Minimally invasive treatment strategies for rectal cancer

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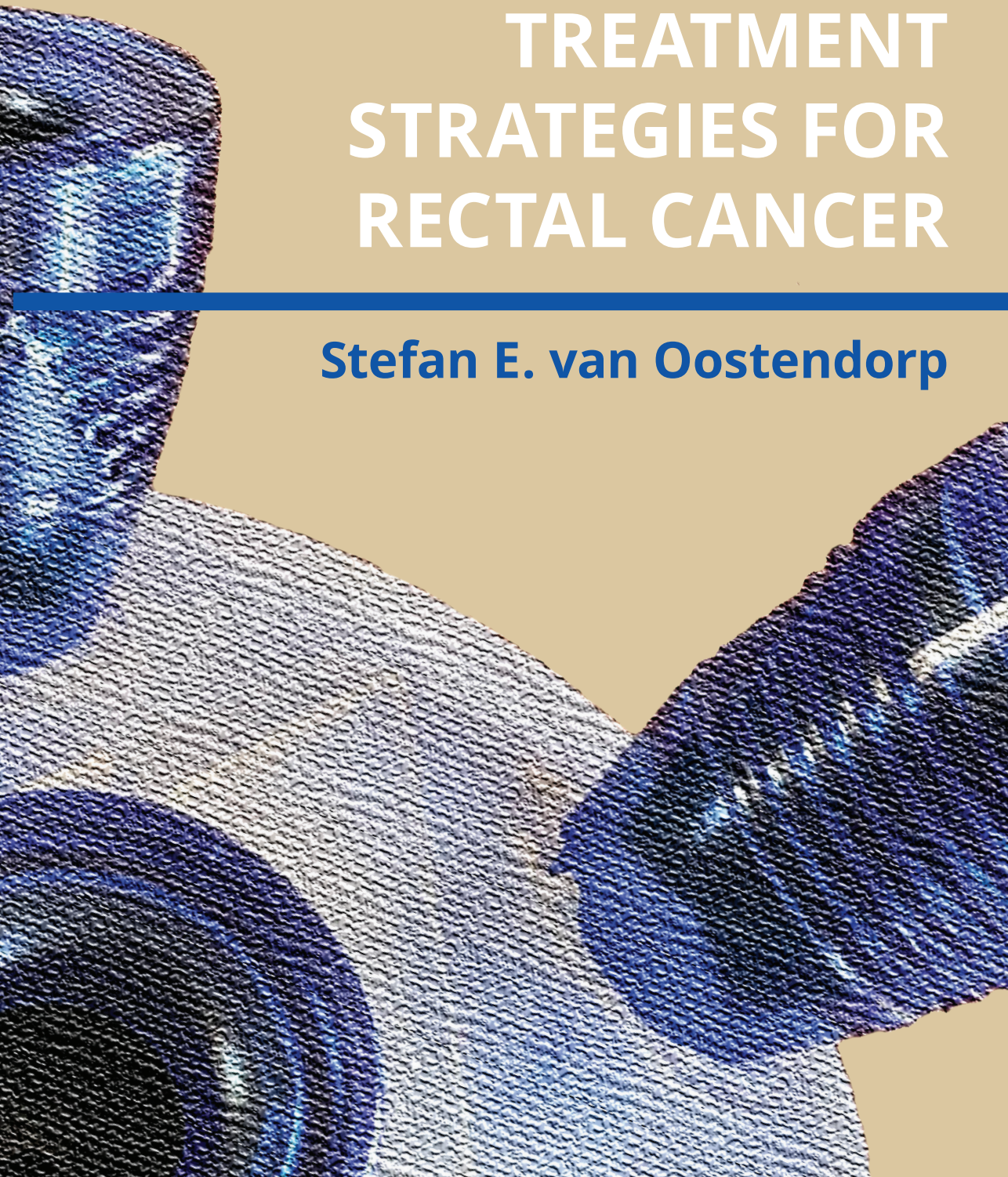

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Stefan E. van Oostendorp

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Minimally invasive treatment strategies for rectal cancer

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door

Stefan Erik van Oostendorp

geboren te Amsterdam

promotor: prof.dr. H.J. Bonjer

copromotor: dr. J.B. Tuynman

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APPENDICES

1

General introduction and outline of thesis

Colorectal cancer is the third most common type of cancer and accounts for 10.2%of all cancers and 9.2% of cancer related deaths worldwide.(1) In the Netherlands, the specific incidence counted 9.412 for colonic cancer and 4.457 for rectal cancer in 2018 respectively.(2) During the last decades the overall 5 year survival has been increasing due to advances in screening, early diagnosis, surgery and adjuvant therapy. Last years a similar five year overall survival is observed for colon and rectal cancer, respectively 66% and 67% . Though the majority of research and developments have addressed rectal cancer due to higher local recurrence rate, difficulty of surgery in the lower pelvis and the more profound impact on patients quality of life . Three persistent major problems in rectal cancer are identified: functional impairment, local recurrence and difficult surgery reflected in high stoma and conversion rate. The descending colon (neorectum) is less capable to fully restore the reservoir function of the rectum and surgery and/or irradiation hampers the innervation of the pelvic floor, sphincter and urogenital organs resulting in functional complaints such as incontinence, frequent bowel movements and sexual dysfunction.(3, 4) In rectal cancer, locoregional recurrence occurs more frequently compared to colon cancer.(5) The bony constraints of the pelvis in combination with intra-abdominal adipositas limit access hampering safe and effective surgery which is reflected in conversion and substantial proportion of non-restorative procedures (creation of an end-colostomy).(6) The funneling shape of the pelvis increasingly endangers a safe resection margin the lower the tumour is located. For low cancers, lymphatic draining is not only cephalic within the mesorectum but also to lateral pelvic lymph nodes. Treatment of recurrent rectal cancer is often palliative or in case of curative intent characterized by highly morbid multivisceral exenterative surgery.(7)

Over the past decades several major *milestones* can be identified which have improved the treatment outcome of patients with rectal cancer: sharp dissection along embryologic planes, laparoscopy and neo-adjuvant radiotherapy. However, defining the optimal strategy to treat rectal cancer in individual cases following these improvements, which are characterized by multidisciplinary involvement including neoadjuvant (chemo) radiotherapy, have become less straight forward. In addition, shared decision making with patients based on individual preference in balancing trade-off between oncologic safety, treatment associated morbidity and quality of life have resulted in a need for tailored treatment strategies.(8)

From a surgical perspective the most renowned milestone has been the principle of total mesorectal excision (TME) which constitutes of sharp dissection along the embryological avascular “Holy” plane circumferencing the mesorectum with preservation of the autonomic nerves as popularized by Heald.(9) The local recurrence rate following TME for rectal cancer dropped to 3.7% at 5 years follow-up in his selected series of patients operated in Basingstoke and has consistently been reproduced in large trials.

(10, 11) TME has become the gold standard for surgical resection of rectal cancer. A second surgical innovation has been the widespread use of minimal invasive approach, mostly laparoscopic, for colorectal cancer resections which results in faster recovery and similar long term outcome as demonstrated by the COLOR II trial.(12) Pathologic evaluation of the TME-specimen, which constitutes of the rectal tube surrounded by the fatty mesorectum containing the lymph nodes, is of paramount importance to assess the quality of surgery and identify patients at risk of local recurrence. Quirke and Nagtegaal have demonstrated the importance of the circumferential resection margin, i.e. distance between plane of dissection and malignant tumour cells, usually defined positive when within 1 millimeter and secondly, the quality of the specimen categorized by the extent of defects of the mesorectal envelope which is ideally covered by its shiny mesorectal fascia.(13, 14)

Another paradigm shift in the treatment of rectal cancer has been the introduction of neoadjuvant (chemo)radiotherapy. Radiotherapy aims to sterilize suspected or potential metastatic locoregional lymph nodes and/or downsizing of the primary tumour in case of a threatened margin to the mesorectal fascia. The Dutch TME trial has shown an improved local control for patients who underwent TME + neoadjuvant therapy compared to TME alone 2.4% versus 8.2% respectively ($p < 0.0001$).(15) An extra paradigm shift has been the rectal preservation strategy as introduced by Habr-Gama et al.; for a minority of patients with locally advanced rectal cancer a complete clinical response after chemo-radiotherapy cancer is observed. Refraining from surgery and implementing a so-called 'Wait and See' strategy has been a popular a safe method(16, 17) Albeit this concerns only a small portion of all rectal cancer patients it has opened the door to the concept of organ preservation and questions the dogma of radical mesorectal excision as only possibility for curative treatment of all rectal cancer beyond low risk early stage tumors.

The annual incidence of rectal cancer in the Netherlands in 2017, two years after the introduction of a nationwide screening program, comprised 4.436 patients.(2) Following this screening program a stage migration towards more early stage cancer has been observed: i.e an increase of smaller cT1/2 tumours.(18) Distinction between dysplastic adenomas and very early cancer can be difficult and endoscopic removal by the gastroenterologist will yield a proportion of cancerous tumours.[Moons/ backs T1] Also in more suspected lesions, a full thickness local excision can be considered as step-up approach. Technical advancements to facilitate access and visualization have increased the possibility to achieve a good quality full thickness local excision since the 1980's when professor G. Buess introduced the Transanal Endoscopic Microsurgery (TEM) allowing local excision of lesions located proximal (cephalic) from the anal canal. (19) Further refinement by replacing the rigid tube (TEM) to a flexible platform by Atallah et al in 2020, where after the technique was named Transanal Minimally Invasive Surgery (TAMIS).(20) TAMIS helped to increase the indication of cases amendable for a local

procedure and improved the quality of the surgical excision as it requires conventional laparoscopic instruments and surgical skill.(20)

Avoidance of radical surgery in the pursuit of organ preservation for rectal cancer gains more interest of patients and physicians.(21) Similar to multimodal therapy for breast cancer, the adjunct of (chemo)radiotherapy either neoadjuvant or adjuvant in combination with more restrictive surgery (local excision) for other than locally advanced rectal cancer is increasingly investigated. The hypothesis is to sterilize possible metastasis in the mesorectum with radiotherapy and only locally excise the primary tumour. Currently, two randomized controlled trials evaluate the safety of local excision with respectively adjuvant or neo-adjuvant (chemo)radiotherapy compared to the gold standard of TME to evaluate whether promising results in terms of oncologic safety from cohorts with suspected selection bias can be reproduced.(22, 23)

In coherence with organ preservation strategies, patients that are subject to radical TME surgery often prefer sphincter preservation as restorative procedure. A proctectomy with creation of an end-colostomy has a higher impact on the quality of life compared to when an anastomosis is performed especially in young patients. (24) In 2009, Lacy and Sylla performed a revolutionizing new procedure nowadays known as Transanal Total Mesorectal Excision (TaTME) which has attracted the attention of the colorectal community ever since. The TaTME technique offers the technical ability to create a lower anastomosis, thus increasing the restorative and sphincter preservation rate. Furthermore, TaTME is suggested to offer improved access which could yield a lower conversion rate and better quality of the specimen with lower rate circumferential margin involvement and by endoluminal visualization more control of the distal margin. (25, 26) For restorative procedures, this technique enables a single-stapled circular anastomosis, in contrast to the conventional cross-stapled anastomosis in a pure laparoscopic approach. Omitting the stapled linear transection of the rectum at the pelvic floor which often requires multiple loads and the “dog-ears” after application of the circular stapler through the linear staple line could reduce the incidence of anastomotic leakage in theory. (27, 28) Nevertheless, the technique is complex which is reflected by a relative long learning curve of 40 to 45 cases based upon histopathologic and peri-operative outcomes. (29, 30) Furthermore, long-term oncologic outcomes have to be awaited before this new technique can be seen as an oncologically safe alternative to the current standard which is a laparoscopic approach.

OUTLINE OF THE THESIS

The **first** part of this thesis focusses on TAMIS local excision and organ preservation. **Chapter 2** summarizes the available recommendations of national or international society guidelines on the possibility of rectal preserving treatment strategies for early

rectal cancer. Pathologic examination following local excision of an early rectal cancer may reveal risk factors. If such factors are present, the Dutch multidisciplinary guideline recommends formal radical resection also named completion surgery to reduce the risk of a local recurrence. The local recurrence rate following completion surgery, adjuvant chemoradiotherapy and refrained additional therapy but follow-up is compared in **chapter 3**. Early identification of potential candidates for rectal preservation is dependent on accurate staging. The accuracy of MRI staging with or without endorectal ultrasound for early rectal cancer in daily practice in the Netherlands is evaluated in **chapter 4**. In the context of shared decision making, physicians consider local excision in frail patients to avoid radical resection, balancing treatment related morbidity and oncologic safety. In **chapter 5** the pros and cons of a local excision as palliative option in relation to alternative strategies are evaluated**.**

The **second** part of the thesis concerns the implementation of transanal minimal invasive surgery for total mesorectal excision whereas the first part concerned local excision. **Chapter 6** summarizes the early experience of centers that published a cohort reporting their results with TaTME. In acknowledgement of the technical complexity of this technique a structured training pathway including on-site proctoring by surgeons experienced in TaTME was developed. In **chapter 7** we describe perioperative morbidity and histopathologic outcomes of the first ten cases from twelve centers that completed this structured training pathway. In the first half of 2019 the occurrence of local recurrences following TaTME led to a national stop in Norway. Therefore, the oncologic outcomes of all 120 patients in the multicenter structured training cohort were externally audited in **chapter 8** after signaling the occurrence of some early local recurrences in conjunction with the warning report from Norway. The long term local recurrence rate in a cohort of patients with a minimal interval of 3 years following index operation from the two centers starting TaTME in the Netherlands, Gelderse Vallei hospital and the VUmc, was studied in **chapter 9**. Extension of the bottom-up TaTME technique into a more advanced procedure which includes en-bloc resection of the pelvic floor and/or sphincter complex is named as a transperineal (extralevatory) abdominoperineal excision. In **chapter 10** we describe the combined experience of five centers with this technique.

The results of this thesis are summarized and discussed in general in **chapter 11** followed by future perspectives on further evaluation and implantation of transanal surgery for rectal cancer.

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PART I

TAMIS local excision

2

Rectal preserving treatment strategies in rectal cancer; synopsis of international guidelines

WAA Borstlap*, **SE van Oostendorp***, CEL Klaver, D Hahnloser, C Cunningham, E Rullier, WA Bemelman, JB Tuynman, PJ Tanis; on behalf of the research committee of the European Society of Coloproctology. *shared first author

Colorectal Disease - 2017

ABSTRACT

Background: The high morbidity associated with rectal resection for rectal cancer serves as an incentive for rectal preserving treatment strategies. This synopsis of national and international guidelines aims to determine current consensus and controversy among treatment recommendations for early rectal cancer.

Methods*:* The databases PubMed, Embase, Trip database, national guideline clearinghouse, BMJ Best practice were systematically searched for relevant papers. Guidelines published before 2010 were excluded. The AGREE-II tool was used for quality assessment.

Results*:* Out of 2278 potential documents, 24 guidelines were included. Consensus exists for local excision of low risk T1 rectal cancer, although there is no uniformity how to stratify risk. It's generally agreed that TME surgery is standard of care for all other stages. If rectal preserving alternatives are mentioned, this is mostly recommended only in patients unfit for radical surgery or in trial setting with a low level of agreement. Guidelines mostly lack any statement on assessing cN0, and surveillance protocols after local treatment. Clinical complete response after chemoradiotherapy is addressed by a minority of guidelines, mostly emphasizing the experimental status of a 'watch and wait' strategy or local excision of the scar.

Conclusion: Rectal preserving treatment strategies for rectal cancer, except for low risk T1 stage, are still considered experimental or only indicated in patients not suitable for standard care according to current guidelines and consensus statements, underlining the need for high quality studies. The definition of cN0 stage and surveillance of the preserved rectum are underexposed issues that need to be explored further.

WHAT DOES THIS PAPER ADD TO THE LITERATURE?

This guideline synopsis provides a systematic overview of national and international guidelines on rectal preserving treatment strategies, thereby identifying lacunae in current evidence and highlighting fields for further research.

BACKGROUND

The treatment of rectal cancer is rapidly developing towards a more patient tailored approach. Focus is also shifting from solely oncological control towards achieving a balance with optimal functional outcome and quality of life. The high morbidity and long-term functional implications that are associated with radical surgery for rectal cancer have encouraged the development of treatment strategies that enable preservation of the rectum. Introduction of transanal approaches for local excision of early rectal lesions (i.e. Transanal Endoscopic Microsurgery (TEM)) and observing those patients who demonstrate clinical complete response after neoadjuvant chemoradiotherapy have contributed to this paradigm shift. Finally, the introduction of screening programs resulted in a migration towards earlier staged rectal cancers, thereby increasing the population of patients who may be treated with organ preservation strategies. There is considerable uncertainty and lack of standardisation in the approach to organ preservation and an urgent need to define standardized treatment strategies on an international level to facilitate an optimal balance between oncological control and treatment-related morbidity and sequelae in terms of functional outcome and quality of life.(1)

The pivotal publication of "watch and wait"(W&W) by Habr Gama et al. showed promising results for patients that achieved a clinical complete response following neoadjuvant chemoradiotherapy, and has led to various initiatives to investigate different strategies of rectal preservation.(2) However, there is still controversy whether these should be implemented as standard of care.

Local excision of low risk early rectal cancer is a commonly accepted rectal preserving treatment. However, defining the risk of an early rectal cancer is still debated. Intermediate and high risk early rectal cancers often pose a treatment dilemma as the increased risk of recurrence after local excision with or without neoadjuvant radiotherapy should be weighed against the morbidity associated with (completion) total mesorectal excision (TME).(3) The aim of this study is to systematically review national and international guidelines in order to provide an overview on the consensus and controversies concerning rectal preservation strategies in the treatment of rectal cancer.

METHODS

Search strategy

A systematic search to identify regional, national and international guidelines and consensus documents on treatment of rectal cancer was performed. In collaboration with a clinical librarian, the search was carried out on November 5th 2015 using Medline (via Pubmed), Embase, Trip database, National Guideline Clearinghouse and BMJ Best

Practice databases. An update of the search was performed at June 2nd 2016 to include updates and/or recently published guidelines. Furthermore, websites of the Ministries of Health of several Western countries were searched manually.

Selection process

Guidelines written in English, Dutch, German, Scandinavian or Latin languages were included. Guidelines published prior to 2010 were excluded. Besides regional and national guidelines, consensus statements of multinational organisations (i.e. European Society of Medical Oncology or the European Association of Endoscopic Surgery) were included as well.

After removal of duplicates, retrieved references were independently screened by two reviewers (WAB, SO) on title and abstract using the online Covidence review manager (Covidence online review manager 2015, www.covidence.org). In case of disagreement, consensus was achieved by discussion. After this second round of screening, an additional check on duplicates, updates, addendums, and withdrawn status was performed. Full-text assessment of the remaining documents was performed independently by two reviewers.

The AGREE-II instrument was used for quality-assessment of the included guidelines. (4) This instrument incorporates 23 items, which were scored independently by the two reviewers from 1 to 7, with 7 as the maximum score. A mean score of each paper was calculated, and those scoring 3.00 or less were deemed to be of low quality and were therefore excluded.

Data extraction

Data extraction and categorization were performed by WAB and SO and discussed to reach consensus. Topics of interest were rectal preserving treatment strategies per clinical/pathological stage, preoperative imaging of early rectal cancers, techniques of local excision, W&W after neoadjuvant chemoradiotherapy, and follow-up schemes after rectal preserving treatment.

Consensus and Level of Evidence

In order to reach consensus, at least two-thirds of the guidelines that made a relevant statement on a specific topic needed to have a similar recommendation on rectal preserving treatment strategies. For the conclusion statements, the highest level of evidence classified to the Oxford centre for Evidence-based Medicine Levels of Evidence 2009 was retrieved from the included guidelines. (http://www.cebm.net/oxford-centre-evidencebased-medicine-levels-evidence-march-2009/) If the included guidelines did not report their recommendations according to the Oxford classification, the level of evidence was manually reassigned.

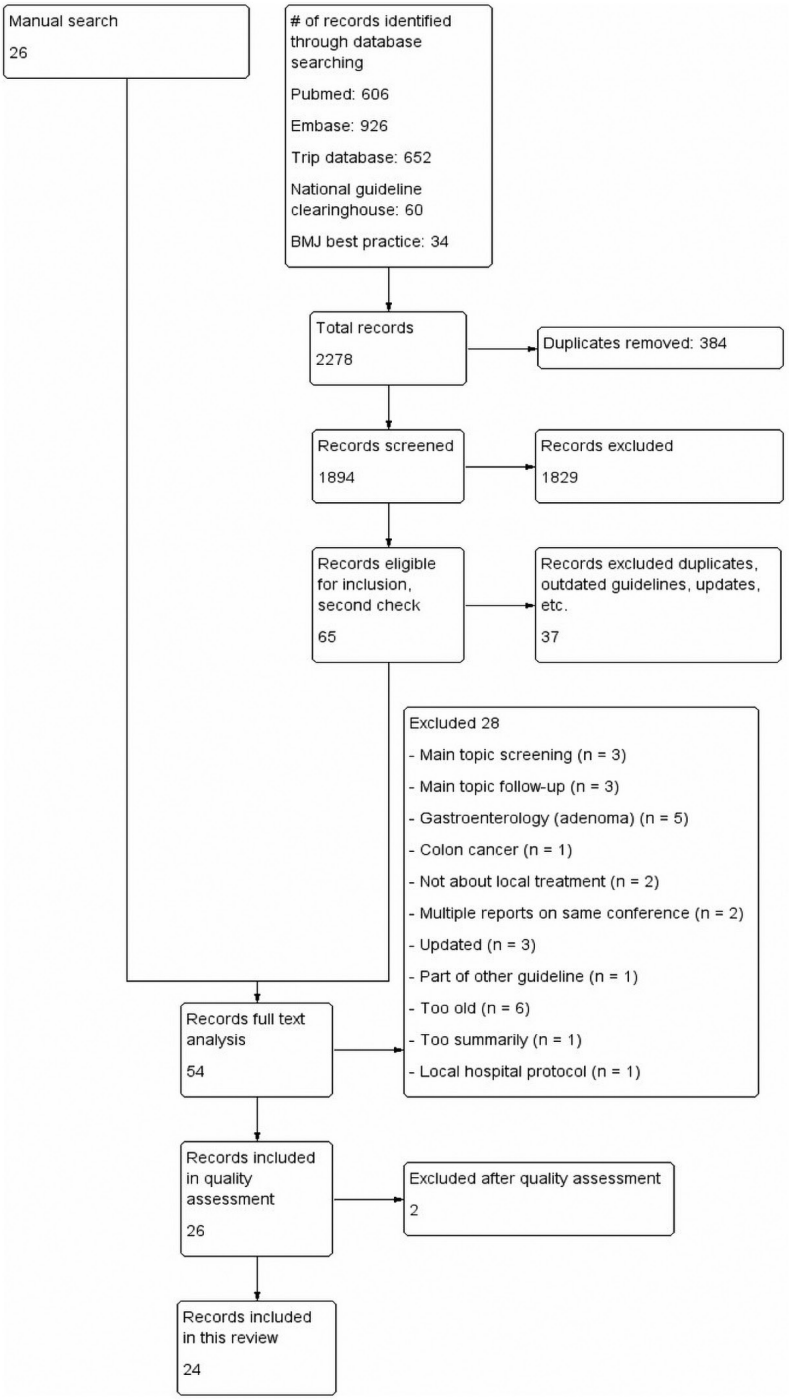

Figure 1 Inclusion Flow-Chart

RESULTS:

Literature search

The search resulted in a total of 2278 articles. After removal of duplicates, 1894 titles were evaluated for potential use, of which 1857 were excluded based on title or abstract. An additional 26 guidelines were retrieved by searching websites of ministries of health and surgical or oncological national societies, and by crosschecking references. Ultimately, 54 guidelines were assessed by full text for inclusion. Another 28 guidelines were excluded based on criteria as provided in Figure 1 (flowchart).

Quality – AGREE-II The remaining 26 guidelines that were assessed for quality consisted of 16 national guidelines [e01][e02][e03][e04][e06][e07][e08][e09][e11][e14][e17][e18][e19][e24][e25] [e27], eight consensus statements [e10][e12][e13][e15][e16][e20][e21][e22], and two sole chapters [e05][e26]. The mean score of the guidelines was 4.70. The Cuban[e04] and Danish[e05] guidelines were excluded due to a mean score of 2.21 and 2.67 respectively. Eventually, a total of 24 guidelines were included.

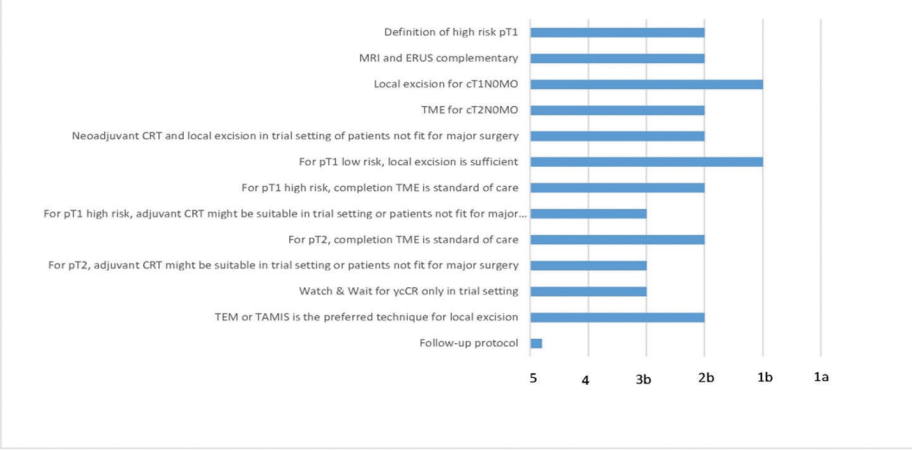

Figure 2: Level of evidence per topic 1a being the highest and 5 the lowest

Table 1 Included guidelines

	Guideline	Country	Year
e1	Colorectaal carcinoom	Netherlands	2014
e2	Cancer colorectal en la argentina	Argentina	2011
e3	Guía de práctica clínica para la detección temprana, diagnóstico, tratamiento, seguimiento y rehabilitación de pacientes condiagnóstico de cáncer de colon y recto	Colombia	2013
e4	Consenso nacional de cáncer de recto (excluded)	Cuba	2013
e5	Danish colorectal cancer group retningslinier Lokal tumorresktion i recum (excluded)	Denmark	2014
e6	Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behnadling og oppfolging av kreft it tykktarm og endetarm	Norway	2015
e7	Thésuarus national de cancérologie digestive, ch 5 cancer du rectum	France	2013
e8	Evidence based guideline for colorectal cancer	Germany	2014
e9	Protocolos clinicos e dretrizes terapeuticas em oncologica	Brasil	2014
e10	Early rectal cancer: the europoean association for endoscopic surgery (EAES) clinical consensus conference	EAES	2015
e11	European guidelines for quality assurance in colorectal cancer screening and diagnosis	European commission	2010
e12	Managment of patients with colorectal cancer: a personalized approach to clinical decision making	European society of medical oncology	2012
e13	Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up	European society for medical oncology	2013
e14	Consensus document for management of colorectal cancer	India	2014
e15	Review of current best practice and priorities for research in radiation oncology for elderly patients with cancer: the International Society of Geriatric Oncology (SIOG) taskforce	International	2014
e16	Practice parameters for early rectal cancer management: Italian society of colorectal Surgery guidelines	Italy	2015
e17	Management of early colorectal cancer	New Zealand	2011
e18	National institute for Health and Care Excellence	UK	2011/14

Table 1 Continued.

	Guideline	Country	Year
e19	SIGN Colorectal	Scotland	2015
e20	ACR Appropriateness Criteria® Local Excision in Early Stage Rectal Cancer	USA	2015
e21	Practice Parameters for the management of Rectal Cancer (revised) ASCRS follow up	USA	2013
e22	EURECCA colorectal: multidisciplinary management: European consensus conference colon &rectum	Europe	2014
e24	NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer	USA	2015
e25	JSCCR guidelines 2014 for the treatment of colorectal cancer	Japan	2014
e26	Early stage rectal cancer	Canada (Alberta)	2013
e27	Cancer colorectal Adénocarcinome	France	2012

SYNOPSIS

1.Staging

In the pre-treatment staging of rectal cancer, MRI and endorectal ultrasound (ERUS) have been described as imaging modalities. Local excision is only recommended in N0 stage rectal cancer, therefore staging with MRI to exclude lymph nodes suspected for metastasis is mandatory. Seven out of the 24 included guidelines, mentioned criteria for lymph node assessment based on MRI [e01][e10][e12][e13][e16][e21][e22]. Irregular border, signal heterogeneity and a round shape were named in all as morphologic characteristics associated with malignancy. Two guidelines mentioned a size >8 mm as a risk factor [e12][e22], and the Dutch guideline mentioned a size >5mm as a risk factor when concomitant suspicious morphologic features were observed [e1]. ERUS is superior in analysing depth of invasiveness for small rectal cancers, thereby differentiating between T1 and T2. MRI is superior to assess ingrowth into the mesorectal fat and mesorectal fascia. Therefore, MRI is recommended for larger lesions. This recommendation was mentioned in 14 guidelines [e06][e07][e08][e10][e12][e13][e14][e16][e17][e20][e21][e22][e26][e27]. In six guidelines MRI was recommended above ERUS, and that ERUS should be reserved for expert centres or solely when local excision is planned [e1][e3][e8][e11][e18][e19]. The NCCN guidelines (USA) did not differentiate between MRI or ERUS and stated that imaging should be performed according to facilitations of local hospitals [e24]. Four guidelines did not mention imaging in the work-up [e2][e9][e15][e25].

MRI and ERUS should be used complementary in the staging of rectal cancer. ERUS is superior when analysing depth of invasiveness in small superficial cancers, and MRI is superior for assessing mesorectal lymph nodes as well as ingrowth into the mesorectum and mesorectal fascia. Consensus. level of evidence: 2b.

2. Treatment based on clinical stage (cTNM)

cT1NOMO

Local excision for clinical staged cT1NOMO was advised in 13 of the included guidelines [e01][e03] [e06][e07][e10][e12][e14][e17][e20][e21][e22] [e24][e25]. Eight guidelines mentioned neo-adjuvant treatment for cT1-2 tumours followed by local excision as an alternative treatment strategy, but only in trial setting [e01][e03][e06][e8][e10][e11][e20] [e21]. Additionally, the ESMO guidelines specifically mentioned contact radiotherapy or brachytherapy as an option for patients not fit for any type of surgery [e12]. Two guidelines advised TME for cT1N0M0, of which the Canadian guideline specifically mentioned that, if a patient consents with a higher risk on recurrence, a local excision is a viable option [e13][e26]. The NICE guideline from the United Kingdom stated that TME should be considered standard therapy for early rectal cancer as the evidence for all other treatment strategies is of inadequate quality [e18]. The European Union guideline refrained from recommendation based on cT1N0MO-stage [e11]. Six guidelines did not make a distinction between clinical- and pathological-staged rectal cancer separately, and therefore were not included in this analysis on clinical stage early rectal cancer [e02][e16][e09][e15][e19][e27].

Local excision is a safe approach for cT1N0M0 rectal cancer. Consensus, highest level of evidence: 1b.

cT2N0M0

None of the seventeen guidelines making a recommendation on this stage advised a local excision alone[e1][e3][e6][e7][e8][e9][e10][e11][e12][e13][e14][e15][e16][e21][e22] [e24] [e25]. One consensus statement[e20] advised neoadjuvant treatment followed by local excision and 10 guidelines mentioned neoadjuvant therapy followed by local excision as an option in trial setting only, in patients not fit for surgery or in patients refusing a TME [e01][e03][e06][e07][e10][e11][e12][e15][e16][e21]. Six guidelines did not address this specific stage [e02][e17][e18][e19][e26][e27].

For cT2N0M0 rectal cancer, TME should be considered standard of care. Consensus, highest level of evidence: 2b.

Local excision following neo-adjuvant therapy can be offered in trial setting or for patients not fit for or refusing major surgery. Consensus, Level of evidence: 2b.

3. Definition of high risk pT1 rectal cancer

Six out of the 24 included guidelines did not make a categorisation into low or high risk pT1 rectal cancer based on tumour characteristics [e9][e14][e15][e17][e18][e19].

Of the remaining guidelines, a pT1 tumour was defined as high risk in 13 out of the 18 guidelines if the pathological examination revealed at least one of the following characteristics: poor differentiation, lymphatic- or venous-invasion and a resection margin of less than 1mm [e01][e02][e06][e07][e08][e10][e11][e12][e16][e21][e22][e24][e25]. Regarding margin status, the Argentinian guideline used a different cut-off of <3 mm as high risk [e02]. A tumour size >3 cm was mentioned as an additional independent risk factor in six of the included guidelines [e1][e2][e7][e8][e17][e21].

Four of the included guidelines based the low/high risk classification of pT1 solely on SM-classification [E3][e13][e26][e27]. In eight guidelines, SM-classification was mentioned as independent factor among the other characteristics (i.e. poor differentiation, lymphatic-, venous invasion) [e6][e7][e10] [e12][e16][e22][e24][e25]. Four of these eight guidelines mentioned SM3 as high risk and four classified anything higher than SM1 as high risk [e6][e7][e10][e16]. The German and the EURECCA guidelines stated that current evidence was of inadequate quality to include SM-classification in the definition of low or high risk pT1 rectal cancer [e8][e22]. In conclusion, 12 out of 18 guidelines mentioned SM-3 as indicator for high risk pT1.

Tumour budding was mentioned as independent characteristic of high risk in four of the included guidelines [e7][e11][e25][e27]. Tumour budding is classified into three grades, which is based on the amount of individual cells and small clusters of tumour cells that infiltrate the interstitium at the tumour resection margin. Grade 1 being less than 4 tumour cells within the microscopic field, grade 2 with 5-9 cells, and grade 3 with more than 10 cells [e25]. Grade 1 budding was considered to be low risk, and Grade 2-3 budding was considered to be high risk pT1.

> *A pT1 rectal cancer is defined as high risk if any of the following characteristics is mentioned in the pathology report: poor differentiation, lymphatic- or venous invasion, a clear resection margin of less than 1mm and sm3. Consensus, Level of evidence: 2b.*

4. Treatment based on pathological stage (pT)

4a. pT1 Low risk (well-moderately differentiated, no venous invasion, no lymphatic invasion, <3-4cm, SM1-2)

Following local excision or polypectomy of a low risk T1 rectal cancer, nineteen [e01][e02][e03][e06][e07][e08][e09][e10][e11][e12][e13][e14][e16][e19][e20][e22][e24][e25][e27] papers stated that no adjuvant therapy (completion surgery or (chemo-) radiotherapy) was indicated. In five guidelines, there were no separate statements for risk categories of pT1, and adjuvant treatment after local excision was not mentioned [e15][e17][e18][e21][e26].

> *For pT1 low risk, local excision is deemed sufficient. Consensus, highest level of evidence: 1b.*

4b. pT1 high risk (poor differentiation, or venous invasion, or lymphatic invasion, or R1, or >3-4cm, or SM3)
Completion TME was recommended by 18 guidelines for high risk pT1 rectal cancer [e01][e02][e03][e06][e07][e08][e10][e11][e12][e13][e14][e16][e19][e20][e22][e24][e25][e27]. The Brazilian guideline [e09] advised adjuvant (chemo)radiotherapy, and nine other guidelines mentioned this as option in trial setting, or for patients not fit for or declining surgery [e07][e8][e10][e12][e13][e20][e22][e24][e27]. In addition, the French Thésaurus [e07] indicated contact radiotherapy as option for frail patients. Five documents [e15][e17][e18][e21][e26] did not clarify a specific advise on treatment for this stage.

> *Standard of care after local excision/polypectomy of high risk pT1 is completion TME. Consensus, Level of evidence: 2b.*
> *Adjuvant (chemo)radiotherapy could be an alternative for completion TME in trial setting, or for patients unfit for surgery. Controversy, highest level of evidence: 3b.*

4c. pT2
Seventeen guidelines [e01][e02][e03][e06][e07][e08][e10][e11][e12][e13][e14][e16][e19][e20][e22][e24][e27] recommended a completion TME after local excision of pT2 rectal cancer. Adjuvant radiotherapy was mentioned as an alternative for TME in the Brazilian guideline[e09] and considered as an alternative option in trial setting, or in patients not fit for surgery or declining surgery in 7 other guidelines [e07][e08][e09][e10][e12][e13][e20]. Six of the included papers did not make a statement on further treatment of locally excised pT2 rectal cancer [e15][e17]e18][e21][e25][e26].

> *Standard of care after local excision of pT2 rectal cancer is completion TME. Consensus, Level of evidence: 2b.*
> *Adjuvant (chemo-)radiotherapy following local excision for pT2 rectal cancer is an alternative for completion TME in selected patients or in trial setting. Controversy, Level of evidence: 3b.*

5. Treatment strategy for complete clinical response to neo-adjuvant treatment (ycCR / ycT0)
W&W was mentioned by 8 guidelines in patients with a clinical complete response (cCR) after chemoradiotherapy that was indicated based on a clinically advanced stage. The Dutch guideline considered TME surgery as standard of care independent of response after chemoradiotherapy [e01], and W&W for ycCR should only be performed in trial setting. Two guidelines [e07][e15] postulated W&W for fragile patients or patients who refuse surgery. Five other guidelines [e08][e13][e18][e21][e24] mentioned the novel concept of close monitoring for ycCR but stated that there is no high-quality supporting evidence yet. None of the included guidelines incorporated an exact definition on how cCR is or should be defined.

Excision of the scar in case of cCR should be considered according to 4 guidelines [e01][e13][e15][e16]. The French Thésaurus [e07] and EAES [e10] consensus statement proposed the excision of the scar in ycCR in the setting of a clinical trial. If local excision of a remaining scar after (chemo)radiotherapy has been performed, only one guideline specified the treatment strategy per specific ypT-stage. The Dutch guideline mentions that after local excision of the scar, surveillance can be considered in case of ypT0-1 if discussed during a MDT meeting in a centre with expertise in rectal preserving treatment. Completion TME is advised in case of ypT2-3 by this guideline.

W&W for ycCR with intensive surveillance by an experienced team can be considered, especially in frail patients and those refusing surgery, but should ideally be performed in the controlled setting of a trial. Local excision of the scar or small residual disease following (chemo)radiotherapy can be considered as alternative to TME surgery, with close surveillance for ypT0-1. Controversy, highest level of evidence: 3b.

6. Technique of local excision

A wide variety of different local excision techniques was described in the included guidelines: snare polypectomy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), transanal excision (TE), transanal endoscopic microsurgery (TEM), transanal minimally invasive surgery (TAMIS), posterior transphincteric resection, posterior proctectomy, and transcoccygial resection. TEM was the preferred technique for local excision according to 11 guidelines [e07][e08][e11][e12][e13][e14][e16][e20][e21][e22][e25]. Three guidelines considered TAMIS as equivalent [e01][e15] or alternative [e10] option for local excision. Endoscopic treatments (i.e. polypectomy, ESD and EMR) were indicated according to some guidelines [e06][e10][e18]. EMR is more commonly used for the resection of benign lesions and ESD is the preferred technique according to gastroenterologists if the lesion proved to be carcinoma and is small enough to be excised endoscopically. The European Commission guideline [e11] considered ESD inferior to TEM for rectal cancer. Conventional transanal excision was indicated as viable option in one guideline [e09], but was considered obsolete by 5 guidelines [e08][e11][e16][e20][e21]. Six guidelines [e03][e14][e17][e26][e27] did not specify which technique of local excision was advised.

A minimally invasive surgical approach is preferred for local excision of early stage rectal cancer, using either TEM or TAMIS. Consensus, highest level of evidence: 2b.

