Transanal Endoscopic Microsurgery

Indications and Results

E.J.R. de Graaf

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Transanal Endoscopic Microsurgery
Indications and Results

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indicaties en resultaten

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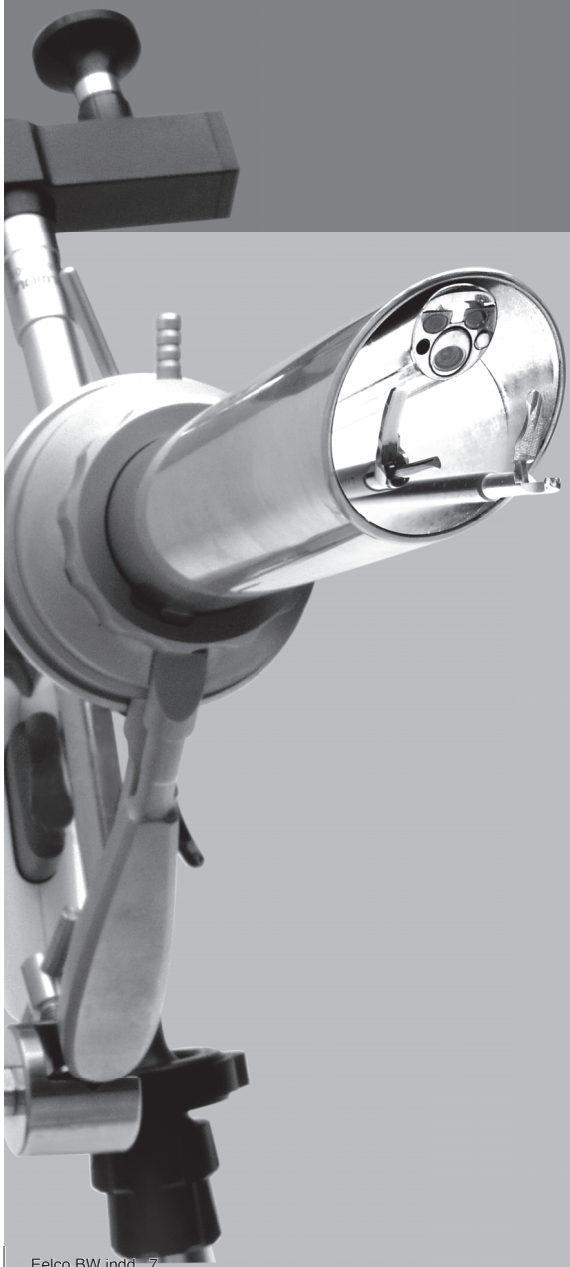
Chapter 1

Transanal endoscopic microsurgery

de Graaf EJR



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A number of surgical techniques have been implemented to remove rectal tumours locally. Transanal endoscopic microsurgery (TEM) is a newly developed, minimally invasive technique for that purpose. Its place among surgical techniques needs to be more clearly defined. This article provides an update on existing local techniques and on TEM in particular.

Existing Local Techniques

History

Exploring the rectum was practised even in ancient times, as is evidenced by the archaeological findings of anal retractors covered in lava at Pompeii[1]. Several surgical techniques have been described to remove pathology that is present, which can be distinguished by their method of approach. Transanal excision (TE), first described in 1739[2], was developed further in the 19th century. The restricted view and the limited range were considered to be disadvantages and were indicated as possible causes for a high recurrence rate. This led to a search for improved local entry. Already in 1826, Lisfranc[3] described a posterior approach. In 1874 Kocher described excision of the os coccygis and in 1876 Cripps described the incision of the sphincter muscle in order to enlarge the passage[4]. However, again there was a high recurrence rate and, moreover, a high rate of severe morbidity and mortality. After Miles had published his theories on the lymphogenic spread of the rectal carcinoma in the Lancet in 1908, it was generally thought that this was the cause of the high recurrence rate after local excision[5]. This signified the end of the research into improving the technique of local entry and a transabdominal approach became the preferred option. In 1885 Kraske strongly opposed its development[6], thereby causing a schism in the surgical world which lasted for many years and which resulted in his name being associated with the dorsal, sphincter-saving approach to the rectum. At that time, Bevan made a last plea for the transsphincteric approach[7]. Mason revived the technique in 1972, which led to this procedure being named after him[8]. An endoscopic approach required use of the urological resectoscope, which was introduced for urological purposes in the 1920s. Its use for the transanal removal of rectal tumours was first described in 1979[9].

Technique

TE has been described in detail by Parks. The patient is positioned in the lithotomy or the jack-knife position. After anal dilatation, a retractor is introduced. In adenomas, the submucosal plane beneath the tumour is infiltrated with an adrenaline solution and in that plane the tumour is excised with a margin of macroscopically

normal mucosa. The defect is sutured or left open. With large lesions the retractor is repositioned step by step until the tumour is excised completely and, using longitudinally placed, interrupted sutures, the defect is closed. In the case of carcinomas, Parks recommended full thickness excision[10, 11]. With the posterior, sphincter-saving technique, the patient is placed in the jack-knife position. The incision extends from the level of the sacrococcygeal joint to the proximal margin of the anal sphincter. The ligamentum anococcygeum and the levator ani muscle are incised lengthwise and the os coccygis is excised. The rectum is opened and the tumour is excised. The rectum and the pelvic floor are closed layer by layer[6]. The posterior, sphincter-splitting technique is essentially the same as the sphincter-saving technique, with the difference that the incision is extended by the sphincter apparatus. The internal and external sphincters are divided and sutured separately. The os coccygis can be excised as well[12, 13]. For transanal use of the resectoscope a plug is used to shut off the anal canal. The resectoscope is inserted through this. It consists of a guiding tube, an obturator, a working element, an optical system, a cutting electrode wire and high frequency cauterization. First, the rectum is distended with irrigation fluid. Then, under direct vision, the tumour is resected piecemeal down to the muscle using the cutting loop. The defect is left open. In the meantime, the apparatus is removed and the fluid and tissue are expelled from the rectum by applying manual pressure on the abdomen[9].

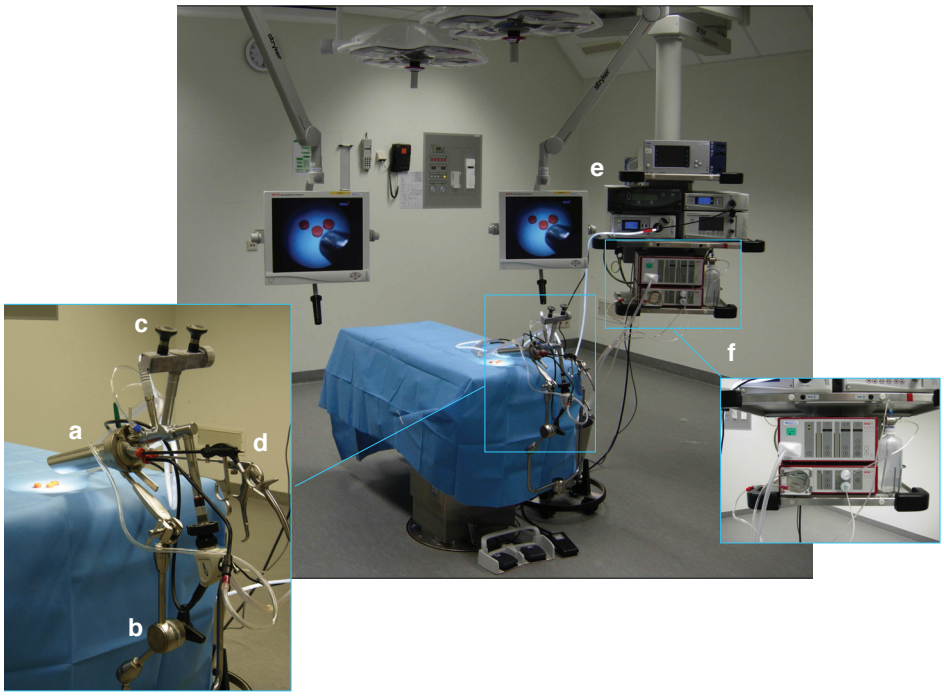
Results

TE is by far the most common procedure. Over the years, many publications have appeared, often containing a substantial numbers of patients. It is an easy procedure to perform. Tumours capturing up to 100 per cent of the circumference of the rectal wall, and located up to 12 cm from the anal verge, are excised. Mortality ranges from 0 to 2 per cent and complication rate from 5 to 25 per cent. Complications are usually mild and can be treated conservatively. The recurrence rate in adenomas is 9 to 60 per cent and in carcinomas 0 to 27 per cent[14-22]. The posterior, sphincter-saving technique is used sparingly. In a review in 1986, only 117 patients in 9 studies are described. It is a technically demanding technique. Tumours ranging from 6 to 15 cm from the anal verge can be removed. Severe complications, such as abscesses, fistulas and disabling faecal incontinence, are present in 24 to 41 per cent: 5 to 6 per cent of which require the formation of a stoma. Mortality is 0 to 1 per cent. There is very little mention of the recurrence rates, which appear to be 3 to 33 per cent in adenomas and 10 to 45 per cent in carcinomas[23-27]. The posterior, sphincter-splitting technique is also used sparingly. In the period up until 1986, only 231 patients in 10 studies had been described. It is technically demanding as well. Tumours ranging between 0 cm and 13 cm from the anal verge can be removed.

The same serious complications as those after the sphincter sparing technique arise here in 11 to 70 per cent with 2 to 28 per cent formation of a stoma. Those cases without serious complications are the result of the preventive creation of a stoma in all patients. Mortality is 0 to 1 per cent. The recurrence rate is 3 to 32 per cent in adenomas and 10 to 29 per cent in carcinomas[24, 27-30]. The results after removal using the resectoscope are described even less frequently. Tumours up to 22 cm from the anal verge can be removed. However, several sessions are necessary and 50 per cent of the patients require 2 or more sessions. Up to 10 sessions may be necessary. Mortality is 0 to 5 per cent. Morbidity is 7.5 to 31 per cent, 7 per cent demanding stoma formation. The recurrence rate is around 27 per cent in adenomas and 35 per cent in carcinomas[31-35].

It is clear that the above-mentioned methods, other than TE, are more technically demanding, do not lead to an increase in the range and size of the tumours to be resected, come with a considerable percentage of severe morbidity and do not lead to a decrease in recurrence rates. These methods do not seem to have added value and this might explain their limited use. They therefore remain outside the scope of this article.

Figure 1. Illustration of the TEM equipment, consisting of a rectoscope (a), fixed to the operating table by means of a Martin arm (b), the stereoscopic optic (c), inserted instruments (d), an electrosurgery unit (e) and a specially developed TEM pump and an insufflation system (f).



Transanal endoscopic microsurgery

History

In 1984 Gerhard Bueß introduced TEM. In fact, he elaborated on the principle of the resectoscope and perfected it. He developed the technique according to a fixed plan of action, including experiments on animals, after which he progressed to a clinical introduction. In addition, he set up training courses for interested surgeons[36-39].

Technique

TEM is a minimally invasive operation. It is a 1-port system introduced transanally. It consists of a rectoscope, a handle and a 4-port working insert. The rectoscope has a diameter of 4 cm and a length of 12 or 20 cm. It is fixed to the operating table by means of a Martin arm, allowing it to be placed in any conceivable position. A working insert is placed. It has a port for a stereoscope. The stereoscope is an optical system for direct vision with a separate lens system for each eye. It is of unmatched quality, resulting in a 3-dimensional view with the maximum depth of vision and resolution, and with a 6-fold magnification, unattainable even with the best camera and monitor. A documentation endoscope can be connected to a monitor for the rest of the operating team. Attached to the working insert is a rubber cap with 3 openings sealed with valves and allowing a maximum of 3 instruments to be inserted simultaneously. The system is airtight. An insufflator and a specially developed TEM pump are connected via a tube system supplying gas insufflation, pressure measurement, irrigation and suction (Figure 1). Gas insufflation and intraluminal pressure measurement take place simultaneously, making it possible to correct also minor fluctuations in pressure. The result is that a stable pneumorectum is guaranteed. The characteristics of the rectoscope, stereoscope and pneumorectum are the key elements in TEM enabling tumours that are larger and more proximal in the rectum and even distally in the sigmoid to be reached and excised, while retaining a good view on the operative field. A high frequency knife, tissue graspers, a rinsing and suction tube, needle holder and scissors are specially designed. Marking dots are placed at a 0.5 to 1 cm margin of macroscopically normal mucosa around the tumour, followed by excision, which is possible in any desired plane, ranging from submucosal to full thickness. The different layers of the rectal wall and the perirectal fat can be clearly identified. After removal of the specimen, the defect is closed transversally with a running suture. Clips are used as knots (Figure 2)[40-42]. Use of the laparoscope and operating without gas are described as alternative options[43-46]. The use of ultracision results in a reduction of blood loss and operative time[47]. The use of a multifunctional instrument, enabling bipolar cutting, monopolar coagulation, rinsing and suction, reduces the number of instruments that are required simul-

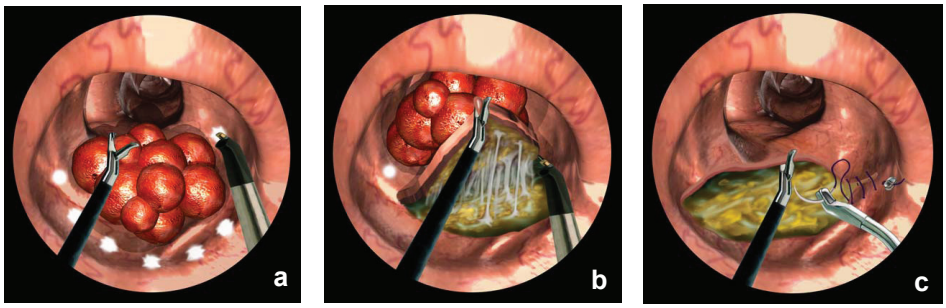


Figure 2. Illustration of the endoscopic view during TEM. The margin of excision is marked (a), after which the tumour is resected (b). The defect is closed transversally using a running suture (c).

taneously and this can positively influence the speed and ease of the operating procedure[48, 49]. There are also alternatives for suturing[50]. To decrease physical strain, especially present in endoscopic techniques with direct vision, the use of a head-mounted display is described[51].

Results

With TEM it was possible to remove tumours up to 25 cm from the anal verge, including circumferential tumours. Either mucosectomy or full thickness excision was possible, allowing proper histological examination. Complete resection was observed in 90 to 92 per cent. Overall morbidity was 4.8 to 9 per cent. In 2.5 to 8 per cent of the patients re-operation was necessary due to a complication, and a stoma was created in 1.9 per cent of the patients. Mortality was 0 to 0.3 per cent. The recurrence rate was 0 to 5 per cent in adenomas, 3 per cent in low risk T1 carcinomas and 8 per cent in all carcinomas[40, 52-63].

These excellent results led to this technique being applied to other indications concerning the rectum, such as nonepithelial tumours and anastomotic strictures, or outside the rectum[64-66].

Discussion

In the 19th century, the limited range in TE was one of the reasons for developing alternative techniques. Paradoxically enough, maximum sizes and distances in the individual reports suggest that the entire rectum can be reached. However, looking at the means in distance and size, it must be concluded that in fact the majority of the tumours is smaller and positioned distally. TEM outclasses TE in these features. The mean distance and size and the maximum distance reached with TEM are superior to TE. Unfortunately, comparative studies on this are lacking. However,

some attempts have been made. Authors have stated that frequently TEM could still be performed even if it was not possible to make a tumour visible between the blades of the anal retractors and consequently could not be resected transanally. These personal experiences led to the view that in approximately 50 per cent of the tumours resected with TEM, TE would not have been possible[56-58].

Another idea to develop alternative techniques was the realization that leaving behind possible lymph node metastases caused a high recurrence rate in carcinomas. If this was the sole cause the recurrent percentage after the removal of rectal adenomas would have to be negligibly small. After TE, this is clearly not the case. Taking the behaviour of adenomatous tissue into consideration, this can only be caused by incomplete resection. Incompleteness of resection is scarcely described after TE. Incidentally, up to 43 per cent is reported, including impossibility of assessment because the tumour was excised in pieces[17]. A high recurrence—or perhaps a residual—percentage is then in fact obvious. Although the majority of recurrences do not seem to cause problems and can be treated with re-excision or Argon coagulation, the finding of a carcinoma as a recurrence and the cumulative risk of morbidity and mortality after repetitive local excisions put the justification of this policy to the test[67]. In TEM, complete resections are described in over 90 per cent and appear to be the reason for an extremely low recurrence rate in adenomas[40-53]. Initially, TEM was intended for the improvement of the results of the local resection of rectal adenomas. Submucosal resection can suffice in adenomas. Full thickness excision is required for rectal carcinoma. Often invasive rectal carcinoma is mistaken for adenoma preoperatively due to negative findings at biopsy and the unreliability of other diagnostic tools[56, 63, 68-70]. From a technical point of view, full thickness excision is perhaps even easier, because by cutting through the rectal wall the rectum is able to expand more and the view of the operating area is improved. Therefore, in most series, full thickness excision is preferred in all patients. Submucosal excision is preferred only in tumours situated within the sphincter complex in order to prevent injury to the sphincter. Completeness of resection of the tumour itself is one of the major factors contributing to adequate tumour control in rectal cancer[71,72]. The extent of radicality is seldom mentioned after TE. When it is mentioned, incomplete resection was observed from 12 to 35 per cent[14, 16, 18, 20]. The degree of radicality is to a large extent determined by the way in which the specimen is processed and assessed by the pathologist. Protocollarization reveals an increased degree of incomplete resection[71, 72]. In that way, the specimens after TE have not been examined and it seems plausible to expect an increased rate of incomplete resection. In TEM, incomplete margins are observed in less than 10 per cent also after protocollarized examination of circumferential margins[63].

Both TE and TEM are safe procedures. TEM is also safe if tumours proximal to the peritoneal reflection are excised, in contrast to the other local techniques. It is remarkable that after TE little attention is given to the consequences of the procedure on the anal sphincter function, whereas in other circumstances it has been shown that anal dilatation has a direct bearing on anal sphincter function[73]. In TEM, faecal incontinence is rarely observed and mostly transiently[60]. Assessment of anorectal physiology in TEM revealed contemporary reduction in internal sphincter tone, seemingly without clinical signs of faecal incontinence[74-77].

In rectal cancer, total mesorectal excision (TME) with autonomic nerve preservation is the surgical technique of choice if curation is intended. However, even in expert hands, mortality is 0 to 7 per cent and morbidity, including genitourinary dysfunction, faecal incontinence and permanent colostomy, 13 to 46 per cent. For adenomas and *in situ* carcinomas, the recurrence rate is 0 per cent[78-84]. Since TE is a safer procedure, it has been the preferred option, accepting the higher recurrence rate. Regarding morbidity and mortality, TEM is superior to TME and regarding recurrence rate, it is superior to TE. Furthermore, compared to TE, larger and more proximally situated adenomas can also be removed. It must be concluded that TEM is the method of choice for removal of rectal adenomas.

For rectal cancer, the choice appears to be more difficult. The same arguments hold for mortality and morbidity. Furthermore, TEM makes complete resection of the tumour possible[63]. Therefore, palliative reasons justify the choice of TEM relatively easily. Historically, and compared to TE, TME is the method of choice when curation is intended. The high morbidity and mortality that accompany it are accepted because of a low recurrence rate. After the introduction of TEM, the choice appears to be more difficult to make. In early rectal cancer, the recurrence rate is 3 to 4 per cent and the survival rate is 96 per cent, after both TME and TEM[54, 85-87]. The minor presence of lymph node metastases and the possibility of complete tumour excision in TEM could be the explanation[63, 85, 88]. After TME, recurrent disease is observed in 4 to 10 per cent and the survival rate is reduced to anywhere between 74 and 87 per cent[78, 81, 82]. So, complete removal of both tumour and lymph nodes simultaneously is not the sole solution. In the search for adjuvant treatment, preoperative radiation has turned out to be valuable in TME[84]. Initial reports on TEM and adjuvant chemoradiation are promising[61]. However, at the present time the argumentation is still too anecdotal to be able to realistically answer the question of curative resection of rectal carcinoma with TEM. The results need to be examined with caution. Thorough scientific foundations that meet the high level of evidence of TME are *conditiones sine qua non* given the devastating results for both the patient and the doctor if the initial therapy turns out to be the incorrect approach.

In spite of its excellent results, TEM is a procedure that appears to have been copied very little throughout the world. There are a number of possible reasons. TEM is unique as an endoscopic operation, because it is the only endoscopic operation in the rectum and the only endoscopic operation using a 1-port system. Development of the specialized equipment and instruments requires time and money. The cost of the equipment is therefore high, and is becoming an increasing problem for hospitals. Furthermore, it requires relatively lengthy and specialized training[38, 41, 89]. TEM is a procedure active on the interface between colorectal and endoscopic surgery, demanding knowledge and skills in both areas, but not yet common property. The indication is seldom brought up. It raises the question which surgeons and hospitals should specialize in this procedure[89].

Technical improvements, such as those described earlier, have become available and simplify the difficult technique of TEM. Moreover, minor improvements, such as disposable tube sets with clear colour codes and improved rinsing needles, have been quietly introduced. This can lead to a reduction in the learning curve and therefore also a reduction in the time, effort and perhaps money invested. An increase of indications for TEM will be another stimulus. Colonic screening for adenomas is considered. In application, it will definitely lead to an increase in rectal adenomas that can be removed locally. To determine the role of TEM in rectal carcinoma, better assessment of its biological behaviour is of crucial importance. Research into genetic pathways is promising[90-94]. After all, when an exact diagnosis of a rectal adenoma or a rectal carcinoma without lymph node metastases can be made preoperatively, without a potential for recurrence or with sensitivity to adjuvant treatment, major surgery could quite suitably be replaced by TEM.

Conclusions

TEM is an elegant technique with excellent results. It seems to be in a position of being the method of choice for the local resection of rectal adenomas for curation and rectal carcinomas for palliation. If curation is intended in rectal cancer, TEM should be exercised with caution. Views on existing techniques and TEM are impeded by a lack of scientific evidence.

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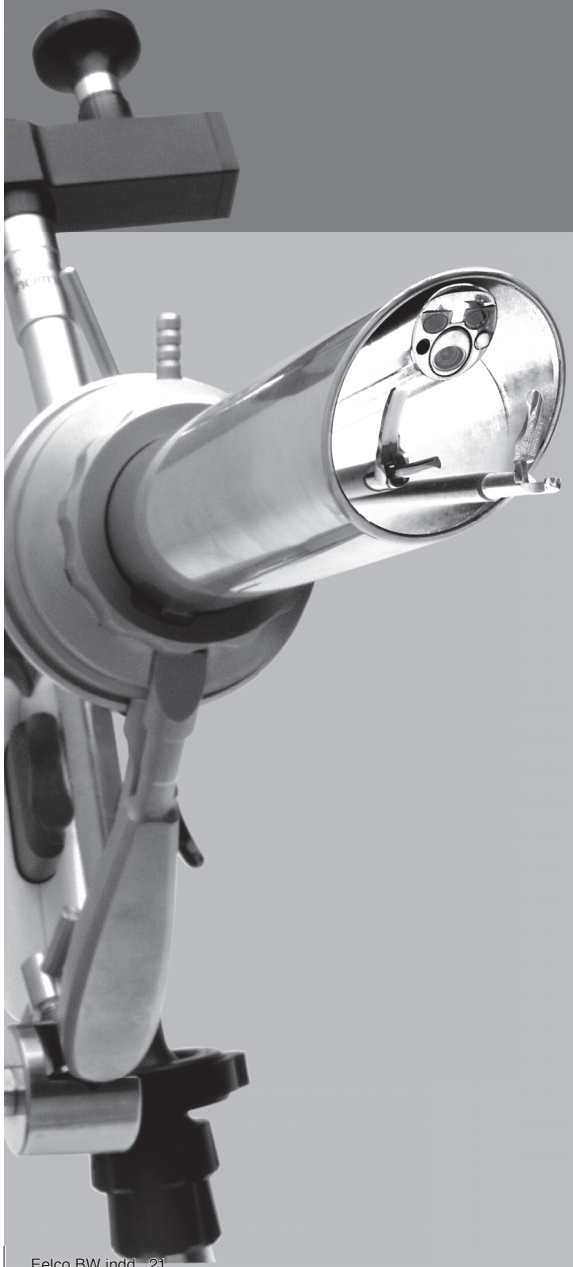
Chapter 2

Aim of the thesis



Aim of the thesis

A number of surgical techniques have been practised to excise rectal tumours locally. Transanal endoscopic microsurgery (TEM) is a newly developed, minimally invasive technique serving that purpose. Its place among surgical techniques needs to be defined.

Chapter 1 contains a review of the relevant literature.

TEM is slowly but surely gaining its place in the surgical armamentarium. However, many questions still remain unanswered.

The aim of this thesis, outlined here in **chapter 2**, is to gain greater insights in both the indications for and the results of TEM.

