registry. Second, with this novel approach, a learning curve is present and complete expertise is not achieved until several cases are performed, leading to better outcomes in surgeons with increased experience. In this article, the experience of the surgeon, learning curve, and case volume of the center were not taken into account, though they definitely influence results. This important issue will be further assessed in a future registry project, specifically focusing on learning curve for TaTME. Also, due to the design of the registry, pathological assessment was not standardized and the specimens were assessed by local pathologists. Although many pathological definitions, as TNM-staging and TME specimen quality, are standardized, this may have led to inconsistencies. Lastly, in this study, we could only perform an internal validation of the predictive model. Future studies should assess the external validity of the formulated predictive model, before definite conclusions can be drawn.

In summary, this study reports a 4% rate of positive CRM in a large cohort of patients and suggests that key predictive factors for positive CRM after TaTME were restricted to 5 tumor characteristics. CRM involvement is a strong predictor of recurrence and survival, and awareness of high risks may facilitate prevention of noncurative surgery in selected patients. Knowledge of these predictive factors will help guide patient selection, facilitate a more constructive discussion with patients regarding their risks and prognosis, and enhance a tailored treatment approach to optimize oncological outcome.

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DISCUSSANTS

Pawel Mroczkowski (Kassel, Germany):

The paper describes a predictive model for CRM-positivity after TaTME. Several issues limit the validity of the conclusions and should be clarified:

- No standardized pathology processing and reporting
- No standardized radiological processing and reporting
- No clinical validation of the data entered in the registry, which is possibly a selection bias
- Number of missing and imputed data is not given
- No standardized time period between NAT and surgery; the relationship between this gap and positive CRM was not analyzed
- Surgeon- and hospital-dependent factors were not analyzed

The concept of the registry is understandable – to achieve as much information as possible about the implementation of a new surgical technique – and the authors are to be congratulated on this. However, the price of this approach is a huge heterogeneity in the data and different oncological concepts, especially TaTME for threatened CRM, and obviously, no ''watch & wait'' option for complete response. The practical use of the proposed nomogram could be also questioned. The presented results do not have the value of a strictly conducted and controlled RCT, but do have the beauty of the real-world surgical data. Limited implementation of RCT in the clinical practice is well known. So, the results achieved by the authors should not be ignored, also inspiring the improvement of other concepts of registries, which will remain relevant for the improvement of surgical knowledge.

Response From Roel Hompes (Amsterdam, The Netherlands):

Thank you very much for your insightful comments. I believe that the first 3 comments were grouped together as they're valid and known limitations of working with registry data. When it comes to pathology reporting, of course, there is no standardized reporting of pathology, as we would have in an RCT. However, we do work with data captured under very standardized definitions, which we provided on the registry. For the pathology reporting, the most inaccurate data could come from the grading of the specimen quality, which we didn't use as a primary endpoint. We also acknowledge that there are variable definitions throughout the participating centers for a ''positive CRM.'' So, although this is a data point on the registry, we also record the distance of the primary tumor or positive lymph node toward that CRM. Therefore, instead of looking at whether the surgeon checked the ''positive CRM'' box, we actually looked at the distance toward the CRM, and determined whether it's a pathological involved margin, based on the definitions we gave in the methods section.

With regards to the radiological outcomes, I think that for surgeons working or dealing with rectal cancer, EMVI is not considered as a standard parameter for preoperative imaging. This is reflected in the registry data, with quite a large proportion of missing data on this variable. There is a recent systematic review by Chand et al (*World J Gastroenterol*, 2016), which has shown that

there is quite a lot of variability in reporting EMVI. So, I think that this is definitely a point for future improvement.

Concerning the selection bias, again, this is not a randomized control trial. It's registry data, where we have to acknowledge, that we can't be certain that all surgeons also included their worst cases. However, we have made every effort to make the data as accurate as possible. It took us 6 months to clean the data. We went through each case, looked at any inconsistencies and missing data, and then emailed each surgeon individually with these queries. At the end of the day, I would like to make the point that this is real-world data and the best data we have so far.

With regards to the data imputation and the missing data, as mentioned, we tried to limit the amount of missing data by contacting surgeons individually. Still, we have used the single imputation and the predictive mean matching for missing data, as discussed with our statistician within our department. We've acknowledged that multiple imputations would be better. However, that would lead us to doing a single imputation ten times, which would mean that we would get ten different datasets and models, and we would struggle to see how we would combine these models. That's why we chose a single imputation, and the range of the data that was imputed was from 1% to 30%; the 30% was particularly relevant for the EMVI data. I agree that 30% appears high, but simulation studies have shown that even if data is imputed up to 80%, one can still get valid prognostic models.

With regards to your question about the interval period between neo-adjuvant therapy (NAT) and surgery, it's again registry-based data, and not standardized. What we saw was a median interval between neoadjuvant treatment and the surgical procedure of 9.5 weeks [IQR 7.7–12.0]. When you look at the literature, I believe that this is an acceptable interval to achieve downstaging. We did analyze whether there is a difference in getting a pathological involved margin, and no relationship was found between a longer waiting time and positive CRM rate (4.2% in $<$8 wk interval vs 4.5% in $>$8 wk interval, $P = 0.815$).

Ultimately, your last question is also very valid. We do have data on the volume of surgeons. This is part of another project that we're doing based on this dataset, which aims to determine the learning curve for various endpoints. We don't have accurate data on hospital volume because we don't know what the denominator (total number of procedures for rectal cancer) is for each individual unit. However, we have a new project based on Dutch population-based data in the pipeline, as this allows us to not only have data on the exact number of TaTME procedure performed, but also on the denominator of total procedures of rectal cancer.

Finally, I think your comments have strengthened insight into the paper, and will, hopefully, improve the overall message of the paper.

Ronan P. O'Connell (Dublin, Ireland):

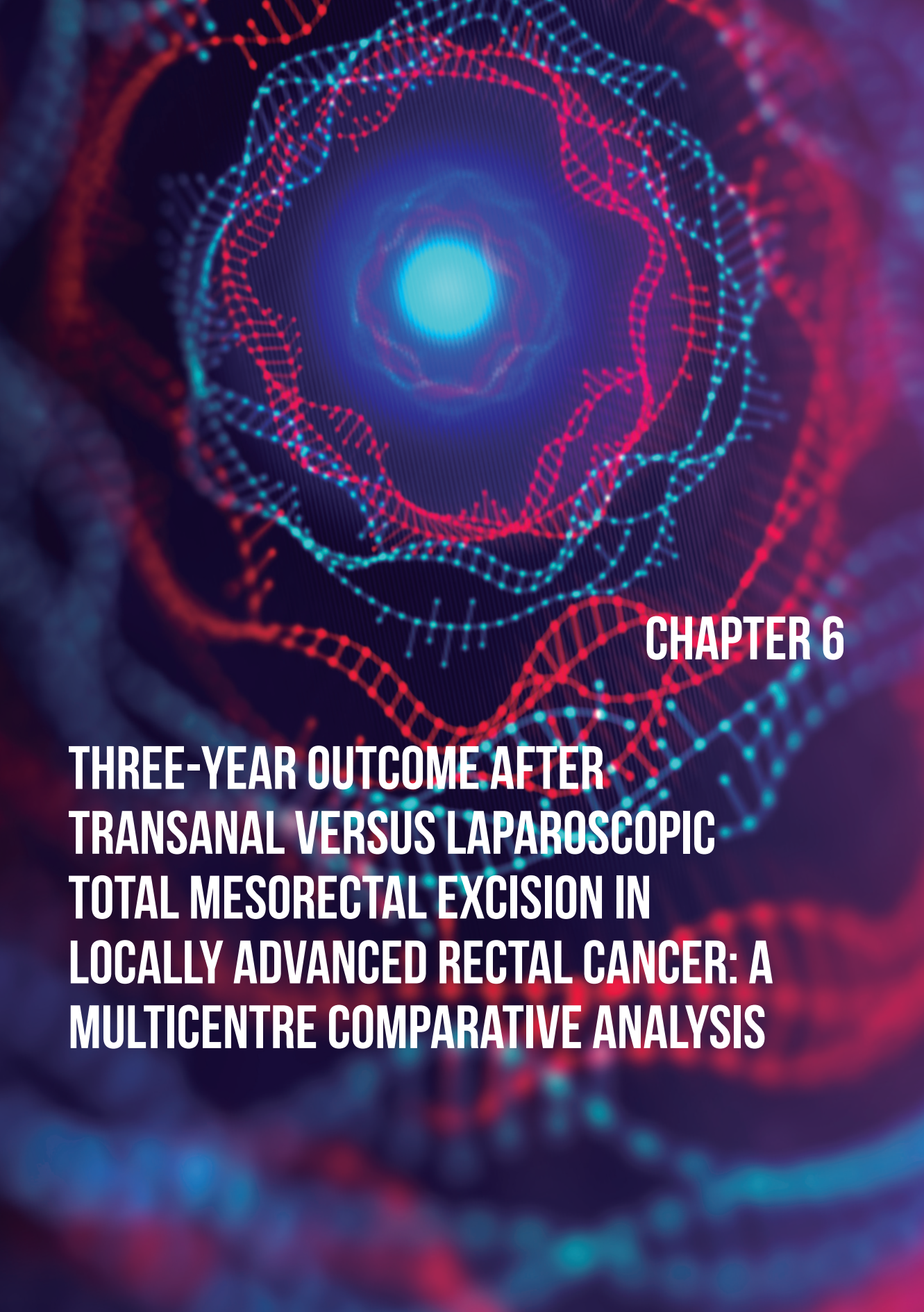
Thank you for presenting these data. You say that they are real-world data and they are real-world data in the registry. However, is the ''real world'' in the real world? That is really one of the concerning things because there is a substantial learning curve to this operation. Many of us have spent our lives learning how to do TaTME properly from above, and now, people are beginning to try to learn the anatomy from completely the opposite end. It is difficult and there are complications that we are seeing with this technique, which we don't generally see with doing it from above. So, the first point is that you say it's ''real world,'' but is it really ''real world''?

The second point is that you have said that patient factors, such as sex or obesity, did not come through as being statistically important, and yet, you state in your introduction that these are selected patients. You have a greater number of men and obese patients. So, how can you then deduce that this is not something that is relevant?

Response From Roel Hompes (Amsterdam, The Netherlands):

I do think that it's the ''real world.'' Within population-based datasets, we do observe that surgeons tend to select the most difficult patients for TaTME. I think that this is an issue we need to address, particularly within the learning curve. We have published data on how TaTME was implemented in the Netherlands (Detering et al, *J Am Coll Surg*, 2019), and there you can clearly see that surgeons in the learning curve are choosing the most difficult patients. This leads to more morbidity, more anastomotic leaks and longer hospital stays. So, I think that this model can give them an idea of which patients should ideally not be chosen within their learning curve, even though they might be the ideal candidates for TaTME.

With regards to your second question, if patient factors, such as sex and obesity, were to be related, I would expect that it would have come through in the analysis. Both of these factors weren't even significant in the univariate analysis. Of course, they are relevant in that they comprise the cases, where one expects to gain the most benefit from the technique.



CHAPTER 6

THREE-YEAR OUTCOME AFTER TRANSANAL VERSUS LAPAROSCOPIC TOTAL MESORECTAL EXCISION IN LOCALLY ADVANCED RECTAL CANCER: A MULTICENTRE COMPARATIVE ANALYSIS

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Three-year outcome after transanal versus laparoscopic total mesorectal excision in locally advanced rectal cancer: a multicenter comparative analysis

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Abstract

Background: For patients with mid and distal rectal cancer, robust evidence on long-term outcome and causal treatment effects of transanal total mesorectal excision (TaTME) is lacking. This multicentre retrospective cohort study aimed to assess whether TaTME reduces locoregional recurrence rate compared to laparoscopic total mesorectal excision (LapTME).

Methods: Consecutive patients with rectal cancer within 12 cm from the anal verge and clinical stage II-III were selected from three institutional databases. Outcome after TaTME (Nov 2011 - Feb 2018) was compared to a historical cohort of patients treated with LapTME (Jan 2000 - Feb 2018) using the inverse probability of treatment weights method. The primary endpoint was three-year locoregional recurrence.

Results: A total of 710 patients were analysed, 344 in the TaTME group and 366 in the LapTME group. At 3 years, cumulative locoregional recurrence rates were 3.6% (95% CI, 1.1–6.1) in the TaTME group and 9.6% (95% CI, 6.5–12.7) in the LapTME group (HR = 0.4; 95% CI, 0.23–0.69; $p = 0.001$). Three-year cumulative disease-free survival rates were 74.3% (95% CI, 68.8–79.8) and 68.6% (95% CI, 63.7–73.5) (HR = 0.82; 95% CI, 0.65–1.02; $p = 0.078$) and three-year overall survival 87.2% (95% CI, 82.7–91.7) and 82.2% (95% CI, 78.0–86.2) (HR = 0.74; 95% CI, 0.53–1.03; $p = 0.077$), respectively. In patients who underwent sphincter preservation procedures, TaTME was associated with a significantly better disease-free survival (HR = 0.78; 95% CI, 0.62–0.98; $p = 0.033$).

Conclusions: These findings suggest that TaTME may improve locoregional recurrence and disease-free survival rates among patients with mid and distal locally advanced rectal cancer.

Keywords: Rectal cancer, Total mesorectal excision, Locoregional recurrence, TaTME

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Background

Each year, 125,000 new cases of rectal cancer are diagnosed in the European Union [1] and mortality ranges between 4 and 10/100,000 per year. The therapeutic approach to rectal cancer is eminently multidisciplinary, but surgery remains the main cornerstone for cure. For mid- and low rectal tumours, total mesorectal excision (TME) along embryological-specific planes is the standard surgical treatment [2]. An intact specimen based on the principles of TME grading, the circumferential resection margin, and the distal resection margin have become the most critical factors in predicting the risk of locoregional recurrence and long-term survival [3–5].

Primary rectal cancer surgery can be performed through an open, laparoscopic, robotic, or transanal approach. The oncological superiority of one approach over the other is still a topic of debate. A recent meta-analysis showed that the risk of a suboptimal TME specimen is higher with laparoscopy compared to open surgery [6]. The transanal TME (TaTME) was developed to improve patient outcomes and the quality of the dissection, which is believed to be especially significant in mid- and low rectal tumours. Studies published to date have reported mesorectal excision completeness rates as high as 92.5 to 96%, and an even significantly higher rate of complete and near-complete mesorectal excisions compared to conventional laparoscopic TME (LapTME) [7–9]. These clinical findings suggest that TaTME is a highly promising technique, although the translation of this data into improved mid- and long-term oncological outcomes has yet to be proven. Unexpectedly, a recent study reported a pattern of rapid and multifocal locoregional recurrence after TaTME [10]. Therefore, this multicenter international study was designed with the goal of comparing the three-year oncological outcome of patients with primary locally advanced rectal cancer treated with TaTME and LapTME in three high-volume rectal cancer centers.

Methods

Study population

Data were obtained from one Spanish center, the Hospital Clinic of Barcelona, and two Dutch centers, the Gelderse Vallei Hospital and the Amsterdam UMC at AMC. LapTME was first introduced at the Hospital Clinic in 1994. In November 2011, TaTME became the standard of care for all patients presenting with rectal cancer that did not require abdominoperineal resection or pelvic exenteration. In February 2017, the transanal approach became standard for patients requiring an abdominoperineal resection. Gelderse Vallei Hospital is a high-volume rectal cancer institution in which TaTME was first used in 2012. At the Amsterdam UMC TaTME became the standard procedure for patients presenting with mid- and low rectal cancer from 2014 onwards. All patients with histologically proven rectal adenocarcinoma treated by TaTME were prospectively registered in a local standardised database or in the International TaTME Registry [11]. Consequently, a multicenter database was created, which included the TaTME cohort and a cohort of patients treated by LapTME between January 2000 and February 2018, through a retrospective analysis of clinical records. All three hospitals used TaTME as a standard procedure for patients with mid- and low rectal cancer until their recent participation in the COLOR III trial, a randomised study in which participants are allocated to either TaTME or LapTME [12].

For this analysis, adult patients with a solitary locally advanced rectal adenocarcinoma, according to the ACOSOG Z6051 definition (cT3/cT4, or cN1/cN2 with any cT) detected by magnetic resonance imaging (MRI) with or without transrectal ultrasonography, within 12 cm of the anal verge treated with TaTME or LapTME were included [13]. The exclusion criteria were: patients with cTisN0 or cT1-2 N0; pelvic malignancy within 5 years; severe, incapacitating disease, i.e. American Society of Anaesthesiologists (ASA) classification IV-V; procedures performed in an emergency setting; tumours previously treated by local excision; unknown cT or cM; metastatic tumours (M1); synchronous tumours; active Crohn's or ulcerative colitis; familial risk-colorectal cancer syndromes; and patients with 30-day mortality when it was judged to have occurred as a direct result of a major active postoperative complication, which is not of primary interest. The Institutional Ethics Committees (Comité de Ética de la Investigación con Medicamentos, Beoordlingscommissie Wetenschappelijk Onderzoek, and Medisch Ethische Toetsings Commissie AMC) approved the TaTME and LapTME techniques years prior to this study in the three institutions noted, and the current study protocol was assessed and accepted by the local Institutional Review Boards. Patients provided written informed consent.

Endpoints

The primary endpoint was three-year locoregional recurrence. Secondary endpoints included systemic recurrence, disease-free survival, and overall survival.

Procedures and definitions

The specific staging, classification methods, and surgical procedures have been described in more detail previously [14–16]. Tumours were considered high if the distal border of the tumour was > 10 cm from the anal verge, mid if it was between 5 and 10 cm, and low in case of a distal border < 5 cm. Patients were eligible for neoadjuvant therapy in cases of cT3b-d/cT4 or cN-

positive tumours below the peritoneal reflection, or if the circumferential resection margin was threatened or involved, although other factors such as extramural venous invasion were also taken into account and discussed by a multidisciplinary team. The indication to receive radiotherapy alone or in combination with chemotherapy was given depending on the institution-specific protocols. Short-course one-week radiotherapy was administered by 25 Gy in five daily fractions. Neoadjuvant long-course chemoradiotherapy was administered by continuous 5-fluorouracil (5-FU) infusion (225 mg/m^2 for 5 days per week) or capecitabine (825 mg/m^2 twice daily for 5 days per week), and a total dosage of 45 Gy, by a weekly dose of 9 Gy divided in 5 days each week, for a total of 5 weeks. The interval between completion of long-course chemoradiotherapy and surgery was 5 to 7 weeks at the beginning of the LapTME cohort recruitment, and, in accordance with current guidelines, was subsequently extended up to 12 weeks and associated with appropriate restaging [1].

The mesorectal specimen was analysed on the basis of four major pathological factors: the integrity of the mesorectum, graded following the Quirke method: complete, near-complete, or incomplete [5]; the circumferential resection margin, considered to be positive when the distance between the deepest portion of the tumour and the resection margin was ≤1 mm, or in the case of a positive lymph node at ≤1 mm of the radical dissection plane; the distal resection margin, considered to be positive if tumour cells were present ≤1 mm from the lower border of the tumour to the cut edge of the specimen; and the number of lymph nodes harvested. Pathological tumour response to neoadjuvant therapy was scored by the Ryan tumour regression grade (three-point TRG): TRG 1, no viable cancer cells, or single cells or small groups of cancer cells; TRG 2, residual cancer outgrown by fibrosis; and TRG 3, significant fibrosis outgrown by cancer, or no fibrosis with extensive residual cancer [17].

Follow-up

Until follow-up was completed after 5 years, patients visited every 3 to 6 months during the first 2 years and every 6 to 12 months during the remaining 3 years. Visits included a history, physical evaluation with digital rectal examination, and determination of the carcinoembryonic antigen level. In Barcelona, imaging studies with thoracic and abdominopelvic CT scans were requested every 6 months during the first 2 years and annually during the remaining 3 years. In both Gelderse Vallei and Amsterdam UMC, imaging study was based on liver ultrasound, and CT scan was performed in case of suspicion of local recurrence or distant metastasis. Pelvic MRI and/or transrectal ultrasound-guided needle biopsy were requested when pelvic recurrence was suspected. Locoregional recurrence was defined as any recurrence in the pelvic area and had to be confirmed at least on imaging.

Statistical analysis

Qualitative variables were expressed as absolute frequencies and percentages. Quantitative variables were reported as means or medians with their 95% confidence intervals (CI), except for follow-up periods, which were expressed as median with range. To allow for an unbiased comparison, an inverse probability of treatment weights approach was used [18]. A logistic regression model was applied, including demographic and clinical preoperative variables such as hospital, age, gender, ASA classification, body mass index (BMI), the distance of the tumour from the anal verge, cT and cN stage, and baseline threatened or involved circumferential resection margin. As the goal was to develop a balanced population that was independent of the outcome assessment, postoperative variables were not included, except for relevant variables that were assessable only after surgery (i.e., pT and pN stage, and pathological response to neoadjuvant therapy). The covariate radiologic extramural venous invasion was excluded from the model due to a significant amount of missing data because this information was not routinely reported until recent years. The covariate type of surgery (categorised as sphincter-saving or abdominoperineal resection) could not be included in the propensity score calculation due to the small number of abdominoperineal resections in the TaTME group.

A well-balanced distribution of the covariates in the weighted sample was confirmed by means standardised differences meeting a standard objective of ±0.10 [19]. The only exception was the covariate hospital, in which a standardised difference of 0.12 was achieved. Since some authors consider the cut-off point for standardised differences to be ±0.20, and given the extensive homogeneity of the rest of covariates (with standardised differences of less than ±0.02), this was finally accepted [20].

The estimation of the survival functions was carried out using the Kaplan-Meier method. The estimation of the effect of surgical procedure was performed using Cox hazard models weighted by the inverse probability of treatment weight adjusting by preservation of the sphincter (sphincter-saving surgery or abdominoperineal resection) with a cut-off at 3 years. Additional analyses using Accelerated Failure Time models were used for the analysis of time to event data in order to estimate the time ratio (TR) for the effect of the surgical procedure on acceleration in the time to the event [21].

Statistical tests were two-sided with a 5% type I error. All the analyses were carried out using SPSS version 25 (IBM) or SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Between 2000 and 2018, 863 patients with primary locally advanced rectal adenocarcinoma met the inclusion criteria and were eligible. Of these, 153 (17.7%) were excluded because data were missing in the covariates selected for the inverse probability of treatment weight. This occurred mainly at the beginning of the LapTME cohort, because either systematization in reporting all the information was scarce, or the necessary investigations to obtain that data were not always performed in that period. Therefore, the final study population consisted of 710 patients, of whom 344 (48.5%) underwent TaTME and 366 (51.5%) LapTME (Fig. 1). The median follow-up in the TaTME and LapTME cohorts was 28.4 (range 0.1–83.6) and 61.1 (range 1.1–205.7) months, respectively. After truncation at 3 years, more than 30% of the patients remained at risk in both groups. Table 1 shows the selected covariates of patients treated with TaTME or LapTME, with standardised differences before and after the inverse probability of treatment weight.

In both groups, similar rates of neoadjuvant therapy administration were observed (71.2% vs. 77.0%; $p = 0.086$). Short-course radiotherapy was given to 59 (24.5%) patients in the TaTME cohort and to 79 (28.1%) patients in the LapTME cohort ($p = 0.408$), while most patients in both groups received long-course chemoradiotherapy: 180 (52.3%) vs. 203 (55.4%) ($p = 0.371$). TaTME was associated with a significant reduction in abdominoperineal resection rates: 2.9% vs. 25.6%, $p < 0.001$. Similar rates of 30-day postoperative complications were observed (31.9% vs. 35.2%; $p = 0.382$).