7. Surveillance protocol following rectal preservation

Of the 24 included guidelines, five mentioned a surveillance protocol after local excision of early rectal cancer [e01][e03][e11][e12][e22]. None of the included guidelines mentioned a follow-up protocol following W&W. The Dutch guideline recommended endoscopic inspection of the scar and pelvic MRI every 3-6 months in the first 2 to 3 years following local excision. The other guidelines recommended the use of

sigmoidoscopy combined with digital exam up to five years. Independently of type of resection, 14 guidelines recommended a surveillance protocol after curative treatment of rectal cancer in general [e01][e02][e03][e07][e08][e09][e11][e12][e13][e19][e22][e24][e25][e27]. Although the differences were small, they all proposed a different follow-up protocol. Six of these specifically stated that for pT1N0 and R0 resection, imaging-modalities and CEA-testing were of no proven value [e01][e11][e12][e13][e14][e16].

No uniform surveillance protocol following rectal preserving treatment of rectal cancer could be derived from the included guidelines. Endoscopic surveillance of the scar after local excision seems to be indicated. Controversy, highest level of evidence: 5.

DISCUSSION

This synopsis included 24 national and international guidelines or consensus documents with a statement on rectal preserving therapies for rectal cancer. Despite the growing attention and expanding application of this treatment strategy, this synopsis reveals that still only consensus exists for local excision of low risk T1 rectal cancer, although there is no uniformity how to stratify risk. It is generally agreed that TME surgery is standard of care for all other stages, and it is most commonly stated that rectal preserving alternatives should only be considered in patients unfit for radical surgery or in trial setting if mentioned at all. Unfit for surgery is never defined. Other topics with low level of agreement, reflecting the insufficient available evidence are MRI based lymph node assessment, W&W in complete responders after neoadjuvant therapy, definition and assessment of ycCR, and surveillance protocols after local treatment. Only a few guidelines included a statement on these topics. The original idea to conduct guideline synopses by the scientific committee of the ESCP was to identify the lacunae in the current evidence on specific topics and define areas of research. Therefore, these lacunae in rectal preserving treatment of rectal cancer will be discussed in the light of upcoming trials or the latest available evidence.

Emerging evidence and topics for further research

Despite the consensus achieved on the type of imaging that should be used for the assessment of rectal cancer, there was no consensus among the included guidelines regarding the definitions of clinical lymph node status if mentioned at all. The reported low sensitivity of 72-91% and 65-76% of endo-ultrasonography and MRI, respectively, has likely contributed to the observed variety among the guidelines (Topic 1).(5-8) Diffusion-weighted-MRI to assess nodal status has shown to increase the sensitivity and specificity. However, more prospective studies and uniformity in definitions are needed to increase the accuracy of preoperative staging modalities.(9, 10)

Consensus was observed on the approach of cT1N0M0 and pT1 low risk carcinomas, which can safely be treated with organ preserving local excision (Topic 2). Moreover,

the definition of characteristics associated with an increased risk on tumour recurrence (and therefore high risk pT1) was univocal among the guidelines regarding differentiation grade, lymphatic or venous invasion, resection margins and SM-classification. Nevertheless, more recently used characteristics such as size of the carcinoma and tumour budding were not embedded in the majority of guidelines (Topic 3). A recent retrospective study and systematic review showed tumour budding to be an independent predictor for increased cancer recurrence.(11, 12) However, a more standardized method of assessment is needed before tumour budding can be implemented in current clinical practice.

Neoadjuvant radiotherapy for clinically staged cT1-3N0M0 should still only be applied in the controlled setting of a clinical trial. Neoadjuvant therapy that would otherwise not have been given for these stages, is associated with an increased risk of complications following surgery, long-term toxicity, and impaired functionality. These disadvantages should be weighed against the oncological safety and probability of preserving the rectum on the long term. Results of the recently published CARTS study showed that organ preservation with neoadjuvant chemoradiotherapy followed by TEM was possible in half of the patients with a cT1-3N0M0, but at the expense of a mortality rate of 3.6% related to the chemoradiotherapy and substantial overtreatment in those patients insufficiently responding.(13) In the UK TREC trial, cT1-2N0M0 patients were randomised between TME and short-course radiotherapy followed by TEM. Next to, the recently published GRECCAR-2 trial successfully randomised patients with good response to neo-adjuvant radiotherapy for a cT2-3 stage between local excision and TME.(14) These trials demonstrate the feasibility of randomising patients with early rectal cancer to standard TME surgery and a rectal preserving strategy. The upcoming multinational STAR-TREC trial will hopefully provide additional high quality evidence to enable evidence based treatment recommendations for rectal preservation based on clinical stage (Topic 4). As shown by Bach et al., a locally excised rectal lesion that is thought to be benign during preoperative work-up, is found to be malignant in up to 40% of the patients.(15) In the presence of high risk features these patients should undergo completion TME according to current guidelines as the associated risk of local recurrence is around 15, but might be as high as 42% if several risk factors are present (Topic 4).(15) The current evidence on adjuvant radiotherapy following local excision for this type of early rectal cancers is limited to small retrospective series with heterogeneous cohorts.(16) The currently recruiting TESAR Trial (NCT02371304) is aiming to provide the needed evidence for this subgroup of patients.(17)

cCR after neoadjuvant therapy is observed in 12% -to 30% of the patients but depends on several factors such as initial stage, type of neoadjuvant treatment and timing of response evaluation.(18, 19) Moreover, it is important to mention that in current literature, there is still substantial variation in the exact definition of a cCR. A combination between digital rectal examination, endoscopy, CEA measurement, CT

and MRI seems to be most accurate in evaluating the response.(20) The exact criteria for cCR were, however, not assessed in the included guidelines. Reported studies on complete responders reflect a selected subgroup of patients with favourable tumour characteristics, which is important to keep in mind when interpreting the data. In a propensity matched analysis, Renehan et al. showed that 60% of the complete responders can be treated in an organ preserving manner.(19) Adequate surveillance is needed to detect the one third of patients with a local regrowth at a salvageable stage. It should be emphasised that the W&W strategy following cCR needs specific expertise and results should be closely monitored as part of a clinical trial or registry. Improving the clinical complete response rate in early rectal cancer is one of the research questions currently being addressed. Furthermore, there is a need to better define how (local excision, digital rectal examination, endoscopy, imaging), and at which interval from radiotherapy cCR should be assessed (Topic 5).

Few studies have directly compared TEM versus TAMIS for local excision of early cancers and both are recommended as local excision technique (Topic 6). One retrospective single-centre cohort study from Melin et al. compared 40 patients undergoing TEM with 29 patients that underwent a local excision with TAMIS.(21) They reported a non-significant trend towards a higher involved margin rate of the TAMIS approach: 2.5% vs. 10.3%, respectively . As the basic principle of both surgical options is comparable, the additional value of an RCT on this topic seems limited.

Regarding surveillance protocols following organ preservation, the paucity found in standardized follow-up protocols among the included guidelines is inevitably a result of the limited evidence available. An intensified schedule, which includes endoscopic inspection of the scar and pelvic MRI for lymph node assessment, seems warranted following rectal preserving strategies. Frequency and duration have to be defined, also from a cost-effectiveness perspective.

CONCLUSION

Although rectal preserving treatment strategies for rectal cancer are mentioned to a certain extent in the majority of national and international guidelines, the exact boundaries and indications of use are still to be defined. Multiple trials are currently recruiting to define the optimal neoadjuvant treatment strategies, improve outcomes and further determine the exact definitions of early rectal cancer. Awaiting these results, rectal preservation should still be seen as an experimental treatment strategy. Uniformity in terms of lymph node assessment on imaging, surveillance protocols and risk assessment based on pathological examination is needed prior to definitive implementation into clinical practice.

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Local recurrence after local excision of early rectal cancer: a meta-analysis of completion TME, adjuvant (chemo) radiation, or no additional treatment

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ABSTRACT

Background: After local excision of early rectal cancer, clinical dilemmas arise when balancing the risks of recurrence and treatment related morbidity, but few data are available to support shared decision-making. The aim of this meta-analysis was to determine oncological outcomes after local excision of pT1-2 rectal cancer followed by no additional treatment (NAT), completion total mesorectal excision (cTME) or adjuvant (chemo)radiotherapy (aCRT).

Methods: A comprehensive search was conducted in PubMed, Embase and the Cochrane Library. Primary outcome was local recurrence (LR). Statistical analysis included weighted average of proportions.

Results: Of 73 included observational cohort studies, 62 evaluated NAT, 13 cTME, and 28 aCRT. The included studies comprised 4 793 patients. The LR rate for NAT in low-risk pT1 tumors was 6.7% (95% CI 4.8-9.3). No LR occurred in low-risk pT1 tumors after cTME or aCRT. The LR rate for high-risk pT1 tumors was 13.6% (95% CI 8.0-22.0) for local excision only, 4.1% (95% CI 1.7-9.4) for cTME, and 3.9% (95% CI 2.0-7.5) for aCRT. The LR rate for pT2 tumors was 28.9% (95% CI 22.3-36.4) after NAT, 4.3% (95% CI 1.4-12.5) after cTME and 14.7% (95% CI 11.2-19.0) after aCRT.

Conclusion: Substantial risk of local recurrence has been reported for NAT after local excision, especially for high-risk pT1 and pT2 rectal cancer. Completion TME provides the lowest recurrence risk. The alternative, aCRT, showed comparable outcomes with cTME in high-risk pT1 tumors, but a higher risk in pT2 tumors. These findings may facilitate shared decision-making in patients with early rectal cancer.

INTRODUCTION

Screening programs for bowel cancer have resulted in a substantial shift towards earlier stages of colorectal cancer.(1, 2) Except for low-risk pT1 tumours, the current standard treatment for rectal cancer is a total mesorectal excision (TME) with or without neoadjuvant (chemo)radiotherapy depending on tumour stage.(3) This radical approach is associated with morbidity, long-term functional impairment and consequently a decrease in quality of life (QoL).(4, 5) The increased incidence of early lesions, treatment related morbidity and the impact of treatment on QoL create a clinical need for organ preservation, especially in patients with early rectal cancer.(3, 6)

Clinical staging by endoscopy, MRI, and endoscopic ultrasound (EUS) has shown low accuracy in distinguishing low-risk T1 from high-risk T1 or early T2 rectal cancers.(7, 8) Therefore, local excision as initial diagnostic procedure is an attractive approach in early rectal cancer. This might turn out to be therapeutic in selected patients based on the histopathological results and is associated with low morbidity and good functional outcomes.(9) For high-risk pT1 tumours, local excision is not considered oncologically safe due to a higher risk of recurrence.(3, 10, 11) Despite the recommendations of guidelines, patients and physicians often refrain from completion TME (cTME) in case of high-risk tumours.(12) Clinical data supporting this strategy are scarce and relatively high recurrence rates have been reported.(11, 13-16) A promising organ sparing alternative after local excision is adjuvant (chemo)radiotherapy (aCRT), which is being evaluated in trials.(17) Solid long-term outcome data of all treatment options are essential to develop a valid clinical decision-making algorithm for both patients and physicians.

The aim of this meta-analysis was to provide an update on a previous meta-analysis and to evaluate the rising amount of data for the three treatment strategies after local excision of pT1-2 rectal cancer, namely no additional treatment (NAT), cTME, and aCRT. (18) For these treatment strategies local recurrence rates, distant recurrence rates and both disease-free and overall survival rates were evaluated.

METHODS

Search strategy

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.(19) Comprehensive searches regarding the treatment options were performed in the bibliographic databases of PubMed, Embase and the Cochrane Library for NAT (Appendix S1) and for cTME and aCRT (Appendix S2). Compared with the previous meta-analysis, NAT was added as a treatment option and an additional subgroup analysis was performed regarding low- and high-risk pT1 tumours.(18) Literature searches were carried out on August 26th 2019

and contained all available records to the date of the search. Studies were reviewed for eligibility by two independent researchers and a third in case of discrepancies.
Studies were considered eligible if pT1-2 rectal carcinomas were included, treated with local excision followed by either NAT, cTME or aCRT, and met the following inclusion criteria: local recurrence rates were reported, a minimum of ten patients were included, articles were published since 1990 in the English language, and median length of follow-up was at least 36 months. Exclusion criteria were neoadjuvant treatment, distant metastasis at the time of local excision and studies that included patients with suspected nodal metastases on MRI. Studies that did not describe pT stage, treatment modality or distinction between colon or rectal cancer were considered ineligible. Animal studies, studies with overlapping data, reviews, and letters were excluded.

Quality assessment

In order to assess the quality of the included studies, the Methodological Index for Non-Randomised Studies (MINORS) instrument was used.(20) Each item was scored independently by two authors from 0 to 2 points; 0 indicating that it was not reported, 1 indicating that it was inadequately reported and 2 indicating that it was reported adequately. In addition to the eight established elements, an item considering allocation bias was added to evaluate whether the treatment of choice was according to a protocol, to surgeon's preference or whether the rationale was not described.

Outcome measures and statistical analysis

Primary outcome was local recurrence, defined as endoluminal recurrence or nodal recurrence in the pelvis. This included patients with isolated local recurrence as well as patients with distant metastases. Secondary outcomes were distant metastases, disease-free survival (DFS) and overall survival (OS). Subgroup analyses were performed to differentiate outcomes for tumour stage (pT1 vs. pT2). Additionally, the current meta-analysis added subgroup analysis regarding low- and high-risk pT1 tumours. Low- and high-risk tumours were analysed separately if the presence of risk factors was described. High-risk tumours were defined as tumours with at least one of the following histopathological risk factors: lymphovascular invasion, poor differentiation, deep submucosal invasion (sm3, Haggitt 4 or ≥1000 μm), tumour budding or positive resection margins (margin <1mm or tumour in resection plane).(21, 22) In low-risk tumours, these factors had to be absent. A weighted average of proportions was calculated using the generic inverse-variance method and a random effects model. After natural log transformation of the individual proportions final results were back transformed. Heterogeneity was assessed by the I^2-statistic, an I^2 of 75%-100% was determined as considerable heterogeneity, hence 75% was used as cut-off value.(23) One pooled analysis regarding NAT in pT2 tumours showed statistically significant heterogeneity (I^2 55%, p<0.01) but was kept in the analyses. Due to heterogeneous and scarce reporting of OS and DFS, no weighted averages were determined for these outcomes, but the range was provided. Survival rates were not incorporated if studies

included patients with other tumour stages than pT1-2, without specified survival rates. Disease-free survival was defined as survival without local or distant recurrence.

RESULTS

Included studies

The literature searches resulted in a total of 14 907 studies. The selection process according to the PRISMA guidelines is presented in figures 1 and 2. A total of 76 cohort studies were included in this systematic review and meta-analysis, compared to nineteen studies in the previous meta-analysis.(18) Sixty-two publications on local excision only were included, comprising 3 050 pT1 and 545 pT2 patients.(11, 13-16, 24-80) Thirteen studies reported outcomes of local excision followed by cTME, comprising 180 pT1 and 70 pT2 patients.(11, 33, 35, 44, 56, 59-61, 73, 78, 81-83) Lastly, 28 studies on aCRT were included and contained 385 pT1 and 444 pT2 patients.(24, 28, 29, 32, 34, 35, 38, 41, 42, 48, 52, 54, 59, 60, 63, 64, 67, 72, 74, 75, 84-91) For the subgroup analysis on low- and high-risk pT1 tumours a total of 29 studies were included regarding low-risk pT1 tumours without additional treatment, one study for cTME, and one for aCRT. The total amount of studies that described high-risk pT1 tumours were 19 for NAT, 7 for cTME, and 12 for aCRT. Twenty-nine of the 62 studies on local excision only described active surveillance during follow-up. For aCRT 14 of the 28 studies reported close follow-up schemes. Ten of the 73 (13.2%) included studies were prospective cohort studies. Eight prospective studies regarded NAT after local excision, one prospective study included cTME patients and three studies evaluated aCRT prospectively. Different local excision techniques were utilised in the included studies. For the NAT treatment group 52 of the 62 studies evaluated surgical modalities of local excision, five of the 62 studies investigated endoscopic local excisions, and 5 studied either both or did not describe the local excision technique. For cTME nine out of thirteen studies evaluated surgical local excision, three studies investigated endoscopic local excision and one study included both surgical and endoscopic techniques. In studies regarding aCRT 24 out of 28 studies evaluated surgical excision techniques, four studies investigated both surgical and endoscopic techniques or did not describe the utilised excision method. Detailed information concerning the characteristics of all included studies is provided in table S1-3 of the supplementary material.

Local recurrence rate

The local recurrence rate of patients with a pT1 tumour without additional treatment was 8.1% (95% CI 6.6-9.9) (Table 1). Completion TME after local excision of a pT1 tumour resulted in a local recurrence rate of 2.8% (95% CI 1.2-6.5). Weighted local recurrences for patients with a pT1 tumour receiving aCRT were 4.8% (95% CI 2.3-9.8).

For low-risk pT1 tumours, NAT showed a local recurrence rate of 6.7% (95% CI 4.8-9.3). No recurrences were reported after cTME and aCRT in patients with low-risk pT1 lesions, based on one study for each treatment strategy (Table 1).

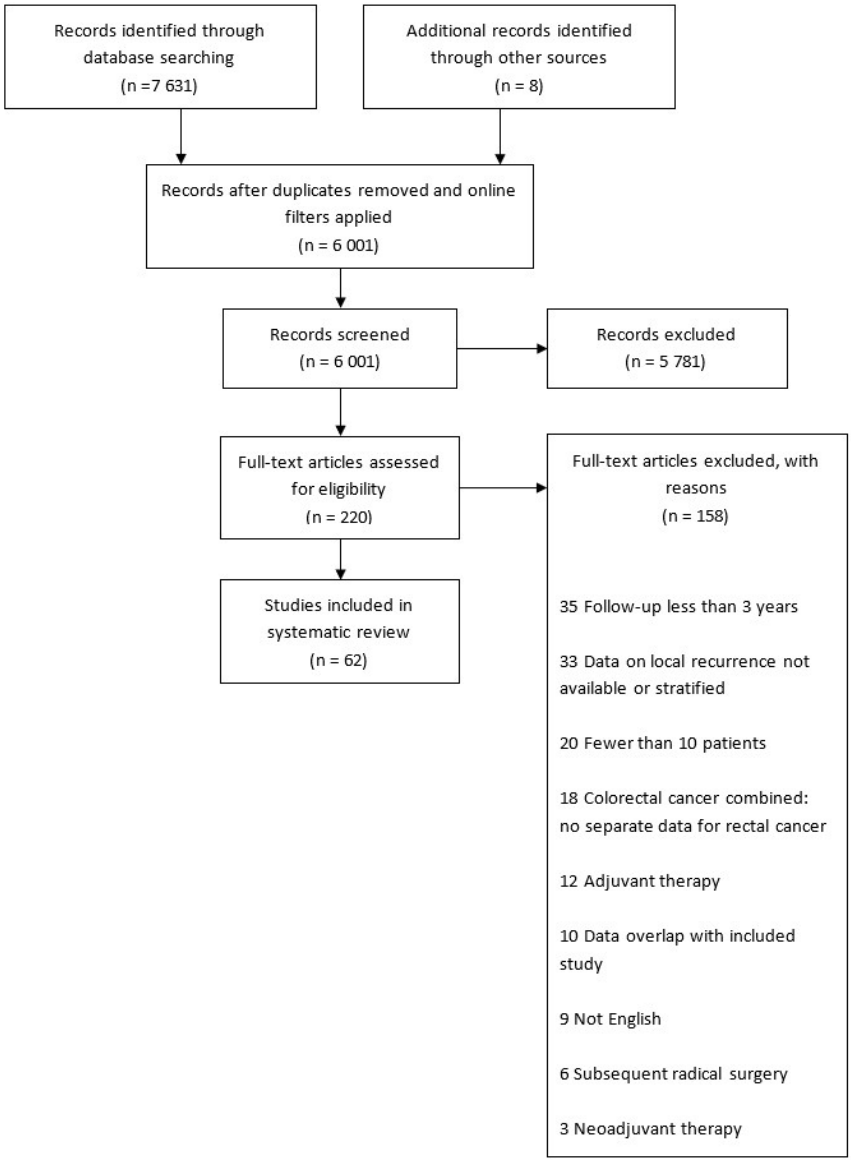

Figure 1 Flow chart of literature search: local excision without additional treatment

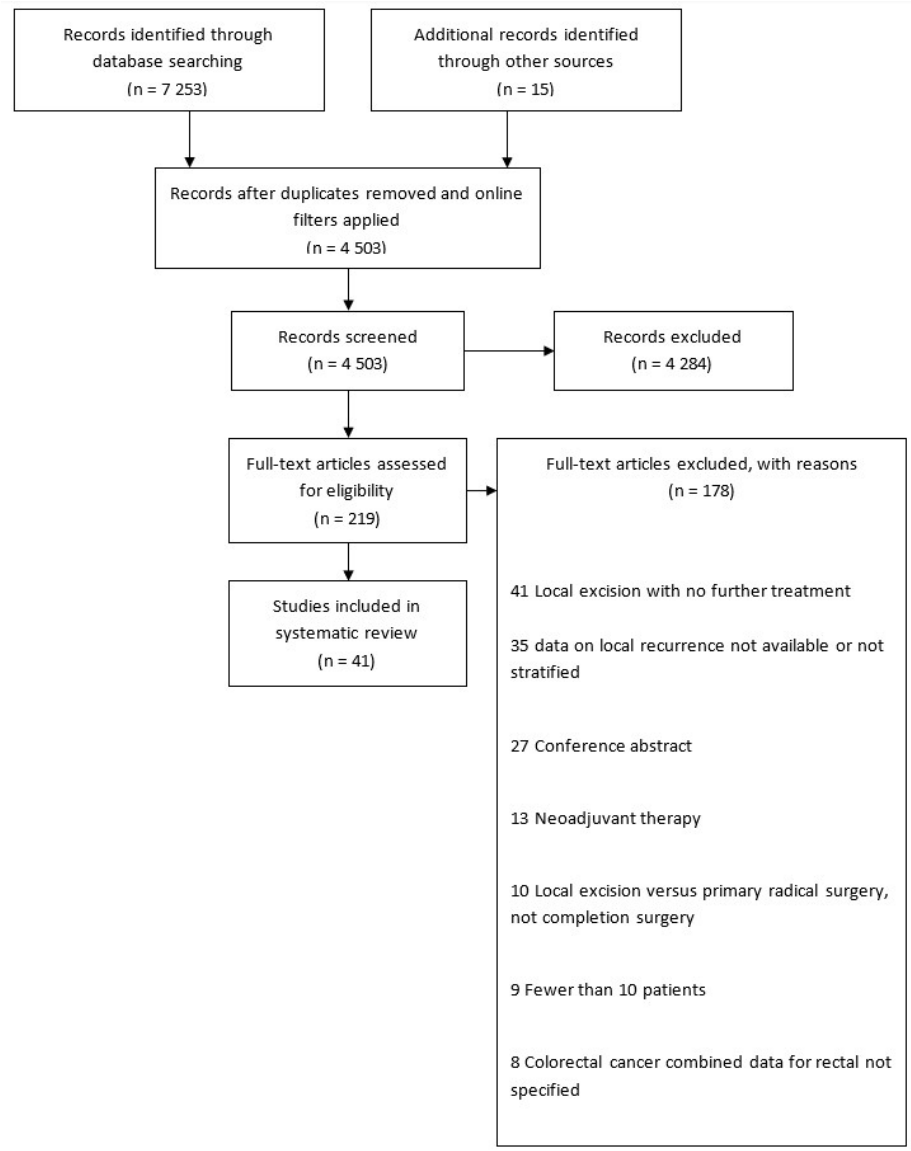

Figure 2 Flow chart of literature search: adjuvant (chemo)radiation or completion total mesorectal excision following local excision of early rectal cancer

Table 1 Local recurrence weighted average in percentages (95 percent CI)

	NAT	event/ total	cTME	event/ total	aCRT	event/ total
pT1	8.1 (6.6 – 9.9)	268 / 3 050	2.8 (1.2 – 6.5)	5 / 180	4.8 (2.3 – 9.8)	24 / 385
pT1 LR	6.7 (4.8 – 9.3)	75 / 1 019	0	0 / 28*	0	0 / 1*
pT1 HR	13.6 (8.0 – 22.0)	44 / 282	4.1 (1.7 – 9.4)	5 / 123	3.9 (2.0 – 7.5)	10 / 254
pT2	28.9 (22.3 – 36.4)	136 / 545	4.3 (1.4– 12.5)	3 / 70	14.7 (11.2 – 19.0)	66 / 444

LR: low-risk, HR: high-risk, NAT: no additional treatment, cTME: completion total mesorectal excision, aCRT: adjuvant (chemo)radiotherapy. *One study.

Weighted local recurrence rates of high-risk pT1 tumours were 13.6% (95% CI 8.0-22.0), 4.1% (95% CI 1.7-9.4), and 3.9% (95% CI 2.0-7.5) for NAT, cTME, and aCRT, respectively. In patients with a pT2 tumour, NAT was associated with an local recurrence rate of 28.9% (95% CI 22.3-36.4). This analysis showed significant heterogeneity (I^2 55%, p<0.01) (Figure S1). After cTME, the local recurrence rate was 4.3% (95% CI 1.4-12.5). In pT2 tumours treated with aCRT, 14.7% (95% CI 11.2-19.0) of the patients had a local recurrence. Local recurrences were defined as patients with either local recurrence only or patients with both local and distant recurrence. These proportions are depicted in Table S4. Study specific local recurrence rates are reported in table S5-10 and figure S1-6.

Distant metastasis

The weighed distant metastasis rate in patients with pT1 tumours that underwent NAT was 3.4% (95% CI 2.5-4.6), for cTME the distant recurrence rate was 4.9% (95% CI 2.4-9.4) and for aCRT 5.0% (95% CI 3.0-8.3) (Table 2, Table S5-7, Figure S6-9). Distant metastasis rates for low- and high-risk tumours are described in table 2. In pT2 tumours, weighed averages of distant metastasis were 6.2% (95% CI 2.8-13.0) for NAT, 7.3% (95% CI 2.8-17.8) for cTME, and 5.8% (95% CI 2.7-11.9) for aCRT.

Table 2 Distant recurrence weighted average in percentages (95 percent CI)

	NAT	event/ total	cTME	event/ total	aCRT	event/ total
pT1	3.4 (2.5 – 4.6)	101 / 2 658	4.9 (2.4 – 9.4)	8 / 165	5.0 (3.0 – 8.3)	14 / 280
pT1 LR	3.2 (2.2 – 4.7)	25 / 783	3.6	1 / 28*	0	0 / 1
pT1 HR	7.2 (3.6 – 13.9)	20 / 233	5.6 (2.5 – 11.8)	6 / 108	3.9 (1.9 – 7.5)	8 / 208
pT2	6.2 (2.8 – 13.0)	28 / 398	7.3 (2.8 – 17.8)	4 / 55	5.8 (2.7 – 11.9)	17 / 254

LR: low-risk, HR: high-risk, NAT: no additional treatment, cTME: completion total mesorectal excision, aCRT: adjuvant (chemo)radiotherapy. *One study.

Survival

Survival data are presented in table 3 and table S5-7. Five year DFS for local excision without additional treatment in pT1 tumours was reported in eight publications (range

66.6%-97.0%) with two out of eight studies reporting 5 year DFS above 85%. Only one study reported a 5-year DFS rate of 81.4% after cTME. For aCRT in pT1 tumours the 5 year DFS was reported in six studies (range 59%-100%) of which five reported DFS of more than 85%. For pT2 tumours 5-year DFS of NAT was reported in three publications as 64.8%, 80.5%, and 92.8%. One study reported a 3-year DFS of 100% after cTME. Four studies reported 5-year DFS rates for treatment with aCRT in pT2 tumours, which ranged from 58% to 78.2%.

The 5-year OS rate for NAT in pT1 tumours was reported in fifteen studies (ranged 65.3%-100.0%), and exceeded 85% in one third of the studies. After cTME 5-year OS was 92.3%. Overall survival following aCRT was reported in six studies (range 63.0%-98.0%), three out of six studies showed OS of over 85%. For pT2 tumours the 5-year OS rate in patients without additional treatment was reported in seven publications (range 30.0%-94.7%), two of these studies described an OS rate of more than 85% (Table 3, S5-7). Five studies reported 5-year OS for pT2 tumours after aCRT (range 58%-93.3%), in two out of five studies OS exceeded 85% (Table 3, S5-7).

Table 3 Five-year overall and disease free survival rates

		NAT	n	Reported survival >85%	cTME	n	aCRT	n	Reported survival >85%
pT1									
	DFS	66.6 - 97.0%	8	2 / 8	81.4%	1	59.0 - 100%	6	5 / 6
	OS	65.3 - 100%	15	5 / 15	92.3%	1	63.0 - 98.0%	6	3 / 6
pT2									
	DFS	64.8 - 92.8%	3	1 / 3	100% *	1	58.0 - 78.2%	4	0 / 4
	OS	30.0 - 94.7%	7	2 / 7	N.R.		58.0 - 93.3%	5	2 / 5

DFS: disease free survival, OS: overall survival, NAT: no additional treatment, cTME: completion total mesorectal excision, aCRT: adjuvant (chemo)radiotherapy, n: number of studies reporting this value. *: 3-year DFS.

DISCUSSION

This meta-analysis shows that patients who undergo NAT after local excision of pT1-2 rectal cancer have a high risk of local recurrence, especially in high-risk pT1 and pT2 lesions. The risk of local recurrence after aCRT for high-risk pT1 tumours seems to be similar to cTME. For pT2 tumours, aCRT seems less effective compared to radical surgery. This is the first meta-analysis evaluating the results of the three treatment options after local excision of rectal cancer, and may support both patients and clinicians in decision-making.

Recently, Antonelli et al. reviewed local recurrence rates for pT1 colorectal tumours that were excised endoscopically without additional treatment. An overall recurrence rate of 9% for rectal cancer was reported.(92) This reported percentage of local recurrence is consistent with the outcomes of this review. The current data showed that high-risk pT1 is associated with a relatively high risk of recurrence of 13.6% after local excision only, which is consistent with other series.(46, 53) An older large cohort of Bach et al. showed an even higher percentage of 19% local recurrence for pT1 tumours. The relatively high 29% local recurrence rate for locally excised pT2 tumours in the study from Bach et al. corresponds to this study's findings.(10) Other studies confirmed high local recurrence rates for pT2 cancer, and cTME is recommended.(93, 94) The data of aCRT after local excision in early rectal cancer are scarce. Most series are hampered by the lack of standardised histopathological evaluation distinguishing low-risk pT1 from high-risk pT1. Jeong et al. evaluated one of the largest cohorts of 83 patients, of whom 3.6% had a local recurrence.(85) A review by Cutting et al. showed local recurrence rates that were comparable to this review, 5.8% for pT1 and 13.8% for pT2 tumours.(95) An earlier meta-analysis by this study group, not incorporating patients without additional treatment, reported a higher percentage of local recurrence of 10% in pT1 tumours, and similar results of 15% local recurrence for pT2 tumours.(18) The largest study of endoscopically resected tumours followed by cTME of Tamaru et al. included 56 pT1 tumours and showed a local recurrence rate of 3.6%.(73) Borschitz et al. described the highest number of cTME's after transanal endoscopic microsurgery and reported a local recurrence rate of 5.3% for high-risk pT1 tumours and 10% for pT2 tumours, which is higher than the pooled outcomes reported in the current review.(11)

The occurrence of distant metastases was comparable for the three treatment strategies, with averages between 3.4% and 5.0% for pT1 lesions and 5.8% to 7.3% for pT2 lesions. This is lower than rates reported elsewhere. In a study of locally excised pT2–3 rectal cancers, distant metastases were observed in 16 per cent at 3 years of follow-up of patients who underwent NAT or transanal endoscopic microsurgery followed by cTME.(96) In the previous review, the weighted average distant recurrence rate was 9 per cent in patients treated with aCRT or cTME.(18) It is not expected that the type of treatment influences the occurrence of distant metastasis, but it is more likely that local recurrence is associated with an increased risk of distant metastases. However, aspects as tumour biology and the occurrence of local recurrence may influence the risk of distant metastasis. These hypotheses cannot be confirmed based on this review, but are in line with other studies.(97, 98)

The intensity of surveillance of patients with NAT differed among the studies. About half of the studies reported endoscopic, MRI and/or EUS surveillance every three to four months during the first two or three years after local excision. A large share of studies (31 of 73) did not report specific follow-up schemes. Active surveillance of both local and distant recurrences is crucial in an organ preserving strategy of high-

risk tumours. Unfortunately, the type (i.e. endoluminal or nodal) and stage of local recurrences were not reported in the vast majority of the included studies. Few studies have reported eligibility and outcomes of salvage treatment in case of local recurrence after local excision.(99-101) Based on this limited evidence, the proportion of patients deemed eligible for salvage surgery varies between 73% and 93%.(13, 100-103) Salvage surgery is associated with more extensive procedures and low rates of sphincter preservation. Weiser et al. described a cohort of 50 patients that underwent salvage surgery; 55% of these patients required an extended pelvic resection.(104) Besides, in three studies regarding salvage treatment, in approximately two-thirds of the patients who underwent salvage surgery the sphincter could not be preserved. (100, 101, 105) Moreover, in patients eligible for curative salvage surgery the survival rates are low. Several studies showed that 5-year OS rates after salvage treatment are around 50%.(100, 104, 106) Limited data is available on cancer specific survival after salvage treatment. Doornebosch et al. reported a 58% 3-year cancer specific survival and Vaid et al. a 53% 5-year cancer specific survival.(13, 103) A systematic review by Jones et al. reported a disappointing 5-year OS rate of 50% after salvage surgery as well, presumably due to the increased incidence of distant metastasis.(99) Conceivably, with adequate follow-up, local recurrences might be detected in an early stage. If case clear resection margins are achieved, 5-year OS was estimated at 59% by Weiser et al. In contrast to a 0% 5-year OS rate in incomplete resections.(104) While the data of the current review seem more robust than previous reports, a substantial gap remains regarding high-quality data and appropriate reporting of long-term outcomes of local treatment of early rectal cancer, which emphasizes the need for clinical trials.(18) The advantages and disadvantages (i.e. morbidity, function, and oncological outcomes) of the three treatment options should be contemplated for each patient individually. The increase in risk of recurrence that is accepted in order to preserve the rectum is unclear and may differ between patients and physicians. Eventually, the decision for rectum preserving treatment depends on both patient preferences and tumour characteristics, and should be based on shared decision-making.

An alternative strategy to accomplish organ preservation is neoadjuvant CRT, which has shown to downsize and even cause complete remission in over 50% of patients. (107, 108) However, patients without complete remission will require TME surgery. This implies that neoadjuvant CRT led to overtreatment of these non-or partially responding patients and likely resulted in increased morbidity. More importantly, since clinical staging by imaging has shown to lack accuracy this treatment strategy incorporates patients with low-risk tumours as well, who could have been treated with local excision only.(7, 8) For this reason, a strategy that consists of local excision of small lesions without signs of risk factors on preoperative imaging seems more attractive. Based on the histopathological risk factors, additional treatment can be patient tailored.

The current meta-analysis is based upon extensive data, including 73 studies, compared to nineteen in the previous meta-analysis.(18) Besides the newly added third treatment strategy, NAT, which included 62 studies, the number of studies evaluating cTME and aCRT doubled to thirteen and 28 studies, respectively. Yet, this study was limited by the heterogeneous character of the included studies and selection bias in allocated treatment. A variety in follow-up protocol, follow-up length, sample size and type of adjuvant treatment was observed. In some studies, patients underwent radiotherapy without concurrent chemotherapy. Besides, NAT was often allocated to patients unfit for surgery or patients that refused additional treatment and presumably led to selection bias. Due to the variability in follow-up, local recurrence rates were not correlated to follow-up length or protocols. Despite these methodological differences it was decided to perform a pooled analysis. Quality assessment according to the MINORS checklist revealed that almost ninety percent of the included studied was carried out retrospectively (Table S11-12). A large amount of studies did not describe the histopathological inclusion criteria in detail. The definitions of histopathological risk factors varied, for instance some studies reported a margin of <1mm as a risk factor, whereas other studies defined this by carcinoma in the resection plane. Moreover, deep submucosal infiltration was determined to be a histopathological risk factor. However, more recent evidence shows that deep submucosal invasion only is not a strong risk factor in multivariate analysis for lymph node metastases.(109) Nevertheless, this subgroup analysis for low- and high-risk pT1 tumours was performed because it provides important information in clinical decision-making, and reporting overall local recurrence rates only would have led to additional bias. Data of pT2 tumours are heterogeneous and will likely include a proportion of patients with nodal disease due to underreporting of inclusion criteria and suspected nodal involvement on preoperative imaging. Besides, in studies on NAT and aCRT patients with unidentified nodal disease might have been included, whereas these patients were excluded in studies on cTME. These issues may have influenced the outcomes. Survival data were not reported sufficiently enough to pool and might have been influenced by the selection of patients for each treatment strategy. For these reasons only ranges could be described and no conclusions could be drawn based on the available data. A potential confounder is the method of local excision. The majority of included studies evaluated surgical local excision techniques. Further research is needed to study differences in outcomes within and between surgical and endoscopic techniques of local excisions.(110, 111) In addition, the location of local recurrence (i.e. endoluminal, mesorectal or lymph node involvement), was generally not reported, but is of value in decision-making for salvage treatment. Despite these limitations, it was attempted to minimize heterogeneity by sustaining strict inclusion criteria and by reporting data for the included subgroups only.

This meta-analysis is the largest set of data evaluating treatment options after local excision. The current data shows that local excision only cannot be recommended for high-risk pT1 and pT2 tumours. Adjuvant chemoradiotherapy might be a good

alternative for high-risk pT1 tumours, although for pT2 tumours a relatively high local recurrence rate is observed. Completion TME surgery for overall pT1 and pT2 tumours is associated with lowest risk for recurrence. Data from high-quality trials with long-term outcomes and sufficient sample sizes are awaited to define the exact value of the three options after local excision of high-risk pT1 and pT2 lesions.(17)

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Organ Preservation and Palliative Options for Rectal Cancer

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INTRODUCTION

Local excision is a well-accepted organ preserving method for early rectal cancer with substantial lower morbidity and impact on quality of life compared to radical surgery. However, only rectal cancers staged as a T1 tumor limited to the superficial third of the submucosa (sm1) and less than 3 cm in diameter without signs of poor differentiation, lymphatic or vascular invasion, budding or clustering in the final pathology are oncologically safely treated with radical local excision (1). These tumors have local recurrence rates of less than 5%. Small locally excised lesions with more risk factors as budding, poor differentiation and lymphovascular invasion or even T2 lesions have been associated with relatively high recurrence rates (2-4). Due to the increased recurrence rate, most guidelines recommend completion radical surgery after local excision of high risk lesions (5).

Local excision for palliation could be considered in patients who are either too fragile for or who refuse radical surgery. This seems to be a valuable option for those that have symptomatic bleeding, changed defecation or even incontinence. However, local excision alone for higher risk tumors in the rectum is not without risks. The relatively high recurrence rate within 2-3 years is a substantial problem, since recurrences are often symptomatic. Combining local excision with radiation for palliative reasons could be an option, but unfortunately data to support this theory are scarce.

Other organ preserving strategies after local excision of high risk lesions are being investigated in prospective cohorts and randomized trials. A potential curative option is adjuvant chemoradiation (CRT) following local excision, which has proven to decrease local recurrence rates and offers acceptable morbidity with organ preservation. The other option is no further therapy, but instead offer close surveillance with salvage radical surgery if a local recurrence presents itself (about 20%).

Several combinations of local excision, radiotherapy, chemotherapy and/or close observation are being investigated for treatment of higher staged tumors. The aim of this chapter is to summarize data of organ preservation options with a focus to palliative options.

TREATMENT OPTIONS

Local excision

Treatment with solely local excision offers the lowest burden for patients, since it is a minimally invasive technique and results in low morbidity and colostomy rates. You et al. reported an overall 30-day morbidity rate of 5.6% compared to 14.6% for radical resections, because of less gastrointestinal and infectious complications, with a

consequent shorter hospital stay after local excision. (6) However, the question remains whether it is a sufficient treatment since local excision only treats the primary tumor and not the potential remaining tumor cells in the mesorectum. The clinically pathological features such as depth of submucosal invasion, differentiation, lymphovascular invasion, budding, and clustering are related to recurrence, whether endoluminal or within the mesorectum. When local excision is carried out, the surrounding muscular wall and mesorectum are left untreated. Therefore, tumor cells are potentially left behind where they may propogate and eventually develop into a clinically detectable local recurrence.