Transanal excision (TE) has been used for the excision of rectal adenomas (RA) for a long time. The need to compare the outcome of this technique to the outcome after TEM is obvious. In **chapter 3,** the outcome after TE of and TEM for RA is investigated.

In minimally invasive surgery, feasibility of a technique is an important aspect. The feasibility of TEM for RA is investigated in **chapter 4**.

TEM makes use of a rectoscope with a diameter of 4 cm, introduced transanally. Therefore evaluation of the impact on faecal continence and the quality of life speaks for itself. In **chapter 5**, both are investigated before and after TEM.

Local excision can be used for mobile rectal cancer (RC). In **chapter 6**, the feasibility of TEM for mobile RC is investigated.

Introduction of TEM revived the debate on the role of local excision as curative treatment for RC. Stage T1 is considered the earliest stage of RC. In **chapter 7**, oncological outcome after TEM and total mesorectal excision (TME) of T1-RC is investigated.

If several surgical techniques are available, differences in faecal continence and the quality of life postoperatively can play a role in decision making. In **chapter 8**, they are investigated after TEM for and TME of early RC.

Chapter 9 summarises the results of the investigations, while **chapter 10** provides a Dutch translation of this summary.

Chapter 3

Transanal endoscopic microsurgery is superior to transanal excision of rectal adenomas

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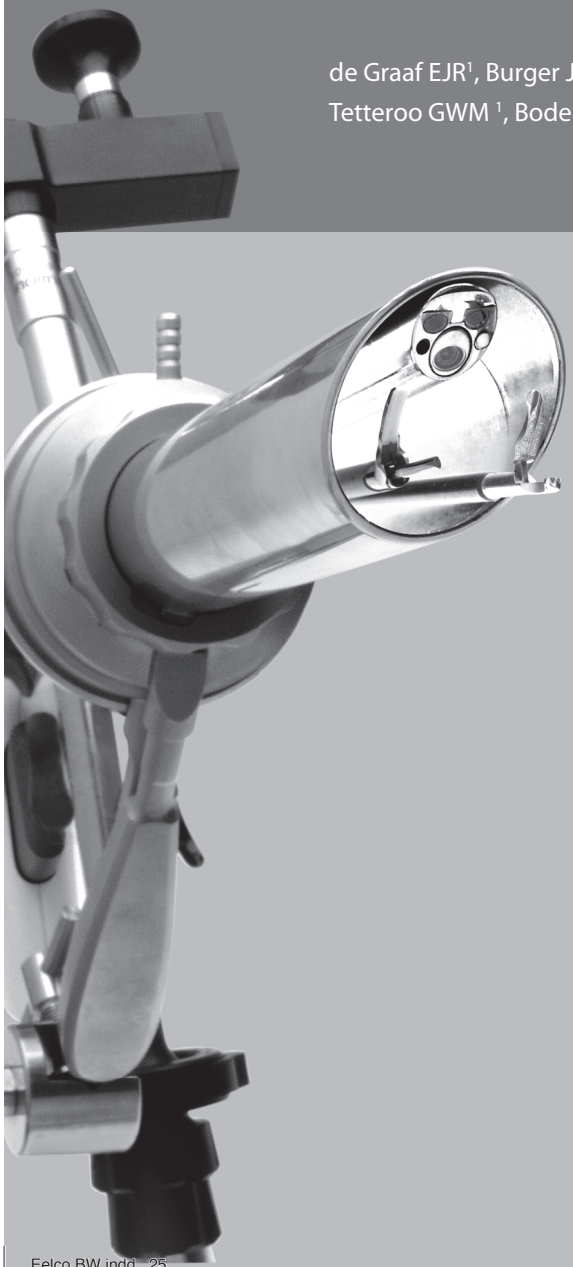

Submitted

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Introduction

Transanal excision (TE) has been the preferred technique for local excision of rectal adenomas (RA) for a fairly long time. It is relatively safe, but its use seems limited to smaller RA in the distal and mid-rectum. And the recurrence rates range from 4 to 57 per cent. Limited view and fragmentation and positive resection margins of the excised specimen are considered the major causes for recurrences[1-11].

In 1983, Gerhard Bueß introduced transanal endoscopic microsurgery (TEM), an endoscopic operation for local excision of RA[12, 13]. The safety of TEM equals that of TE, however, it also enables the excision of larger RA as well as RA in the proximal rectum and distal sigmoid colon and has recurrence rates ranging from 3 to 16 per cent. These possibilities are attributed to the technical features of TEM that create a clear and stable view throughout the rectum and enable precise excision of the specimen in 1 piece with complete margins[7, 9-11, 14-21].

Results after TE and TEM for RA have seldom been compared and limitations in study design have led to unclear results[7, 9, 11]. We investigated 2 matched groups of RA after TE and TEM.

Patients and methods

Data of all patients that were referred for local excision of RA between January 1990 and February 2007 were researched. RA with the same range in size and diameter for both techniques were selected. Patients had been evaluated according to a protocol including history, physical examination with digital rectal examination, colonoscopy with biopsy, rigid rectoscopy and endorectal ultrasound. Distance was defined as distance from the anal verge to the inferior margin of the tumour and diameter as the largest diameter of the tumour recorded. The size was determined by multiplying the largest diameter and the diameter squared of the tumour.

Patients underwent bowel preparation and were given antibiotic prophylaxis. For TE, the patient was positioned to the surgeon's preference, an anal retractor was positioned, after which the tumour was excised. For TEM, the patient was positioned according to the location of the tumour in supine, prone jack-knife, left or right lateral position. Both of the TE and TEM techniques are extensively described elsewhere[1, 13, 16].

The parameters studied were operation time, blood loss, morbidity, mortality, length of hospital stay and recurrence. Operation time was defined as the time from introduction of the anal retractor or rectoscope to completion of the last suture. Specimens were pinned on cork with fine pins at short distance through the margin of macro-

Table 1. Patient and tumour characteristics of this study.

	TE	TEM	P
Patients			
women : men	32: 18	115: 93	0.56
age (yrs)	76 (50-87)	69 (29-91)	< 0.001
ASA 1: 2: 3: 4	7: 4: 3: 1	109: 65: 41: 1	0.58
Rectal adenomas	43	216	
diameter (cm)	2.5 (0.5-5)	3 (0.5-5)	0.24
size (cm^2)	5.3 (0.3-25)	6.3 (0.3-25)	0.46
captured circumference (%)	20 (5-75)	35 (5-75)	0.15
distance (cm)	4 (0-15)	8 (0-15)	< 0.001
0-5 cm (n)	27	32	
5-10 cm (n)	9	118	
10-15 cm (n)	7	82	
clear margins (%)	50	88	< 0.001
fragmentation (%)	23.8	1.4	< 0.001

TE = transanal excision; TEM = transanal endoscopic microsurgery; ASA = American Association of Anesthesiology; clear margins = >1 mm margin of normal tissue microscopically; data given are numbers with percentages in parentheses or medians with ranges in parentheses.

scopically normal mucosa. Regarding the excised specimen fragmentation and resection margin status were studied. Excisional margin status was scored as clear (margin > 1 mm of normal tissue microscopically) and unclear (margin ≤ 1mm and indeterminate). Excision was considered indeterminate if the pathology report described it as such or the specimen could not be reconstructed because of fragmentation.

Follow-up included surveillance endoscopy at 1 and 4 years postoperatively and every 5 years thereafter. Additional rectoscopy was performed 6, 18, 24 and 36 months and in case of suspected local recurrence. The last follow-up date was determined by the last endoscopy. Local recurrence was defined as recurrent tumourous tissue within the proximity of the scar tissue of the earlier operation. Histological confirmation was mandatory.

All data were collected in a database and analyzed with SPSS statistical software (version 11.5 for Windows, SPSS, Chicago). Percentages and continuous data were compared between groups using the Chi-square test or Fisher's exact test and the Mann-Whitney test, respectively. The cumulative percentages of tumour recurrence over time were calculated using the Kaplan–Meier method, and comparisons between groups were made by the log rank test. The limit of significance was P = 0.05 (two-sided).

Results

A total of 366 RA were identified. Ten RA were excluded because of missing data. After both TE and TEM, the range in distance was 0 to 15 cm. After TE, the range in

Table 2. Operation characteristics of this study.

	TE	TEM	P
Rectal adenomas	43	216	
Operation time (min)	47.5 (5-135)	35 (2-180)	< 0.001
Blood loss (cc)	some	some	
Co-operations	0	13 (6.1)	
right-sided colectomy		7	
laparoscopic right-sided colectomy		1	
transverse colectomy		1	
left-sided colectomy		1	
sigmoid colectomy		1	
total mesorectal excision		1	
ankle fracture		1	
Morbidity	4 (10)	11 (5.3)	< 0.001
minor			
urinary retention	1	1	
urinary tract infection		1	
rebleeding	3	3	
anastomotic stricture	0	1	1.00
wound dehiscence		3	
pneumonia		1	
major			
wound dehiscence	0	1 (0.4)	1.00
Mortality (%)	0	1 (0.4)	1.00
Hospital stay (days)	3 (1-62)	2 (1-26)	0.07

Minor morbidity = treated conservatively; major morbidity = needing re-intervention; data given are numbers with percentages in parentheses or medians with ranges in parentheses.

diameter was 0.5 to 5 cm and after TEM 0.3 to 20 cm. Therefore, all RA excised with TE were selected and the selection for RA excised with TEM was limited to RA with a diameter from 0.5 to 5 cm. Before 1996, all patients underwent TE. From January 1996 TEM was intended in all RA and only 6 TE procedures have been performed as conversion from TEM. TE was performed by 5 surgeons. TEM was performed exclusively by 2 surgeons (EDG and GT). Before starting TEM in our hospital both surgeons were trained in intensive TEM courses and did not have experience with TEM. Forty-three RA were excised with TE in 40 patients and 216 RA in 208 patients with TEM. Patient and tumour characteristics are depicted in Table 1. Patients that underwent TE were older ($P < 0.001$), but both groups were similar in co-morbidity, classisfied according to the American Association of Anesthesiology (ASA). Median distance of RA excised with TEM was located more proximal, due to a difference in the proportion of tumours in the different parts of the rectum between the 2 groups ($P < 0.001$). Clear margins were observed in 50 per cent after TE and in 88 per cent after TEM ($P < 0.001$). Fragmentation of the specimen was observed in 23.8 per cent after TE and 1.4 per cent after TEM ($P < 0.001$). In cases of fragmentation after TE, unclear margins were observed more frequently (one fragment and unclear margins

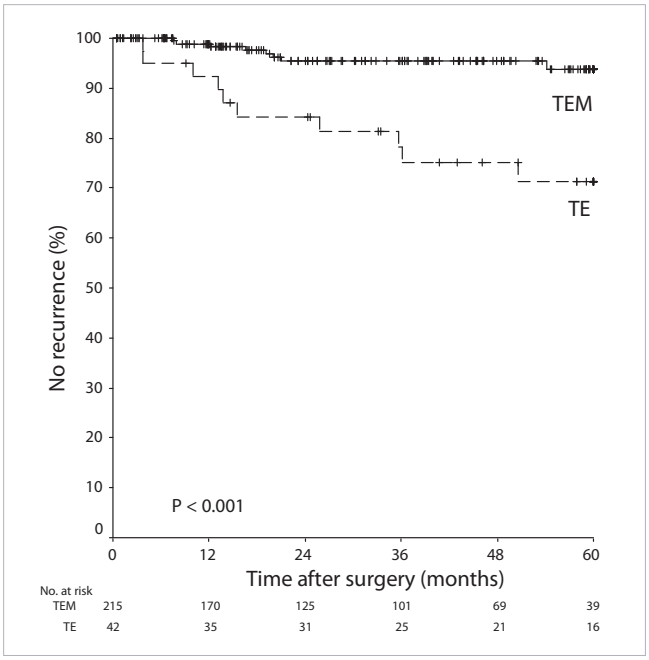


Figure 1. Local recurrence of rectal adenomas after transanal excision (TE) and transanal endoscopic microsurgery (TEM).

35.5 per cent versus fragmented and unclear margins 90 per cent; P = 0.003). After TEM this was 11.7 per cent and 33.3 per cent respectively (P = 0.32).

Operation characteristics are depicted in Table 2. Operation time was longer after TE compared to TEM (47.5 minutes versus 35 minutes; P < 0.001). After TE, 4 complications in 4 patients (10 per cent) were observed and after TEM, 11 complications in 11 patients (5.3 per cent; P < 0.001). All complications could be treated conservatively, except for a wound dehiscence with opening of the peritoneum in 1 patient after TEM that was re-sutured laparoscopically with a diverting ileostoma, removed after 6 weeks (severe morbidity 0.4 per cent).

Median follow-up was 59 months (range 2-120) after TE and 32 months (range 0.4-95) after TEM. Ten local recurrences after TE and 8 after TEM were diagnosed, leading to a cumulative recurrence rate of 28.7 per cent and 6.1 per cent respectively at 5 years (P < 0.001; Figure 1). RA excised with TE and with clear margins had a local recurrence rate of 0 per cent, compared to 59.6 per cent with unclear margins (P < 0.001; Figure 2). After TEM the local recurrence rate was 1.9 and 10.3 per cent (P = 0.3; Figure 2) respectively. To exclude as much as possible the possible impact of distance, recurrences were analysed per part of the rectum. Median distance, diameter and size were similar in the 2 groups per part of the rectum. In the distal rectum recurrence rate after TEM was 14.2 per cent and after TE 37.7 per cent (HR 0.51, 95

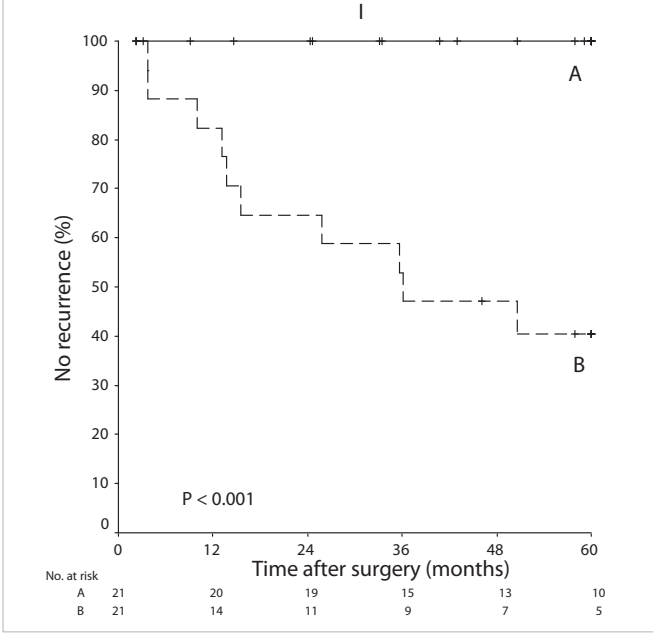
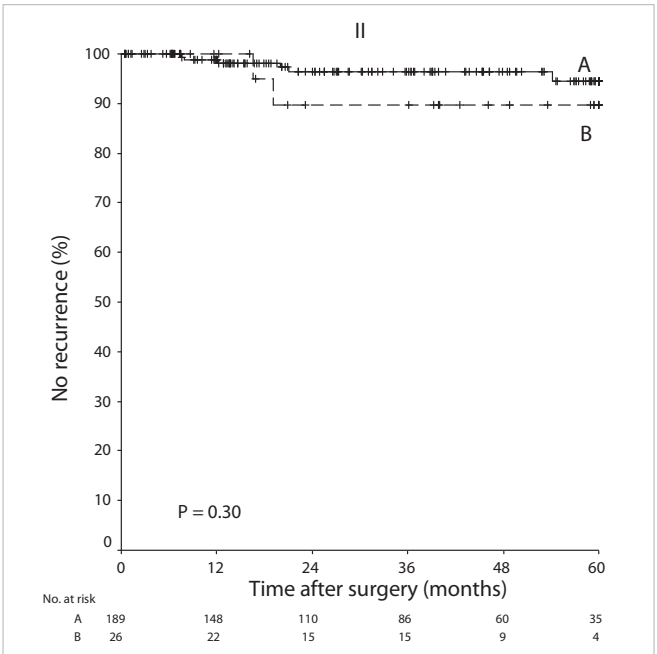


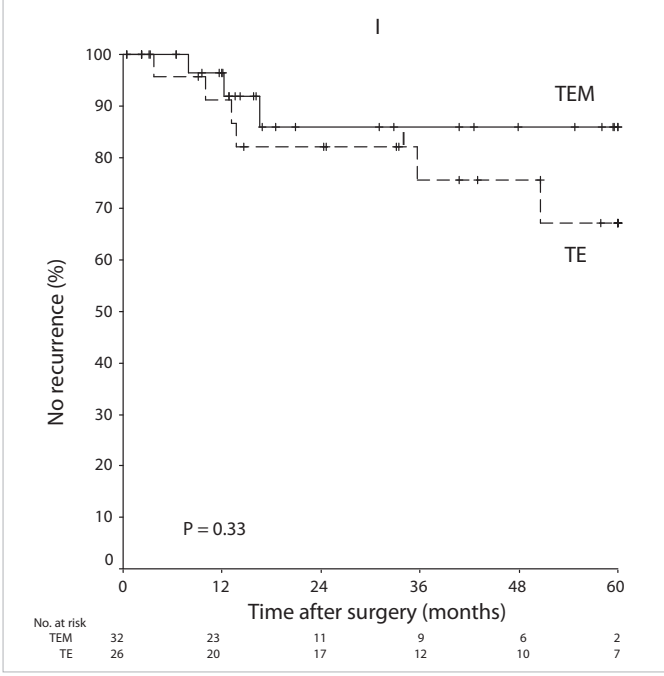
Figure 2. Local recurrence of rectal adenomas after transanal excision (TE, I) and transanal endoscopic microsurgery (TEM, II) with clear (A) and unclear (B) margins.



per cent confidence interval 0.13-2.1; P = 0.33). In the mid-rectum this was 4.8 and 11.1 per cent respectively (HR 0.47, 95 per cent confidence interval 0.05-4.2; P = 0.48) and in the proximal rectum 5.3 and 42.8 per cent respectively (HR 0.04, 95 per cent confidence interval 0.01-0.43; P < 0.001; Figure 3).
After TE 9 recurrences were once again RA, treated with snare polypectomy (n = 3), renewed TE (n = 4) or TEM (n = 2). One recurrence was an invasive carcinoma (2.3 per cent). The patient underwent abdomino-perineal excision (T2N0, complete margins) and remained disease free up with a follow-up now of 46 months. After TEM all 8 recurrences were once again RA, treated with snare polypectomy (n = 5) and renewed TEM (n = 3).

Discussion

Both TEM and TE are considered safe methods of treatment for excision of RA. After TE, Moore found 17 per cent morbidity, including 7 per cent major morbidity, compared to 15 per cent, including 5 per cent major morbidity, after TEM without postoperative mortality. Langer observed complications in 11.8 per cent after TE without major morbidity and 7.6 per cent after TEM including 2.5 major morbidity. There was no mortality either. After radical resection (RR) he observed a complication rate of 55.5 per cent, including 20 per cent major complications, and mortality of 3.7 per cent. Winde described a morbidity rate of 17 per cent after TE, 12.2 per cent after TEM and 35.7 per cent after RR. No mortality was observed. In all of these 3 studies morbidity after TEM was less than after TE but the differences were not significant. Major morbidity, needing re-intervention, were minimal after both techniques with limited consequences as no mortality was observed. Moreover, TE and TEM are significantly saver compared to RR[7, 9, 11]. Middleton came to the same conclusions in his systematic review after calculating a morbidity rate of 10.3 per cent after TEM and 17 per cent after TE[10]. Impact of both techniques on faecal continence and quality of life, representing long-term morbidity, was reported by Winde indirectly in 6.6 per cent after TE, 4.8 per cent after TEM and 25 per cent after RR respectively[7]. It was recently studied thoroughly. After both TEM and TE of RA, no deteriorating effect on faecal continence was observed and, once the RA had been excised, quality of life improved[22-24]. In this study the morbidity of 5.3 per cent after TEM was significantly lower than the morbidity of 10 per cent after TE. This is the first study to find TEM to be significantly safer than TE. Maybe this can be explained by 2 comparable groups with regard to diameter, size and distance. TEM patients with larger RA and RA located in the distal sigmoid, were left out. In other studies RA, excised with TEM, were larger and located more proximal in the rectum compared to TE[9] or considered



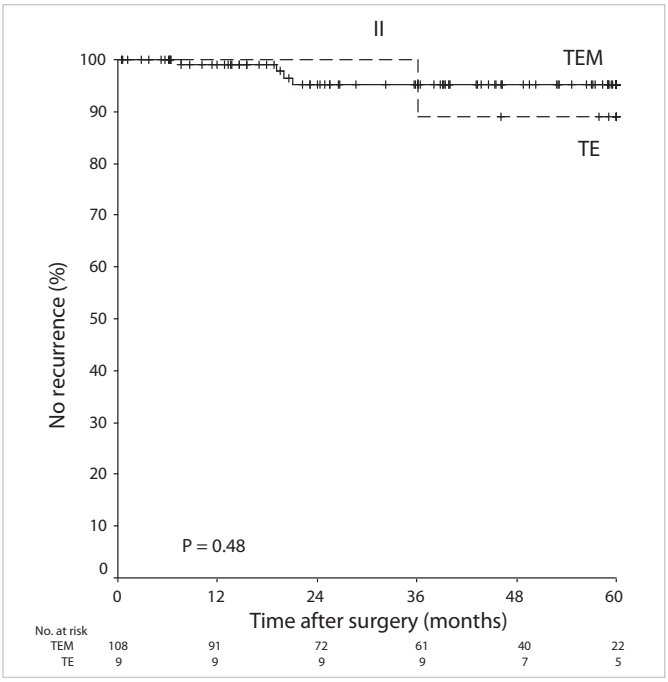
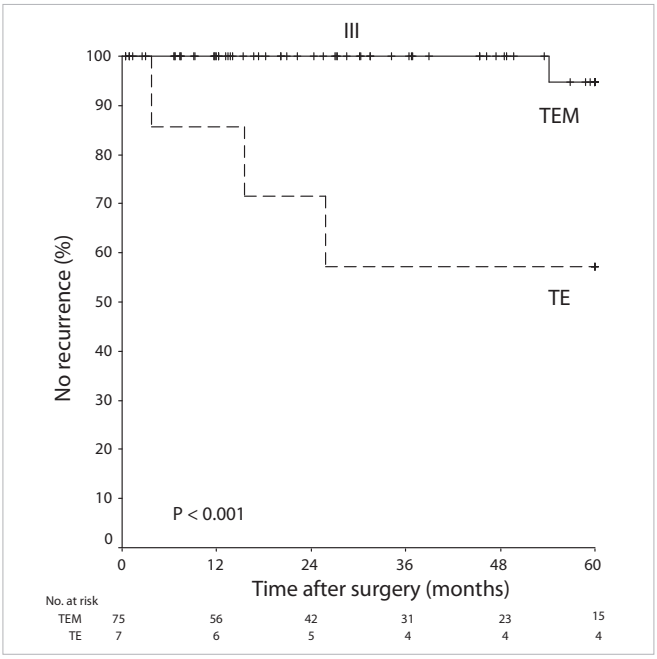


Figure 3. Local recurrence of rectal adenomas after transanal excision (TE) and transanal endoscopic microsurgery (TEM) in de distal (I), middle (II) and proximal part (III) of the rectum.



unsuitable for TE in 53 to 100 per cent[20, 21]. These RA have an increased risk on peroperative problems, conversion rates and postoperative morbidity[14, 18, 25]. Remarkably, also in the latter studies morbidity was still within the ranges mentioned.