Histopathological outcomes and adjuvant therapy

Despite an absence of significant differences in the original multi-category mesorectal specimen variable, a

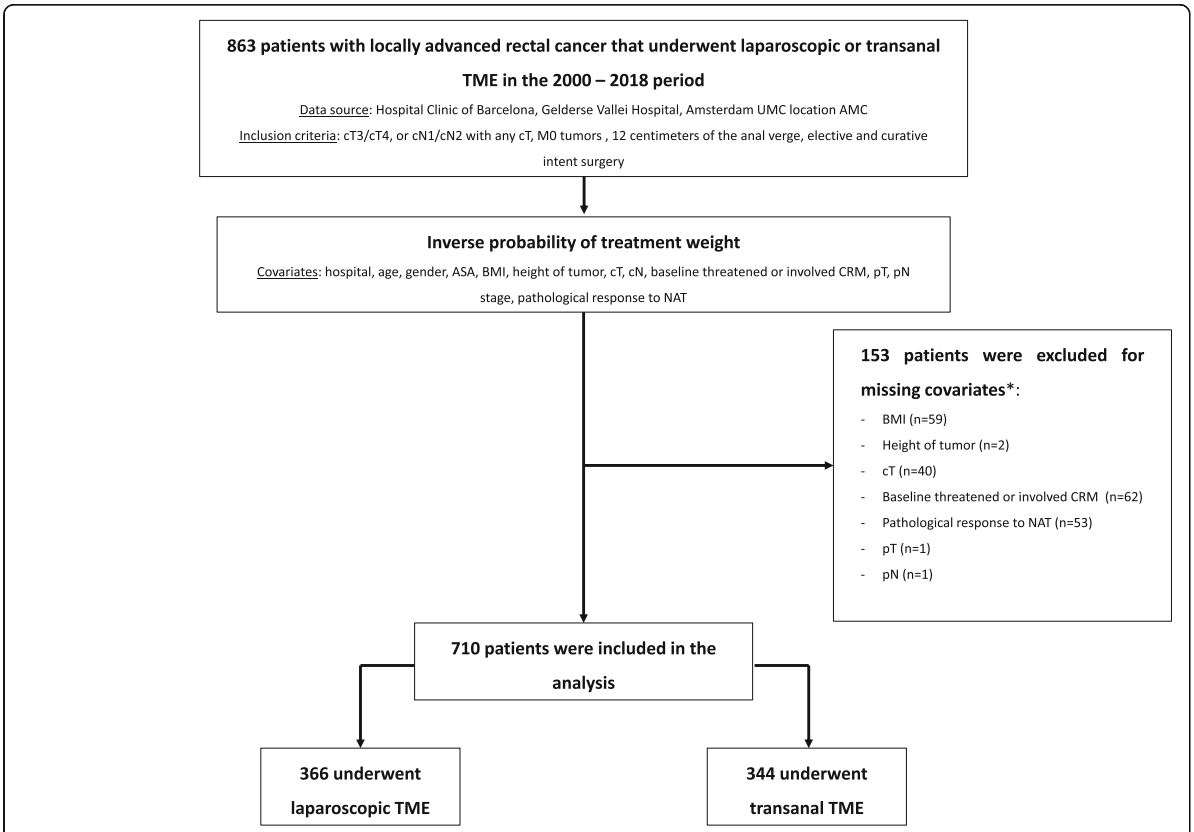

Fig. 1 Flow diagram of study population. Abbreviations: TME, total mesorectal excision; AMC, Amsterdam University Medical Centers; ASA, American Society of Anesthesiologists; BMI, body mass index; CRM, circumferential resection margin; NAT, neoadjuvant therapy; LapTME, laparoscopic total mesorectal excision; TaTME, transanal total mesorectal excision

Table 1 Selected covariates of patients treated with laparoscopic or transanal total mesorectal excision for rectal cancer, with standardised differences before and after inverse probability of treatment weighting

Variable	Surgical approach		Standardised differences	
	TaTME, No. (%)	LapTME, No. (%)	Before IPTW	After IPTW
Total, No.	344	366		
Center				
Barcelona	194 (56.4)	212 (57.9)	0.1189	0.1238
Gelderse Vallei	90 (26.1)	79 (21.5)		
AMC	60 (17.4)	75 (20.4)		
Age, years (mean, 95% CI)	66.5 (65.2–67.7)	66.4 (65.2–67.6)	0.0071	< 0.0001
Gender				
Female	104 (30.2)	137 (37.4)	0.1526	−0.007
Male	240 (69.7)	229 (62.5)		
ASA				
I	44 (12.7)	68 (18.5)	0.0682	0.0002
II	239 (69.4)	227 (62.0)		
III	61 (17.7)	71 (19.4)		
BMI, kg/m^2 (mean, 95% CI)	25.5 (25.1–25.9)	26.4 (25.7–27.0)	−0.161	−0.017
Distance from AV, cm (mean, 95% CI)	7.2 (6.9–7.5)	6.5 (6.1–6.8)	0.2487	0.0024
Clinical T-stage				
cT1	0 (0.0)	4 (1.1)	0.0726	0.0047
cT2	27 (7.8)	41 (11.8)		
cT3	289 (84.0)	266 (76.6)		
cT4	28 (8.1)	35 (10.0)		
Clinical N-stage				
cN0	148 (43.0)	113 (30.8)	−0.288	0.0005
cN1	155 (45.0)	181 (49.4)		
cN2	41 (11.9)	72 (19.6)		
Baseline threatened/involved CRM	94 (27.3)	101 (27.6)	−0.006	−0.009
Pathologic response to NAT[a]				
TRG 1	93 (38.2)	103 (36.5)	−0.144	−0.003
TRG 2	76 (31.2)	85 (30.1)		
TRG 3	74 (30.4)	94 (33.3)		
Pathological T-stage			−0.144	−0.003
pT0	40 (11.6)	35 (9.5)	−0.144	−0.003
pTis	1 (0.2)	0 (0.0)		
pT1	26 (7.5)	20 (5.4)		
pT2	85 (24.7)	95 (25.9)		
pT3	179 (52.0)	179 (48.9)		
pT4	13 (3.7)	37 (10.1)		
Pathological N-stage				
pN0	251 (72.9)	243 (66.3)	−0.144	−0.003
pN1	57 (16.5)	76 (20.7)		
pN2	33 (9.5)	47 (12.8)		
Variable	**Surgical approach**		**Standardised differences**	
	TaTME, No. (%)	**LapTME, No. (%)**	**Before IPTW**	**After IPTW**

Table 1 Selected covariates of patients treated with laparoscopic or transanal total mesorectal excision for rectal cancer, with standardised differences before and after inverse probability of treatment weighting *(Continued)*

Variable	Surgical approach		Standardised differences	
	TaTME, No. (%)	LapTME, No. (%)	Before IPTW	After IPTW
pN3	0 (0.0)	0 (0.0)		
pN1c	3 (0.8)	0 (0.0)		
Sphincter saving surgery[b]	334 (97.0)	272 (74.3)	NA	NA

Abbreviations: TaTME, transanal total mesorectal excision; LapTME, laparoscopic total mesorectal excision; IPTW, inverse probability of treatment weighting; AMC, Amsterdam University Medical Centers; ASA, American Society of Anesthesiologists; BMI, body mass index; AV, anal verge; CRM, circumferential resection margin; NAT, neoadjuvant therapy; TRG, tumour regression grade; NA, not applicable

[a] Including only patients treated with NAT. The TRG system developed by Ryan et al. was used[17]

[b] Not included in the IPTW calculation due to the large differences between groups. It was used as an adjustment cofactor in Cox models

significant higher rate of complete or near-complete was observed in the TaTME cohort: 98.5% vs. 93.5%, p = 0.0003. The rate of circumferential resection margin involvement and incidence of intra-operative rectal perforation were also lower in the TaTME group (Table 2). These findings translated into an overall better composite endpoint of poor pathological outcome for TaTME.

Survival and recurrence analyses

Three years after surgery, the rates of locoregional recurrence were 3.6% in the TaTME group and 9.6% in the LapTME group Hazard Ratio (HR) = 0.4 (95% CI, 0.23–0.69; p = 0.001) (Fig. 2). After stratifying for sphincter-saving surgery or abdominoperineal resection, a lower rate of locoregional recurrence was maintained in those patients who underwent TaTME with sphincter preservation HR = 0.42 (95% CI, 0.24–0.73; p = 0.002). No difference was observed in patients with low rectal cancer HR = 0.9 (95% CI, 0.28–2.93; p = 0.866). In patients with cancer of the mid rectum, the rates of locoregional recurrence were 5.3% in de TaTME group and 12.3% in the LapTME group HR = 0.39 (95% CI, 0.2–0.76; p = 0.006). Systemic metastases were reported in 16.4% of the patients in the TaTME group and in 19.8% of the patients in the LapTME group HR = 0.93 (95% CI, 0.7–1.24; p = 0.615).

At 3 years, the disease-free survival rates were 74.3% in the TaTME group and 68.6% in the LapTME group HR = 0.81 (95% CI, 0.65–1.02; p = 0.078) (Fig. 3). However, when the analysis was limited to patients with sphincter preservation, an improved disease-free survival was observed in patients who underwent TaTME HR = 0.78 (95% CI, 0.62–0.98; p = 0.033). The overall survival rates were 87.2% in the TaTME group and 82.2% in the LapTME group HR = 0.74 (95% CI, 0.53–1.03; p = 0.076). Significant differences in overall survival could not be demonstrated in patients who underwent TaTME with sphincter preservation HR = 0.73 (95% CI, 0.52–1.02; p = 0.068). The survival and recurrence subgroup analyses are shown in Fig. 4.

Within 3 years after primary rectal cancer surgery, 35 locoregional recurrences were observed in the LapTME cohort, with a corresponding number of 12 in the TaTME cohort. Of those patients, 25 (six in the TaTME group and 19 in the LapTME group) presented with at least one of the following risks factors: T4 tumour, N2 disease, incomplete mesorectal specimen, or positive circumferential resection margin. The median time to locoregional recurrence could not be calculated since the event rate was less than 50%. However, the Accelerated Failure Time analysis identified a longer time-ratio in the TaTME group TR = 2.3 (CI, 1.34–4.00; p = 0.026). No multifocal pattern of recurrence was diagnosed.

Discussion

In this multicenter cohort of 710 patients with clinical stage II-III rectal adenocarcinoma, TaTME provided a three-year 60% risk reduction for locoregional recurrence compared to LapTME. In patients undergoing surgery with sphincter preservation, the three-year disease-free survival rate was higher for patients treated with TaTME than for patients treated with LapTME. These benefits could be explained by an improved quality of the mesorectal specimen, with fewer positive resection margins, and lower rate of rectal perforations [4, 22, 23].

The performance of an optimal TME is technically demanding, and the histopathological equivalence of the laparoscopic and open approaches has been recently questioned [13, 24]. Fleshman et al. compared LapTME to open TME and included similar patients as the current study, except for the fact that every patient received neoadjuvant therapy. They found that LapTME did not meet the criteria for noninferiority in a composite score of complete or near-complete TME, and negative circumferential and distal resection margins [13]. It is important to note that Fleshman et al. did not find any difference in survival within 2 years after surgery [25]. Still, the study was not designed as an equivalence trial for survival and recurrence, and the absence of numerical distinctions might not be indicative of any dissimilarity.

Table 2 Pathologic and adjuvant therapy outcomes after inverse probability of treatment weighting

Variable	Surgical approach		*P* Value
	TaTME, No. (%)	LapTME, No. (%)	
Total, No.	344	366	
AJCC pathological stage			
0	38 (11.0)	32 (8.7)	0.8616
I	90 (26.1)	92 (25.1)	
II	123 (35.7)	119 (32.5)	
III	93 (27.0)	123 (33.6)	
IV	0 (0.0)	0 (0.0)	
Mesorectal specimen			
Complete	318 (93.2)	242 (89.3)	0.1678
Near-complete	20 (5.8)	13 (4.8)	
Incomplete	3 (0.8)	16 (5.9)	
Distance to CRM, mm (median, 95% CI)	10.0 (10.0–12.0)	7.5 (6.0–10.0)	0.0131
CRM involvement	32 (9.5)	56 (16.2)	0.0038
Distance to DRM, mm (median, 95% CI)	20.0 (20.0–25.0)	19.5 (15.0–20.0)	0.248
DRM involvement	6 (1.8)	7 (2.0)	0.6135
Rectal perforation	2 (0.8)	8 (3.2)	0.0262
Composite poor pathological outcome[a]	35 (10.6)	69 (24.7)	< 0.001
Perineural invasion	44 (13.0)	47 (18.3)	0.0109
Lymphovascular invasion	68 (21.4)	44 (17.0)	0.0182
Budding			
no	155 (82.8)	38 (52.7)	0.0002
low	23 (12.3)	32 (44.4)	
moderate	2 (1.0)	0 (0.0)	
high	7 (3.7)	2 (2.7)	
Differential grade			0.5589
good	20 (6.3)	15 (4.8)	0.5589
moderate	254 (80.3)	240 (77.4)	
poor	17 (5.3)	22 (7.1)	
Number of lymph node harvested (median, 95% CI)	15.0 (15.0–16.0)	14.0 (14.0–15.0)	0.0133
Adjuvant chemotherapy	42 (12.2)	61 (17.1)	0.0508
Adjuvant radiotherapy	4 (1.1)	15 (4.2)	0.0002

Abbreviations: TaTME, transanal total mesorectal excision; LapTME, laparoscopic total mesorectal excision; AJCC, American Joint Committee on Cancer; CRM, circumferential resection margin; DRM, distal resection margin

[a] Complete or near-complete TME, and negative CRM and DRM

Nevertheless, several clinical studies and meta-analyses have reported improved histopathological outcomes with TaTME compared to LapTME [26, 27]. However, the translation of these potentially advantageous data into improved mid- and long-term oncological outcomes is still scarce. The outcomes of the present study indicate that TaTME not only allows patients to benefit from the short-term advantages of minimally invasive surgery, but might also be superior in ensuring mid-term locoregional recurrence and disease-free survival in selected patients.

The reported improvement in locoregional recurrence rates was at the expense of patients with cancer of the mid rectum, but unexpectedly this was not confirmed in patients with cancer of the low rectum. This apparent disparity could be explained by a high proportion of patients, not estimable due to retrospective access to the data, in the LapTME group with low rectal tumours who underwent open perineal dissection using the transanal way to facilitate the most challenging part of the procedure. According to a randomised trial, transanal perineal dissection has been shown to decrease the risk of

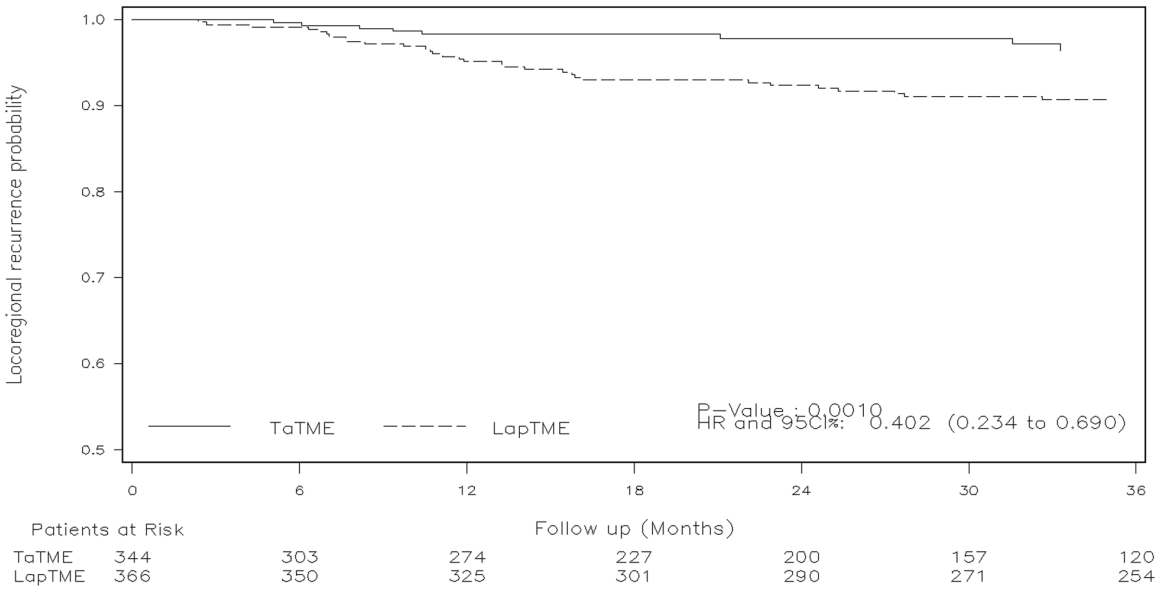

Fig. 2 Three-year locoregional recurrence between TaTME and LapTME in patients with locally advanced rectal cancer. Abbreviations: TaTME, transanal total mesorectal excision; LapTME, laparoscopic total mesorectal excision; HR, hazard ratio; CI, confidence interval

circumferential resection margin involvement by more than 4-fold compared to a purely abdominal TME [28]. Although further investigation is required, these combined data suggest that the surgical therapy of mid and low rectal cancer should include a perineal approach. This might be performed with conventional open surgical instruments or through TaTME in the low rectum. Given the difficulties of approaching mid rectal cancers using an open transanal technique (the Transanal Abdominal Transanal (TATA) procedure) and the inferiority of a pure transabdominal laparoscopic approach as suggested by the present data, TaTME might

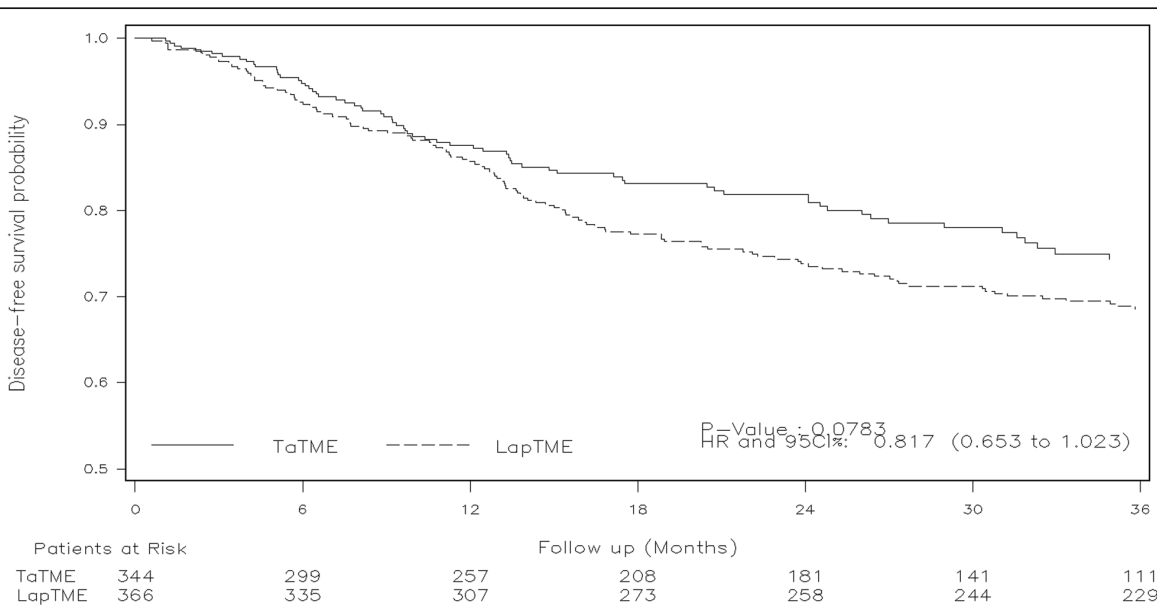

Fig. 3 Three-year disease-free survival between TaTME and LapTME in patients with locally advanced rectal cancer. Abbreviations: TaTME, transanal total mesorectal excision; LapTME, laparoscopic total mesorectal excision; HR, hazard ratio; CI, confidence interval

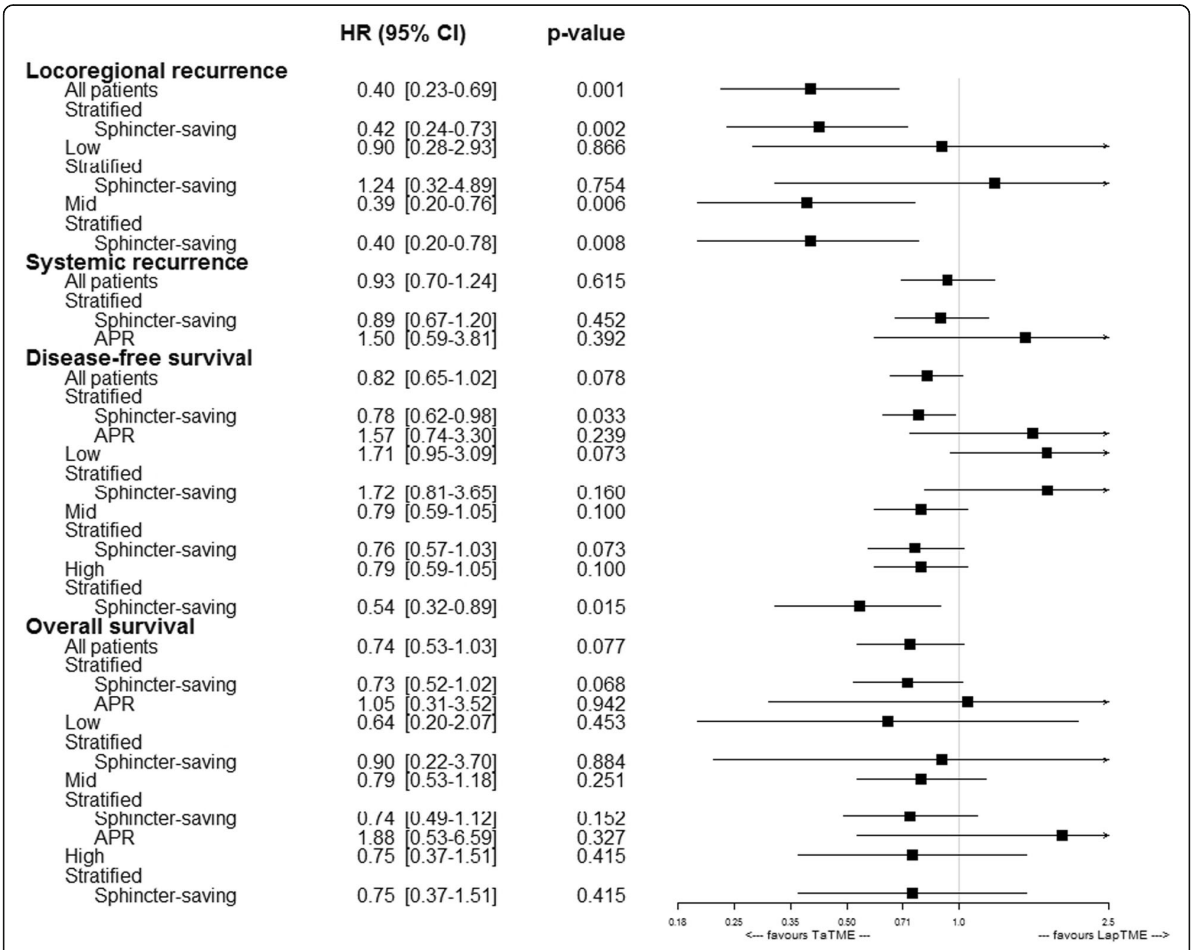

Fig. 4 Subgroup analyses of survival and recurrence among patients with locally advanced rectal cancer treated with TaTME or LapTME. Abbreviations: HR, hazard ratio; CI, confidence interval; APR, abdominoperineal resection; TaTME, transanal total mesorectal excision; LapTME, laparoscopic total mesorectal excision

be the preferred technique when the tumour is in the mid rectum. Robot assisted transabdominal laparoscopy might potentially achieve similar results, but this has still to be confirmed.

Although knowledge in the literature is still scarce and follow-up periods are relatively short, the reported data that TaTME might be associated with a lower risk of locoregional recurrence are substantiated by several observational studies. Tuech et al. analysed 56 consecutive patients with low rectal cancer treated with TaTME and reported a locoregional recurrence rate of 1.7% with a median follow-up of 29 months [29]. Veltcamp Helbach et al. analysed 80 patients with mid- or low rectal cancer who underwent TaTME, and the locoregional recurrence rate after 2 years was 2.5% [16]. With a median follow-up of 31.9 months, Lelong et al. reported a 0% locoregional relapse rate [30]. More recently, Hol et al. analysed 159 consecutive patients undergoing TaTME with a complete and minimum follow-up of 3 years, reporting three- and five-year local relapse as low as 2 and 4%, respectively [31].

However, a recent study questioned the oncologic validity of the transanal approach. Larsen et al. reported, on behalf of the Norwegian Colorectal Cancer Group, that 9.5% of the 110 patients who underwent TaTME presented with an unexpected pattern of early locoregional recurrence, characterised by rapid, multifocal growth in the pelvic cavity and sidewalls [10]. The authors suggested that this atypical pattern of relapse may be a consequence of transanal pursestring failure, with spillage of the malignant cells that are aerosolised by the transanal insufflator. However, neither in the present study nor any of the published studies to date has revealed an unexpected pattern of recurrence. Moreover, the Accelerated Failure Time analysis of our study identified

TaTME as a protective factor on patients' locoregional recurrence time, suggesting a longer time to pelvic relapse in that group compared to patients treated with LapTME.

This clinical research study was based on real-world clinical practice and involved several groups of surgeons to enhance external validity. However, a significant limitation is its nonrandomised design. Observational studies are more susceptible to biases, even more so with surgical interventions where the risk of treatment assignment partiality is increased during the early phase of the learning curve. To avoid this allocation bias, we decided to use the inverse probability of treatment weight method, which has been shown to deliver results more comparable to an RCT than other techniques such as propensity score stratification and, unlike matching, retains most participant data [32]. After weighting, the covariates of the sample obtained were well-balanced and independent of treatment assignment. The only exception was the covariate type of surgery, which was applied as an adjustment cofactor in the Cox models. Nevertheless, we were unable to correct for unknown cofounders, and the analysis by subgroup depending on the type of surgery should be interpreted with caution due the low number of abdominoperineal resections in the TaTME cohort.

Another limitation is the inherent retrospective design which used historical controls. Besides, the extramural venous invasion variable could not be included in the propensity score model due to the large amount of missing data. This occurred predominantly in the LapTME group because the radiological extramural venous invasion has recently begun to be described. Variables such as budding, perineural and lymphovascular invasion displayed a heterogeneous distribution. However, the increased risk of recurrence that this may carry seems to be offset across the groups. Nonetheless, despite our extensive corrections, the presence of cofounders that might bias the results cannot be excluded. Finally, a representative non-selected group of patients who were treated for locally advanced rectal tumours was included. However, the surgical teams have extensive experience performing transanal procedures, and the results may not be generalised to other clinics that have recently started to perform TaTME.

Conclusions

The results of this multicenter observational trial support a possible role for TaTME in improving locoregional recurrence and disease-free survival rates among patients with locally advanced rectal cancer. Further investigation in a randomised clinical trial is warranted.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12885-020-07171-y.

Additional file 1: Supplementary file 1. DF_AC (ICMJE Form from Dr. Antoni Castells).

Additional file 2: Supplementary file 2. DF_AML (ICMJE Form from Dr. Antonio M. Lacy).

Additional file 3: Supplementary file 3. DF_AO (ICMJE Form from Dr. Ana Otero).

Additional file 4: Supplementary file 4. DF_CS (ICMJE Form from Dr. Colin Sietses).

Additional file 5: Supplementary file 5. DF_FBL (ICMJE Form from Dr. F. Borja de Lacy).

Additional file 6: Supplementary file 6. DF_JR (ICMJE Form from Mr. José Ríos).

Additional file 7: Supplementary file 7. DF_JVL (ICMJE Form from Dr. Jacqueline van Laarhovene).

Additional file 8: Supplementary file 8. DF_PJT (ICMJE Form from Dr. Pieter J. Tanis).

Additional file 9: Supplementary file 9. DF_RB (ICMJE Form from Dr. Raquel Bravo).

Additional file 10: Supplementary file 10. DF_RH (ICMJE Form from Dr. Roel Hompes).

Additional file 11: Supplementary file 11. DF_RvP (ICMJE Form from Dr. Roy van Poppel).

Additional file 12: Supplementary file 12. DF_SV (ICMJE Form from Dr. Silvia Valverde).

Additional file 13: Supplementary file 13. DF_SXR (ICMJE Form from Dr. Sapho X. Roodbeen).