Many cohorts and population-based studies have provided data concerning oncological outcome after local excisions for T1 and T2 tumors. A meta-analysis of local excision as sole treatment, covering all published data from 1990 to 2018, revealed local recurrence rates of 10% in 2120 patients with a T1 tumor, and 32% in 357 patients with a T2 tumor as shown in Table 1 [Tuynman et al in preparation (7)]. Distant failures occurred in 6% of 1805 patients, and 12% of 230 patients with respectively T1 and T2 tumors. The substantial increase in recurrences of T2 tumors indicates the reduced effectiveness of local excision for more advanced early rectal cancer.

Table 1 Recurrence rates.

	T1	T2	T3
Local recurrence			
LE	10% (n=2120)	32% (n=357)	58% (n=19)
LE + adjuvant	7% (n=278)	16% (n=382)	33% (n=27)
Distant recurrence			
LE	6% (n=1805)	12% (n=230)	31% (n=13)
LE + adjuvant	5% (n=214)	7% (n=254)	4% (n=23)

n = number of patients included in this analysis; LE = local excision; adjuvant = (chemo)radiation

The recurrence rates after local excision of T3 cancer are expected to be even higher and are the reason that local excision for T3 is not supported by clinical guidelines as treatment strategy with curative intent. As expected, data is scarce concerning this group of advanced disease. Some publications report a few cases of patients who refused radical surgery or were deemed unfit for major surgery. In seven publications which address this subject, an overall recurrence rate of 68% (15 of 22 patients) was reported (8-14).

This increase in recurrences might be an acceptable clinical outcome if a radical resection is not desirable nor possible in frail patients who present unacceptably high risk of perioperative morbidity and mortality. Therefore, expected longevity and predicted survival rates are important factors when a deliberate choice for a sub-standard operation is carried out by performing local excision. Allaix et al. (15) reported

5-year survival rates of 76% in 32 patients after TEM, and 96% of 33 patients after anterior resection or APR. However, radical resection was indicated in all patients. Those who underwent a TEM procedure were either not fit for surgery or refused radical surgery. A meta-analysis showed overall 5-year survival rates of 65% to 100% for T1 tumors, and 30% to 95% for T2 tumors (7). The majority of all recurrences appears within 3 years after initial treatment. Salvage treatment usually consists of major surgery or less effective radiotherapy, and it is often associated with complications.

In conclusion, local excision for rectal cancer is accompanied by low morbidity rates and good functional outcome. However, it is also associated with poor oncological outcome in high risk tumors which increases with tumor (T) stage. In case of low risk T1 tumors, local excision alone is a viable and accepted treatment strategy.

Local excision with adjuvant therapy

Especially for infirm patients, local excision is an attractive strategy compared to radical surgery concerning morbidity. Therefore, other additional options to improve the associated oncological compromise have been studied. One of these explored options is addition of adjuvant (chemo)radiation following local excision. This might increase oncological outcomes including survival, while still offering organ preservation.

A meta-analysis reported average local recurrence rates of 7% in 278 patients with T1, and 16% in 382 patients with T2 tumors (Table 1). Distant recurrence rates were 5% in 214 patients, and 7% in 254 patients with respectively T1 and T2 tumors (7). In particular, it was noted that recurrence rates of T2 tumors decreased remarkably with the addition of adjuvant therapy compared to local excision alone. Overall recurrence rate of local excision with adjuvant (chemo)radiation of T3 tumors was 38% (12 of 32 patients) (8, 9, 12, 14, 16-19).

A United States National Cancer Database analysis showed a 5-year survival rate of 79.7% for T2N0M0 tumors, similar to radical surgery (20). After exclusion of 90-day mortality, survival was significantly worse than after radical surgery. Others report 5-year overall survival rates are 63% to 98% for T1 tumors, and with 61% to 93% slightly lower for T2 tumors (7). Compared to local excision alone, the survival benefit of adjuvant therapy seems to be substantial for T2 tumors. However, due to serious heterogeneity of the studies, direct conclusions cannot be established. Nevertheless, the addition of adjuvant CRT after local excision seems to be a promising strategy as tailored approach for tumors at high risk of recurrence, such as T1 tumors with risk features or T2 tumors.

The TESAR trial, was initiated in 2015 to gain insight into the oncological and functional outcome of local excision with adjuvant chemoradiotherapy (21). In this study, local excision of intermediate and high risk T1 tumors and T2 tumors without adverse features,

is followed by randomization of patients between either adjuvant chemoradiotherapy or completion TME. The hypothesis is that both treatments offer similar recurrence and survival rates, while adjuvant chemoradiation offers better quality of life and functional outcome. The trial remains ongoing at the time of this writing.

Summarized, addition of adjuvant therapy to local excision potentially improves recurrence rates and survival in locally excised rectal cancer staged as T1 with risk features or T2 tumors. T3 tumors seem to benefit from adjuvant therapy as well, but oncological outcome remains poor with high recurrence rates.

Neoadjuvant therapy followed by local excision

The incorporation of neoadjuvant chemoradiotherapy and subsequent local excision is a possible treatment strategy. Neoadjuvant therapy might lead to downstaging and shrinkage of the primary lesion, which could enable local excision of what were initially larger tumors. More importantly, such a protocol targets the mesorectum via irradiation, which could sterilize occult nodal disease.

Local recurrence rates of 7-17% have been reported for T2 and T3 tumors treated with neoadjuvant chemotherapy prior to local excision (22-24). This is substantially lower than the previously mentioned rates of local excision alone, and slightly better than adjuvant therapy. Focusing on survival, an American National Cancer Database analysis revealed 5-year overall survival of 76.1% for T2N0M0 tumors (20). This was similar to radical surgery, and local excision with adjuvant chemoradiation. Allaix et al. reported a comparable 5-year survival rate of 77,8% in 11 patients, which was equal to local excision alone (15). Based on these numbers, neoadjuvant and adjuvant therapy seem to be equally effective strategies.

However, morbidity of neoadjuvant treatment is highly underestimated. Local excision after neoadjuvant chemoradiation is associated with higher risk of wound dehiscence (61% vs. 23%), post procedural pain (52% vs. 15%), and an increase of hospital readmissions (44% vs. 7%) compared to local excision alone (25). Another series reported the increase in wound-related morbidity following TEM (26). This series by Marks et al. included 43 patients with neoadjuvant therapy, of whom 36 received chemoradiation. The remaining 7 patients were deemed not fit for chemotherapy, and therefore underwent radiotherapy only. In total, 11 (25.6%) patients suffered wound complications. None of the 19 patients treated with TEM *alone* had wound complications.

Despite the increased short-term morbidity associated with neoadjuvant therapy, the promising oncological outcomes account for ongoing studies on this subject. An example is the multicenter international randomized STAR-TREC trial (27). In this study, small cT1-3 N0 lesions are randomized between primary TME and rectal preserving

therapy. In the rectal preservation arm, neoadjuvant chemo-radiotherapy is followed by local excision in case of good clinical response. In case of complete clinical response, cross-over to a Watch and Wait regime is offered. The hypothesis behind this protocol is that chemoradiation could be sufficient as sole treatment for early stage rectal cancer.

This hypothesis is supported by the group of Professor Angelita Habr-Gama (São Paulo, Brazil) among others. They described complete responses up to 22.4% of the irradiated tumors, omitting the need for surgery and enabling a Watch and Wait follow-up regimen (28, 29). In another publication, they reported improvement of absolute survival after chemoradiotherapy alone in the setting of complete clinical response, compared to incomplete responses to neoadjuvant therapy followed by radical surgery in octogenarians (age 80), regardless of whether they were fit or if they had significant comorbid conditions (30). Absolute survival advantage, after chemoradiotherapy without versus with radical surgery, was 10.1% for fit octogenarians, and 13.5% for comorbid octogenarians after one year.

In summary, the addition of neoadjuvant chemoradiation appears to improve oncological outcome of local excisions. However, the increased morbidity after neoadjuvant radiotherapy requires caution. Complete responses after chemoradiation are found in less than one of four patients. Nevertheless, this might offer opportunities to improve survival and organ preservation, if the good responders can be identified.

Palliative Radiotherapy

The administration of short course radiotherapy can be regarded in an attempt to avoid surgical intervention. Radiotherapy is often used for palliative relieve of symptoms associated with tumor growth, such as pain, obstruction, bleeding, or tenesmus. A systematic review was performed in 2014 to assess the efficacy of radiotherapy on palliation (31). Improvement of symptoms occurred in 75% of patients. However, all included studies used different dosages.

More recently, a study was published administering 5 fractions of 5 Gy in 5 days for palliation of locally advanced rectal cancer (32). They reported reduction or resolution of pain in 87.5%, and of bleeding in 100% of cases. Colostomy free rates were 100% after 1 year, 71.4% after 2 years, and 47.6% after 3 years. Toxicity of this dose was low.

Endorectal brachytherapy has been shown to be effective in patients with inoperable tumors and in the palliative setting. When used as a boost, it seems to improve the pCR (complete response) but does not impact recurrence rates or overall survival. Local administration of radiotherapy by brachytherapy for palliation, is an option whose use is derived from experience with prostate and cervical cancer. Brachytherapy as local treatment of rectal cancer has been reviewed, but data are sparse.

In a study by Hoskin et al., fifty patients with either inoperable or incurable tumors were treated with brachytherapy as sole treatment or as a boost to external beam radiotherapy (EBRT)(33). A clinical response was achieved in 75% of all patients, including 14 complete responses. Median survival for patients treated with definitive EBRT and brachytherapy boost was 25 months and 7 months for patients treated with a palliative intent. Of the 28 patients with rectal bleeding at presentation, 57% achieved a complete clinical resolution with a median response duration of 10 months. The HERBERT trial also examines the efficacy of the combination of EBRT followed by high-dose-rate endorectal brachytherapy boost in elderly and medically inoperable patients with rectal cancer. The first results have shown that response occurred in 29 of 33 patients (87.9%), with 60.6% complete response (CR). The local progression free survival and overall survival rates were 42% and 63%, respectively, at 2 years (34).

In conclusion, radiotherapy as sole treatment for infirm and otherwise inoperable patients seems to be a valid option as palliative treatment with significant improvement of tumor related symptomology. The combination of external beam radiotherapy with endoluminal brachytherapy shows especially high response rates. More data on long-term outcome after radiotherapy is needed to evaluate toxicity.

Radical surgery

Currently, radical surgery following the principal of total mesorectal excision (TME) remains the best available treatment of rectal cancer, in terms of oncological outcome. However, the risk of anastomotic leakage is substantial with 3-10%, which might be catastrophic, particularly in frail, elderly patients (35). Therefore, resection with creation of an end-colostomy (Hartmann's procedure) might be a valid option in this setting.

From an epidemiological standpoint, the majority patients diagnosed with rectal cancer are older than 75 years of age. Therefore, a significant subset may be considered for palliative treatment rather than curative-intent therapy due to frailty, severe comorbidities and/or reduced life expectancy. A systematic review by Manceau et al. concluded that severity of comorbidities had more influence on postoperative complications than advanced age (35). This suggests that age on its own should not be a discriminator.

Unfortunately, few studies report exclusively on this older, comorbid population. Postoperative 30-day mortality in patients with colorectal cancer aged between 75-84 years, is approximately 9%. For patients older than 85 years of age, 30-day mortality is 20%, which increases when surgical intervention is performed in the emergent setting (36, 37). Mamidanna et al. described a higher 30-day mortality of 31% which increased to 51% at 12 months follow up in patients older than 80 years (38). However, this data includes procedures with restoration of bowel continuity. Survival rates in

younger patients are more promising. For T1 rectal cancer, 5-year overall survival is approximately 80%, and for T2 tumors 77% (6, 20, 39).

In conclusion, radical surgery offers the best oncological outcome. By opting for a Hartmann procedure, anastomosis related morbidity and mortality could be avoided in high-risk patients, whilst still maintaining superior oncological outcomes.

CONCLUSION; TAILORING PALLIATIVE TREATMENT

Local excision is associated with low morbidity rates, but when compared to radical resection, local excision has inferior oncological outcome for rectal tumors other than low risk T1. Although theoretically attractive, addition of neoadjuvant (chemo)radiation results in relatively high morbidity. Local excision with tailored adjuvant treatment seems to be a promising option for T1 and T2 tumors. Local excision alone for tumors staged T2 or higher stage seems to be associated with unacceptably high recurrence rates that could be very symptomatic. Therefore, local excision is not advised as part of palliative treatment.

The best treatment should be highly tailored to each individual patient and discussed with the patient, the family, and a multi-disciplinary tumor board. If it is only for short-term symptom relief, short course radiotherapy might be the best option. If next to low morbidity, a recurrence free period is also of relevance, a more invasive treatment strategy might be the best option. This could include local excision with adjuvant therapy for T1-2 tumors. As an alternative, endoluminal brachytherapy with or without external beam radiotherapy could be administered for palliative treatment of rectal cancer. For patients who are deemed medically fit to tolerate radical surgery and want optimal oncological control, then radical surgery seems to be the best option. For patients where the risk of anastomotic leak is unacceptably high, rectal extirpation without configuration of an anastomosis (with permanent end-colostomy) seems to be a valid option with the best oncological control and a relatively good quality of life.

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MRI cT1-2 rectal cancer staging accuracy: a population-based study.

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ABSTRACT

Background: Adequate MRI based staging of early rectal cancers is essential for decision making in an era of organ-conserving treatment approaches. The aim of this population-based study was to determine the accuracy of routine daily MRI staging of early rectal cancer, whether or not combined with endorectal ultrasound (ERUS).

Method: Patients with cT1-2 stage rectal cancer who underwent local excision or total mesorectal excision (TME) without downsizing (chemo)radiotherapy were selected from the Dutch ColoRectal Audit, between 1 January 2011 and 31 December 2018. Accuracy of imaging was expressed as sensitivity, specificity, and positive- and negative predicting value (PPV/NPV).

Results: Of 7 382 registered patients with cT1-2 stage rectal cancer, 5 539 patients were included (5 288 MRI alone, 251 MRI + ERUS; 1 059 cT1 and 4 480 cT2). Patients with pT1 were overstaged by MRI alone in 54.7% (792/1 448) and by MRI and ERUS in 31.0% (36/116). Understaging of pT2 occurred in 8.2% (197/2 388) and in 27.9% (31/111), respectively. MRI alone overstaged pN0 in 17.3% (570/3 303) and the PPV of cN0 stage was 76.3% (2 733/3 583). Of the 834 patients with a pT1N0 stage, potentially suitable for local excision, 253 patients (30.3%) were correctly staged as cT1N0, and 484 (58.0%) and 97 (11.6%) patients were overstaged as cT2N0 and cT1-2N1, respectively.

Conclusion: Dutch population-based analysis of patients who underwent local excision or TME surgery for cT1-2 rectal cancer with preoperative MRI staging reveals substantial overstaging, indicating the weaknesses and opportunities for organ preservation strategies.

INTRODUCTION

Rectal cancer management depends on clinical locoregional staging as performed by endoscopy, endorectal ultrasound (ERUS) and magnetic resonance imaging (MRI). The decision-making process to treat rectal cancer patients either with rectal sparing local excision or radical excision with or without the addition of preoperative (chemo-) radiotherapy (RT) is dictated by clinical staging and identification of risk factors such as T-stage, suspicious lymph nodes and extramural venous invasion.(1) The use of MRI for determining indication for preoperative radiotherapy and extent of subsequent rectal resection in patients with intermediate or high risk rectal cancer has significantly influenced rectal cancer care worldwide.(2)

Introduction of bowel cancer screening programs has resulted in stage migration with an increase in early stage rectal cancer, i.e. cT1-2N0 stage.{logan 2013} This opens opportunities for organ preservation, avoiding substantial morbidity and decrease in function associated with radical rectal resection.(3) But, to safely aim for an organ preservation strategy, correct patient selection with optimal staging is a prerequisite. {logan 2013} Superficial lesions (T1) without risk features and/or suspicious lymph nodes might be considered suitable for upfront local excision as part of an organ preserving strategy. However, the final pathology result might reveal a more advanced tumour stage or presence of adverse features leading to a completion total mesorectal excision (TME) or adjuvant chemoradiotherapy (CRT) within current trials.(4, 5) Another approach aiming at organ preservation for patients with early cancer is upfront (C)RT with subsequent response assessment and tailored further treatment (e.g. TME surgery, local excision, watch and wait strategy) within current trials. Although this approach is promising, a substantial proportion (about 50%) of patients is at risk for overtreatment, especially given the current limitations in clinical staging.(6, 7)

To avoid both under- and overtreatment, optimising clinical staging is of utmost importance. MRI based staging of rectal cancer has proven its value in more advanced stages of the disease, but is known for its limited accuracy in early rectal cancers and assessment of lymph node status.(8)The diagnostic value largely depends on MRI scanning protocols and experience of the radiologist. In early lesions, the addition of ERUS has been advocated to improve clinical staging, but this seems highly operator dependent.(9) At present, population-based data on the accuracy of clinical tumour and nodal staging of early rectal cancer in daily practice is lacking.

Therefore, the aim of this population-based study was to determine the diagnostic accuracy of routine MRI staging in patients who underwent local excision or TME surgery for cT1-2 rectal cancer, whether or not combined with ERUS, and with trends over time.

METHODS

Data were derived from the Dutch ColoRectal Audit (DCRA). This audit collects detailed information on the patient, tumour, treatment and short-term (≤90 days) outcome characteristics of all patients undergoing resection for primary colorectal cancer in the Netherlands. Specific details of the DCRA regarding data collection, data quality, data validation and methodology have been published previously.(10)

Patient selection

All patients who underwent local excision or TME surgery for primary cT1-2 staged rectal cancer and were registered in the DCRA between January 1st, 2011 and December 31th, 2018 were potentially eligible. Only patients who were staged by MRI, with or without ERUS, were included. Exclusion criteria were downsizing therapy (e.g. short course radiotherapy (SCRT) with delayed surgery or CRT), a registered (y)pT0 stage, emergency surgery, staging by other modalities than MRI ± ERUS. Patients who underwent SCRT with immediate surgery (SCRT-IS; ≤2 weeks interval to surgery) were considered eligible. For this study, no ethical approval or informed consent was required under Dutch law.

Data extraction and outcome parameters

The following data were extracted from the DCRA-database: patient- and tumour characteristics, diagnostic- and staging characteristics, and procedural characteristics. Data on ERUS was available in the DCRA dataset until 2017. Removal of this variable was related to the low uptake of ERUS at a national level and registration burden. Pathological T and N-stage were extracted as the gold standard for comparison with radiological staging. Overstaging and understaging of staged rectal cancer patients was defined as higher pTN stage compared with cTN stage, for understaging and lower pTN stage compared to the cTN stage for overstaging, respectively. Outcome parameters included sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the preoperative MRI for tumour- and nodal staging.

Dutch colorectal cancer guidelines

The Dutch colorectal cancer guideline of 2008 was revised in 2014.(11, 12) For cT staging of rectal cancer, both Dutch guidelines stated that for non-superficial tumours, MRI is recommended as part of the standard work-up. ERUS can be considered in addition to MRI for differentiating between T1 and T2 stage. Regarding nodal staging, the Dutch guideline of 2008 stated that lymph nodes with a size of >5 mm on MRI should be considered suspicious for nodal metastasis. The revised guideline of 2014 stated that nodal disease should be considered in lymph nodes with a size of 5-9 mm and the presence of at least two of three malignant morphological characteristics, or in lymph nodes measuring >9mm.

Statistical analysis

Descriptive statistics were used to describe baseline characteristics which were defined as absolute numbers of cases and percentages. Staging was evaluated for patients who underwent MRI alone, and those who underwent combined imaging by MRI and ERUS. To calculate diagnostic performance of imaging, cT and cN staging was compared with pT and pN staging. For T-staging, both local excisions and TME were included, and only TME was included for analysis of N-staging. Sensitivity, specificity, PPV and NPV were calculated for cT1 and cT2 and cN0, cN1 and cN2 stage with 95% confidence intervals (CI). These outcome parameters were also calculated per year, graphically plotted, and analysed for time trends using the Linear-by-Linear Association test for the total study period (2011-2018) and comparing two time periods (<2014 vs. ³2014) for revision of the National colorectal cancer guideline in 2014. Regarding N-staging, nodal positivity (N+) was used without discriminating N1 from N2 stage. P-values of <0.05 were considered statistically significant. Statistical analyses were performed in SPSS 24.0 Statistics for Windows (Armonk, NY: IBM Corp).

Table 1. Patient-, tumour- and treatment characteristics for patients with cT1-2 rectal cancer diagnosed by MRI ± ERUS in the period from 2011-2018, who subsequently underwent TME surgery without downsizing preoperative radiotherapy.

Patient		Count	Percentage
Sex	Male	2 997	61.9
	Female	1 848	38.1
	Missing	2	
Age	<75	3 508	72.4
	≥75	1 336	27.6
	Missing	3	
ASA	I - II	4 000	82.5
	III+	846	17.5
	Missing	1	
Charlson score	0	2 619	54.0
	1	1 044	21.5
	2+	1 184	24.4
BMI	<30	3 889	81.6
	≥30	879	18.4
	Missing	79	
Preoperative MRI staging	MRI	4 700	97.0
	MRI including ERUS	147	3.0
Distance from anus*	≤5 cm	1 564	33.7
	6-10 cm	1 820	39.3
	≥10 cm	1 252	27.0
	Missing	211	
cT score	cT1	577	11.9
	cT2	4 270	88.1

Table 1. Continued.

Patient		Count	Percentage
cN score	cN0	3 746	77.4
	cN1	942	19.5
	cN2	81	1.7
	cNX / unknown	69	1.4
	Missing	9	
cM score	cM0	4 542	93.9
	cM1	82	1.7
	cMX / unknown	215	4.5
	Missing	8	
Neoadjuvant radiotherapy	No	3 227	66.6
	SCRT-IS	1 620	33.4
Procedure	(L)AR	3 115	64.3
	APR	1 044	21.5
	Hartmann	578	11.9
	Other**	110	2.3
pT stadium	pT1	1 057	21.8
	pT2	2 331	48.1
	pT3	1 403	28.9
	pT4	56	1.2
pN stadium	pN0	3 465	71.5
	pN1	1 046	21.6
	pN2	294	6.1
	pNX / unknown	42	0.9
CRM	Positive (≤1mm)	119	2.7
	Negative	4 222	97.3
Number of lymph nodes retrieved	≤10	1 060	21.9
	>10	3 779	78.0
	Unknown	8	0.4
Number of positive lymph nodes	0	3 492	72.1
	1-3	1 034	21.4
	>3	317	6.5
	Missing	4	

# Percentages for the variables are calculated out of the total number of actual results available, excluding the missing values.
ASA = American Society of Anaesthesiologists-Classification, BMI = Body Mass Index, MDT= multidisciplinary meeting, MRI = Magnetic Resonance Imaging, Multidisciplinary Team, cT stage = clinical tumour stage, cN stage = clinical nodal stage, SCRT-IS = Short Course Radiotherapy-Immediate Surgery (≤2 weeks), pT stage = pathological tumour stage, pN stage = pathological nodal stage.
* Note: this was not defined in the DCRA until 2016 and mostly based on endoscopic measurement of the distance to the anal verge, while since 2016 this is defined as the distance to the ARJ on sagittal MRI
** Note: including proctocolectomy and total colectomy

RESULTS

A total of 7 382 patients with cT1-2 rectal cancer, were identified between 2011 and 2018. Patient selection is displayed in Supplement Figure 1. During the study period, the use of MRI for clinical staging in this patient population increased from 90.4% (2011) to 92.6% (2018). A total of 5 539 patients remained for final analysis after exclusion of preoperative (chemo)radiotherapy with an interval of >2 weeks to surgery, emergency setting and staging by other means than MRI ± ERUS. Staging was performed by MRI alone in 5 288 patients, and 251 patients had combined imaging by MRI and ERUS. The use of ERUS in combination with MRI increased from 0.2% in 2011 to 5.4% in 2017. Clinical T stage was cT1 in 19.1% (n=1 059) and cT2 in 80.9% (n=4 480). The patient-, tumour- and treatment characteristics of the included patients are displayed in Table 1, stratified for type of surgery. The median number of examined lymph nodes increased from 11 lymph nodes in 2011 to 15 lymph nodes in 2018 (Supplement Figure 2). The proportion of pN+ remained similar over time (median 28%), as well as the total number of positive lymph nodes in case of pN+ (median 2).

Diagnostic performance for tumour staging

The diagnostic performance of preoperative MRI alone and with the addition of ERUS was assessed per tumour and nodal stage for each year in the period from 2011-2018 and shown in Table 2. Of 942 patients with a cT1 stage, 656 patients (69.6%) had a pT1 stage, 197 (20.9%) a pT2 stage and 85 (9.0%) a pT3 stage. Of 4 346 patients with a cT2 stage, 792 patients (18.2%) had a pT1 stage, 2 191 (50.4%) a pT2 stage and 1 311 (30.2%) a pT3 stage. Overstaging of pT1 tumours occurred in 54.7% and under staging of pT2 tumours in 8.2%. The sensitivity and specificity of MRI alone were 45.3% and 97.6% for T1 tumours, and 91.8% and 25.7% for T2 tumours, respectively (Table 3). Overall, staging of cT1-2 rectal cancer by MRI alone was accurate in 2 847 patients (53.8%); 792 patients (15.0%) were clinically overstaged, and 1 649 (31.2%) were clinically understaged. When combining the results of cT1-2 tumours evaluated by MRI alone, 26.4% had pT3 stage and 1.1% pT4 stage.

In patients who were staged by both MRI and ERUS, overstaging of pT1 occurred in 31.0% (36/116) and understaging of pT2 in 27.9% (31/111). Sensitivity and specificity of combined MRI and ERUS was 69.0% and 72.6% for T1 tumours, with corresponding percentages of 72.1% and 61.4% for T2 tumours, respectively.

The trends for sensitivity, specificity, PPV and NPV per individual clinical tumour stage over the study period are demonstrated in Figure 1. The PPV of MRI for staging cT1 tumours showed a significant increase of 32.1% in 2011 compared to 2018 (p<0.05). NPV showed a significant decrease from 89.6% to 80.7% in the same timeframe (p<0.05) (Figure 1a). For cT2 tumours, the specificity showed a significant increase of 9.4% from 2013 to 2018 (p<0.05) and a significant increase of PPV of 4.5% from 2012 to 2018 (p<0.05) (Figure 1b).

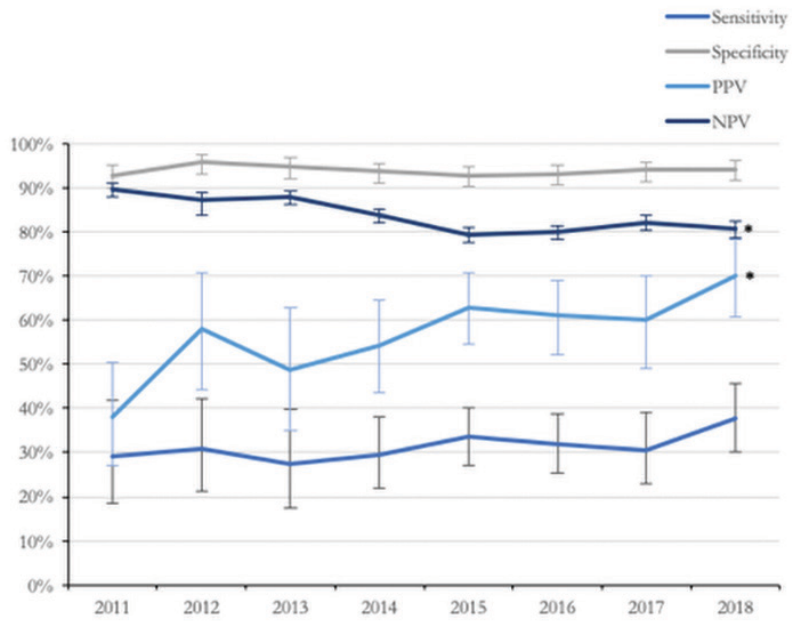

Figure 1A. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MRI for diagnosis of cT1 rectal cancer over time (2011-2018).
*Statistically significant difference (p<0.05) tested over the total study period.

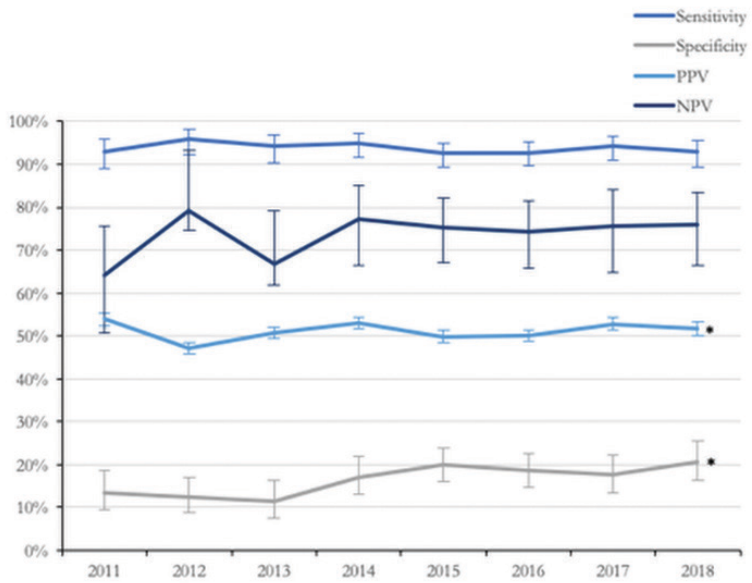

Figure 1B. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MRI for diagnosis of cT2 rectal cancer over time (2011-2018).
*Statistically significant difference (p<0.05) tested over the total study period.

Table 2a. Clinical versus pathological tumour- and nodal staging by MRI alone

Clinical versus pathological tumour staging					
	pT1	**pT2**	**pT3**	**pT4**	**Total**
cT1	656	197	85	4	942
cT2	792	2 191	1 311	52	4 346
Total	1 448	2 388	1 396	56	5 288

Clinical versus pathological nodal staging					
	pN0	**pN1**	**pN2**	**pNX**	**Total**
cN0	2 733	672	178	32	3 615
cN1	524	311	89	6	930
cN2	46	15	18	0	79
cNX	36	24	3	4	67
Total	3 339	1 022	288	42	4 691*

MRI = Magnetic Resonance Imaging, cT stage = clinical tumour stage, cN stage = clinical nodal stage, pT stage = pathological tumour stage, pN stage= pathological nodal stage. *Note: 9 cases of cN/pN were missing.

Table 2b. Clinical versus pathological tumour- and nodal staging, by MRI + ERUS

Clinical versus pathological tumour staging				
	pT1	**pT2**	**pT3**	**Total**
cT1	80	31	6	117
cT2	36	80	18	134
Total	116	111	24	251

Clinical versus pathological nodal staging				
	pN0	**pN1**	**pN2**	**Total**
cN0	106	22	3	131
cN1	10	1	1	12
cN2	1	0	1	2
cNX	2	0	0	2
Total	119	23	5	147

MRI = Magnetic Resonance Imaging, cT stage = clinical tumour stage, cN stage = clinical nodal stage, pT stage = pathological tumour stage, pN stage= pathological nodal stage.

Table 2c. Diagnostic accuracy of clinical staging of combined T and N stage, by MRI alone.

Pathological tumour and nodal staging versus clinical staging				
	pT1N0	**pT2N0**	**pT1-2N1**	**Total**
cT1N0	253	87	47	387
cT2N0	484	1 312	289	2 085
cT1-2N	97	279	177	553
Total	834	1 678	513	3 025*

MRI = Magnetic Resonance Imaging, cT stage = clinical tumour stage, cN stage = clinical nodal stage, pT stage = pathological tumour stage, pN stage= pathological nodal stage. *Note: 1 675 (35.6%) patients were staged as T3-4N0-2.

Tumour staging for local excisions

In patients who were staged by MRI alone and underwent a local excision, overstaging of pT1 occurred in 23.5% (100/426) and understaging of pT2 in 45.2% (66/146) (Supplement Table 1). For the local excision group, sensitivity and specificity of MRI alone was 76.5% and 56.2% for T1 tumours, and 54.8% and 74.9% for T2 tumours, respectively (Supplement Table 2).

For patients who underwent local excision and were staged by MRI and ERUS, overstaging of pT1 occurred in 12.3% (10/81) and understaging of pT2 in 59.1% (13/22). Sensitivity and specificity of MRI and ERUS was 87.7% and 39.1% for T1 tumours, and 40.9% and 87.8% for T2 tumours, respectively (Supplement Table 2).

Diagnostic performance for nodal staging

Preoperative nodal staging was available for 4 769 (98%) TME patients. Missing cN stage in this patient population decreased from 3.5% in 2011 to 0.7% in 2018. Overall nodal stage was accurate in 3 066 patients (65.4%) by MRI alone; 977 (20.8%) were clinically understaged, and 570 (12.2%) were clinically overstaged (Table 2a). Using MRI alone, accuracy of a cN0 stage was 69.0%, with corresponding sensitivity of 82.7% and specificity of 33.8%. Overstaging of pN0 occurred in 17.3% (570/3 303), and understaging of pN1-2 in 66.3% (850/1 283). Combined MRI with ERUS resulted in 131 patients with a cN0 stage, of whom 25 patients had a pN1-2 stage (19%). Accuracy for cN0 stage by MRI with ERUS was 75.2%, with corresponding sensitivity of 90.6% and specificity of 10.7% (Table 2b).

Within this population of cT1-2 rectal cancer TME patients assessed by MRI, a decreasing trend in diagnosis of cN1-2 disease was observed after revision of the guideline in 2014 (Figure 2). The sensitivity of nodal staging by MRI showed a significant increase from 74.0 percent in 2012 to 87.6 percent in 2018 (p<0.05). For PPV, a significant decrease from 2014 till 2018 was observed (80.8% vs. 75.3%, p<0.05). Additional time-trend analysis

showed a significant decrease of specificity over the total study period (p=0.031) and comparing the two-time periods, <2014 and ³2014 (p=0.039).

Diagnostic accuracy of combined tumour and nodal staging by MRI

The clinically relevant combined staging of T and N stage was evaluated (Table 2c). Of the 834 patients with a pT1N0 stage, potentially suitable for local excision only, 253 patients (30.3%) were correctly staged as cT1N0, 484 (58.0%) patients were overstaged as cT2N0 and 97 (11.6%) patients were overstaged as cT1-2N1 (Table 2c). In 387 patients with cT1N0 stage, 5.2% (n=87) of the patients were incorrectly stages as pT2N0 stage and in 9.2% (n=47) of the patients as pT1-2N1 stage. Patients with pT1-2N1 stage, were correctly staged by MRI alone in 34.5% (n=177).

Table 3a. Accuracy of MRI alone (sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV))

	Accuracy MRI alone tumour staging (% (95% CI))				
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
cT1	32.3 (29.4-35.3)	94.2 (93.4-94.9)	60.6 (56.7-64.2)	83.3 (82.7-83.9)	80.7 (79.5-81.8)
cT2	94.2 (93.1-95.1)	16.8 (15.4-18.4)	50.8 (50.3-51.3)	76.0 (72.4-79.2)	53.7 (52.3-55.2)
	Accuracy MRI alone nodal staging (% (95% CI))				
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
cN0	82.7 (81.4-84.0)	33.8 (31.2-36.4)	76.3 (75.5-77.0)	43.2 (40.6-45.8)	69.0 (67.7-70.4)
cN1	31.2 (28.3-34.1)	82.9 (81.6-84.1)	33.7 (31.1-36.3)	81.2 (80.6-81.9)	71.7 (70.3-73.0)
cN2	6.3 (3.8-9.8)	98.6 (98.2-98.9)	22.8 (15.0-33.0)	94.1 (93.9-94.2)	92.9 (92.1-93.6)

MRI = Magnetic Resonance Imaging, CI = confidence interval, cT stage = clinical tumour stage, cN stage=clinical nodal stage, pT stage = pathological tumour stage, pN stage= pathological nodal stage, PPV= Positive predicting value, NPV= Negative predicting value.

Table 3b. Accuracy of MRI + ERUS (sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV))

	Accuracy MRI + ERUS tumour staging (% (95% CI))				
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
cT1	25.7 (12.5-43.3)	79.5 (70.8-86.5)	28.1 (16.7-43.4)	77.4 (73.4-81.0)	66.7 (58.4-74.2)
cT2	79.8 (69.9-87.6)	24.1 (13.9-37.2)	61.7 (57.4-65.9)	43.8 (29.6-59.0)	57.8 (49.4-65.9)
	Accuracy MRI + ERUS nodal staging (% (95% CI))				
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
cN0	90.6 (83.8-95.2)	10.7 (2.3-28.2)	80.9 (78.6-83.0)	21.4 (7.5-47.7)	75.2 (67.3-82.0)
cN1	4.4 (0.1-22.0)	91.0 (84.4-95.4)	8.3 (1.2-40.1)	83.5 (82.0-84.8)	77.2 (69.6-83.8)
cN2	20.0 (0.5-71.6)	99.3 (96.1-99.9)	50.0 (6.8-93.2)	97.2 (95.7-98.2)	96.6 (92.1-98.9)

MRI = Magnetic Resonance Imaging, CI = confidence interval, cT stage = clinical tumour stage, cN stage=clinical nodal stage, pT stage = pathological tumour stage, pN stage= pathological nodal stage, PPV= Positive predicting value, NPV= Negative predicting value.

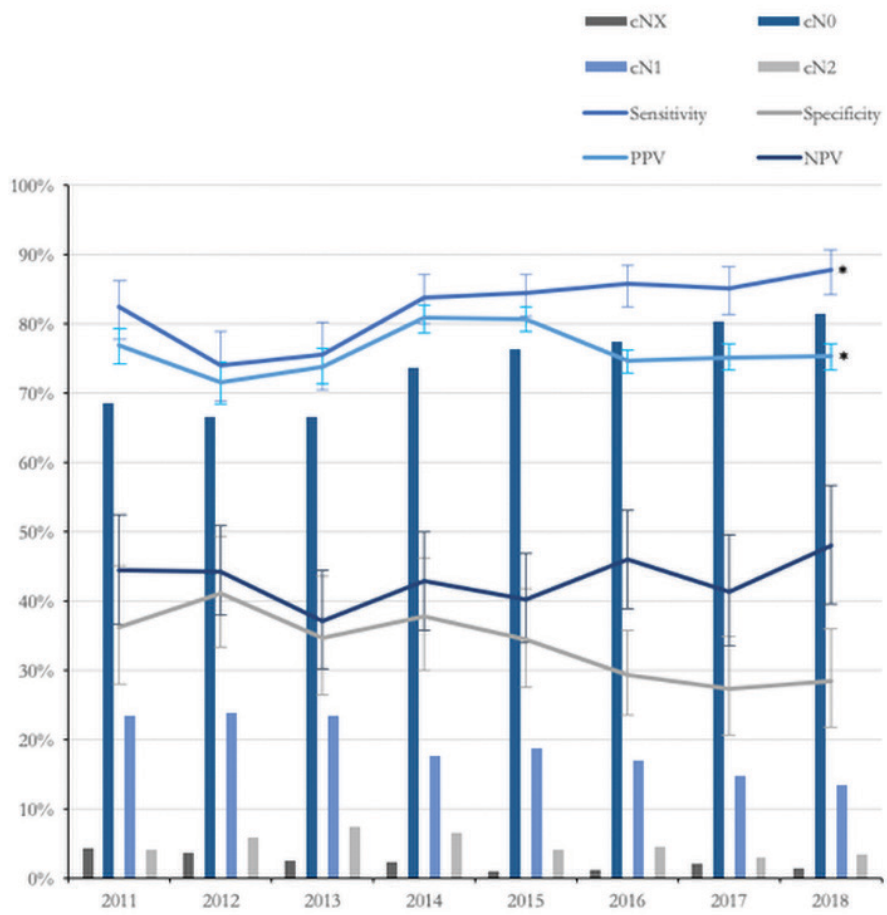

Figure 2. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for clinical mesorectal lymph node staging based on MRI (cN0 and cN1-2 vs. pN0 and pN1-2) in patients with MRI based cT1-2 rectal cancer for each year (2011-2018).
Note: cN stage plotted in all surgically resected rectal cancer patients. Confidence Intervals (CI) are depicted for Sensitivity, specificity, PPV, and NPV values.
*Statistically significant difference (p<0.05) tested over the total study period.