Recurrence rates after TE of RA ranges from 4 to 57 per cent and after TEM for RA from 3 to 16 per cent[1-11, 14-21]. Both Whitehouse and McCloud investigated detailed large numbers of RA, excised with TEM. Age, size, distance, previous treatment, severity of dysplasia, thickness of excision, operating surgeon and the instrument used for excision were not found to be associated with recurrence. Only resection margin status stepped forward as a significant factor. Whitehouse showed that unclear margins were significantly more often the case in patients that had a recurrence than in those that had not**.** McCloud observed a highly significant difference in recurrence rate after TEM of 0 per cent after clear margins compared to 35.7 per cent after unclear margins. In both studies there was a trend towards a higher percentage of recurrences and of unclear margins in larger RA, impossible to unravel statistically[19, 20]. Frequently, both for RA and rectal cancer, excisional margin status is recognised as a key factor in the risk of recurrences. Quirke showed a direct relationship between margin status and local recurrence after RR for rectal cancer. It led to a change in surgical technique towards the concept of total mesorectal excision with increased percentages of complete excision and decreased percentages of local recurrences[26, 27]. After local excision of RA, clear margins range from 47 to 77 per cent after TE and from 62.7 to 94.5 per cent after TEM[8, 9, 11, 18-21]. Galandiuk reported a local recurrence rate of 18 per

cent after TE of RA. He found that a positive resection margin was highly significant in terms of local recurrence rates: 34 per cent of RA with positive resection margins recurring, as opposed to only 3 per cent of RA with negative resection margins. The number of RA with incomplete margins was not mentioned[5]. Winde compared 98 RA after TEM and 90 after TE. Recurrence rates were 6.1 per cent and 22 per cent. No data were given on excisional margin status and possible relation to recurrence[7]. Langer compared 54 RA, excised with TE, 57 RA, excised with TEM, and 8 RA, excised with RR. He observed unclear margins in 53 per cent after TE and 24 percent after REM. Surprisingly, the difference did not reach statistical significance; the difference was not stated after RR. He also found recurrence rates of 31.5 per cent after TE, 8.9 per cent after TEM and 3.7 per cent after RR. The difference was significant between TE and TEM/RR, and was not significant between TEM and RR[9]. Moore compared 49 RA after TEM and 43 RA after TE, similar in size. He found a significant difference in clear margins of 83 per cent after TEM and 61 per cent after TE and in nonfragmented specimens of 88 and 74 per cent respectively. Recurrence rate was 5 per cent after TEM and 27 per cent after TE. Unfortunately, he did not investigate the correlation of excisional margin status and risk on recurrence[11]. In this study clear margins were observed in 50 per cent after TE and 88 per cent after TEM, fragmentation in 23.8 per cent and 1.4 per cent respectively and, in case of fragmentation, unclear margins significantly more frequently both after TE and TEM. Recurrence rate after TE was 23.3 per cent and after TEM 3.7 per cent, significantly different. And RA after TE with clear margins had a significantly lower local recurrence rate of 0 per cent compared to 47.4 per cent after unclear margins. After TEM the local recurrence rate was lower after clear margins (3.2 per cent) compared to unclear margins (7.7 per cent). The latter difference did not reach statistical significance, most probably because of low numbers in the subgroup with unclear margins. The present study is the first study to show clearly the differences in outcome between TE and TEM with regard to excisional margin status, fragmentation and recurrence in RA similar in size.

In this study there was a difference in distance between the 2 groups. To overcome the possible impact, recurrences were analysed per part of the rectum. Then median distance, diameter and size were similar in both groups per part of the rectum. Independent of the part of the rectum local recurrences after TEM were observed less frequently, showing that distance is not a risk factor as also shown by both Whitehouse and McCloud[19, 20]. After TEM the recurrence rate is also limited in the distal rectum. And TEM is feasible in this part. In the study by Whitehouse, no TEM for an adenoma in the distal rectum was converted[20].

In all studies TEM steps forward as the better technique in one or more of the parameters studied. The level of evidence is limited but we do not think in the future there is much change on randomized studies comparing TE and TEM for RA. Once

mastering TEM and experiencing and appreciating its technical features, most surgeons become enthusiastic and abandon TE. The sentiments are very well expressed by Saclarides in his invited commentary on the study of Moore[11]: "I do not think that this is possible. I remember the days of conventional local excision, bent over uncomfortably at the waist, trying to adjust overhead lights down a long, dark tunnel so that I could excise something with indistinct margins that I could not see very well, and, along the way, inadvertently grasping the cancer and fragmenting it into several pieces. I cannot go back to the old ways". In the TEM-equipment major improvements have been carried out as well as alternatives in the set-up suggested[16]. An example of the latter is the use the use of ultracision harmonic scalpel, accelerating operation time substantially[28]. In this study the instrument was used progressively. The operation time of TEM was shorter than that of TE.

Conclusions

Transanal endoscopic microsurgery is superior to transanal excision of rectal adenomas. TEM is safer, faster and more capable of excision of the specimen in one piece with clear margins. Consequently, a lower recurrence rate is observed.

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Chapter 4

Transanal endoscopic microsurgery is feasible for adenomas throughout the entire rectum: a prospective study

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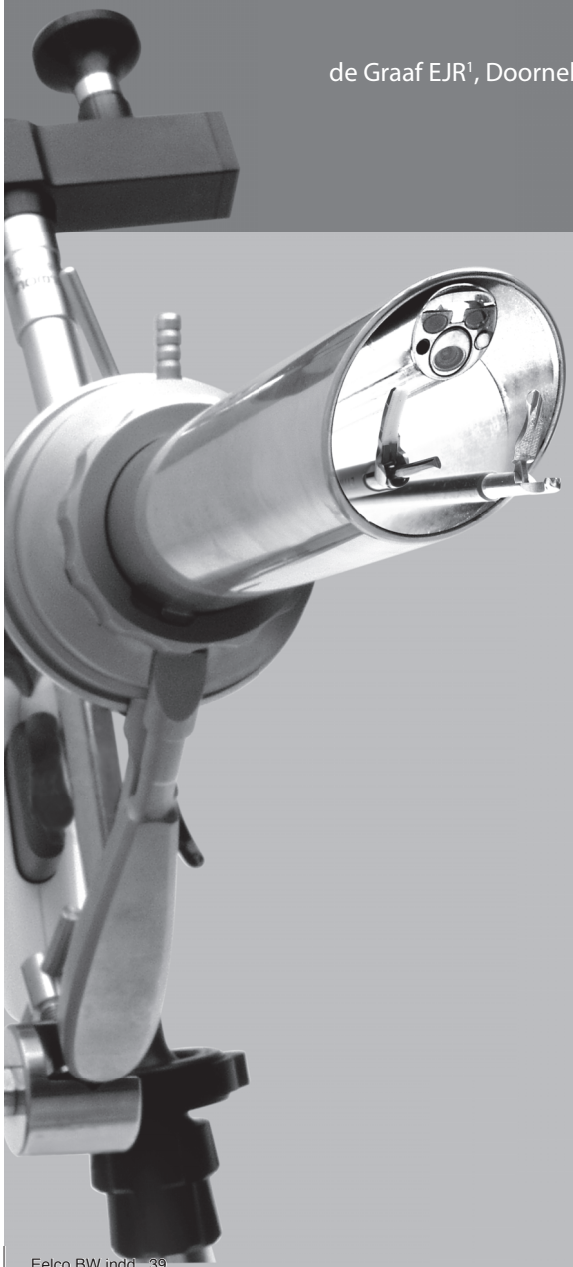

Submitted

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Introduction

Transanal excision (TE) has been the most frequently used technique for local excision of rectal adenomas (RA) for a fairly long time. It is relatively safe, however, its use seems limited to smaller RA in the distal and mid-rectum. The recurrence rates can be as high as 60 per cent with invasive cancer as a recurrence up to 4 per cent. Fragmentation and positive resection margins are considered major causes for recurrences[1-6].

In 1983, Gerhard Bueß introduced transanal endoscopic microsurgery (TEM), an endoscopic operation for local excision of RA[7-9]. Excellent results are described with minimal morbidity, mortality and recurrences; also in larger RA and RA in the proximal rectum and distal sigmoid colon. These results are attributed to the technical features of TEM that create a clear and stable view and enable excision in 1 piece with complete margins[5, 9-18].

An additional major advantage of TEM could be that one surgical technique can remove all RA. However, feasibility of TEM for all RA has not been investigated. We therefore conducted a prospective study of the feasibility of TEM for RA throughout the entire rectum.

Patients and methods

All patients that were referred for surgical treatment of RA between January 1996 and February 2007 were offered TEM. All patients were evaluated according to a standard protocol including history, physical examination with digital rectal examination, colonoscopy with biopsy, rigid rectoscopy and endorectal ultrasound (ERUS). For each patient, both the distance and the location of the tumour were assessed as well as the rate of captured circumference of the rectal wall by the tumour. Distance was defined as the distance from the dentate line to the lower margin of the tumour. In particular, the location of the tumour was assessed because the patient should be positioned with the tumour downward, during surgery.

Patients underwent full preoperative mechanical bowel preparation and were given antibiotic prophylaxis. The patients were operated under general anaesthesia and placed according to the location of the RA in supine, prone jack-knife, left or right lateral position. All RA were excised full thickness except for RA within the anal canal. Patients were allowed to resume a full diet on the day of the operation and were dismissed the first or second postoperative day after uneventful recovery.

TEM (Wolf GmbH, Knittlingen, Germany) is a minimal invasive operation. The technique is described extensively elsewhere[9]. During the study period, various exci-

sional devices were used, of which the results have already been published[19]. Nearly all TEM operations were performed by 2 surgeons (EDG and GT). Only from 2006 onward, did surgical residents perform TEM occasionally, always under direct supervision of the above-mentioned surgeons. Before performing TEM, all surgeons were trained in intensive TEM courses. None of the surgeons had any clinical experience with TEM before the start of this study.

The parameters studied were operation time, peroperative problems, conversions, blood loss, morbidity, mortality, length of hospital stay, resection margin status and recurrence rate. Operation time was defined as the time from introduction of the rectoscope to completion of the last suture. Peroperative problems were defined as any event during the procedure that was not expected and unwanted. Any time needed to correct the problem was recorded. If conversion was necessary, its cause was recorded. Type of conversion was to the surgeon's preference.

All specimens were pinned on cork with fine pins at short distance through the margin of macroscopically normal mucosa. Longitudinal and transversal diameter both of the specimen and the base of the tumour were measured at that time. Subsequently, the whole was fixed in 4 per cent formalin solution buffered in saline and sent to the pathology department. Resection margin status was investigated by serial transversal sectioning every 0.5 cm. All sections were evaluated by a pathologist. Margin status was scored as complete (> 1 mm of normal tissue microscopically) or incomplete (≤ 1 mm and indeterminate). If an invasive carcinoma was found, the patient was excluded from the study.

Follow-up included surveillance endoscopy at 1 and 4 years after TEM and every 5 years thereafter. Additional rectoscopy was performed 6, 18, 24 and 36 months after TEM and in case of suspected local recurrence. The last follow-up date was determined by the last endoscopy. Local recurrence was defined as recurrent tumourous tissue within the proximity of the scar tissue of the earlier operation. Histological confirmation was mandatory.

All data were collected in a database and analyzed with SPSS statistical software (version 11.5 for Windows, SPSS, Chicago). Percentages and continuous data were compared using the Chi-square test, Fisher's exact test and the Mann-Whitney test. Multiple regression was used simultaneously to evaluate factors regarding their effects on operation time, the latter variable transformed logarithmically in order to get an approximate normal distribution. Spearman's correlation coefficients are given. The cumulative percentage of patients with recurrence over time was calculated using the Kaplan–Meier method, and comparisons between groups were made using the log rank test. The limit of significance was $P = 0.05$ (two-sided).

Results

A total of 353 RA were excised in 342 patients. Patient and tumour characteristics are presented in Table 1.

During 42 procedures peroperative problems occurred (11.9 per cent). The median time to correct was 5 minutes (range 0-65). In 28 of the RA, the peritoneum was opened during excision (8.7 per cent). In 18 of the RA, this did not interfere with the progress of the operation and the defect was closed within the running suture when closing the rectal wall. In 10 of the RA, the operation was interrupted to close the opening with time needed ranging from 5 to 15 minutes. It mainly involved more proximal and larger tumours ($P < 0.001$ and $P = 0.009$, respectively), however, it never lead to conversion or increased morbidity. In 9 of the RA (2.5 per cent), the multifunctional instrument[20] was not functioning properly for various reasons resulting in substantial bleeding in 3 patients (range 300-1000 cc). In 6 of the RA (1.7 per cent), technical problems related to the TEM device occurred; malfunctioning of the needle for rinsing occurred in 4 RA and malfunction of gas flow measurement in 2 RA. In 1 patient with a history of radical excision for an adenoma, repeated TEM

Table 1. Patient and tumour characteristics of this study.

Patients	
women : men	175 : 167
age (yrs)	69 (29-91)
ASA 1: 2: 3: 4	170: 103: 68: 1
Adenomas	353
recurrent	111
longitudinal diameter (cm)	3 (0-20)
transverse diameter (cm)	3 (0-16.5)
area (cm^2)	9 (0-330)
captured circumference (%)	40 (5-100)
distance (cm)	8 (0-24)
0-5 cm	84
5-10 cm	151
10-15 cm	99
> 15 cm	16
most proximal (cm)	25.8
location	
anterior	75
posterior	100
left lateral	90
right lateral	77
circular	11
Specimens	
longitudinal diameter (cm)	4 (0.5-21.5)
transverse diameter (cm)	4 (0.5-16.5)
area (cm^2)	16 (0.25-346.5)

ASA = American Association of Anesthesiology; data given are numbers or medians with ranges in parentheses.

for recurrences and again a suture line recurrence, approximation of the margins of the defect was not possible and the defect was left open (0.3 per cent). The patient recovered uneventfully. Repositioning for completion of excision was never necessary.

Conversion was performed in 34 out of 353 RA (9.6 per cent; Table 2, Figure 1 and Figure 2). It depended on distance from the dentate line (P = 0.007). In 15 RA (4.2 per cent), another type of local excision was performed and a transabdominal procedure was performed in 19 (5.4 per cent). Conversion to another type of local excision was mainly in RA in the distal rectum (P < 0.01), whereas conversion to transabdominal procedures was mainly in RA in the proximal rectum and distal sigmoid (P < 0.001). In addition, circumferentially located RA had a higher risk on conversion (P = 0.001). During the study the conversion rate decreased for the surgeon that performed the majority of TEM operations (EDG) (P = 0.004) and RA, actually treated with TEM, increased regarding all specimen and tumour characteristics (P ranging from 0.04 to 0.003). Distance did not change. Conversion rate did not differ between the 2 surgeons participating in this study.

Table 2. Cause versus type of conversion in this study.

	prolapsing	no pneumorectum	not within reach	too bulky	n
Local procedures					
Gabriel's procedure	5				5
Lone Star excision		4			4
transanal excision		2			2
Altemeier's procedure	2				2
"open" TEM			2		2
Abdominal procedures					
lap. ass. snare polypectomy			2		2
TME		1	4	5	10
sigmoid colectomy			6	1	7
n	7	7	14	6	34

"Open" TEM = removing the working insert, inverting the tumour into the rectoscope tube and excising the tumour; TME = total mesorectal excision; data given are numbers.

Operation characteristics of the 2 operating surgeons (EDG and GT) are shown in Table 3 and Figure 3. Operation time correlated with the area of the specimen, was dependent on the operating surgeon (both P < 0.001; Figure 3) and decreased with increase in experience (P < 0.001). It was not related to distance. Mild morbidity, treated conservatively, was observed in 19 patients (6.4 per cent). Wound abscesses spontaneously drained peranally, after digital rectal examination or with the use of a rectoscope. Anastomotic stenosing was corrected with Hegar dilatation. Severe morbidity, needing surgical re-intervention was observed in 4 patients (1.3 per cent). Suture line dehiscence and rebleeding after TEM for RA proximal to the peritoneal

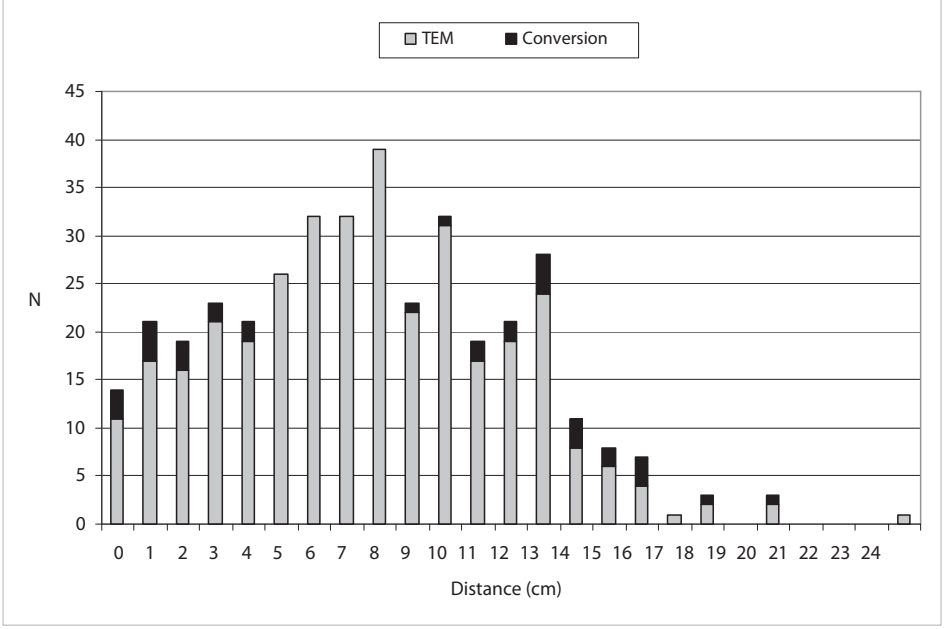

Figure 1. Relation of distance and conversion in this study.

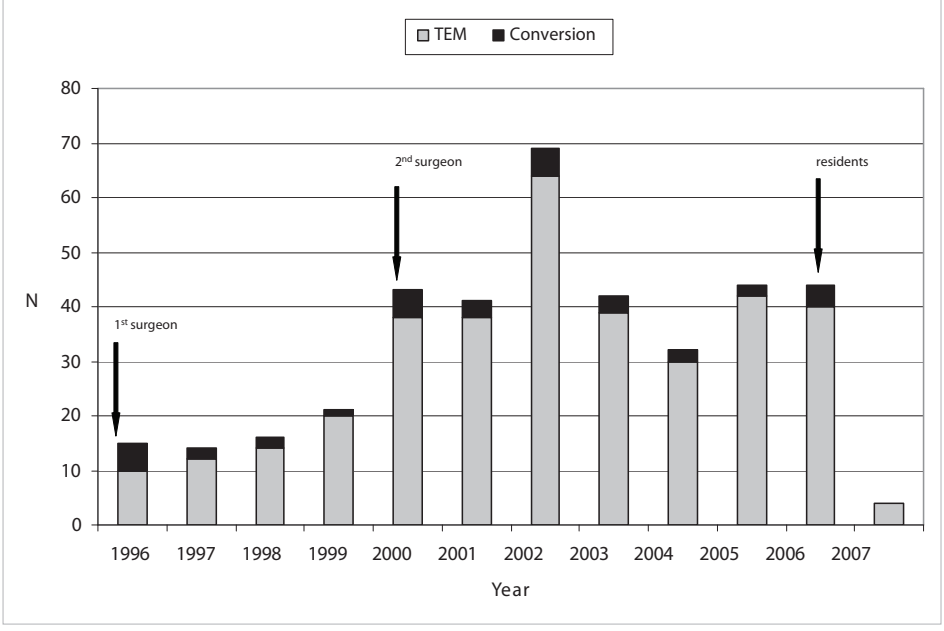

Figure 2. Number of TEM operations and conversions per year in this study.

Table 3. Operation characteristics of 319 adenomas in 309 patients that actually underwent transanal endoscopic microsurgery.

Operation time (min)	45 (2-260)
Blood loss (cc)	25 (0-1000)
Co-operations	15 (4.9)
right-sided colectomy	7
laparoscopic right sided colectomy	1
transverse colectomy	2
left-sided colectomy	1
sigmoid colectomy	1
TME	1
laparoscopic cholecystectomy	1
ankle fracture	1
Morbidity (%)	23 (7.8)
mild	19 (6.4)
urinary retention	5
urinary tract infection	2
rebleeding	3
anastomotic stricture	1
wound abscesses	7
pneumonia	1
severe	4 (1.3)
wound dehiscence	1
rebleeding	1
recto-vaginal fistula	1
partial sphincter excision	1
Mortality (%)	2 (0.6)
Hospital stay (days)	4 (2-28)

Mortality = in 294 patients that were only treated with TEM; mild morbidity = could be treated conservatively; severe morbidity = needed re-intervention; data given are medians with ranges in parentheses or numbers with percentage in parentheses.

fold were corrected via laparotomy with covering ileostomy. A rectovaginal fistula was closed with TEM after creation of a covering ileostomy laparoscopically. Partial sphincter excision with faecal incontinence occurred in the first segmental excision from 0 to 11 cm in the 66th patient from the start of the study. A covering ileostomy and sphincterplasty was performed. The covering ileostomy was removed in all patients. Two elderly patients died suddenly (0.6 per cent).

Follow-up data were available for 315 RA. The median follow-up was 27 months (range 0-123). Local recurrence occurred in 21 RA (6.6 per cent). The cumulative recurrence rate was 9.1 per cent at 3 years after TEM (95 per cent confidence interval 5-13; Figure 4). The median time from operation to recurrence was 12 months (range 4-54). All but 1 recurrences occurred within 34 months (94.1 per cent). An invasive carcinoma was never observed as a recurrence.

Complete margins were observed in 85 per cent and incomplete margins in 15 per cent. In comparison with RA with complete margins, RA with incomplete margins

had a larger longitudinal diameter (P < 0.001), a larger transverse diameter (P < 0.001), a larger tumour area (P < 0.001), a larger rate of captured circumference of the rectal wall (P < 0.004) and were more proximally located (P < 0.001). Resection margin status was not dependent on the surgeon. Resection margin status was a predictor for recurrence (complete margins 6.1 per cent (95 per cent confidence interval 3-9) versus incomplete 25.2 per cent (95 per cent confidence interval 11-40; P = 0.0004; Figure 5). Metachronous rectal tumours were found in 8 patients (2.5 per cent).

Fifty-nine patients were lost for follow-up (17.2 per cent). In 1 patient with multiple adenomas throughout the colon, TEM was performed as a first step for 2 presumed RA. Histology of the specimen showed 1 adenoma and 1 T1 rectal carcinoma. Consequently proctocolectomy with ileo-anal pouch anastomosis was performed. Four patients refused follow-up, 8 patients did not show up and could not be traced, 7 patients died of unrelated causes and in 39 patients follow-up was discontinued because of age and/or severe co-morbidity.

Recurrences were treated with snare polypectomy (n = 9), Lone Star excision (n = 2), re-TEM (n = 9) and abdomino-perineal excision (n = 1). In the last patient, local recurrence at the dentate line caused progressive stenosing with functional complaints not responding to Hegar dilatation.

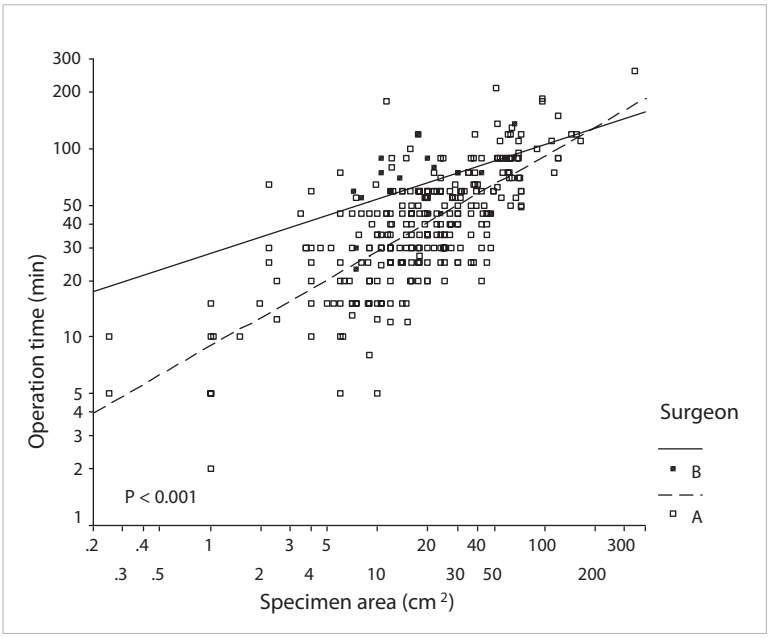

Figure 3. Operation time of TEM related to the area of the specimen and the surgeon. Note the logarithmic scaling of both axes.

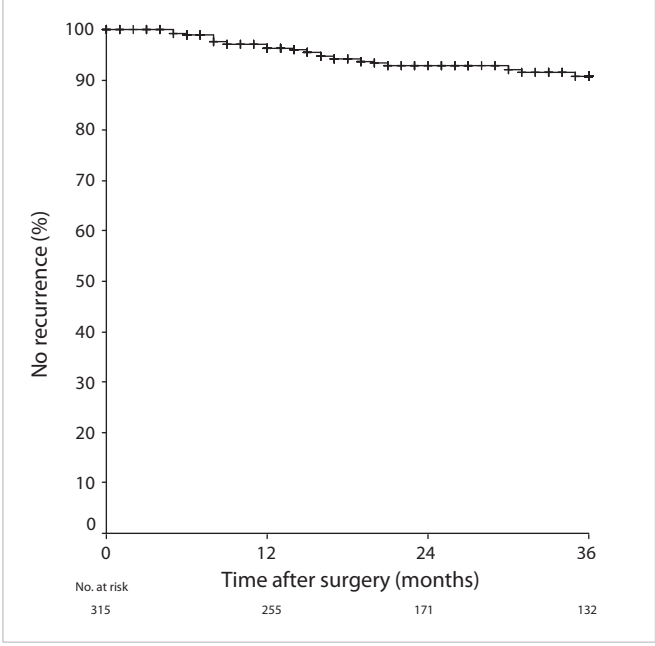

Figure 4. Recurrence rate in all adenomas that underwent transanal endoscopic microsurgery in this study.