Additional file 14: Supplementary file 14. DF_TV (ICMJE Form from Dr. Tjaakje Visser).

Additional file 15: Supplementary file 15. DF_WAB (ICMJE Form from Dr. Willem A. Bemelman).

Abbreviations

TME: Total mesorectal excision; TaTME: Transanal total mesorectal excision; LapTME: Laparoscopic total mesorectal excision; MRI: Magnetic resonance imaging; ASA: American Society of Anaesthesiologists; M1: Metastatic tumours; TRG: Tumour regression grade; BMI: Body mass index; CI: Confidence interval; TR: Time ratio; HR: Hazard ratio; TATA: Transanal abdominal transanal procedure

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Authors' contributions

All authors have read and approved the manuscript. Furthermore, the specific contributions from each author were: Study conception and design: FBL, SXR, JR, JVL, RH, AC, AML. Acquisition of data: FBL, SXR, AOP, TV, RVP, SV. Analysis of data: FBL, JR. Interpretation of data: FBL, JR, SXR, RH, CS, AC, WAB, PJT, AML. Drafting of manuscript: FBL, JR, SXR. Critical revision: JVL, AOP, RB, TV, RVP, SV, RH, CS, AC, WAB, PJT, AML.

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Availability of data and materials

The datasets used and analysed, together with the generated syntaxes (coding), during the current study are available from the corresponding author and Mr. José Ríos on reasonable request.

Ethics approval and consent to participate

The Institutional Ethics Committees approved the TaTME and LapTME techniques years prior to this study in the three institutions noted, and all patients signed informed consent. The Ethics Committee of the Hospital Clinic of Barcelona (named *Comité Ético de Investigación Clínica*), where the Principal Investigator (FBL) belongs, approved the feasibility of the study (*reference HCB/2016/0640*). The current study protocol was assessed and accepted by the local Institutional Review Boards.

Consent for publication

Not applicable.

Competing interests

Dr. F. Borja de Lacy, Drs. Sapho Xenia Roodbeen, Mr. Jose Ríos, Dr. Jacqueline van Laarhoven, Dr. Ana Otero-Piñeiro, Dr. Raquel Bravo, Dr. Tjaakje Visser, Dr. Roy van Poppel, and Dr. Silvia Valverde have no conflicts of interest or financial ties to disclose. Dr. Roel Hompes reports an educational grant from Stryker, personal fees from Applied Medical outside the submitted work. Dr. Colin Sietses reports personal fees from Medtronic, personal fees from Olympus, and personal fees from AFS medical, outside the submitted work. Dr. Antoni Castells reports personal fees from Amadix, Goodgut and Universal Diagnostics, and grants from SAF2014 and AECC, outside the submitted work. Dr. Willem A. Bemelman reports grants from VIFOR, grants from Medtronic, and grants from Braun, outside the submitted work. Dr. Pieter J. Tanis reports personal fees from Johnson & Johnson, personal fees from Olympus, and personal fees from B Braun, and research grant from Life Cell, outside the submitted work. Dr. Antonio M. Lacy reports personal fees from Medtronic, personal fees from Olympus, personal fees from Applied Medical, and personal fees from Conmed, outside the submitted work.

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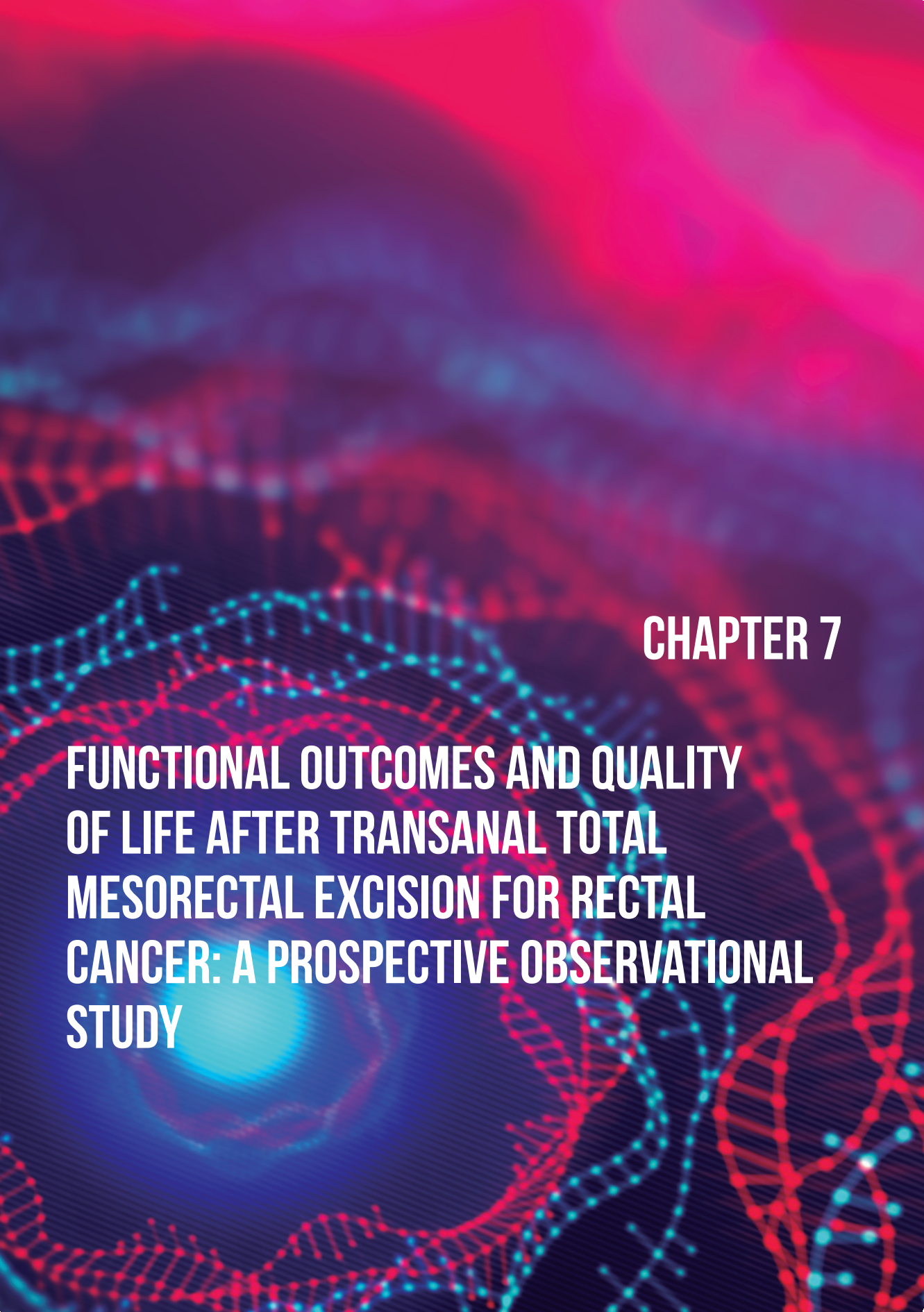

CHAPTER 7

FUNCTIONAL OUTCOMES AND QUALITY OF LIFE AFTER TRANSANAL TOTAL MESORECTAL EXCISION FOR RECTAL CANCER: A PROSPECTIVE OBSERVATIONAL STUDY

Original Article

Functional outcomes and quality of life after transanal total mesorectal excision for rectal cancer: a prospective observational study

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STRUCTURED ABSTRACT

Background: Few studies have addressed the functional impact after transanal total mesorectal excision.

Objective: To evaluate function and health-related quality of life among patients with rectal cancer treated with transanal total mesorectal excision.

Design: Consecutive patients treated between 2016 and 2018 were selected. Their function and quality of life was studied preoperatively, at 3 and 12 months after surgery.

Setting: Prospective case series.

Patients: Patients were eligible if they had primary anastomosis, the diverting stoma had been reversed, and in the absence of anastomotic leakage. Forty-five patients were finally included. A total of 31 (68.8%) and 32 patients (71.1%) completed the 3- and 12-months surveys, respectively.

Interventions: Standard transanal total mesorectal excision.

Main outcome measures: The primary endpoint was functional and quality of life outcomes using validated questionnaires. Secondary endpoints included values obtained with endoanal ultrasounds, anorectal manometries, and rectal sensation testing.

Results: Wexner and Low Anterior Resection Syndrome scores significantly increased 3 months after surgery but returned to baseline values at 12 months. The rate of "major Low Anterior Resection Syndrome" at the end of follow-up was 25.0% (+11.7% compared to baseline, p=0.314). Sexual and urinary functions remained stable throughout the study, although a meaningful clinical improvement was detected in male sexual interest. Among quality of life domains, all deteriorations returned to baseline values 12 months after surgery, except worsening of flatulence symptoms, and improvement in insomnia and constipation. At 12 months, an expected decrease in the mean width of the internal sphincter, the anal resting pressure, and the tenesmus threshold volume was found.

Limitations: Limited sample size, absence of a comparative group, significant missing data in female sexual difficulty, and in ultrasounds and manometries at 3 months.

Conclusions: Patients undergoing transanal total mesorectal excision report acceptable quality of life and functional outcomes 12 months after surgery.

INTRODUCTION

For patients with rectal cancer, surgery based on the total mesorectal excision (TME) has decreased the locoregional recurrence risk to less than 10% and increased the five-year overall survival to about 75%.[1, 2] The oncologic improvements must be complemented with the evaluation of health-related quality of life (HRQL), especially in the setting of the multiple strategies developed to enhance sphincter preservation. Unfortunately, rectal cancer surgery carries serious side effects (such as incontinence or sexual dysfunction) with a direct impact on HRQL.[3, 4] According to Trenti et al, patients undergoing low anterior resection for rectal cancer experience defecatory dysfunctions at a rate of 70 to 90%, which can develop from both TME and radiation therapy.[5]

Transanal TME (TaTME) was developed to improve the quality of the TME, which is believed to be especially significant in the low pelvis.[6] Nevertheless, few studies have addressed functional impact after TaTME, and concerns remain due to a lower anastomotic level and the need for a transanal platform that allows for prolonged anal stretch and dilation.[7-9] A recent meta-analysis with more than 800 patients concluded that TaTME and conventional laparoscopic TME (LapTME) were associated with significant but similar effects in terms of function and quality of life.[10] However, only one third of the studies included reported the patients' baseline prior to undergoing surgery. There was also a lack of information about the stage of the learning curve in each of the surgical teams.[11] Therefore, this single-arm prospective study was designed with the aim of evaluating the impact of TaTME on function and HRQL using standardized questionnaires. All patients underwent a baseline evaluation, and only cases that were performed after the surgeon's learning curve was complete were included. Since questionnaire-based instruments are considered to deliver subjective data that may differ depending on the patient's perception, endoanal ultrasounds and anorectal manometries were also performed.[12]

MATERIAL AND METHODS

Study population

In Hospital Clinic of Barcelona, where TaTME became the standard of care in 2011, all patients undergoing surgery for rectal cancer are assessed from a functional and quality of life point of view. For this study, we conducted a prospective case series analysis of

all consecutive adult patients with rectal cancer treated with the standardized TaTME technique between September 15, 2016 and September 15, 2018. The exclusion criteria were: no primary anastomosis, diverting stoma not reversed, cognitive impairment that prevented the correct understanding of the surveys, anastomotic leak, emergency or palliative surgery, previous local excision, surgery other than conventional anterior resection, patients with active Crohn's disease or ulcerative colitis, and exitus or loss of follow-up before completing at least the first postoperative (3 months) assessment. The local Ethical Committee approved the feasibility of the trial, and all patients signed informed consent.

Procedures

All surgeries were performed by a two-teams approach and by the same specialized surgical team.[9] Patients were considered candidates for primary anastomosis if they had acceptable pre-treatment anorectal sphincter function, which was assessed by medical history, digital rectal examination, endoanal ultrasound and anorectal manometry. Defunctioning stoma was constructed in patients with risk factors for anastomotic leak but at the discretion of the senior surgeon. During the first follow-up visit, patients with bowel diversion and an intact anastomosis without stricture, assessed at least with digital rectal examination and imaging with contrast enema, were considered for reconstruction. In cases requiring adjuvant chemotherapy, stoma reversal was usually delayed until systemic treatment completion.

Follow-up and health-related quality of life instruments

Functional and HRQL validated surveys, which were filled out either by paper or email, were completed the day before the operation (baseline), then 3 and 12 months after restorative surgery (considering restorative surgery as either primary TaTME without diverting stoma, or stoma closure if it had been primarily constructed). On the index date, individual reminders were sent.

To assess bowel function, the Wexner Score and the Low Anterior Resection Syndrome (LARS) instruments were used. The LARS score was divided into “No LARS” (0 to 20 points), “minor LARS” (21 to 29 points), and “major LARS” (30 to 42 points).[13] The International Index of Erectile Function (IIEF-5) and the Female Sexual Function Index (FSFI) were used to evaluate sexual function in males and females, respectively.

To analyze urinary function, the International Consultation on Incontinence Questionnaire (ICIQ) was used.

The European Organization for Research and Treatment of Cancer (EORCT) tools were used to analyze HRQL: the generalized QLQ-C30 version 3.0, and the disease-specific for colorectal cancer QLQ-CR29.[14-16] The EORTC QLQ-C30 entails 30 items that cover five functional scales, three symptom scales, six individual symptoms, and a global HRQL index. The EORTC QLQ-CR29 includes 29 items that cover five functional and 18 symptom scales. Following the EORTC scoring manual and in order to compare means, the individual scores were converted to scale scores ranging from 0 to 100.[15, 16] Besides the statistical method described below, within the EORTC questionnaires there is a lack of consensus on what a clinically relevant change means. We considered a minimally important difference (MID) for deterioration as a range between 5 and 10 mean points.[17] Differences greater than 10 were considered to be substantial. Both EORTC tools were translated and validated for use among the Spanish population participants.

Endoanal ultrasounds, anorectal manometries, and rectal sensation testing

Endoanal ultrasound was performed with a 2D ultrasound scanner with a 10 MHz rotating endoprobe. For anal manometry and rectal sensation studies, we used a low compliance, four-channel water-filled catheter, with a radial distribution of the ports, connected to a polygraph (PC Polygraph HR Synectics Medical) and to a computer acquisition system (Pentium-II-software Polygram MS-DOS). These objective data were also gathered at the time of diagnosis (within four weeks before surgery), then 3 and 12 months after TaTME or stoma closure.

Statistical analysis

The results were described as mean and standard deviation, and non-parametric as median and range. Qualitative variables were expressed as relative and absolute frequencies. To answer the research questions, a comparison of the means between baseline measurements and values at 3 and 12 months were completed to assess quality of life before and after surgery. Comparison of the variable means were calculated with a Paired Samples T-Test, by calculating the mean differences between baseline and 3-month post-surgery, as well as between baseline and 12 months post-surgery. Since radiotherapy and low tumors (<5cm from anal verge) have been identified as risk factors for bowel

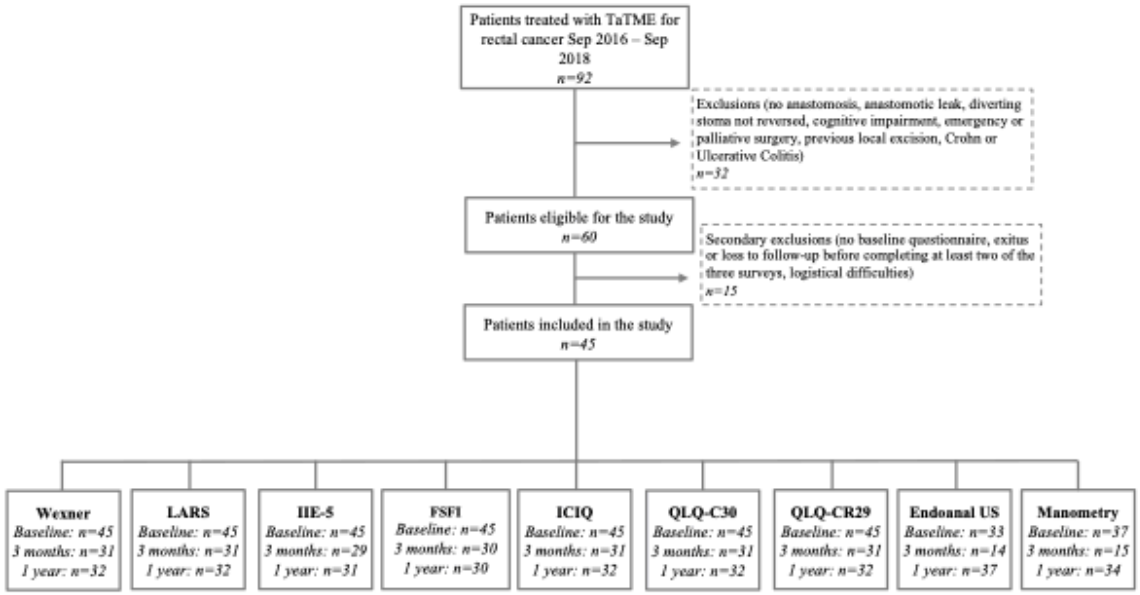
dysfunction, a subanalysis using ANOVA and Chi-Square tests was performed. However, because the LARS categorical variable contains pre- and post-test measurements, the McNemar's Chi-Square test was applied to adjust for the fact that the assumption of variable independence is violated. A two-sided Type I Error equal to 0.05 was used in all statistical analyses. Data were analyzed using the IBM SPSS Statistics program, version 24 (IBM Corp., Armonk, NY, USA).

RESULTS

Between September 15, 2016 and September 15, 2018, 92 patients were treated with TaTME for primary rectal cancer. After applying inclusion and exclusion criteria, 60 patients were eligible for this study. Of these, 15 patients were excluded due to an absence of baseline data, not completing at least two of the three surveys, or logistic difficulties. Thus, 45 patients were finally included in this analysis. Table 1 shows the baseline characteristics of the patients included. The rates of conversion, complete or incomplete mesorectum, and positive circumferential resection margin excluding T4 tumors were 2.2% (n=1), 95.5% (n=43), and 7.3% (n=3) respectively. The median operative time was 140.5 (range 235.0) mins.

Response rate to surveys was 100% (n=45) for baseline, 68.8% (n=31) at 3 months, and 71.1% (n=32) at 12 months. The endoanal ultrasound compliance was 77.3% (n=33) for baseline, 31.1% (n=14) at 3 months, and 82.2% (n=37) at 12 months. For anorectal manometries, compliance was 82.2% (n=37) at baseline, 33.3% (n=15) at 3 months, and 75.5% (n=34) at 12 months (see flowchart in Figure 1). Within the completed questionnaires, the completion rate was generally high (>95%) for all domains. The only exception was sexual function in women and dyspareunia. The domain scores of these two items could not be calculated in >85% of the female participants, thus impairing the comparison of mean differences between all follow-up times and baseline.

Figure 1: Flow diagram of study population



TaTME, transanal total mesorectal excision; LARS, Low Anterior Resection Syndrome; IIEF-5, International Index of Erectile Function; FSFI, Index of Female Sexual Function; ICIQ, International Consultation on Incontinence Questionnaire; QLQ, Quality of Life Questionnaire; US, ultrasound

Table 1: Patient, tumor, and operative characteristics

Factor	**Total = 45**
Mean age, years (SD)	67.1 (11.3)
Gender	
Female	23 (51.2%)
Male	22 (48.8%)
Previous pelvi-perineal surgery	5 (11.1%)
Hemorrhoidectomy	1 (2.2%)
Rectal prolapse repair	1 (2.2%)
Vaginal prolapse repair	1 (2.2%)
Rectovaginal fistula repair	1 (2.2%)
Prostatectomy	1 (2.2%)
Mean BMI, kg/m^2 (SD)	26.1 (4.4)
Mean tumor height from AV, cm (SD)	9.1 (3.6)
Clinical T-stage	
cT0	1 (2.2%)
cT1	8 (17.7%)
cT2	15 (33.3%)
cT3	17 (37.7%)
cT4	4 (8.8%)
Clinical N-stage	
cN0	33 (73.3%)
cN1	9 (20.0%)
cN2	3 (6.6%)
Neoadjuvant therapy	18 (40.0%)
Short course radiotherapy	1 (2.2%)
Long course chemoradiotherapy	17 (37.7%)
Mean anastomotic height from AV, cm (SD)	5.1 (2.2)
Type of anastomosis	
Stapled*	40 (88.8%)
Hand-sewn	5 (11.1%)
Anastomosis configuration	
End-to-end	21 (46.6%)
Side-to-end	24 (53.3%)
Primary diverting stoma	21 (46.7%)
Stoma closure	45 (100%)
Median time to stoma closure, months (range)	5.4 (0.23-9.9)

BMI, body mass index; AV, anal verge

*stapled anastomosis was performed as a double pursestring single-stapled

Bowel, sexual, and urinary functions

A significant increase in Wexner score from baseline was found at 3 months but returning to baseline values 12 months after surgery. “Major LARS” was reported in 13.3% (n=6) patients before surgery, in 61.3% (n=19) patients at 3 months (p=0.007), and in 25.0% (n=8) patients at 12 months (p=0.314). Specifically, the most commonly reported symptom of the LARS score was incontinence for flatus, with 53.1% (n=17) of patients presenting with it more than once a week 12 months after surgery. The most common answer for number of bowel movements per day at 12 months was 1-3 (46.8%, n=15).

As shown in Supplementary Table 1, preoperative radiotherapy and low tumors were associated with a higher rate of “major LARS” before surgery (27.8% vs. 3.7% (p=0.020) and 60.0% vs. 7.5% (p=0.001), respectively). At 12 months, the proportion of patients with “major LARS” in radiated or low tumors was still higher, but the difference was not statistically significant (29.4% vs. 20.0% (p=0.539) and 40.0% vs. 22.2% (p=0.399), respectively).

Among the 24 patients with “no or minor LARS” 12 months after surgery, 45.8% (n=11) used constipating medications, or had undergone pelvic floor rehabilitation or neurostimulation. Of the whole cohort, one patient (2.2%) decided to undergo a permanent stoma for severe bowel dysfunction.

Sexual dysfunction was infrequent, as expressed stables scores in both IIEF-5 and FSFI surveys. Throughout the study, no significant impact was found in ICIQ scores either. Bowel, sexual, and urinary outcomes are shown in Table 2.

Table 2: Bowel, sexual, and urinary functions

HRQL instruments	Baseline	3 months		12 months	
		Mean score or percentage	Mean paired differences	Mean score or percentage	Mean paired differences
Wexner score	6.4 (3.9)	11.3 (5.3)*	+4.0 (4.5)	9.0 (6.0)	+1.4 (5.4)
LARS					
No LARS (0 - 20 points)	51.1% (n=23)	9.7% (n=3)*	-	40.6% (n=13)	-
Minor LARS (21 - 29 points)	35.5% (n=16)	29.0% (n=9)	-	34.4% (n=11)	-
Major LARS (30 - 42 points)	13.3% (n=6)	61.3% (n=19)*	-	25.0% (n=8)	-
IIEF-5	12.7 (6.9)	13.1 (7.8)	+2.7 (6.2)	10.5 (5.9)	+0.3 (1.9)
FSFI	10.8 (11.3)	13.8 (19.5)	+0.6 (1.9)	12.0 (11.0)	+0.008 (1.9)
ICIQ	1.8 (2.8)	2.1 (3.5)	+0.3 (2.2)	2.5 (3.3)	+0.6 (2.2)

Data are presented as mean (SD) paired differences on Paired Sample T-Test, except for LARS score which is presented in the validated three-form multicategory [18]. HRQL, health-related quality of life; LARS, Low Anterior Resection Syndrome; IIEF-5, International Index of Erectile Function; FSFI, Index of Female Sexual Function; ICIQ, International Consultation on Incontinence Questionnaire

*Difference from baseline values with $p<0.05$

Health-related quality of life

In the EORTC QLQ-C30, the majority of the items remained stable at 3 and 12 months Table 3). Among the functional scales, the only exception was cognitive functioning, accounting for memory and concentration, at 3 months (mean decrease of -12.3 (SD 26.2) points (p=0.035)) but returning to baseline values at 12 months. Among the individual symptoms, an improvement was found in insomnia and constipation 12 months after surgery (p=0.038 and p=0.025, respectively).

In the EORTC QLQ-CR29, the weight functional scale significantly decreased 3 months after surgery (p=0.022) but returned to baseline values at 12 months (Table 4). In the symptom scales, a worsening in stool frequency, buttock pain, dry mouth, flatulence, and embarrassment was found at 3 months. After 12 months, all these subdomains returned to preoperative values except for flatulence, which remained significantly higher than baseline (p=0.012).

Endoanal ultrasounds

At baseline, mean width of the internal sphincter was 2.5 mm (SD 0.6). Three months after surgery, the internal sphincter had become thinner (2.3 mm (SD 0.5), p=0.831), and 3 (21.4%) lacerations were observed. The low compliance rate of endoanal ultrasounds at 3 months should be noted, especially in the setting of the statistically significant results observed at 12 months: mean width of internal sphincter of 2.3 mm (SD 0.5) (p=0.007), and nine (26.5%) lacerations (two anterior, two posterior, and five lateral). The mean width of the external sphincter remained stable throughout the study, and no injuries were detected.

Anorectal manometries and rectal sensation testing

Maximum resting pressure decreased from 53.8 mmHg (SD 21.5) at baseline to 33.3 mmHg (SD 19.2) (p<0.001) at 12 months. Maximum squeeze pressure and maximum squeeze duration remained stable. A significant decrease in tenesmus threshold was found at 12 months. These outcomes are depicted in Supplementary Table 2.

