General introduction
and outline of this thesis
Innovative procedures, concerns remained about whether sphincter preserving surgery could compromise the completeness of excision. Aligned with the newest pathology insights, TME was developed. Nevertheless, after Dixon reported the results of a 400 patients study, anterior resection became the standard treatment for rectal cancer of the middle and upper rectum with a mortality rate of 2.6 percent and a five-year survival of 64 percent. Concurrently, with the advent of stapling devices, APR resection by a combined abdominal and perineal surgical approach with an extensive excision of the anus, rectum and associated lymph nodes: the abdominoperineal resection (APR). With the introduction of this technique local recurrence rates decreased from 95 to 29.5 percent.

A major disadvantage of Miles technique was the necessity for a permanent colostomy. A technique that moved away from this necessity was described by Balfour et al in 1910: an abdominal approach to popular belief. Allegedly, Faget performed the procedure for what he thought was a bilateral ischiorectal abscess, but this turned out to be perforated rectal cancer. In spite of this 'accident', the interest in lateral tumour spread and identified that there was a high positive predictive value of circumferential margin involvement for the subsequent development of locally recurrent cancer and poor survival. Subsequently, it became clear that distal margins of 2 cm did not compromise survival or local recurrence. Around that same time, Heald published his first experience with 'total mesorectal excision', TME.

In 1906 however a British surgeon named Miles discovered, by doing postmortem examination, that rectal cancer was excised solely by perineal approach until 1906. While this procedure resulted in low morbidity, it was also associated with early recurrence rates as high as 95 percent. Recurrences occurred in the pelvic peritoneum, the mesocolon and in the lymph nodes situated over the bifurcation of the left common iliac artery. Subsequently, he concluded that tumour spread occurred in all directions, the cylindrical concept, and that involved lymph nodes were responsible for the development of locally recurrent diseases. Consequently, Miles developed an 'en bloc' excision technique.

Building on successive innovations in procedures, research in pathological outcomes and survival rates after rectal cancer surgery gained further traction in the early 1980s. Quirke et al. renewed the interest in lateral tumour spread and identified that there was a high positive predictive value of circumferential margin involvement for the subsequent development of locally recurrent cancer and poor survival. Subsequently, it became clear that distal margins of 2 cm did not compromise survival or local recurrence. Around that same time, Heald published his first experience with 'total mesorectal excision', TME. Aligned with the newest pathology insights, TME was developed.
General introduction

The first perineal resection for rectal cancer was performed by Faget in 1739 by accident, according to popular belief. Allegedly, Faget performed the procedure for what he thought was a bilateral ischiorectal abscess, but this turned out to be perforated rectal cancer. [1] In spite of this ‘accident’, rectal cancer was excised solely by perineal approach until 1906. While this procedure resulted in low morbidity, it was also associated with early recurrence rates as high as 95 percent.

In 1906 however a British surgeon named Miles discovered, by doing postmortem examination, that recurrences occurred in the pelvic peritoneum, the mesocolon and in the lymph nodes situated over the bifurcation of the left common iliac artery. Subsequently, he concluded that tumour spread occurred in all directions, the cylindrical concept, and that involved lymph nodes were responsible for the development of locally recurrent diseases. Consequently, Miles developed an ‘en bloc’ resection by a combined abdominal and perineal surgical approach with an extensive excision of the anus, rectum and associated lymph nodes: the abdominoperineal resection (APR). [2] With the introduction of this technique local recurrence rates decreased from 95 to 29.5 percent. [3] Associated mortality rates were 31 percent, mainly due to blood loss and infectious complications, as blood transfusion and antibiotics were not yet available. [2]

A major disadvantage of Miles technique was the necessity for a permanent colostomy. A technique that moved away from this necessity was described by Balfour et al in 1910: an abdominal approach with the performance of an end-to-end anastomosis: the anterior resection. Due to a high mortality rate caused by anastomotic leakage, this technique did not gain wide acceptance initially. Nevertheless, after Dixon reported the results of a 400 patients study, anterior resection became the standard treatment for rectal cancer of the middle and upper rectum with a mortality rate of 2.6 percent and a five-year survival of 64 percent. Concurrently, with the advent of stapling devices, APR with an end colostomy was limited to 11%. Notwithstanding the adoption of these - at the time - innovative procedures, concerns remained about whether sphincter preserving surgery could compromise the completeness of excision. [4]