Discussion

The world's largest single-institute prospective series on TEM for RA to date is presented in this study. TEM has gradually surpassed all other local surgical techniques for excision of RA as expressed by the number of studies, number of patients treated, aspects studied, level of evidence and results. Total morbidity ranges from 3 to17 per cent, severe morbidity 1.2 to 2.5 per cent and mortality 0 to 1.1 per cent, which are not different from TE and significantly less than after radical excision[5, 14, 16-19, 21-27]. In this study co-morbidity rate was not a criterion and ASA 3 patients were largely present. Total morbidity was 8 per cent, severe morbidity 1.3 per cent and mortality 0.6 per cent, highlighting again the safety of TEM for RA.

Despite all of this, implementation of TEM in the surgical armamentarium has been relatively slow. This is remarkable because both median diameter and distance of RA, excised with TEM, were often larger[5, 14, 27]. Furthermore, subjective assessment stated that RE would have been necessary because TE would not be capable of excision in 50 to 100 per cent of the patients without TEM [12, 18]. Thus, compared to TE, TEM also seems to prevent a laparotomy more often from a technical point of view. Unfortunately, in all series mentioned, a selection bias may have or has been introduced, and therefore the question as to whether TEM can be applied to all RA still remains unanswered. Another aspect of feasibility in endoscopic surgery is conversion rates.

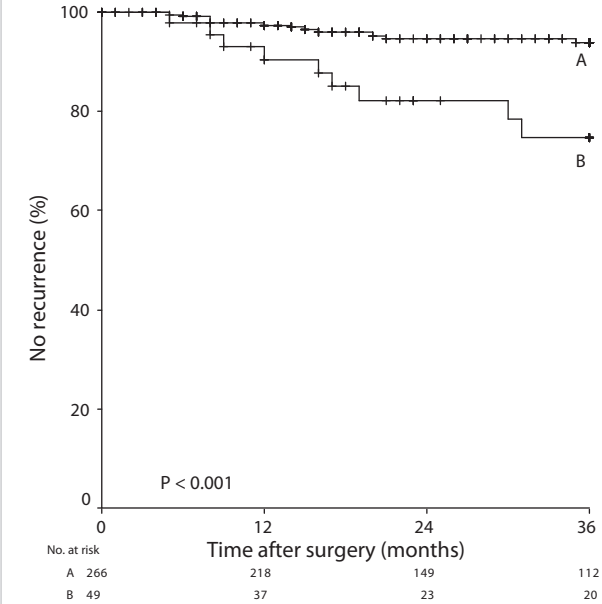

Figure 5. Recurrence rate in adenomas that underwent transanal endoscopic microsurgery with complete (A) and incomplete margins (B).

Salm described retrospectively a conversion rate to laparotomy of 11.6 per cent decreasing to 1.2 per cent with experience[10]. In his systematic review Middleton concluded to a median conversion rate of 5.7 per cent[16]. Said retrospectively described a consecutive series of 260 RA, excised with TEM. Eligibility regarding type of RA was well-defined but it was unclear if all referred RA were included. Also Said's rationale for alternative techniques in 18 RA (7 per cent) was not disclosed [11].

It must be concluded that our study is the first to study the feasibility of TEM for all RA prospectively. All referred RA were included without exception and TEM was intended in all RA. Conversion rate in this study was 9.6 per cent, meaning RA were excised with TEM in more than 90 per cent (Table 2). Another type of local excision was performed in 4.2 per cent. These RA were located in the distal rectum. In our explorative study, all tumours in the distal rectum were converted and we shared the opinion that TEM did not seem feasible in this part of the rectum[8, 28]. This was partly due to the inability to create a stable pneumorectum by gas leakage along the rectoscope. Gradually, we realised that detailed positioning of the patient as necessary for other types of perineal surgery, could be a cause. Refraining led to enclosing of the rectoscope by the buttocks, reduction of gas leakage and decrease of conversion rate. If we still encountered gas leakage in larger RA in the distal rectum, we started submucosal dissection distally with help of the Lone Star retractor and continued with TEM proximally. We did not consider this as a conversion.

Conversion was limited to 14 of 84 RA in the distal rectum (16.6 per cent; Figure 2), conversion rate decreased with increasing experience, and if converted, the alternative procedures could be performed safely. Our opinion is that TEM is feasible in the distal rectum. In the mid-rectum, feasibility is obvious with only 1 conversion to RE because of a bulky tumour at a distance of 9 cm (Figure 2). We had to convert to a transabdominal procedure in only 5.4 per cent. All of these RA were located in the proximal rectum and distal sigmoid colon. In time conversion rate further decreased resulting in an increase in all tumour characteristics of RA treated with TEM, except for distance. The latter is logical since TEM was intended in all RA throughout the rectum. Often, to our surprise, larger and circumferentially located RA could be excised with TEM. If not for this study we often wondered if we would have considered TEM. This mechanism with reduction in conversion rate to laparotomy when experienced was also observed by Salm[10]. Operation time was substantial in these patients but without impact on morbidity. It must be concluded that nearly all RA can be removed safely with TEM throughout the entire rectum.

Opening of the peritoneum was the most frequent and most striking encountered peroperative problem and occurred in 8.7 per cent. The operation was not or hardly delayed because of this; it did not cause insurmountable problems, resulting in conversion, and it did not have any impact on morbidity and mortality. Proximity of both distal and proximal margins and a larger rate of captured circumference of the RA were obvious risk factors. Both Bretagnol and Gavagan also explored the consequences of opening the peritoneum. They found no impact on morbidity either[18, 21]. Therefore opening of the peritoneum should not be considered a reason for conversion a priori, denying many patients the advantages of TEM.

During this study, operation time had decreased with increased experience, was correlated with the area of the specimen and was related to the operating surgeon (all $P < 0.001$). It was not related to distance (Figure 3). Because all operating surgeons began with the same level of (in)experience, this is most likely the effect of a learning curve. However, a significant reduction of operation time and blood loss using ultracision harmonic scalpel compared to both the monopolar knife and the multifunctional instrument has been reported, also by us. We used ultracision harmonic scalpel progressively during this study. This might also have played a role in the decrease of operation time[5, 19, 20].

Conclusions

This study demonstrates that TEM is safe and feasible for rectal adenomas throughout the entire rectum. Opening of the peritoneum can occur but does not have any

impact on morbidity and does not lead to conversion. Conversion rate is minimal, also in the distal rectum, particularly with increasing experience. Recurrence rate is minimal, especially after complete excision. In our opinion TEM should be the surgical method of choice for local excision of all rectal adenomas.

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Chapter 5

Impact of transanal endoscopic microsurgery on functional outcome and quality of life

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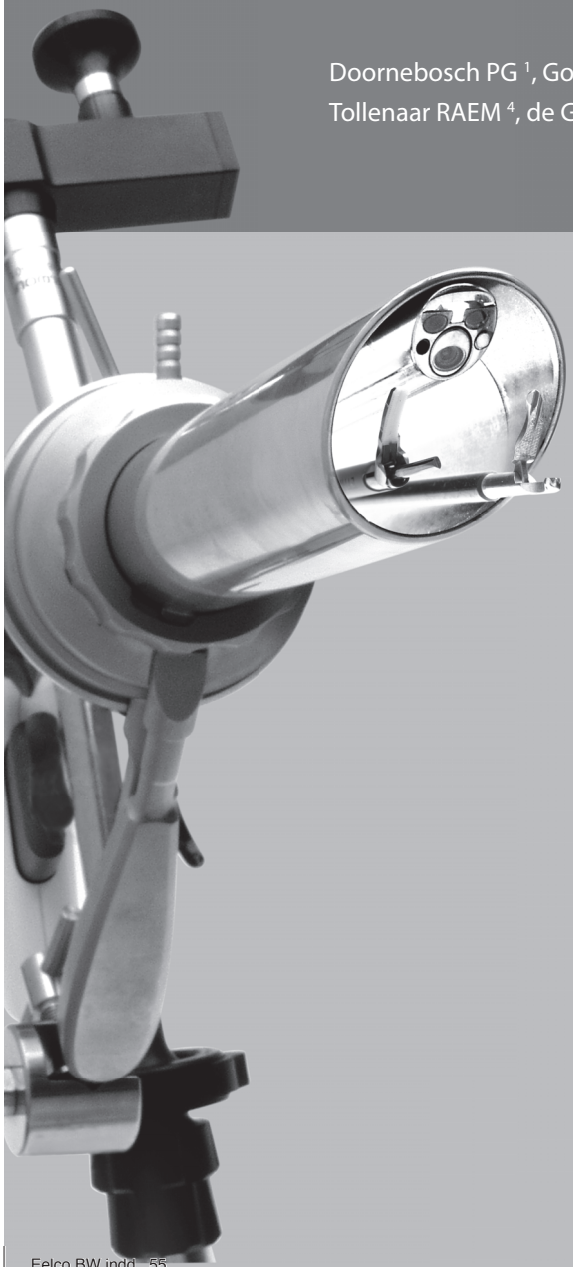

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Introduction

Local excision of benign rectal tumours is safer compared to radical surgery and is considered to be the treatment of choice[1-3]. Several techniques have been developed for local excision, with the transanal technique according to Parks as the most frequently implemented[1, 4]. Other techniques employed are the dorsal transcoccygeal approach (Kraske) and the dorsal transsphincteric approach (York-Mason)[5-9]. Each procedure has its own advantages and disadvantages, while not one of the procedures mentioned is able to achieve local excision of tumours throughout the entire rectum. Transanal endoscopic microsurgery (TEM) has, however, demonstrated to be a safe procedure capable of overcoming this shortcoming. In early publications, even distal sigmoid tumours could be locally excised with excellent results. Moreover, recurrence rates are minimal compared to other local techniques. As a result the indication for local excision of rectal tumours has expanded dramatically[10-13].
Few studies have addressed functional outcome following TEM, and with an operation rectoscope with a length of 12 or 20 centimetres and a diameter of 40 mm, scepticism towards postoperative faecal continence remains. In manometric studies after TEM there seems to be a detrimental, temporary impact on internal sphincter functioning, although without clinical significance[14-16].
Cataldo et al recently performed a prospective study on faecal continence and incontinence-specific quality of life after TEM, using standardized surveys[17]. They stated TEM does not result in significant alterations. These results are promising, especially with a relative short duration of follow-up of 6 weeks in this study. As known from other types of rectal surgery, incidence of faecal incontinence diminishes with time[18]. This could imply results after TEM may even improve with longer follow-up.
Quality of life is increasingly recognised as the ultimate endpoint when assessing clinical outcomes after different surgical interventions because it measures the patient's subjective perspective. The precise impact of the TEM procedure on quality of life has not been well studied. This prospective study was set out to provide a comprehensive insight into the impact of TEM on functional outcome and quality of life.

Patients and methods

Between January 2004 and January 2006, a consecutive series of 50 patients were referred for a TEM procedure. All patients were evaluated preoperatively according to a standard protocol including rigid rectoscopy, tumour biopsy and endorectal ultrasound. If TEM was considered feasible, patients were eligible for this study. In-

formed consent had to be given before inclusion. Local medical ethical committees approved this study. A full-thickness excision was performed on every patient. The portion of the tumour located within the sphincter musculature was removed with a partial-thickness excision. Before and a minimum of 6 months after the TEM procedure, patients were asked to fill out a questionnaire to assess anorectal functioning and the quality of life. All data were collected by an independent research coordinator not previously involved in the patients' care. We recorded the demographics, operative details, postoperative length of stay, postoperative complications and functional outcome for each participant.

We evaluated functional outcome by means of a detailed questionnaire based on the Faecal Incontinence Severity Index (FISI)[19]. This system, developed by Rockwood, uses 2 basic components: the type of incontinence and its frequency. FISI scores range from zero (total continence) to 61 (complete incontinence to solid stool on a daily basis). We used the validated weighting scores that are based on patients input.

Quality of life was evaluated using both the EuroQol EQ-5D and the Faecal Incontinence Quality of Life (FIQL) score. The EuroQol EQ-5D consists of a so-called Index score representing the societal value of the health state, and has a scale ranging from zero (no quality of life) to 100 (optimal quality of life). The EuroQol EQ-5D also uses a visual analogue scale, the EQ-VAS, representing the patient perspective. This scale ranges from zero (no quality of life) to 100 (optimal quality of life). The EuroQoL EQ-5D scores were compared with a sex- and age-matched, community based sample of healthy persons without co-morbidity[20]. The FIQL score as described by Rockwood measures specific quality of life issues, expected to affect patients with faecal incontinence[21]. This instrument is composed of 29 questions within 4 domains: lifestyle issues, coping/behaviour, depression/self-perception, and embarrassment. The scores in the FIQL range from a minimum score of 1 to a maximum of 4, for all of the scales (1 = quality of life alteration present most of the time, 4 = none of the time). Data are presented as medians and standard deviations.

Changes within groups were evaluated using the nonparametric one-sample Wilcoxon's signed-rank test. Comparison of these changes between groups was conducted using the Mann-Witney U test. The Spearman's correlation coefficient was used for correlation between the different findings. A P-value ≤ 0.05 was considered statistically significant.

Results

Informed consent was obtained from all of the 50 patients who were eligible to participate. Three of these patients were excluded. TEM could not be performed

because of a bulky tumour and of technical problems in 2 of the patients. The third patient underwent low anterior resection for locally recurrent disease within 6 months of the TEM. The remaining 47 patients completed both questionnaires and were included for analysis. All of these patients were alive without evidence of recurrent disease. The group consisted of 22 males and 25 females. Median age was 67 years (range 40-84). Preoperative diagnosis was villous adenoma in all patients. Median distance from the distal tumour margin to the dentate line was 7 cm (range 0-15) and median tumour size was 20 cm^2 (range 4-53). The median rate of captured circumference of the rectal wall was 40 per cent (range 5-80) (Table 1). Median operative time, defined as beginning when the rectoscope was inserted and ending when it was removed, was 55 minutes (range 10-140). Complications developed in 4 of 47 patients (8.5 per cent). Two patients had urinary retention, 1 patient a urinary tract infection and 1 suffered from a low haemoglobin rate requiring blood transfusion. No reoperations were necessary and mortality rate was zero. Median length of stay was 4 days (range 3-9) (Table 2). Definite histopathological examination of the resected specimens revealed an adenoma in 44 patients and an invasive carcinoma in 3 patients (pT1 in 2 patients and pT2 in 1 patient). These 3 patients were reluctant to major surgery and were observed with rectoscopy and endorectal ultrasound every 3 months without signs of recurrence at 6 months after TEM. In 3 adenomas, excisional margin was considered microscopic irradical, resulting in 94 per cent of tumours being radically excised.

Six months after surgery, mean FISI scores were found to be decreased (preoperative 10 versus postoperative 7; $P < 0.01$), depicting an improvement in faecal con-

Table 1. Patient and tumour characteristics.

n	47
Women: men	25: 22
Age (yrs)	67 (40-84)
Distance (cm)	7 (0-15)
Size (cm^2)	20 (4-53)
Captured circumference (%)	40 (5-80)

Data given are numbers or medians with ranges in parentheses.

Table 2. Procedure related characteristics.

Operation time (min)	55 (10-140)
Morbidity	8.5
urinary retention	2
urinary tract infection	1
blood transfusion	1
Re-operations	None
Hospital stay (days)	4 (3-9)

Data given are numbers or medians with ranges in parentheses.

tinence (Figure 1). Overall when preoperative and postoperative FISI scores were compared, 24 patients improved, 16 patients were unchanged and 7 deteriorated. Operation time or tumour size did not influence the change in FISI score. There was a significant correlation between the decrease in FISI score and tumour distance (P = 0.02). Reduction of FISI was significantly greater in patients with a tumour location within 7 centimetres from the dentate line (P = 0.01; Table 3). Mean scores and ranges of the EuroQol EQ-5D are presented in Table 4. Mean general quality of life score from the patients' perspective (EQ-VAS) was found to be significantly higher 6 months after TEM (P < 0.02). The observed changes in EQ-VAS showed no correlation with the postoperative alterations in FISI scores or tumour characteristics. The mean preoperative EQ-VAS score in our group was lower compared to the mean EQ-VAS score of the sex- and age-matched general population (P = 0.02). Postoperative EQ-VAS score was comparable to the general population. The mean index score (social perspective) remained the same (P = 0.09). Both pre- and postoperative EQ-5D index scores were similar to those of the sex- and age-matched general population. Comparing the change from baseline in FIQL scores, a statistically significant improvement was observed in 2 of the 4 domains (embarrassment; P = 0.03 and lifestyle; P = 0.05). The domains of lifestyle, coping/ behaviour, and embarrassment were correlated with the FISI (all P < 0.05; Table 5). Overall, EQ-5D and FIQL scores were not affected by age and gender of the patients. Surgical aspects and tumour characteristics did not influence the outcome.

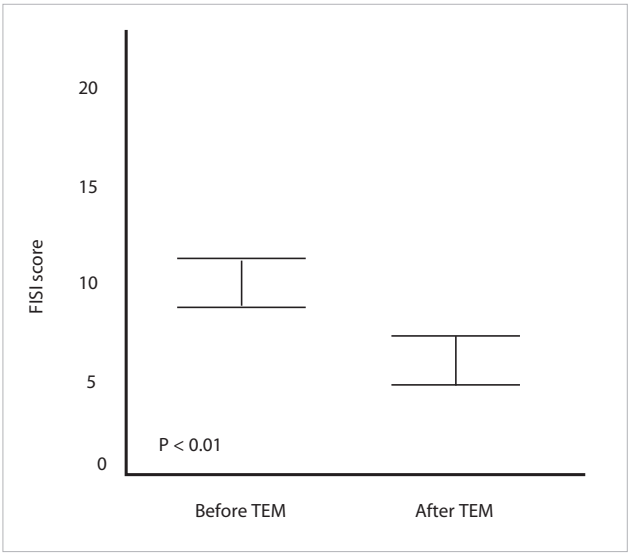

Figure 1. Mean Faecal Incontinence Severity Index (FISI) scores (± SEM) before and after transanal endoscopic microsurgery (TEM).

Table 3. Mean Faecal Incontinence Severity Index (FISI)-scores.

FISI score	Preoperative	Postoperative	P
Overall	10 (2)	6 (2)	< 0.01
Duration of operation < 55 minutes (n = 24)	9 (4)	7 (3)	0.24
Duration of operation > 55 minutes (n = 23)	12 (3)	4 (2)	0.17
Tumours < 7 cm from dentate line (n = 21)	16 (5)	5 (2)	0.01
Tumours > 7 cm from dentate line (n = 26)	6 (2)	7 (3)	0.43
Median tumour size < 20 cm^2 (n = 27)	12 (4)	6 (3)	0.12
Median tumour size > 20 cm^2 (n = 20)	8 (3)	6 (3)	0.32

Lower values indicate better anorectal functioning; numbers in parentheses are standard deviations.

Table 4. Mean EuroQoL EQ-5D scores.

	Control group	Preoperative	Postoperative	P
EQ-VAS	82 (7)	77 (14)	82 (11)	0.02
Index score	86 (6)	84 (11)	89 (9)	0.09

EQ-VAS represents the patients' perspective on quality of life; index score represents the societal value on quality of life; higher scores indicate higher quality of life; both scores are compared with a healthy sex- and age-matched control group; numbers in parentheses are standard deviations.

Discussion

In rectal adenomas, TEM has emerged as the procedure of choice, because of its safety and low local recurrence rates. TEM has proven its safety, especially when compared to radical surgery[22, 23]. However, possible adverse effects of TEM need to be addressed. The use of a rectoscope with a diameter of 4 centimetres, introduced transanally, has led to substantial scepticism regarding impact on anorectal functioning. In earlier studies, we already showed TEM to be superior to total mesorectal excision regarding postoperative defecation disorders, although this did not result in an improved quality of life[24]. In the present study, TEM resulted in improved faecal continence as measured by the Faecal Incontinence Severity Index (FISI). This apparent paradox may be attributed to preoperative tumour symptoms such as mucinous or bloody discharge, prolapse, tenesmi and/or urge, giving rise to incontinence-like symptoms. Postoperative improvement of continence was most significant in tumours within 7 centimetres from the dentate line, but disappeared in our study in tumours above 7 centimetres from the dentate line. Kreis et al performed manometric studies after TEM and found a significant reduction in anal resting pressure 1 year postoperative and a temporary reduction in anal squeezing pressure, resulting in a temporary rise in urge-incontinence[25]. Kennedy et al found a significant reduction in anal resting pressure 6 weeks after TEM[26]. This reduction was significantly correlated with duration of the procedure, but mean continence score was not changed after TEM. Both of the above studies however did not use validated questionnaires on

Table 5. Mean Faecal Incontinence Quality of Life (FIQL) scores.

FIQLS	Preoperative	Postoperative	P
Lifestyle	3.7 (0.3)	3.9 (0.3)	0.05
Coping	3.6 (0.5)	3.8 (0.4)	0.10
Depression	3.7 (0.3)	3.9 (0.4)	0.08
Embarrassment	3.1 (0.3)	3.7 (0.4)	0.03

Higher scores indicate higher quality of life; numbers in parentheses are standard deviations.

faecal continence, and therefore comparison with our study is difficult. Cataldo et al reported on the impact of TEM on functional outcome and incontinence-specific quality of life, using the same questionnaires[17]. No significant alteration was found in faecal continence after TEM. The discrepancy between both studies may be explained by the relative short interval between the TEM procedure and postoperative questioning of 6 weeks in the Cataldo series. Furthermore, in his study, indications for TEM were heterogeneous, which may have influenced those results. The positive effect of TEM on faecal continence in our series may be explained by the differences in preoperative FISI scores between both studies (present series mean 10, Cataldo series mean 2.4), which depicts more continence problems among the patients in our series. Another explanation may be the differences in tumour distance from the dentate line (present series median 7 cm, Cataldo series median 11 cm). In addition, the tumours in our series were larger (present series median 20 cm^2, Cataldo series median 8.75 cm^2). More extensive resections were performed in our series because of larger tumours that were located within the sphincter apparatus more often. These latter tumours were already shown to influence recto inhibitory reflex, reflex sphincter contraction, rectal sensitivity and compliance[16]. Further analysis within our series upon this issue showed tumour distance from the dentate line of only less than 7 centimetres to be a significant contributing factor. These results however are based upon low number of patients and therefore solid conclusions cannot be drawn. Even though in our study, TEM resulted in a significant improvement in continence, the postoperative FISI was still worse compared to the Cataldo series (mean 7 versus mean 2.4).

Cataldo found TEM to have no significant affect on the quality of life. In our series, however, mean general quality of life score from the patients' subjective perspective, EQ-VAS, was significantly higher after TEM. This improvement could not be explained by improved FISI scores, but probably by lower preoperative EQ-VAS scores as compared to healthy controls. Another explanation might be the rejoice phenomena, that is when patients are relieved the tumour has been excised, and in most cases an adenoma was found[27]. However, because of the low number of invasive carcinomas in our series, this is purely theoretical. The societal value of general quality of life, EQ-5D, remained unchanged. Measuring quality of life using the

Faecal Incontinence Quality of Life (FIQL) questionnaires, resulted in a significant improve in two of the four FIQL domains (embarrassment and lifestyle). Moreover, the domains of lifestyle, coping and behaviour, and embarrassment were all significantly correlated with the FISI.

In conclusion, how are these results to be interpreted? This study supports the hypothesis rectal tumours give rise to incontinence-like symptoms, especially in low-lying rectal tumours. After the tumour is excised using the TEM technique, faecal continence improves. TEM itself does not improve continence, but also does not deteriorate faecal continence. Mean quality of life from the patients' perspective following TEM is improved. Based on, as far as we know, the only two studies addressing anorectal functioning and the quality of life after TEM in one study, it can be concluded TEM does not impair faecal continence. Also, quality of life is not negatively influenced by the TEM procedure itself, and therefore TEM is the procedure of choice in all rectal adenomas.