DISCUSSION

In this Dutch population-based study during the period 2011-2018, among 7 382 patients with a registered cT1-2 stage rectal cancer, 9% and 66% of patients underwent local excision and TME after MRI staging without downstaging preoperative therapy, respectively. Within this combined population, 12% of the patients also underwent ERUS for preoperative staging. The overall performance of MRI ± ERUS to stage early

rectal cancer was disappointing. The diagnostic value of preoperative MRI showed some improvements in tumour- and nodal staging over time, but still indicating potential areas for improvement. The accuracy of MRI based clinical staging for pT1 patients was 70%, and patients with a pT2 cancer were understaged in 8%. Most striking was the overstaging of pT1 tumours in 54% when using MRI alone, and still a 31% when ERUS was added to the MRI. On the other hand, patients with a cT1 tumour appeared to be pT1 in 70% and pT2 in 21%. Accuracy of cN0 stage was 69%, overstaging of pN0 occurred in 17.3%, and understaging of pN1-2 in 66.3%. Of the 834 patients with a pT1N0 stage, only 253 patients (30.3%) were correctly staged by MRI as cT1N0 and 484 (58.0%) patients were overstaged as cT2N0, indicating the potential role for upfront local excision.

In the present study, the diagnostic value of MRI for tumour- and nodal staging was specifically determined for the early tumour stages. Most studies reporting on diagnostic performance of MRI include all stages of rectal cancer. The meta-analysis from Al-Sukhni et al., including 21 studies, and Bipat et al., including 90 studies, demonstrated overall sensitivities ranging from 69-87%, and specificities of 75-82% for T-staging by MRI.(13, 14) Preoperatively treated rectal cancer patients with downsizing therapy were excluded in the meta-analysis by Zhang et al., comprising a total of 35 studies.(15) Subgroup analyses for T1 and T2 tumours showed sensitivities of 58% and 80% (45.3% and 91.8% in our study) and specificities of 97% and 74% (97.6% and 25.7% in our study), respectively. In accordance with our results, a high specificity of cT1 stage and a high sensitivity for cT2 stage were found.

The diagnostic value of nodal staging by MRI remains subject of debate. The revised Dutch colorectal cancer guideline of 2014 specifically included more strict criteria to consider a lymph node positive on MRI.(12) Remarkably, a significant decrease of specificity for nodal staging (p=0.039) was observed, meaning that an increased tendency towards overstaging was observed over time in this population of early rectal cancers, despite current guideline recommendations. In a study by Zhou et al. including 52 patients with T1-3 stage rectal cancer, preoperative nodal staging by MRI revealed an accuracy of 59.6%, sensitivity of 56.5% and specificity of 82.8%.(16) Balyasnikova et al. evaluated 65 early rectal cancer patients and reported an accuracy of 84%, PPV of 71% and NPV of 90% for MRI based nodal staging.(17) Our study confirms the overstaging by MRI for nodal disease in this specific group with early tumours with 56% of the cN1 being pN0. A possible explanation of overstaging might be based on the use of size criteria for nodal staging and hospital variation in guideline adherence. Overstaging of positive nodal disease when using >5 mm as a size criterion, which was a guideline recommendation stated in the colorectal cancer guideline of 2008, has been reported in 30-40%.(18) In the TESAR-trial, a trial investigating the therapeutic options after local excision of early rectal cancer with risk features, lymph nodes are considered benign with a size smaller than 10 mm independent of morphologic features.(5)

Radiologists have a learning curve to become proficient in staging of early rectal cancer by MRI. Rafaelsen et al. found a higher sensitivity (96% vs. 77%, $p<0.05$) and specificity (74% vs. 40%, $p<0.05$) when comparing more experienced gastrointestinal radiologists to general radiologists when assessing all stages of rectal cancer.(19) This implies that specific training programs and accreditation for radiologists is likely to improve the accuracy of early rectal cancer staging.(20) Furthermore, tumour staging improves with the use of higher field strength MRI and review of images ideally by consensus of two or more expert radiologists.(15, 16) Recently, the national SPECC (significant polyps and early colorectal cancer) initiative in the UK expressed the need to improve staging of early rectal cancer, which includes better focus on standardization of MRI protocols, consensus guidelines, (size) criteria used for nodal staging, structured MRI reporting, and increasing the performance and experience in smaller centres.(3, 20)

The European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus document explicitly mentions the role for (additional) ERUS, given its superior diagnostic performance for differentiating T1 from T2 tumours. (21) In the present study, the addition of ERUS only slightly improved nodal staging in comparison with MRI alone, and showed overstaging of pT1 and understaging of pT2, but numbers were small because of the restricted use of ERUS in the Netherlands. As these modalities are complementary to each other, the encountered accuracy should be interpreted as such and not as sole accuracy of MRI or ERUS. A recent study showed that ERUS outperformed MRI in overall T, T1, T3 and overall nodal staging ($p<0.01$).(22) These results support the thought that ERUS is better in detecting smaller lesions in the thinner colorectal wall (submucosa and serosa) in contrast to the muscularis propria (T2) at which level the MRI performs better. However, Mondal et al. showed no benefit of ERUS in patients' selection for local therapy, with <10% change of management when ERUS being considered next to clinical, endoscopically and MRI staging findings.(23)

Given the diagnostic difficulties in MRI staging as found in current analysis, the upfront chemoradiotherapy strategies for patients have a risk of overtreatment since many small T1 will be included which could treated with local excision only. The potential of upfront (chemo)radiotherapy as organ preservation is currently investigated in the setting of an international controlled trial.(6, 24)Another more pragmatic strategy aimed at organ preservation for cT1-2 tumours with limited size is a diagnostic/therapeutic local excision. Exact histopathology will reveal the final staging, and for the majority, a radical local excision with endoscopic submucosal dissection (ESD) or transanal minimally invasive surgery (TAMIS) already constitutes definitive treatment for the low risk T1 tumours. If the final pathology shows intermediate-risk early cancers (high-risk pT1 or low-risk pT2), additional treatment options should be considered: completion TME surgery, adjuvant chemoradiotherapy or close surveillance including MRI for local and/or nodal regrowth, however these two last mentioned options are to this date still considered as experimental. Implementing diagnostic/therapeutic local excision

by ESD or TAMIS for all cT1-2 tumours requires patient as well as surgeon and MDT education. Patients should be aware of the possibility that completion TME is advised after final pathology reveals high risk features. However, completion TME is regarded as a slightly riskier procedure because it is associated with higher morbidity and colostomy rates, and risk of incomplete specimens, compared to primary TME.(25) However, these increased risks seems less evident with transanal TME.(26) In addition, the potential problems of subsequent completion surgery should be considered before deciding on local excision, and full thickness excisions should be avoided in those areas at risk for breach of completion TME surgery (anterior rectum and close to the sphincter). The alternative therapeutic approaches, adjuvant chemoradiotherapy and close surveillance with endoscopy and MRI, are the experimental arms in the ongoing TESAR trial.(5, 24)

The strength of this population-based study is that it offers real life data concerning the diagnostic accuracy of the preoperative assessment of MRI staging of early rectal cancer in daily practice in the Netherlands. However, some limitations of this study need to be addressed. Patients who underwent endoscopic polypectomy of a T1 cancer, or were referred to dedicated units in pursue of a rectal preserving strategy were not included, which might have influenced overall diagnostic accuracy of MRI and ERUS. The decision-making process regarding the use of an additional ERUS for staging, was not registered in the DCRA dataset. Furthermore, no data was available regarding the different MRI protocols used to stage rectal cancer in the centres. Also, the current available variables in the DCRA do not allow for analyses on the percentage of patients that eventually could have been spared TME surgery based on all currently known high risk features to guide this decision, or needed completion TME if routine upfront local excision would have been implemented.

This large population-based study demonstrates the diagnostic value of preoperative MRI in patients who underwent local excision or TME surgery for early rectal cancer in routine daily practice in the Netherlands between 2011 and 2018. This revealed a substantial rate of overstaging of pT1N0 tumours, which eliminated the option of an organ-preserving approach instead of TME surgery in eligible patients.

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Data-availability
The data, analytic methods, and study materials of this study are accessible from the Dutch ColoRectal Audit (DCRA) but are not publicly available. The data is made accessible to other authors upon reasonable request and with permission of the Dutch ColoRectal Audit.

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PART II

Transanal total mesorectal excision (TaTME)

6

TaTME compared to LaTME for mid and low rectal cancer; current evidence.

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ABSTRACT

Background: Transanal Total Mesorectal Excision (TaTME) is potentially the answer to refractory challenges in rectal cancer surgery. The surgical dissection in the deep pelvis is facilitated by a down to up approach with modern laparoscopic techniques. Potential benefits are decrease in short-term morbidity including anastomotic leakages, in conversion and colostomy rate, and better quality of specimens including less R1 rates. Long-term oncological outcome data is lacking and needs to be reviewed thoroughly. Initial (comparative) series show promising results, however there is a lack of audited data and comparative data between Laparoscopic TME(LaTME) and TaTME. This review compares available data of LaTME and TaTME.

Methods: A systematic review was performed in PubMed to identify papers reporting TaTME series with minimal 15 patients. A comparative set of recent large RCT data on laparoscopic TME was constructed. Weighted averages were derived from the extracted data. Primary endpoints were short-term morbidity, anastomotic leakage, conversion, pathological outcomes and local recurrences(LR).

Results: The search yielded 1.093 papers, of which after the selection process resulted in the inclusion of 23 series on TaTME. To make a comparison, the four latest RCT's on LaTME were identified as a referential group. The international TaTME registry paper was presented separately to make a third comparative group. Average morbidity 31.5% and 39.6% and anastomotic leakage 6.9% versus 8.0% both in favor of TaTME. Conversion rate was 2.0% versus 15.7% for TaTME and LaTME respectively. Complete mesorectal integrity 86.2% vs 81.5% and CRM+ 4.6% vs. 7.9%. Five urethral injuries (0,7%) were reported. Long-term outcomes of local recurrences were reported in a minority of studies with heterogeneous follow-up intervals.

Conclusion: This review summarizes the data and potential benefits of TaTME. Compared to LaTME, TaTME decreases short-term morbidity, conversion, suboptimal quality of the specimen and involved CRM rate. Due to concerns about underreporting of poor outcomes, a well-designed randomized controlled trial with quality assurance and report on oncological safety is needed before widespread implementation can be justified.

BACKGROUND

Transanal total mesorectal excision (TaTME) is the potential answer to refractory challenges in the surgical resection of mid and low rectal cancer. Since the first reports of this approach by its pioneers in 2010, the technique has gained wide attention in the surgical community.(1, 2) The technique facilitates dissection of the very distal rectum and mesorectum providing excellent view of the anatomy in the deep pelvis. Especially difficult cases (e.g. obese, male patients with bulky distal tumors) seem to benefit from the transanal approach. Nevertheless, no randomized evidence is present to support any benefits. Also, in systematic reviews as well as reported in registries the benefits of TaTME compared to LaTME seem modest and long-term oncological outcome is awaited.(3-5) Current problems in TME surgery are short-term morbidity including anastomotic leakage, conversions to open surgery in 10-25%, unintended end colostomies, poor specimen quality, circumferential resection margin involvement, distal margins rates and local recurrences.

Laparoscopic TME surgery is associated with substantial short-term morbidity of 30-40%. This includes anastomotic leakage rates around 8%.(6, 7) The conversion rate in LaTME is still above 10% as reported in recent trials and even with robotic surgery this percentage remains between 10 and 20 percent, especially in obese patients.(8-11) Conversion to open surgery occurs due to difficult dissection and is associated with higher morbidity and worse oncological outcome.(12-15)

Currently an increase focus is seen towards sphincter preserving therapy.(16, 17) The open intersphincteric resection and transanal dissection creates the possibility of saving the sphincter avoiding end colostomies, but laparoscopic TME still results in a relatively high rate of APR, which has negative impact on quality of life. Transanal minimal invasive access with high-quality images creates the potential to achieve a higher rate of sphincter saving procedures. Nevertheless, data regarding unintended AP resections are scarce and only within a randomized comparison it will be possible to evaluate this aspect. High-quality surgery with respect to the embryological avascular planes aims to achieve an intact mesorectal envelope and offers good local control, especially with neoadjuvant radiotherapy if indicated.(18, 19) An involved circumferential resection margin remains a concern since this is a substantial risk factor for LRs. Laparoscopic surgery with an intent for TME result in an involved circumferential resection margin of 17% as is shown in national registries.(20) Potentially the mesorectum is not totally removed in TME surgery as shown by the presence of residual mesorectum in 40% upon evaluation by MRI 6 months after surgery in 46.9%.(21)

The TaTME technique could improve outcomes for patients with mid and low rectal cancer overcoming the limitations of dissection the angulated rectum deep within the pelvis.(1, 12) Especially the known difficult LaTME resection will probably benefit from

the TaTME approach such as male sex, low tumor, high BMI and bulky or anteriorly situated tumours.(22) In these situations deep mesorectal dissection, safe resection margins (both distal and circumferential) and safe stapled transection, without the need for multiple firings, may not be achieved requiring conversion to open surgery.(12, 20) Furthermore, in (ultra)low anterior resections for tumours situated close to but not grown into the pelvic floor, the rate of end-colostomy (APR) for technical considerations outstands the rate in which it is an oncological necessity.(16) TaTME may overcome these challenges by improved visualization and ergonomics. By enabling a more precise distal dissection in the embryological planes, theoretically the autonomic nerves can be preserved possibly leading to improved functional outcomes.(23, 24)

In this review we focus to current evidence of laparoscopic rectal surgery and TaTME with respect to morbidity including anastomotic leakage, conversion, colostomy, involved resection margins and local recurrences.

METHODS

We performed a PubMed search with a similar syntax as recently published to identify studies, published since January 2005, reporting on outcomes of TaTME.(4) The final search was performed at 25 January 2018 with the following syntax:

((((excision*[tiab] OR resection*[tiab] OR TME[tiab] OR TaTME[tiab] OR TAMIS[tiab] OR NOTES[tiab] OR proctectom*[tiab]) AND (transanal*[tiab] OR trans-anal*[tiab])) OR ((excision*[ot] OR resection*[ot] OR TME[ot] OR TaTME[ot] OR TAMIS[ot] OR NOTES[ot] OR proctectom*[ot]) AND (transanal*[ot] OR trans-anal*[ot]))) AND ((((“Neoplasms”[Mesh] OR neoplas*[tw] OR tumor*[tw] OR tumour*[tw] OR cancer*[tw] OR malignan*[tw] OR oncolog*[tw] OR carcinom*[tw] OR adenocarcinom*[tw]) AND (“Rectum”[Mesh] OR rectum[tiab] OR rectal[tiab] OR colorect*[tiab] OR mesorect*[tiab])) AND (“surgery”[Subheading] OR surgery[tiab] OR surgical[tiab] OR operati*[tiab])) OR (“Rectal Neoplasms/surgery”[Mesh:noexp])))

For this paper, case-series, cohorts and comparative studies, with a minimum of 15 patients that underwent Transanal TME for rectal cancer were included. The transanal approach had to be an endoscopic technique, therefore papers on open transanal approach (TaTa) were excluded. Moreover, animal and cadaver studies were not included. Language in which the cohorts were reported was restricted languages with the Latin alphabet.

The international registry of TaTME was isolated from the other retrieved series on TaTME, because of its different design and the rather large proportion of indications

other that rectal cancer such as IBD, completion proctectomy and Hartmann reversal. (25)

In addition, to provide the most recent evidence from randomized clinical trials regarding laparoscopic TME, data from the laparoscopic arms of large, n= >200, multi-center RCT's published after 01-01-2015 were isolated and recorded.

Primary endpoints were type of surgery, morbidity, anastomotic leakage, defined as (partial) dehiscence, intraoperative complication as urethral injury, intraoperative bleeding, stoma-rate, conversion, clinicopathological parameters as quality of the mesorectum, circumferential resection margin and distal margin involvement and long-term oncological outcome as LRs.

Statistical analysis

Because a minority reported comparative data on TaTME and laparoscopic TME, no direct comparative meta-analysis could be performed. Instead, for the retrieved laparoscopic and TaTME studies, a separate weighted average was provided for the retrieved baseline characteristics and outcomes. The calculated weighted percentages and crude data (events and adjusted total population per outcome) of the laparoscopic TME and retrieved TaTME series, as well as the TaTME registry are presented in tables.

For the primary endpoints, if possible, a separate weighted average of the proportions was determined by means of the generic inverse-variance method. This is a method for aggregating multiple effect sizes to minimize the variance of the weighted average, giving more weight to the effect of large studies than to small ones. Analyses were performed with the inverse-variance method, using a random-effects model. Heterogeneity was assessed by use of the I^2 statistic. The software used for statistical analysis was R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The PubMed search on TaTME resulted in 1093 papers. Selection by title/abstract excluded 1058 studies which resulted in 35 papers for full text analysis. Of those, nine papers were excluded for N= < 15.(26-34) Other reasons of exclusion were the use of another technique or non-availability of full-text for two other articles.(35, 36) Eventually, 24 papers on TaTME were included in this paper, of which overlap existed by 2 papers from the same clinic.(37, 38) Since the latter paper focused on pathological outcomes, from this paper only the pathological data were extracted; quality of mesorectum, CRM and DRM positivity (38). Because of its unique design the TaTME registry was not pooled with the other series in the meta-analysis.(25) *Figure 1 flowchart and Appendix Table 2 search results.*

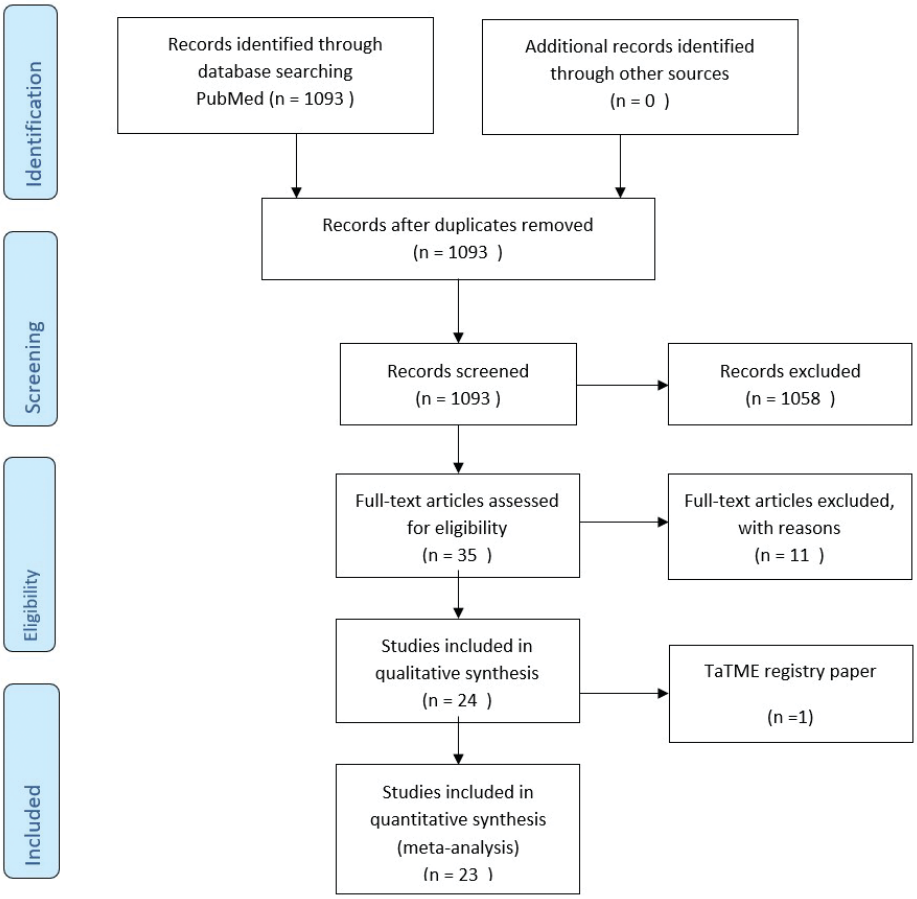

Figure 1 Flow-chart of flowchart of TaTME search

The selection of the open/robotic versus laparoscopic TME multicenter RCT's with an arm of N= >200 resulted in the ROLARR, COLOR II, ALaCaRT and ACOSOG Z6051.(8, 9, 39-41)

TaTME series and registry

The 23 included TaTME cohorts varied in design and inclusion criteria and reported clinical and pathological outcomes of 1107 patients, *Appendix Table 3 TaTME*.(37, 38, 42-62) Fourteen single center series (37, 43-47, 51, 53-55, 57-60), of which one published 2 papers (37, 38), 7 dual or multicenter (42, 48, 50, 53, 56, 61, 62) and one paper of an implementation pathway(49) were included. One of the single center papers included solely advanced or recurrent low rectal cancers.(59) Furthermore, for the pathological data of the largest single center experience, Hospital Clinic, we extracted the data of their latest paper on pathological endpoints. (38) The indication for TaTME was merely

rectal cancer varying from <5 to 15 centimeter from the anal verge, however some included a few benign cases. Due to heterogeneous inclusion criteria regarding intent for continuity; pooling for APR or LAR rate could not be performed. *Table 1 weighted averages.* Baseline characteristics, Surgical and postoperative outcomes of the TaTME series can be found online: http://ales.amegroups.com/public/system/ales/supp-ales.2018.04.02-2.pdf.

The TaTME registry encompasses 1594 patients who received an anastomosis after TaTME, of which 1540 procedures were for rectal cancer, and in the appendix an additional 161 abdominoperineal resections were reported.(25)

Table 1 – weighted averages

Outcome	TaTME	Laparoscopic TME	Registry
Baseline			
Population N=	1107	1411	1594
Male sex	65.3% (710/1088)	65% (923/1411)	68% (1080/1594)
Age (years, RoM)	63.7 (55.0 - 70.0)	64.7 (57.7 - 66.8)	63.7
BMI (RoM)	26.2 (24.2 - 29.5)	26.3 (26.1 - 27.0)	26.3
Neoadj treatment	65.3% (680/1041)	61.9% (874/1411)	56% (895/1594)
Surgery			
Colostomy (definite)	7.4% (75/1007)	27.0% (378/1398)	12% (211/1755) *
Conversion	2.0% (22/1083)	13.7% (192/1403)	5.6% (90/1594)
Duration of surgery (min, RoM)	249.1 (166 - 368.6)	242.9 (210 - 266)	252 (30 - 733)
Intraoperative complications	4.2% (36/865)	12.1% (141/1164)	30.6% (487/1594)
Intraoperative bleeding	1.7% (10/585)	3.5% (41/1164)	4.2% (67/1594)
Urethral injury	0.7% (5/694)	NR	0.8% (12/1594)
Pathology			
Mesorectal integrity			
Complete	86.2% (871/1010)	81.5% (1139/1398)	85.5% (1193/1540)**
Partial	12.6% (111/1010)	11.9% (166/1398)	10.8% (150/1540) **
Incomplete	2.8% (25/1010)	4.1% (58/1398)	3.4% (47/1540) **
CRM Positive	4.6% (51/1118)	7.9% (102/1290)	4.1% (60/1451)
DRM Positive	0.7% (7/1013)	1.0% (7/702)	0.7% (10/1445)
Postoperative outcomes			
Short-term morbidity (30 day)	31.% (317/100)	39.6% (462/1167)	34.8% (555/1594)
Anastomotic Leakage (30 day) ***	6.9% (67/975)	8.0% (88/1104)	7.8% (124/1594)
Length of stay (days, RoM)	7.5 (4 - 4)	7.9 (7.3 - 8.2)	8 (2-94)
Mortality (30 day)	0.6% (7/110)	0.9% (13/1407)	0.6% (9/1594)

*, included 161 APR; **, minus 54 benign; ***, defined as dehiscence. RoM, range of reported means or medians; DRM, distalresection margin; CRM, circumferential resection margin; BMI, body mass index; TaTME, transanal total mesorectal excision; LaTME, laparoscopic TME.

Laparoscopic TME

The laparoscopic TME arms of the before mentioned RCT's covered short-term and pathological outcomes of 1411 patients.(8, 9, 39-41) Only the COLOR II trial reported the long-term outcomes: 5% local recurrences after 3 years.(39) Patient demographics were comparable, but Fleshman *et al.* reported an neo-adjuvant therapy rate of 98% which was rather high compared with the 46-59% rate reported by the other trials, *Appendix Table 4 LaTME*.(41)

The 4 studies reported an abdominoperineal resection(APR) percentage of 11-29%, and had a weighted colostomy rate of 27%, *table 1 weighted averages.* Conversion to open surgery was done in 13.7% and laparoscopic TME resulted in 8% anastomotic leakage. The retrieved crude data can be found in *Appendix Table 4 LaTME*.

Short-term morbidity and anastomotic Leakage

The reported short-term morbidity (30-day) of the retrieved TaTME series varies between 8.7% and 52% with a weighted average of 31.5% versus an average of 39.6% short-term morbidity in laparoscopy. *Table 1 weighted averages* In the meta-analysis of short-term morbidity, an average rate of 0.32 (95% CI 0.28 – 0.36, I^2= 25.8%) of TaTME versus 0.39 (95% CI 0.33 - 0.46, I^2= 80.6%) laparoscopy was calculated, but with serious risk at heterogeneity for laparoscopic TME. *Figure 2a and 2b.*

The incidence of anastomotic leakage, defined as (partial dehiscence) was more or less equal for weighted average of laparoscopic (8.0%), TaTME (6.9%) and the Registry (7.8%), *table 1 weighted averages*. Interestingly, anastomotic failure, including pelvic abscess, fistula and sinus reached 15.8 % if the 30- day was extended to 3 months.(25) The meta-analysis of the weighted average of the proportions can be found in *figure 3a and 3b.*

For TaTME specific intraoperative complications such as pelvic (sidewall or prescaral) bleeding and urethral injury, 10 (1.7%) and 5 (0.7%) cases were reported. The international TaTME registry report 4.2% intraoperative bleeding and 0.8% (n=12) urethral injuries, *table 1 weighted averages.* The 30.6% intraoperative complication rate included technical aspects, such as difficulties with the transanal platform.(25)

Conversion

Conversion to open surgery is encountered less frequently in TaTME, 2.0% versus 13.7%. The registry reports an intermediate conversion rate of 5.6 percent. *Table 1 weighted averages.* Meta-analysis by inverse variance with a random effects model resulted in a 0.03 (95% confidence interval 0.02-0.05) rate of conversion in TaTME with low risk of heterogeneity (I^2 = 0%), *Figure 4a*. In laparoscopic TME this was 0.13 (95% CI 0.09-0.16, I^2 = 69.6%) with risk of heterogeneity, *Figure 4b*.

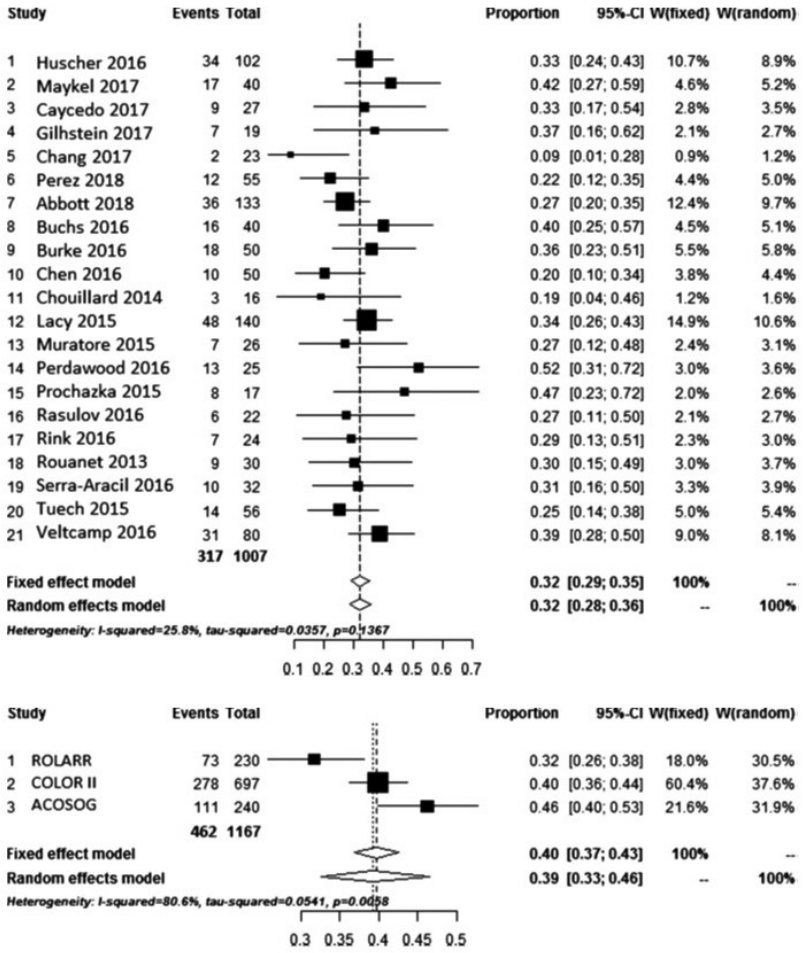

Figure 2 Morbidity Meta-analysis of the single proportions by inverse variance with a random effects model. Proportions are shown with 95% CI. (A) TaTME morbidity; (B) LaTME morbidity. TaTME, transanal total mesorectal excision; LaTME, laparoscopic TME.

Colostomy

The four RCT's of laparoscopic TME encompassed an average of 20% abdominoperineal resection (APR) for TME surgery, with a definitive stoma rate of 27%. *Table 1 weighted averages* and *Appendix Table 4 LaTME*. The retrieved TME series varied in inclusion criteria for APR's, intersphincteric TME and low anterior resections. Therefore, an average APR-rate could not be calculated, but the reported definitive stoma rate was 7.6%. The registry paper focused on anastomotic leakage and excluded APR's. However, the supplement stated 161 registered APR's leading to an 12% definitive stoma rate in which also total proctocolectomies or completion proctectomies for benign indications were included.(25)

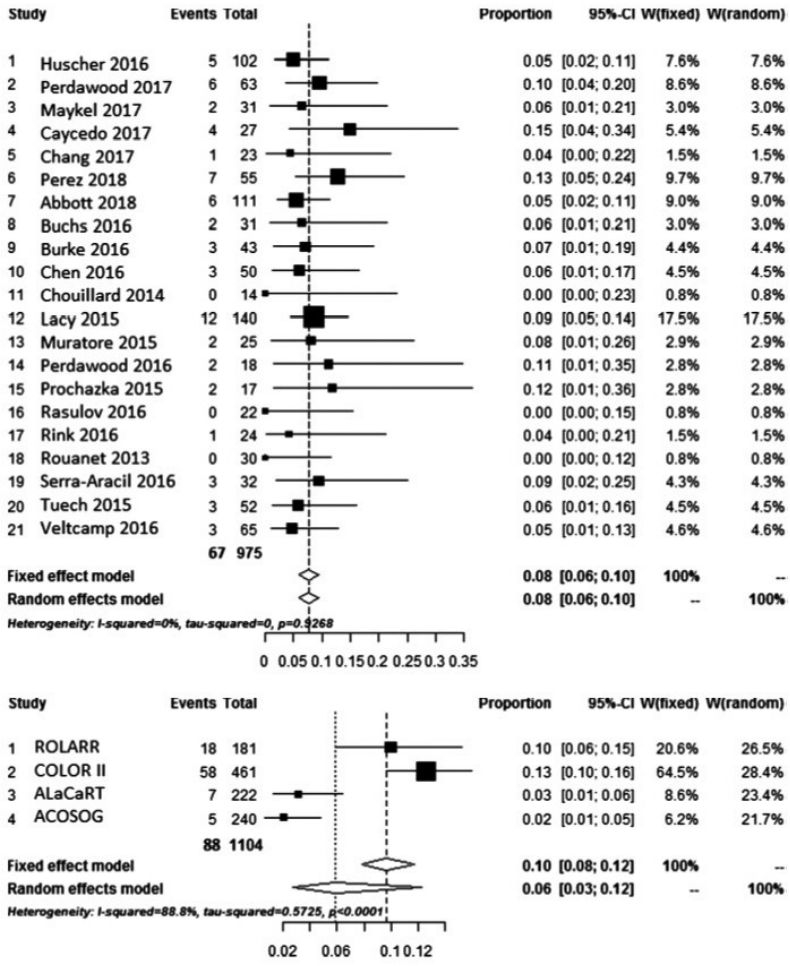

Figure 3 Leakage Meta-analysis of the single proportions by inverse variance with a random effects model. Proportions are shown with 95% CI. (A)TaTME leakage; (B) LaTME leakage. TaTME, transanal total mesorectal excision; LaTME, laparoscopic TME.

Irradicallity

The integrity of the mesorectum, defined by Quirke, was complete in 81.5% in laparoscopy and 86.2% in TaTME. *See table 1 weighted averages.* Distal resection margin positivity was 1.0% and 0.7% for LaTME and TaTME respectively. The weighted rate of a positive circumferential resection margin (CRM), was 7.9% versus 4.6% in the Laparoscopic TME and TaTME groups respectively. See *table 1 weighted averages.* For the pathological outcomes of the latest paper from the group of Lacy *et al.* was used.(38) Meta-analysis of complete mesorectum and CRM+ for both approaches are shown in *Figures 5a-5b and 6a-6b.* The percentage of complete is 86% vs 80% in the transanal versus pure laparoscopic approach, but with a high I^2 of 90.8% in laparoscopic TME.

The weighted average of the proportions shows a positive CRM of 0.08 (95% CI of laparoscopic 0.06 – 0.11, I^2=58%) in laparoscopy compared to 0.06 in TaTME (95% CI 0.04 – 0.07, I^2=0).

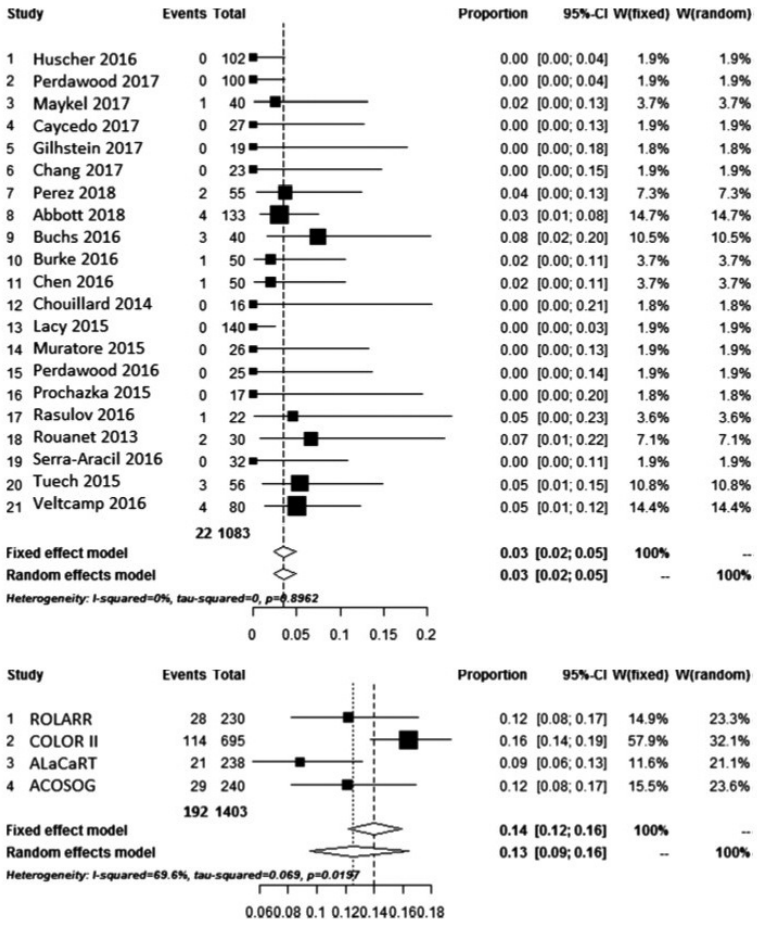

Figure 4 Conversion Meta-analysis of the single proportions by inverse variance with a random effects model. Proportions are shown with 95% CI. (A) TaTME conversion; (B) LaTME conversion. TaTME, transanal total mesorectal excision; LaTME, laparoscopic TME.

Local recurrence

Local recurrence(LR) rate was reported 5% the 3-year follow-up paper in COLOR II-trial (39). None of the other laparoscopic TME trials reported 3-year follow-up yet. Neither the TaTME papers reported 3 years follow-up with LR percentages. However, an incidence of 17 local recurrences was reported. (37, 46, 51, 59, 61, 62). Of these 17

local recurrences, 5 were reported by Rouanet et al. who included locally advanced rectal cancer or local recurrences in his TaTME-series.(59)

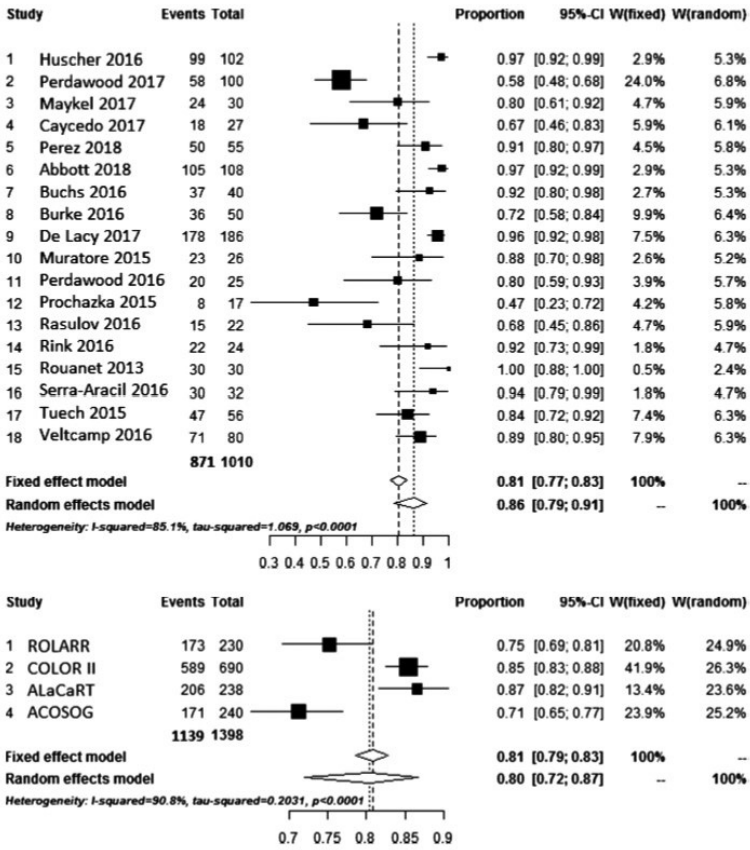

Figure 5 Mesorectum complete Meta-analysis of the single proportions by inverse variance with a random effects model. Proportions are shown with 95% CI. (A) TaTME mesorectum complete; (B) LaTME mesorectum complete. TaTME, transanal total mesorectal excision; LaTME, laparoscopic TME.