Table 3: Scores of function, symptom and global health-related quality of life on EORTC QLQ-C30

Items	Baseline	3 months		12 months	
		Mean score	Mean paired differences	Mean score	Mean paired differences
Global quality of life[+]	75.4 (27.8)	74.3 (16.8)	+0.7 (23.9)	73.3 (17.4)	-3.9 (26.8)
Physical function[+]	89.9 (16.0)	83.6 (13.3)	-5.5 (20.1)	88.2 (14.5)	-0.5 (14.0)
Role function[+]	86.4 (21.4)	75.6 (22.5)	-10.1 (30.4)	81.4 (20.7)	-1.33 (25.4)
Emotional function[+]	80.4 (20.1)	66.6 (30.1)	-11.9 (36.2)	75.3 (28.6)	-8.6 (27.0)
Cognitive function[+]	90.0 (12.0)	76.3 (19.6)*	-12.3 (26.2)	89.7 (14.9)	-0.6 (12.2)
Social function[+]	87.8 (16.5)	78.9 (21.4)	-8.3 (23.9)	84.6 (19.3)	-4.0 (20.0)
Fatigue[ŧ]	22.2 (21.6)	31.2 (23.1)	+10.6 (26.4)	21.2 (19.9)	-0.7 (25.3)
Nausea and vomiting[ŧ]	3.8 (11.5)	3.6 (15.5)	-0.2 (13.9)	2.8 (12.2)	-0.9 (11.7)
Pain[ŧ]	16.0 (19.8)	21.1 (25.1)	+5.5 (20.5)	13.2 (19.0)	-3.6 (13.1)
Dyspnea[ŧ]	18.1 (7.6)	13.5 (21.5)	-4.5 (21.5)	11.1 (10.8)	-7.3 (11.7)
Insomnia[ŧ]	26.1 (21.4)	18.2 (28.1)	-7.3 (31.1)	13.2 (31.8)*	-14.4 (31.5)
Appetite loss[ŧ]	11.0 (27.8)	14.8 (23.4)	+2.3 (20.3)	5.0 (29.8)	-8.6 (25.0)
Constipation[ŧ]	16.1 (20.1)	9.0 (29.8)	-6.5 (34.4)	3.2 (32.5)*	-13.0 (33.5)
Diarrhea[ŧ]	23.7 (24.3)	25.0 (28.2)	+1.6 (44.8)	14.3 (21.7)	-9.6 (24.9)
Financial difficulties[ŧ]	3.8 (18.2)	2.6 (26.3)	-0.6 (25.9)	2.3 (14.3)	-1.1 (15.1)

Data are presented as mean (SD) paired differences on Paired Sample T-Test.

+ a high value is positive for the individual

ŧ a high value is negative for the individual

*Difference from baseline values with $p<0.05$

Table 4: Function and symptom scores on EORTC QLQ-CR29

Items	Baseline	3 months		12 months	
		Mean score	Mean paired differences	Mean score	Mean paired differences
Body image[+]	91.2 (11.1)	79.1 (26.4)	-10.1 (24.3)	88.8 (15.0)	-2.2 (10.2)
Anxiety[+]	66.6 (33.3)	62.5 (38.4)	-7.2 (28.3)	66.6 (32.6)	-5.3 (39.2)
Weight[+]	81.0 (26.6)	66.6 (32.6)*	-14.4 (28.1)	71.7 (33.5)	-8.0 (30.8)
Sexual function in men[+]	41.6 (33.3)	59.2 (27.7)	+14.8 (29.3)	57.1 (31.7)	+19.0 (32.5)
Sexual function in women[+]	88.8 (19.2)**	100 (-)**	-	83.3 (23.5)**	-
Urinary frequency[ŧ]	12.7 (17.4)	10.5 (11.2)	-1.6 (13.5)	7.6 (7.7)	-5.2 (9.8)
Blood and mucus in stool[ŧ]	16.3 (21.2)	20.9 (17.8)	+3.0 (28.0)	7.1 (12.6)	-6.6 (19.2)
Stool frequency[ŧ]	25.3 (22.4)	29.4 (30.2)*	+16.6 (28.0)	20.7 (19.0)	+7.9 (22.4)
Urinary incontinence[ŧ]	9.6 (16.8)	13.9 (21.7)	+7.9 (20.8)	9.0 (15.0)	-2.7 (13.6)
Dysuria[ŧ]	11.5 (17.6)	11.2 (18.8)	+4.7 (19.1)	6.5 (13.3)	-5.5 (21.2)
Abdominal pain[ŧ]	19.0 (24.2)	30.6 (25.8)	+8.6 (28.8)	10.3 (15.6)	-8.0 (19.9)
Buttock pain[ŧ]	14.5 (22.9)	30.6 (33.9)*	+18.8 (29.8)	9.0 (17.7)	-5.3 (18.4)
Bloating[ŧ]	11.7 (29.6)	19.5 (23.9)	+5.7 (37.1)	19.3 (25.2)	-1.3 (35.3)
Dry mouth[ŧ]	22.6 (26.1)	37.5 (28.3)*	+15.9 (36.0)	24.4 (22.2)	+0.0 (25.4)
Hair loss[ŧ]	9.3 (16.6)	15.3 (19.6)	+4.3 (15.2)	3.9 (14.3)	-2.6 (13.3)
Taste[ŧ]	10.9 (20.8)	12.5 (21.5)	+4.3 (28.9)	2.6 (9.0)	-5.3 (15.7)
Flatulence[ŧ]	15.3 (22.0)	52.4 (30.8)*	+25.4 (30.1)	40.0 (28.8)*	+18.8 (33.0)
Fecal incontinence[ŧ]	16.2 (18.8)	27.0 (30.9)	+7.8 (32.3)	19.5 (19.4)	+6.0 (19.6)
Score skin[ŧ]	14.2 (20.4)	30.4 (32.3)	+11.1 (28.0)	14.7 (21.6)	+1.4 (18.7)

Embarrassmentŧ	10.2 (21.2)	27.0 (34.3)*	+29.6 (35.9)	4.4 (11.4)	-9.5 (28.1)
Stoma care problemsŧ	13.4 (29.8)	41.7 (41.9)	+16.6 (23.5)	8.4 (16.6)	+8.3 (16.6)
Impotenceŧ	48.0 (38.4)	45.5 (37.2)	-0.0 (52.7)	66.7 (27.2)	+0.0 (27.2)
Dyspareuniaŧ	22.3 (19.2)	33.4 (-)**	-	0.0 (0.0)**	-

Data are presented as mean (SD) paired differences on Paired Sample T-Test.

+ a high value is positive for the individual

ŧ a high value is negative for the individual

*Difference from baseline values with $p<0.05$

** Less than 3 women answered this subdomain at each time point, thus impairing the statistical comparison

DISCUSSION

In this study, TaTME was associated with a deterioration in bowel function and individual subdomains of the HRQL 3 months after surgery. Twelve months after surgery, deterioration for all domains returned to baseline except for flatulence symptoms. Moreover, insomnia and constipation symptoms significantly improved at the end of the follow-up. In patients undergoing TaTME, sexual and urinary functions remained stable. The outcomes in bowel function were objectively confirmed by a decrease in the internal sphincter width, the anal resting pressure, and the tenesmus threshold volume.

"Major LARS" has been shown to improve during the first postoperative year, but a significant number of patients may suffer these severe symptoms for years.[5] Koedam et al reported "major LARS" after TaTME in 80% of the patients one month after surgery, but with a drop to 33% after six months.[18] This is consistent with the results of this study, with a final 25% rate of "major LARS" one year after surgery. A longer analysis has shown a time-dependent improvement in both LARS and Wexner scores in patients treated with TaTME, with only 10% of patients presenting with "major LARS" after one year.[19] However, the low rate of neoadjuvant radiotherapy (20%), a well-known factor for increased risk of postoperative incontinence, in that study should be noted.

The studies above suggest that TaTME might be associated with a lower rate of "major LARS" than the previously published rate of 45-62% with conventional TME.[5, 20, 21] Nevertheless, several comparative studies have showed similar postoperative bowel dysfunction between TaTME and LapTME.[22-25] Recently, this equivalence has been reinforced in a meta-analysis (RR 1.13, 95% CI 0.94 – 1.35, p=0.18).[10] To our knowledge, only one cohort study showed worse outcomes with TaTME, with a significant increase in buttock pain, diarrhea, clustering of stools, and urgency.[26] Still, the study lacked a preoperative functional analysis, which is mandatory for causal inference in all but randomized controlled trials.

The plane of dissection during TME is closely connected to the autonomic nervous system that innervates the urologic and sexual organs. From the original COLOR II study, Andersson et al concluded that micturition symptoms occurred but gradually returned to baseline values six months after surgery, regardless of whether patients were treated by open or laparoscopic approach.[27] Problems with male sexual function were more frequent, with a rate of erectile dysfunction one year after TME of around 11-20%. The scores on urinary and sexual surveys of the present study, as well as on the specific symptom scales on the EORTC QLQ-CR29, did not deteriorate throughout follow-up. Although the result was not statistically significant, sexual interest in men increased by a mean of 19 points compared to baseline values. These outcomes should be interpreted in the context of a randomized controlled trial that reported a higher rate of sexual activity in male patients treated with TaTME than with conventional LapTME, with non-significant improvement of the erectile function (IIEF-5 17 vs. 7, p=0.119).[24] These outcomes support the theoretical basis that TaTME might allow for enhanced preservation of neural tissue during rectal dissection, although this should be tested in a randomized controlled trial.

The vast majority of items in both the EORTC QLQ-C30 and QLQ-CR29 returned to baseline values one year after TaTME or stoma closure. This is similar to the findings from observational studies and phase III clinical trials including patients after radical TME surgery.[27-29] When considering the meaningful clinical difference in absolute means within the EORTC questionnaires, the results of the COLOR II trial showed a drop of more than 10 points in most functional and symptoms scales, as well as in the global HRQL index, four weeks after open and laparoscopic TME.[28] Nonetheless,

outcomes gradually returned to baseline 12 months after surgery. In the present study, substantial differences (mean difference >10 points, with or without time-dependent statistical significance) were detected in several items. Role, emotional, and cognitive functions had deteriorated at 3 months, as well as fatigue, body image, weight, stool frequency, buttock pain, dry mouth, flatulence, score skin, embarrassment, and stoma care problems. Several of these items are directly associated with the LARS and correlates with the 3-month deterioration observed in the analysis of both the LARS and Wexner scores. As expected, substantial differences had disappeared in the majority of bowel dysfunction-derived symptoms 12 months after TaTME.

One strength of this study is the collection of baseline data, allowing each participant to serve as his/her own control. Another strength is the combination of questionnaire-derived data, imaging techniques, and anorectal manometry, which provides a comprehensive assessment of anorectal function. Endoanal ultrasounds revealed a significant decrease in the width of the internal anal sphincter and 26% lacerations, with no alterations in the external sphincter. Similarly, Leao et al. recently analyzed 20 patients undergoing TaTME and reported no injuries to the external anal sphincter but 20% partial lacerations in the internal sphincter.[19] In 1998, a study concluded that transabdominal low anterior resection was associated with an internal anal sphincter injury of 18% (10.2% minor lacerations and 7.2% major lacerations).[30] The majority of those patients presented with a thinned sphincter after surgery, which seems be related to innervation damage during intestinal mobilization. In contrast, the use of transanal dilation platforms has been associated with anal stretching and damage to the sphincter apparatus, which might explain the slightly higher rate of internal sphincter lacerations in our series.[31, 32] Persistent damage to the smooth musculature of the internal anal sphincter is expected.[33, 34] Nevertheless, the outcomes of several observational studies suggest that the majority of these internal sphincter injuries are not associated with a significant clinical impact on continence, although this requires further investigation.[19, 33, 34]

To our knowledge, this is the first study that assessed the impact of TaTME on anorectal manometries and rectal sensation testing. We noted a decrease in resting pressure, which is a reflection of the internal anal sphincter function, and in tenesmus threshold volume. This is consistent with the outcomes reported by De Nardi et al, with

more than a 50% decrease of both anal resting pressure and tenesmus threshold in 39 patients treated for rectal cancer.[35] Unlike that study, we found a stable squeeze pressure, which reflects the stability of the external anal sphincter. This finding was expected since the external sphincter is innervated by somatic nerves that are not at risk during conventional low anterior resection.

This single-center study has several limitations. Firstly, despite its prospective design, it is a small sample single-arm trial and the results are difficult to interpret in the absence of a comparative group. Secondly, the amount of missing data in female sexual difficulty and dysfunction items was significant. This weakness has also been detected in several trials, including the COLOR II study, and must be addressed by means of different strategies, e.g. interviews in person.[27, 36] Thirdly, the compliance rate of about 30% in both endoanal ultrasounds and anorectal manometries at 3 months impaired accurate parameter estimation. Therefore, inferences from this study should be drawn with caution, and solid conclusions will be reached in studies designed to prevent or control for confounding.

CONCLUSION

Patients undergoing TaTME reported acceptable HRQL and functional outcomes one year after restorative surgery. The validated scores were comparable to those achieved with conventional TME techniques, although a lower impairment in genitourinary function may exist. Therefore, until completion of ongoing randomized controlled trials, evidence supports the use of TaTME from a quality of life perspective.

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Supplementary material

Supplementary Table 1: Low Anterior Resection Syndrome assessment in patient with and without radiotherapy

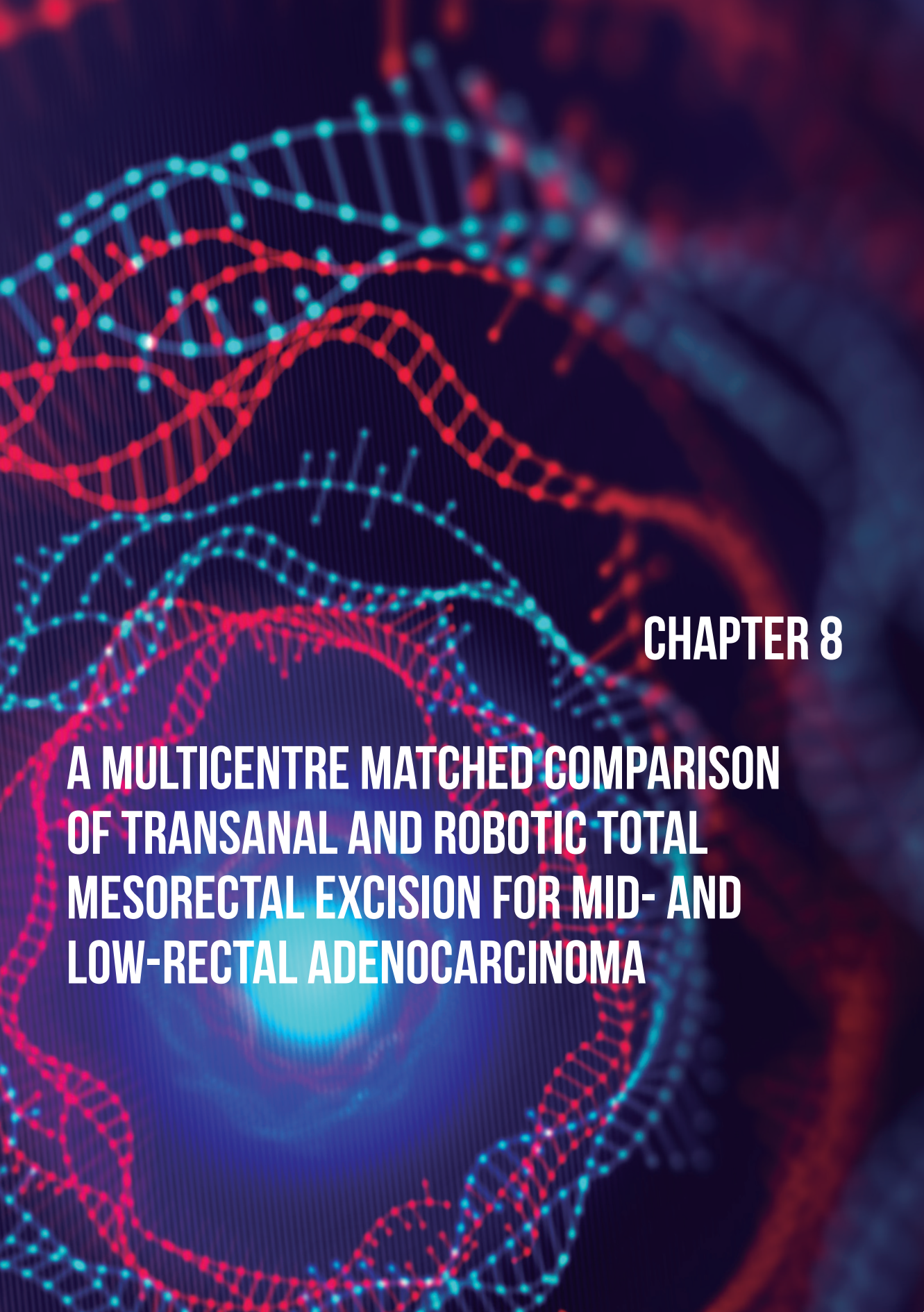
Factor	Baseline*	3 months	12 months
No LARS (0 -20 points), (%)			
No radiotherapy	82.6 (n=19)	80.0 (n=4)	80.9 (n=17)
Radiotherapy	17.4 (n=4)	20.0 (n=1)	19.0 (n=4)
Minor LARS (21 - 29 points), (%)			
No radiotherapy	43.7 (n=7)	64.2 (n=9)	50.0 (n=6)
Radiotherapy	56.2 (n=9)	35.7 (n=5)	50.0 (n=6)
Major LARS (30 - 42 points), (%)			
No radiotherapy	16.6 (n=1)	50.0 (n=13)	58.3 (n=7)
Radiotherapy	83.3 (n=5)	50.0 (n=13)	41.6 (n=5)

LARS, Low Anterior Resection Syndrome
*Difference between groups with $p<0.05$

Supplementary Table 2: Anorectal manometry and rectal sensation testing

Factor	Baseline	3 months		12 months	
		Mean values	**Mean paired differences**	**Mean values**	**Mean paired differences**
Maximum resting pressure, mmHg	53.8 (21.5)	30.0 (15.6) *	-22.3 (16.7)	33.3 (19.2) *	-18.8 (21.3)
Maximum squeeze pressure, mmHg	154.9 (83.3)	131.8 (81.0)	-29.7 (55.3)	131.3 (67.3)	-25.8 (41.5)
Maximum squeeze duration, seconds	23.5 (11.1)	26.2 (13.0)	+4.6 (11.3)	24.1 (15.0)	+0.4 (12.7)
Tenesmus threshold, mL	90.6 (44.5)	40.0 (13.4) *	-48.0 (58.4)	53.9 (22.9) *	-38.4 (37.5)

Data are presented as mean (SD) paired differences on Paired Sample T-Test
*Difference from baseline values with $p<0.05$



CHAPTER 8

A MULTICENTRE MATCHED COMPARISON OF TRANSANAL AND ROBOTIC TOTAL MESORECTAL EXCISION FOR MID- AND LOW-RECTAL ADENOCARCINOMA

A Multicenter Matched Comparison of Transanal and Robotic Total Mesorectal Excision for Mid and Low-rectal Adenocarcinoma

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Objective: To compare the quality of surgical resection of transanal total mesorectal excision (TA-TME) and robotic total mesorectal excision (R-TME).

Background: Both TA-TME and R-TME have been advocated to improve the quality of surgery for rectal cancer below 10 cm from the anal verge, but there are little data comparing TA-TME and R-TME.

Methods: Data of patients undergoing TA-TME or R-TME for rectal cancer below 10 cm from the anal verge and a sphincter-saving procedure from 5 high-volume rectal cancer referral centers between 2011 and 2017 were obtained. Coarsened exact matching was used to create balanced cohorts of TA-TME and R-TME. The main outcome was the incidence of poor-quality surgical resection, defined as a composite measure including incomplete quality of TME, or positive circumferential resection margin (CRM) or distal resection margin (DRM).

Results: Out of a total of 730 patients (277 TA-TME, 453 R-TME), matched groups of 226 TA-TME and 370 R-TME patients were created. These groups were well-balanced. The mean tumor height from the anal verge was 5.6 cm (SD 2.5), and 70% received preoperative radiotherapy. The incidence of poor-quality resection was similar in both groups (TA-TME 6.9% vs R-TME 6.8%; $P = 0.954$). There were no differences in TME specimen quality (complete or near-complete TA-TME 99.1% vs R-TME 99.2%; $P = 0.923$) and CRM (5.6% vs 6.0%; $P = 0.839$). DRM involvement may be higher after TA-TME (1.8% vs 0.3%; $P = 0.051$).

Conclusions: High-quality TME for patients with rectal adenocarcinoma of the mid and low rectum can be equally achieved by transanal or robotic approaches in skilled hands, but attention should be paid to the distal margin.

Keywords: rectal cancer, robotics, transanal total mesorectal excision

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Total mesorectal excision (TME) has been established as the standard for oncologic resection of rectal carcinoma,[1] and quality of the proctectomy has a direct impact on local recurrence and overall survival.[2,3] The past 2 decades has seen significant advances in the treatment of rectal cancer, particularly with minimally invasive laparoscopic and robotic approaches. Despite advances in surgical technique and neoadjuvant therapy, obtaining a negative circumferential resection margin (CRM) resection with intact TME had remained challenging, particularly for patients with tumors in the distal rectum.[4]

Proponents of robotics in colorectal surgery argue that the combination of stereoscopic view, motion scaling, and tremor cancellation allow a more precise dissection in a confined operative field such as the pelvis.[5,6] More recently, transanal TME (TA-TME) has emerged as a new technique for performing TME for rectal cancer with curative intent.[7,8] TA-TME expanded on Marks transabdominal transanal approach to sphincter preservation surgery in the distal rectum by using an advanced transanal platform, the most common of which has been the transanal minimally invasive surgery (TAMIS) platform.[9,10] Advocates of the TA-TME argue the technique offers excellent access to the distal rectum, allows establishment of a distal negative resection margin, and has advantages in dealing with difficult pelvic anatomy.[11] The ''bottom-up'' technique of TA-TME has been proposed as a way to overcome the inherent challenges of operating in a narrow pelvis and perhaps improve the ability to perform sphincter-preserving surgery for cancers of the distal rectum.

Results from the TA-TME registry demonstrated a significant proportion (92.6%) of patients that received a high-quality resection, including a complete or near-complete TME specimen, and negative CRM and distal margins,[12] exceeding results from the American College of Surgeons Oncology Group Z6051 trial for both open and laparoscopic groups.[13] Indeed, the incidence of CRM involvement in the TA-TME registry is also superior to both laparoscopic and robotic arms of the RObotic versus LAparoscopic Resection for Rectal cancer trial.[14] However, there are few direct comparisons between TA-TME and conventional transabdominal approaches (including open, laparoscopic, and robotic) to date.[15–18] Therefore, the objective of this study was to compare quality of surgical resection between the transanal and robotic approaches for patients undergoing curative resection for mid and low-rectal cancer.

METHODS

Study Population

Data were obtained from 5 high-volume rectal cancer specialist institutions [3 centers performed robotic TME (R-TME), 3 centers performed TA-TME, including 1 performing both] from 4 countries. The study population was limited to consecutive cases performed between 2011 and 2017, because before this time, the TA-TME approach had not been developed. Patients were included if they had biopsy-proven adenocarcinoma of the rectum $\leq$10 cm from the anal verge and underwent TME with sphincter preservation by either transanal or robotic approaches. The exact surgical technique was

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surgeon-specific, but was ultimately classified based on which technique (robotic or transanal) was employed for the TME portion of the operation. For example, a robotic approach mobilization of the splenic flexure, descending colon, and beginning of the TME plane at the sacral promontory, but with the majority of TME performed by the transanal approach, was defined as a TA-TME. There were 10 patients who underwent TA-TME who had robotic abdominal assistance, and 5 with robotic-assisted transanal approach; therefore this subgroup was not separately analyzed. The rest of the TA-TME procedures had laparoscopic abdominal dissection. All TA-TME procedures were performed using the GelPOINT Path Transanal Access Platform (Applied Medical, Inc., Rancho Santa Margarita, CA). Robotic procedures were performed using the *Da Vinci Si or Xi* platforms (Intuitive Surgical, Sunnyvale, CA). Exclusion criteria included histology other than adenocarcinoma, upper rectal lesions (>10 cm from the anal verge), patients undergoing abdominoperineal excision, and patients undergoing TME via the laparoscopic approach. Abdominoperineal excisions were excluded from this analysis as the TA-TME approach was no longer performed for this indication by the participating institutions.

All patients included in the study underwent preoperative locoregional staging with magnetic resonance imaging (MRI). Tumor height was defined using rigid proctoscopy and defined as the distance from the lower border of the tumor and the anal verge. Neoadjuvant therapy was generally administered to patients with T3 and higher or with clinical nodal involvement. In instances of long-course chemoradiation, the interval to surgery was between 8 and 12 weeks, although the exact regimen and protocol differed between institutions.

Outcomes and Variable Definitions

The main outcome measure of this study was a composite of quality of the mesorectal excision, CRM, and distal resection margin (DRM). The quality of TME specimen was defined as per the Quirke classification.[2] A positive CRM was defined as <1 mm between deepest tumor invasion to the mesorectal fascia. Due to the variability in the way the CRM was defined in pT4 tumors, CRM involvement was calculated only for pT0-3 tumors. A positive DRM was defined as <1 mm between the lower aspect of tumor and distal cut edge of specimen. A high-quality resection was defined as a complete or near-complete TME specimen, coupled with negative CRM and DRM. This composite outcome has been used in randomized trials comparing open and laparoscopic TME.[13,19] Postoperative morbidity and mortality were recorded up to 30 days after surgery. Anastomotic leak was defined as per the International Study Group of Rectal Cancer grading system.[20] Response to neoadjuvant radiotherapy was not included in this analysis due to the differing grading systems used by the contributing institutions.

Statistical Analysis

Coarsened exact matching (CEM) was used to account for differences in patient-level factors between those undergoing TA-TME and R-TME. CEM is similar to propensity score matching in that it facilitates more comparable evaluation of study groups by creating proportionality among variables that are hypothesized to affect the outcome of interest. Rather than matching based on the logit score, CEM divides subjects into distinct strata, and matched according to relevant variables (eg, discrete height strata of 0–4, 4–7, and 7–10 cm from the anal verge). The matched subjects are then assigned a weight specific to their stratum and proportional to all subjects in each stratum. CEM has the advantage of being able to balance comparison groups while minimizing the confounding effects of individual variables and avoids the need for the iterative balance checking process that may introduce error, as in propensity score matching, while still maintaining a relative level of similarity between observations.[21] When directly compared with propensity score matching, CEM has been shown to result in less variance and bias.[22] In this study, CEM was used to account for baseline differences in age, male sex, body mass index, tumor size, tumor height from the anal verge, clinical T-stage, and neoadjuvant radiotherapy. Patients in either group who do not have any suitable matches were removed from the analysis. Matching was only performed based on clinical and not pathologic T-stage as only clinical stage would have been available during the decision process to potentially perform either transanal or robotic approach. Clinical N-stage was not included as there were different criteria used between the centers (ie, size, morphology, etc) which resulted in significant variability.