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Chapter 6

Transanal endoscopic microsurgery for rectal cancer

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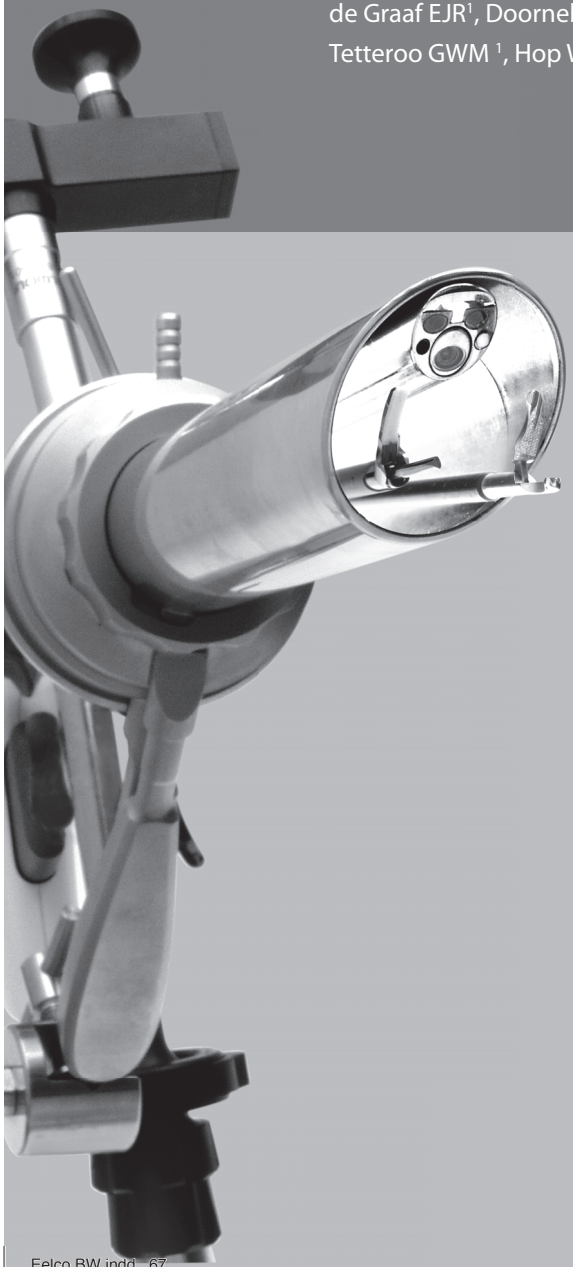

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Introduction

Total mesorectal excision (TME) with autonomic nerve preservation is the surgical technique of choice if cure is intended in rectal cancer. However, even in expert hands, mortality is 1 to 7 per cent and morbidity, including genitourinary dysfunction, faecal incontinence and permanent colostomy, 13 to 46 per cent. Moreover, disabling recurrent disease is observed in 4 to 10 percent and 5-year survival is reduced to 74 to 87 per cent[1-5].

Because of limited mortality and morbidity, local resection is advocated. The method of choice is the transanal route. Mortality is 0 to 2 per cent and morbidity 15 to 25 per cent. Only distal and smaller tumours can be excised with limited view. There are positive margins in 12 to 60 per cent and local recurrence rate is 0 to 27 per cent[6-10].

Because of these disadvantages, the sphincter-saving Kraske technique, the sphincter-splitting York-Mason technique and the transanal use of the transurethral resectoscope have been introduced. They are technically demanding, mortality is 1 to 5 per cent and morbidity, often severe, ranges from 18 to 34 per cent. As a result, these techniques are used sparingly and tumour control in rectal cancer is described only anecdotically[11, 12]. The most natural conclusion is that resection transanally is the local technique of choice with less mortality and morbidity, but only possible in distal and smaller tumours with inferior tumour control compared with TME. Until now, these facts have led to the cautious application of local excision of rectal cancer and it is used mostly only for palliation.

In 1984, Bueß introduced transanal endoscopic microsurgery (TEM) as an alternative technique for local resection of rectosigmoid tumours. Mortality was 0 to 0.3 per cent and overall morbidity 4.8 to 8 per cent. Complete margins were observed in 92 per cent. In adenomas, the recurrence rate was 3.5 per cent and in T1 tumours 3 to 4 per cent. These excellent results were assessed, even though tumours up to 24 cm from the dentate line and circumferential tumours were excised. Either mucosectomy or full thickness excision was possible and in 1 piece, allowing for a proper histological examination. These facts were thought to be due to the excellent view obtained due to the characteristics of the equipment[13-17].

Following these results, TEM was introduced in 3 Dutch hospitals, in the first instance for adenomas and for rectal cancer cases only for palliation. At a later stage, the technique was also used for T1 tumours with a curative intention. In this study, results after TEM for rectal cancer are presented.

Patients and methods

From 1996 to 2001, TEM was performed in 76 patients with 76 carcinomas. The characteristics of the enrolled patients and tumours are shown in Table 1. All patients were analysed according to a standard protocol including history, physical examination with digital rectal examination, blood tests, colonoscopy with biopsy, rigid rectoscopy, anorectal endosonography, chest X-ray and liver ultrasound. Rigid rectoscopy was performed to measure the distance from the dentate line to the lower margin of the tumour and in particular to assess the exact location of the tumour because, at operation, the patient should be positioned with the tumour downward. The rate of captured circumference of the rectal wall and the area of the tumour - the multiplication of length and width of the base of the tumour - were measured at the time of operation. The longest distance refers to the most proximal margin reached.

Table 1. Patient and tumour characteristics.

Patients	
women : men	27 : 49
age (yrs)	74 (42-92)
ASA 1: 2: 3	22: 34: 20
Tumours	
stage	
Tis	32
T1	21
T2	18
T3	5
distance (cm)	8 (0-17)
longest	22
captured circumference (%)	33 (5-90)
area (cm^2)	9 (0-77)

ASA = American Association of Anesthesiology; data given are numbers or medians with ranges in parentheses.

TEM is a minimal invasive operation. The central component of the 1-port system consists of a rectoscope, handle and a 4-port working insert. It is introduced transanally and fixed to the operating table with a Martin arm allowing positioning in any conceivable position. A stereoscope with a documentation endoscope and a maximum of 3 instruments can be introduced in the working insert. An insufflator and specially developed TEM pump are connected via a tube system and provide gas insufflation, pressure measurement, irrigation and suction. An electrosurgery unit is used for cutting and coagulation. The system is airtight, which is necessary for creating a pneumorectum. Use of a multifunctional instrument is advocated to reduce the number of instruments[13, 18, 19]. Marking dots are placed at a 0.5 to 1 cm margin around the tumour, followed by excision, possible in any desired plane,

submucosal to full thickness. The different layers of the rectal wall and the perirectal fat can be clearly identified. After removal of the specimen, the defect is closed transversally with a running suture. Clips are used as knots. The specimen is pinned on cork, fixed in formalin and sent to the pathologist. Circumferential margins were investigated.

Patient data were stored in a central, digital database. For statistics, percentages and continuous data were compared using the Chi-square test and Mann-Whitney test, respectively. Multiple regression was used to evaluate factors simultaneously regarding their effect on operation time, the latter logarithmically transformed. Correlation coefficients given are Spearman's. The cumulative percentage of patients with recurrence over time was assessed using the Kaplan-Meier life-table method. P values given are two-tailed; $P = 0.05$ was considered the limit of significance.

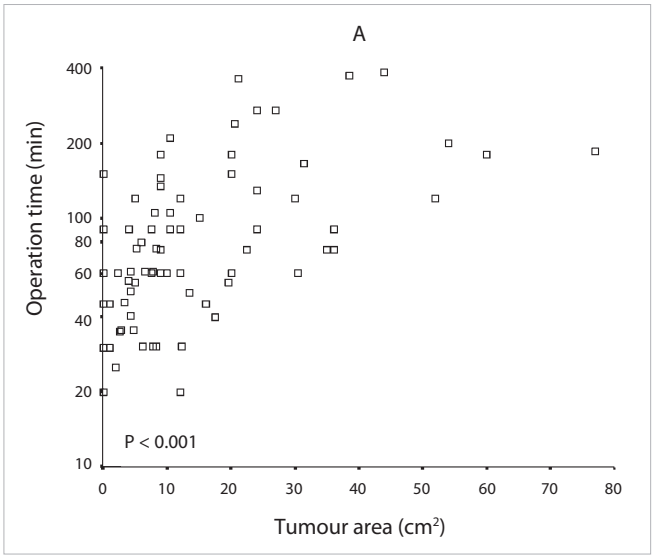
Results

Median operation time was 75 min (mean 101; range 20-385) and mean blood loss a few cc (median few; range few-1000). Operation time was independently influenced by area ($r = 0.57$; $P < 0.001$) and depth of infiltration ($r = 0.49$; $P < 0.001$) and not by distance ($r = 0.15$; $P = 0.15$; Figure 1). In 13 patients, we encountered peroperative problems (17 per cent). Opening of the peritoneum, always at the side of the resection and never through the tumour, was observed in 7 patients. It was either sutured directly or at the end of the operation within the running suture. Six substantial technical problems were encountered. All could be corrected with the time loss varying between 0 to 40 min. In 1 patient, the defect could not be closed due to fibrosis caused by an earlier anterior resection. Recovery was uneventful. Median hospital stay, from the day of operation, was 4 days (mean 5.7; range 1-106). Mortality was 1.3 per cent ($n = 1$). It was a 87-year-old lady with a cardiac history and a T3 rectal carcinoma. TEM was performed because of severe blood loss, requiring blood transfusions. She died of a cardiac arrest on the fourth postoperative day. There were 15 patients with 16 postoperative complications. In 13 patients, complications were mild and treated conservatively (17 per cent). In 2 patients, a severe complication occurred. These were an abscess and rebleeding needing reoperation with a protective stoma (3 per cent)(Table 2).

Indications for local treatment were adenoma ($n = 43$), *in situ* carcinoma ($n = 13$) and invasive carcinoma ($n = 20$) at biopsy. Postoperative histology showed *in situ* carcinoma in 32 tumours, T1 carcinoma in 21 tumours, T2 carcinoma in 18 tumours, and T3 carcinoma in 5 tumours, meaning false-negative preoperative histology of invasive rectal cancer in 27 of 56 tumours (Table 3).

Because 1 patient died and 8 patients underwent additional surgery, 67 patients were available for follow-up (Table 4). At follow-up, a digital rectal examination, rigid endoscopy and anorectal endosonography were performed every 3 months. Four patients were lost during the follow-up because they refused (n = 1) or died, not related to cancer (n = 3). Median follow-up was 10 months (range 1-52; mean 13.9 months; Table 5).

The local recurrence rate for all patients at 3 years was 18 per cent. Numbers at risk for stage T1-3 were too small to determine any representative recurrence rates. Only



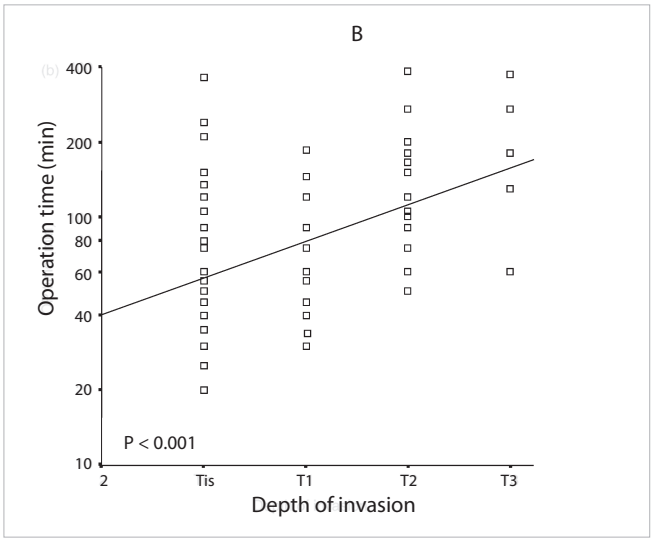
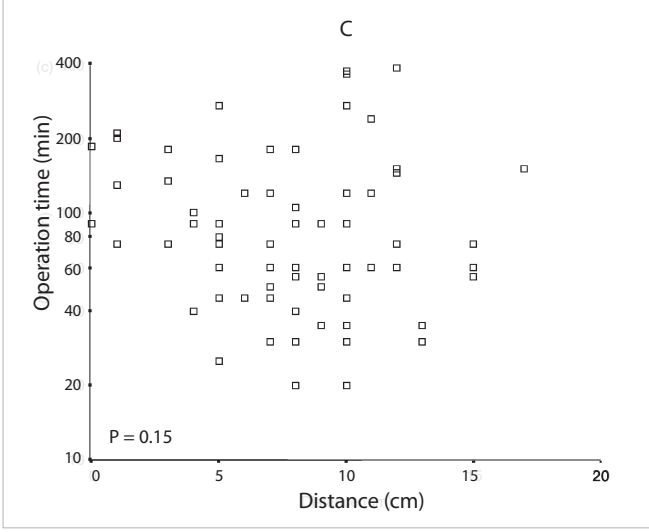


Figure 1. Operation time was influenced by tumour area (A) and depth of infiltration (B) and not by distance (C).



for *in situ* tumours numbers were large enough at 12 months with a recurrence rate of 0 per cent. Numbers of recurrences observed so far: *in situ* tumours 1; T1 tumours 2; T2 tumours 3, and in T3 tumours no local recurrences have been observed. (Table 4 ; Table 5; Figure 2). No distant recurrences or cancer-related deaths were observed. Incomplete margins were observed in 7 tumours (9 per cent). Carcinomas with incomplete margins were significantly larger (9 versus 24 cm^2; P = 0.03; Figure 3).
No correlation could be demonstrated between the risk of recurrence and complete or incomplete margins of excision.

Discussion

Transanal endoscopic surgery has been proven to be an excellent technique for the local resection of rectal adenomas. Its safety and low recurrence rate compared with other local techniques have been previously described. With TEM, tumours from the dentate line to the lower sigmoid, including circumferential tumours, can be excised. This avoids the need to master several, often technically demanding, local techniques which have the added limitations of increased mortality and morbidity. Without TEM, up to 50 per cent of the tumours could not have been excised locally and laparotomy would have been inevitable[21-24]. In the present study, mortality was 1.3 per cent and severe morbidity 3 per cent in an elderly group of patients with substantial comorbidity, with 20 patients (33 per cent) considered unfit for TME preoperatively (Table 2 and Table 4). This study confirms and underlines earlier findings that TEM is a superior technique that is feasible outside of specialised centres.

Table 2. Complications.

Complication	n	Treatment
Pelvic pain	1	Conservative
Urinary tract infection	3	Conservative
Urinary retention	2	Conservative
Cardiac	2	Conservative
Faecal incontinence	1	Conservative
Rebleeding	4	Conservative (3) Re-operation (1)
Abscess	3	Conservative (2) Re-operation (1)

Table 3. Histological diagnosis pre- and postoperative.

		Postoperative				n
		Tis	T1	T2	T3	
Pre-operative	Adenoma	20 (1)	12 (2)	10 (1)	1	43
	Tis	9 (2)	4			13
	T1-3	3	5	8	4 (1)	20
n		32	21	18	5	76

Numbers between parentheses are numbers of incomplete excision.

TEM is considered a difficult technique, demanding extensive training before starting. All participating surgeons in this study were trained extensively. Major technical and other interruptions were encountered at operation in 17 per cent. All of these were solved without the need for laparotomy or diverting stoma. We strongly believe that, without such training, more problems would have resulted and would not have been solved without additional surgery[20, 25, 26].

Key elements in TEM are the excellent view provided and the pneumorectum. When the views via the documentation endoscope and the stereoscope are compared, the latter has a much larger range of vision, up to 180 per cent. Moreover, the view from the stereoscope is of unmatched quality, since it can be viewed directly with the human eye, resulting in a 3-dimensional view with the maximum depth of vision and resolution, and with a 6-fold magnification, this is unattainable even with the best cameras and monitor[17]. These advantages are essential for TEM use, because viewing and manipulation of the instruments has to be performed in a parallel plane. In a collapsed rectal cavity, a tumour is stowed away in the folds of the rectal wall. Inflation enlarges the view because it enables the exposure of the tumour on the unfolded and extended rectal wall. Therefore, creation of a pneumorectum is the second key element in the technique. Because the rectal cavity is relatively small, pressure measurement and gas insufflation are carried out separately, using 2 tubes and 2 connections. This enables both continuous gas insufflation and frequent pressure measurement. As a consequence, a very stable pneumorectum and operative field are guaranteed[20].

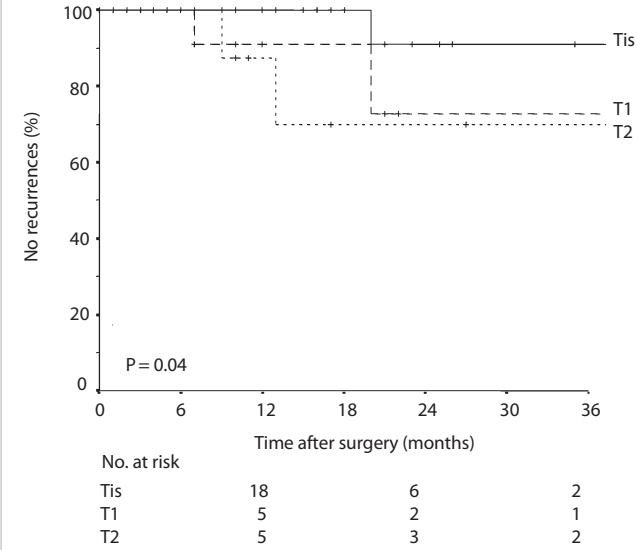


Figure 2. Recurrence rates.

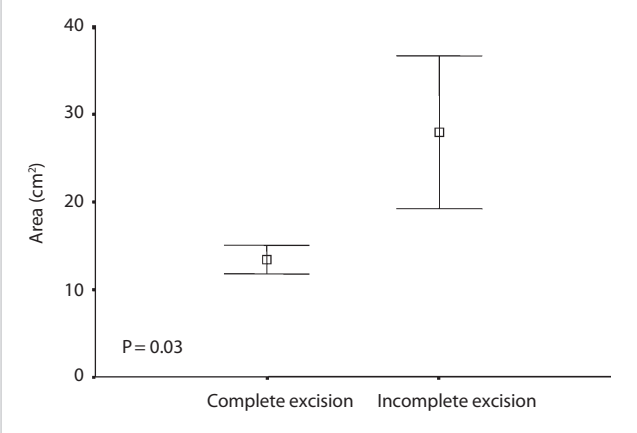


Figure 3. Mean area (± S.E.M.) of complete versus incomplete excised tumours.

TEM has been developed for adenomas. However, because of its success, it is tempting to determine its role in the treatment of rectal cancer. Rectal cancer is mistaken for adenoma preoperatively, due to negative findings at biopsy. This mistake correlates with the size of the tumour. Because in TEM there is apparently no limitation in the area of the tumour, the surgeon has to frequently make decisions on tumour control after unintended local excision of rectal cancer, as was the case in this study in 27 tumours (Table 4).

In situ carcinomas do not have the potential for metastatic spread and local excision is justified in all cases[27]. The minimal local recurrence rate and the absence of distant

Table 4. Selection of patients for follow-up.

	Died postop.	TME	Follow-up		
			indicated/unfitt	unfitt	refused
Tis			32		
T1		2	19		
T2		6		8	4
T3	1			3	1
n	1	8	51	11	5

n = sum as number.

Table 5. Length of follow-up.

	n	Follow-up (months)		
		median	mean	range
Tis	32	14	15.5	1-41
T1	19	7	12.5	1-47
T2	12	10.5	15.5	1-52
T3	4	2	5	1-15
Total	67	10	13.9	1-52

Total = sum as number, median, mean or range.

recurrences or cancer-related deaths in this study support this statement. There is growing support to redefine it as severe dysplasia, as already practised within the World Health Organization (WHO), advised by the same panel as the International Union Against Cancer (IUCC)[28, 29].

In invasive rectal cancer, TME is the gold standard. At the start of this study, in all patients with invasive tumours and fit for major surgery, additional TME was performed. In 2 patients with T1 tumours, no residual cancer tissue nor lymph node metastasis were found in the TME specimen, as experienced in earlier reports[15, 16, 21, 22, 24]. In T1 tumours, lymph node metastases are found in 0 to 10 per cent at the time of radical operation[30-32]. After TEM for T1 tumours, local recurrence rates of 0 to 4.2 per cent and survival rates of 79 to 96 per cent, no different from TME, have been reported[23, 33, 34]. Therefore, we decided not to re-operate for the T1 tumours.

After transanal excision, local recurrence is 0 to 27 per cent for T1 tumours[6, 9, 10]. Tumour selection criteria, surgical technique in use and statistical pitfalls can be held responsible for differences in the local recurrence rates. Local recurrence can be expansion of lymph node metastases, left behind after surgery. Local excision should be confined to rectal cancers without any lymph node metastasis at the time of operation. Depth of infiltration is a major risk factor for the presence of metastasis, as discussed before. The use of histopathological criteria to predict nodal involvement is advocated. Well or moderate differentiation, no blood- or lymphatic-vessel invasion, and no mucinous component are defined as low risk criteria. Presence of

lymph node metastasis in T1 low-risk rectal tumours is 7 per cent, no different from T1 tumours as a group, possibly reflecting the vast majority of low-risk tumours within T1 tumours[6, 9,3 2]. Anorectal endosonography is used to demonstrate local lymph node involvement in rectal cancer. A disadvantage of this technique is the moderate negative predictive value of 84 per cent for all rectal cancers and its lack of value for T1-rectal cancers[35]. It is used for decision-making in T1 tumours, but the minimal amount of lymph node metastasis in this tumour stage probably camouflages the inadequacy of anorectal endosonography, enabling a low local recurrence rate[33].

Local recurrence can also be due to an expansion of residual tumour tissue because of incomplete excision. In 91 per cent of the specimens, the circumferential margins were free of tumour. This finding is similar to other series and compares well with findings after TME[21, 36]. After transanal excision, data on the completeness of excision are difficult to obtain, but incomplete excision has been reported in 12 to 60 per cent. Both after TME and transanal excision, the frequency of local recurrence is significantly higher for patients with incomplete excisions[6, 8, 10, 37-40]. It is advocated that adenomas can be resected submucosally and with smaller margins of macroscopically normal mucosa than rectal cancers. However, because rectal cancer is often mistaken for adenoma preoperatively, every tumour should be excised full thickness and with wide margins. In this study, mild dysplasia at the mucosal margin was the only histopathological finding when the excision was incomplete. Mild dysplasia per definition is not visible macroscopically[29]. Because this was the only finding, it proves that all tumours were excised in macroscopically normal mucosa. In larger tumours, incomplete excision was observed more frequently. In larger tumours, one perhaps tends to excise with a smaller margin, because of fear for the size of the defect being created. It must be concluded that incomplete margins after TEM are of theoretical origin rather than of technical. It confirms the excellent view in TEM, all the more since tumours up to 22 cm from the dentate line and up to 77 cm^2 have been excised in one piece, unrivalled by any other local technique (Table 1).

For T1 tumours, survival rates after TME, transanal excision and TEM are similar, even in studies with high local recurrence rates[6, 10]. Local recurrence after local excision can be salvaged by radical resection, with no extra mortality and morbidity compared with radical resection as the first option, in contrast with local recurrence after TME. Local recurrences after TME are usually associated with severe local symptoms, are difficult to palliate and lead to a miserable death. Survival after local recurrence after TME is very limited, whereas survival for patients who underwent a salvage operation after local recurrence following a local resection seems comparable to that for patients who did not[10, 41]. Thus, local recurrence after local resection should be viewed differently. A prerequisite is an intensive follow-up with digital and en-

doscopic rectal examination, as well as an anorectal endosonography every 3 to 4 months to diagnose local recurrences at an early stage[10].

Proper statistical analysis is of crucial importance in evaluating the results. Calculated percentages have to be looked at with great care in less than 100 cases with a few incidents, since the actual percentages can vary considerably due to the large confidence intervals. We could find no studies on local resection of rectal cancer with numbers exceeding 50 per T stage. The same was true for local excision of higher stages of tumours. Moreover, different regimes of adjuvant treatment are added, preventing a reliable analysis of the results[9].

In patients who are unfit for major surgery, TME is not a real option and local resection can be performed to relieve patients from distressing symptoms and improve local control with limited mortality and morbidity. This study shows that TEM is capable of doing this.

TEM is a safe technique, capable of excising rectal cancer, independent of the size and distance of the tumour. Incomplete excision is rarely observed. TEM should therefore be the method of choice when considering a local excision of rectal cancer. Local tumour control in T1 tumours seems comparable to TME with the same survival rates. In higher stages, the results are unclear. There is a lack of properly constructed, randomised trials with sufficient numbers of patients and length of follow-up to circumvent possible statistical pitfalls. However, the possibilities of TEM justify proper evaluation of its role in local excision for rectal cancer.