DISCUSSION

This is the latest systematic review of all the cohorts larger than 15 patients, describing the short-term results of TaTME. Because the comparison with LaTME is most important in evaluating the potential benefits of TaTME and comparative prospective clinical trial are still lacking we have added the result of the 4 latest randomized trials evaluating LaTME. TaTME compared to LaTME is beneficial in terms of conversion rate and clinicopathological outcomes, morbidity and anastomotic leakage seems comparable. End

colostomy (APR) rate and local recurrences could was not reliably reported by the retrieved studies, due to design and lack of long-term follow-up.(37, 38, 42-62) Before widespread implementation can be justified, careful evaluation is warranted because morbidity has not decreased, and the rate of local recurrence is still a concern and needs thorough evaluation in an RCT with quality control of surgery and data.(63)

The short-term overall morbidity in TaTME was 31.5% which is beneficial compared to the registry data of 34.8% and pooled LaTME of 39.6%. This 31.5% rate of the TaTME cohorts must be interpreted with caution since morbidity was not reported in a standardized way such as the Clavien-Dindo classification. A concern in (laparoscopic) rectal cancer surgery remains anastomotic leakage which was 8% in the latest laparoscopic RCT data. It was imposed that leakage could be decreased by TaTME as a consequence of a new way of making an anastomosis without the need for cross stapling leaving dog-ears which are prone to ischemia.(25, 64) However, the current data do not suggest a decrease with a reported 30-day leak rate 7%. The open rectal stump which results after the dissection needs to be fused with the descending colon to create the anastomosis. This can be performed either by a hand sewn colo-anal anastomosis for very low anastomosis or by a stapled colo-rectal anastomosis with a circular stapling technique with the aid of a second purse string to close up the open rectal stump, which is described in detail in the 2016 paper in Techniques of coloproctology.(64) TaTME potentially leads to more bacterial load as showed by Velthuis et al. and needs further investigation of the rate of anastomotic failure or pelvic abscess.(65) The registry reported an anastomotic failure rate of 15.7% when late complications of the anastomosis such as fistula, chronic abscess or presacral sinuses were included.(25) These numbers are comparable to the anastomotic leak rate, defined as not only early dehiscence but includes presacral abscess or sinus, which builds up to 20% beyond the 30 day cut-off.(6)

This paper shows a promising conversion rate of 2% in TaTME in the cohort series compared to 5.6% in the TaTME registry compared to 12.2 - 16.6% for LaTME as reported in the ROLARR and laparoscopic arms of the COLOR II, ALaCaRT and ACSOG-Z6501 trials.(8, 9, 40, 41) The main reasons for conversion to open surgery are extensive adhesions, intra-operative complications such as major bleeding, the inability to make progress in sharp dissection of the mesorectal envelope or to achieve a clear distal margin below the tumor.(12) Risk-factors that contribute to difficulty are male sex, high body mass index(BMI) , visceral obesity, narrow pelvis, bulky tumours or more advanced stage of the tumours and these patients might be candidates for a down to up approach of mesorectal excision.(10, 11, 66)

The average 20% APR-rate in laparoscopic TME surgery for rectal cancer as stated before impacts quality of life. This extensive procedure with resection of the sphincter complex is not always required from oncological point of view, which is mostly the

risk of CRM+ due to ingrowth in the sphincter complex or m. levator ani, but is also performed for technical reasons such as the inability to get a satisfactory distal margin intraoperatively.(16) Definitive colostomy–rate is even higher, adding some sphincter sparing Hartmann procedures without restoration of bowel continuity. TaTME enables lower sphincter saving, or intersphincteric, dissections with a colo-anal anastomosis in selected cases.(16) Unintended APR rate resulting in end colostomy was an endpoint which could not be evaluated. The RCT series did not report the incidence of planned versus unplanned; one study reported an end colostomy rate of 79,7% in LaTME for the low rectum(0-5 cm from the AV).(9)

The circumferential resection margin positivity, an important predictor of local recurrence, was found to be less frequently involved in TaTME.(67) This can be contributed by improved visualization of the surgical plane and improved ergonomics in the dissection of especially the lower (meso)rectum.(1, 2)

The integrity of the mesorectal envelope surrogates surgical quality by pursuing a smooth specimen which is correlated to local recurrence.(68) This review shows that TaTME results in better mesorectal integrity for TaTME as shown in *table 1 weighted averages*. Positive distal resection margins are rarely encountered since the tumor can be directly visualized by the transanal endoscopic view.(4) Furthermore, in case of a stapled anastomosis, the donuts of the EEA-31 hemorrhoid stapler add an extra 16 mm margin in addition to the original specimen.(64) Local recurrences are not well reported in the TaTME cohorts. Overall, 17 local recurrences were reported with a varying follow-up (9.7-29.0 months). The registry has not reported long-term oncological outcome and will probably underreport this fact because of the voluntary non-audited design. The trial data of LaTME reports a 5% local recurrence rate at 3-year follow-up.(39)

The lack of long-term outcome underlines the importance of a prospective trial with quality assurance and with auditing of the long-term data. Potentially tumor spill due to inadequate closure of the rectum or due to seeding due to manipulation could be a concern of the TaTME technique.

The cohorts and registry contain unaudited data and publication bias, therefore concern has risen about unreported poor outcomes. Urethral injuries have been mentioned at symposia and training sessions frequently, but fail to be equivalently reported in manuscripts.(4, 25, 69) Other potential injuries such as side wall injury with the risk at major haemorrhage or autonomous nerve injury and a too low stapled anastomosis resulting in poor outcomes are also concerns especially in the learning curve. These potential disastrous complications warrant restraint of wide-spread rigorous implementation of the technique without proper training and auditing.(22, 70, 71)

Although this review contains the most up-to-date overview of the available data substantial limitations are present which precludes any conclusion about the value of TaTME. Only cohort data with selection bias, publication bias and lack of audit. The registry data contains similar bias since data is missing and no audit of the data is present. Comparing RCT with cohort data is only presented due to lack of other comparative data and only serves as an indication. RCT's often have better results compared to registries since the learning curve is less an issue whereas the TaTME data is biased by a learning curve which has shown to be associated with increased morbidity and worse specimens. The learning curve of laparoscopy has been set at 50-60 patients previous decade, measured by conversion and morbidity.(72, 73) Koedam et al. analyzed the individual learning curve of a surgeon starting TaTME, and concluded is achieved after 40 cases and 60 more are required to get to the level competent to teach others.(77)

To shorten this learning curve, a training pathway has been designed which covers e-learning, live surgery, hands on cadaver course and on-site proctoring.(32, 70, 71) The international TaTME consensus meeting on the design of a training-pathway concluded due to the technical demanding aspect of TaTME this approach should be reserved for dedicated colorectal surgeons who have extensive experience in both laparoscopic colorectal surgery and TAMIS for local excision.(70) The results of the Australian & New Zealand training and implementation program that were included in this review reported the outcomes of 12 surgeons that performed 108 cases TaTME for rectal cancer with a 5.4% anastomotic leak rate, 1.9% CRM+, 0% DRM+ and an intact TME specimen in 107 cases (98.2%) suggesting high quality surgery.(49)

Another need is quality assurance to ensure proficiency and safety and avoid patients and results of trials to be hampered by suboptimal performance of not sufficiently trained surgeons.(74, 75) A well designed trial with these components, in order to capture the real advantage and potential harms of a technique within a training pathway and a patient safety environment, avoids underreporting of poor outcomes and a randomized trial is best suited to rule out bias of excellence centers.

It is well recognized that randomization often discourages patients and surgeons which are in favor of one technique but no other trial design yet has been able to reproduce the level of evidence an adequately powered and executed RCT provides.(76)

CONCLUSION

Continuous cohort reports on TaTME indicate a benefit in conversion rate compared to laparoscopic TME and potential increase in sphincter preservation. However, morbidity including anastomotic leakage and by this novel approach introduced specific

complications as urethral or pelvic side-wall injury need prospective audit. A significant learning curve is present in the implementation and hampers fair comparison. Long-term oncological outcome does not seem to improve so far but randomized controlled trial with proper quality assurance is best suited to provide data on short-term outcomes as well long-term oncological safety.

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7

Structured training pathway and proctoring; multicenter results of the implementation of transanal total mesorectal excision (TaTME) in the Netherlands

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ABSTRACT

Background: Transanal Total Mesorectal Excision (TaTME) is a new complex technique with potential to improve the quality of surgical mesorectal excision for patients with mid and low rectal cancer. The procedure is technically challenging and has shown to be associated with a relative long learning curve which might hamper widespread adoption. Therefore a national structured training pathway for TaTME has been set up in the Netherlands to allow safe implementation. The aim of this study was to monitor safety and efficacy of the training program with 12 centers.

Methods: Short term outcomes of the first ten TaTME procedures were evaluated in 12 participating centers in the Netherlands within the national structured training pathway. Consecutive patients operated during and after the proctoring program for rectal carcinoma with curative intent were included. Primary outcome was the incidence of intraoperative complications, secondary outcomes included postoperative complications and pathological outcomes.

Results: In October 2018, 12 hospitals completed the training program and from each center the first 10 patients were included for evaluation. Intraoperative complications occurred in 4.9% of the cases. The clinicopathological outcome reported 100% for complete or nearly complete specimen, 100% negative distal resection margin and the circumferential resection margin was positive in 5.0% of patients. Overall postoperative complication rate was 45.0%, with 19.2% Clavien-Dindo ≥ III and an anastomotic leak rate of 17.3%.

Conclusions: This study shows that the nationwide structured training program for TaTME delivers safe implementation of TaTME in terms of intraoperative and pathology outcomes within the first ten consecutive cases in each center. However, postoperative morbidity is substantial even within a structured training pathway and surgeons should be aware of the learning curve of this new technique.

INTRODUCTION

Transanal total mesorectal excision (TaTME) has been proposed as a potentially better alternative to the laparoscopic standard TME for mid and distal rectal cancer.(1-4) The bottom up approach for the deep pelvic region increases exposure and facilitates the distal mesorectal excision. Especially those difficult cases such as obese patients, low rectal cancer and (male) patients with a narrow pelvis seem to benefit from this approach.(5, 6) TaTME has been introduced in 2010 and has had enthusiastic uptake throughout the world.(7, 8) Current evidence from non-randomized studies shows that the TaTME technique for mid and low rectal cancer has similar short term clinical outcomes compared to laparoscopic TME (Lap TME) in terms of complications including anastomotic leakage, margin involvement and specimen quality. Especially the conversion rate seems to benefit from TaTME compared to Lap TME (2% versus 12%) as shown in both registry and systematic reviews.(8, 9) The circumferential resection margin (CRM) involvement after TaTME has shown to be slightly lower as observed in conventional or robotic TME in pooled analysis by weighted averages: 4.6% versus 7.9% versus 5.1% respectively.(8-10) However, direct comparison in large trials have yet to confirm this difference and demonstrate oncological safety. Within the international TaTME registry, a relative high percentage of intraoperative and postoperative complications has been presented including an anastomotic failure rate of 15.7%.(9, 11) Since the TaTME has only recently been introduced a learning curve is probably partly a reason for the relative high morbidity rate. TaTME seems technically demanding because of the required single port surgery skills and due to a different approach to the anatomy: down-to-up.(12) The traditional landmarks are missing and surgeons inexperienced in this technique may encounter TaTME specific related complications. A well trained TaTME surgeon might show benefits, but for those less trained and capable surgery by TaTME will probably result in worse short- and long-term outcomes. A meta-analysis of TaTME cohorts showed a quality difference in low- versus high-volume centers, indicating a potential learning curve.(2, 12)

The technical challenges and accompanying learning curve of the TaTME technique resulted in the off sprout of dedicated courses all over the world. In the Netherlands a structured training pathway was set up in 2014 including a multiple step program of e-learning, didactic courses, detailed anatomy instruction, observation of a TaTME live procedure, a hands-on cadaver workshop and the first cases proctored by TaTME experts. The current training pathway was set up to ensure adequate skills to participate in the COLORIII study, an international multicenter study evaluating the TaTME technique in terms of short- and long- term outcome powered upon oncological safety.

The aim of the present study was to capture the safety, clinical and pathological outcomes of the implementation of TaTME in centers within the structured training pathway by collecting the data from the first ten patients in each participating center.

MATERIALS AND METHODS

Training pathway

The education and training pathway was set up in The Netherlands in 2014 as a structured program for postgraduate colorectal surgeons with known experience in laparoscopic TME surgery who had the intention to implement the TaTME technique in their center. In order to successfully introduce the TaTME technique minimal pre-requisites were set out in order to enter the pathway. 1. Adequate skills and experience; prior training and experience in laparoscopic rectal cancer surgery with at least 50 laparoscopic TME cases. 2. Prior TAMIS experience; knowledge and skills of the transanal single port technique. 3. Case volume; the number of TaTME cases a year should be at least 20 /year /center to ensure sufficient exposure of the entire team. 4. Adequate medical instruments including a continuous air insufflation system, an adequate transanal platform and the possibility to perform a two-team approach.

This training program comprises of a 2-day hands-on course in which a maximum of ten surgeons can participate enabling intensive interaction and individual tutoring. The course incorporates three different elements; didactic sessions, live TaTME surgery and a hands-on training including box trainers and a cadaveric course. Didactic sessions included topics as theoretical background of TaTME, extensive pelvic anatomy by an anatomist, procedure specific pitfalls (urethral injury, wrong plane of dissection e.g.), patient selection, setup of surgical equipment and step-by-step procedure training. Part of the education was available online (www.rectalcancersurgery.eu and www.iLappSurgery.com). The second part consisted of a multidisciplinary team (MDT) discussion of a case and a live TaTME case, performed at the Amsterdam University Medical Centers – location VUmc. Both surgeons and scrub nurses were invited as observers and technique was interactively demonstrated with informed consent of the patients.

The third part of the training was a full day hands-on training including box-training for the single port technique skills and training the purse string. The final part was to practice an entire TaTME procedure on a cadaver in pairs, with experienced faculty providing help. At time of writing over 200 surgeons from all over the globe have participated in one of our 22 courses since its launch in 2014.

The implementation of the technique in the center of the trainees was done by a structured clinical proctoring program until adequate proficiency was reached in agreement with the proctor to proceed alone. The group of proctors consists of eight surgeons who have each performed over 50 cases of TaTME and are trained in surgical education. Patients were informed to undergo a proctored TaTME. After each case evaluation with the team was done. If requested by proctor or participating surgeon,

an additional case of proctoring could occur in order to guarantee the quality as much as possible.

In October 2018, hospitals that have successfully completed the proctoring program were approached to share the data of the first ten TaTME procedures performed on patients with rectal cancer with curative intent. All of the 12 hospitals that were eligible to participate in our study agreed on participation.

TaTME Surgical procedure

The technique has been highly standardized as previously described.(13) First, the laparoscopic transabdominal phase starts with standard medial to lateral mobilization of the splenic flexure. Next the patient is positioned in Trendelenburg and a medial to lateral approach to the sigmoid and rectum is performed, after the ligation of the superior artery including sigmoidal branches with preferably sparing of the left colic artery. Thereafter the dissection is continued in the TME plane dorsally, both sides laterally and the beginning anteriorly. Identification of ureters and hypogastric plexus and nerve bundles has been mandatory. After ligation of the vessels, the transanal phase is started simultaneously with insertion of the transanal port and establishing pneumorectum with abdominal clamping of the distal sigmoid to avoid a pneumocolon. After closure with a purse string of the rectum below the tumor and ideal above the anorectal junction, the rectal tube is rinsed with povidone-iodine solution. After a full-thickness endoscopic transection of the rectum is achieved, the posterior TME plane, anterior plane and both lateral planes are dissected, the latter with the help of abdominal retraction of the rectum. Anastomosis is preferably constructed with a circular stapling technique either side-to-end or end-to-end, specimen retraction is preferably done by a pfannenstiel incision.

Patients

The Medical Ethics Review Board of the VU Medical Center in Amsterdam approved the study protocol and waived the need for informed consents. The first ten consecutive patients from each participating hospital with clinical suspicion of rectal cancer in whom a TaTME was performed with curative intent were eligible for this study. In October 2018, 12 hospitals completed our proctoring program and were all willing to participate in this study. All participating surgeons followed the structured TaTME training in the VU medical center prior to the proctoring program. Data were provided anonymously by the participating surgeon and checked by research assistants. No cases were excluded and all cases were consecutively. For the evaluated cases, all data was collected anonymously with entry as case numbers. In order to calculate the distance from the anal verge (AV) when only distance from anorectal junction was provided, the tumor distance measured from the anorectal junction was corrected by adding four centimeters for males and females.(14-17) The part of the rectum in which

the tumor was situated was defined by distance from the AV as 0-6 cm, 7-11 cm 12-15cm for low, mid and high rectum respectively.(15)

Outcomes

Primary outcomes were intraoperative complications. Secondary outcomes included operation time, conversion to laparotomy and postoperative complications, length of stay and pathological outcomes (e.g. circumferential and distal resection margin, completeness of mesorectum according to classification of Quirke et al.).(18) In order to show a potential learning curve, outcomes of the first five procedures were compared to the outcomes of the sequential five procedures.

Statistical analysis

A p-value <0.05 was considered statistically significant. For analysis of comparing results between the first and sequential five procedures, Chi-Square test (Fisher's exact test when appropriate) in case of categorical variables and Students T-test in case of continues variables were used. Mann-Whitney U test was used for continuous variables that were not normally distributed. Statistical analysis was performed using SPSS version 22 for Windows and Mac (SPSS, Chicago, Illinois, USA).

RESULTS

Baseline characteristics

A total of 120 patients was included of which 53 operated with attending proctor and 67 without attending proctor. Baseline characteristics are shown in Table 1. The majority of patients was male (n = 91, 75.8%). The mean BMI was 26.9kg/m^2 (standard deviation (SD) 4.0) and age 65.4 years (SD 9.9). Tumors were located in the lower rectum in 45%, middle rectum in 46.7% and upper rectum in 8.3% (Mean 6.9 cm from AV). Patients received either radiotherapy (n=41, 34.2%), chemoradiotherapy (n=36, 30.0%) or no neoadjuvant treatment (n=43, 35.8%). The majority of tumors was classified as cT3 (73.7%) on MRI in the preoperative work-up. When comparing the first and sequential cohort of 60 patients, ASA classification was significantly higher in the second group (p= 0.021) Remaining baseline characteristics did not differ significantly.

Operative details

Table 2 shows the intraoperative outcomes of all patients. Transanal TME with primary anastomosis and diverting ileostomy was performed in 64.1% of patients (n= 77). In one patient a transverse loop colostomy was performed due to clinical signs of obstruction prior to the TaTME. The most common anastomotic technique performed was mechanical stapling (94.9%) with a side-to-end or end-to-end anastomosis in 36.7% and 63.3% of patients respectively. Mean operative time was 293 minutes (SD 93.4). Intraoperative complications were reported in six patients (4.9%).

Table 1 Patient characteristics

		Structured training program n=120
Sex	*Male*	91 (75.8)
	Female	29 (24.2)
BMI (mean) (±SD)		26.9 (±4.0)
Age (years) (mean) (±SD)		65.4 (±9,9)
History of abdominal surgery	*No*	91 (75.8)
	Yes	29 (24.2)
History of transanal surgery	*No*	115 (95.8)
	Yes	5 (4.2)
ASA	*I*	25 (21.4)
	II	75 (64.1)
	III	17 (14.5)
	Missing data	3 (2.5)
Tumor height (AV) (cm) (mean) (±SD)		6.9 (±3.1)
Tumor stage	*T1*	6 (5.1)
	T2	23 (19.5)
	T3	87 (73.7)
	T4	2 (1.7)
	Missing data	2 (1.7)
Mesorectal fascia involvement	*No*	97 (82.2)
	Yes	21 (17.8)
	Missing data	2 (1.7)
Preoperative therapy	*None*	43 (35.8)
	RT	41 (34.2)
	CRT	36 (30.0)

Numbers in parentheses are percentages, unless mentioned otherwise
Abbreviations: *BMI* = Body Mass Index (kg/m^2), *SD* = standard deviation, *ASA* = American Society of Anesthesiologists, *cm* = centimeters, *AV* = anal verge, *RT* = radiotherapy, *CRT* = chemoradiotherapy

Two of this six complications occurred during the transanal phase (1.7%); a rectal perforation and difficulty dissecting the right lateral plane resulting in completing the dissection laparoscopically. Two pelvic bleeding, iatrogenic injury to the small bowel and combined ureter and bladder injury occurred in four patients during the laparoscopic phase (3.3%). In 5 out of 120 cases (4.2%) conversion to laparotomy was necessary, due to portal hypertension, a combined ureter and bladder injury, difficulties due to a BMI of 40 in combination with a small male pelvis and difficulty mobilizing the splenic flexure during the laparoscopic phase. The fifth conversion was done due to a difficult

Table 2 Operative details

		Structured training program n=120
Type of surgery	*LAR*	110 (91.7)
	Intersphincteric	10 (8.3)
Anastomosis	*No*	22 (18.3)
	Yes	98 (81.7)
Stoma type	*None*	20 (16.7)
	Diverting ileostomy	77 (64.1)
	*Colostomy^*	23 (19.2)
Technique anastomosis	*Hand sewn*	5 (5.1)
	Stapled	93 (94.9)
Type anastomosis	*Side-to-end*	36 (36.7)
	End-to-end	62 (63.3)
Specimen removal	*Pfannenstiel*	68 (57.6)
	Transanally	31 (26.3)
	Stoma site	3 (2.5)
	Laparotomy	5 (4.2)
	Small transverse incision	11 (9.3)
	Missing data	2 (1.7)
Operative time (min) (mean) (±SD)		293.0 (±92.6)
Blood loss (ml) (median) (range)		100.0 (0-4050)
Conversion*		5 (4.2)
Intraoperative events	*Urethral injury*	0 (0.0)
	Pelvic bleeding	2 (1.7)
	Rectal perforation	1 (0.8)
	Small bowel injury	1 (0.8)
	Ureter injury	1 (0.8)
	Technical problems#	1 (0.8)

Numbers in parentheses are percentages, unless mentioned otherwise
^ includes 1 in situ loop transversostomy
* includes 1 early conversion
# Complete unilateral dissection, unable to safely progress contralateral
Abbreviations: *LAR* = low anterior resection, *SD* = standard deviation, *min*= minutes, *ml* = milliliters

transanal phase; an inability to find a safe lateral plane due to a combination of a curved anatomy and the initial transanal unilateral dissection with connection to the peritoneal cavity. The first four conversions occurred during the abdominal phase and

without attending proctor, the latter with attending proctor. In summary, intraoperative complications occurred twice during the abdominal phase (1.7%), and in four cases (3.3%) during the transanal phase. For the non-converted cases, specimen removal was mostly performed through a pfannenstiel incision (57.6%) and secondly by transanal extraction (26.3%).

Table 3 Postoperative details

		Structured training program n=120
Hospital stay (days) (median) (range)		7 (3-43)
Postoperative complications CD	*None*	66 (55.0)
	Minor (CD I-II)	31 (25.8)
	Major (CD ≥ III)	23 (19.2)
	IIIa	*7 (30.4)*
	IIIb	*16 (69.6)*
Anastomotic leakage <30 days^		17 (17.3)
Anastomotic treatment^	*Endosponge*	5 (5.1)
	Temporary ileostomy	4 (4.1)
	Unintended colostomy	4 (4.1)
	Suture	2 (2.0)
	Drainage	1 (1.0)
	Novel anastomosis	1 (1.0)
30-day mortality		0 (0.0)

Numbers in parentheses are percentages, unless mentioned otherwise
^ Only patients selected with anastomosis (n=98)
Abbreviations: CD = Clavien-Dindo classification

Postoperative outcomes

Median hospital stay was reported as 7 days (range 3 - 43) (Table 3). Overall postoperative morbidity rate was 45.0% (n=54). Major complications within 30 days, graded as Clavien-Dindo IIIa or IIIb were seen in 19.2% (n=23) of patients. No Clavien-Dindo gr IV or V complications were reported. A primary anastomosis was performed in 81.7% of the cases(n=98) of whom 17 patients (17.3%) encountered anastomotic problems. Treatment in these cases occurred by colostomy (4), diverting ileostomy (4), resuture (2), drainage (1), novel anastomosis (1) and endosponge (vacuum therapy) (5). Four patients with a primary end colostomy developed a presacral abscess despite of the absence of an anastomosis which was treated by transanal drainage (2), CT-guided drainage (1) and endosponge (1). Overall, twenty patients had anastomotic problems or presacral abscesses of which 81% (n=17) was seen in patients with primary anastomosis.

Table 4 Pathology reports

		Structured training program n=120
Pathology stage	*pT0*	9 (7.6)
	pT1	16 (13.6)
	pT2	32 (28.8)
	pT3	59 (50.0)
	n.a.	2 (1.7)
Quality of specimen (Quirke)^	*Complete*	107 (89.2)
	Nearly complete	13 (10.8)
	Incomplete	0 (0.0)
CRM involvement		6 (5.0)
DRM involvement*		0 (0.0)
Lymph nodes harvested (mean) (±SD)		17.0 (±7.2)
Lymph nodes positive (median) (range)		0 (0-7)

Numbers in parentheses are percentages unless mentioned otherwise
^From Quirke et al. Lancet 2009 (reference 18)
*1 missing patient
Abbreviations: *CRM* = circumferential resection margin, *DRM* = distal resection margin, *SD* = standard deviation

Pathologic outcomes

The quality of specimens according to Quirke's classification was complete or nearly complete in all patients (89.2% and 10.8% respectively). A positive circumferential resection margin (tumor invasion <1mm from non peritonealized surface of the rectum) was reported in 5.0% of patients. Distal resection margins was negative (>1mm) in all 120 patients.

Short-term training

No significant differences in operative time between the first cohort of proctored and second cohort of unproctored five procedures per center were found (283.6 and 302.5 minutes respectively, p=0.266). (Table 5) In both groups three intraoperative adverse events occurred suggesting no major increase in intraoperative difficulties resulting in visceral injuries or an increase in conversion rate. A complete specimen (Quirke) was excised more frequently in the second cohort which was a significant difference; 80.0% versus 98.3% for procedure 1-5 and 6-10 respectively (p = 0.001). The circumferential resection margin involvement was slightly higher in the second half of procedures (1.7% versus 8.3%) but this did not reach significance. Postoperative morbidity was equal for the first and second cohort as can be seen in table 5. Severe short-term morbidity, defined as Clavien-Dindo ≥ III, was equally distributed. Moreover, anastomotic problems were encountered in 9 of 48 and 8 of 50 cases respectively.

Table 5 Learning effect within structured training program

		Patients 1-5 (60)	Patients 5-10 (60)	p-value
Sex (male)		45 (75.0)	46 (76.7)	.831
BMI (mean) (±SD)		26.5 (±3.5)	27.3 (± 4.5)	.269
Age (years) (mean) (±SD)		64.9 (± 10,3)	66.0 (± 9.5)	.540
ASA	*I*	15 (26.3)	10 (16.7)	0.017
	II	39 (68.4)	36 (60.0)	
	III	3 (5.3)	14 (23.3)	
Tumor height (AV) (cm) (mean) (±SD)		6.7 (3.1)	7.1 (3.0)	0.519
Tumor stage	*T1*	3 (5.1)	3 (5.1)	1000*
	T2	12 (20.3)	11 (18.6)	
	T3	43 (72.9)	44 (74.6)	
	T4	1 (1.7)	1 (1.7)	
Mesorectal fascia involvement	*No*	49 (83.1)	48 (81.4)	.810
	Yes	10 (16.9)	11 (18.6)	
Preoperative therapy	*None*	18 (30.0)	25 (41.7)	.406
	RT	22 (36.7)	19 (31.6)	
	CRT	20 (33.3)	16 (26.7)	
Type of surgery	*LAR*	53 (88.3)	57 (95.0)	.186
	Intersphincteric	7 (11.7)	3 (5.0)	
Operative time (min) (mean) (±SD)		283.6 (±80.1)	302.5 (±103.6)	.266
Conversion		1 (1.7)	4 (6.8)	.207*
Intraoperative complications		3 (5.0)	3 (5.1)	.1000*
Hospital stay (days) (median) (range)		8 (3-43)	7 (3-25)	.521*
Postoperative complications CD	*None*	31 (51.7)	35 (58.3)	.750
	Minor (CD I-II)	17 (28.3)	14 (23.4)	
	Major (CD ≥ III)	12 (20.0)	11 (18.3)	
Anastomotic leakage <30 days^		9 (18.8)	8 (16.0)	.719
Quality of specimen (Quirke)#	*Complete*	48 (80.0)	59 (98.3)	.001
	Nearly complete	12 (20.0)	1 (1.7)	
	Incomplete	0 (0.0)	0 (0.0)	
CRM involvement		1 (1.7)	5 (8.3)	.207*

Numbers in parentheses are percentages, unless mentioned otherwise
^ Only patients selected with anastomosis (n=98)
* Fisher's Exact Test or Fishers-Freeman-Halton Test or Mann-Whitney U Test
# From Quirke et al. Lancet 2009 (reference 18)
Abbreviations: *BMI* = Body Mass Index (kg/m^2), *SD* = standard deviation, *ASA* = American Society of Anesthesiologists, *RT* = radiotherapy, *CRT* = chemoradiotherapy, *LAR* = low anterior resection, *min* = minutes, *CD* = Clavien-Dindo classification, *CRM* = circumferential resection margin

Table 6 Structured training program compared to other studies

		Structured training program n=120	High volume n ≥ 30 cohorts n=478^	TaTME registry n=1594*	Lap TME trials n=1411#
Sex (male)		75.8	67.4	67.8	65
Age (years) (mean)		65.4	63.8	63.7	64
BMI (mean)		26.9	26.1	26.3	26.1-27
Neoadjuvant (c)RT		64.2	73.0	56.1	61.9
Tumor height (cm) (AV) (mean)		6.9	6.5	4.0$	NA
cT3 or cT4		75.4	69.3	69.0	NA
Conversion		4.2	2.7	5.6	13.0
Anastomotic leakage		17.3	NA	15.7	7.9
pT3 or pT4		50.0	45.1	43.5	NA
Quality of specimen (Quirke)&					
	Complete	89.2	89.7	85.8	87.0
	Nearly complete	10.8	9.0	10.8	13.0
	Incomplete	0	1.3	3.4	4.0
	Missing			9.7	6.0
CRM involvement		5.0	4.5	4.1	8.0
DRM involvement		0.0	NA	0.7	NA

All numbers are percentages, unless mentioned otherwise
^ From Deijen et al. Tech Coloproctology 2016 (reference 2)
* From Penna et al. Ann Surg 2018 (reference 9)
# From van Oostendorp et al. Annals of lap and Endoscop Surg 2018 (reference 8)
$ Median from anorectal junction
& From Quirke et al. Lancet 2009 (reference 18)
Abbreviations: TaTME = Transanal Total Mesorectal Excision, Lap TME = Laparoscopic Total Mesorectal Excision, BMI = Body Mass Index (kg/m2), (c)RT = (chemo)radiotherapy, cm = centimeters, AV = anal verge, CRM = circumferential resection margin, DRM = distal resection margin

DISCUSSION

This study shows the outcome data during the initial phase of a structured TaTME training and proctoring curriculum in the Netherlands in 12 centers, and within each center the first ten patients resulting in a total of 120 patients. We have demonstrated that the implementation within a structured training pathway is relatively safe with a low rate of intraoperative complications of 4.9% and good quality of resection and specimen. The resection quality as addressed by pathology showed that complete or nearly complete specimen was obtained in 100%, similar to negative distal resection margin. Circumferential resection margin was positive in 5.0% of patients. Postoperative complications according to Clavien-Dindo ≥III occurred in 19.2%. These results suggest that the structured training pathway does result in safe introduction of the technique without major intraoperative complications and safe results comparable to those obtained from laparoscopic TME surgery.(8, 19)

Compared to the international TaTME registry, especially the intraoperative event rate seems low; the registry reports 30.6% intraoperative adverse events rate, of which a vast majority (18%) regarded technical problems leaving 12.6% to visceral injuries (1.8%) of which 12 urethral injuries (0.8%), incorrect dissection planes (5.7%) and pelvic haemorrhage (4.2%).(9) Concern exists for underreporting since publications bias of cohort studies is present and rumors about intraoperative complications as urethral injury, pelvic sidewall injury, rectal tube perforation and venous CO2 embolisms are discussed at conferences and courses frequently but fail to be represented in the available literature. The proctor guided implementation of TaTME in the current series showed that intraoperative complications were encountered in 5.0% and conversion to laparotomy was necessary in 4.2%, suggesting that a proctor based introduction potentially lowers the frequency of intraoperative difficulties and adverse events. To illustrate this, no injuries to the urethra (0%) occurred and visceral injury was encountered in 3 of 120 cases (2.5%). An incorrect dissection plane was reported in one patient (0.8%) which is considerably lower than the 5.7% of the previously mentioned registry. Abbott et al.(20) recently published the results of implementing TaTME Australia and New Zealand using a training pathway which includes on-site proctoring and showed a safe introduction with low conversion rate (3%), no intraoperative visceral complications but did report two rectal wall perforations.

Postoperative morbidity was reported as 45% overall complications, including 19.2% major complication and 17.3% leakage rate. Although the structured training seems to provide intraoperative safety the postoperative event rate is high. Several reasons may account for this. First, all pelvic abscess and subclinical leaks were included and regarded as a anastomotic leakage. Second this is audited cohort data from multicenter cohort within a learning curve. Most likely the learning curve is associated with prolonged operating time and bacterial spill may negatively influence morbidity rate.(12,

21) It is shown that he learning curve of TaTME is associated with an increase in major surgical postoperative complications (Clavien-Dindo ≥III) in the first forty cases.(12) In this study the anastomotic leak rate was 27.5% for the first 40 cases and decreased to 5% for the next forty cases. In addition, the international registry data also shows a relative high anastomotic leak rate; 15.7%.(9, 12) Similar leakage rates have been reported by the Dutch national audit (90 days; 20%).(9, 22-24) The delayed leak and/or presacral abscess potentially may come as a consequence of the open rectal stump which raises a concern for bacterial contamination as demonstrated by Velthuis et al.(21) but needs further prospective investigation. Third reason for the experienced relative high morbidity is the selected patient group with 45% distal tumors and 64.2% was treated with neoadjuvant therapy. These distal tumor resections are more prone to morbidity.

Within the included centers no difference in intraoperative complications, postoperative morbidity or anastomotic leak rate was present when comparing the first proctored cohort of five to the second cohort of non-proctored patients. This suggests that the learning effect was not present for adverse outcomes in our training program and that therefore five cases seems efficient. However, evaluating a surgical learning curve needs higher number of cases (80) to allow a CUSUM analysis.(12, 25-27) Future studies will address learning curves within centers that have undergone a structured training curriculum.(2, 8, 28, 29) In laparoscopic surgery learning curve ranging from 100-150 cases as self-taught learning curve and 40-60 with proctoring/teaching programs is reported.(25, 28-30) The UK LapCo training program showed the safe widespread implementation of supervised training for laparoscopic colorectal surgery.(31) Within this program outcomes between experienced consultant trainers and trainees was similar regarding adverse events.(31, 32) In addition; a meta-analysis of Kelly et al.(33) on 19 studies reporting a total of 14.344 colorectal resections showed no significant increase in anastomotic leak rate, conversion or worse pathological outcomes in procedures performed by trainees.

In our series the primary end colostomy percentage of 18.8 is lower than the 34% in COLOR II.(23) However, compared to the 9% colostomy rate from the TaTME registry this seems a high rate.(11) Transanal total mesorectal excision possibly enables an increase of the creation of an anastomosis in lower rectal cancer which previously would have been subject for end colostomy. In further detail, this (very) low colo-rectal or colo-anal anastomosis might be suitable for patients without the oncologic necessity for an abdominoperineal resection but in whom it is technically impossible to create an anastomosis by only transabdominal laparoscopy. For this category the preoperative function of the anal sphincter is important in the consideration whether to make an anastomosis or an end-colostomy.(11) This can probably be attributed to patient selection in the beginning of implementation in the Netherlands, as surgeons

try to avoid major APE surgery for patients and select low rectal cancer for TaTME in order to achieve a primary anastomosis.

Long-term oncological outcomes in terms of local recurrences have to be awaited due to the limited duration of follow-up in this series. As CRM involvement seems to be a strong predictor of local recurrence, the encountered 5.0% is lower compared to 6.3-12.1% as reported by the recent Laparoscopic TME RCT's (Table 6) .(8, 10, 23, 34-37)The quality of the specimen as defined by Quirke et al. was incomplete in 0 out of 120 cases, with a significant increase of a complete specimen when comparing the proctored cohort versus the non-proctored cohort patients: 80% versus 93.3% respectively (p= 0,01). (18, 34) A non-significant difference of CRM involvement was observed (1.7% vs 8.3% p=0.207). This increase of CRM while oppositely improving the quality of specimen might be attributed to tumor characteristics which were not captured in this study. It might be contributed to a higher proportion of anterior located tumors where, due to tapering of the mesorectum towards the pelvic floor, the bowel wall is directly adjacent to the mesorectal fascia without any intermediary mesorectal fat. Distal resection margin was free in all cases suggesting a high rate of R0 resection in our series.

Some limitations of this study should be mentioned; the small sample size and the lack of more than ten patients per center. Nevertheless, the main purpose of this study was to show the feasibility and safety of the training and proctoring program; the low intraoperative complications and promising pathological outcomes indicates that competency to safely perform a TaTME is achieved. By extending the cohort to larger numbers per center; too many inclusions could therefore be seen as unethical, especially in case if we had encountered major intraoperative complications or R1 resections in the second half of the patients. We do feel that additional audit, quality control and potentially extension of the amount of procedures with a proctor should be deliberated in future series. At time of data accrual, all centers who completed the program have participated in this study.

CONCLUSION

This study describes the safe introduction of TaTME in the Netherlands within a structured training program deemed necessary due to the high complexity of this novel surgical approach. Intraoperative complication rate was low and TaTME specific complications such as pelvic sidewall injury and urethral transection occurred rarely. However, postoperative morbidity and anastomotic leak rate emphasize the need for careful implementation and need for randomized data as well as long-term outcomes on local recurrences.

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8

Locoregional recurrences after transanal total mesorectal excision of rectal cancer during implementation

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ABSTRACT

Background: Transanal total mesorectal excision (TaTME) has been proposed as an approach in patients with mid and low rectal cancer. The TaTME procedure has been introduced in the Netherlands in a structured training pathway, including proctoring. This study evaluated the local recurrence rate during the implementation phase of TaTME.

Methods: Oncological outcomes of the first ten TaTME procedures in each of 12 participating centres were collected as part of an external audit of procedure implementation. Data collected from a cohort of patients treated over a prolonged period in four centres were also collected to analyse learning curve effects. The primary outcome was the presence of locoregional recurrence.

Results: The implementation cohort of 120 patients had a median follow up of 21.9 months. Short-term outcomes included a positive circumferential resection margin rate of 5.0 per cent and anastomotic leakage rate of 17 per cent. The overall local recurrence rate in the implementation cohort was 10.0 per cent (12 of 120), with a mean(s.d.) interval to recurrence of 15.2(7.0) months. Multifocal local recurrence was present in eight of 12 patients. In the prolonged cohort (266 patients), the overall recurrence rate was 5.6 per cent (4.0 per cent after excluding the first 10 procedures at each centre).

Conclusion: TaTME was associated with a multifocal local recurrence rate that may be related to suboptimal execution rather than the technique itself. Prolonged proctoring, optimization of the technique to avoid spillage, and quality control is recommended.

INTRODUCTION

The transanal total mesorectal excision (TaTME) technique has been introduced for patients with low rectal cancer, with the aim of improving clinical outcomes, such as a greater degree of radical resection, lower rates of anastomotic leakage, more sphincter-saving procedures, better functional results and, most importantly, similar or lower local recurrence rates.(1, 2) Direct visualization facilitates purse-string suture placement. The technique has been met with tremendous enthusiasm in the colorectal surgical community, and more than 300 centres worldwide have implemented the technique.(3) In expert centres, TaTME is associated with promising pathological and clinical outcomes.(4-8) The first long-term outcome data from two expert centres showed a favourable low recurrence rate of 2 per cent after 3 years.(9)

Despite these positive results, it is also acknowledged that TaTME is a difficult technique and has a long learning curve with associated morbidity.(10, 11) The international TaTME registry(3) and a systematic review(4) have shown that widespread adoption results in less favourable clinical outcomes than reported in the initial cohorts treated in expert centres. The TaTME registry(3), representing more than 300 centres voluntarily entering data, recorded an anastomotic failure rate of 15.6 per cent among 1594 patients, which is higher than rates from expert centres. In addition, a population-based study(12) documented an overall morbidity rate of 42.3 per cent, anastomotic leakage in 16.0 per cent and a circumferential resection margin (CRM)-positive rate of 4.4 per cent. These latter studies show that the promise of TaTME has not yet been met on a large scale.