Data are represented as n (%) for categorical variables and mean [standard deviation (SD)] for continuous variables. Univariate analyses were performed using Student *t* test for continuous variables and chi-square test for categorical variables. The main outcome analyses were also stratified by rectal segment (low rectum, 0–5 cm; mid rectum, 5–10 cm). Independent predictors of a poor-quality resection were determined using multiple logistic regression. Covariates for the multiple regression model were chosen a priori based on known risk factors for involved CRM or incomplete TME: male sex, body mass index, tumor height, neoadjuvant radiotherapy, and more advanced tumors (higher grade, larger size, and T3-4).[23,24] Multiple regression analyses were only performed using the propensity-matched cohort to further minimize bias.[25] Subgroup analyses were performed in patients without pathologic complete response as it would affect CRM and DRM involvement. Statistical significance was defined as $P < 0.05$. All analyses were performed using STATA 15.1 (StataCorp, College Station, TX).

RESULTS

There was a total of 730 patients included in this study (453 robotic and 277 transanal). There were significant differences in patient and tumor characteristics between the 2 groups in the unmatched cohort (Tables 1 and 2). After matching, 226 patients in the TA-TME group were matched to 370 patients in the R-TME group. Patient and tumor characteristics were well-balanced after matching (Tables 1 and 2), in particular, pathologic T-stage and tumor height from the anal verge. There remained a significant difference in clinical N-stage, despite matching, but this variable was not included in the CEM, and there were no differences in pathologic N-stage. The mean tumor height from the anal verge was 5.6 cm (SD 2.5). There were 53.6% of the tumors located within 4 and 7 cm from the anal verge (TA-TME 53.9% vs R-TME 53.4%; $P = 0.676$). Neoadjuvant radiotherapy consisted of long-course chemoradiotherapy in 96.2% of cases as short-course radiotherapy was administered in only 12 patients (7 R-TME, 5 TA-TME). There was no difference in operative time between the 2 groups, despite more hand-sewn anastomoses and diverting stomas in the TA-TME group. Postoperative morbidity was also similar between the 2 groups, including the incidence of anastomotic leak and re-operations.

Pathologic outcomes between the 2 groups in the matched cohort were similar (Table 2). There was a higher incidence of pathologic complete response in the TA-TME group compared with R-TME. The proportion of patients that achieved a high-quality resection was similar in both groups (TA-TME 93.1% vs R-TME 93.2%; $P = 0.954$), and also when stratified by low (TA-TME 92.8% vs R-TME 92.1%; $P = 0.819$) and mid-rectal (TA-TME 93.3% vs R-TME 94.5%; $P = 0.699$) tumors. There was no difference in these outcomes on subgroup analysis if patients with pathologic complete response were excluded. When analyzed by individual elements, there were no differences in the incidence of CRM involvement, or TME quality (99.1% complete or near-complete in TA-TME vs

TABLE 1. Patient, Tumor, and Operative Characteristics

	Unmatched Cohort			Matched Cohort		
	TA-TME (n = 277)	**R-TME (n = 453)**	***P***	**TA-TME (n = 226)**	**R-TME (n = 370)**	***P***
Mean age, yrs (SD)	63.4 (12.2)	59.7 (13.2)	<0.001	62.1 (11.7)	62.5 (11.1)	0.684
Male sex	175 (63.2%)	284 (62.6%)	0.896	142 (62.8%)	235 (63.5%)	0.867
Mean BMI, kg/m^2 (SD)	27.9 (4.6)	25.6 (3.9)	<0.001	26.1 (3.8)	25.8 (4.0)	0.332
ASA class 3+	58 (20.9%)	105 (23.2%)	0.481	47 (20.7%)	70 (18.9%)	0.576
Mean height from AV, cm (SD)	5.9 (2.5)	5.5 (2.6)	0.064	5.6 (2.5)	5.6 (2.6)	0.919
Rectal segment			0.018			0.727
Low (0–5 cm)	126 (45.5%)	247 (54.7%)		117 (51.8%)	197 (53.2%)	
Middle (5–10 cm)	151 (54.5%)	205 (45.3%)		109 (48.2%)	173 (46.8%)	
Mean tumor size, cm (SD)*	2.8 (1.9)	3.3 (2.1)	<0.001	2.8 (1.9)	3.0 (2.1)	0.350
Clinical T-stage			0.626			0.915
cT1-2	55 (19.9%)	96 (21.2%)		50 (22.0%)	78 (21.1%)	
cT3	197 (71.1%)	308 (68.0%)		154 (67.9%)	251 (67.8%)	
cT4	25 (9.0%)	49 (10.8%)		23 (10.1%)	41 (11.1%)	
Clinical N-stage			<0.001			<0.001
cN0	136 (49.1%)	125 (27.6%)		95 (42.0%)	100 (27.0%)	
cN1-2	141 (50.9%)	328 (72.4%)		131 (58.0%)	270 (73.0%)	
Pretreatment threatened/involved CRM	85 (30.7%)	133 (29.4%)	0.704	68 (30.1%)	108 (29.2%)	0.815
Neoadjuvant (chemo)radiotherapy	198 (71.5%)	302 (66.7%)	0.174	160 (70.7%)	256 (69.2%)	0.678
Mean operating time, min (SD)	189.8 (87)	185.8 (95.3)	0.617	189.9 (89.3)	189.1 (98.2)	0.988
Anastomosis			0.011			0.023
None	9 (3.2%)	28 (6.2%)		8 (3.5%)	24 (6.5%)	
Stapled	164 (59.2%)	298 (65.8%)		129 (57.1%)	237 (64.0%)	
Hand-sewn	104 (37.6%)	127 (28.0%)		89 (39.4%)	109 (29.5%)	
Diverting stoma	253 (91.3%)	351 (77.5%)	<0.001	212 (93.8%)	299 (80.8%)	<0.001
Conversion	3 (1.1%)	6 (1.3%)	0.774	3 (1.3%)	4 (1.1%)	0.787
30-d postoperative complications	93 (33.6%)	158 (34.9%)	0.719	74 (33%)	130 (35%)	0.550
Anastomotic leak*	29 (10.5%)	51 (11.3%)	0.741	25 (11.1%)	37 (9.5%)	0.612
Grade B	14 (5.1%)	31 (6.8%)	0.329	13 (5.8%)	26 (7.0%)	0.541
Grade C	15 (5.4%)	20 (4.4%)	0.539	12 (5.3%)	11 (3.0%)	0.151
Postoperative ileus	29 (10.5%)	61 (13.5%)	0.232	25 (11.1%)	49 (13.2%)	0.433
Urinary retention/UTI	15 (5.4%)	31 (6.8%)	0.441	10 (4.4%)	21 (5.7%)	0.505
Superficial SSI	7 (2.5%)	13 (2.9%)	0.783	5 (2.2%)	10 (2.7%)	0.711
Acute kidney injury	15 (5.4%)	33 (7.2%)	0.386	12 (5.3%)	27 (7.3%)	0.341
Other	8 (2.9%)	25 (5.5%)	0.097	6 (2.7%)	16 (4.3%)	0.294
Re-operation within 30 d	23 (8.3%)	28 (6.2%)	0.275	17 (7.5%)	23 (6.2%)	0.536
30-d mortality	0 (0%)	2 (0.4%)	0.268	0 (0%)	2 (0.3%)	0.268

*Only including patients with anastomosis (unmatched cohort TATME n = 268, R-TME n = 425; matched cohort TATME n = 218, R-TME n = 346).
ASA indicates American Society of Anesthesiologists; BMI, body mass index.

99.2% in R-TME; $P = 0.923$). There was a trend towards higher incidence of DRM involvement in the TA-TME group. Of the 4 total patients with a positive DRM, 3 had pT3 tumors that received neoadjuvant chemoradiation and were located within 1 cm of the anorectal ring and required intersphincteric resection. The DRM and CRM were focally positive in these cases. The quality of TME in these cases was complete (n = 3) or near-complete (n = 1). These results were similar when stratified by low and mid-rectal tumors, except that the distance to the distal margin was longer in the TA-TME group for low-rectal tumors. On multiple regression analysis, only tumor height and advanced T-stage were independent predictors of a poor surgical resection for both models (Table 3).

DISCUSSION

Despite advances in multimodal therapy, surgical technique resection quality remains a crucial factor for curative-intent treatment of patients with rectal adenocarcinoma. Local recurrence is highly dependent on a negative CRM and excision of an intact mesorectal envelope.[26,27] Yet, these surgical benchmarks remain highly variable due to deficiencies in technique, anatomical challenges, and tumor-related characteristics.[4] R-TME has been adopted by many to overcome the challenges to a quality oncologic resection.[6] More recently, a TA-TME approach has been developed as another method for oncologic proctectomy.[7] To date, there are few data comparing these 2 techniques.

The results of this study suggest that the incidence of high-quality TME for mid and low-rectal cancer is similar between the transanal and robotic approaches. The results in the R-TME group mirror other large robotic series.[14,28,29] In the ROLARR trial, the incidence of CRM involvement was 5.1%, although 30% of tumors were located in the upper rectum and only 47% received neoadjuvant radiotherapy.[14] Comparatively, there was 6% CRM involvement in the R-TME group in this study, but we only included sphincter-saving procedures for lesions in the mid and low rectum, and 69% of patients in the robotic arm received preoperative radiotherapy. In contrast, there was a higher incidence of CRM involvement in the TA-TME group in this study (5.6%) compared with that of the PELICAN registry (2.4%), although the proportion of patients with a poor composite outcome was similar (6.6% in this study and 7.4% in the PELICAN registry).[12] The reasons for this are unclear, except that there were more advanced tumors and a higher proportion of patients that received neoadjuvant radiotherapy in the present study. This is further reinforced by the fact that were 0.8% of patients in the TA-TME group that had an incomplete TME grade compared with

TABLE 2. Pathologic Outcomes

	Unmatched Cohort			Matched Cohort		
	TA-TME (n = 277)	R-TME (n = 453)	*P*	TA-TME (n = 226)	R-TME (n = 370)	*P*
Tumor grade*			0.402			0.395
Low	218 (92.0%)	369 (90.0%)		176 (92.2%)	303 (89.9%)	
High	19 (8.0%)	41 (10.0%)		15 (7.8%)	34 (10.1%)	
Lymphovascular invasion*	35 (14.8%)	58 (14.0%)	0.800	31 (16.2%)	49 (14.5%)	0.603
Pathologic T-stage			0.035			0.063
pCR/pT0	50 (18.1%)	52 (11.4%)		39 (17.3%)	40 (10.9%)	
pT1	18 (6.5%)	34 (7.5%)		15 (6.6%)	28 (7.7%)	
pT2	74 (26.7%)	102 (22.5%)		62 (27.4%)	81 (22.1%)	
pT3	121 (43.7%)	243 (53.5%)		100 (44.3%)	199 (54.4%)	
pT4	14 (5.0%)	23 (5.1%)		10 (4.4%)	18 (4.9%)	
Pathologic N-stage			0.041			0.215
pCR/pN0	192 (69.3%)	272 (60.0%)		150 (66.4%)	219 (59.2%)	
pN1	59 (21.3%)	124 (27.4%)		53 (23.5%)	105 (28.4%)	
pN2	26 (9.4%)	57 (12.6%)		23 (10.1%)	46 (12.4%)	
Lymph node harvest	16.1 (6.1)	16.9 (7.1)	0.111	16.1 (5.9)	16.8 (7.1)	0.186
Pathologic complete response	40 (14.4%)	43 (9.5%)	0.040	35 (15.4%)	33 (8.9%)	0.014
CRM involvement (excl. pT4 tumors)						
Overall	14 (5.3%)	29 (6.7%)	0.452	12 (6.3%)	21 (6.2%)	0.839
Low rectal tumors	7 (5.9%)	16 (6.8%)	0.731	6 (5.4%)	12 (6.3%)	0.740
Mid rectal tumors	7 (4.9%)	13 (6.7%)	0.481	6 (5.7%)	9 (5.5%)	0.947
Distal resection involvement						
Overall	6 (2.1%)	1 (0.2%)	0.009	4 (1.8%)	1 (0.3%)	0.051
Low-rectal tumors	5 (4.2%)	1 (0.4%)	0.010	3 (2.7%)	1 (0.5%)	0.116
Mid-rectal tumors	1 (0.7%)	0 (0%)	0.243	1 (0.9%)	0 (0%)	0.207
Mean distance to distal margin, mm (SD)*						
Overall	17.4 (11.9)	14.8 (13.9)	0.011	16.9 (12.3)	15.1 (13.2)	0.097
Low-rectal tumors	12.2 (9.9)	9.5 (10.1)	0.012	12.2 (10.2)	9.6 (10.3)	0.033
Mid-rectal tumors	21.7 (13.1)	21.4 (15.5)	0.816	22.0 (13.3)	21.3 (15.5)	0.707
TME grade						
Overall			0.148			0.278
Complete	254 (91.7%)	431 (95.1%)		209 (92.5%)	356 (95.4%)	
Near-complete	20 (7.2%)	18 (4.0%)		15 (6.6%)	14 (3.8%)	
Incomplete	3 (1.1%)	4 (0.9%)		2 (0.9%)	3 (0.8%)	
Low-rectal tumors			0.149			0.322
Complete	113 (89.7%)	233 (94.3%)		106 (90.6%)	185 (93.9%)	
Near-complete	12 (9.5%)	11 (4.5%)		10 (8.5%)	9 (4.6%)	
Incomplete	1 (0.8%)	3 (1.2%)		1 (0.9%)	3 (1.5%)	
Mid-rectal tumors			0.507			0.337
Complete	146 (93.6%)	197 (96.1%)		103 (94.5%)	168 (97.1%)	
Near-complete	8 (5.1%)	7 (3.4%)		5 (4.6%)	5 (2.9%)	
Incomplete	2 (1.3%)	1 (0.5%)		1 (0.6%)	0 (0%)	
High-quality resection (excl. pT4 tumors)						
Overall	244 (92.8%)	396 (92.1%)	0.744	201 (93.1%)	328 (93.2%)	0.954
Low-rectal tumors	110 (91.5%)	217 (91.5%)	0.911	103 (93.3%)	174 (92.1%)	0.819
Mid-rectal tumors	134 (93.7%)	179 (92.7%)	0.730	98 (92.8%)	154 (94.5%)	0.699
High-quality resection (excl. pT4 tumors and pCR)						
Overall	206 (92.4%)	356 (92.2%)	0.864	167 (92.3%)	297 (93.1%)	0.727
Low-rectal tumors	95 (91.5%)	189 (92.2%)	0.388	92 (92.9%)	156 (92.3%)	0.880
Mid-rectal tumors	111 (93.4%)	167 (92.2%)	0.980	75 (91.5%)	143 (94.7%)	0.343

*Only including patients without pCR (unmatched cohort TATME n = 237, R-TME n = 410; matched cohort TATME n = 191, R-TME n = 337).
pCR indicates pathologic complete response.

4.1% in the PELICAN registry, despite higher CRM involvement in the present study. The data in this study also represent consecutive cases from each of the 5 centers, which encompass the early learning curve of the TA-TME technique, whereas there may be response bias in voluntary registry data. Regardless, the results of both the TA-TME and R-TME groups in this study are superior to those of large population-based registries. Rickles et al[4] reported that the overall incidence of CRM positivity in the National Cancer Database was 17.2%. The risk of a positive CRM was higher for patients undergoing complete proctectomy (20.9% vs 13.4% for partial proctectomy), suggesting that patients with tumors in the middle or low rectum are at particularly high risk. Similar results were seen in Canadian[30] and Dutch[31] registries.

The incidence of DRM involvement was also unexpectedly high in the TA-TME group, which was surprising given the fact that the distal margin is usually advocated to be controlled with greater precision from the transanal approach.[32] It should be noted that these cases were all advanced tumors that had received neoadjuvant chemoradiation and were located within 1 cm of the anorectal ring and had both positive DRM and CRM, despite the proper plane of

TABLE 3. Independent Predictors of a Poor-quality Resection (Incomplete TME or Positive CRM or DRM)

	Model 1: Excluding pT4	Model 2: Excluding pT4 and pCR
	OR (95% CI)	
Transanal TME	0.75 (0.36, 1.54)	0.86 (0.38, 1.94)
Height from anal verge, per cm increase	0.83 (0.75, 0.92)	0.83 (0.75, 0.92)
Male sex	1.11 (0.53, 2.33)	1.20 (0.54, 2.63)
BMI, per kg/m^2 increase	1.00 (0.92, 1.09)	1.02 (0.94, 1.12)
Neoadjuvant radiotherapy	1.03 (0.41, 2.58)	1.19 (0.42, 3.42)
pT3 (vs pT1-2)	4.81 (1.96, 11.78)	4.71 (1.83, 12.11)
Tumor size, per cm increase	1.03 (0.87, 1.22)	1.17 (0.89, 1.51)

CI indicates confidence interval; OR, odds ratio.

dissection. These patients refused upfront abdominoperineal excision and required an intersphincteric dissection and hand-sewn coloanal anastomosis. Frozen section was not performed for any of these cases, which may have prevented these occurrences.[33,34] DRM may have also been involved due to residual tumor cells beyond the regressed tumour edge after neoadjuvant therapy.[35] While there were more involved DRM, the mean distance from the lower edge of the tumor to distal transected edge was greater in the TA-TME group. Despite the greater visualization of the distal edge of the tumor from the transanal approach, surgeons should not be too zealous in preserving rectal length, and instead must remain cautious as the possibility of distal positive margins and thus inadequate oncologic clearance still exists.

These results represent those of expert centers that have performed a high-volume of TA-TME and/or R-TME. The exact number of cases that is required to obtain proficiency for TA-TME is unclear, but there are data to suggest differences in the quality of surgical resection between institutions that have performed at least 30 cases and those with less.[36] The learning curve for robotic TME has also been estimated to be between 42 and 75 cases, although prior laparoscopic experience may shorten it to 25 cases.[37–39] The TA-TME cases represent the total experience of the 3 participating centers, including the early experience, compared with R-TME, which has been performed for longer. While beyond the scope of this study, there may have been a learning curve effect that resulted in the higher than expected CRM and DRM involvement seen in the TA-TME group. However, these results may not be generalizable to centers that perform a low volume of cases of either approach, or who are in the early phases of their learning curve. This is especially important as the TA-TME approach is difficult to learn and can commonly result in wrong plane surgery during the early cases.[40] However, it should be noted that only 1 center contributed cases in both transanal and robotic approaches. There are few surgeons that are equally skilled at both techniques. These results demonstrate that equally good outcomes can be obtained with either approach, suggesting that 1 approach is not necessarily better than the other. An open comparison group was not included as this approach is reserved for patients requiring extensive en bloc resection or recurrent tumors. Similarly, laparoscopic TME for mid and low-rectal cancer was no longer routinely performed by the participating centers in favor of the robotic and transanal approaches.

Short-term morbidity was also similar between the 2 techniques, with no differences in complications, anastomotic leaks, and reoperations. Postoperative metrics, including length of stay or readmissions in the present study, were not assessed due to the different healthcare settings between the international centers, making it difficult to make adequate comparisons.

One potential advantage of the TA-TME technique is the ability to transect the distal margin under direct vision. This allows double purse-string anastomosis, which may be associated with lower incidence of anastomotic leak.[41] It also avoids the need for multiple staple firings to transect the distal rectum, which has also been associated with increased anastomotic leakage.[42] However, most risk factors for anastomotic leak are nonmodifiable.[43,44] Immunofluorescence perfusion assessment was not routinely performed by all centers and inconsistently recorded. It remains to be seen if this could reduce leak rates.[45]

The results of this study should be interpreted in view of several other limitations. The most obvious is that these results were based on an observational study design. We attempted to create a balanced cohort of patients undergoing TA-TME and R-TME; however, there were several important variables that were not included in this study. Tumor response to neoadjuvant radiotherapy was not analyzed, given that there was significant variation in the classification scheme of tumor regression between participating centers as the Dworak et al,[46] Mandard et al,[47] and Ryan et al[48] classifications were all used. This variable has been previously identified as an important predictor of incomplete TME quality.[24] There were also more pathologic complete responses in the TA-TME group, which could have affected margin involvement. However, the quality of surgical resection remained similar for both approaches in subgroup analysis excluding patients with pathologic complete response. Operative duration may also be a poor proxy for operative difficulty, especially early in the learning curve. Not all patients received a repeat postradiotherapy MRI before surgical resection, therefore assessment of preoperative CRM involvement was variable and not included in this analysis. There also remains the possibility of residual bias from other unmeasured confounders. There was also a higher incidence of hand-sewn anastomoses and diverting ileostomies in the TA-TME group, despite a similar tumor height distribution between the 2 groups. It is unclear whether this bias is from case selection or if it is inherent to the TA-TME procedure. There may have also been changes over the study period that may have affected the quality of the surgical resection. Certainly, transanal equipment, such as the high-flow insufflator, have improved, which, in turn, likely enhanced TA-TME dissection quality, as has the implementation of structured TA-TME training programs.[49] The robotic platform has also evolved with the introduction of the *DaVinci Xi* system, which may have further refined the R-TME approach.

CONCLUSIONS

In summary, high-quality TME for patients with rectal adenocarcinoma of the mid and low rectum can be equally achieved by transanal or robotic approaches in skilled hands. Tremendous care must be taken to avoid an involvement distal margin for tumors in

close proximity to the anorectal ring, especially in the TA-TME approach. These results suggest that surgeons do not need to abandon 1 approach in favor of the alternate if their outcomes are in line with the published data. Rather, surgeons performing open TME that wish to adopt a minimally invasive approach or those performing laparoscopic TME that have difficulty for mid and low-rectal tumors can choose either approach depending on pre-existing skillset, available equipment, and mentoring.

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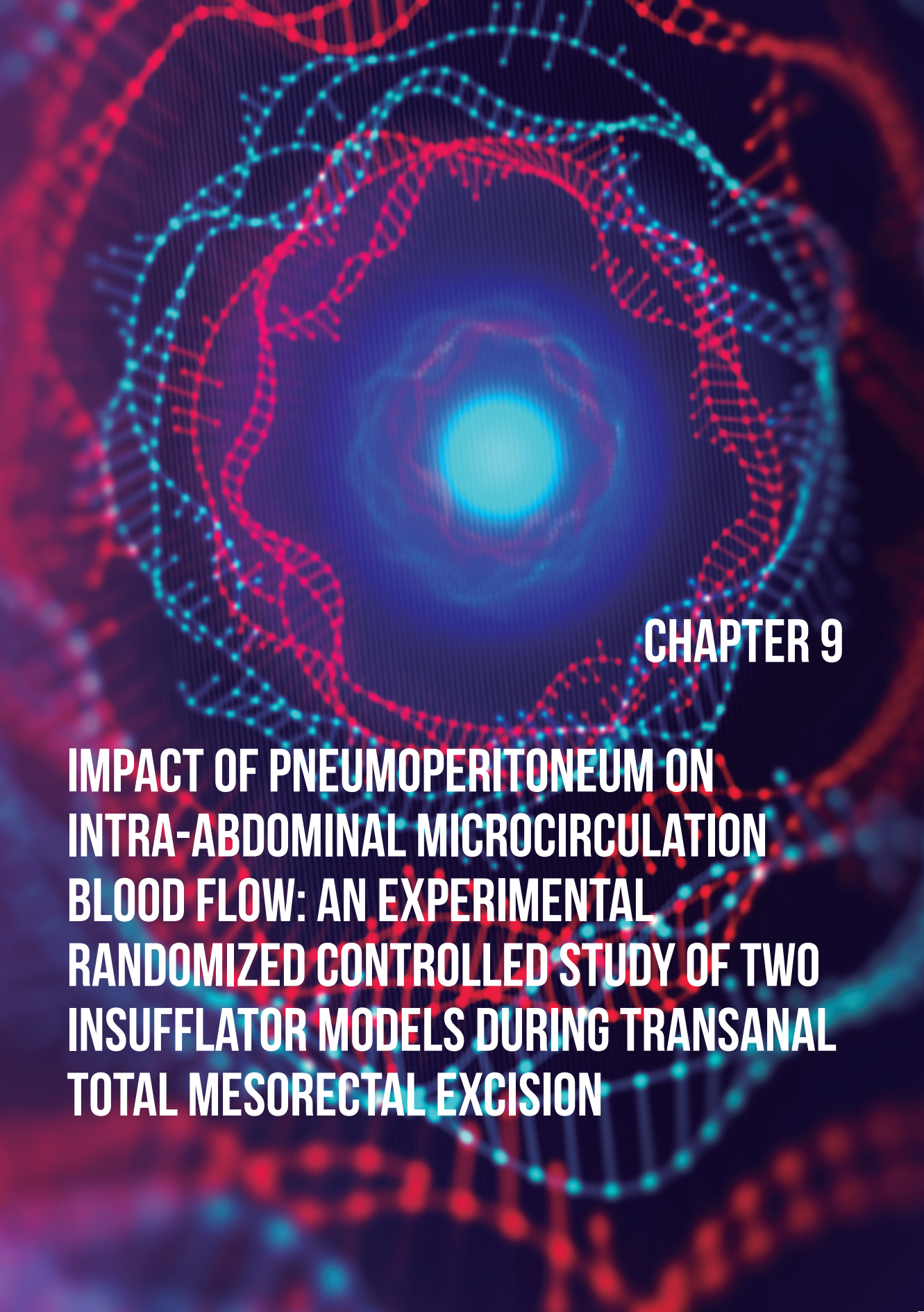

CHAPTER 9

IMPACT OF PNEUMOPERITONEUM ON INTRA-ABDOMINAL MICROCIRCULATION BLOOD FLOW: AN EXPERIMENTAL RANDOMIZED CONTROLLED STUDY OF TWO INSUFFLATOR MODELS DURING TRANSANAL TOTAL MESORECTAL EXCISION

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Impact of pneumoperitoneum on intra-abdominal microcirculation blood flow: an experimental randomized controlled study of two insufflator models during transanal total mesorectal excision

An experimental randomized multi-arm trial with parallel treatment design

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Abstract

Objective To compare changes in microcirculation blood flow (MCBF) between pulsatile and continuous flow insufflation.