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Chapter 7

Transanal endoscopic microsurgery and total mesorectal excision of T1 rectal cancer with curative intention

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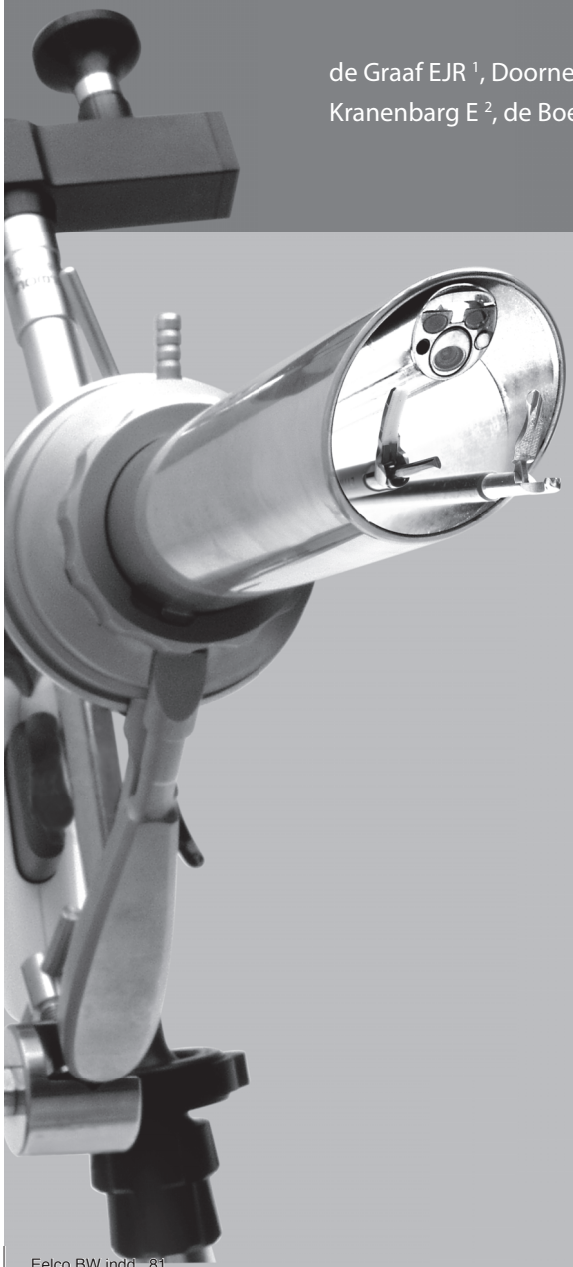

Submitted

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Introduction

In rectal cancer, total mesorectal excision (TME) is the gold standard. This optimised and standardized surgical technique, together with neo-adjuvant radiotherapy, has improved oncological outcome[1, 2]. Counterbalancing this improvement is the high rate of postoperative mortality and severe morbidity[3-6]. Local excision reduces both mortality and morbidity significantly and is therefore considered an alternative surgical option. Transanal excision (TE) has been implemented for a fairly long time, but transanal endoscopic microsurgery (TEM) is slowly but surely gaining ground as method of choice. Both techniques are safe with predominantly minor morbidity and negligible mortality. Re-operations and formation of a stoma are seldom needed[7-17].

Quirke showed that standardized processing of the specimens after TME revealed a higher percentage of incomplete excision with significant correlation to an increased risk on both local and distant recurrences and on decreased survival. This resulted in the concept of TME and adjustment of histological examination of the TME specimen[1, 2, 18]. The role of local excision of rectal cancer with curative intent concentrates on T1 rectal cancer. After both TE and TEM, margin status has been demonstrated to be a predictor for local recurrence, however, this has only been shown in case studies[19-21]. Comparing local excision and TME is dominated by other factors, passing over the role of margin status and standardized pathology as basis, and outcome show a confusing variety[8, 11, 14, 15, 22-27].

An increasing rate of local excision of T1 and T2 rectal cancer is observed, despite the low level of evidence with controversial outcome[15]. Moreover, the incidence of T1 and T2 rectal cancer will most likely also increase in the near future[28]. The preceding warrants the need for more studies on the subject.

The aim of this study was to compare the impact of margin status prospectively, assessed with standardized pathology after TEM and TME for T1 rectal cancer.

Patients and methods

The Dutch TME trial started in 1996. Patients with mobile rectal cancer were randomly assigned either to short term preoperative radiotherapy followed by TME or to TME alone to determine whether the addition of preoperative radiotherapy increases the benefit of TME. The study protocol included standardized processing of the specimen, described in detail elsewhere[29]. In IJsselland hospital, a tertiary referral centre for TEM and participating in the Dutch TME trial, patients with T1 rectal cancer were also selected for TEM, amenable to the same study protocol,

completed with rigid rectoscopy and endorectal ultrasound. Eligibility for this study was in accordance with the Dutch TME trial protocol with some exceptions. Patients that underwent TME who had synchronous distant metastases, only discovered at laparotomy, were not excluded, because if TEM had been therapy of choice, the metastases would not have been disclosed. Furthermore, patients who previously underwent pelvic operations or resections of left-sided large bowel or rectum were not excluded. For TEM patients World Health Organisation Performance Score (WPS) was not a criterion (in the Dutch TME trial WPS limited to 2 or less was an inclusion criterion). TEM patients were only eligible if there were no signs of lymph node metastases and circumferential margins were complete.

If T1 rectal cancer was diagnosed preoperatively in IJsselland hospital, patients were offered both TEM and TME. If T1 rectal cancer only emerged at histology of the excised specimen, patients were offered follow-up only or additional TME. If margins were incomplete after TEM and it was decided for follow-up, TEM was repeated to obtain complete margins. The TEM technique is described in detail elsewhere[10].

Tumour size after TEM as well as TME was assigned as the largest diameter. TEM specimens were pinned onto a cork board before fixation. Fixation, serial transverse slicing, embedding, staining, sectioning and examination of the specimens were done according to descriptions detailed elsewhere[18, 29]. Both groups were followed according to the Dutch TME trial protocol also extensively described elsewhere [29]. Moreover, rigid rectoscopy and endorectal ultrasound were performed at every visit except for the colonoscopy visit in the TEM patients. Endpoints studied were morbidity, mortality, margin status, local recurrence, surgery for local recurrence, distant recurrence, overall survival and cancer specific survival. Local recurrence was defined as evidence of a tumour within the lesser pelvis. Distant recurrence was defined as evidence of a tumour in any other area. In all patients in this study informed consent had been obtained.

Data were analyzed with SPSS statistical software (version 14.0 for Windows, SPSS, Chicago). Chi-square tests were used to compare proportions. Mann-Whitney tests were used to compare continue variables. Univariate analyses of cumulative probability of local and distal recurrence, as well as overall and cancer-specific survival were carried out by the Kaplan-Meier method, and the evaluation of differences between the two groups was performed with the log-rank test. The Cox proportional hazards model was used to calculate hazard ratios and 95 per cent confidence intervals in the univariate and multivariate analyses. A two-sided P value of 0.05 or less indicated statistical significance.

Results

In the 1530 Dutch patients entered in the TME trial 76 patients with T1 rectal cancer were present (5 per cent). One patient was excluded because of a second malignancy. Seventy-five patients were eligible for this study. In 1 patient a R1 resection was performed (1.3 per cent). In 86 patients TEM was performed for T1 rectal cancer. In 5 patients excision was not complete (5.8 per cent). Six patients, including 2 patients with incomplete margins, chose for additional TME and were excluded. Eighty patients were entered in the study, including the remaining 3 patients with incomplete margins. TEM was repeated in these patients. Only fibrosis and no residual tumour tissue were found and it was considered a complete excision. Patient and tumour characteristics are depicted in Table 1. Both groups were comparable, except that TEM patients were in worse condition pre-operatively ($P < 0.001$). Operation characteristics are depicted in Table 2. TEM proved to be safer compared to TME reflected by operating time, blood loss, hospital stay, morbidity, re-operations and stoma formation (all factors $P < 0.001$). Complications after TEM were present in 5 patients (5.8 per cent). Three patients suffered from a urinary tract infection. One patient with a cardiac history suffered from cardiac pain and dysrythmia leading to medical treatment on cardiac care. In 1 patient after a segmental resection anastomotic stenosis with disabling complaint occurred. Hegar dilation proved unsuccessful resulting in renewed TEM for correction (1.2 per cent). Histology only showed fibrosis. After TME, 48 patients suffered from 72 complications (64 per cent). The majority was severe, leading to re-interventions in 13.3 per cent of all patients predominantly because of anastomotic leakage (6.9 per cent), re-bleeding (9.3 per cent) and ileus (6.7 per cent). In 58 patients a primary anastomosis was constructed, in two patients a Hartmann's procedure was performed and in 15 patients an abdomino-perineal excision. In 59 patients, a stoma was constructed at the original TME operation (78.7 per cent) including deviating ileostomies in 44 patients. A

Table 1. Patient and tumour characteristics of the patients enrolled in the study.

	TEM	TME	P
n	80	75	
Age (yrs)	71 (44-92)	67 (48-83)	ns
Female: male	32: 48	27: 48	ns
WPS : 0: 1: 2/3	42: 18: 20	60: 14: 0	0.001
Tumour diameter (cm)	3.0 (0.5-13)	2.5 (0.5-7.5)	ns
Tumour distance (cm)	8.0 (0-15)	7.0 (0-15)	ns
0-5	17	14	
5-10	44	34	
10-15	18	25	

WPS = World Health Organisation Performance Score; data given are numbers or medians with ranges between parentheses.

Table 2. Operation characteristics of the patients enrolled in the study.

	TEM	TME	P
Operating time (min)	40 (10-125)	180 (70-360)	< 0.001
Blood loss (ml)	0 (0-250)	1000 (50-15000)	< 0.001
Hospital stay (days)	3 (2-13)	14 (7-121)	< 0.001
Morbidity (%)	5 (5.1)	48 (64)	< 0.001
surgical complications			
abdominal wound dehiscence	0	1 (1.3)	
perineal wound dehiscence	0	1 (1.3)	
intestinal necrosis	0	1 (1.3)	
ileus	0	5 (6.7)	
anastomotic leakage	0	4 (6.9)	
re-bleeding	0	7 (9.3)	
other	1 (1.2)	3 (4)	
infections			
abdominal wound	0	8 (10.7)	
perineal wound	0	2 (2.7)	
urinary tract	3 (3.4)	10 (13.3)	
intra-abdominal abscess	0	2 (2.6)	
sepsis	0	4 (5.3)	
other	0	2 (2.6)	
febris e causa ignota	0	1 (1.3)	
general complications			
venous thrombosis	0	1 (1.3)	
pulmonary	0	6 (8)	
embolism	0	3 (4)	
cardiac	1 (1.2)	2 (2.6)	
other	0	7 (9.3)	
delirium	0	1 (1.3)	
multi organ failure	0	1 (1.3)	
Re-operations (%)	1 (1.2)	10 (13.3)	< 0.001
Stoma formation (%)	0	61 (81.3)	
at first operation	0	59 (78.7)	< 0.001
at re-operation	0	2 (2.6)	
Mortality (%)	0	3 (4.0)	0.07

Morbidity = number of patients with one or more complications; anastomotic leakage in 4 out of 58 patients with a primary anastomosis; data given are numbers or medians with ranges or percentages between parentheses.

stoma was constructed during re-operation in another 2 patients (2.6 per cent). Ten out of 44 deviating ileostomies have never been reversed and in 5 patients after reversal again a stoma was constructed resulting in 41 per cent of the TME patients having a definite stoma at the time of evaluation versus zero TEM patients. Mortality after TEM was 0 per cent and after TME 4 per cent.

Median follow up after TEM was 42 months (range 1-127) and after TME 84 months (range 30-115). At 5 years, local recurrence rate was 24 per cent after TEM compared to 0 per cent after TME (HR 79.266 (95 per cent confidence interval 1.208-5202), P < 0.0001; Figure 1). Overall survival was 75 per cent after TEM and 77 per cent after TME (HR 0.988 (95 per cent confidence interval 0.482-2.023), P = 0.973; Figure 2).

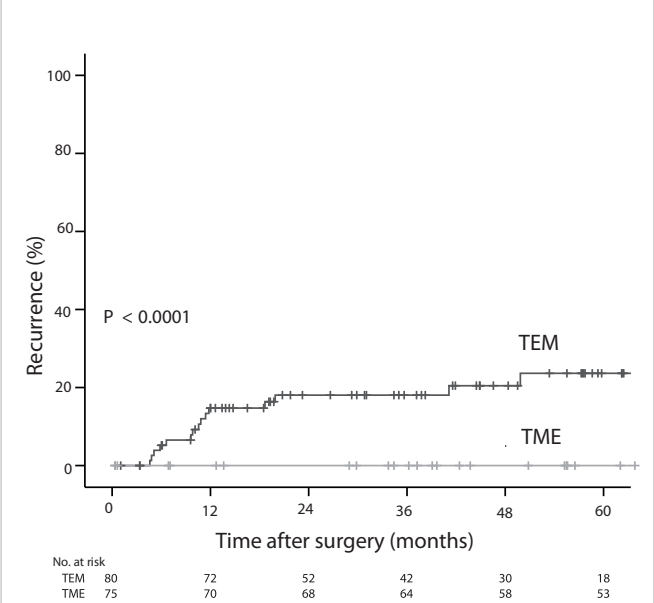

Figure 1. Local recurrence rates of patients after TEM and TME for T1 rectal cancer.

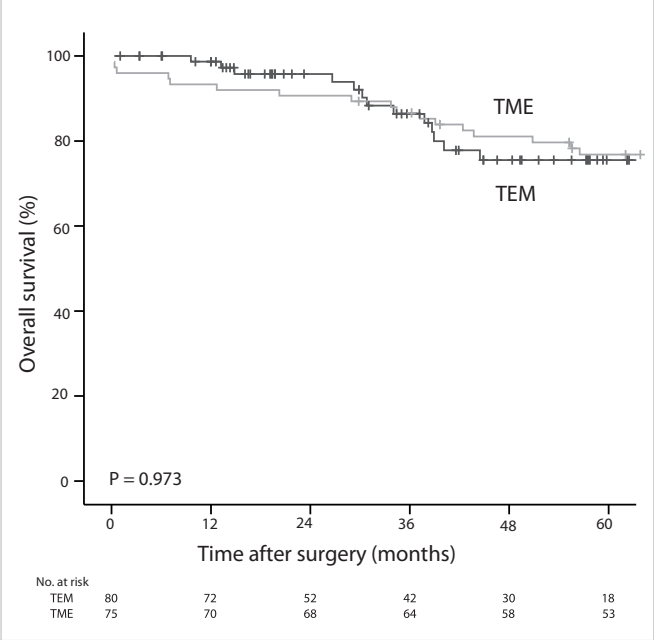

Figure 2. Overall survival of patients after TEM and TME for T1 rectal cancer.

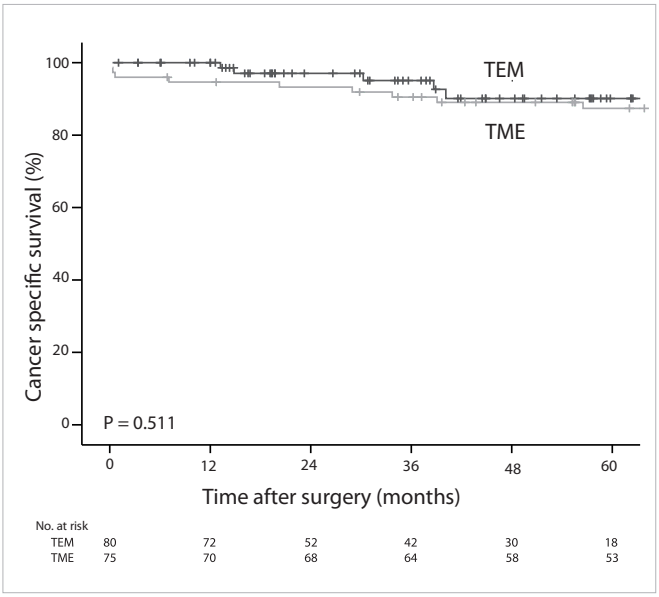

Figure 3. Cancer specific survival of patients after TEM and TME for T1 rectal cancer.

Cancer specific survival was 90 per cent after TEM and 87 per cent after TME (HR 0.691 (95 per cent confidence interval 0.230-2.080), P = 0.511; Figure 3). After TEM 15 local recurrences were observed of which 13 were diagnosed within the first 18 months (86.7 per cent), 1 at 42 months and 1 at 50 months (Table 3a). Median time to local recurrence was 10 months (range 5-50). In 12 patients (80 per cent) salvage surgery was performed, limited to TME, without mortality and without renewed local recurrences. Distant metastases developed in 6 patients (7.5 per cent). Median follow-up of this subgroup was 33 months (range 13-69) in which 5 patients died cancer-related (6.3 per cent). None of the TEM patients without local recurrence developed distant metastases or died cancer-related. After TME 6 patients developed distant metastases (7.9 per cent) and 9 patients died cancer related (11.8 per cent; Table 3b). Median follow-up of this subgroup was 20 months (range 0.3-57). No local recurrences were observed in the TME patients. In regard to both overall survival and cancer-specific survival, none of the following were risk factors for either: surgical technique used, age, gender or general condition.

A TME with primary anastomosis was performed in 3 of 6 patients that decided for additional TME after TEM, 1 patient had an abdomino-perineal excision, 1 received Hartmann's procedure and the last one an ileo-anal pouch anastomosis. There was no mortality. In all specimens no residual tumour tissue and complete margins were observed. Median time of follow up was 39 months (range 4-77). Neither local nor distant recurrences were observed.

Table 3a. Characteristics of local and distant recurrences after TEM for T1 rectal cancer.

Patient	Local recurrence	Time after TEM (months)	Therapy	TNM	Margins	Distant recurrences	Time after TEM (months)	Follow up (months)	Survival status
1	Yes	5	LAR	pT3N0	R0	-	-	16	A
2	Yes	5	APR	pT2N0	R0	-	-	34	DNCR
3	Yes	6	APR	pT2N0	R0	-	-	33	DNCR
4	Yes	7	LAR	pT2N0	R0	-	-	69	A
5	Yes	10	APR	pT3N0	R0	-	-	69	A
6	Yes	10	LAR	pT3N0	R0	-	-	16	A
7	Yes	11	LAR	pT3N1	R0	-	-	19	A
8	Yes	12	LAR	pT3No	R0	-	-	20	A
9	Yes	40	Cth, APR	pT0N0	R0	-	-	49	A
10	Yes	5	LAR	pT3N0	R0	Liver, lung	5	13	DCR
11	Yes	12	LAR, Cth	pT3N2	R1	Liver	27	39	DCR
12	Yes	19	Hp	pT2N0	R0	Liver	19	40	DCR
13	Yes	5	None	cT3	-	Liver	5	15	DCR
14	Yes	20	CTh	cT4	-	Liver	22	30	DCR
15	Yes	50	CTh	cT4	-	Lung	50	52	A

APR = abdomino-perineal resection; AR = anterior resection; Cth = chemotherapy; Hp = Hartmann's procedure; - = not applicable; p = pathological; c = clinical; R0 = microscopically radical; R1 = microscopically irradical; A = Alive; DCR = died cancer-related; DNCR = died not cancer-related.

Table 3b. Characteristics of local and distant recurrences after TME for T1 rectal cancer.

Patient	Local recurrence	Time after TME (months)	Type of re-operation	TNM Salvage surgery	Margins	Distant recurrences	Time after TME (months)	Follow up (months)	Survival status
1	No	-	-	-	-	No	0.3	0.3	DCR
2	No	-	-	-	-	No	0.4	0.4	DCR
3	No	-	-	-	-	No	0.6	0.6	DCR
4	No	-	-	-	-	Skin	5	7	DCR
5	No	-	-	-	-	Peritonitis carcin	0	20	DCR
6	No	-	-	-	-	Liver, bone	28	29	DCR
7	No	-	-	-	-	Liver, lung, brain	29	34	DCR
8	No	-	-	-	-	Liver	23	39	DCR
9	No	-	-	-	-	Lung	16	57	DCR

- = not applicable; A = Alive; DCR = died cancer-related; DNCR = died not cancer-related.

Discussion

Reduced morbidity and mortality compared to TME is often the motive for local excision in rectal cancer. After TME, morbidity varies from 10 to 62 per cent. Morbidity is often severe, especially if preoperative radiotherapy is added, with perineal wound

complications in 18 to 29 per cent, anastomotic leakage in 11 per cent, need for one or more re-operations in 14 per cent, creation of a (temporary) stoma in 53 to 60 per cent, genito-urinary dysfunction in 10 to 57 per cent and faecal incontinence in 38 to 62 per cent, having major impact on quality of life. Mortality after TME ranges from 3.3 to 25.8 per cent[1-6]. Morbidity ranges from 8.2 to 11.4 per cent after TEM. This morbidity is predominantly minor and temporary, occasionally leading to re-operation and formation of a stoma and without functional disorders having impact on quality of life. Mortality after TEM is negligible[7, 9-17, 30]. Morbidity and mortality in this study are in line with literature and unmistakably demonstrate the safety of TEM and the consequences of TME. This is accentuated all the more when considering the patients in the TEM group had worse conditions at the moment of operation.

However, choice for type of surgical treatment in curation of rectal cancer has to be based on more than differences in morbidity and mortality between 2 surgical options. It must as much hold an optimal limitation of cancer recurrence. With regard to latter, outcome after local excision of rectal cancer shows a confusing variety, even if limited to T1 rectal cancer. As a result, it is looked at with caution[8, 9, 11, 12, 14-17, 22-27, 31]. Therefore, it is presented as another alternative for treatment only in carefully selected patients, usually with low risk T1 rectal cancer, in accordance with many national guidelines[32, 33].

Microscopic completeness of excision is *conditio sine qua non* to limit recurrences after TME for rectal cancer. Standardized histological examination revealed a higher percentage of incomplete resection with significant correlation to an increased risk on both local and distant recurrences and on decreased survival. This resulted in the concept of TME and adjustment of histological examination of the TME specimen[1, 2, 18]. The application of this logical sequence of thoughts for the local excision of rectal cancer speaks for itself. In 1990 Graham concluded in his review that after local excision positive surgical margins were associated with an increased local recurrence rate and decreased survival[19]. And in case studies on TEM margin status has proven to be a predictor for recurrence as well[20, 21]. However, in studies comparing TE with TME or TEM with TME for T1 rectal cancer, the method of histological investigation remains unclear and the presence of incomplete or doubtful margins was not an exclusion criterion per se. Furthermore, analysis of their impact is blurred by variable use of other criteria for patient selection and subgroups of patients undergoing additional TME, radiation or chemo-radiation[8, 11, 14, 15, 22-27]. Moreover, limited pathological investigation can lead to misleading thoughts on complete excision also after local excision. Hanloser reports residual tumour tissue in 29 per cent of patients in additional TME specimens after prior TE. Additional TME was performed mainly for other reasons because incompleteness was the indication in only 9.6 per cent of the patients[34]. Vice versa standardized pathology can lead to a reduced rate of

complete excision. Free circumferential margins were only observed in 49 per cent after TE of T1 rectal cancer in the study by Steele[20]. Complete excision is still present in 91 per cent after TEM for mobile rectal cancer and with standardized pathology[35]. This ability of TEM to completely excise rectal tumours could account for the finding that after TEM for T1 rectal cancer, oncological outcome seems similar to TME[8, 11, 22, 24], whereas after TE, results can be inferior to TME[11, 14, 15, 23, 25-27]. Therefore, completeness of excision after standardized pathology after TEM for T1 rectal cancer as sole criterion needed to be investigated and was the point of departure for this study.

Regarding survival, no differences were found after TEM or TME, proving that after complete excision with TEM of T1 rectal cancer, survival remains untouched. This is in line with all other comparative studies of TEM and TME[8, 11, 22, 24]. However, contrary to a 100 per cent complete excision rate of all patients eligible for follow-up after TEM that was assessed with standardized pathology, local recurrence rate was 24 per cent in this study. This seems higher than the 4.1 to 10 per cent observed by other TEM centres[8, 11, 22, 24] and the 4 to 18 per cent after TE[11, 14, 15, 23, 25-27]. The question is if we are looking at real differences or variations within the same confidence interval in smaller and underpowered studies[17].

If rectal cancer is excised completely with TEM, the remaining mechanism for local recurrence is outgrowth of lymph node metastases, already present at operation but left behind because TEM is not capable of excising them as well. Their presence in T1 rectal cancer after radical excision is reported in 3 to 33 per cent. This large variety seems caused by the use of different criteria for tumour selection and by the use of different surgical techniques[16, 26, 34, 36-41]. Furthermore, preoperatively determining the presence of lymph node metastases has proven to be difficult. Endorectal ultrasound, computed tomography and magnetic resonance imaging show very limited value in detection[16, 42, 43]. This gave cause to study histological criteria to predict their presence. Favourable criteria would be associated with little risk on lymph node metastases and therefore little risk on local recurrence. Apart from T-stage and margin status, mostly age, diameter, distance, fragmentation, histological grading, lymphovascular invasion and level of submucosal invasion have been investigated. Probably for the same limitations regarding tumour selection and surgical technique used, mutually divergent and conflicting results are described[11, 16, 21, 26, 34, 36-41, 44, 45]. Nevertheless, the addition of combinations of favourable criteria is recommende in reviews and national guidelines[9, 12, 16 , 17, 32, 33]. Perhaps molecular analysis of biopsies could break new ground. The level of caspase-3 activity in biopsies has shown to be a predictor for local recurrence after TME and should be evaluated after TEM for rectal cancer as well[46]. Recently, we described 5 specific chromosomal and genomic events discriminating rectal adenomas from carcinomas and 1 event that could be

related to the presence of lymph node metastasis, reproducible in biopsies. Clinical validation is an urgent step to take[47, 48].