The long-term oncological safety of TaTME remains to be proven. Although the first report with long-term outcome data showed a low level of local recurrence, the question remains whether such results can be achieved with more widespread adoption of TaTME.(9) As TaTME is substantially different from abdominal techniques in terms of open access to the tumour, purse-string closure and a subsequent endoluminal approach to the mesorectal dissection, it is especially important to assess long-term outcomes properly. RCTs such as COLOR III(13) and GRECCAR 11(14) are investigating long-term outcomes of TaTME, and are currently including patients. Recently, concern has been raised by the first report(15) of national Norwegian data which showed an increase in the incidence of local recurrence with an extensive or multifocal pattern following TaTME, leading to a national halt to TaTME.(16)

In the Netherlands, a structured training pathway, including proctoring sessions by dedicated trainers, has been set up to ensure safe implementation of TaTME and minimization of learning curve effects.(17) A collective review of the short-term outcomes of the first ten patients in 12 proctored centres revealed a major morbidity rate of 19.2 per cent and involved CRMs in 5.0 per cent of patients.(17) The aim of the present study was to evaluate the oncological outcomes of the initial patients who

underwent TaTME within the structured training pathway. In addition, a cohort treated over a prolonged period after the implementation of TaTME in four high-volume centres was evaluated to analyse learning curve effects in terms of local recurrence rates.

METHODS

Structured training pathway

The structured training pathway was set up in the Netherlands in 2014 as a programme for postgraduate colorectal surgeons in centres with an annual volume of total mesorectal excision (TME) surgery for rectal cancer of 20 procedures or more and with known proficiency in laparoscopic TME. The clinical data from patients in the structured training pathway was collected prospectively, as described previously.(17) The first five procedures were discussed with and assisted by an experienced proctor, after which the following procedures were performed independently. The first ten patients in each of centres that completed the structured training pathway were included to evaluated clinical outcomes during the implementation of TaTME.(17) In addition, a larger cohort of patients from four centres that continued TaTME after training, with a procedure volume greater than 45, was collected to assess learning curve effects. Long-term clinical data were obtained as part of an external audit to assure high quality and completeness of the data set. The anonymized operative notes and full imaging reports of locoregional recurrences were obtained and audited by senior TaTME surgeons. All patients consented to a TaTME procedure as required under the Dutch national patient–physician relation regulations. The Medical Ethics Review Board of Amsterdam UMC, Location VUmc, approved the study and waived the need for additional informed consent for the present study

Outcomes

The primary outcome of this study was the incidence of local recurrence confirmed by either imaging (MRI, CT or PET–CT) and/or pathology (biopsy, salvage surgery). A local recurrence was defined as a mass in the pelvis with a biopsy positive for adenocarcinoma, or growth on sequential imaging in the absence of histopathological confirmation. A multifocal local recurrence was defined by the presence of two or more separate foci of recurrence in the pelvic area, as seen on MRI or PET–CT. Secondary outcomes included location of local recurrence and distant metastasis, treatment of recurrence and distant metastasis, and overall mortality. All potential risk factors were evaluated for an association with recurrence. Pelvic sepsis was defined by the occurrence of early anastomotic leakage, early pelvic abscess or late complications (leakage, abscess or presacral sinus occurring more than 30 days after operation).(18) Complications were graded according to the Clavien–Dindo classification.(19) Rectal perforation, purse-string failure and an insufficient anastomosis requiring reinforcement or refashioning were deemed to increase the risk of spillage of tumour

cells into the pelvis. A positive CRM was defined by the presence of tumour cells 1 mm or less from the circumferential plane.

Statistical analysis

Categorical data are shown as number with percentage, whereas continuous outcomes are recorded as mean(s.d.) or median (range). Dichotomous and categorical values were analysed using Pearson's χ^2 square test or Fisher's exact test. Comparison of continuous data was done using the independent Student's *t* test, or Mann–Whitney *U* test if the data were not distributed normally.

Univariable logistic regression analysis was performed to identify potential risk factors for local recurrence. Multivariable analysis was not possible because the event rate did not exceed the threshold for entry of multiple univariable significant predictors into a multivariable model. Case–control analysis between the present TaTME group and the laparoscopic TME group from the original COLOR II study was performed by matching sex, age, tumour height, neoadjuvant chemoradiotherapy, type of procedure (low anterior resection or abdominoperineal resection) and pathological risk factors, R1 and CRM and pT4 category.(20, 21) Patients with a final pT4 category or positive margins were excluded to enable evaluation of the technique as a potential individual risk factor for recurrence. For all tests, two-sided $P \leq 0.050$ was considered statistically significant. Statistical analyses were done using SPSS® version 24 for Windows® and Mac® (IBM, Armonk, New York, USA).

RESULTS

Baseline characteristics and clinical outcomes

A cohort of 120 patients, comprising the first ten patients in each of 12 centres who underwent TaTME between March 2015 and October 2018, was included. Median follow-up was 21.9 (range 2.0–46.7) months. The median interval between the first and tenth procedures in each hospital was 12.5 (range 3.5–35.5) months. Baseline characteristics have been published previously and are shown in *Table 1*.(17)

Short-term outcomes are summarized in *Table 2*. The overall 30-day morbidity rate was 45.0 per cent, including an anastomotic leakage rate of 17 per cent and pelvic sepsis in 17.5 per cent. The involved CRM rate was 5.0 per cent; no patient had an involved distal resection margin. The quality of the specimen was rated as complete in 89.2 per cent of procedures and nearly complete in 10.8 per cent; none of the specimens were considered incomplete.

Table 1 Patient characteristics

	No. of patients* (n=120)
Age (years)†	65.4(9.6)
Sex ratio (M : F)	91 : 29
BMI (kg/m²)†	26.9(4.1)
ASA fitness grade	
I	26 (21.7)
II	77 (64.2)
III	17 (14.2)
Tumour height from anal verge (cm)†	6.9(3.1)
Clinical tumour category	
ycT1	7 (5.8)
ycT2	24 (20.0)
ycT3	89 (74.2)
Clinical node category	
cN0	52 (43.3)
cN1	44 (36.7)
cN2	24 (20.0)
Persistent MRF+ after RT‡	6 (5.0)
Preoperative therapy	
None	43 (35.8)
RT	41 (34.2)
CRT	36 (30.0)
Transanal total mesorectal excision	
Low anterior resection	110 (91.7)
Intersphincteric resection	10 (8.3)

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.). ‡All patients with a persistent theatened mesorectal fascia (MRF+) initially had cT3 tumours (3 anterior, 2 lateral, 1 unknown). RT, radiotherapy; CRT, chemoradiotherapy.

Table 2 Short-term clinicopathological outcomes

	No. of patients (n=120)
Intraoperative events	
Purse-string failure	1 (0.8)
Perforation	1 (0.8)
Reinforcement	3 (2.5)
30-day mortality	0 (0)
30-day overall morbidity	54 (45.0)
Major morbidity (Clavien–Dindo grade ≥ III)	23 (19.2)
30-day anastomotic leakage	17 of 98 (17)
Pelvic sepsis (early leak, abscess and late sinus*	21 (17.5)
Pathological tumour category	
(y)pT0	11 (9.2)
(y)pT1	16 (13.3)
(y)pT2	34 (28.3)
(y)pT3	59 (49.2)
(y)pT4	0 (0)
Quality of specimen (Quirke)*	
Complete	107 (89.2)
Nearly complete	13 (10.8)
Incomplete	0 (0)
CRM involvement ≤ 1 mm	6 (5.0)
DRM involvement < 5 mm	0 (0)

Values in parentheses are percentages. *All patients (anastomosis and colostomy). CRM, circumferential resection margin; DRM, distal resection margin.

Long-term outcomes

Long-term outcomes are shown in *Table 3*. Twelve of 120 patients (10.0 per cent) developed local recurrence, which was multifocal in eight patients. The median interval to local recurrence was 15.9 months, ranging from 6.0 to 26.4 months (*Table 4*). The recurrences were located presacrally (2), anterior (1), at the rectal stump (1) or in multiple regions in the pelvis (8). Nine of the 12 patients with local recurrence presented with or developed distant metastasis, whereas only 14 of 108 patients without local recurrence had distant metastases diagnosed ($P < 0.001$).

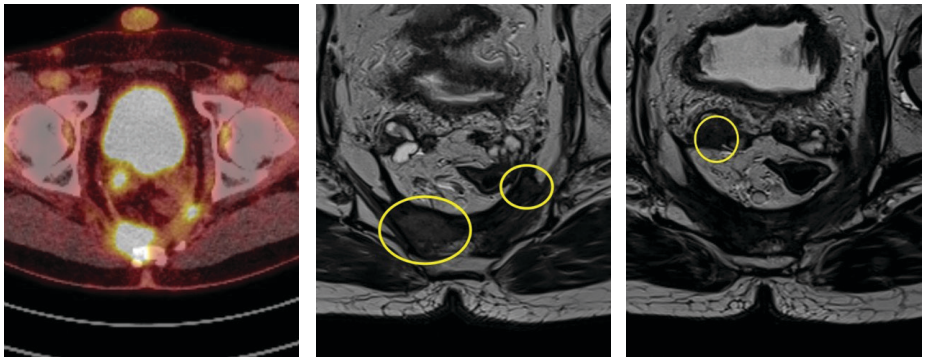

Figure 1 Images from a patient with multifocal recurrence after transanal total mesorectal excision
a PET images showing multifocal recurrence. **b**,**c** T2-weighted axial MRI images showing left lateral and presacral local recurrence (**b**) and recurrence in right seminal vesicle (**c**).

Table 3 Long-term outcomes

	No. of patients* (n=120)
Follow-up (months)	
Mean(s.d.)	23.4(9.5)
Median (range)	21.9 (2.0–46.7)
Local recurrence (total)	12 (10.0)
Multifocal local recurrence	8 of 12 (67)
Interval to local recurrence (months)†	15.2(7.0)
Overall distribution of disease (recurrence and metastasis)	
Isolated local	3 (12)
Local + liver	4 (15)
Local + lung	2 (8)
Local + liver + lung	2 (8)
Local + lung + peritoneal + brain	1 (4)
Liver + lung	4 (15)
Isolated liver	5 (19)
Isolated lung	5 (19)
Disease-free surival	94 (78.3)
Overall survival	115 (95.8)

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.).

The local recurrences were distributed over the 12 participating sites as follows: three in one centre, two in three centres, one in three centres and none in five centres. There

was no relationship between the time to include ten procedures and the incidence of local recurrence.

Details of the 12 patients who developed local recurrence are shown in *Table 5.* Two patients initially presented with a synchronous liver metastasis which was treated by a liver-first approach. One of these developed lung metastasis simultaneous with the local recurrence. Pathological examination showed two poorly differentiated tumours, and three patients had an involved margin, one due to perineural growth that intersected the circumferential plane.

Table 4 Location and treatment of local recurrences

	No. of patients (n=12)
Interval to local recurrence (months)	
Mean(s.d.)	15.2(7.0)
Median (range)	15.9 (6.0–26.4)
Location	
Presacral	2
Anterior	1
Rectal stump	1
Multiple sites	8
Focality (no. of sites)	
1	4
2	4
3	4
Treatment	
Exenteration†	4
CRS + HIPEC	1
Abdominoperineal resection + IORT	1
Palliative chemotherapy	5
Further CRT; multivisceral resection planned	1

†Also intraoperative radiotherapy (IORT) in one patient. CRS + HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; CRT, chemoradiotherapy.

Treatment of recurrences

Of the 12 patients with local recurrence, five with unresectable and/or systemic disease received palliative treatment. Six patients had local exenterative surgery with curative intent. Four patients underwent exenteration (1 combined with intraoperative radiotherapy (IORT)), one had abdominoperineal excision with IORT and one had

cytoreductive surgery with hyperthermic intraperitoneal chemotherapy as salvage surgery. At the time of writing, the final patient was receiving further chemoradiotherapy before salvage surgery.

Risk factors for recurrence

Risk factors for recurrence were identified by univariable logistic regression analysis. Prognostic factors associated with local recurrence (12 patients) were: positive CRM (odds ratio (OR) 11.67; *P* = 0.006), intraoperative complication (OR 7.00; *P* = 0.005), (y)pT3 category (OR 6.02; *P* = 0.025) and pelvic sepsis (OR 4.12; *P* = 0.029) (*Table S1*, supporting information). Risk factors associated with multifocal recurrence (8 patients) were: intraoperative complication (OR 12.11; *P* = 0.013), positive CRM (OR 9.00; *P* = 0.022), pathological N-positive status (OR 6.88; *P* = 0.022), (y)pT3 category (OR 3.34; *P* = 0.150) and pelvic sepsis (OR 5.59; *P* = 0.023) (*Table S2*, supporting information).

Proctoring effect

There were four patients with local recurrence among the first five proctored TaTME procedures per centre (4 of 60 overall) and eight occurred in the second five proctored TaTME procedures (8 of 60) (*P* = 0.362). Clinicopathological outcomes for the first and second five procedures per centre were an intraoperative complication rate of 3 *versus* 5 per cent respectively, an anastomotic leakage rate of 19 *versus* 16 per cent, and involved CRM rate of 2 *versus* 8 per cent.

Comparative case-matched analysis of transanal *versus* laparoscopic total mesorectal excision

To focus on the procedure itself rather than pathological risk factors for local recurrence, case-matched pairing of patients with good-quality specimens and no CRM involvement yielded two groups of 109 patients with similar baseline characteristics, abdominoperineal resection rate and incidence of anastomotic leakage (*Table S3*, supporting information). The pathological outcomes were comparable in terms of stage, and no patient in either matched group had a non-radical resection or incomplete specimen. The overall local recurrence rate was higher for TaTME than laparoscopic TME: 8.3 per cent (nine patients) and 1.8 per cent (2) respectively.

Long-term outcomes of four hospitals with experience of more than 45 procedures

A prolonged cohort from four hospitals with experience of more than 45 procedures included a total of 266 patients who underwent TaTME for primary rectal cancer. Median follow-up was 23.8 (range 1.0–62.4) months. The crude local recurrence rate was 15.0 per cent after the first ten procedures in each centre, 4.2 per cent after procedures 11–40, and 3.8 per cent for procedure 41 onwards (*Table 6*). Overall, 15 patients (5.6 per cent) in this cohort of 266 patients who underwent TaTME developed local recurrence.

Table 5 Details of patients with local recurrence

Patient no.	Baseline data (sex, age, tumour height, cTNM stage)	Neoadjuvant treatment, MRF status*	Surgery	Anastomotic leakage	Pathological stage	Differentiation	CRM (mm)	Follow-up details	Treatment	Outcome
1	M, 68 years, 2 cm from AV, cT2 N0 M0	No, MRF–	LAR + diversion	No	pT3 N0	W/M	10	18 months LR (multifocal) + M (hepatic)	Metastasectomy, APR + IORT	M+ (pulmonary), palliative chemotherapy. Alive at 35 months
2	F, 50 years, 8 cm from AV, cT3 N2 M1 (hepatic)	CRT, MRF–	Liver-first laparoscopic segmentectomy VI + VII. LAR + diversion	Yes	pT3 N0	W/M	5	19 months LR (unifocal)	Exenteration	Further recurrence after 3 months. Alive at 28 months
3	F, 54 years, 3 cm from AV, cT3 N0 M0	No, MRF–	LAR + diversion	No	pT3 N0	W/M	3	26 months LR (unifocal) + M (hepatic)	Metastasectomy, exenteration	Disease-free. Alive at 39 months
4	M, 65 years, 4 cm from AV, cT3 N1 M0	CRT, MRF–	LAR, no stoma	No	pT2 N1	Poor	3	12 months LR (multifocal)	Exenteration (R1)	M+ (hepatectomy) after 5 months, palliative chemotherapy. Died 36 months after TME
5	M, 55 years, 8 cm from AV, cT3 N0 M0	5 × 5, MRF–	LAR, no stoma	Yes	pT3 N1	W/M	4	7 months LR (multifocal) + M (hepatic)	Palliative	Alive at 23 months
6	M, 40 years, 8.3 cm from AV, cT3 N2 M0	CRT, MRF–	LAR + diversion	No	pT3 N2	W/M	7	14 months LR (multifocal) + M (pulmonary)	Further CRT, systemic chemotherapy	Progression, palliative. Alive at 25 months
7	M, 85 years, 2 cm from AV, cT3 N2 M0	CRT, MRF–	LAR + colostomy	No	pT3 N0	Poor	0	10 months LR (unifocal)	Palliative	Died 15 months after TME

Table 5 Continued.

Patient no.	Baseline data (sex, age, tumour height, cTNM stage)	Neoadjuvant treatment, MRF status*	Surgery	Anastomotic leakage	Pathological stage	Differentiation	CRM (mm)	Follow-up details	Treatment	Outcome
8	M, 51 years, 5 cm from AV, cT3 N2 M1 (hepatic)	CRT, MRF–	Liver-first laparoscopic segmentectomy IVb. LAR + diversion	No	pT3 N1	W/M	< 1	8 months LR (multifocal) + M (pulmonary)	Pulmonary RT. Response to induction chemotherapy. Recurrent M+ (pulmonary)	Palliative chemotherapy. Alive at 34 months
9	F, 54 years, 3 cm from AV, cT3 N1 M0	CRT, MRF–	LAR + diversion	No	pT3 N1	W/M	> 10	25 months LR (multifocal)	Induction chemotherapy + further CRT. CRS + HIPEC (R0)	Alive 36 at months
10	M, 60 years, 7 cm from AV, cT3 N1 M0	5 × 5, MRF–	LAR + diversion; air leak reinforced by sutures	Yes	pT3 N0	W/M	> 10	20 months LR (multifocal)	Induction chemotherapy + further CRT. Exenteration (R0)	Alive at 22 months
11	F, 75 years, 5 cm from AV, cT3 N1 M0	5 × 5, MRF–	LAR, no stoma; air leak reinforced by sutures	Yes	pT3 N1	W/M	0†	19 months LR (multifocal) + M (pulmonary). Also previous 10 months M (hepatic)	Work-up to plan treatment for LR + M (pulmonary)	Alive at 22 months
12	M, 73, 10cm AV, cT3 N1 M0	5 ×5, MRF–	LAR + diversion	No	pT3 N1	W/M	7	6 months LR (unifocal) + M (pulmonary, peritoneal, brain)	Palliative	Alive at 18.5 months

*After neoadjuvant treatment if applicable. †Perineural growth. MRF, mesorectal fascia; CRM, circumferential resection margin; AV, anal verge; MRF–, MRF not threatened; LAR, low anterior resection; W/M, well to moderate; LR, local recurrence; M, distant metastasis; APR, abdominoperineal resection; IORT, intraoperative radiotherapy; CRT, chemoradiotherapy; TME, total mesorectal excision; 5 × 5, short-course radiotherapy (RT) 5 × 5 Gy; CRS + HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Table 6 Local recurrence according to number of transanal total mesorectal excision procedures at each centre in prolonged cohort

	Local recurrence rate			
	Procedures 1–10	**Procedures 11–40**	**Procedures ≥ 41**	**Total**
Centre A	2 of 10	2 of 30	0 of 31	4 of 71 (6)
Centre B	1 of 10	2 of 30	3 of 28	6 of 68 (9)
Centre C	2 of 10	0 of 30	1 of 7	3 of 47 (6)
Centre D	1 of 10	1 of 30	0 of 40	2 of 80 (3)
Overall	6 of 40 (15)	5 of 120 (4.2)	4 of 106 (3.8)	15 of 266 (5.6)

Values in parentheses are percentages.

DISCUSSION

In this study, the local recurrence rate during the learning curve was 10.0 per cent, despite the low positive CRM rate and the presence of a structured training pathway, including on-site proctoring. The multifocal pattern of recurrence seemed to be substantially different from that after abdominal TME (open, laparoscopic or robotic) and confirmed the pattern encountered in Norway(15), which calls for further evaluation of the safety of TaTME. TaTME has been shown to be a difficult technique with a relatively long learning curve and associated morbidity.(10) Therefore, it was expected that some learning curve-related problems would be encountered in the present cohort, despite the presence of a structured training pathway aimed at minimizing harm during implementation.

The effect of the learning curve is demonstrated by the relatively high rate of anastomotic leakage and relatively high rate of local recurrences in the longer term. The present cohort size in each centre was inadequate for cumulative sum analysis with the endpoint local recurrence, but an increased recurrence rate among the first ten patients was clearly shown. This could reflect difficulties with poor execution of the technique causing unwanted tumour spillage. These data also demonstrate that the structured training as set out in this programme was not capable of diminishing all adverse outcomes, and should therefore be made more extensive for centres implementing this technique in the future. Proctoring of more than ten procedures should be advised until proficiency is met according to independent competency assessment using video analysis.(22)

Execution of the procedure rather than the technique itself may explain the observed recurrences. This is supported by the results of univariable analysis, which identified

intraoperative events as the biggest risk factor. Two expert centres reported a 3-year local recurrence rate of 2.0 per cent.(9) In the present study, long-term outcomes from four centres with experience of more than 45 TaTME procedures after training indicated that the first ten procedures (early experience) are more at risk of local recurrence than the following 30. The 4.0 per cent local recurrence rate achieved after exclusion of the first ten procedures at each centre is more in line with the results reported by Hol et al. for the two expert centres starting this technique in the Netherland.(9) Longer follow-up is needed to confirm the present recurrence rates, which should be interpreted with caution owing to inclusion of more challenging cases.(23)

The learning curve for implementation of new surgical techniques and its influence on long-term oncological outcome is an important issue. Data are scarce, but a study of laparoscopic TME surgery demonstrated a significantly higher recurrence rate among the first 100 procedures compared with the following 200 (10.5 *versus* 4.9 per cent respectively).(24) Robotic-assisted TME surgery is being implemented worldwide, but data on the learning curve have focused on duration of operation, involved CRM rates and/or complications, and not on long-term recurrence rates. A series by Polat et al., reporting the first 77 procedures, documented a recurrence rate of 9.5 per cent despite a relatively low positive margin rate. This relatively high local recurrence rate was probably related to suboptimal technical execution within the learning curve.(25)

The full report of the National Norwegian audit of 157 TaTME procedures revealed 12 local recurrences (7.6 per cent) after a median follow-up of 19 months, with an estimated local recurrence rate of 11.6 per cent at 2.4 years according to Kaplan–Meier analysis.(16) Wasmuth et al. stated that TaTME was responsible for the increased local recurrence rate, and that poor outcome could not be attributed to the learning curve effect because several of these recurrences occurred late in the series.(16) However, four high-volume centres performed 152 procedures over 4 years, which breaks down to an average annual volume of 9.5 procedures. This raises the question of whether the learning curve had been completed owing to the low exposure. A high rate of positive margins despite low tumour stage, the high rate of permanent stomas and perioperative morbidity may be indicative of suboptimal TaTME procedures. An unsupervised learning curve without proctoring, as shown by experienced single-port surgeons, takes over 40 procedures.(10, 11)

The crucial difference in the TaTME technique is the endoluminal approach and potential direct contact with the tumour, whereas in the other abdominal techniques distal closure is assured by stapling below the tumour.(26) Poor tumour handling and inadequate closure of the lumen by failing purse strings could lead to tumour cells spilling into the pelvic dissection area during the procedure causing (multifocal) recurrences. This could be a similar mechanism to that described in early reports of laparoscopy demonstrating port-site metastasis.(27) Careful evaluation led to the

acknowledgement of tumour cell aerosolization combined with a chimney effect at the trocar sites. After implementation of sufficient training and clinical trials, it has now been proven that laparoscopy is safe when executed proficiently.

The multifocal local recurrence shown in this series and reported by Larsen and co-workers seems to be a new pattern.(15) In the Dutch TME trial(28), the multifocality of recurrences was not evident on review of the imaging of patients with local recurrence. Other data regarding the incidence of multifocal local recurrences are scarce; large trials have not reported multifocality as a separate entity. In the present study, seven of 12 patients with local recurrence developed distant metastasis, similar to rates found in the Dutch TME and COLOR II trials, in which 50–60 per cent of patients with local recurrence also had distant metastasis.(21, 29) The question remains whether recurrence is related to the biology of the cancer rather than the surgical technique driving distant haematogenous spread of the disease.(30)

The explanation for both the high rate of multifocal recurrences and the local recurrence rate of 10.0 per cent, despite a relatively low CRM positivity rate of 5.0 per cent in this implementation cohort, could be multifactorial. Theoretically, unsuccessful execution of a TaTME procedure might result in inadequate purse-string closure of the lumen. During the subsequent pelvic dissection, spilled tumour cells might be scattered as a result of the continuous high-flow insufflation used in the dissection area in TaTME, leading to multifocal local recurrence. A high rate of positive bacterial cultures during TaTME, as reported by Velthuis and colleagues(31), might provide support for this hypothesis. The authors have preliminary data showing that cancer cells can be cultured from rectal wash-out (J. Tuynman; unpublished observation). Although the exact aetiology remains to be proven, all COLOR III sites have been instructed to secure the purse-string closure with a second over-running suture after the rectotomy with a secondary wash-out.(32) Intraoperative perforation of the rectal tube in conventional TME might be regarded as a similar mechanism whereby tumour cells can seed in the pelvic cavity. In the present risk analysis, occurrence of intraoperative complications was the strongest predictor of multifocal local recurrence and second strongest for overall local recurrence. A previous study by Eriksen and colleagues(33) showed a tremendous negative impact of perforation on 5-year local recurrence, with the incidence rising from 9.9 per cent to 28.8 per cent in the presence of perforation ($P < 0.001$). The relatively high rate of pelvic sepsis (17.5 per cent) in the present learning curve cohort might also have contributed to the increased recurrence rate. A consistent hypothesis is that pelvic sepsis leads to an increased inflammatory reaction, and increased levels of growth factors associated with stimulation of adhesion and seeding of tumour cells.(34-36)

A potential weakness of this cohort study is the possible inclusion of some patients with advanced-stage disease in the learning curve cohort. Overall, selection bias could be present within these data, but all patients who underwent TaTME for primary

rectal cancer were included consecutively and the data were audited externally by an independent clinical researcher. Furthermore, case-matched analysis of TaTME and laparoscopic TME procedures, excluding CRM-positive and T4 tumours, demonstrated that TaTME during the learning curve was the only risk factor for local recurrence and not the pathology, showing that case selection was not an issue in the present cohort. Video analysis with surgical quality assessment could have revealed potential risk features for local recurrence. Quality assessment of every procedure is the central ingredient in the current COLOR III trial(22), in which all data including MRI and the entire video of each procedure are captured centrally.

As stated in the IDEAL framework, a new innovation or technique should be evaluated stepwise, and not be implemented broadly before standardized indications and procedures have been developed. In this way, adverse effects and consistent outcomes can be established during the learning curve, which new centres can set as a benchmark.(37) The surgical community should focus on demonstrating oncological safety rather than surrogate endpoints for new innovative surgical techniques for patients with cancer. High-quality data accrual in a clinical (randomized) trial is key, including establishing a safety commission and frequent external data monitoring.(38) The international TaTME guidance also states that TaTME should be implemented only in centres with a high volume of TME practice and with adequate training, including individual proctoring.(2)

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9

Long-term oncological results after transanal total mesorectal excision for rectal carcinoma

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ABSTRACT

Introduction: Transanal total mesorectal excision (TaTME) for mid and low rectal cancer has shown to result in benefits in short-term outcomes, mostly reflected by lower conversion rates and with improved quality of the specimen. However, robust long-term oncological data supporting the encouraging clinical and pathologic outcomes are lacking.

Methods: All consecutive patients undergoing TaTME with curative intent for mid- or low rectal cancer in two reference centers in the Netherlands with a complete and minimum follow-up interval of 36 months from date of surgery were included. Primary outcome was local recurrence rate. Secondary outcome were disease free survival, overall survival and development of metastasis.

Results: In this series of 159 consecutive patients operated between January 2012 to April 2016, the 3 years local recurrence rate was 2.0% and the 5 years local recurrence rate was 4.0%. Median time to local recurrence was 19.2 months. Disease free survival at 3 years was 92% and at 5 years was 81%. Overall survival at 3 years was 83.6% and at 5 years was 77.3%.

Conclusion: The long-term follow-up of the current cohort confirms the oncological safety and feasibility of TaTME in two high volume reference centers for rectal carcinoma. However, further robust and audited data must confirm current findings before widespread implementation of TaTME.

INTRODUCTION

Transanal Total Mesorectal Excision (TaTME) has the potential to lower the local recurrence rate after radical resection of mid and low rectal cancer. Currently available evidence shows an improvement in the quality of the surgical specimen and reduced number of R1 resections by lower distal margins in initial cohort studies (1-3). Therefore, TaTME has the potential to lower the local recurrence rate after radical resection of mid and low rectal cancer. However, long-term data of local recurrence rates confirming the encouraging pathologic outcomes are lacking (4). Over the past decades, adaptation of Total Mesorectal Excision (TME) as surgical principle has reduced local recurrence rates and improved cancer free survival rates (5). Combined with neoadjuvant chemoradiation the local recurrence rates have been reduced to 5% as demonstrated in a large randomized clinical trial (6).

Even though laparoscopic surgery has improved the short-term results after rectal cancer surgery, the expected oncological benefits are modest as shown in large randomized trials (6-8). Laparoscopic TME is considered as a difficult technique which might influence the results of surgery. Especially the lower part of the rectum is at risk, specifically in male patients with a narrow small pelvis in which there is a limited space to mobilize the rectum with intact mesorectum. But also neoadjuvant therapy and local excision will influence the results of laparoscopic TME surgery.

In TaTME, the rectum is approached both from above and below, preferably at the same time (1). Because the distal part of the rectum is approached from below it is more accessible and the surgical planes are better visualized. The technique appears to be feasible and short-term outcomes seem promising in expert centers. However, the learning curve is extensive which might influence the results in low volume centers (3, 9)**.** Recently, Norway TaTME data revealed 9,5% local recurrences leading to a nationwide stop and thorough investigation (10). Nevertheless, the 9,5% local recurrence rate disturbed the surgical colorectal community and the results of the official investigations are eagerly awaited. Other single center series have reported local recurrence rates ranging from 2.3% - 5.7% with median follow up between 15 -32 months (2, 11-15). In this study we describe the long-term oncological results after TaTME surgery in a large consecutive cohort with a minimal of 36 months follow-up from the two hospitals that started TaTME in the Netherlands.

METHODS

Patients

Between January 2012 and May 2016, all patients in the Gelderse Vallei Hospital, Ede, the Netherlands and Amsterdam UMC, location VUmc, Amsterdam, the Netherlands

with histological proven distal- or midrectal carcinomas, operated electively by TaTME approach were included. Exclusion criteria were recurrent and/or locally advanced tumors with persistent threatened margins after neoadjuvant radiotherapy, and palliative resections.

Preoperative assessment included MRI for local staging, computed tomography of the abdomen and computed tomography or conventional x-ray of the thorax for distance metastasis detection, and blood analysis with serum CEA analysis. Each patient was discussed by a local multidisciplinary cancer board. Patients at medium risk, being cT3b+ N0 or cT2–3 N1 tumors received preoperative radiotherapy with 5 consecutive days of 5Gy daily dose. Patients with N2 disease or tumors with threatened margins (<1.0 mm) to the mesorectal fascia were treated with chemo radiation therapy with 25 days of 2 Gy daily dose, combined with administration of oral 5-fluorouracil.

Surgical procedure

TaTME was performed as described before (2). The first patients were operated by a single surgeon, performing both phases of the procedure sequentially. After the initial learning curve the two team approach was introduced, with simultaneous abdominal and the transanal dissection. The splenic flexure was mobilized in the majority of the patients. Ligation of the inferior mesenteric vein was done near the pancreas.

The transanal phase consists of a thorough washout and the introduction of the anal platform, in the majority of the cases the GelPOINT Path Transanal Access Platform (Applied Medical, Rancho Santa Margarita California, USA) was used. In the first consecutive patients, a regular laparoscopic CO2 insufflator was used. This was replaced in all other patient by the AirSeal insufflator (ConMed, Utica, New York, USA). The purse strings location changed from the initial position directly behind the dentate line to a 3 cm higher position above the anorectal junction (if applicable for the location of the tumor, in proximal tumors it was placed below the tumor). Dissection was performed in a standardized fashion, starting the dissection dorsally and ventrally, thereafter dissecting the lateral plane. The abdominal and transanal team joined anteriorly. Specimen extraction was performed after wound protection through a Pfannenstiel incision. The anastomosis was made preferably side to end using a 31 EEA or 33 EEA hemorrhoid stapler (Medtronic, Dublin, Ireland).

Statistics and data collection

Baseline data was collected regarding age, sex, ASA classification, BMI, distance of the tumor from the anal verge, preoperative clinical staging, and preoperative chemo radiation therapy. Pathological outcome included pathological staging, macroscopic completeness of the resection, number of lymph nodes harvested and CRM. All patients have had follow-up carried out according to the Dutch National Guidelines for Colorectal Cancer for a period of 5 years at the outpatient clinic. For this cohort a full 36 month

follow-up was available for all patients. Primary outcome was loco regional recurrence. Secondary outcome included distant metastasis disease-free and overall survival. Recurrence disease was defined as the presence of loco regional recurrence, distant metastases or death from rectal cancer. All data collection and statistical analysis were carried out using SPSS Statistics version 24 (IBM, Chicago Illinois, USA). After analysis of numbers and percentages or median and range for each variable, a univariate binary regression analysis was performed for possible risk factors for local recurrence. Kaplan Meier survival analysis was performed for local recurrence free survival rates, disease free survival rates and overall survival rates.

Ethics

The study was approved by the participating centers. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

Patients characteristics and clinical outcomes

From January 2012 to May 2016 a total of 159 consecutive patients underwent TaTME. 110 underwent surgery in Gelderse Vallei Hospital, Ede, the Netherlands and 49 in Amsterdam UMC, location VUmc, Amsterdam, the Netherlands. The follow-up data was complete for all patients. Mean age was 66.9(10.2) years old and 66.7 percent of all patients were men. Neoadjuvant radiotherapy was administered in 112 patients (70.4%) and 117 received a primary anastomosis during surgery (73.6%). In 39 patients (24.5%) encountered postoperative complications graded as Clavien Dindo grade 3 or higher. Characteristics and short-term clinical outcomes are summarized in table 1.

Oncologic outcomes

Pathological analysis showed a complete mesorectum in 139 patients (87.4%), nearly complete in 16 (10.1%) and an incomplete mesorectum in 4 patients (2.5%). Pathological staging showed T0 in 13 patient (8.2%), T1 in 15 (9.4%), T2 in 74 (46.5%), T3 in 55 (34.6%) and T4 in 2 (1.3%). N stage was N0 in 118 patient (74.2%), N1 in 28 (17.6%) and N2 in 13 (8.2%). There was involvement of the circumferential resection margins (<1mm) in 1 patient (0.6%) and none had involvement of the distal margin (<5mm).

The mean long-term follow up was 54.8 months (range 36-88 months). The overall local recurrence rate was 3.8%, median time to local recurrence was 19.2 months (5.9-30.0). Figure 1 shows a Kaplan Meier (KM) curve of local recurrence. Local recurrence rate at 3 years was 2.0% and at 5 years was 4.0%. An overview of all six local recurrence cases and treatment can be seen in table 4.

Table 1. Patient characteristics and clinical outcome

			n=159
Sex		*Male*	106 (66.7)
		Female	53 (33.3)
BMI (mean) (±SD)			26.4 (4.3)
Age (years) (mean) (±SD)			66.9 (10.2)
ASA		*I*	33 (20.8)
		II	100 (62.9)
		III	26 (16.4)
Height from AV (cm)	mean (±SD)		5.7 (3.5)
	median (range)		6 (0-15)
Height from AV <4cm		yes	47 (29.6))
Clinical Tumor stage		*T1*	2 (1.3)
		T2	39 (24.5)
		T3	103 (64.8)
		T4	11 (6.9)
		Tx	4 (2.5)
Clinical Nodal stage		*N0*	82 (51.6)
		N1	47 (29.6)
		N2	26 (16.4)
		Nx	3 (1.9)
Synchronous Metastasis		*M+*	7 (4.4)
MRF threatened (before RT)		*No*	125 (78.6)
		Yes	34 (21.4)
Preoperative therapy		*RT*	112 (70.4)
		CRT	43 (27.0)
Anastomosis		*primary anastomosis*	117 (73.6)
		end-colostomy	42 (26.4)
Performed operation		*LAR TaTME*	133 (83.6)
		ISR/APE TaTME	26 (16.4)
Intra-operative complications		*rectal perforation*	2(1.3)
		purse-string failure	1(0.6)
		carbon dioxide (CO2) embolus	1(0.6)
Postoperative morbidity		*No complications*	46 (47.8)
		Minor Clavien Dindo 1-2	44 (27.7)
		Severe Clavien Dindo ≥3	39 (24.5)
		Reoperation	36 (22.6)
Anastomotic leakage			10 (6.3)
Presacral abcess			14 (8.8)

Numbers in parentheses are percentages, unless mentioned otherwise
Abbreviations: BMI = Body Mass Index (kg/m2), SD = standard deviation, ASA = American Society of Anesthesiologists, cm = centimeters, AV = anal verge, MRF = mesorectal fascia RT = radiotherapy, CRT = chemoradiotherapy, LAR= Low anterior resection, ISR= Intersfincteric resection, APE = abdomino perineal excision

Table 2. Pathologic and long term outcomes

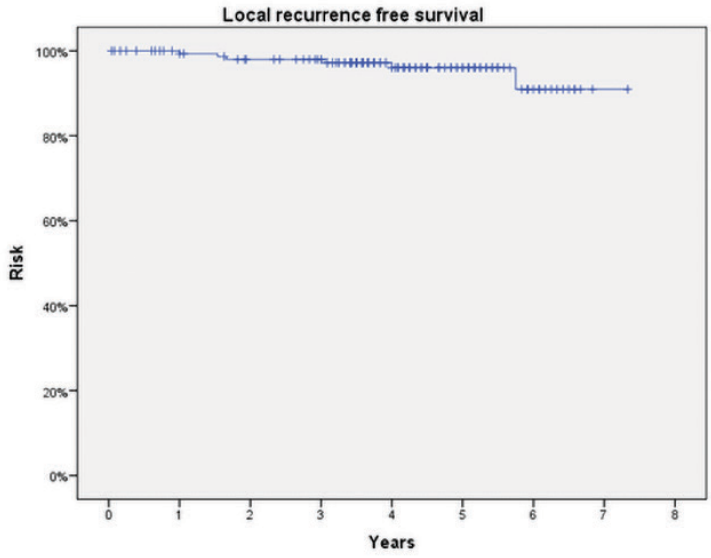
		n =159
Pathologic T-stage	*(y)pT0*	13 (8.2)
	(y)pT1	15 (9.4)
	(y)pT2	74 (46.5)
	(y)pT3	55 (34.6)
	(y)pT4	2 (1.3)
Pathologic N-stage	*N0*	118 (74.2)
	N1	28 (17.6)
	N2	13 (8.2)
Quality of specimen (Quirke)	*Incomplete*	4 (2.5)
	Nearly complete	16 (10.1)
	Complete	139 (87.4)
CRM +	*<1 mm*	1 (0.6)
DRM +	*<5mm*	0 (0.0)
Follow-up (months)	*Mean (±SD) **	54.8 (13.1)
	*Median (range) **	52.0 (36.0-88.0)
Local Recurrence overall	*no*	153 (96.2)
	yes	6 (3.8)
Interval to local recurrence (months)	*Median (range)*	19.2 (5.9-30.0)
Distant metastasis	*no*	137 (86.2)
	yes	22 (13.8)
Interval to distant metastasis (months)	*Median (range)*	6.9 (1.1-50.4)
Disease recurrence	*no*	133 (83.6)
	yes	26 (16.4)
Interval to disease recurrence	*months*	8.2 (1.1-50.4)
Overall survival		124 (78.0)
Deceased		35 (22.0)
Interval to death (months)	*Median (range)*	28.0 (0.5-61)

Numbers in parentheses are percentages, unless mentioned otherwise
* Mean/mediang-range Does not include diseased patients

Disease free survival at 3 years was 92% and at 5 years was 81%. Figure 2 shows a KM curve of disease free survival. Distant metastases were seen in 22 (13.8%) patients and were diagnosed after a median of 6.9(1.1-50.4) months. Overall survival at 3 years was 83.6% and at 5 years was 77.3%. See figure 3 for KM curve of overall survival. Results from pathologic examination and long-term results are summarized in table 2.