Building on successive innovations in procedures, research in pathological outcomes and survival rates after rectal cancer surgery gained further traction in the early 1980s. Quirke et al. [5] renewed the interest in lateral tumour spread and identified that there was a high positive predictive value of circumferential margin involvement for the subsequent development of locally recurrent cancer and poor survival. Subsequently, it became clear that distal margins of 2cm did not compromise survival or local recurrence. [6] Around that same time, Heald [7] published his first experience with ‘total mesorectal excision’, TME. Aligned with the newest pathology insights, TME was developed...
anticipating the importance of complete excision under direct vision of the envelope of lymph vascular fatty tissue surrounding the rectum and its mesorectum.[8] The term mesorectum is used to describe all peri-rectal connective tissue including the posterior sheath of the endopelvic fascia containing the peri-rectal neurovascular structures.[9] Possible lymph metastasis are mainly located in this mesorectum. TME was thought to realise radical resection, with even sphincter preserving surgery in patients with distal tumours. Heald et al. [10] proved this theory by reporting a five-year local recurrence rate of 3.7% and five-year survival rate of 87%. Although overall recurrence rates decreased as a result of TME, neoadjuvant (chemo)radiotherapy was added to primary surgery in following years in order to decrease the risk of local recurrence, increase sphincter preserving therapy by tumour downstaging and improve local control.[11-14]

Laparoscopic rectal surgery
TME surgery as Heald described in 1982 has remained the basic principle for rectal cancer surgery. Notwithstanding the advancement TME has brought to rectal cancer surgery, the procedure is still - in 2018 - considered highly challenging to perform in comparison to colon surgery, due to the limited workspace in the lower pelvis. Overcoming this hindrance is one of the main reasons that laparoscopic approach, as compared to open approach, is considered more suitable for rectal surgery. Meta-analyses of several randomised controlled trials (RCT’s) stated that laparoscopic surgery is a safe alternative for open surgery in patients with rectal cancer, resulting in improved short-term outcomes such as shorter duration of hospital stay, reduction of intra-operative blood loss and number of transfused patients and earlier resumption of oral intake. Oncological quality and survival rates were similar however, to the rates of open surgery.[15-17] The COLOR-II study group[18] supported these findings with improved recovery after laparoscopic surgery. More recently, this group published results of an international trial conducted in 30 hospitals comparing laparoscopic surgery with open surgery for rectal cancer. In this trial, locoregional recurrence rate, disease-free survival rate and overall survival rate after three years were similar in the laparoscopic-surgery group as in the open-surgery group with 5,0%, 74,8% and 86,7% respectively.[19]

Transanal TME
Although short-term benefits after laparoscopic surgery have been demonstrated, oncological quality and survival rates remain comparable to conventional TME. Moreover, there is potential to refine TME surgery and overcome remaining challenges during rectal dissection. For example, conversion is currently inevitable in some cases with figures ranging from 0% to 30.3%, which has proven to result in an increase in postoperative complications.[16,20,21] This can mostly be attributed to technical reasons such as bulky tumours, narrow male pelvis, body mass index >25 and tumour height which hinders the ability to achieve clear resection margins in these patients.
Transanal TME (TaTME) could overcome these issues because of an alternative surgical approach of the tumour: a laparoscopic and endoscopic (transanal) approach is combined to optimise the angle for tumour dissection.

The concept of endoscopic surgery, or NOTES (natural orifice transluminal endoscopic surgery) was described as early as the 1900s with transurethral resection of prostatic hypertrophy and transvaginal hysterectomy.[22,23] With NOTES, the peritoneal cavity is not approached by an incision via the abdominal wall, but by a visceral incision aiming for a ‘scar-less’ procedure. It was not until 1983 however, that NOTES was introduced through the transanal canal by Buess et al.[24] The transanal endoscopic microsurgery (TEM) served as an alternative to laparoscopic excision for benign rectal lesions and selected early stage rectal carcinomas. This technique offers superior visualisation, improved access to distal lesions, increased rates of negative margins, and decreased fragmentation of specimens and lower recurrence rates. Based on these experiences, natural-orifice transluminal endoscopic surgery (NOTES) emerged as a promising new alternative to open and laparoscopic colorectal surgery.

Following the adoption of TEM, in 2010 Atallah et al. [25] published their first cases of TAMIS (transanal minimally invasive surgery): a technique in which patients with T1N0 lesions were operated with a hybrid between TEM and (single-port) laparoscopy. This resulted in shorter operative time compared to TEM surgery (86min vs 120-140min respectively), but more importantly in a complete absence of observed short-term postoperative morbidity or mortality. A year later, Sylla et al. [26] used this technique to perform total mesorectal excision in a patient with a T2N2 rectal cancer with preoperative chemoradiotherapy: Transanal total mesorectal excision (TaTME or TAMIS TME) was born.