Focussing on prevention of local recurrence after local excision of rectal cancer is caused by the fact that local recurrence after radical excision is difficult to treat with many renewed local recurrences and with poor prognosis[49]. Anecdotal cases show that additional radical excision within 30 days in patients at possible high risk for local recurrence after local excision seems to avoid local recurrences; seem to not compromise oncological outcome; and could be used as a treatment option once subgroups of patients with increases risk on local recurrence can be identified adequately[21, 34]. Literature on salvage surgery for local recurrence after local excision is very limited. It only concerns TE as technique used. Results seem mediocre because extensive surgery is sometimes needed with the presence of renewed recurrences and poor survival[9, 16, 23, 44, 50-52]. No studies addressing the same topic with TEM as surgical technique so far have been published[12]. Salvage surgery is only mentioning oblique as uncomplicated and without renewed recurrences. In this study, salvage surgery was indicated in 12 patients. In all patients, excision along the mesorectal fascia was possible without the need for excision of adjacent pelvic organs. Excision was complete in all but 1 patient. Never renewed local recurrences were observed. Maybe the elegant and precise technique of TEM is the key element for this difference[10]. Or perhaps it was the early detection due to the intensive follow-up. About 90 per cent of recurrences were diagnosed within 18 months. Moreover, about 25 per cent of the local recurrences were diagnosed only with endorectal ultrasound as described by others[16, 53]. In 3 patients, no salvage surgery was performed. One patient (nr 13; Table 3a) had an early recurrence at 5 months with concomitant diffuse liver metastasising. Retrospectively it was assumed to be an adenoma preoperatively. Postoperatively no analysis after possible local and distant metastases had been performed. Given the time frame, the metastases were most probably already present at the time of TEM. One patient (nr 14; Table 3a) was not followed intensively according to the protocol. Earlier detection could have possibly improved treatment options. One patient (nr 15; Table 3a) was followed intensively, but local recurrence was located presacrally at the level of the promontory. Therefore currently additional magnetic resonance imaging of the lesser pelvis is performed at 1, 2 and 3 years.

In stage III rectal cancer, short-term radiotherapy has shown to be beneficial in contrast with stage I[2]. After 40 Gy radiotherapy and TME, fewer patients with stage III rectal cancer are observed[54]. Contact radiotherapy alone with 80 to 100 Gy is reported to achieve adequate local control in T1 rectal cancer[55, 56]. Possible positive effects combining local excision and postoperative radiotherapy have been reported[26, 57, 58]. Preoperative radiotherapy and TEM is reported to be successful too[59]. Promising re-

sults of neo-adjuvant chemoradiation in mobile rectal cancer with downstaging or even complete remission are described[60-63]. Within the group of patients with local recurrence in this study 2 patients were treated with neo-adjuvant chemoradiation. Complete response was observed in 1 patient (nr 9; Table 3a).

Conclusions

TEM is much safer than TME for T1 rectal cancer. Survival rates of these 2 techniques are of equal standing. After TEM local recurrence rate is substantial, but its appearance is difficult to predict and its impact is difficult to assess. Salvage surgery is possible and (neo-) adjuvant treatment seems effective and mandatory. Future studies are needed to research these issues in an effort to spare as many patients as possible from the adverse effects of TME.

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Chapter 8

Quality of life after transanal endoscopic microsurgery and total mesorectal excision in early rectal cancer

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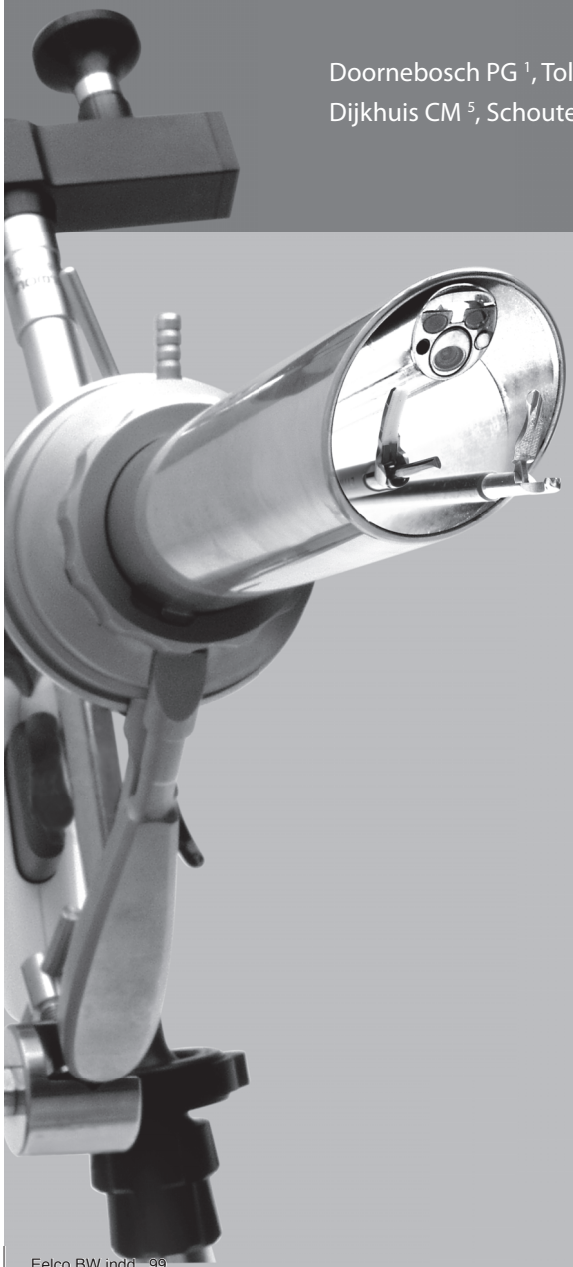

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Introduction

Surgery for rectal cancer remains the only treatment modality offering a chance of cure. From the oncological point of view total mesorectal excision (TME) is the gold standard. This standardized and optimized surgical technique has lowered the recurrence rates and probably improved survival[1-5]. Sphincter-saving procedures are preferred, even in very distal rectal carcinomas, in which low coloanal anastomosis or intersphincteric techniques are used[6-8].

Unfortunately, most patients suffer adverse consequences from such radical surgery. The operative dissection of the rectum may damage the pelvic autonomic nerves, disturbing bladder and sexual function[9-11]. The closer the anastomosis is to the anal canal, the worse the surgical and functional outcomes are[12, 13]. Furthermore, construction of a permanent colostomy following abdominoperineal resection may be associated with clinically significant psychological problems[14]. Finally, especially in the elderly, mortality after TME is substantial[15, 16].

In an attempt to avoid the morbidity and mortality of TME, local excision has been considered a therapeutic option in the treatment of well-selected patients with early rectal cancer. Several techniques have been developed of which transanal excision according to Parks, transsphincteric (or York-Mason) excision, transsacral (or Kraske) excision, and transanal endoscopic microsurgery (TEM) are the techniques most described[17-23].

Points of discussion after local excision for early rectal cancer include the wide range of local recurrence rates from 0 to 24 per cent, its impact on survival and the results of salvage surgery[24-27]. In the studies regarding TEM for T1 rectal cancer local recurrence rates are low and survival comparable to radical surgery[28-31]. In performing TEM a rectoscope with a diameter of 4 centimetres is used which may cause sphincter dysfunction. Manometry may show internal sphincter dysfunction but this is temporary[32].

Quality of life is increasingly recognized as a crucial factor when assessing clinical outcomes after different surgical interventions because it measures the patient's perspective[33-35]. If oncological outcome is the same in early rectal cancer after TEM and TME, quality of life becomes the key factor in clinical decision making. Quality of life after TEM has been little studied. A recent report found no significant alterations in faecal continence or quality of life after TEM[36].

In this study we present an analysis of quality of life after TEM for T1 carcinomas compared with a sex- and age-matched sample of patients with T+N0 rectal cancer after sphincter saving surgery with TME and a sex- and age-matched sample of healthy persons.

Patients and methods

A consecutive series of 54 patients having TEM for a T1 carcinoma was studied. All patients underwent surgery at IJsselland Hospital between 1996 and 2003. Patients were analysed according to a standard protocol. The technique of TEM has been extensively described in an earlier report[37]. Patients who underwent immediate radical surgery and patients with proven local or distant recurrences were excluded. Validated questionnaires were sent to eligible patients. All results were compared with a sex- and age-matched sample of patients obtained from a consecutive series of 111 patients who had undergone curative (R0) sphincter saving surgery for stage I and II rectal cancer by TME between 1997 and 2002 at a university centre and 2 district hospitals. None of these patients had a diverting ileostomy and all were disease-free at the time of evaluation. Both groups were compared with a sex- and age-matched community based sample of healthy persons.

The EuroQol EQ-5D, EQ-VAS and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-CR38 cancer specific questionnaires were used. The EuroQol EQ-5D consisted of a so-called 'index score' that represents 'the societal value' of the health state, and a visual analogue scale. The EQ-VAS represented the patient perspective. Regarding patients' quality of life and social perspective, both groups were compared with a sex- and age-matched control group of healthy persons[38]. Disease-specific quality of life after TEM and TME was measured according to the official scoring procedures for the EORTC QLQ-C30 and EORTC QLQ-CR38 questionnaires.

The EORTC QLQ-C30 was developed to assess the quality of life of cancer patients. It contains 30 items that can be computed in 5 functional scales (physical, role, emotional, cognitive and social functioning), 3 symptom scales, and 6 single items (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulties)[39]. EORTC QLQ-CR38 was designed especially for the evaluation of colon cancer therapy from a patient perspective[40]. It is subdivided into 2 functional scales (body image and sexual functioning), 7 symptom scales (micturition problems, gastrointestinal tract symptoms, chemotherapy side effects, defaecation problems, stoma related problems and male and female sexual problems), and 3 single-item measures (sexual enjoyment, weight loss and future perspective). The validity and reliability of these questionnaires have been established in Dutch patients with colorectal cancer. In both QLQ-C30 and the QLQ-CR38 scores are summed within scales from 0 to 100. A higher score indicates better functioning for all functioning scales and for 2 of the single items including sexual enjoyment and future perspective. A higher scale on all symptom scales and the remaining single item (weight loss) indicate a lower level of symptomatology[41].

Statistical analysis

When appropriate, patient groups were compared using the χ^2 test or Fisher's exact test. Continuous variables were compared using the Mann-Whitney U-test. Comparisons between groups were also performed, using ANOVA, allowing for gender, age and time of follow-up. A P-value < 0.05 was considered statistically significant.

Results

Of the original group of 54 patients, 18 could not be included. Eleven had died during follow-up, 3 due to disease-related causes (all local recurrence and distant metastasis). Three patients were excluded because of local recurrence, and 1 because of distant recurrence. One patient was excluded because a right hemicolectomy was performed. Two patients could not be contacted as they had moved abroad and their new address was not available.

The questionnaires were sent to the remaining 36 patients. Thirty-one questionnaires were returned, resulting in an overall response rate of 86 per cent. Of the respondents, 18 of which were male, and the median age was 71 years (range 46-90). In the TME group, 31 patients were included, 18 of which were male, and the median age was 70 years (range 51-87 years).

Patient and tumour characteristics of both groups are represented in Table 1. The median time interval between the operation and the mailing was 28 months (range 5-91). From the patient perspective, mean general quality of life score (EQ-VAS) was similar after TEM, TME and controls (Table 2). From the social perspective, the mean EQ-5D index score did not differ between the 3 groups. Scores of the EORTC QLQ-CR30 (Table 3) showed no difference in any of the variables. The EORTC QLQ-CR38

Table 1. Baseline characteristics of the 31 TEM responders, compared with 31 age- and sex-matched patients after TME.

	TEM	TME
n	31	31
Male : female (%)	58 : 42	58 : 42
Age (yrs)	71 (46-90)	71 (51-87)
Length of follow-up (mths)	31 (5-91)	39 (9-62)
Tumour stage		
T1	31 (100)	3 (10)
T2		8 (26)
T3		20 (64)
Preoperative radiotherapy	0	6 (18)
Co-morbidity	6 (19)	6 (19)

TEM = transanal endoscopic microsurgery, TME = total mesorectal excision; data are numbers or percentages or median numbers with ranges or percentages in parentheses.

Table 2. General quality of life scores.

	TEM	TME	General population
EQ-VAS	76 (20-100)	70 (30-100)	76 (68-84)
EQ-5D	81 (-18-100)	76 (26-100)	76 (67-86)

EQ-VAS = Quality of life from the patient perspective; EQ-5D = Quality of life from the social perspective; TEM = transanal endoscopic microsurgery; TME = total mesorectal excision; general population = a sex- and age-matched, community-based sample of healthy persons without co-morbidity; data are mean scores with ranges in parentheses.

(Table 4) showed a significant difference between the 2 groups regarding defaecation problems. TEM patients had less defaecation problems than TME patients ($P < 0.05$). A trend towards better sexual functioning after TEM was seen, especially in male patients, although it did not reach statistical significance.

Discussion

The aim of surgical treatment of rectal cancer is to remove the primary lesion with an adequate margin of normal tissue with as much of the lymphatic drainage as possible. The risk of lymph node metastases depends on pathological criteria including depth of tumour infiltration and histological grading. According to this, when the tumour only invades the submucosa (pT1), lymph nodes are involved in 3 to 14 per cent of patients[42, 43]. Thus patients with minimally invasive histological favourable lesions are suitable for local excision alone. Nevertheless there is concern regarding the oncological outcome after local excision for early rectal cancer[25, 26, 44]. After transanal excision followed by local recurrence the role of salvage surgery is uncertain[27].

The main problem when reviewing the literature on local excision for early rectal cancer is the diversity of techniques used and the variation in patient selection. Compared with other local techniques, TEM has emerged as the method of choice for T1 early rectal cancer as it yields lower recurrence rates[45]. Moreover, results comparable to radical surgery can be achieved with TEM[28, 29]. Nevertheless, definite evidence for the justification of TEM in T1 disease is still lacking. When TEM is considered a therapeutic option, this should be discussed in detail with the patient before obtaining consent.

It seems reasonable to assume that quality of life after local excision using the TEM technique is better than after radical resection. However, no prospective trial has been initiated to investigate this. After radical surgery, several studies have shown that functional results, especially bladder and sexual functioning, are often impaired[9-11].

Table 3. Disease specific quality of life scores (EORTC QLQ-C30).

	TEM		TME	
	mean	median (range)	mean	median (range)
Physical function	78	87 (0-100)	83	90 (20-100)
Role function	81	100 (0-100)	80	83 (0-100)
Emotional function	82	92 (0-100)	82	92 (17-100)
Cognitive function	84	100 (0-100)	86	100 (17-100)
Social function	60	67 (0-100)	69	67 (0-100)
Global health status	73	83 (33-100)	74	75 (17-100)
Fatigue	76	89 (0-100)	80	81 (11-100)
Nausea/vomiting	90	100 (0-100)	95	100 (17-100)
Pain	80	100 (0 -100)	89	100 (0 -100)
Dyspnoea	87	100 (0-100)	87	100 (0-100)
Sleep disturbance	76	100 (0-100)	82	100 (0-100)
Appetite loss	93	100 (33-100)	97	100 (33-100)
Constipation	93	100 (33-100)	85	100 (0-100)
Diarrhoea	86	100 (0-100)	89	100 (0-100)
Financial worries	94	100 (33-100)	94	100 (0-100)

A high subscale score indicates low distress and good functioning; TEM = transanal endoscopic microsurgery; TME = total mesorectal excision; all not significantly different.

In the present study, quality of life after TEM is compared to radical resection. To our knowledge this is the first study to address this subject. Although retrospective and hence limited, several useful findings have been identified. After both TEM and TME patients have ranked their quality of life as high as that in the population-based reference group. Moreover, quality of life was no different between TEM and TME patients. This finding might be due to methodological shortcomings of the study design including its retrospective nature, the relatively small number of patients and the lack of assessment before treatment. Another explanation could be the fact that several patients were only diagnosed to have a carcinoma after the TEM procedure. At that point patients are offered the choice between an additional TME and follow-up. When the patient chooses follow-up the rectum is re-examined every 3 months by digital rectal examination, rigid rectoscopy and endoanal ultrasound. This may heighten the feeling of being at risk for local recurrence with an impact on quality of life. Furthermore, the relatively high quality of life observed among our patients after TME might be explained by the fact that the measurement followed the diagnosis of a life-threatening disease, which may have changed their perceptions of their expectations and priorities with regard to life fulfilment. Successful treatment therefore might result in a higher quality of life as reported by the patient. This effect, known as 'rejoice', has been noted from the beginning of quality-of-life research[46].

Table 4. Disease specific quality of life scores (EORTC QLQ-CR38).

	TEM		TME	
	mean	median (range)	mean	median (range)
Micturition problems	79	77 (22-100)	81	78 (44-100)
Gastrointestinal problems	81	87 (33-100)	80	80 (40-100)
Weight loss	92	100 (33-100)	94	100 (33-100)
Body image	90	100 (44-100)	88	100 (0-100)
Defaecation problems	91	90 (57-100)*	77	80 (47-100)*
Stoma problems	-	-	-	-
Chemotherapy side-effects	89	100 (22-100)	90	89 (22-100)
Sexual function	27	17 (0-100)	24	17 (0-83)
Sexual enjoyment	61	67 (0-100)	53	67 (0-100)
Male sexual problems	62	83 (0-100)	46	42 (0-100)
Female sexual problems	89	92 (33-100)	81	83 (33-100)
Future perspective	71	67 (0-100)	72	67 (0-100)

A high subscale score indicates low distress and good functioning; TEM = transanal endoscopic microsurgery; TME = total mesorectal excision; * $P < 0.05$.

Functional outcome after major rectal surgery is frequently impaired. Most studies report a sustained reduction in resting sphincter pressure after sphincter-saving surgery with TME. However, there is strong evidence that direct sphincter trauma is not a major cause for dysfunction. Several manometric studies have suggested neurogenic injury rather than morphologic damage as the explanation for post-operative functional disorder[47]. The changes in resting sphincter pressure during restorative proctocolectomy with either handsewn or stapled anastomosis have been studied[48]. In both techniques the resting pressure was reduced in a sequential manner during the surgical procedure, with an immediate decrease in pressure after division of the superior rectal artery, a further reduction after full mobilization of the rectum, followed by another equally large drop at the final stage after construction of the anastomosis by either technique.

Because of the 4 cm diameter of the rectoscope, continence following TEM is a concern. Although a significant decrease in both anal resting and squeeze pressure occurs initially, these return to preoperative values at a mean of 4 months after TEM[32, 36, 49]. A possible explanation might be that TEM preserves the neural autonomic pathways regulating sphincter tone. In the present study after TEM patients had significantly fewer defaecation problems, as found with the EORTC QLQ-CR38 questionnaire. In a recent study a correlation between alterations of the anal sphincters and the functional outcome was not demonstrated[50]. Thus the question arises whether postoperative compliance and sensory perception are the determining functional factors. It is well known that the functional outcome after low anterior resection improves with time. It has been shown that this is associated with an increase of

compliance[51-53]. The better functional outcome in TEM patients may be due to the fact that the rectum remains unaffected. Several authors have suggested that radiation to soft tissues of the pelvis worsens postoperative neorectal function[54]. In the present study, only 18 per cent of TME patients had preoperative radiotherapy. This low percentage might mitigate the differences in functional outcome in this study.
Sexual problems after radical surgery for rectal cancer are common, and efforts to prevent and treat it should be increased[9]. In our study there was a trend towards better sexual function after TEM especially in male patients; although it did not reach statistical significance.
On the basis of this study, despite its methodological shortcomings, it can be concluded that there is no difference in impact on quality of life after TEM and TME. Defaecation problems after TEM are less frequent than after TME. This difference could play a role in the choice of surgical therapy for early rectal cancer.

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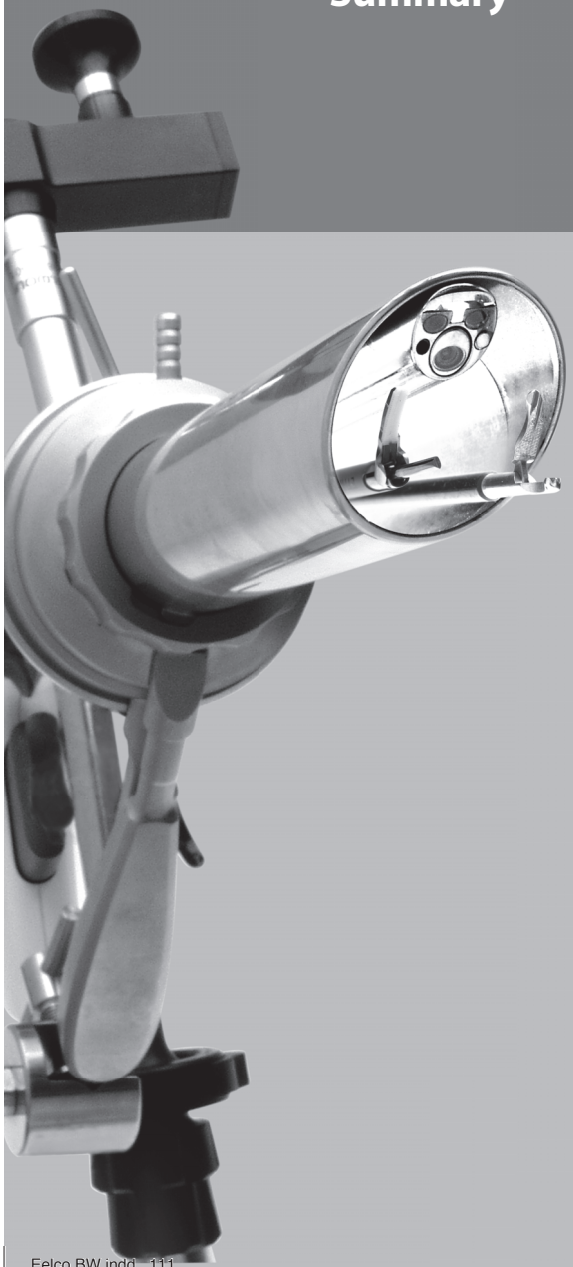
Chapter 9

Summary



Summary

Chapter 1 provides a general introduction and a review of the relevant literature on transanal endoscopic microsurgery (TEM). A number of surgical techniques have been implemented to remove rectal tumours locally. TEM is a newly developed, minimally invasive technique for that purpose. Its place among surgical techniques needs to be more clearly defined.
Local excision of rectal tumours is associated with low mortality and morbidity, making it the preferred choice in rectal adenomas (RA) and for palliation of rectal cancer (RC). Transanal excision (TE) is used for a fairly long time. However, its use is limited to smaller tumours in the distal and mid-rectum and the recurrence rates in RA are substantial. Other local techniques are technically demanding and seem less safe and without added value. This can explain their limited use.
Due to the technical characteristics of TEM, an excellent and stable view is obtained, also of larger and more proximal tumours in the rectum. TEM seems as safe as TE and to prevent a laparotomy more frequently compared with TE. After TEM, the excised specimens almost always have clear margins, in contrast to the specimens after TE. In RA, TEM results in hardly any recurrences. Due to the possibilities, TEM can also be adequately used for palliation of RC. The results following TEM for RC with curative intention are promising but they are only described anecdotically.
It is concluded that TEM is an elegant technique with excellent results. It is slowly but surely gaining its place in the surgical armamentarium and imposes itself as a method of choice for the local excision of RA and of RC for palliation. Proper judgement of literature is impeded by a lack of scientific argumentation.

In **chapter 2**, the aim of the thesis is presented.

In **chapter 3**, the results after TE and TEM for RA are compared. So far, this has been compared sparsely and with unclear results. We investigated 2 matched groups of RA after TE and TEM.
From 1990 to 2007 43 RA were excised with TE in 40 patients and 216 RA excised with TEM in 208 patients, matching for diameter and distance.
Operation time was longer after TE compared to TEM (47.5 minutes versus 35 minutes; $P < 0.001$). Morbidity after TE was 10 per cent and after TEM 5.3 per cent ($P < 0.001$). Mortality after TE was 0 per cent and after TEM 0.4 per cent ($P = 1.0$). Clear margins of the excised specimen were observed in 50 per cent after TE and 88 per cent after TEM ($P < 0.001$). Fragmentation of the excised specimen was observed in 23.8 per cent after TE and 1.4 per cent after TEM ($P < 0.001$). In cases of fragmentation after TE, unclear margins were observed more frequently (one fragment and

unclear margins 35.5 per cent versus fragmented and unclear margins 90 per cent; P = 0.003). After TEM, this was 11.7 per cent and 33.3 per cent, respectively (P = 0.32). Local recurrence rate after TE was 23.3 per cent and after TEM 3.7 per cent (P < 0.001). After TE, RA with clear margins had a local recurrence rate of 0 per cent, compared to 47.4 per cent after unclear margins (P < 0.001) and after TEM the local recurrence rates were 3.2 and 7.7 per cent (P = 0.3), respectively. Independent of the part of the rectum, local recurrences after TEM were observed less frequently (P < 0.001).
It is concluded that TEM is superior to TE of RA and should be the method of choice for local excision of RA.