Summary background data Transanal total mesorectal excision (TaTME) was developed to improve the quality of the resection in rectal cancer surgery. The AirSeal IFS® insufflator facilitates the pelvic dissection, although evidence on the effects that continuous flow insufflation has on MCBF is scarce.

Methods Thirty-two pigs were randomly assigned to undergo a two-team TaTME procedure with continuous ($n=16$) or pulsatile insufflation ($n=16$). Each group was stratified according to two different pressure levels in both the abdominal and the transanal fields, 10 mmHg or 14 mmHg. A generalized estimating equations (GEE) model was used.

Results At an intra-abdominal pressure (IAP) of 10 mmHg, continuous insufflation was associated with a significantly lower MCBF reduction in colon mucosa [13% (IQR 11;14) vs. 21% (IQR 17;24) at 60 min], colon serosa [14% (IQR 9.2;18) vs. 25% (IQR 22;30) at 60 min], jejunal mucosa [13% (IQR 11;14) vs. 20% (IQR 20;22) at 60 min], renal cortex [18% (IQR 15;20) vs. 26% (IQR 26;29) at 60 min], and renal medulla [15% (IQR 11;20) vs. 20% (IQR 19;21) at 90 min]. At an IAP of 14 mmHg, MCBF in colon mucosa decreased 23% (IQR 14;27) in the continuous group and 28% (IQR 26;31) in the pulsatile group ($p=0.034$).

Conclusion TaTME using continuous flow insufflation was associated with a lower MCBF reduction in colon mucosa and serosa, jejunal mucosa, renal cortex, and renal medulla compared to pulsatile insufflation.

Keywords Transanal total mesorectal excision · Randomized controlled trial · Continuous insufflation · Colored microspheres

The transanal total mesorectal excision (TaTME) assisted by laparoscopy was developed for the treatment of rectal cancer [1]. TaTME can be performed either via one-team or two-teams approach, the latest decreasing operative time [2]. This technique allows for an easier pelvic dissection and has been accepted by the surgical community due to its potential of increasing the quality of the specimen [1].

Laparoscopy is based on the insufflation of the peritoneal cavity in order to enlarge the working area, visualize and manipulate the organs. However, this pneumoperitoneum is associated with variations in systemic hemodynamics, pulmonary mechanics, and a decrease of intra-abdominal organs' microcirculation blood flow (MCBF) [3, 4]. The primary mechanism is the compression of the vessels due to increased intra-abdominal pressure (IAP) with a cranial shift of the diaphragm. Conventional CO_2 insufflators are based on autoregulated pulsatile flow fluctuation, and animal and human studies have demonstrated that laparoscopic

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insufflation with pulsatile flow affects vessel tone regulation, triggering hypoperfusion and reperfusion injury, inducing oxidative stress, cellular injury, and organ dysfunction [5–10].

The transanal approach of the TaTME can be technically demanding, and the difficulty is even higher with conventional insufflators because of the throb of the surgical field and poor visualization due to smoke. New technological developments recently appeared, such as a new valve-free CO_2 insufflator (AirSeal IFS®, SurgiQuest, Conmed Corporation, Milford, CT, USA), with a continuous flow and immediate response to minimal IAP variations, avoiding the billowing effect and with a constant smoke evacuation [11]. The AirSeal IFS® consists of three devices: the Intelligent Flow System (IFS), the AirSeal trocar, and the AirSeal Mode Evacuation (ASM-Evac) Tri-lumen Filter Tube Set. The AirSeal valve-free trocar includes CO_2 nozzles that act as pressure gas barriers and preserve the set IAP pressure, in contrast to the trapdoor valves of conventional trocars. The ASM-Evac Tri-lumen Filter consists on one lumen for CO_2 influx, one lumen for CO_2 outflux to the IFS, and a third lumen for concurrent uninterrupted pressure assessment. Once the fixed pressure is reached, the CO_2 flow is spontaneously diminished to 3 L/min, while preserving the fixed pressure. Nepple et al. proved that pneumoperitoneum generated by the AirSeal IFS® was more stable than with the conventional insufflators, even under suction maneuvers [12].

Among the many factors that have been proposed to contribute to hypoperfusion and oxidative stress, the pressure level and the duration of the pneumoperitoneum seem to be the most significant [13]. This study aimed to assess the role of a third variable: the type of gas flow, pulsatile versus continuous, through the use of the conventional or the AirSeal IFS® insufflators. We hypothesized that the continuous flow, by avoiding erratic fluctuations in IAP, would have less effect on vessel tone regulation and thus less impact on organ hypoperfusion. Therefore, the primary objective was to compare intra-abdominal MCBF between the two insufflation systems in pigs undergoing a two-team TaTME procedure. A secondary objective was to investigate changes in systemic hemodynamics, gas exchange, and endothelium-derived mediators.

Methods

Animal model

The Institutional Review Board of the Hospital Clinic approved this randomized multi-arm parallel trial for the Care and Use of Laboratory Animals. The study was conducted following the Principles of Laboratory Animal Care. The University of Barcelona Committee on Ethics in Animal Experimentation and the Catalan Department of the Environment Commission on Animal Experimentation granted ethical approval for the study (Reg. 0006S/11367/2015). Thirty-two healthy female Yorkshire pigs weighing 25–28 kg were studied between October 2015 and March 2016. All animals fasted 12 h before surgery, with free access to water. They were sedated with 4 mg/kg ketamine + 2 mg/kg xylazine + 0.1 mg/kg midazolam and anesthetized by intravenous sodium thiopental (10 mg/kg) and fentanyl (50 µg), before proceeding to endotracheal intubation. Lung-protective mechanical ventilation strategy (tidal volume 8 mL/kg, plateau airway pressure ≤ 30 cmH_2O, positive end-expiratory pressure 4 cmH_2O, and FiO_2 0.4 in air) was established. Appropriate respiratory rate changes were allowed to maintain end-tidal CO_2 ($PetCO_2$) between 30 and 40 mmHg. Anesthesia was maintained with desflurane (MAC ~ 2.5). Cisatracurium (0.75 mg/Kg/h) and continuous infusion of fentanyl (10 µg/kg/h) were administered for muscle relaxation and analgesia, respectively. Fluid therapy was based on 5 mL/kg/h of isotonic saline; a bolus of 1 mL/kg of 6% hydroxyethyl starch was administered, when needed, to maintain constant cardiac output avoiding flow-dependent changes in mediator release and vascular resistance. Core temperature was monitored (PiCCO™; Pulsion Medical Systems, AG, Munich, Germany) and maintained between 36.5 and 38 °C. Once anesthetized, the animals were placed and maintained in supine position.

Animal instrumentation

Under aseptic conditions, a 5-French PICCO catheter and a 7-French bilumen catheter were introduced into the right common carotid artery and in the right jugular vein respectively, to obtain hemodynamic parameters and blood sampling. For MCBF determination, colored microspheres (Dye Trak, Triton Technology, San Diego, CA, USA) were injected by a catheter that was inserted through the left carotid artery to the left ventricle guided by morphology and ventricular pressure curve. To obtain arterial reference sampling of microspheres, a catheter was placed in the right femoral artery.

Randomization and experimental procedure

After instrumentations, animals were stabilized for 30 min (stabilization was defined as MAP ≥ 70 mmHg and HR ≤ 80 b/min and normal arterial blood gases). Randomization to one of the two types of CO_2 insufflation used in both the abdominal and the transanal fields [continuous vs. pulsatile, the latter being performed with the UHI-4 device (Olympus, Hamburg, Germany)] was done using a random-number table. The table contained five-digit numbers arranged in

rows and columns. Sequentially numbered sealed envelopes were used by a surgeon not directly involved in the study, opening them the night before each intervention and informing the principal investigator (FBL). Therefore, a random allocation sequence was developed, and animals were randomized into two experimental groups ($n = 16$ for each one). Each group was stratified according to two different levels of pressure in both fields, 10 mmHg ($n = 8$) or 14 mmHg ($n = 8$). IAP was monitored continuously through the laparoscope, together with digital monitorization through an intra-abdominal catheter (Angiocath, BD Medical Systems, Sandy, UT) connected to a pressure transducer (Edwards Lifesciences, Irvine, CA).

Primary objective: intra-abdominal microcirculation blood flow

Colored microspheres with a 15-μm diameter were used. The delivery of microspheres depends on the tissue perfusion at the time of microspheres injection, and tissue concentration is therefore proportional to the flow *per unit volume or mass of tissue* at the level of the capillaries. Due to the movement of microspheres out of the capillaries into the interstitial space, retention of microspheres is excellent. The specific description of the technique has been detailed elsewhere [14].

The microspheres were administered at three time points: (1) baseline, after stabilization and before insufflation (T1); (2) 60 min after starting insufflation (T2); (3) 90 min after starting insufflation (T3). Following the last microsphere injection, the animals were euthanized with a deep overdose of sodium thiopental and intravenous potassium chloride. After certifying a correct position of the catheter above the aortic valves, tissue samples were carefully harvested from the organs of interest: ascending colon mucosa (CM) and serosa (CS), mesentery of the colon (MC); jejunum mucosa (JM) and serosa (JS), mesentery (M); renal cortex (RC) and renal medulla (RM). The trapped microspheres in each tissue and blood sample were quantified using flow cytometry [14].

Secondary objectives: systemic hemodynamics, blood gases, and endothelium-derived mediators

Hemodynamic variables included cardiac index (CI), which was monitored by thermodilution technique in triplicate, and continuously by pulse contour analysis; heart rate (HR); mean arterial pressure (MAP); global end-diastolic index (GEDI, a reliable preload index), through the PICCO system [15]; and systemic vascular resistance index (SVRI), which were continuously recorded using computerized interface data (PICCO).

Blood gases and pH corrected for temperature were measured with a blood gas analyzer (Rapidjoint 405, Bayer Health Care Systems) calibrated daily with tonometer whole human blood. The pulmonary gas exchange was evaluated by calculation of the alveolar/arterial oxygen difference as $PA\text{-}aO_2 = (713 \times FiO_2 - PaCO_2/0.8) - PaO_2$. Also, the collapse of lung tissue (atelectasis) was estimated by an increased $Pa\text{-}ET_{CO_2}$ gradient [16].

At the three time points, the measured endothelium-derived mediators were:

Whole blood nitrite-to-nitrate: vascular function is affected by both perpendicular transmural pressure (myogenic response) and parallel frictional force (shear stress) [17]. Nitric oxide (NO) release from the endothelium may act as a brake to limit arteriolar vasoconstriction [18]. Nitrite (NO_2^-) and nitrate (NO_3^-) anions are part of the endogenous NO metabolism, representing an indirect measurement of the activation of nitric oxide synthase and NO release during pneumoperitoneum. Therefore, samples (10 ml) containing NO_2^- and NO_3^- were quantitatively reduced to NOx in a solution containing vanadium (III) chloride. Next, NOx was quantified by a chemiluminescence detector after reaction with ozone in a NO analyzer (NOA 280i, Sievers, GE Instruments, CO, USA).

Plasma renin activity (PRA): the oliguria caused by IAP is due to compression of the renal vessels and parenchyma, but also the β-adrenergic stimulation and activation of the renin–angiotensin–aldosterone system, resulting in renal cortical vasoconstriction [19]. PRA, an estimation of plasma renin form released in response to β-adrenergic stimulation, measures the rate of formation of active peptide angiotensin II which is a potent endogenous vasoconstrictor that may enhance microcirculation vasoconstriction, and was quantified by RIA technique (GammaCoat Plasma Renin Activity, DiaSorin Inc., MN, USA).

Surgical technique

Two teams working simultaneously performed the surgical procedure. The transabdominal part was initiated with insufflation of CO_2 through a Veress needle and insertion of four laparoscopic ports. The goal of this team was to divide inferior mesenteric vessels and dissect the descending colon.

The transanal team started with the introduction of the transanal platform (Gelpoint path, Applied Medical, Inc., Rancho Santa Margarita, CA). Pneumorectum was initiated and the rectal lumen was closed with a purse-string suture. After the rectotomy, the mesorectal fascia was reached and the dissection continued upwards. When the two teams met ("rendez-vous"), both continued working together until the rectum and sigmoid were entirely free. Then the surgical procedure was finished, without specimen retrieval or anastomosis performance. As the effects of IAP on microcirculation are time dependent, all surgeries were terminated at 90 min (T3). In case of finishing the task before,

pneumoperitoneum was maintained until reaching the final time point (T3).

Statistical analysis

Descriptive results were presented as the median with interquartile range [IQR: 25th, 75th percentiles]. A generalized estimating equations (GEE) model, with an estimation of within-subject correlation from AR(1) approach to account for the repeated measurements, was used. This methodology considers for statistical analyses all follow-up of each experimental animal, not time-to-time independently. We performed three different models to evaluate the effect of the use of continuous or pulsatile insufflation, IAP (10 mmHg or 14 mmHg) and their combination. All models included one of these independent factors, time, and the interaction of factor by time. These analyses were performed by a non-parametrical approach through a rank-transformation of the dependent variables.

A two-sided Type I Error equal to 0.05 was used in all statistical analyses. All calculations were performed with SPSS version 25 (IBM) software. Due to the experimental proof of concept of this study, no formal sample size calculation was performed, and no methods for multiplicity were done.

Researchers who evaluated biochemical variables and organ blood flow were blind to the knowledge of the groups of samples.

Results

During the study period, a total of 32 animals were randomly assigned to either TaTME with continuous or pulsatile CO_2 insufflation. All animals survived until the end of the experiment. However, one case in the continuous-14 group was excluded from the final analyses due to a bilateral empyema that was discovered when the correct positioning of the catheter above the aortic valves was certified. Moreover, in two pigs the biopsies could not be analyzed due to technical problems with the spectrophotometer and were finally excluded from the MCBF analysis.

The TaTME procedure was completed in all cases with no intraoperative events. The median duration until the complete release of the specimen was 76 min (IQR 73;80) in the set of pulsatile groups, compared with 71 min (IQR 64.2;72) in the set of continuous groups ($p = 0.001$).

Microcirculation blood flow

Table 1 shows MCBF in the median percentage of change, while absolute median outcomes are presented in Supplementary Table 1. Throughout the study, a significant reduction of MCBF from baseline was found in every organ. At an IAP of 10 mmHg, continuous insufflation was associated with a significantly lower MCBF reduction in colon mucosa, colon serosa, jejunal mucosa, renal cortex, and renal medulla. At an IAP of 14 mmHg, MCBF in colon mucosa decreased 23% (IQR 14;27) in the continuous group and 28% (IQR 26;31) in the pulsatile group (p = 0.034) (Figs. 1, 2, 3, 4, 5).

Systemic hemodynamics, blood gases, endothelium-derived mediators

The secondary outcomes are shown in Table 2 (median percentage of change) and Supplementary Tables 2 and 3 (absolute medians). HR significantly increased only in the pulsatile-14 group at 60 min ($p < 0.001$) compared to baseline. At an IAP of 14 mmHg and 60 min, HR decreased 5.4% (IQR − 18;20.6) in the continuous group and increased 18.3% (IQR 12.6;31.7) in the pulsatile group, $p = 0.027$ (Supplementary Fig. 1).

Pa-ET_{CO_2} gradient increased at all times when the pulsatile insufflator was used, although no significant differences were found between groups. At an IAP of 10 mmHg, NOx remained stable in the pulsatile group, while it significantly decreased in the continuous group ($p < 0.001$), compared to baseline. At 14 mmHg and 90 min, the decrease in NOx concentration was greater in the continuous group: 13% (IQR 1.9;16) versus 1.1% (IQR − 6.3;9.6); $p = 0.013$ (Supplementary Fig. 2). PRA concentration showed a non-significant decrease in the continuous-10 group at an IAP of 10 mmHg ($p = 0.814$), and a non-significant increase in both groups at an IAP of 14 mmHg (continuous $p = 0.107$, pulsatile $p = 0.280$), compared to baseline values.

Discussion

A lower impact over MCBF on colon mucosa, colon serosa, jejunal mucosa, renal cortex, and renal medulla was found when continuous flow insufflation was used during TaTME. Therefore, continuous insufflation not only seems to facilitate the pelvic dissection from a purely surgical point of view, but it might potentially prevent the development of hypoperfusion and reperfusion injury in selected organs.

The effects of pneumoperitoneum during laparoscopic surgery have been well reported and might have significant consequences for the patient, resulting in morbidity and even mortality [6, 7, 20, 21]. These adverse effects can be both regional and systemic. Mechanical compression and humoral-mediated vasoconstriction are suggested to be responsible for the regional effect [20]. Moreover, the increase of IAP might result in hypoperfusion, oxidative stress, and organ dysfunction [10]. To this cascade of events, variations on systemic hemodynamics must be

Table 1 Microcirculation blood flow of intra-abdominal organs

	IAP 10 mmHg		IAP 14 mmHg	
	60 min	90 min	60 min	90 min
CM				
Cont	−13 (−14;−11)*ŧ	−15 (−16;−14)*ŧ	−23 (−27;−14)*ŧ	−26 (−31;−19)*
Puls	−21 (−24;−17)*ŧ	−20 (−24;−16)*ŧ	−28 (−31;−26)*ŧ	−31 (−32;−25)*
CS				
Cont	−14 (−18;−9.2)*ŧ	−14 (−18;−11)*ŧ	−27 (−29;−14)*	−31 (−32;−15)*
Puls	−25 (−30;−22)*ŧ	−26 (−32;−24)*ŧ	−33 (−38;−25)*	−35 (−39;−25)*
MC				
Cont	−19 (−21;−15)*	−21 (−25;−17)*	−25 (−26;−23)*	−29 (−33;−20)*
Puls	−20 (−25;−15)*	−18 (−19;−17)*	−32 (−37;−28)*	−35 (−40;−33)*
JM				
Cont	−13 (−14;−11)*ŧ	−13 (−18;−8.1)*ŧ	−21 (−28;−16)*	−24 (−27;−21)*
Puls	−20 (−22;−20)*ŧ	−24 (−25;−23)*ŧ	−31 (−33;−22)*	−32 (−34;−26)*
JS				
Cont	−17 (−20;−15)*	−19 (−21;−16)*	−26 (−30;−24)*	−30 (−35;−23)*
Puls	−22 (−24;−15)*	−25 (−27;−20)*	−31 (−36;−26)*	−34 (−37;−30)*
M				
Cont	−14 (−15;−10)*	−13 (−23;−9.3)*	−29 (−40;−23)*	−30 (−43;−28)*
Puls	−17 (−21;−12)*	−19 (−20;−15)*	−31 (−33;−28)*	−33 (−34;−25)*
RC				
Cont	−18 (−20;−15)*ŧ	−18 (−22;−15)*ŧ	−31 (−33;−30)*	−32 (−36;−29)*
Puls	−26 (−29;−26)*ŧ	−32 (−34;−29)*ŧ	−33 (−39;−30)*	−35 (−41;−33)*
RM				
Cont	−13 (−17;−12)*	−15 (−20;−11)*ŧ	−25 (−28;−18)*	−25 (−28;−22)*
Puls	−18 (−21;−17)*	−20 (−21;−19)*ŧ	−24 (−27;−23)*	−26 (−30;−24)*

Data are presented as median percentage of change (IQR)

CM colon mucosa, *CS* colon serosa, *MC* mesentery of the colon, *JM* jejunum mucosa, *JS* jejunum serosa, *M* mesentery, *RC* renal cortex, *RM* renal medulla, *Cont* continuous insufflation, *Puls* pulsatile insufflation

*Difference from baseline values with $p < 0.05$

ŧDifference between groups with $p < 0.05$

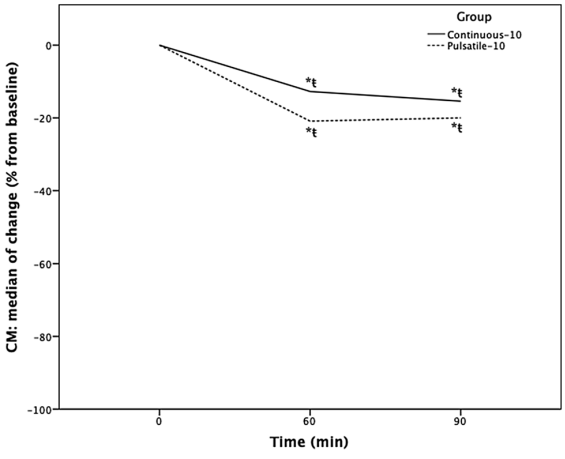

Fig. 1 Microcirculation blood flow at colon mucosa at an IAP of 10 mmHg

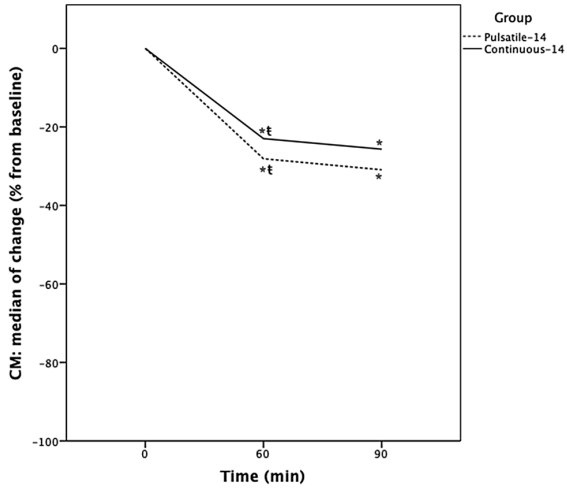

Fig. 2 Microcirculation blood flow at colon mucosa at an IAP of 14 mmHg

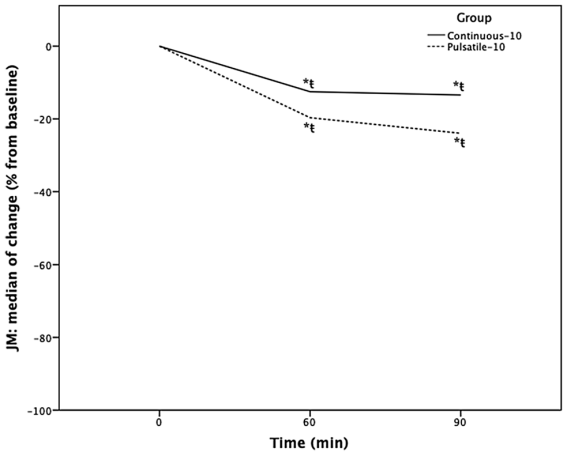

Fig. 3 Microcirculation blood flow at jejunal mucosa at an IAP of 10 mmHg

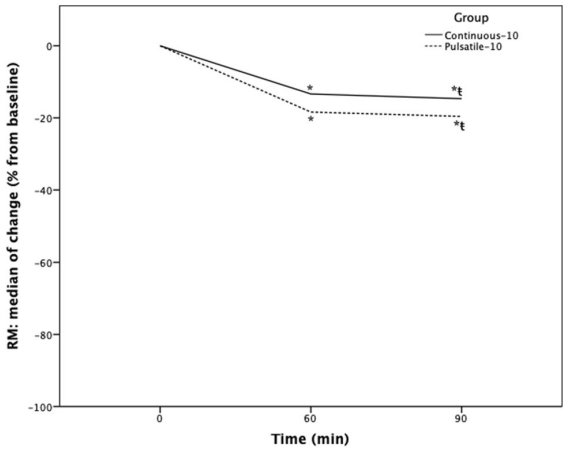

Fig. 5 Microcirculation blood flow at renal medulla at an IAP of 10 mmHg

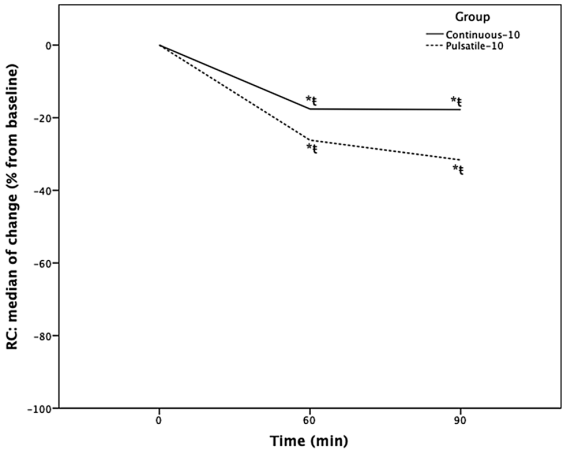

Fig. 4 Microcirculation blood flow at renal cortex at an IAP of 10 mmHg

added, and the effect of the cranial shift of the diaphragm, which directly affects pulmonary mechanics. Besides, our group previously reported that shear stress might have a significant impact on MCBF and its redistribution, despite a lower mean IAP level [22]. The shear stress and its essential role in acute vessel tone regulation depend on the hemodynamic frictional force on the surface of the endothelium. Fluctuations in pneumoperitoneum, more common with pulsatile insufflation, are believed to create increase shear stress gradients and induce greater vessel adaptations in response to acute MCBF variations. On the other hand, the constant pressure of the pneumoperitoneum during continuous insufflation theoretically may have a minor impact on hemodynamic shear stress, blood flow, and endothelial function compared to pulsatile insufflation. Also, continuous insufflation systems have been associated with lower CO_2 employment, absorption, and elimination [23].

In the literature, several studies have analyzed the safety of continuous flow insufflation during laparoscopy. Sroussi et al. reported safe gynecological surgeries with low IAP (7 mmHg), with lower maximal values of ET_{CO_2}, systolic blood pressure, and peak airway compared to pulsatile insufflation [24]. Annino et al. studied the effect of the valve-free insufflator during robotic partial nephrectomy, obtaining improved outcomes in operative time and warm ischemia time [25]. The published data suggest that working with this novel insufflation system might decrease the negative effects in arteriolar blood flow, which could potentially improve patients' outcomes. However, results from controlled clinical trials are pending [26].