Whereas in standard open or laparoscopic technique the rectum is approached transabdominally, from top-to-bottom, with TaTME the rectum is mobilised transanally under direct endoscopic visualisation using endoscopic instruments, beginning at the most distal margin of the mesorectum, known as the most difficult part of laparoscopic surgery, working upwards. As this approach presumes enhanced visualisation, TaTME holds the potential to offer various substantial benefits over conventional TME surgery such as sphincter preservation in more distal tumours, enhanced complete mesorectal excision, improved functional outcomes and less involvement of circumferential resection margins.

Although no randomised trials have yet been published on TaTME, small cohort studies have demonstrated the feasibility of this technique with acceptable short-term morbidity and
pathological outcomes.[27-31] In anticipation of rapidly growing interest and adoption of transanal TME worldwide, training and proctoring programs are currently being introduced all over the world, in order to minimise the ‘dip’ in the adoption curve previously seen in laparoscopic experience.[32,33] Furthermore, the thus far promising results of TaTME have led the Colorectal cancer group (COLOR) to instigate the COLOR III trial; an international, multicentre, non-inferiority, randomised trial to compare TaTME and conventional laparoscopic TME as the surgical treatment for mid and low rectal carcinomas.[34]

The past century had seen groundbreaking innovations and new techniques in surgical and neo-adjuvant treatment for rectal cancer. Nevertheless, mortality rates for men and women in central and eastern Europe are still substantial; 20.3 and 11.7 per 100,000 patients respectively.[35] In the Netherlands, more than 13,000 new patients are diagnosed with colorectal cancer annually with approximately 33% of the tumours localised in the rectum.[36] TaTME, the focus of this thesis, holds the potential to play a role of paramount importance in treating these patients and bringing mortality rates further down in years to come.
Outline of this thesis

This thesis focuses on Transanal TME in the Netherlands as a new and promising alternative to laparoscopic TME for rectal cancer patients. It outlines the implementation (part 1), evolution (part 2) and current status (part 3) of this technique in the surgical treatment of rectal cancer.

Part 1 | Implementation of TaTME
Chapter 2 focuses on the presence and clinical significance of peritoneal bacterial contamination after TaTME, which was in the early phase of implementation of the technique. In this study, three bacterial cultures were taken after completion of the TaTME procedure in 23 consecutive patients in order to determine the risk of postoperative locoregional infections. After this prospective study, we published the short-term intra- and postoperative results and oncological outcomes of 80 patients who underwent TaTME in the VU medical centre and Gelderse Vallei hospital (chapter 3).

Part 2 | Evolution of TaTME
With the knowledge of a better visualisation on the tumour during the transanal part of TaTME, and therefore possible improvement of a more complete resection of the mesorectum, we investigated the residual mesorectum on postoperative MRI between laparoscopic and transanal TME, outlined in chapter 4. The focus of chapter 5 is to give an overview of all published research data regarding morbidity and safety of TaTME. In total 33 studies were analysed in a systematic review. In order to evaluate a possible influence of a learning curve, studies were divided in low-volume (<30 cases) and high-volume centres (>30 cases). Outcomes were measured by among others, complication rates and oncological results.

Functional outcomes after TME are highly variable and up until now, there is lack of data on quality of life following TaTME. Chapter 6 focuses on the difference in quality of life and functional outcomes between laparoscopic TME and TaTME measured by a set of five questionnaires. As the technique evolved, TaTME was considered as an alternative for conventional TME in completion surgery. In chapter 7 TaTME is compared to abdominal TME following local excision of early rectal tumours in patients who required completion surgery. Surgical, pathological and short-term postoperative outcomes were evaluated.
Part 3 | Current status of TaTME

Chapter 8 gives us an update on the use of the flexible multiple-access port for transanal minimally invasive surgery (TAMIS). It was published as a sequel to an initial article in 2012 regarding its implementation and describes the current status of the ‘TAMIS-platform’ and its use for multiple surgical indications. In chapter 9 we show the evaluation of the learning curve in a single centre with 140 consecutive patients receiving TaTME. End-points were operation time and major postoperative morbidity measured by CUSUM analysis.

Because previous literature has shown the relevance and significant influence of surgical training for laparoscopic colon surgery with fewer postoperative complications we wanted to set up a training pathway for TaTME in the Netherlands. Chapter 10 describes the short-term outcomes of the first ten TaTME patients of the participating centres that followed our structured training pathway and proctoring.

Chapter 11 summarises and discusses the main results of this thesis and describes the future perspectives of TaTME as a treatment for rectal cancer.
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