Risk factors for local recurrence

Univariate binary logistic regression analysis for local recurrence showed no significant difference for sex, obesity, low tumor, threatened MRF, preoperative radiotherapy, (y)pT4 stage, (y)pN2 stage, positive CRM, incomplete mesorectum, intra-operative perforation, intra-operative purse-string failure, carbon-dioxide embolus, synchronous metastasis, anastomotic leakage and reoperation. There was a significant risk for pathologic stage T3 or 4 tumors, RR 0.103 (0.012-0.904), p=0.040, complications grade 3 or higher according to Clavien Dindo RR 0.148 (0.026-0.844), p=0.031 and presence of presacral abscess RR 0.077 (0.014-0.430), p=0.003. The patient with intra-operative purse-string failure did not develop pre-sacral abscess or local recurrence. Results of the univariate analysis for risk factors are summarized in table 3.



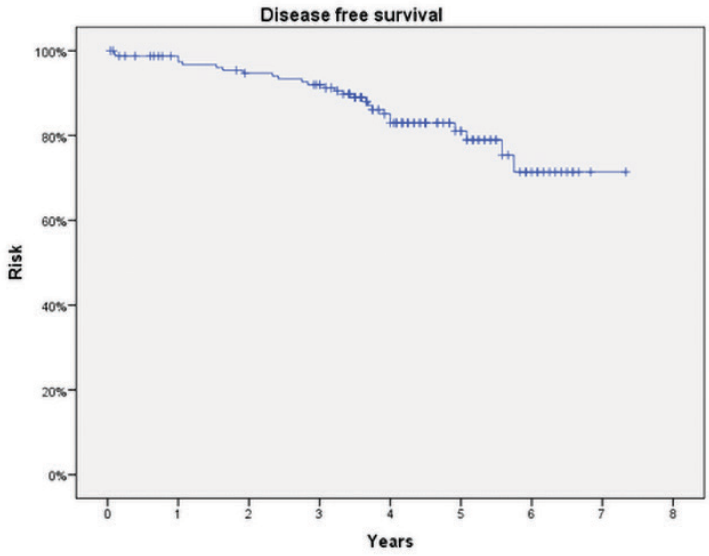
Years	0	1	2	3	4	5	6	7
No at Risk	159	149	140	133	80	41	14	1

Figure 1: Kaplan Meier curve of local recurrence free survival after TaTME

Table 3. Univariate analysis of risk factors for local recurrence

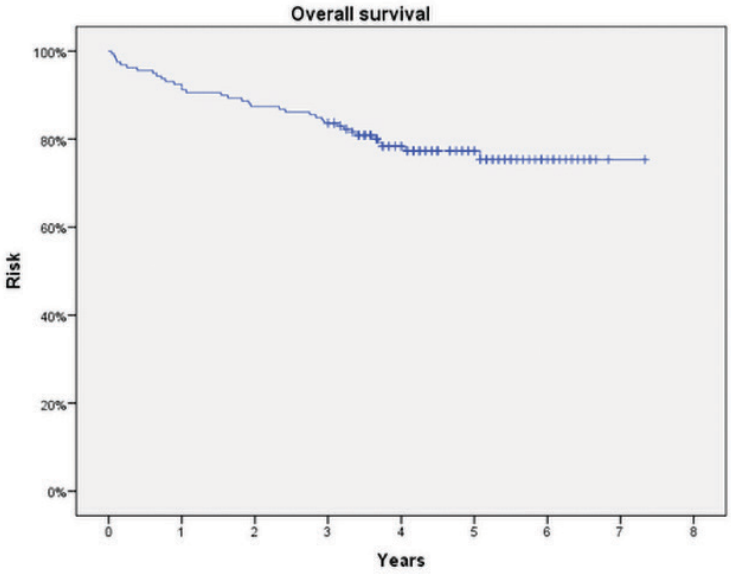
		LR	Total	RR	95% CI lower	95% CI upper	P-value
Sex	*Female*	3	53	ref			
	Male	3	106	2,06	0,401	10,573	0,386
BMI >25	*no*	4	66	ref			
	yes	2	93	2,935	0,522	16,522	0,222
Low tumor <4cm from AV	*no*	4	112	ref			
	yes	2	47	0,833	0,147	4,713	0,837
MRF threatened on MRI	*no*	4	125	ref			
	yes	2	34	0,529	0,093	3,018	0,473
Preoperative radiotherapy	*no*	2	47	ref			
	yes	4	112	1,200	0,212	6,787	0,837
pathologic stage T3-4	*no*	1	102	ref			
	yes	5	57	0,103	0,012	0,904	**0,040**
pathologic stage T4	*no*	6	157	ref			
	yes	0	2		0,000		0,999
pathologic stage N2	*no*	5	146	ref			
	yes	1	13	0,426	0,046	3,943	0,452
CRM+	*no*	5	158	ref			
	yes	1	1	0,000	0,000		1,000
incomplete mesorectum	*no*	6	155	ref			
	yes	0	4		0,000		0,999
Intra-operative perforation	no	6	157	ref			
	yes	0	2		0,000		0,999
Purse-string failure	no	6	158	ref			
	yes	0	1		0,000		1,000
CO2 embolus	no	6	158	ref			
	yes	0	1		0,000		1,000
Synchronous metastasis	*no*	5	152	ref			
	yes	1	7	0,204	0,021	2,029	0,175
complications CD 3 or higher	*no*	2	120	ref			
	yes	4	39	0,148	0,026	0,844	**0,031**
anastomotic leakage	*no*	5	149	ref			
	yes	1	10	0,313	0,033	2,965	0,311
presacral abscess	*no*	3	145	ref			
	yes	3	14	0,077	0,014	0,430	**0,003**
reoperation	*no*	3	123	ref			
	yes	3	36	0,275	0,053	1,426	0,124

Abbreviations: BMI = Body Mass Index (kg/m2), AV = Anal verge, MRF= mesorectal fascia, CRM+ = involvement of the circumferential resection margins (<1mm), CD = Clavien Dindo.



Years	0	1	2	3	4	5	6	7
No at Risk	159	147	139	133	80	41	14	1

Figure 2: Kaplan Meier curve of disease free survival after TaTME



Years	0	1	2	3	4	5	6	7
No at Risk	159	147	139	133	80	41	14	1

Figure 3: Kaplan Meier curve of overall survival after TaTME

Table 4. Overview of cases with local recurrence

	Surgery	p Stage	Complications	R	Neoadjuvant	Interval	Location	Treatment	Survival
1	2012	T3N2	Presacral abscess	R0	radiotherapy	18 months	presacral	palliative chemotherapy	57 months
2	2013	T2N1	none	R0	none	8 months	presacral	stoma and palliative chemotherapy	alive, remission
3	2014	T3N0	Presacral abscess	R1	chemoradiation	6 months	presacral	palliative treatmet	12 months
4	2016	T3N0	Anastomotic leakage	R0	chemoradiation	30 months	presacral	APE	alive
5	2014	ypT0N0	Presacral abscess	R0	radiotherapy	19 monhts	Vesiculae	APE and debulking	alive
6	2015	pT3N1	none	R0	none	27 months	presacral	CRTX, excenteration	alive

Abbreviations:APE = abdomino perineal excision, CRTX=chemoradiation therapy

DISCUSSION

In this series of 159 TaTME procedures for rectal cancer is shown that TaTME is associated with low local recurrence rate; the 3 year local recurrence rate is 2.0% with complete follow-up and 4.0% after 5 years. The median time to local recurrence was 19.2 months (5.9-30.0 months). By our knowledge this is the largest series with a complete and long follow-up of more than 3 years after TaTME (4). This report shows that TaTME is oncological safe when performed in specialist centers with dedicated colorectal surgeons.

The encountered 3 years local recurrence rate in this study is relatively low compared to the laparoscopic TME long-term outcome data of the COLOR II, ALaCART and ACOSOG Z6051 trials which show a 3 year local recurrence rate of 5% (6-8). In accordance to previous literature high tumor stage, severe postoperative complications and presence of a presacral abscess were risk factors for local recurrences (16). A multivariate analysis was not possible due to the low number of events.

One of the potential benefits of TaTME for mid- and low rectal cancer is better specimen quality and better radicality. Incomplete mesorectum is a known risk factor for local and overall recurrence (17). In our study 97.5% of the specimens had a good quality specimen, which is comparable to our previous study by Velthuis et al. in which 100% of the specimens after TaTME had a good quality specimen, while in the traditional laparoscopic group 80% had good quality (18).

Despite TaTME was introduced in 2010, ample data on long-term outcome currently limited. In contrast, a considerable amount of case-series describing single center experiences focus merely on short-term and pathological outcomes (19). Although there is a growing interest for TaTME in rectal cancer surgery, it is still not widely implemented and concerns persist regarding the adequacy of oncological resection. The results of our study adds long-term outcome data to support the potential benefits of TaTME for mid- and low rectal cancer: increased quality of the mesorectum, low number of positive CRM and corresponding low local recurrence rate.

Although the results from our study are encouraging, it only includes data from the two hospitals that started TaTME in the Netherlands which are high volume tertiary referral centers. The oncological results of widespread adaptation of TaTME remains to be proven. Early adopters of TaTME recognized the high complexity of the procedure (20). Therefore, several countries started a nationwide structured training program including proctoring to deliver safe implementation of the procedure (21, 22). The technique has a learning curve associated with substantial morbidity. Surgeons have to perform at least 40 cases in order to reach competency, based on acceptable morbidity or good pathologic outcome (9, 23). Furthermore, higher volumes are associated with better

outcome in terms of conversion, severe complications and quality of the mesorectum (3). Our results do not support the concern that TaTME leads to an increased risk for local recurrence, as suggested by Norwegian data (10)**.** It is to be imagined that poor quality TaTME does negatively influence local recurrence rates. A review focusing on outcomes of TaTME in low volume centers was associated with relatively high recurrence rate of 8.9% versus 2.8% in high volume centers (3). Another possible explanation for the higher

This indicates that a learning curve might seriously hamper both short- and long-term outcome. Inadequate dissection, perforation and/or insufficient closure of the rectum before dissection all have the potential for tumor spill (24).

The IDEAL framework aims to prevent surgical innovation to be implemented too early (25). Whilst the technique is still in the developmental stage and no global consensus and standardization has been reached, one could argue that the surgical community has proceeded to the early exploration with many starting this technique. This means exposing patients to potential intra-operative complications and short-term morbidity. Furthermore, long-term oncological safety of the technique must be approached with caution, comparable to the port-site metastasis setback seen in laparoscopic surgery (26). The international TaTME registry showed to be a useful instrument in the aim to capture real-time data of the early adaptation of TaTME and has signaled a 15.7% anastomotic failure rate (27). The long-term follow up data of the international registry are awaited although completeness of data will be a potential problem and bias.

Although the results of our study are promising, oncological safety after TaTME surgery remains to be proven in a multicenter international setting. The next crucial step in implementing this technique is an international randomized controlled trial such as the COLOR III trial, which is currently enrolling and is designed to assure high quality evidence by implementing a pretrial showing surgical competency, central review of MRI, assessment of procedural video, re-evaluation of the specimen and obligatory upload and central review of MRI 3 years after surgery (28).

This consecutive TaTME cohort study in 159 patients with complete follow-up 36 months or more shows that TaTME is associated with relatively low local recurrence rate of 2.0% after 3 years and 4.0% after 5 years. This shows that in experienced hands with high volume TaTME is safe and is associated with good long-term outcome.

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10

Transperineal minimally invasive APE: preliminary outcomes in a multicenter cohort.

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ABSTRACT

Background: Abdominoperineal excision (APE) for rectal cancer is associated with a relatively high risk of positive margins and postoperative morbidity, particularly related to perineal wound healing problems. It is unknown whether the use of a minimally invasive approach for the perineal part of these procedures can improve postoperative outcomes without oncological compromise. The aim of this study was to evaluate the feasibility of minimally invasive transperineal abdominoperineal excision (TpAPE)

Methods: This multicenter retrospective cohort study included all patients undergoing TpAPE for primary low rectal cancer. The primary endpoint was the intraoperative complication rate. Secondary endpoints included major morbidity (Clavien-Dindo ≥3), histopathology results and perineal wound healing.

Results: A total of 32 TpAPE procedures were performed in five centers. A bilateral extralevator APE (ELAPE) was performed in 17 patients (53%), a unilateral ELAPE in 7 (22%), and an APE in 8 (25%). Intraoperative complications occurred in five cases (16%), severe postoperative morbidity in three cases (9%). There were no perioperative deaths. A positive margin (R1) was observed in four patients (13%) and specimen perforation occurred in two (6%). The unilateral extralevator TpAPE group had worse specimen quality and a higher proportion of R1 resections than the bilateral ELAPE or standard APE groups. The rate of uncomplicated perineal wound healing was 53% (n= 17) and three patients (9%) required surgical reintervention.

Conclusions: Transperineal abdominoperineal excision seems to be feasible with acceptable perioperative morbidity and a relatively low rate of perineal wound dehiscence, while histopathological outcomes remain suboptimal. Additional evaluation of the viability of this technique is needed in the form of a prospective trial with standardization of the procedure, indication, audit of outcomes and performed by surgeons with vast experience in transanal total mesorectal excision.

INTRODUCTION

Radical surgery with adherence to the principles of total mesorectal excision (TME) is the key for local control in rectal cancer surgery (1, 2). A meticulous TME dissection avoids involvement of the circumferential resection margin (CRM) which is directly related to local recurrence (3-5). For low rectal cancer, achieving a complete TME is more difficult, due to tapering of the mesorectal fat surrounding the rectum in combination with limited access to the narrow bony pelvis (6-9). To achieve safe oncological margins, tumours with threatened margins located in the low rectum are commonly subject to an abdominoperineal excision (APE) (10, 11).

Despite more extensive surgery in which the anus and sphincter complex are excised en-bloc with the rectum, the clinical and oncological outcomes after APE are far from optimal. As shown in the Dutch TME trial, the rate of involved CRM (CRM+) was substantially higher for APE compared to anterior resection, 30.4% vs 10.7% (p=0.002) respectively (12). Coning of the specimen towards the pelvic floor with a "waist" at the puborectal sling was put forward as the main culprit for the higher CRM+ rates and formed the rationale for a cylindrical excision (13). In this so called extralevator APE (ELAPE), a wider distal dissection route is followed which includes en-bloc excision of the levator ani muscles leading to a lower rate of CRM+ and tumour perforation (13-16). The wider and thereby more radical excision comes at the cost of a larger defect of the pelvic floor and skin (17-20). Previous studies and meta-analyses have reported major morbidity rates between 10-30% and perineal wound healing problems from 11 up to 50% (21-26). Especially in irradiated patients, perineal wound healing is problematic and sometimes requires primary or secondary reconstruction with musculocutaneous flaps to achieve perineal closure (26-30).

A minimally invasive transperineal approach to the perineal part of an APE has potential advantages over the standard technique, although data on this new technique are limited [33]. This multicenter series describes the combined initial experience of five expert centers in four countries with a transperineal minimally invasive APE technique (TpAPE) for locally advanced low rectal cancer. The primary aim was to assess the feasibility by reporting on intraoperative complications. Secondary aims were to assess the histopathological outcomes and postoperative morbidity including the incidence and management of perineal wound complications.

MATERIALS AND METHODS

Patients

A consecutive cohort of patients who underwent TpAPE for primary rectal cancer was identified at five centers (two in The Netherlands, one in Taiwan, one in Canada and

one in the United Kingdom). This group consisted of patients that had either a bilateral ELAPE, an unilateral ELAPE or APE with resection of the entire external sphincter (31, 32). Intersphincteric APE's were excluded. A retrospective analysis of prospective institutional databases was performed, and individual patient data were provided by an anonymized data-sheet. The annual volume of rectal cancer surgery varied amongst the participating centers, but all perform over 50 resections (including transanal minimally invasive local excision, partial mesorectal excision, low anterior resection, APE, ELAPE, and recurrent rectal cancer).

Surgical technique

The patient is placed in a lithotomy position to enable simultaneous abdominal and perineal dissection. The abdominal phase is performed by a standard laparoscopic medial to lateral mobilization of the left colon. The inferior mesenteric vein is ligated near the lower border of the pancreas and the inferior mesenteric artery ligated with preservation of the left colic artery. The mesorectal plane is opened with autonomous nerve preservation and dissection is continued up to connection with the perineal team. The perineal phase commences with a purse string closure of the anus. Afterwards, a radial perineal incision at approximately 1 cm from the closed anus is made into the subcutaneous fat. A single port can be inserted after creating a 2-3 cm deep opening of the ischioanal fat around external sphincter and connected to a continuous high flow insufflation and smoke exfiltration system. The most frequently used single port devices are the Gelpoint Mini and Gelpointh path (Applied Medical, Rancho Santa Margarita, California, USA). Standard laparoscopic instruments including a diathermic hook or spatula are needed for the endoscopic perineal phase. Dissection continues cephalad until the pelvic floor (levator ani muscle) is reached. Continuation externally along the levator ani muscle is tailored on a case by case level. For uni- or bilateral ELAPE procedures, the pelvic floor is followed on one or both sides up to the fascia of the obturator internus muscle and transected at this level. For a standard APE the pelvic floor is usually transected a few centimeters out from the puborectal sling. The transection usually starts at the level of the coccyx and thereafter going forward. By cutting the pelvic floor muscle, and the overlying pelvic floor fascia connection is made with the abdominal team without coning in on the tumor. Identification of the correct anterior plane, remains the most difficult step. It is crucial to identify the transverse perineal muscles to enter this plane just posteriorly to these muscle fibres to find the avascular plane in front of the posterior vaginal wall or prostate and then continuous cephalad in front or behind Denonvillier's fascia pending anterior location of the tumour. The specimen is extracted trough the perineal wound. The perineal defect is then closed primarily, with a subcutaneous gluteal turnover flap (33) or by aid of (biological) mesh upon individual basis.

Outcomes

The primary endpoint was feasibility of the technique in terms of intraoperative complications (34). Secondary endpoints included 30-day major morbidity (Clavien Dindo ≥3), perineal wound healing, and histopathological outcomes. CRM+ was defined as presence of tumour cells ≤ 1mm of the surgical plane. The specimen quality was graded according to Quirke (2). Perforation was defined as a tear or hole from the surface of the surgical specimen (mesorectum or at the level of the sphincters) into the rectal lumen.

Statistical analysis

All data are presented as N (%) for binary data and for continuous outcome as mean ±SD and median range as well since normal distribution is not expected in this small cohort. To explore the potential impact for the extent of the procedure, which increases from APE via an unilateral ELAPE to a bilateral ELAPE, a comparative analysis for these procedures was performed. For the comparative analysis, a Fisher's exact test was used for categorical variables and the non-parametric Mann-Whitney U test or Kruskal-Wallis test for continuous variables. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 24 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics (table 1)

A total of 32 patients were included (24 males, mean age 65.7 [±12.8]) from 5 different expert colorectal cancer centers with a case load varying between 1 and 12 procedures. The first procedure in this series was performed in June 2014 and the last in July 2018. Seventeen patients had cT3 stage rectal cancer and seven were cT4 stage. (Table 1) Nodal involvement was diagnosed in 14 patients (44%). In one patient, a suspected para-aortic lymph node metastasis was present and, therefore, categorized as distant (M+) disease. No other peritoneal, liver or lung metastasis were encountered in the preoperative work-up. The majority of cases was found to have a threatened margin to the mesorectal fascia (MRF) (n=12, 66%) on baseline magnetic resonance imaging (MRI) and the tumour was located at or below the level of the anorectal junction in twenty-two cases (69%). Extension of low tumours into the sphincter complex was seen in ten patients, ingrowth into the levator ani muscles and anterior involvement (prostate or vagina) was encountered in four and two cases, respectively. A substantial part of the patients received neoadjuvant chemoradiotherapy (n=20, 63%).

Table 1 Patient and tumour characteristics

		n=32
Sex	*Male (%)*	24 (75.0)
	Female (%)	8 (25.0)
BMI (mean) (±SD)		26.4 (3.3)
Age (mean) (±SD)		65.7 (12.8)
ASA	*I*	1 (3.1)
	II	25 (78.1)
	III	6 (18.8)
Tumour heigth from ARJ(cm)*	*mean (±SD)*	0.50 (0.87)
	median (range)	0 (0-3.0)
T-stage (%)	*cTis*	1 (3.1)
	cT2	7 (21.9)
	cT3	17 (53.1)
	cT4b	7 (21.9)
N-stage (%)	*N0*	18 (56.3)
	N1	8 (25.0)
	N2	6 (18.8)
M-stage (%)	*M+*	1 (3.1)**
Mesorectal Fascia involved	*Yes*	21 (65.6)
	No	11 (34.4)
EMVI	*Yes*	8 (25.0)
	No	18 (56.3)
	Unknown	6 (18.8)
Ingrowth	*No*	16 (50.0)
	Spinctercomplex	10 (31.3)
	M. levator ani	4 (12.5)
	Prostate / vagina	2 (6.3)
Neoadjuvant Radiotherapy (%)	*No*	9 (28.1)
	5x5 short interval	3 (9.4)
	long course Chemorad	20 (62.5)

Numbers in parenthesis are percentages, unless mentioned otherwise
Abbreviations: BMI = Body Mass Index (kg/m2), SD = standard deviation, ASA = American Society of Anesthesiologists, RT = radiotherapy, CRT = chemoradiotherapy, ARJ = anorectal junction
*: 22 of 32 located at or below level of ARJ
**: para-aortic M+

Table 2 Operative details

		n=32
Type of surgery	*APE, levators left in situ*	8 (25.0)
	Unilateral ELAPE	7 (21.9)
	Bilateral ELAPE	17 (53.1)
Beyond TME resection	*No*	24 (75.0)
	Prostate / Vagina	6 (18.8)
	Seminal vesicles	1 (3.1)
	Ovaries	1 (3.1)
	Pelvic sidewall	0 (0)
Operative time (min)	*mean (±SD)*	278 (78)
	median (range)	249 (175-450)
Bloodloss (ml)	*mean (±SD)*	203 (115)
	median (range)	200 (50-400)
Conversion	*to open perineal dissection*	1 (3.1)
	to laparotomy	0 (0)
Intraoperative events	*Urethral injury*	1 (3.1)
	Pelvic sidewall injury	1 (3.1)
	Co2 embolism	1 (3.1)
	Rectal tube perforation	2 (6.3)
Omentoplasty performed	*yes*	6 (18.8)
Perineal reconstruction	*Primary closure*	18 (56.3)
	*Gluteal turnover flap**	3 (9.4)
	*Gluteus maximus flap***	3 (9.4)
	Non-absorbable mesh	1 (3.1)
	Absorbable mesh	7 (21.9)

Numbers in parenthesis are percentages, unless mentioned otherwise
*Deepithelialized cutaneous turnover flap, **musculocutaneous flap

A bilateral extralevatory APE was performed in 17 cases (53%), a unilateral ELAPE in 7 cases (22%), and an APE without resection of the levator ani muscle in 8 patients (25%) (table 2). A beyond TME resection (n=8, 25%) was performed for tumours that invaded other organs or those at risk of CRM+ and consisted of additional (partial) resection of the prostate (n=5), vagina (n=1), seminal vesicles (n=1) and ovaries (n=1). An omentoplasty was performed in six patients (19%), all without use of indocyanine green, to assess the perfusion of the mobilized greater omentum. The perineal defect was predominantly closed by primary closure (n=18, 56%), and in the other 15 cases, either a musculo-cutaneous gluteal flap (n=6, 19%), an absorbable mesh (n=7, 22%) or a non-absorbable mesh (n=1, 3%) was used for perineal reconstruction.

Primary endpoint

Intraoperative complications occurred in five patients (16%) and consisted of one carbon dioxide embolus, one urethral injury, one pelvic side wall injury and two intraoperative rectal perforations. No conversions to laparotomy were reported and conversion to an open perineal approach was necessary once, due to the inability to progress with the dissection, despite abdominal assistance in a two-team approach (table 2).

Secondary endpoints

There was no 30-day mortality. Major 30-day postoperative morbidity was reported in three patients (9%). This consisted of a compartment syndrome of the lower leg requiring fasciotomy, a deep pelvic abscess due to omental infarction with return to theatre and a urinoma following urethral injury which was managed with percutaneous drainage (table 3). Perineal wound healing was impaired in 47% (n=15) of patients in this cohort; one flap failure (3%), four break through abscesses (deep perineal infection) (13%), and ten superficial skin infections (31%). One superficial dehiscence and one flap failure were treated by negative pressure therapy, three breakthrough abscesses needed packing, and one abscess required drainage followed by secondary healing. One patient with a superficial skin infection that was initially not severe developed a late perineal hernia with wound dehiscence requiring secondary reconstruction. The median time to perineal wound healing was 14 days for those without perineal infection and 45 days in complicated perineal recovery (p = 0.002).

Table 3 Postoperative details

		n=32
Mortality (30 day)		*0 (0.0)*
Total post-operative complications CD	*None*	*11 (34.4)*
	Minor (CD I-II)	*18 (56.3)*
	Major (CD ≥ III)	*3 (9.4)*
Perineal wound healing	*uncomplicated*	*17 (53.1)*
	complicated	*15 (46.9)*
Nature of healing complicatoins	*Superficial infection*	*10 (31.3)*
	Break through abscess	*4 (12.5)*
	Flap failure	*1 (3.1)*
Days to heal (days) Median (range)	*Uncomplicated*	*14 (5-60)*
	Complicated	*45 (21-140)*

Numbers in parenthesis are percentages, unless mentioned otherwise

CRM+ (R1) upon pathological evaluation was seen in fpir cases (13%) and intraoperative specimen perforation occurred in two procedures (6%). The positive margin was anterior in three out of the four R1 resections. A complete or nearly complete specimen was obtained in the vast majority of cases (n=28, 90%) (table 4.).

Comparative analysis

Comparative analysis based on the extent of the procedure (conventional APE, uni- or bilateral ELAPE) revealed that intraoperative complications were higher in the ELAPE groups (table 5). There were three severe complications in the unilateral ELAPE (pelvic sidewall injury, urethral injury, rectal tube perforation), two in the bilateral ELAPE (CO_2 embolus, rectal tube perforation) and no intraoperative complications in the APE group (p 0.071). Severe postoperative complications were distributed equally among the three procedures. A composite of optimal pathology, defined as circumferential and distal resection margin-without perforation and a complete/near complete specimen, was achieved in 84.4% cases in this series. An unsuccessful resection was seen in two out of seven (29%) unilateral ELAPE procedures which was higher than in conventional APE (13%) and bilateral ELAPE (16%) but did not reach statistical significance.

Table 4 pathological assessment

		n=32
Pathology stage	*(y)pT0*	4 (12.5)
	(y)pT1	0 (0)
	(y)pT2	9 (28.1)
	(y)pT3	19 (59.4)
Succesfull resection	*Yes*	5 (15.6)
	No	27 (84.4)
Quality of specimen (Quirke)*	*Complete*	15 (48.4)
	Nearly complete	13 (41.9)
	Incomplete	3 (9.7)
CRM involvement (<1mm)	*Yes*	4 (12.5)
	No	28 (87.5)
Perforation	*Yes*	2 (6.3)
	No	30 (93.8)
Lymphnodes harvested	*mean (±SD)*	13.6 (7.9)
	median (range)	12 (2-34)
Pathologic N stage	*(y)pN0*	20 (62.5)
	(y)pN1	9 (28.1)
	(y)pN2	3 (9.4)

Numbers in parenthesis are percentages, unless mentioned otherwise
*1 missing

Table 5 Comparative

		APE n=8	unilateral ELAPE n=7	Bilateral ELAPE n=17	p-value
Baseline					
Sex	*Male (%)*	7 (87.5)	6 (85.7)	11 (64.7)	0.488
	Female (%)	1 (12.5)	1 (14.3)	6 (35.3)	
Age	*Mean (±SD)*	70.3 (7.1)	69.3 (13.7)	62.0 (14.0)	0.241
	Median (range)	71 (55-80)	70.0 (47-86)	63.0 (33-83)	
BMI	*Mean (±SD)*	28.3 (2.5)	25.0 (3.6)	26.1 (3.3)	0.121
	Median (range)	28.2 (25.5-31.5)	24.9 (20.3-30.7)	25.6 (20.2-33.0)	
ASA	*<III*	7 (87.5)	4 (57.3)	15 (88.2)	0.202
	≥III	1 (12.5)	3 (42.7)	2 (11.8)	
Tumour stage (cT)	*≤ T3*	7 (87.5)	3 (42.7)	15 (88.2)	0.054
	T4	1 (12.5)	4 (57.3)	2 (11.8)	
Mesorectal Fascia threatened	*yes (%)*	3 (37.5)	6 (85.7)	12 (70.6)	0.146
	no (%)	5 (62.5)	1 (14.3)	5 (29.4)	
Height with respect to ARJ	*At or below (%)*	6 (75.0)	2 (28.6)	14 (82.4)	**0.045**
	Above (%)	2 (25.0)	5 (71.4)	3 (17.6)	
Intra operative outcomes					
Operative time (minutes)	*Mean (±SD)*	256 (50)	245 (50)	297 (83)	0.250
	Median (range)	242 (175-300)	245 (175-300)	300 (180-450)	
Intra-operative complications	*yes (%)*	0 (0)	3 (42.9)	2 (11.8)	0.071
	no (%)	8 (100)	4 (57.3)	14 (82.4)	
Pathological outcomes					
Quality of specimen (Quirke)	*Complete*	6 (75.0)	5 (71.4)	4 (25.0)	**0.022**
	Nearly complete	1 (12.5)	1 (14.3)	11 (68.8)	
	Incomplete	1 (12.5)	1 (14.3)	1 (6.3)	
CRM involvement	*yes (%)*	1 (12.5)	2 (28.6)	1 (5.9)	0.306
	no (%)	7 (87.5)	5 (71.4)	16 (94.1)	
Perforation	*yes (%)*	0 (0)	2 (28.6)	0 (0)	**0.042**
	no (%)	8 (100)	5 (71.4)	17 (100)	
Sucessfull resection	*yes (%)*	7 (87.5)	5 (71.4)	15 (84.4)	0.679
	no (%)	1 (12.5)	2 (28.6)	2 (15.6)	
Postoperative outcomes					
Severe 30 day morbidity (CD≥3)	*yes (%)*	1 (12.5)	1 (14.3)	1 (5.9)	0.781
	no (%)	7 (87.5)	6 (85.7)	16 (94.1)	
Days to perineal wound healing	*Mean (±SD)*	44.0 (39.0)	25.8 (16.6)	51.2 (36.9)	0.354
	Median (range)	33 (5-106)	22 (7-45)	42 (6-140)	
Perineal wound healing	*Uncomplicated*	3 (37.5)	4 (57.1)	10 (58.8)	0.709
	Superficial infection	5 (50.0)	1 (14.3)	5 (29.4)	

Table 5 Continued.

	APE n=8	unilateral ELAPE n=7	Bilateral ELAPE n=17	p-value
Omental/ Break- through abscess	1 (12.5)	2 (28.6)	1 (5.9)	
Flap failure	0 (0)	0 (0)	1 (5.9)	

Numbers in parenthesis are percentages, unless mentioned otherwise
CD= Clavien-Dindo, n.p. = not performed

DISCUSSION

This multicenter case series suggests that minimally invasive TpAPE is feasible with acceptable intraoperative complications, no short-term mortality and a 9% severe postoperative complication rate within 30 days.

The postoperative major morbidity rate of 9% compares favorably to major morbidity rates between 10 and 30% and perineal wound infection ranging from 11 up to 50% reported in large series and meta-analysis, but the current study is limited by the small sample size and inherent case selection bias (21-26). Five intraoperative complications were reported, four of which were related to wrong plane surgery with sequential perforation, urethral, and pelvic sidewall injury. This illustrates the complexity of this technique and further evaluation of safety and development of the technique are warranted.

The minimally invasive transperineal approach with the application of a single port diminishes the need for a large perineal skin incision to facilitate sufficient exposure to complete the extra-sphincteric dissection and resection of the pelvic floor as required. The down-to-up approach offers good visualization and access to the extralevator plane and does not require rotation of the patient to a prone position and/or resection of the coccyx to complete the posterior plane. In addition, the anterior plane between the specimen and the prostate or vagina can be dissected endoscopically which prevents externalization and rotation of the specimen.

Using the conventional open approach for an APE, perineal wound breakdown is a major issue as summarized in a meta-analysis of Musters *et al.* (35). Impaired perineal healing after primary closure occurred in 15.3% of APE and 14.8% of ELAPE procedures, both without neoadjuvant treatment, which increased to 30.2% and 37.6%, respectively, for APE and ELAPE with neoadjuvant radiotherapy (35). Moreover, in the LOREC APE registry (UK), up to 31% perineal wound breakdown for APE and ELAPE was encountered

(23). Dehiscence often requires intensive treatment with prolonged wound packing, vacuum therapy and in case of pelvic sepsis, image-guided percutaneous drainage (36), which is reflected in a substantial increase in length of stay, readmission rate, and costs (26, 37). In the current series, in 5 patients (16%), a breakthrough abscess or flap failure occurred, and 3 out of 32 patients (9%) needed a surgical reintervention under general anesthesia for a perineal wound complication. Interestingly, in addition to the aforementioned patients, 12 other patients developed a superficial skin infection which could be managed conservatively, i.e. by dressings, antibiotics, or removal of sutures. Due to the reduced length of the incision, a superficial infection after a minimally invasive transperineal approach is probably less likely to culminate in a complete breakdown of the perineal area which seems to occur more frequently after a conventional open perineal approach.

The introduction of ELAPE by Holm *et al.* in 2007 has shown potential to decrease the rate of intraoperative tumour perforation and CRM+ rates (13, 14, 19). Randomized data only comes from small randomized clinical trials and supports the potential oncologic benefit of reduced R1 resection in ELAPE (18, 38). Future larger size trials are awaited to add more robust data, especially on tailoring the extent of surgery to uni- or bilateral ELAPE. In this series, CRM+ was more frequently encountered in unilateral ELAPE than APE or bilateral ELAPE: 29% versus 13% and 6%, respectively, (p= 0.306). Intraoperative tumour perforation occurred twice, both in unilateral ELAPE. In three out of four R1 resections, the positive margin was found in the anterior dissection plane which shows that also in an extensive proctectomy, an anterior tumour location is at high risk of a positive margin. This is in line with data from the Mercury II study and transanal total mesorectal excision (TaTME) registry and, therefore, these cases should not be performed early in the learning curve (9, 39). In retrospect, an anterior exenteration with en-bloc resection of the posterior vaginal wall or prostate might have been more suitable. Eliminating these cases provides an acceptable involved margin rate of 3% (1 out of 29).

Comparable results regarding this technique were reported by Yasukawa et al., who described a comparative cohort of 21 minimally invasive TpAPE versus 29 conventional APE with a positive margin rate (2/21 versus 3/29), a lower severe perineal wound infection rate (0/21 versus 5/29) and reduced length of stay (median 14 versus 23 days) with no conversion, no mortality, and no increase in major morbidity (31).

The current study is limited by several factors that result from its design. With a total of 32 cases from 5 large rectal cancer referral centers, selection bias is indisputably present. Furthermore, the learning curve is likely to partly explain the suboptimal outcomes (40). Although all the surgeons were highly experienced in TaTME, the extension of the down-to-up approach to Tp (EL)APE adds to the procedural complexity. In addition, with institutional variation in treatment algorithms for both initial resection

and management of complications including variety in follow-up protocols, further standardized studies are warranted with appropriate institutional review board approval. In particular, since this technique is promising regarding wound healing and recovery, standardized registration of time to perineal wound healing is essential. However, before initiation of (larger) studies on the potential improvement in perineal wound healing, further evaluation should focus on the safety in terms of intraoperative morbidity and oncologic safety within a prospective well-designed trial.

CONCLUSION

Tp (EL) APE seems to be feasible with acceptable perioperative morbidity and a low rate of perineal wound dehiscence, while histopathological outcomes remain suboptimal. High complexity necessitates extensive experience in both TaTME and conventional ELAPE. Additional evaluation of this technique is needed, ideally in the form of a prospective trial with standardization of the procedure, indications and prospective audited data collection to further explore the safety and viability of this technique.

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11

General summary and future perspectives

The aim of this thesis was to explore the current state of transanal minimally invasive surgery (TAMIS) in the treatment of rectal cancer. Whilst TAMIS as technique for local excision has been accepted and positively evaluated since the introduction of transanal endoscopic microsurgery (TEM) by Gerhard Buess in 1988, advancement of the TAMIS approach further beyond the rectal wall to achieve a radical transanal total mesorectal excision (TaTME) was first published only in 2010.(1, 2) Hence the perspectives in forthcoming future of both techniques vary substantially.

The perioperative safety of the TAMIS technique for local excision itself has been established over the past decades. Current focus lies in extending the role from benign adenomas and early rectal cancer (T1 limited to the most superficial part of the submucosa) towards local excision of more advanced rectal tumours potentially in combination with (neo)adjuvant chemoradiotherapy in the pursue of organ preservation. For TaTME perioperative safety has not been consistently reproduced at a comparative level as the standard laparoscopic approach and long-term outcomes are scarce and limited to cohort studies.(3, 4)

Despite the absence of high-quality evidence supporting the oncologic safety of TAMIS local excision in combination with radiotherapy, various strategies have been already incorporated in institutional practices. In **chapter 2** we summarized the role of these strategies in the available guidelines across the globe. Interestingly, the position of organ preserving strategies in the retrieved guidelines diverges from equally safe as primary TME resection to only in frail patients unfit for radical surgery. The retrieved variability is likely due to absence of robust evidence. However, for pT1 high risk tumours and beyond, organ preservation is generally considered experimental and should ideally be performed within the setting of a clinical trial.(5) Over the last years, national screening programs dedicated to detect colorectal neoplasms in an early stage caused an increase in early stage rectal cancer amendable for local excision. Additionally, advancements in endoluminal resection techniques enables surgeons and especially gastroenterologists to perform a local excision in early cancers more often.(6) Microscopic evaluation of the specimen by the pathologist is necessary to identify presence of risk features that would require additional surgery to reduce the risk of a local recurrence.(7, 8) Although robust data of risk predictors for local recurrence justifying a more radical surgical resection is lacking this is considered standard therapy to date, with adjuvant chemoradiotherapy as potential alternative treatment to reduce the recurrence risk and intensive follow-up and early salvage for those refraining additional treatment.

In **chapter 3** we conducted a critical appraisal and meta-analysis of the published literature to congregate the local recurrence rate of three strategies following local excision of early rectal cancer that show presence of risk factors. First, subsequent completion surgery, which is recommended by most guidelines, offers best local control but is also associated with high end-colostomy rate and hampered functional and

urogenital function. The second strategy concerns patients who refrain from additional treatment but undergo surveillance which showed a 3.5 and 7-fold increased risk to develop a local recurrence for high risk pT1 and pT2 respectively. This supports the current national guideline recommendation of completion surgery upon pathologic examination of such tumours that were initially treated by local excision. The third strategy involves adjuvant chemoradiotherapy which, based upon the meta-analysis, mimics the local recurrence rate of completion TME for high risk pT1 tumours and reduces the LR rate for pT2 from 28.9% (no additional treatment) to 15.1% which is considerably higher than the gold standard (completion TME pT2 4.1%). Although this is an extensive review of the available literature, bias is suspected to be present on several levels. First, selection and publication bias of respectively more ideal candidates and good outcomes are commonly present in retrospective case series. Secondly, a Dutch national database study recently signalled that in a rather large proportion, 71%(!), completion TME is declined despite presence of an indication for radical surgery according to the national guideline.(9) Presumably patient and physician preference play a large role in the decision of final treatment strategy. More importantly, these strategies are based on, at best, moderate quality of evidence and will be continuing to do so for the short future. The prospective TESAR trial, which centrally reviews pathology, offers the possibility of organ preservation by adjuvant chemoradiotherapy within the safe setting of an audited clinical trial.(10) A third arm of close surveillance was added for those declining further treatment which will render prospective audited data. Another important domain to explore is the exact location, extension and consequence of disease recurrence among the three strategies. In theory, salvage surgery for a local recurrence following local excision only or with adjuvant chemoradiotherapy may be limited to a "normal" TME resection (low anterior resection or APR). This might be more favourable compared to post (completion)TME recurrent rectal cancer which frequently needs pelvic exenteration.(11)

In frail and elderly patients with a limited life expectancy a higher risk to develop a local recurrence could potentially be tolerated. Especially if these patients are at high risk of peri-operative complications due to comorbidity, the trade-off between oncologic (long-term) safety and immediate procedure related morbidity is different from the trade-off in young and fit patients. It might be tempting in those cases to choose local excision over radical resection in case of a more advanced rectal tumour (cT2-3). However, local excision for larger tumours may yield irradical resection of the primary tumour and will leave regional metastatic spread in the mesorectal lymph nodes in situ. Considering the unacceptably high local recurrence rate, local excision as palliation should therefore be regarded as ineffective as elaborated in **chapter 4**. For immediate symptom relief in frail patients, palliative radiotherapy might be preferable. For patients who are not considered terminal, a laparoscopic radical resection by an experienced colorectal surgeon proceeded by multidisciplinary prehabilitation will serve patients interest best.