Our group has extensive experience with experimental gastrointestinal microcirculation studies [20, 22, 27]. However, to our knowledge, this is the first study focused on analyzing the impact of pneumoperitoneum on MCBF with continuous flow insufflation. In this RCT, pneumoperitoneum caused an expected decrease in bowel mucosal and serosal blood flow. Moreover, a lower decrease of the mesenteric capillary beds flow in bowel biopsies was observed with the continuous insufflation, especially at 10 mmHg of IAP. It is clear that elevated IAP decreases mesenteric blood flow, which could result in intestinal damage [28]. During laparoscopic procedures, IAP should be maintained under 15 mmHg, and if the lower adverse effects of IAP obtained with the continuous insufflation improve postoperative organ function justifies further investigation.

Table 2 Systemic hemodynamics, gas exchange measurements, whole blood nitrite-to-nitrate concentration and plasma renin activity

	IAP 10 mmHg		IAP 14 mmHg	
	60 min	90 min	60 min	90 min
HR				
Cont	−1.9 (−3.9;3.98)	5.06 (−3.7;10)	−5.4 (−18;20.6)[t]	−5.4 (−26;17.6)
Puls	−3.1 (−15;−0.74)*	0.62 (−8;7.46)	18.3 (12.6;31.7)*[t]	10.3 (−3;23)
MAP				
Cont	9.18 (−1.2;15.1)	1.33 (0.00;8.1)	7 (0.93;33.8)*	4 (−9.1;17.6)
Puls	0.77 (−5.9;12.9)	0.67 (−13;10.3)	2.19 (−10;12.4)	−5.5 (−18;4.75)
SVRI				
Cont	−5.0 (−10;10.1)	2.09 (−13;13.5)	10.5 (−19;20.1)	−2.9 (−20;17.6)
Puls	−4.9 (−14;14.8)	−0.43 (−30;7.78)	2.9 (1.32;23.8)	10.4 (−3.4;21.2)*
CI				
Cont	−6.2 (−11;15.9)	−4.5 (−8.7;10.4)	−4.9 (−10;7.88)	−0.15 (−7.9;12−3)
Puls	1.42 (−7.6;7.11)	1.44 (−9.3;10.4)	−6.6 (−8.7;−0.81)*	−14 (−16;−5.1)*
GEDI				
Cont	−1.3 (−6.4;3.22)	−2.7 (−8.1;1.01)	−0.0 (−9.2;6.21)	−0.17 (−6.3;2.89)
Puls	−0.9 (−11;10.4)	−2.6 (−10;4.25)	−1.6 (−5.3;5.15)	−0.18 (−7.1;8.44)
PaO_2				
Cont	−16 (−21;−9.8)*	−9.1 (−21;−3.9)*	−10 (−20;1.05)*	4.21 (−16;9.65)
Puls	−17 (−26;−9.6)*	−12 (−26;−6.6)*	−12 (−20;−1.9)*	−10 (−19;4.09)*
$PaCO_2$				
Cont	14.3 (2.48;22.2)*	18 (8.39;28.9)*	14.3 (10.1;41.1)*	20.4 (13.8;37.3)*
Puls	16.2 (2.14;81.9)*	18.2 (7.64;84.5)*	15.4 (4.36;17.2)*	16.7 (−4.8;20.7)*
Pa-ET_{CO_2}				
Cont	5.72 (2.7;7.41)*	2.7 (−1.5;6.08)	0.00 (−5.6;8.82)	0.00 (−2.8;11.8)
Puls	6.61 (0.00;12.5)*	2.94 (1.47;6.92)*	6.25 (2.86;8.89)*	4.44 (0.00;14.6)*
$P_{A\text{-}a}O_2$				
Cont	0.27 (0.16;0.52)*	0.1 (0.06;0.32)*	0.11 (−0.04;0.59)*	−0.08 (−0.2;0.37)
Puls	0.37 (0.15;0.66)*	0.13 (0.1;0.51)*	0.34 (−0.01;0.77)*	0.31 (−0.07;0.61)*
NOx				
Cont	−8.5 (−21;−2.3)*	−9.2 (−32;−0.78)*	−15 (−19;−7.8)*	−13 (−16;−1.9)*[t]
Puls	−4.8 (−13;3.9)	−4.3 (−19;11.2)	−5.9 (−8.7;−2.1)*	−1.1 (−6.3;9.68)[t]
PRA				
Cont	−31 (−67;5.56)	−19 (−56;114)	40 (0.00;71.4)	114 (−10;286)
Puls	−15 (−48;105)	0.00 (−46;109)	110 (−27;234)	33.7 (−39;484)

Data are presented as median percentage of change (IQR)

HR heart rate, *MAP* mean arterial pressure, *SVRI* systemic vascular resistance index, *CI* cardiac index, *GEDVI* end global diastolic ventricular index, PaO_2 arterial oxygen tension, $PaCO_2$ arterial carbon dioxide tension, *PA-a* O_2 alveolar/arterial tension difference for oxygen, *Pa-Et*CO_2 arterial to end-tidal CO_2 gradient, *NOx* nitrite/nitrate, *PRA* plasma renin activity, *Cont* continuous insufflation, *Puls* pulsatile insufflation

*Difference from baseline values with $p < 0.05$

[t]Difference between groups with $p < 0.05$

The question is whether the decreased mesenteric blood flow caused by pneumoperitoneum produces relevant intestinal ischemia in healthy subjects, or only in high-risk patients. From the evidence-based knowledge, it seems that only patients with underlying vasculopathy or those critically ill are at risk [3]. Moreover, during TaTME, a colorectal anastomosis is usually performed. It is considered a high-risk anastomosis, especially in cases treated with neoadjuvant chemoradiotherapy. Tygat et al. found a direct relationship between applied CO_2 IAP and impaired intestinal healing after enterotomy closure in rats [29]. Laparoscopic surgery has proven benefits for the patient, but caution should be taken in those surgeries where high-risk intestinal anastomoses are performed. The documented reduction in the adverse effects of pneumoperitoneum in colon biopsies suggests that working with continuous flow

could also be potentially helpful in diminishing the undesirable effects of elevated IAP on anastomotic healing.

In the present study, continuous insufflation was associated with a lower MCBF reduction in renal cortex and renal medulla at an IAP of 10 mmHg. During pneumoperitoneum, there is a decrease in renal blood flow, which can be up to 40% depending on the IAP level [30]. Nguyen et al. compared laparoscopic and open gastric bypass in a randomized controlled trial and found that laparoscopy was associated with a decrease in urinary output of 64%, although postoperative renal function was not affected [31]. Once again, it seems that the impairment of both renal flow and function might have clinical effects only in patients with preoperatively deficient renal function.

Even with the ventilation control by the anesthesiologist, which minimizes the amount of CO_2 during pneumoperitoneum, both CO_2 levels and IAP affect venous return, decrease cardiac output, and might increase HR, MAP and SVRI [3]. In this RCT, no differences were found in CI, MAP, and GEDI between groups, although the effect in HR was statistically significant at an IAP of 14 mmHg. This might be explained by a decreased neurogenic sympathetic activity in the continuous insufflation group, with theoretically lower vasoactive peptides and angiotensin levels. However, no increase in SVRI was observed, which goes against the neurogenic sympathetic activity theory. Andersson et al. questioned the effect of vasoactive peptides and catecholamines in SVRI during pneumoperitoneum and highlighted the role of myogenic activity in vascular resistance [32]. Though there were no differences in blood gases, the difference in Pa-ET_{CO_2} gradient could be related to the alveolar collapse of dependent pulmonary regions (atelectasis) induced by diaphragmatic movements and cyclic alveolar opening and closing resulting in units with low ventilation/perfusion ratio. In patients with pathological respiratory conditions and long-lasting surgical procedures, this could be cause of impaired gas exchange.

Several studies among patients treated by laparoscopy have shown a relationship between capillary vasoconstriction and endothelial NO release [33, 34]. In contrast to those studies, results from this RCT indicate that nitrite and nitrate anions remained somewhat stable in the pulsatile groups, while there was a decrease in the continuous insufflation groups. The may support the theory that pulsatile insufflation promotes pulsatile blood flow, which has been shown to increase NO production [35]. On the other hand, continuous insufflation may limit vasoconstriction and capillary pulsatility, although other vascular regulatory models such as metabolic and myogenic mechanisms need to be integrated for a complete understanding of the complex capillary network.

Altintas et al. reported an increase in renin levels in the renal vein after laparoscopy [36]. This, together with the previously commented myogenic response and the purely effect of IAP, triggers renal vasoconstriction. Despite an absence of statistical significance, the observed increase in PRA levels at 14 mmHg was even lower in comparison to the literature [37, 38]. Interestingly, a reduction in PRA levels was found in the continuous-10 group. One theoretical explanation is that, at a low IAP, the lesser reduction in renal MCBF obtained with the continuous insufflation might also carry a decreased impact of humoral factors such as the renin–angiotensin–aldosterone system.

The AirSeal IFS® insufflator was developed to facilitate the transanal dissection, since the combination of the IFS, the AirSeal trocar, and the ASM-Evac Tri-lumen Filter Tube Set allows swift insufflation with a steady pressure, even during suction or smoke evacuation. However, its direct effect on MCBF and hemodynamics required investigation [11, 39]. Moreover, since the AirSeal IFS® prevents the collapse of the working cavity, an expected shorter effective surgical time was found in the continuous groups. This decreased real-surgical time required for completing the task suggests that, in clinical practice, operative time could be shortened and therefore minimize the risk of reduced functional residual capacity and increased Pa-ET_{CO_2}, which promote atelectasis [40].

An important limitation of this study is the fact that the sample size is small, as is usual in this type of experimental studies. Moreover, the technical problems with the spectrophotometer forced us to exclude two piglets. However, following ethics in animal research, our purpose was to use the minimum number of animals required, rather than replace. Therefore, further studies are required to draw reliable conclusions. Another limitation is that all the animals were healthy, which hinders the translation of the outcomes to an often-vulnerable surgical population. Moreover, by microsphere technique protocol, the animals were euthanized at the end of the procedure. Consequently, it is not possible to make a comparison in postoperative organ function. The results of this study should be interpreted with caution since the clinical and physiological significance of the observed difference may have little impact on medical practice in healthy subjects. Nevertheless, the potential risks when dealing with unhealthy patients (with underlying vasculopathy, liver, pulmonary or cardiac diseases, chronic renal insufficiency, deficient nutritional state, or even patients with Inflammatory Bowel Disease) suggest that the pneumoperitoneum-related effects in this subset of patients may be of clinical importance.

In summary, this experimental RCT showed that TaTME using the continuous flow insufflation was associated with a lower MCBF decrease in colon mucosa, colon serosa, jejunal mucosa, renal cortex and renal medulla, compared to pulsatile insufflation. For this promising but challenging surgery, the valve-free with continuous flow insufflator facilitates the dissection and might also carry a decreased risk of

hypoperfusion and reperfusion injury. Even though there is a lack of evidence-based knowledge, this appears to be a substantial matter especially in patients with pre-existing impairment of intra-abdominal blood flow or limited reserve capacity.

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Author contributions Conception and design: FBL, PT, RD, AML. Administrative support: none. Provision of study material or patients: FBL, PT, RD, AML. Collection and assembly of data: FBL, PT, MCA, JST, RB, AI, RP. Data analysis and interpretation: FBL, PT, JR, AML. Manuscript writing (including critical revising): all authors. Manuscript final approval: all authors.

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Compliance with ethical standards

Conflict of interest Apart from the funding previously mentioned, Dr. AM Lacy is a consultant for Medtronic, Conmed Corporation, Olympus Medical, Touchstone International Medical Science Co. Ltd., Applied Medical, and Johnson & Johnson. Dr. de Lacy, Dr. Taurà, Dr. Arroyave, Dr. Trépanier, Mr. Ríos, Dr. Bravo, Dr. Ibarzabal, Dr. Pena and Dr. Deulofeu have no other conflicts of interest or financial ties to disclose.

Ethical approval The Institutional Review Board of the Hospital Clinic approved this trial for the Care and Use of Laboratory Animals. The University of Barcelona Committee on Ethics in Animal Experimentation and the Catalan Department of the Environment Commission on Animal Experimentation granted ethical approval for the study (Reg. 0006S/11367/2015).

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Supplementary material

Supplementary Table 1: Absolute medians of microcirculation blood flow (expressed as ml/g/min)

		IAP 10 mmHg			IAP 14 mmHg		
		Baseline	60 min	90 min	Baseline	60 min	90 min
CM							
	Cont	6.0 (3.6;6.4)	5.2 (3.0;5.6)	5.1 (3.0;5.4)	4.7 (3.1;6.4)	3.9 (2.4;4.5)	3.7 (2.3;4.3)
	Puls	5.1 (2.9;7.6)	4.0 (2.3;6.0)	3.9 (2.4;5.8)	4.9 (3.5;6.6)	3.5 (2.3;4.6)	3.4 (2.2;4.5)
CS							
	Cont	9.1 (6.0;10.8)	7.5 (5.4;9.6)	7.2 (5.4;9.4)	8.9 (7.2;10.2)	7.3 (5.4;9.9)	7.1 (5.0;9.6)
	Puls	5.6 (5.2;7.9)	3.9 (3.9;6.2)	3.8 (3.7;6.04)	6.4 (5.5;7.3)	4.2 (3.7;5.3)	4.1 (3.6;5.2)
MC							
	Cont	2.7 (2.4;2.9)	2.2 (1.9;2.9)	2.2 (2.9;2.8)	3.0 (2.6;3.2)	2.2 (1.9;2.4)	2.0 (1.7;2.4)
	Puls	2.2 (2.1;2.3)	1.8 (1.8;2.0)	1.8 (1.7;2.0)	2.7 (2.1;3.5)	1.9 (1.4;2.5)	1.9 (1.3;2.3)
JM							
	Cont	3.4 (3.2;4.0)	3.1 (2.8;3.5)	3.1 (2.6;3.59)	4.1 (3.2;6.2)	3.1 (2.3;5.3)	3.0 (2.4;5.1)
	Puls	3.0 (2.5;3.3)	2.3 (1.9;2.7)	2.1 (1.9;2.5)	3.0 (2.2;5.2)	2.3 (1.6;3.7)	2.1 (1.5;3.7)
JS							
	Cont	10.4 (7.8;11.7)	8.8 (6.6;9.6)	8.5 (6.3;9.4)	8.8 (6.2;12.4)	6.6 (4.4;9.3)	6.5 (4.2;8.6)
	Puls	6.8 (5.5;7.1)	4.9 (4.1;6.4)	4.8 (4.0;6.1)	7.8 (5.8;9.0)	5.1 (3.9;7.1)	4.9 (3.8;6.7)
M							
	Cont	3.3 (2.1;4.3)	2.6 (1.8;3.9)	2.5 (1.9;4.7)	5.6 (3.4;7.4)	3.3 (1.3;6.0)	3.2 (1.3;6.2)
	Puls	2.0 (1.8;2.2)	1.5 (1.5;2.1)	1.5 (1.4;1.9)	2.6 (1.4;4.1)	2.2 (0.9;3.0)	1.9 (1.0;2.8)
RC							
	Cont	11.9 (8.0;12.8)	9.7(6.6;10.5)	9.3 (6.4;10.4)	9.8 (9.3;11.1)	7.1 (5.9;7.5)	6.8 (6.0;7.3)
	Puls	8.2 (4.7;11.1)	5.7(3.4;7.8)	5.3 (3.2;7.3)	9.5 (7.9;10.7)	5.6 (4.9;7.2)	5.4 (4.8;7.0)
RM							
	Cont	7.5 (4.6;10.4)	6.3 (3.8;9.1)	6.4 (3.9;8.7)	6.2 (4.2;9.1)	5.1 (3.2;6.5)	4.9 (3.2;6.4)
	Puls	5.7 (5.2;6.0)	4.7 (4.1;4.7)	4.6 (3.6;4.8)	7.5 (6.4;7.8)	5.7 (4.6;6.4)	5.6 (4.6;5.9)

Data are presented as median (IQR); CM, colon mucosa; CS, colon serosa; MC, mesentery of the colon; JM, jejunum mucosa; JS, jejunum serosa; M, mesentery; RC, renal cortex; RM, renal medulla; Cont, continuous insufflation; Puls, pulsatile insufflation.

Supplementary Table 2: Absolute medians of systemic hemodynamics and gas exchange measurements

		IAP 10 mmHg			IAP 14 mmHg		
		Baseline	60 min	90 min	Baseline	60 min	90 min
HR							
	Cont	80.5 (73.5;90.0)	80.0 (73.5;90.5)	83.5 (75.0;93.0)	81.0 (68.0;92.0)	85.0 (72.0;87.0)	80.0 (65.0;90.0)
	Puls	87.5 (74.5;96.0)	76.5 (68.0;89.0)	82.0 (74.0;96.5)	80.5 (68.5;90.0)	98.0 (86.0;106)	93.5 (74.5;99.5)
MAP							
	Cont	88.5 (76.0;92.5)	88.0 (78.0;105)	84.5 (76.0;102)	88.0 (74.0;106)	99.0 (89.0;107)	93.0 (80.0;104)
	Puls	93.0 (85.5;98.5)	96.5 (88.0;101)	92.0 (80.5;96.5)	96.5 (81.0;108)	102 (75.5;109)	89.0 (71.5;108)
SVRI							
	Cont	1792 (1227;2344)	1566 (1163;2340)	1694 (1117;2256)	2545 (1492;2969)	2537 (1808;3204)	2597 (1448;3221)
	Puls	2780 (2312;3046)	2770 (2515;2840)	2286 (2144;2732)	1958 (999;2995)	1881(1205;3185)	1822(1184;3168)
CI							
	Cont	3.8 (3.5;4.2)	3.9 (3.1;4.5)	3.7 (3.3;4.4)	2.9 (2.2;3.7)	2.7 (2.3;4.2)	2.6 (2.0;4.3)
	Puls	2.6 (2.2;3.1)	2.6 (2.4;2.8)	2.6 (2.4;3.0)	4.3 (2.6;5.9)	2.6 (2.4;2.8)	2.6 (2.4;3.0)
GEDI							
	Cont	609 (585;701)	616 (556;675)	605 (558;646)	563 (553;578)	555 (510;690)	569 (498;604)
	Puls	567 (558;572)	595 (506;649)	556 (518;625)	594 (512;650)	623 (509;664)	619 (553;652)
PaO_2							
	Cont	228.1 (202;279)	199.5 (169;222.8)	213.9 (152.1;252)	228 (172;269.4)	202 (182;228)	211 (184;250)
	Puls	218.4 (201.5;250.4)	175.7(154.9;234.5)	179.4(159.6;232.5)	208 (184.5;269.5)	195.5(173;226.3)	192(184.5;244.1)
$PaCO_2$							
	Cont	34.3 (31.8;42.4)	41.4 (38.6;45.5)	44.2 (39.5;46.9)	34.1 (31.4;38.5)	40.2 (37.5;46)	43.1 (39.5;44.9)
	Puls	33.4 (26.7;36.9)	39.9 (36.5;42.5)	41 (36.9;44.3)	40.4 (36.3;47.5)	43.3 (40.3;49.5)	44.8 (40;49.9)
Pa-ET_{CO2}							
	Cont	36.5 (34.5;37)	37.5 (35;38.5)	36 (34.5;38)	36 (34;39)	38 (34;39)	38 (37;39)
	Puls	34.5 (34;37)	38.5 (34;40.5)	37 (35;38.5)	36 (35;48)	41 (36;51)	42 (36;49)
$P_{A\text{-}a}O_2$							
	Cont	77.1 (37.8;105)	105 (86.3;133)	95.4 (49.3;145)	92.9 (46.1;142)	104 (68.3;129)	91.6 (56.1;127)
	Puls	101 (53.5;120)	129 (71.7;155)	123 (71.1;1.152)	89.5 (33.8;119)	99.9 (79.2;118)	92.6 (65.6;112)

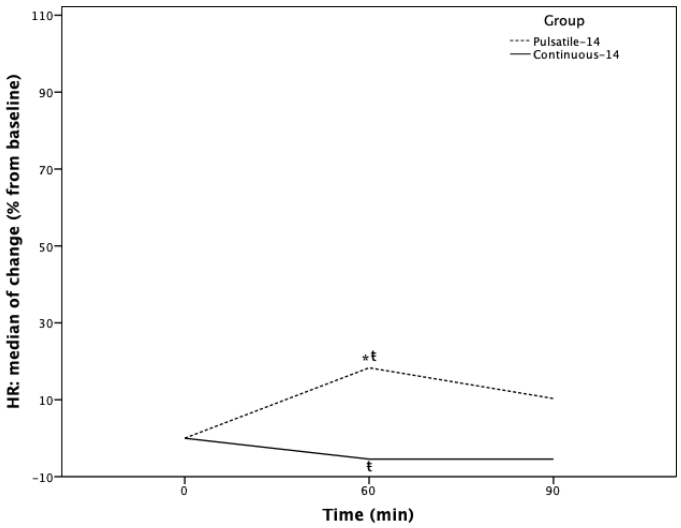
Data are presented as median (IQR). HR, heart rate (beat/min); MAP, mean arterial pressure (mm Hg); SVRI, systemic vascular resistance index ($dyn.s.cm^{-5}.m^2$); CI, cardiac index ($L.min^{-1}.m^{-2}$); GEDVI, end global diastolic ventricular index ($ml.m^{-2}$); PaO_2, arterial oxygen tension (mm Hg); $PaCO_2$, arterial carbon dioxide tension (mm Hg); PA-a O_2: alveolar/arterial tension difference for oxygen (mm Hg); Pa-$EtCO_2$: arterial to end-tidal CO_2 gradient (mm Hg); Cont, continuous insufflation; Puls, pulsatile insufflation.

Supplementary Table 3: Absolute medians of whole blood nitrite-to-nitrate concentration and plasma renin activity

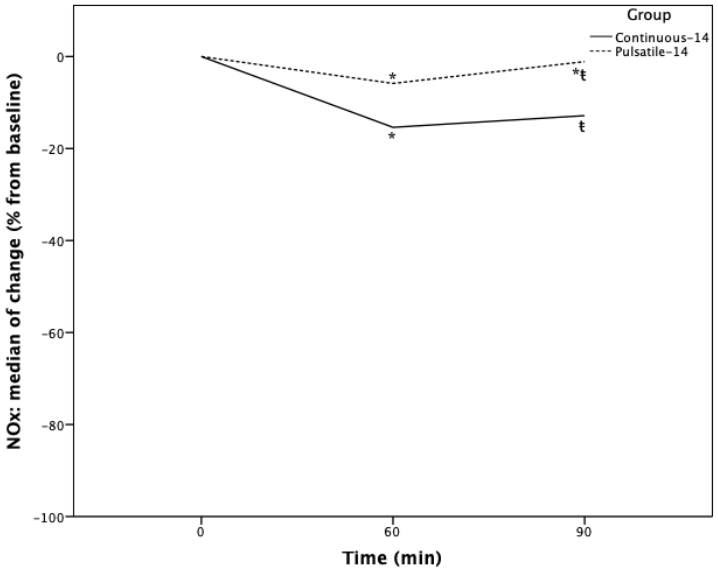
		IAP 10 mmHg			IAP 14 mmHg		
		Baseline	60 min	90 min	Baseline	60 min	90 min
NOx							
	Cont	62.6 (37.7;88.6)	49.4 (36.7;65.3)	48.6 (36.6;72.8)	51.5 (28.5;112)	58.3 (22.5;100)	48.7 (23.8;95.6)
	Puls	40.9 (26.6;59.5)	39.6 (25.9;57.9)	37.0 (28.0;54.9)	48.2 (34.3;79.5)	49.8 (38.0;78.7)	48.4 (39.3;85.2)
PRA							
	Cont	0.27 (0.08;0.53)	0.11 (0.08;0.23)	0.17 (0.09;0.33)	0.07 (0.07;0.10)	0.12 (0.09;0.16)	0.26 (0.09;0.30)
	Puls	0.13 (0.07;0.19)	0.09 (0.07;0.16)	0.13 (0.07;0.21)	0.30 (0.15;0.86)	0.59 (0.11;3.03)	1.01 (0.10;2.25)

Data are presented as median (IQR). NOx, nitrite/nitrate (μM); PRA, plasma renin activity (ng/mL/h); Cont, continuous insufflation; Puls, pulsatile insufflation.

Supplementary Figure 1: Heart rate at an IAP of 14 mmHg



Supplementary Figure 2: Nitrite-to-nitrate at an IAP of 14 mmHg



CHAPTER 10

SUMMARY, DISCUSSION, AND FUTURE PERSPECTIVES

SUMMARY, DISCUSSION, AND FUTURE PERSPECTIVES

SUMMARY

Chapter 3 provides a historical overview of the TaTME procedure. The review includes the development, safety and feasibility, proposed benefits and risks of the procedure, implementation and education models, and future direction for research and implementation of the TaTME in colorectal surgery. While satisfactory short-term results have been reported, the procedure is in its infancy, and long-term outcomes and definitive results from controlled trials are pending.

In **Chapter 4**, the histopathological results of the first 186 consecutive patients treated at the Hospital Clinic of Barcelona are reported. Mesorectal resection quality was complete in 95.7% (n=178), almost complete in 1.6% (n=3) and incomplete in 1.1% (n=2). Positive circumferential and distal resection margins were 8.1% (n=15) and 3.2% (n=6), respectively (including T4 tumours). This demonstrates that TaTME provides high-quality histopathological results, which has been proven as a surrogate marker for survival.

Chapter 5 presents the results of an original study performed in collaboration with the Amsterdam UMC at AMC. The aim of the study was to determine the incidence of positive CRM after TaTME surgery for rectal cancer, together with formulating a predictive model. Patients recorded on the international TaTME registry between July 2014 and January 2018 were selected. The final analysis included 2653 patients. The incidence of positive CRM was 107 (4.0%). Only pre-operative tumour related features were identified as predictive risk factors for CRM involvement after TaTME, with no patient-related factors could be found. The predictive model showed adequate discrimination (area under the

receiver operating characteristic curve >0.70). Currently another study is being performed to assess the external validation of the predictive model.

Chapter 6 consists on a comparative analysis between TaTME and conventional laparoscopic TME. We decided to conduct a multicenter observational study using a propensity score designed to deliver results with high level of evidence. The inverse probability of treatment weight method enabled an estimation of the causal treatment effect of TaTME on survival and recurrence in patients with stage II-III rectal cancer. A reduction in three-year locoregional recurrence was found in patients who underwent TaTME compared to conventional laparoscopic surgery. Unexpectedly, an improvement in the locoregional recurrence rate was only detected in patients with mid rectal cancer. When the analysis was limited to patients who underwent sphincter preservation procedures, TaTME was associated with a higher disease-free survival rate.

In **Chapter 7**, the function and health-related quality of life among 45 patients with rectal cancer treated with TaTME are presented. Validated questionnaires, imaging techniques and anorectal manometries were performed. Wexner and LARS scores significantly increased 3 months after surgery but returned to baseline values at 12 months. The rate of "major LARS" at the end of follow-up was 26.6% (+13.3% compared to baseline, p = 0.314). Sexual and urinary functions remained stable throughout the study, although a meaningful clinical improvement was detected in male sexual interest. Among health-related quality of life domains, all deteriorations returned to baseline values 12 months after surgery, except worsening of flatulence symptoms, and improvement in insomnia and constipation. At 12 months, an expected decrease in the mean width of the internal sphincter, the anal resting pressure, and the tenesmus threshold volume was found.

Chapter 8 consists on the first comparative analysis between TaTME and robotic TME. The main outcome was the incidence of poor-quality surgical resection, defined as a composite measure including incomplete quality of TME, or positive

CRM or DRM. Data of patients with for rectal cancer below 10cm from the AV and a sphincter-saving procedure from five high-volume rectal cancer referral centres between 2011-2017 were obtained. After using the coarsened exact matching method, two groups of 226 (TaTME) and 370 (robotic TME) patients were created. The incidence of poor-quality resection was similar in both groups (TaTME 6.9% vs. robotic TME 6.8%, p=0.954). There were no differences in TME specimen quality (complete or near complete TaTME 99.1% vs. robotic TME 99.2%, p=0.923), neither CRM involvement (5.6% vs. 6.0%, p=0.839).

Chapter 9 consists on the evaluation of the effects produced by a new continuous CO_2 insufflation system especially designed for the performance of TaTME. Thirty-two pigs were randomly assigned to undergo a two-team TaTME procedure with continuous (n=16) or conventional pulsatile insufflation (n=16). Each group was stratified according to two different pressure levels in both the abdominal and the transanal field, 10 mmHg or 14 mmHg. Continuous flow insufflation was associated with a lower microcirculation blood flow reduction in colon mucosa and serosa, jejunal mucosa, renal cortex, and renal medulla compared to pulsatile insufflation.

DISCUSSION AND FUTURE PERSPECTIVES

Transanal Total Mesorectal Excision and the limitations of surgical trials

The consensus across research institutions and scientific organizations is that TaTME has the potential to improve the quality of resection in rectal cancer surgery. This conviction grows stronger as more evidence comes to light. Given the promising results, several colorectal units worldwide have embraced TaTME as part of their routine practice. However, a recent Norwegian report has questioned the oncological safety of the transanal approach by reporting a 9.5% local relapse rate, characterized as rapid and multifocal (56). We systematically searched the PubMed database, from its creation to October 2018, for published articles with relevant evidence regarding survival or recurrence after TaTME for patients with rectal cancer, with no language restrictions. The literature search yielded 120 records. After screening the title, abstract, and full-text review when appropriate, four studies were finally included (58-61). A case-control study with no test for confounding and three case series were found, thus impairing an estimation of the causal treatment effect of TaTME on the risk of death or recurrence. All four studies indicated that TaTME might be associated with a low risk of locoregional recurrence. However, in most of the trials, follow-up periods were relatively short. An updated search in February 2020 yielded four case series studies in addition to the Norwegian study (52, 62-64). All of them supported the association between TaTME and an improved oncological outcome, including a multicentre study that reported two-year cumulative locoregional recurrence as low as 3% (95% CI 2 – 5) in 767 consecutive patients from six tertiary referral centres (52). Of these studies, all but one lacked a concurrent control group, which substantially limits the evaluation of intervention effects in a binary analysis, and therefore no meta-analyses were performed.

At present, the strongest argument against considering TaTME as the treatment of choice for patients with rectal cancer remains undoubtedly the lack of RCTs. Randomization is regarded as the most effective experimental design in clinical

trials. It controls for confounding of unknown variables and allows for a comparison of the effect with placebo. An RCT with pharmacological intervention can be properly implemented because medication is a standardized intervention, not dependent on the prescribing doctor. However, a surgical intervention is by definition a highly complex procedure in which a good outcome depends on the surgical team's expertise. In this respect, the complexity of the treatment and the learning curve play a significant role. Moreover, the possibility of blinding is impaired, internal validity decreases external validity, and testing against placebo might be unethical. Randomized controlled trials should still be considered the best research method, but the results of the different trial designs should be regarded as mutually complementary. Furthermore, in TaTME, the results of the COLOR III trial are not expected for the next five or six years, and the surgical community is in strong need of oncologic data (65). For this reason, we decided to conduct the multicentre study presented in **Chapter 6**, using a propensity score designed to deliver results with a high level of evidence (66). The inverse probability of treatment weight method enabled an estimation of the causal treatment effect of TaTME on survival and recurrence in patients with stage II-III rectal cancer. A reduction in three-year locoregional recurrence was found in patients who underwent TaTME compared to conventional laparoscopic surgery. Unexpectedly, an improvement in the locoregional recurrence rate was only detected in patients with mid rectal cancer. When the analysis was limited to patients who underwent sphincter preservation procedures, TaTME was associated with a higher disease-free survival rate.

The findings of this work are a response to a number of research issues with relevant and practical implications. The first major contribution is the much-needed empirical data on the oncological benefits of TaTME, at least as evident in high-volume centres. The analysis of 186 consecutive patients showed high-quality histopathological results, which has been proven as a surrogate marker for survival (24, 67). Contrary to conventional TME techniques, the predictive risk factors for positive CRM after TaTME were restricted to five tumour characteristics. Moreover, on the basis of the study presented in **Chapter 6**,

we demonstrated that TaTME provided favourable oncological outcomes in patients with locally advanced rectal cancer, without reporting any unexpected early pattern of locoregional recurrence. Given the difficulties of approaching the mid rectum through an open transanal TATA technique, we concluded that the treatment of primary mid rectal cancer should include a transanal approach through TaTME. The data support the use of a transanal approach in low rectal cancer, which can be attempted either by means of conventional open instruments or through TaTME. Outcomes should be tested in a more heterogenous environment, but the results of this thesis indicate that TaTME might improve locoregional recurrence and disease-free survival rates for advanced stages of rectal cancer.

While the oncological safety of TaTME is being globally investigated, there is a lack of information concerning its impact on patient function and health-related quality of life. Thus, a second important implication of this work are the reported functional outcomes of 45 consecutive patients that underwent TaTME for rectal cancer. A recent systematic review and meta-analysis on the subject was published, but with the significant limitation that only one third of the studies included reported the patients' baseline prior to undergoing surgery. The analysis presented in **Chapter 7** included baseline data and used validated questionnaires as well as imaging techniques and anorectal manometries, thus providing a comprehensive assessment. An acceptable function and health-related quality of life one year after surgery were found. The outcomes were comparable to those achieved with conventional surgical techniques for rectal cancer. The only exception was a lesser impairment in genitourinary function, which seems to support the theoretical basis that TaTME allows for enhanced preservation of neural tissue during rectal dissection.

A third implication derives from the finding that using the new valve-free CO_2 insufflators with continuous flow insufflation, especially designed for performing TaTME, is associated with a lower reduction of blood flow in the colon mucosa and serosa, jejunal mucosa, renal cortex, and renal medulla

compared to conventional pulsatile insufflation. These new insufflators facilitate transanal dissection by providing a stable environment and continuous smoke evacuation. Consequently, this enhanced visualization is critical for avoiding damage to anatomical structures or dissecting through incorrect planes. The decreased risk of hypoperfusion and reperfusion injury demonstrated in the experimental study presented in **Chapter 9** adds further value to the technique, although more studies should be undertaken to establish a case profile that is clearly beneficial.

The future of rectal cancer treatment

Several RCTs have demonstrated that screening programs reduce colorectal cancer incidence and mortality (68-71). However, once the tumour has grown in the rectum, the TME remains the cornerstone for the treatment of curable rectal cancer. In selected cases of locally advanced cancer, neoadjuvant therapy with radiotherapy or chemoradiotherapy provides an added benefit by reducing tumour burden (72). These strategies have enhanced rectal cancer outcome and survival, but at the cost of often resulting in significant effects on quality of life and defecatory, sexual, and urinary functions (73, 74). Moreover, radical surgery in the elderly and in patients with pre-existing comorbidities is associated with higher postoperative morbidity and mortality rates (75, 76). These facts, and especially the unpleasant side effects of traditional rectal surgery, have generated interest in finding alternative treatment methods that offer the possibility of preserving the organ.

The first alternative strategy is based on the proof that neoadjuvant chemoradiotherapy results in complete eradication of rectal cancer in the resected specimen – what is known as pCR – in approximately 10 - 25% of the patients (29, 77). Attempts were made to identify features related to a complete clinical response (cCR) prior to radical surgery, such as whitening of the mucosa, telangiectasia, or the absence of residual ulceration (78). The patients

with cCR are considered candidates for enrolment in strict active surveillance ("watch and wait") programs with the possibility of deferral of surgery or salvage intervention (79). The benefits of these policies are clear in terms of avoiding morbidity, functional sequelae, and the frequent need for temporary or permanent stomas. A recent retrospective analysis of 197 patients with cCR revealed overall survival rates of 82% at five years, and a risk of less than 10% of developing recurrences after two years of follow-up (80). Moreover, more than 90% of the local recurrences had an endoluminal component, which may facilitate detection through digital rectal examination or endoscopic evaluation. However, stronger evidence is needed to elucidate the oncological risk inherent to the "watch and wait" policy, to better define the factors that lead to higher cCR rates, or to identify the best way to reassess the response to neoadjuvant treatment, among others.

Local excision is a feasible and safe treatment option for low risk early rectal cancer (defined as well-moderately differentiated T1 adenocarcinoma with no lymphatic or vascular invasion and with free resection margins) (81). Considering the benefits of this minimally invasive organ-preserving treatment, several trials were designed with the objective of assessing whether local excision after chemoradiotherapy provides adequate oncological control. The CARTS study demonstrated that organ preservation was possible in 50% of patients with cT1-3N0 distal rectal cancer treated with chemoradiotherapy and local excision (82). In Spain the TAU-TEM study group is performing a RCT with similar endpoints but including patients with T2 and T3 tumours with mesorectal invasion lower than 4mm, which is currently recruiting (83). Finally, the STAR-TREC, opened in 2017, is a RCT of three arms (standard TME surgery vs. long-course chemoradiotherapy followed by local excision vs. short course radiotherapy followed by local excision) for patients with cT1-3bN0 rectal cancer (84).

Nevertheless, the main limitation of local excision is that the deeper the invasion of the submucosa, the higher the risk of positive nodal disease. Moreover, current measures for prediction of recurrence are only available after the local excision

has been performed (85). Therefore, current studies also explore the role of local excision followed by adjuvant therapies in more advanced cancer stages. The TESAR trial is a multicentre RCT comparing radical surgery vs. adjuvant chemoradiotherapy after local excision for intermediate risk early rectal cancer (86). This phase III trial is currently recruiting, and outcomes are expected for 2023.

When radical surgery is definitely required, TME can be performed by an open, laparoscopic, robotic or transanal approach. Currently, and despite the available literature and results from studies such as the ones described in this thesis, there is a lack of consensus on the 'gold standard' approach, with each of these options offering specific advantages (37, 38, 40-42, 45). Future studies will ascertain the level of evidence of each of these surgical approaches, as well as establish clearer guidelines for treating T4 tumours, those located adjacent to the anal sphincter, and those with a deficient response to neoadjuvant therapies.

From an oncological point of view, it is important to do research into the management of lateral pelvic lymph nodes in advanced rectal cancer. In Asia, current guidelines consider these lymph nodes as part of the regional territory, and an extended lymphadenectomy is usually performed based on a reduced local recurrence in the lateral area (87, 88). By contrast, in Western countries this dissection is not routinely performed, since several trials have found that the most common site of local recurrence is the presacral area (89, 90). Despite the existing controversies, the ultimate aim is to improve local control and surgical care, and efforts should be made to evaluate the importance of pelvic sidewall lymph node dissection for patients with mid and low rectal cancer.

The future of rectal cancer treatment is exciting. The constant evolution of procedures and technologies, the growing collaboration between professionals from different specialties, and the development of organ-preserving strategies are leading us to a situation where each patient will be placed at the centre of an individualized therapeutic plan. And colorectal surgeons are key participants in this modern and tailored multidisciplinary care.

The landscape of academic surgery

The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule defines "health research" as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (91). A narrower definition proposed by the Countway Library of Medicine includes descriptions such as "find better ways to prevent and treat disease" or "an important way to help improve the care and treatment of people worldwide". Research is one of the three aspects of the comprehensive mission of academic medical centres, besides patient care and education.

In an increasingly globalized and competitive world, in which the search salaries and financial demands places restrictions on the search for excellence, several pressure mechanisms may have a negative impact on research. A recent article by Massarweh et al. places surgery at a special risk due to its significant influence on hospital revenues and stresses the importance that this might have for the faculty (92). Imbalances between research and clinical productivity could result in unmotivated staff members or even employee burnout, eroded relationships, or in insufficient support for junior colleagues' development (92). The medical community and especially the leaders of academic canters need to acknowledge this situation and develop innovative solutions. The danger is that at some point we, and consequently the people we teach, forget the principles and standards of quality research. Health research is an essential component to extend the quality of life, a valuable tool that provides information about diseases and contributes to the common good of society. And, as John Alverdy once wrote, we have the fundamental responsibility of protecting it (93).

CHAPTER 11

CONCLUSIONS

CONCLUSIONS

The observations arising from the studies included in this thesis led to the following conclusions:

- TaTME may improve locoregional recurrence and disease-free survival rates among patients with mid and distal locally advanced rectal cancer.

- The surgical treatment of primary mid and distal rectal cancer should include a transanal approach. While both conventional and TaTME perineal surgery appear to be oncologically safe in distal tumours, TaTME might be the preferred method in mid rectal cancer for anatomic matters.

- The improved survival outcomes observed with TaTME appear to be derived from higher quality TME specimens. Specifically, lower rates of incomplete mesorectum and CRM involvement.

- Contrary to conventional TME techniques, where the risk of CRM involvement depends on patient and tumour-related factors, the predictive risk factors for positive CRM after TaTME were restricted to five tumour characteristics. In other words, adverse patient characteristics such as obesity and male gender are less problematic with TaTME than with other approaches.

- Patients undergoing TaTME reported acceptable health-related quality of life and functional sequelae one year after surgery. The outcomes were comparable to those achieved with conventional TME techniques, with a possible lower impairment in genitourinary function.

- Both TaTME and robotics appear to deliver high quality TME specimens. RCTs and carefully designed observational trials are required to contrast or even combine data from these two approaches, including cost analyses.

- Working with the CO2 insufflation system specially designed for the performance of TaTME was associated with lower microcirculatory consequences in the intestine and kidney. This suggests a possible role in the prevention of hypoperfusion and reperfusion injury in selected organs, compared to conventional insufflation systems.

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RESUMEN

RESUMEN

El **capítulo 3** proporciona una descripción histórica del procedimiento TaTME. La revisión incluye el desarrollo, la seguridad y la viabilidad, los beneficios y riesgos propuestos del procedimiento, la implementación y los modelos educativos, y la dirección futura para la investigación e implementación del TaTME en cirugía colorrectal. Si bien los datos a corto plazo son satisfactorios, están pendientes los resultados a largo plazo y los resultados definitivos de los estudios randomizados controlados.

En el **capítulo 4** se informan los resultados histopatológicos de los primeros 186 pacientes consecutivos tratados en el Hospital Clínic de Barcelona. La calidad de la resección mesorrectal fue completa en 95,7% (n = 178), casi completa en 1,6% (n = 3) e incompleta en 1,1% (n = 2). Los márgenes de resección circunferencial y distal positivos fueron 8,1% (n = 15) y 3,2% (n = 6), respectivamente (incluidos los tumores T4). Esto demuestra que TaTME proporciona resultados histopatológicos de alta calidad, factor que ha sido ampliamente definido como marcador subrogado de recurrencia y supervivencia.

En **capítulo 5** se presentan los resultados de un estudio realizado en colaboración con el Hospital de Amsterdam UMC en AMC. El objetivo del estudio fue determinar la incidencia de CRM positivo después de la cirugía TaTME para el cáncer de recto, junto con el desarrollo de un modelo predictivo. Se seleccionaron pacientes registrados en el international TaTME registry entre julio de 2014 y enero de 2018. El análisis final incluyó 2653 pacientes. La incidencia de CRM positivo fue de 107 (4,0%). Se identificaron como factores de riesgo predictivos para la afectación de CRM sólo las variables relacionadas con el tumor, sin incluir los factores dependientes del paciente como el género masculino o la obesidad. El modelo predictivo mostró una discriminación adecuada (área bajo la curva > 0,70). Actualmente, se está realizando otro estudio internacional para evaluar la validez externa del modelo predictivo.

El **capítulo 6** consiste en un análisis comparativo entre TaTME y TME laparoscópica convencional. Decidimos realizar un estudio observacional multicéntrico utilizando el inverse probability of treatment weight como modelo de propensity score, lo que permitió una estimación del efecto causal del tratamiento de TaTME sobre la supervivencia y la recurrencia en pacientes con cáncer de recto estadio II-III. Se encontró una reducción en la recurrencia locorregional de tres años en pacientes tratados mediant TaTME en comparación con la cirugía laparoscópica convencional. Inesperadamente, la mejor tasa de recurrencia locorregional se detectó sólo en pacientes con cáncer de recto medio. Cuando el análisis se limitó a los pacientes intervenidos mediante procedimientos de preservación esfinteriana, TaTME se asoció con una mayor tasa de supervivencia libre de enfermedad.

En el **Capítulo 7** se analiza la función y calidad de vida de 45 pacientes con cáncer de recto tratados mediante TaTME. Se utilizaron cuestionarios estandarizados y validados, técnicas de imagen y manometrías anorrectales. Las escalas de Wexner y LARS aumentaron significativamente 3 meses después de la cirugía, pero volvieron a los valores basales a los 12 meses. La tasa de "LARS mayor" al final del seguimiento fue del 26,6% (+ 13,3% en comparación con el valor inicial, p = 0,314). Las funciones sexuales y urinarias se mantuvieron estables durante todo el estudio, aunque se detectó una mejoría clínica significativa en el interés sexual masculino. Entre los dominios de calidad de vida relacionados con la salud, todos los deterioros volvieron a los valores basales 12 meses después de la cirugía, excepto el empeoramiento de los síntomas de flatulencia y la mejora del insomnio y el estreñimiento. A los 12 meses, se encontró una disminución esperada en los valores medios de grosor del esfínter interno, presión de reposo anal y volumen umbral del tenesmo.

El **capítulo 8** consiste en el primer análisis comparativo entre TaTME y TME robótico. El objetivo primario fue la incidencia de resección quirúrgica de baja calidad, definida como una variable compuesta que incluye calidad incompleta de TME, margen de resección circunferencial (CRM) positivo, o margen de

resección distal (DRM) positivo. Se obtuvieron datos de pacientes con cáncer de recto hasta 10 cm del margen anal y cirugía conservadora de esfínteres de cinco centros de referencia entre 2011 y 2017. Después de utilizar el método de coarsened exact matching se crearon dos grupos de 226 (TaTME) y 370 pacientes (TME robótico). La incidencia de resección de baja calidad fue similar en ambos grupos (TaTME 6,9% versus TME robótico 6,8%, p = 0,954). No hubo diferencias en la calidad de mesorrecto (TaTME completo o casi completo 99,1% vs. TME robótico 99,2%, p = 0,923) ni en el CRM afecto (5,6% vs. 6,0%, p = 0,839).

El **capítulo 9** consiste en la evaluación de los efectos producidos por un nuevo sistema de insuflación continuo de CO_2 especialmente diseñado para la técnica TaTME. Treinta y dos cerdos fueron asignados al azar para someterse a un procedimiento TaTME de dos equipos con insuflación continua (n = 16) o convencional pulsátil (n = 16). Cada grupo se estratificó de acuerdo con dos niveles de presión diferentes tanto en el campo abdominal y transanal, 10 mmHg o 14 mmHg. La insuflación de flujo continuo se asoció con una menor reducción de la microcirculación en la mucosa y serosa del colon, la mucosa yeyunal, la corteza y la médula renal en comparación con la insuflación pulsátil.

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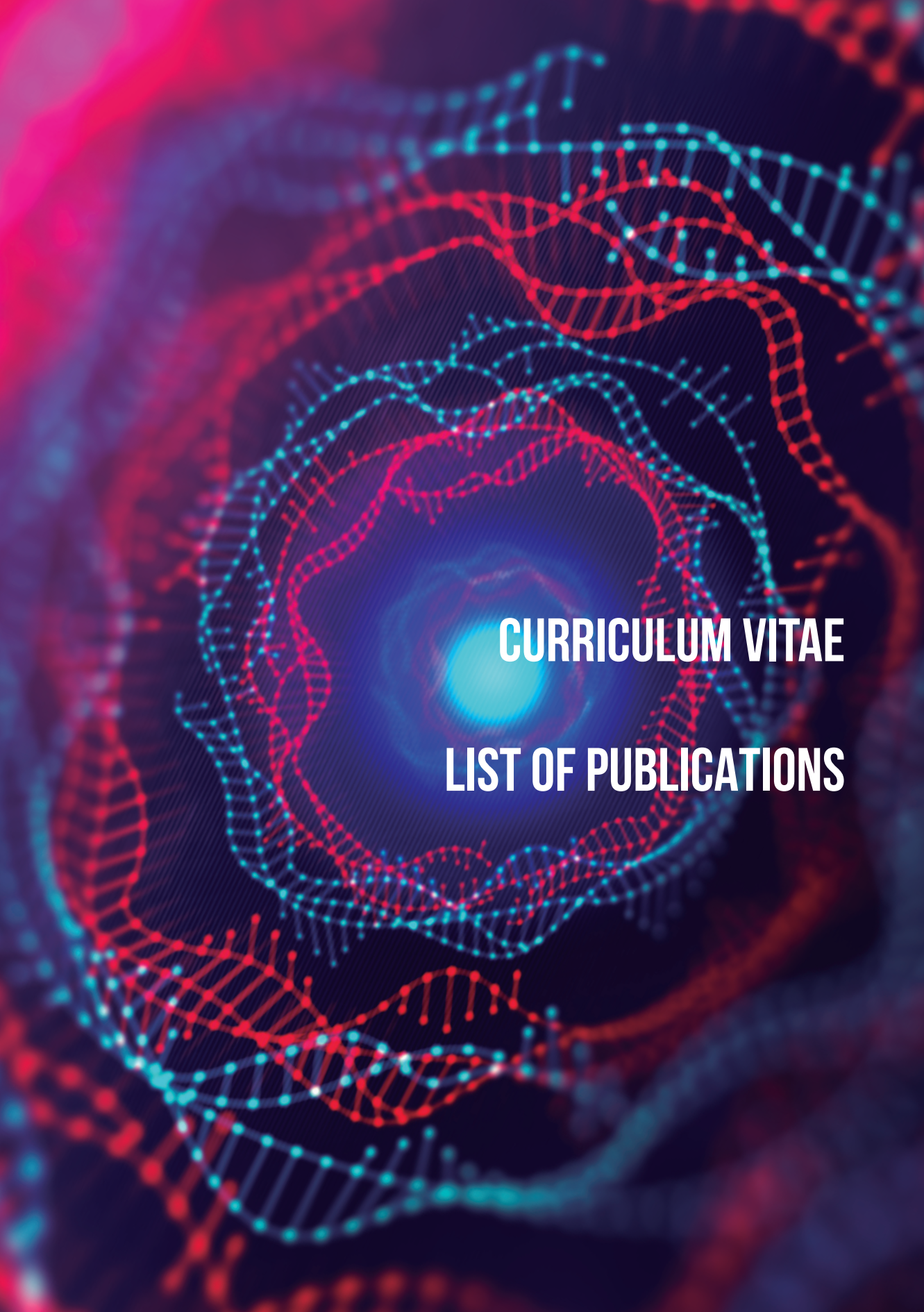

CURRICULUM VITAE

LIST OF PUBLICATIONS

CURRICULUM VITAE

F. Borja de Lacy nació en Barcelona el 20 de marzo de 1988. Tras alcanzar el título de Bachiller en la escuela Aula Escola Europea y cursar los estudios universitarios, obtuvo la Licenciatura de Medicina y Cirugía por la Universidad de Barcelona en 2012. Tras aplicar al examen MIR, realizó la residencia de Cirugía General y Digestiva el Hospital Clínico de Barcelona entre los años 2013 y 2018. Su formación quirúrgica se focalizó principalmente en cirugía colorectal y esófago-gástrica, con especial interés en su desarrollo mediante técnicas mínimamente invasivas. Actualmente es adjunto del servicio de Cirugía Gastrointestinal del Hospital Clínico y se encuentra en proceso de especialización en patología colorectal y cirugía oncológica. Durante estos años F. Borja de Lacy ha tenido la oportunidad de desarrollar la vertiente investigadora en Barcelona y durante dos estancias en hospitales académicos de Holanda. En 2017 surgió la oportunidad de comenzar un proyecto de doctorado en la Universidad de Barcelona con los Dres. A. Castells y A.M. de Lacy, dedicándose durante cuatro años a tiempo parcial a la investigación sobre el tratamiento del cáncer de recto mediante el abordaje transanal.

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Happiness is not in the mere possession of money; it lies in the joy of achievement, in the thrill of creative effort.

Franklin D. Roosevelt

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