If it is anticipated that the patient is unlikely to recover from an anastomotic leakage, a non-restorative resection with end-colostomy seems appropriate.

Accurate preoperative staging of rectal cancer is of immense importance to offer precise tailored treatment such as organ preservation. Without accurate staging, it can lead to prevent potential under and overtreatment. Multidisciplinary teams rely on the mandatory preoperative MRI to triage patients with rectal cancer in need of neoadjuvant (chemo)radiotherapy. Whilst MRI is excellent to identify enlarged lymph nodes and to determine the growth of the tumour beyond the rectal wall, it underperforms in daily practice to distinguish T1 stage (limited to submucosa) from T2 stage as shown in **chapter 5**. Therefore large excisional biopsy by local excision is suggested which may turn out therapeutic in a proportion of patients. These cases constitute of T1 low risk tumours who are thereby spared from a TME resection whilst the large biopsy can further direct additional treatment for other than T1 low risk tumours.

The second part of this thesis concerns the Transanal Total Mesorectal Excision (TaTME) procedure, which involves a hybrid approach of a transabdominal laparoscopic phase and a transanal endoscopic single port phase. The simultaneous access to the pelvic cavity from above and below is claimed beneficial in the meticulous dissection along the holy plane (inner side of the mesorectal fascia) to achieve a complete specimen with clear margins. By completing the most difficult part of the operation which is the dissection deep in the narrowing pelvis from below, conversion to laparotomy is seldom required as the distal margin can be confirmed by direct endoluminal visualization. Additionally, this approach technically enables the construction of a very low stapled circular anastomosis due to the diathermic transection with a double purse string instead of cross-stapling through a linear stapled transection of the rectal tube. A systematic review of twenty-three cohort studies that describe a minimal series of fifteen patients that underwent TaTME for primary rectal cancer was conducted to congregate the early results of the centres that initially adopted this technique and these results were compared to the outcomes from the laparoscopic arm of four large randomized controlled trials in **chapter 6**. The included series of TaTME, all inherently limited by selection bias, showed that postoperative morbidity, anastomotic leakage, circumferential resection margin involvement and specimen quality were comparable to the rates as seen in the laparoscopic arms of the RCT's. Indisputably the rate of conversion to laparotomy was improved from 16% in the laparoscopic TME to 2% in TaTME. The end- colostomy rate was not pooled due to anticipated selection bias and the local recurrence rate could not be derived due to study design and lack of adequately reported follow-up. Nevertheless, this study shows that in the centres from the studies involved, which all have a dedicated colorectal cancer program, acceptable short-term results of a highly complex novel procedure in a selected group of patients could be achieved.

As suggested by early adaptors and agreed upon in multiple TaTME consensus meetings, extensive postgraduate training even for consultant colorectal surgeons to start with this highly complex technique is imperative.(12) In the Netherlands a structured pathway was set-up to prevent centres making iterative mistakes during the implementation of TaTME in their practice; cornerstone was the on-site presence of an experienced proctor to coach the apprentice during the first five cases. The short-term results of the first ten patients in twelve centres that participated in a structured training pathway are described in **chapter 7**. Intraoperative complications were low and the pathologic results were good both indicating that the correct planes were identified. However, a considerably high morbidity and especially anastomotic leakage rate occurred in this multicentre cohort reporting the very early experience.

A disturbing yet honest report coming from Norway on an increased local recurrence rate with a multifocal pattern urged an external audit of the local recurrence rate in the aforementioned implementation cohort which revealed a similar picture as shown in **chapter 8**. At a median follow-up of 21.9 months, twelve local recurrences (12 of 120, 10%) occurred of which eight were multifocal. An unexpected high rate, since by an involved CRM rate of 5% the expected corresponding LR rate was estimated at 2.5%. The observed relation of intraoperative events that consisted of some sort of open connection between the pelvic cavity and the rectal lumen (purse string failure, rectal perforation or defects after firing the anastomosis) and the multifocal recurrence pattern hint that tumour spill due to suboptimal execution could be responsible for the increased local recurrence rate. Extension of the cohort in four centres with a cumulative experience of more than 45 procedures per centre showed that the local recurrences of 15 % (6 of 40) were concentrated in the very early experience (case 1-10) in each centre and dropped in the succeeding series enormously, thereby bringing down the overall local recurrence proportion to 5.4% (15 of 266).

In a cohort of patients that underwent TaTME in the two centres that started this procedure in the Netherlands with a minimum interval of 36 months since the operation showed the 3-years local recurrence rate to be 2.0% as shown in **chapter 9**. This shows that the technique appears to deliver good long-term outcomes in expert hands of high volume rectal cancer programs and supports the previously mentioned hypothesis that the long-term outcomes are vulnerable to imperfect execution. To indisputably demonstrate long-term oncologic safety of TaTME is non-inferior to standard laparoscopic approach a randomized controlled trial is necessary.

Expansion of the principles of the bottom-up principle for an abdominal perineal excision (APE) has resulted in a transperineal endoscopic resection of the complete sphincter complex and pelvic floor en-bloc with the rectum. The early experience of this transperineal (extra levatory) APE technique in five centres are collectively described in **chapter 10**. No postoperative mortality occurred and the major morbidity rate

(9%) seems favourable compared to the conventional technique. However, despite extensive experience in TaTME, intraoperative complications were reported in 5 of 32 procedures and a positive CRM was observed in 4 specimens which is somewhat disappointing. Especially in the subgroup of unilateral extra levatory tpAPE pathology remained suboptimal. Nevertheless, subjective benefits of intraoperative exposure of the correct surgical planes and improvements in perineal wound healing justify further exploration of this approach in further studies. Further standardization and prospective data collection are vital in further assessment of the safety of this tpAPE technique.

Future perspectives

For decades, research in rectal cancer has mainly focused on which approach renders an optimal total mesorectal excision, how to minimize associated morbidity following TME, increase the restorative procedure rate, minimize anastomotic leakage and assess the value of neo-adjuvant radiotherapy to TME in terms of local control.(13-15) Despite efforts in decreasing the local recurrence rate to 5% and increasing DFS and OS to 68%, long-term functional outcome has not improved leaving at least 50% of the patients with urinary, sexual and defecation problems.

Therefore, the last decade more research is focused towards organ preservation for patients with rectal cancer. Several institutes have explored the possibility to reduce the need for radical resection (TME) in (early stage) rectal cancer by adding (neo)adjuvant radiotherapy in combination with transanal local excision thriving for organ preservation rather than radical surgery. Both neoadjuvant and adjuvant chemoradiotherapy combined with local excision seem promising and are explored. Unfortunately, to date only few randomized controlled trials have been conducted to properly assess oncologic safety. (16, 17) Although the possibility organ preservation seems appealing for patients, in case of insufficient response or signs of regrowth patients qualify for immediate completion TME or later salvage TME which then both come at a cost of increased morbidity and decreased ability of sphincter preservation compared to a primary TME. More direct comparative studies are expected in the coming years including patient reported outcomes of quality of life and function. Improvements in endoluminal surgery have resulted in advanced techniques, such as endoscopic submucosal dissection (ESD) for gastroenterologists and TAMIS for surgeons. Nevertheless, a surprisingly high proportion of pT1 (8.1%) locally excised tumours develop a local recurrence as demonstrated in chapter 4, even in low risk pT1 this amounted 6.7%. In a cohort of 88 patients with pT1 cancer treated by TEM endoluminal recurrences were reported in more than half of 18 locoregional recurrences despite a radical excision, i.e. absence of a positive margin.(18, 19) Lezoche et al. have suggested that quality of the local excision, in particular the extend beyond the rectal wall of a full thickness excision could be related to incidence of local recurrence.(20) Another explanation analysis could be potential seeding of viable tumour cells into the excision defect which calls for further investigation.

Also for radical rectal resection, physicians and industry continuously seek technical advancements in their aim to improve the quality of surgical cancer care. However, history repeats as the current concern on increased local recurrences following TaTME reminds of port-site metastases in the early phase after the introduction of laparoscopy.(21) It seems that the TaTME technique might have been disseminated prematurely since long-term outcomes were not yet available. At least than 170 units have started this technique according to the latest international TaTME registry paper, and this is very likely to be an underestimation since participation in not mandatory and the actual number might have reached 300-400 globally.(22)

In 2019, Norway declared a moratorium of TaTME following a disturbing high incidence of multifocal local recurrences that were presented to the referral centres for recurrent rectal cancer.(23) A national audit revealed a 11.6% estimated local recurrence rate in a cohort of all 157 Norwegian patients that were operated by the TaTME technique. This indicates that individual hospitals are potentially unable to signal unfavourable long-term outcomes and thorough long-term outcome registration was lacking. In explanation, signalling was initiated by the centres facing an increase in referred recurrent rectal cancer cases, rather than by the centres who performed this technique.(24) Also in the Netherlands, external audit was an important aspect to track the local recurrence rate in the structured training pathway cohort. (25) In daily practice, a substantial proportion of patients are no longer in the follow-up of the operating surgeon due to return to a more nearby community hospital for further follow-up or referral to a tertiary hospital in case of metastasis or local recurrence. In contrast, several dedicated high volume rectal cancer centres that early adopted the TaTME technique recently published cohort studies reporting excellent long-term outcome data of an expanded experience (N ³ 100) with local recurrence between 2 and 5%.(26-32) Especially considering that the initial streak in each centre consists of an unsupervised and merely autodidact experience, these cohorts rest assure that excellent outcomes can be achieved with TaTME. Hompes et al. are commended for implementing an international registry which has enabled prospective data collection of TaTME procedures performed by any surgeon across the globe.(33) The registry has been able to early signal an anastomotic failure rate of 15.7% and an increase of positive margins as more centres contributed cases, but has not published long-term outcomes to date. The amount of unregistered cases, missing data and loss to follow-up in this voluntary non-audited database is a limitation that must be acknowledged. Pending robust long-term outcome data from large prospective randomized trials which are not expected in the next three years, population-based studies are better equipped to capture the complete study population by excluding publication bias. However, population-based databases are frequently limited to a predefined dataset, restricted follow-up (30 days) and are not able to correct for previous experience/ learning curve.(3) Therefore cohort series are the only source of long-term outcome data. The difference in the local recurrence rate reported in the cohort series (3-5%) and

the external audits in Norway and the Netherlands (10%) puzzles and has placed TaTME under a magnifying glass for the foreseeable future. Potentially TaTME could turn out to be a non-transferable technique for every surgeon due to the complexity and specific required skills. Alternatively, the discrepancy can also be a consequence of selection and publication bias of non-audited cohort series in combination with a shorter time to overcome the learning curve in more high volume practices that adopted early. Lastly, the cohorts report on a prolonged series in which an increased rate of local recurrences in the first experience might be present as well but fades out as more cases are added enlarging the total amount of cases (denominator).

Patients who are deemed to benefit most from TaTME are obese, male sex, anterior tumour location, situated in the distal rectum and/or post radiotherapy. Unfortunately, exactly these patients encounter the largest risk of a positive circumferential margin following TaTME as can be deducted from the prediction model generated by Roodbeen et al. based on 2653 cases from the TaTME registry. Therefore, it is recommended to commence with less challenging cases such as a T2 mid rectal tumour in a non-irradiated female patient when starting TaTME.(12) In the context of the recent data from Norway and the Netherlands, from an ethical standpoint it might however be questionable to expose "easy cases" to TaTME since these patients could alternatively receive curative resection by a conventional laparoscopic transabdominal approach without exposure to a surgeons TaTME learning curve. It is relevant to mention here that in the Netherlands, the structured training pathway organized by the VUmc is put on hold pending reaffirming data on the oncologic safety of TaTME. It is important to reiterate that dedicated high volume rectal cancer centres have been able to achieve excellent results in recent published cohort series which is reassuring in response to the Norway moratorium.(26-32) Continuation of the procedure is therefore appropriate but should be performed in the context of a clinical trial to provide reliable data. That data is heavily awaited in order to establish the viability of TaTME and secondly identify the group of patients that will benefit most from this approach which might result in narrowing the indication of TaTME. A contemporary trial incorporates surgical quality assurance to ensure the participating sites have completed their learning curve and are competent in both TaTME and comparator (laparoscopic TME) in order to make a fair comparison. Additionally, central MRI review and collection of procedural videos are essential ingredients a well-designed randomized controlled trial with extensive quality assurance. The assumption that suboptimal execution can cause serious consequences such as described in chapter 8 has amplified the importance of video registration to assess the prevalence of intraoperative errors. In such a prospective study a potential causal relation with the increased (multifocal) local recurrence rate may be demonstrated.

The surgical community will nonetheless have to take lessons from the setback seen in Norway and the Netherlands which is described in this thesis. Individual physicians

might be tempted to preliminary adopt new interventions strategies in order to not miss the boat. Also patients might pursue new treatment options of which the expectations are exaggerated by investigator bias and selection bias. More strict regulation of the implementation of innovative procedures by professional associations could prevent exposure of too many patients to innovative strategies before safety and efficacy is reproducibly established. It is striking that new surgical treatment developments lack the strict regulations as to which pharmaceutical companies have to comply to when introducing a new drug. (USA: FDA and Europe EMA) Even medical devices, although to a much lesser degree than drugs, are regulated by national authorities before allowed to be used in healthcare. To remedy this lack of formal regulation, the international group of surgeons exploring TaTME thrived to adhere to the IDEAL framework for safe stepwise introduction.(34, 35) This includes the aforementioned registry and establishment of a highly engaged network of TaTME surgeons sharing novel complications as urethral injury, carbon dioxide emboli and videos of other potential pitfalls. Continuous adjustments of the technique have been discussed in international consensus meetings to improve safety, define indications and minimal requirements for effective implementation of the technique.(12, 36-38) Additionally, emphasis on the necessity for extensive training of fellow surgeons interested in this technique lead to the initiation of various hands-on cadaver courses which are ideally followed by proctored implementation and continued mentorship.(39-44) Atallah et al. recently argued that the vast majority of participants in training courses in the USA lack sufficient case volume to be able to reach sufficient technical competency and made a plead for more strict entry criteria and (obligatory) proctoring.(45) Surgical associations are likely best equipped to regulate training curriculums including entry criteria, oversee the subsequent implementation into daily practice and assess performance disparities between individual hospitals and the golden standard of care.

New innovations in this multidisciplinary field are on the foreseeable horizon to improve treatment of rectal cancer such as laparoscopic articulating instruments, robotic systems, integrated intraoperative navigation, fluorescent labelled tumour markers, MRI-guided radiotherapy but also include the exciting area of targeted immunotherapy. (46) To ensure that new promising options are sustainably incorporated in guidelines, thorough scientific evaluation is essential. Alike established (multi)national authorities regulating drugs and medical devices, surgical societies may need to implement regulative frameworks for novel techniques including appointment of independent oversight to protect foremost patients but also innovations itself from too early implementation often instigated by too high expectations from patients, health care providers and industry.

In the next decade robotic assisted surgery is expected to expand due to expiry of the patent of the current monopolist and subsequent entry of alternative platforms from multiple companies at more competing costs. Also for robotic assisted colorectal

surgery structured training and proctoring programs have been launched but similar to TaTME these are not mandatory.(47, 48, 49) Robotic-assisted TME studies have focussed on procedural success in terms of primarily conversion and secondary in complications and pathologic outcomes (complete specimen and radical margins) whilst long-term local recurrence rates are underexposed and randomized data from the ROLARR trial is awaited.(15, 50-53) Especially since more units will be able to implement robotic assisted surgery in daily practice, robust scientific evaluation of benefits and liabilities of the technique, especially in the implementation phase will show the validity and true merit of such, relatively costly, equipment.

The outcomes of transanal TME have been scrutinized in detail. An international group of engaged surgeons continuously and transparently publish their data. The magnifying glass that lies on TaTME by this group exposed caveats of the technique with proposed preventive measures and improvements, but has also highlighted the danger that comes with a learning curve when implementing a new technique. Throughout the surgical literature, the initial procedures of various techniques are well-described regarding peri-operative outcomes but are seldom included in studies assessing long-term safety and efficacy. Prof R.J. Heald acknowledged the importance of focusing on oncologic outcome in his landmark paper on TME in the Lancet in 1986:

> *,,In assessment of any new procedure, however, the fundamental yardstick is long-term tumour-free survival. This personal series was undertaken in the belief that a reduction of the bowel wall margin to conserve sphincters is safe provided that mesorectal excision is complete. Since every other consideration is secondary to those of cancer clearance and survival the results are presented only in terms of recurrence and mortality."*(54)

Transanal total mesorectal excision should currently be regarded as a promising but complex solution for difficult rectal cancer cases. In the coming decade randomized controlled trials (55, 56) will have to show definitive oncologic safety and the indication for TaTME is likely further refined. Expanding the role of TAMIS local excision will likely increase beyond low risk early rectal cancer upon patient request. Whereas shared decision making is currently based on suboptimal evidence, several ongoing trials (10, 57) with prospective oncologic and patient reported outcomes will offer more reliable data enabling a better informed trade-off by individual patients between oncologic risk, morbidity, function and quality of life.

In summary, introduction of innovations in rectal cancer surgery must follow the IDEAL framework to ensure proper and sustainable implementation. Structured training pathways, proctoring, quality assurance and external audited data within trials should be mandatory before new strategies can be considered standard care. Surgical societies may fulfil a more regulative role to ensure new strategies are sufficiently studied to prevent prematurely dissemination which might endanger patients and techniques

itself. Increasing international collaboration facilitates the formation of networks capable to collectively produce robust data.

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APPENDICES

NEDERLANDSTALIGE SAMENVATTING

Het doel van dit proefschrift was om de huidige toepassing van transanale minimaal invasieve chirurgie voor de behandeling van een tumor in de endeldarm te analyseren. Deze benadering voor de lokale behandeling (TAMIS) van een tumor in een nog vroeg stadium is breed geaccepteerd en wordt toegepast sinds de introductie van de TEM-procedure door Gerhard Buess in 1988. Uitbreiding van de transanale minimaal invasieve techniek voor een resectie voorbij de darmwand en met medeneming van het omliggende mesorectale vet (TaTME) werd pas 22 jaar later, in 2010, voor het eerst beschreven. Hierdoor verschilt het perspectief van TAMIS vs. TaTME ten aanzien van de toepassing en ontwikkelingen in de nabije toekomst aanzienlijk.

In de laatste decennia is de perioperatieve veiligheid van TAMIS uitgebreid onderzocht en ligt de huidige focus op uitbreiding van de indicatie voor de toepassing van een lokale excisie voor verder gegroeide tumoren, al dan niet in combinatie met chemo-radiatie voorafgaand of volgend op de lokale behandeling. Voor de TaTME techniek voor de radicale resectie van het rectum en drainerende lymfeklieren in het omliggend vet zijn de intra-operatieve veiligheid en postoperatieve complicaties echter nog onvoldoende gereproduceerd en zijn de oncologische resultaten op de lange termijn nog schaars.

In **hoofdstuk 2** worden de adviezen omtrent de toepassing van een lokale excisie voor de behandeling van een endeldarmtumor zoals opgenomen in de nationale richtlijnen van over de hele wereld samengevat. Ondanks dat er nog geen onomstreden bewijs is dat een lokale excisie al dan niet in combinatie met (chemo)radiotherapie op de langere termijn even goed is als een radicale resectie, loopt de positie van deze zogenoemde orgaan sparende behandelstrategie opvallend genoeg uiteen van een gelijkwaardig alternatief in enkele richtlijnen tot alleen toegestaan in studieverband of bij patiënten die een grote operatie niet aan kunnen. De algemene opvatting is desalniettemin dat voor tumoren van stadium pT1 met hoog risico factoren een orgaan sparende therapie nog experimenteel is en idealiter dient plaats te vinden in de context van een klinische studie. Door nationale screening programma's en verbeteringen in endoscopische technieken door zowel de MDL-arts als chirurg is er een toename te verwachten in de lokale excisie van tumoren. Microscopische analyse door de patholoog is essentieel om risicofactoren te identificeren. Wanneer deze factoren aanwezig zijn dan bestaat de standaardbehandeling uit het verrichten van een aanvullende radicale resectie (totale mesorectale excisie (TME)) teneinde het risico op een lokaal recidief te reduceren. Aanvullende bestraling zou het risico op een lokaal recidief kunnen reduceren als alternatief voor een majeure operatie. Voor patiënten die een aanvullende behandeling afslaan is intensieve monitoring nodig om in geval van een lokaal recidief een zogenoemde 'salvage' operatie mogelijk te maken.

In **hoofdstuk 3** worden de gepubliceerde uitkomsten van de drie hiervoor genoemde strategieën volgend op een lokale excisie van een vroeg rectum carcinoom (complementerende TME, adjuvante radiotherapie en geen aanvullende behandeling) in een meta-analyse onderzocht. De complementerende radicale resectie, volgens de richtlijnen beschouwd als standaardbehandeling, biedt de beste lokale controle maar resulteert in een aanzienlijk percentage colostoma's en functionele en urogenitale klachten. Geen aanvullende behandeling maar alleen surveillance laat een respectievelijke 3.5- en 7-voudige toename in risico op het ontwikkelen van een lokaal recidief zien voor hoog risico pT1 en pT2 stadium tumoren in vergelijking met een complementerende TME. Dit ondersteunt de aanbeveling uit de huidige richtlijn om een complementerende radicale resectie. De derde strategie, aanvullende adjuvante chemoradiotherapie, lijkt voor hoog risico pT1 tumoren de uitkomsten van een complementerende resectie te benaderen. Voor pT2 tumoren geeft aanvullende bestraling (15.1%) een aanzienlijk mindere reductie op een lokaal recidief ten opzichte van de gouden standaard van chirurgie (4.1%) maar is wel ontegenzeggelijk beter dan geen aanvullende behandeling (28.9%). De resultaten uit dit uitgebreide systematisch literatuuroverzicht zijn gelimiteerd door publicatie- en selectie bias. Positieve resultaten worden eerder gepubliceerd en in cohort studies opgenomen. Daarnaast heeft een recente Nederlandse populatiestudie door Van Groningen *et al.* laten zien dat ondanks dat er volgens de richtlijn een indictie was voor een aanvullende resectie na lokaal behandeling vroeg rectum tumoren, 71% van de patiënten deze behandeling niet heeft ondergaan. Hoogstwaarschijnlijk spelen er bij patiënten als ook bij behandelaren zwaarwegende motieven om geen aanvullende behandeling te doen. De precieze afwegingen in de besluitvorming zijn helaas onbekend maar berusten in ieder geval op data van matige kwaliteit. Daarom lopen er momenteel meerdere prospectieve studies om deze lacune op te vullen waarbij er wordt gekeken naar behandeling gerelateerde oncologische veiligheid, complicaties als ook patiënt gerapporteerde kwaliteit van leven en functionele uitkomsten.

Voor oudere patiënten die een beperkte levensverwachting hebben kan mogelijk een hoger risico op het ontwikkelen van een lokaal recidief worden geaccepteerd. Een lokale excisie wordt daarom ook wel voorgesteld bij meer geavanceerde cT2-3 tumoren waarbij de lymfeklieren ongemoeid worden gelaten. Zeker wanneer deze patiënten een hoog risico op complicaties rondom de operatie hebben door bijkomende ziekten is de afweging tussen oncologisch perspectief en mogelijk complicaties van een grote operatie anders dan bij jonge, fitte patiënten. In **hoofdstuk 4** beschrijven we dat ook bij patiënten die niet als terminaal worden beschouwd een laparoscopische resectie, al dan niet met aanleg van een colostoma, door een ervaren colorectaal chirurg in de context van een multidisciplinair team om de patiënt optimaal voor te bereiden, de eerste keus in behandeling is gezien het onacceptabel hoge recidief kans bij slechts een lokale excisie.

Juiste selectie van patiënten met endeldarmkanker is van groot belang om de juiste route van behandeling in te gaan. Inadequate stadiëring kan leiden tot zowel onder- als overbehandeling. Multidisciplinaire behandelteams gaan primair af op de volgens de richtlijn verplichte MRI scan om te bepalen of een patiënt in aanmerking komt voor bestraling voorafgaand aan een operatie. Met behulp van de MRI blijkt men goed in staat om pathologische lymfeklieren en uitbreiding van de tumor buiten de darmwand in het omliggend vet te beoordelen. Daarentegen blijkt zoals beschreven in **hoofdstuk 5** het MRI-onderzoek in de dagelijkse praktijk niet voldoende in staat om onderscheid te maken tussen een laag en hoog risico vroeg stadium endeldarm tumor. Een groot excisiebiopt middels een hoog kwaliteit lokale excisie kan een waardevolle stap in de stadiëring zijn; in geval van een laag risico tumor is de behandeling klaar en in geval van een hoog risico tumor dient in principe een aanvullende chirurgische behandeling, of adjuvante radiotherapie in studieverband, van de resterende endeldarm en het mesorectum te volgen.

Het tweede deel van dit proefschrift beslaat de transanale totale mesorectale excisie (TaTME) die bestaat uit een hybride minimaal invasieve (kijkoperatie) met een transabdominale fase en een endoscopische transanale fase. Door het kleine bekken zowel vanaf boven als beneden te benaderen zou een meer zorgvuldige dissectie langs de juiste vlakken bewerkstelligd kunnen worden wat een beter resectiepreparaat met vrije marges oplevert. Verder is er vrijwel geen noodzaak meer voor een conversie naar een laparotomie (traditionele open buikoperatie) en kan er met de transanale techniek op een lager niveau een nieuwe verbinding van de dikke darm en anus worden gemaakt. In **hoofdstuk 6** presenteren wij een systematisch literatuuroverzicht van publicaties met resultaten van de eerste serie patiënten uit centra die deze TaTME techniek vroeg hebben omarmd en vergelijken deze met uitkomsten van de laparoscopische abdominale techniek uit vier grote gerandomiseerde studies. In de gevonden studies, die gelimiteerd zijn door selectie van mogelijk 'gunstige' patiënten, waren het aantal complicaties, naadlekkages, radicaliteit en kwaliteit van het preparaat vergelijkbaar met de resultaten van de gouden standaard. Ontegenzeggelijk was in de TaTME series het percentage conversie naar laparotomie lager dan met de laparoscopische techniek: 2% versus 16%. Uit de geïncludeerde studies kon door het verschil in opzet en duur van opvolging na de operatie nog niets geconcludeerd worden over het percentage colostoma's of lokaal recidieven.

De groep chirurgen van over de hele wereld die kort na de eerste demonstratie de TaTME techniek hebben geëxploreerd, is het erover eens dat zelfs voor ervaren colorectaal chirurgen uitgebreide training geïndiceerd is wanneer men met TaTME wil beginnen vanwege de hoge moeilijkheidsgraad. In Nederland is daarom een gestructureerd implementatie programma opgezet voor nieuwe centra om te voorkomen dat deze dezelfde fouten zouden maken als de pioniers gedurende de implementatie van deze operatie. Naast uitgebreide presentaties, live demonstratie en kadavertraining was

het belangrijkste element in het implementatieprogramma de aanwezigheid van een collega-chirurg die ervaren is met de TaTME techniek gedurende de eerste vijf procedures in het eigen ziekenhuis. De korte termijn uitkomsten van twaalf centra die hebben geparticipeerd in dit gestructureerde implementatie programma, beschreven in **hoofdstuk 7**, lieten zien dat er een gering percentage complicaties tijdens de operatie was en dat de pathologische resultaten goed waren hetgeen erop wijst dat de juiste vlakken werden gevolgd. Echter, er was een aanzienlijk percentage postoperatieve complicaties als ook een meer dan verwacht aantal naadlekkages in dit multicenter cohort bestaande uit de eerste tien procedures in elk van de twaalf participerende centra.

Een alarmerend rapport uit Noorwegen over een hoog aantal lokaal recidieven met een ongebruikelijk en uitgebreid patroon gaf aanleiding om onmiddellijk het voorkomen van lokaal recidieven te onderzoeken in het cohort van de eerste 10 patiënten uit de 12 ziekenhuizen. In **hoofdstuk 8** had zich bij een mediaan interval van 22 maanden sinds de operatie bij twaalf patiënten een lokaal recidief ontwikkeld, een ruw percentage van 10%, waarvan het merendeel een multifocaal patroon had. Een zeer onverwacht percentage, aangezien het verwachte percentage 2.5% bedroeg bij een positieve circumferentiële resectie marge status van 5%. Een correlatie tussen het optreden van een situatie tijdens de operatie waarbij er een open verbinding tussen het lumen van de darm en het wondbed in het kleine bekken kon zijn (door falen van de tabakszak hechting, perforatie van de darm of een defect van de anastomose) geeft een mogelijke aanwijzing. Spill van tumorcellen bij een technisch suboptimaal uitgevoerde operatie zou mogelijk de oorzaak kunnen zijn voor de verhoogde lokaal recidief kans.

In **hoofdstuk 9** wordt beschreven dat in de twee ziekenhuizen die in Nederland zijn begonnen met de TaTME techniek in een groep van 159 patiënten die inmiddels minimaal 36 maanden na de operatie waren, het 3-jaars lokaal recidief percentage slechts 2.0% bedroeg. Dit laat zien dat met de TaTME techniek in een context van gespecialiseerde centra in rectumchirurgie met een hoog volume goede resultaten behaald kunnen worden, juist ook op langere termijn. Hierdoor bestaat het vermoeden dat door de complexiteit van deze procedure de oncologische uitkomsten kwetsbaar zijn voor een suboptimale uitvoering van de transanale techniek.

Uitbreiding van het principe van een minimaal invasieve “bottom-up” techniek voor de benadering van een abdomino-perineale excisie (APE) waarin ook de kringspier en bekkenbodemspier en-bloc met de endeldarm wordt geëxcideerd heeft geleid tot de transperineale (extra levatoire) abdomino-perineale excisie. De collectieve eerste ervaring met deze techniek bij 32 patiënten uit vijf internationale centra wordt beschreven in **hoofdstuk 10**. Er was geen perioperatieve mortaliteit en het aantal ernstige postoperatieve complicaties (9%) is minder dan we kennen van studies met de conventionele techniek. Daarentegen trad er tijdens de operatie in vijf gevallen

een complicatie op en werd er bij vier patiënten een positief snijvlak gevonden ondanks uitgebreide ervaring van de chirurgen met de TaTME techniek. Door de operateurs subjectief gerapporteerd beter zicht op de operatievlakken tezamen met het grote potentieel in perineale wondgenezing rechtvaardigen verder onderzoek naar de toepassing. Echter verdere standaardisatie van de techniek en prospectieve datacollectie zijn essentieel in verdere evaluatie van de toepasbaarheid en veiligheid van de endoscopische transperineale APE.

Nabeschouwing

Decennia lang heeft onderzoek naar de behandeling van endeldarmkanker zich gefocust op met welke benadering (open of laparoscopisch) een optimale TME behaald kan worden, interventies om het optreden van naadlekkages en consequenties te verminderen, het percentage stoma's te reduceren en de waarde van radiotherapie in het risico op de ontwikkeling van een lokaal recidief. Hoewel het lokaal recidief percentage sterk verminderd is tot omstreeks 5% en ook de ziektevrije en algemene overleving zijn verbeterd zijn de functionele gevolgen op lange termijn, zoals mictie, seksuele en incontinentie problematiek nog altijd aanzienlijk voor patiënten die zijn geopereerd wegens endeldarmkanker.

Daarom is er de laatste jaren veel aandacht voor orgaanpreservatie. Verschillende instituten hebben de mogelijkheid onderzocht om de radicale resectie van een endeldarmcarcinoom te vervangen door bestraling voorafgaand of volgend op een lokale excisie van een tumor. Helaas zijn dit geen gerandomiseerde studies maar vooral cohort series van mindere kwaliteit. Daarom is toepassing op bredere schaal nog prematuur. Vanuit patiënten is er veel interesse in de mogelijkheid van een endeldarm sparende behandeling maar men dient zich te realiseren dat de oncologische veiligheid op langere termijn nog onzeker is. Daarom adviseren wij om een dergelijke behandeling alleen te doen in de context van een klinische prospectieve studie waarbij er een gestandaardiseerd follow-up schema is, het bestaan en verschil in uitkomst voor mogelijke verschillende subtypen vroeg rectum tumoren wordt onderzocht, en er bovendien systematisch patiënt-gerapporteerde kwaliteit van leven en functionele uitkomsten worden uitgevraagd.

In het tweede deel van dit proefschrift komt de innovatie van een transanale benadering voor de TME resectie, wat sinds de jaren 80 de hoeksteen in de behandeling van endeldarmkanker is, uitgebreid aan bod. Helaas lijkt de geschiedenis zich te herhalen, want waar in de jaren 90 de laparoscopische benadering (kijkoperatie of ook wel sleutelgat chirurgie) gepaard ging met buikwandmetastasen door enting van tumorcellen in de toegangspoorten worden recent multifocale lokaal recidieven in het kleine bekken na een TaTME operatie gemeld. In Noorwegen is de TaTME tot een halt geroepen nadat bleek dat er een onacceptabel hoog lokaal recidief percentage was gevonden. Ook in Nederland is er in de eerste serie in ziekenhuizen die participeerden in

een trainings- en implementatieprogramma een verhoogd aantal recidieven gevonden, hoewel het risico op zo'n lokaal recidief sterk vermindert naarmate de centra meer ervaring opdoen. De twee ziekenhuizen die in Nederland zijn begonnen met TaTME hadden bij patiënten die inmiddels minimaal drie jaar na de operatie (n=159) waren, een lokaal recidief percentage van 2%. Ook andere expert centra vanuit meerdere landen hebben recent bemoedigende resultaten gepubliceerd. Dit ondersteunt de hypothese dat de operatie an sich veilig is mits zorgvuldig en technisch perfect uitgevoerd en dat mindere uitkomsten mogelijk veroorzaakt worden door suboptimale uitvoering. Patiënt selectie, hoog volume, technische uitvoering en adequate training lijken essentiële aspecten voor een veilige implementatie. In Nederland is het trainingsprogramma voor nieuwe centra gestopt in afwachting van robuuste data uit prospectieve studies die de veiligheid van de TaTME benadering ondubbelzinnig aantonen.

Er vallen belangrijke lessen te trekken uit de invoering van orgaan preservatie en zeker TaTME door de chirurgische gemeenschap. Zowel artsen als patiënten zijn geneigd om een nieuwe behandeling mogelijk prematuur te omarmen. Enerzijds willen artsen meegaan in nieuwe ontwikkelingen en niet de boot missen. Anderzijds vragen ook patiënten om nieuwe behandelingsopties, met daarbij een te hoog verwachtingspatroon gevoed door studies die onderhevig zijn aan selectie- en publicatiebias. Een nieuwe chirurgische behandeling wordt niet strikt gereguleerd door een nationale of Europese instantie (bijv. FDA in de Verenigde Staten of EMA in Europa) in tegenstelling tot wanneer een farmaceutisch bedrijf een nieuwe medicijn of een nieuw chemotherapeuticum heeft ontwikkeld en wil introduceren op de markt. Een internationale groep van chirurgen die bij de initiële ontwikkeling van de TaTME betrokken zijn heeft dit vroegtijdig herkend en een consensus document met daarin een raamwerk opgesteld om handvatten te bieden de techniek veilig te implementeren. Daarin staan onder andere aanbevelingen omtrent minimale aantallen ingrepen. Echter uit een survey blijkt dat van deelnemers van een TaTME cursus in de Verenigde Staten het overgrote deel deze aantallen niet haalt en dus te weinig aanbod heeft om zich daadwerkelijk te bekwamen in deze techniek. Nationale chirurgische beroepsverenigingen lijken het best toegerust te zijn om de implementatie van nieuwe ontwikkelingen te reguleren door middel van verplichte trainingscurricula, volume normen en audit van uitkomsten.

In de komende 10-20 jaar zullen technische innovatie binnen de zorg en de (colorectale) chirurgie in het bijzonder elkaar snel opvolgen. De implementatie van de TaTME heeft mede door de enorme transparantie van een nauw samenwerkende internationale groep van chirurgen onder een vergrootglas gelegen en heeft daarmee mogelijke valkuilen blootgelegd. Daarbij heeft vroege communicatie er hopelijk voor gezorgd dat deze valkuilen door anderen voorkomen konden worden. Bovendien zijn voor TaTME de lange termijn (oncologische) consequenties bestaande uit suboptimale uitkomsten aangetoond als gevolg van de leercurve voor TaTME. In de chirurgische literatuur worden van nieuwe operatietechnieken de technische details en eerste postoperatieve

uitkomsten goed beschreven maar de lange termijn uitkomsten van juist de eerste patiënten die de nieuwe techniek ondergingen zijn vaak onderbelicht.

Samenvattend zijn er betere richtlijnen nodig om innovaties in de (chirurgische) behandeling van endeldarm kanker veilig en met robuuste onderbouwing in de dagelijkse praktijk te implementeren. Gestructureerde training, begeleiding, waarborging van competentie en externe audit van uitkomsten binnen klinische prospectieve studies zouden verplicht moeten zijn voordat een behandeling in de dagelijkse praktijk kan worden geïmplementeerd. Een (nationale) chirurgische beroepsvereniging lijkt de aangewezen entiteit om een meer regulerende rol te spelen om te voorkomen dat veelbelovende behandelingen vroegtijdig wijdverspreid worden toegepast wat niet alleen mogelijk patiënten schaadt maar ook de techniek of behandeling zelf.

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CURRICULUM VITAE

Stefan van Oostendorp was born on 17 October 1990 in the Prinsengrachtziekenhuis in Amsterdam. He grew up with his parents and brother Justin in the Valeriusstraat which turned out to be both a great football pitch as well a perfect area for blikje-trap (a Dutch ammendment of hide & seek involving a football). After primary school (2e Dalton) he went to the Barlaeus Gymnasium from which he graduated in 2009. In September 2009 he started medic al school upon acceptance in the decentral selection process at the Vrije Universiteit.

During the bachelor phase Stefan spend his time playing hockey, watching games of Ajax, and drinking beers with friends from his fraternity (Forvm). During his junior internship in the VUmc he discovered the thrill of surgery and decided to pursue a career as surgeon. Together with dr. Leo Geeraedts as mentor he started on a comprehensive review on prehospital haemorrhage control which almost resulted in a back-up thesis. Further surgical internships in the RKZ Beverwijk(regular), SLAZ (semi-physician) and VUmc (facultative 10 weeks of traumatology) confirmed the earlier experienced excitement about surgery. A productive scientific internship under guidance of dr. Jurriaan Tuynman resulted in two publications and laid the foundation for this thesis. After working as a surgical resident not in training for one year in the RKZ Stefan started as PhD-student in September 2017 under supervision of professor Bonjer and dr. Tuynman. After finishing the majority of his papers, he worked from June 2020 for 6 months as a non-trainee resident in the Spaarne Gasthuis. After being accepted as surgical resident to the training program in region 1 (VUmc), Stefan returned to RKZ Beverwijk to start his surgical training by dr. H. Cense per January 2021.