In **chapter 4**, feasibility of TEM for RA is investigated. TEM for RA is safe with low recurrence rates. However, no data are available on feasibility of TEM in RA throughout the entire rectum. We investigated this in a prospective study.
From 1996 to 2007 353 consecutive RA in 342 patients were evaluated according to a standard protocol. TEM was intended in all RA.
Median tumour diameter was 3 cm and median distance from the dentate line 8 cm. The peritoneum was opened peroperatively without any adverse effects in 8.7 per cent. Conversion rate was 9.6 per cent (alternative local procedure 4.2 per cent, transabdominal procedure 5.4 per cent). Conversion rate correlated with distance (P = 0.007) and degree of experience of the operating surgeon (P = 0.004). Median operation time was 45 minutes and correlated with specimen area, operating surgeon and degree of experience of the operating surgeon (all P < 0.001). It did not correlate with distance. Clear margins were observed in 85 per cent. RA with unclear margins were larger (P < 0.001) and were located more proximal (P < 0.001). Morbidity was 7.8 per cent and mortality 0.6 per cent. Median hospital stay was 4 days. Median follow-up was 27 months. Recurrence rate at 3 years was 9.1 per cent. Median time from operation to recurrence was 12 months (range 4-54). Margin status was a predictor for recurrence (clear margins: 6.1 per cent versus unclear 25.2 per cent; P < 0.001).
It is concluded that TEM is safe and feasible for RA throughout the entire rectum. Opening of the peritoneum can occur but does not have any impact on morbidity and does not lead to conversion. Especially with increasing experience conversion rate is limited. Recurrence rate is low, especially after clear margins. In our opinion TEM should be the method of choice for local excision of all RA.

In **chapter 5**, faecal continence and quality of life before and after TEM are investigated. TEM is performed via a rectoscope with an outer diameter of 4 cm, introduced transanally. The impact on faecal continence and quality of life is unknown. We investigated this in a prospective study.

Between 2004 and 2006, 47 patients were studied prior to and at least 6 months after TEM. Faecal continence was determined using the Faecal Incontinence Severity Index. Quality of life was measured using the EuroQol EQ-5D questionnaire and the Faecal Incontinence Quality of Life score. Six months after surgery, median Faecal Incontinence Severity Index score was found to be decreased ($P < 0.01$), depicting an improvement in faecal continence. This improvement was most significant in tumours within 7 cm from the dentate line ($P = 0.01$). From the patients' perspective, post-operative quality of life was found to be higher ($P < 0.02$). A significant improvement was observed in 2 of the 4 Faecal Incontinence Quality of Life score domains: Embarrassment ($P = 0.03$) and Lifestyle ($P = 0.05$). The domains of Lifestyle, Coping/behaviour and Embarrassment were correlated with the Faecal Incontinence Severity Index (all $P < 0.05$).
It is concluded that TEM has no deteriorating effect on faecal continence. Moreover, once the tumour has been excised using TEM, quality of life is improved.

In **chapter 6**, feasibility of TEM in mobile RC is investigated.
From 1996 to 2001, TEM was performed in 76 patients with 76 rectal cancers: in 20 patients for palliation, 56 patients because at biopsy an invasive cancer was not present.
Median operation time was 75 minutes and mean blood loss a few cc. Operation time correlated with tumour area ($P < 0.001$) and depth of infiltration ($P < 0.001$) and not with distance ($P = 0.15$). In 13 patients, we encountered peroperative problems (17 per cent). All could be corrected without the need for conversion. Median hospital stay was 4 days. Mortality was 1.3 percent. Fifteen patients experienced 16 post-operative complications (19.7 per cent). In 13 patients, complications were mild and treated conservatively (17.1 per cent). In 2 patients, a severe complication occurred, needing re-operation with construction of a protective stoma (2.6 per cent). Post-operative histology showed *in situ* cancer in 32 tumours, T1 cancer in 21 tumours, T2 cancer in 18 tumours, and T3 cancer in 5 tumours. Margins of the excised specimens were clear in 91 per cent of RC. RC with unclear margins were significantly larger (9 versus 24 cm^2; $P = 0.03$). Numbers of patients per T stage and length of follow-up were too limited for adequate estimation of recurrence rates and survival.
It is concluded that TEM is capable of excision of mobile RC. It can therefore be used for palliation. This study also demonstrates that biopsies are not sufficient to assess the nature of rectal tumours, referred for TEM. The question on the use of TEM for curative treatment of RC could not be answered .

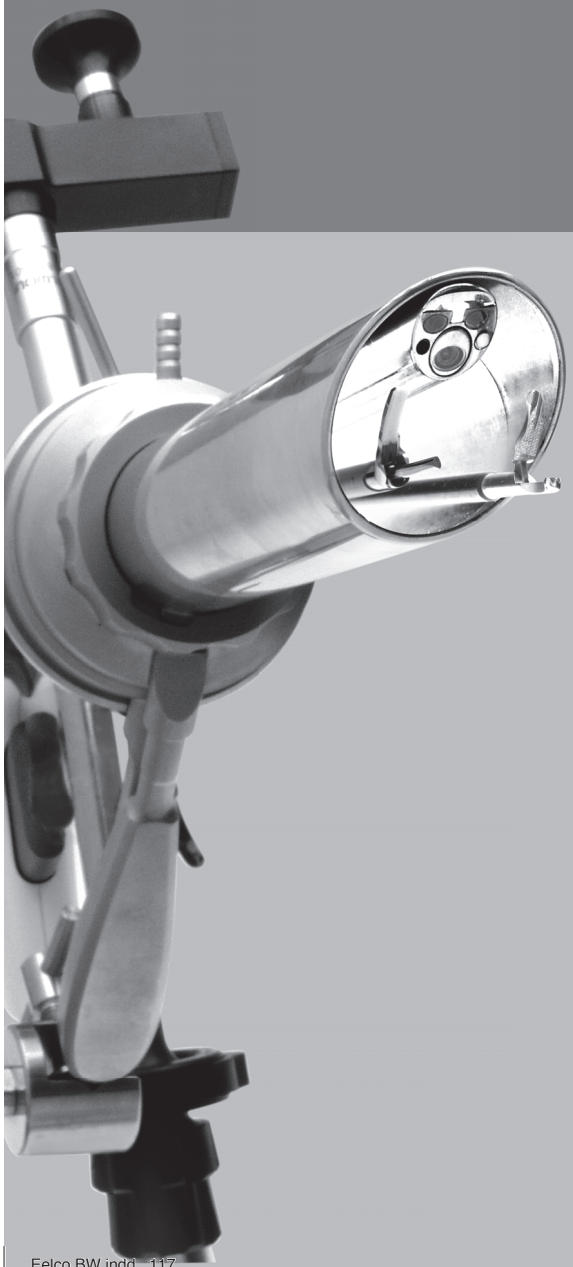
In **chapter 7**, oncological outcome after TEM and total mesorectal excision (TME) for T1-RC is investigated. After TME for RC, pathology is standardized with margin

status as a predictor for recurrence. This has yet to be implemented after TEM and was investigated prospectively for T1-RC.
Eighty patients after TEM were compared to 75 patients after TME. The study protocol included standardized pathology. TEM patients were eligible when circumferential margins were complete. TEM was safer than TME as reflected by operating time, blood loss, hospital stay, morbidity, re-operation rate and stoma formation (all factors $P < 0.001$). Mortality after TEM was 0 per cent and after TME 4 per cent. At 5 years after TEM and TME, both overall survival (TEM 75 per cent versus TME 77 per cent, $P = 0.973$) and cancer specific survival (TEM 90 per cent versus TME 87 per cent, $P = 0.511$) were of equal standing. Local recurrence rate after TEM was 24 per cent and after TME 0 per cent ($P < 0.0001$).
It is concluded that for T1-RC TEM is much saver than TME. Survival rates of these 2 techniques are of equal standing. After TEM local recurrence rate is substantial, but its appearance is difficult to predict and its impact is difficult to assess. Salvage surgery is possible and (neo-) adjuvant treatment seems effective and mandatory. Future studies are needed to research these issues in an effort to spare as many patients as possible from the adverse effects of TME.

In **chapter 8**, faecal continence and quality of life after both TEM and TME are investigated. TME is the gold standard in RC when curation is intended. TEM is a much safer technique and might be considered as an alternative, assuming that oncological outcome is comparable. The impact of both procedures on quality of life has never been compared. In this study, we compared quality of life after TEM and TME.
Fifty-four patients underwent TEM for T1-RC. Only patients without known locoregional or distant recurrences were included, resulting in 36 eligible patients. The questionnaires used included the EuroQol EQ-5D, EQ-VAS, EORTC QLQ-C30 and EORTC QLQ-CR38. The results were compared with a sex- and age-matched sample of T+N0 RC patients who had undergone sphincter saving surgery by TME and a sex- and age-matched community-based sample of healthy persons.
Thirty-one patients after TEM returned completed questionnaires (overall response rate 86 per cent). Quality of life was compared with 31 TME patients and 31 healthy controls. From the patients' and social perspective quality of life did not differ between the 3 groups. Compared with TEM, significant defaecation problems were seen after TME ($P < 0.05$). A trend towards worse sexual functioning after TME, compared to after TEM, was seen, especially in male patients.
It can be concluded that TEM and TME for RC do not seem to differ in quality of life postoperatively, but daefecation disorders are more frequently encountered after TME. This difference could play a role in the choice of surgical therapy in RC, however, further studies are needed to confirm our findings.

Chapter 10

Samenvatting



Samenvatting

Hoofdstuk 1 vormt de algemene inleiding en geeft een literatuur overzicht over transanale endoscopische microchirurgie (TEM). Een aantal chirurgische technieken worden gebruikt voor de locale excisie van rectum tumoren. TEM is een nieuw ontwikkelde, minimaal invasieve techniek voor die reden. Haar plaats dient gedefinieerd te worden.
Locale excisie van rectum tumoren gaat gepaard met lage morbiditeit en mortaliteit. Daardoor is zij de methode van keuze voor rectum adenomen (RA) en voor de palliatie van rectum carcinomen (RC). Transanale excisie (TE) wordt van oudsher gebruikt. Echter, TE is slechts toepasbaar op kleinere tumoren in het distale en middelste deel van het rectum en het recidief percentage voor RA is fors. Alternatieve locale technieken zijn moeilijker en lijken minder veilig en geen toegevoegde waarde te hebben. Dit kan hun beperkte gebruik verklaren.
Als gevolg van de technische karakteristieken van TEM wordt een duidelijk en stabiel beeld verkregen, ook van grotere en meer proximaal gelegen tumoren. TEM lijkt even veilig als TE en veel vaker een laparotomie te voorkomen dan TE. Na TEM is er bijna altijd sprake van vrije snijvlakken in tegenstelling tot de snijvlakken na TE. Het resultaat is dat na TEM voor RA zeer weinig recidieven worden gezien. Door haar mogelijkheden kan TEM ook goed gebruikt worden voor de palliatie van RC. De resultaten na TEM voor RC met een curatieve intentie zijn veelbelovend maar zijn slechts zeer beperkt beschreven.
De conclusie is dat TEM een elegante techniek is met zeer goede resultaten. Zij verovert haar plaats in het chirurgische armamentarium langzaam maar zeker en dringt zich op als therapie van keuze voor de locale excisie van RA en voor de palliatie van RC. Een goede beoordeling van de literatuur wordt belemmerd door een gebrek aan wetenschappelijke bewijsvoering.

In **hoofdstuk 2** wordt het doel van het proefschrift beschreven.

In **hoofdstuk 3** worden de resultaten na TE en TEM voor RA vergeleken. Tot nu toe is dit weinig gedaan en met onduidelijke resultaten. Wij onderzochten 2 bij elkaar passende groepen van RA na TE en TEM.
Van 1990 tot 2007 werden 43 RA geëxcideerd met TE bij 40 patiënten en 216 RA geexcideerd met TEM bij 208 patiënten, met een vergelijkbare diameter en afstand.
De operatie tijd was langer na TE vergeleken met TEM (47.5 minuten versus 35 minuten; $P < 0,001$). De morbiditeit na TE was 10 procent en na TEM 5.3 procent ($P < 0,001$). De mortaliteit na TE was 0 procent en na TEM 0,4 procent ($P = 1,0$). Vrije snijvlakken van het resectie preparaat werden in 50 procent na TE en in 88 pro-

cent na TEM gevonden (P < 0,001). Fragmentatie van het resectie preparaat werd in 23.8 procent na TE en in 1.4 procent na TEM gevonden (P < 0,001). In het geval van fragmentatie na TE, werden niet-vrije snijvlakken vaker gevonden (1 stuk en niet-vrije snijvlakken 35.5 procent versus gefragmenteerd en niet-vrije snijvlakken 90 procent; P = 0,003). Na TEM betrof dit respectievelijk 11.7 procent en 33.3 procent (P = 0,32). Het locale recidief percentage na TE was 23.3 procent en na TEM 3.7 procent (P < 0,001). Na TE was het locale recidief percentage bij RA met vrije snijvlakken 0 procent, vergeleken met 47.4 procent bij RA met niet-vrije snijvlakken (P < 0,001) en na TEM was het locale recidief percentage respectievelijk 3.2 procent en 7.7 procent (P = 0,3). Onafhankelijk van het deel van het rectum was het locale recidief percentage na TEM lager (P < 0,001).
De conclusie is dat TEM superieur is aan TE en de therapie van keuze moet zijn voor de locale excisie van RA.

In **hoofdstuk 4** is de geschiktheid van TEM voor RA onderzocht. TEM voor RA is veilig en met een laag locaal recidief percentage. Echter, het is niet bekend of TEM geschikt is voor alle RA in het gehele rectum. Dit werd door ons onderzocht in een prospectieve studie.
Van 1996 tot 2007 werden 353 RA bij 342 opeenvolgende patiënten beoordeeld volgens een gestandaardiseerd protocol. Alle RA werden in opzet met TEM geëxcideerd.
De mediane diameter van de RA was 3 cm en de mediane afstand vanaf de linea dentata 8 cm. Bij 8,7 procent werd peroperatief het peritoneum geopend zonder nadelige effecten. Met name vormde het nooit de aanleiding tot conversie. Het conversie percentage was 9,6 procent (alternatieve locale operatie techniek 4,2 procent, transabdominale operatie techniek 5,4 procent). Het conversie percentage correleerde met de afstand (P = 0,007) en de mate van ervaring van de operateur (P = 0,004). De mediane operatie tijd bedroeg 45 minuten en correleerde met de oppervlakte van het resectie preparaat, de operateur en de mate van ervaring van de operateur (allen P < 0,001). De operatie tijd correleerde niet met de afstand. De snijvlakken waren vrij in 85 procent. RA met niet-vrije snijvlakken waren groter (P < 0,001) en waren proximaler in het rectum gelokaliseerd (P < 0.001). De morbiditeit was 7,8 procent en de mortaliteit 0,6 procent. De mediane opnameduur was 4 dagen. De mediane follow-up was 27 maanden. Na 3 jaar bedroeg het locale recidief percentage 9,1 procent. De mediane tijd tot het recidief was 12 maanden. De status van de snijvlakken bleek van voorspellende waarde op het krijgen van een recidief (vrije snijvlakken 6,1 procent tegenover niet-vrije snijvlakken 25,2 procent; P < 0,001).

De conclusie is dat TEM veilig is en geschikt voor bijna alle RA in het gehele rectum. Vooral met toegenomen ervaring, is het conversie percentage beperkt. Het recidief percentage is laag, met name na excisie met vrije snijvlakken. Naar onze mening dient TEM de therapie van keuze te zijn voor de locale excisie van alle RA.

In **hoofdstuk 5** is de fecale continentie en de kwaliteit van leven voor en na TEM onderzocht. TEM maakt gebruik van een rectoscoop met een buitenwaardse diameter van 4 cm, welke transanaal ingebracht wordt. Het is onbekend wat het effect is op de fecale continentie en de kwaliteit van leven. Dit werd door ons prospectief onderzocht.
Tussen 2004 en 2006 werden 47 patiënten voorafgaand en tenminste 6 maanden na TEM onderzocht. De fecale continentie werd vastgesteld met behulp van de "Faecal Incontinence Severity Index". De kwaliteit van leven werd gemeten met behulp van de EuroQol EQ-5D vragenlijst en de "Faecal Incontinence Quality of Life" score.
Zes maanden na TEM bleek de mediane "Faecal Incontinence Severity Index" score afgenomen ($P < 0,01$), hetgeen een verbetering in de fecale continentie impliceert. Deze verbetering trad met name op bij tumoren binnen een afstand van 7 cm van de linea dentata ($P = 0,01$). Vanuit het perspectief van de patiënt, was de kwaliteit van leven postoperatief hoger ($P < 0,02$). Een significante verbetering werd waargenomen in 2 van de 4 "Faecal Incontinence Quality of Life" score domeinen: "Embarrassment" ($P = 0,03$) en "Lifestyle" ($P = 0,05$). De domeinen van "Lifestyle", "Coping/ behaviour" en "Embarrassment" correleerden met de "Faecal Incontinence Severity Index" (allen $P < 0,05$).
De conclusie is dat TEM geen verslechtering van de fecale continentie geeft. Bovendien, nadat de tumor met behulp van TEM is geëxcideerd, neemt de kwaliteit van leven toe.

In **hoofdstuk 6** is de geschiktheid van TEM bij mobiele RC onderzocht.
Van 1996 tot 2001 werd TEM uitgevoerd bij 76 patiënten met 76 RC. Bij 20 patiënten als palliatie en bij 56 patiënten omdat in de biopten geen invasief carcinoom aanwezig was.
De mediane operatie tijd was 75 minuten en het gemiddelde bloedverlies enkele cc's. De operatietijd correleerde met de tumor oppervlakte ($P < 0,001$) en de infiltratie diepte ($P < 0,001$) en niet met de afstand ($P = 0,15$). Bij 13 patiënten traden peroperatieve problemen op (17 procent). Alle problemen konden gecorrigeerd worden zonder de noodzaak tot conversie. De mediane opnameduur was 4 dagen. Bij 15 patiënten traden 16 complicaties op (19,7 procent). In 13 patiënten waren de complicaties mild en konden conservatief behandeld worden (17,1 procent). Bij 2 patiënten trad een ernstige complicatie op. Een heroperatie met plaatsen van een

tijdelijk stoma was daarvoor nodig (2,6 procent). De mortaliteit was 1,3 procent (n = 1). De histologie toonde een in situ carcinoom bij 32 tumoren, een T1 carcinoom bij 21 tumoren, een T2 carcinoom bij 18 tumoren en een T3 carcinoom bij 5 tumoren. De snijvlakken van het resectie preparaat waren vrij bij 91 procent van de RC. RC met niet-vrije snijvlakken, waren significant groter (P = 0,03). De aantallen patiënten T-stadium en de follow-up duur waren te beperkt voor de adequate bepaling van de recidief percentages en de overleving.
De conclusie is dat TEM geschikt is voor mobiele RC. Daarom kan zij gebruikt worden voor palliatie. Ook toont de studie aan dat alleen biopteren niet voldoende is om de aard van de tumor vast te stellen bij patiënten, verwezen voor TEM. De vraag naar het gebruik voor TEM voor RC met curatieve intentie kan op grond voor de resultaten van deze studie niet worden beantwoord.

In **hoofdstuk 7** is het oncologische resultaat na TEM en totale mesorectale excisie (TME) voor T1-RC onderzocht. Na TME voor RC is het pathologisch onderzoek gestandaardiseerd waarbij de betrokkenheid van de snijvlakken de recidief kans voorspelt. Na TEM wordt dit nog niet toegepast en werd prospectief onderzocht voor T1-RC.
Tachtig patiënten na TEM werden vergeleken met 75 patiënten na TME. Gestandaardiseerd pathologisch onderzoek van het resectie preparaat was onderdeel van het studie protocol. TEM patiënten kwamen in aanmerking als de circumferentiële snijvlakken vrij waren.
TEM was veiliger dan TME, uitgedrukt in operatietijd, bloedverlies, opnameduur, aantal heroperaties en het aantal aangelegde stoma's (alle factoren P < 0,001). De mortaliteit na TEM was 0 procent en na TME 4 procent. Na 5 jaar waren na TEM en TEM zowel de totale overleving (TEM 75 procent versus TME 77 procent, P = 0,973) als de kanker specifieke overleving (TEM 90 procent versus TME 87 procent, P = 0,511) gelijkwaardig aan elkaar. Het locale recidief percentage was na TEM 24 procent en na TME 0 procent (P < 0,0001).
De conclusie is dat voor T1-RC TEM veiliger is dan TME. De overleving is gelijkwaardig. Na TEM is het locale recidief percentage fors. Het optreden daarvan is moeilijk te voorspellen en de impact onduidelijk. Chirurgie is mogelijk en (neo-) adjuvante behandeling lijkt effectief en noodzakelijk. Meer studies naar deze belangrijke punten zijn nodig in een poging om zo veel mogelijk patiënten te behoeden voor de nadelige gevolgen van TME.

In **hoofdstuk 8** is de fecale continentie en de kwaliteit van leven zowel na TEM als ook na TME voor RC onderzocht. TME is de gouden standaard in de behandeling van RC, als curatie nagestreefd wordt. TEM is een veel veiliger techniek en zou als al-

ternatief overwogen kunnen worden, aangenomen dat het oncologische resultaat vergelijkbaar is. De impact van beide procedures op de kwaliteit van leven is nog nooit vergeleken.

Vier en vijftig patiënten ondergingen TEM voor T1-RC. Alleen patiënten zonder locoregionaal recidief of afstandsmetastasen werden geïncludeerd, resulterend in 36 geschikte patiënten. De EuroQol EQ-5D, EQ-VAS, EORTC QLQ-C30 en EORTC QLQ-CR38 waren de vragenlijsten die gebruikt werden. De resultaten werden vergeleken met een qua geslacht en leeftijd vergelijkbare steekproef van patiënten met T+N0 RC, die sphincter sparende chirurgie met behulp van TME hadden ondergaan, en een qua geslacht en leeftijd vergelijkbare steekproef van gezonde personen uit de bevolking.

Door 31 patiënten na TEM werden de ingevulde vragenlijsten teruggestuurd (antwoord percentage 86 procent). De kwaliteit van leven werd vergeleken met 31 patiënten na TME en 31 gezonde controle personen. Vanuit het perspectief van de patiënt en het sociale perspectief verschilde de kwaliteit van leven niet tussen de 3 groepen. Vergeleken met TEM werden meer defecatie problemen gezien na TME ($P < 0,05$). Na TME werd, in vergelijking met TEM, een trend richting slechter seksueel functioneren waargenomen, in het bijzonder bij mannelijke patiënten.

De conclusie kan zijn dat TEM en TME niet verschillen in kwaliteit van leven postoperatief . Wel worden vaker defecatie problemen gezien na TME. Dit verschil kan een rol spelen in de keuze van chirurgische therapie bij RC.

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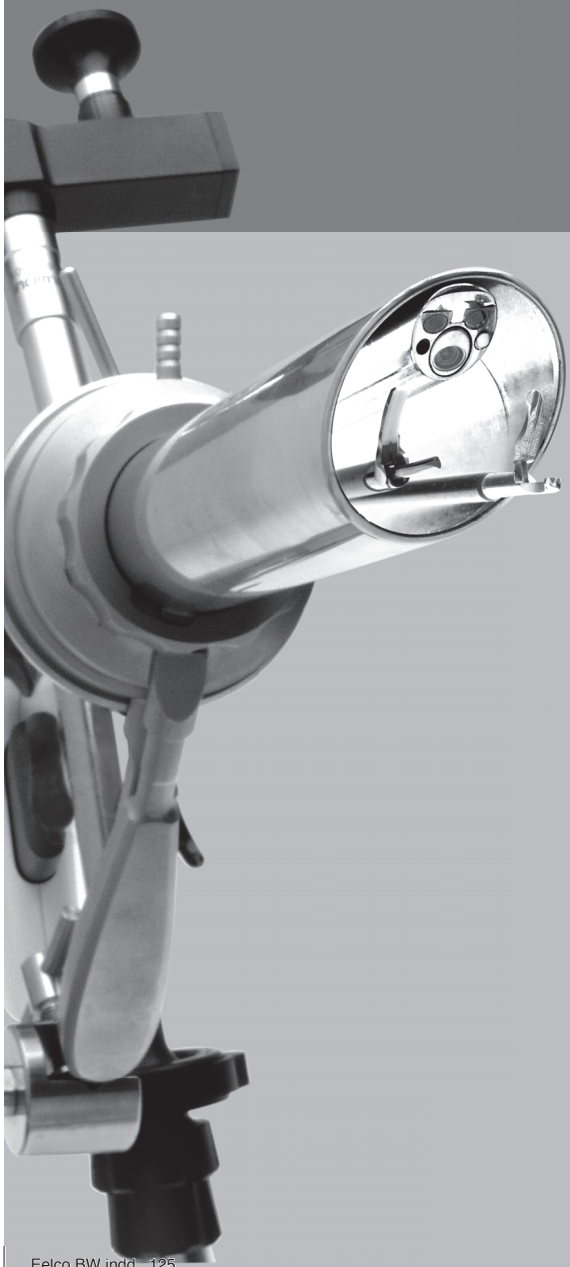

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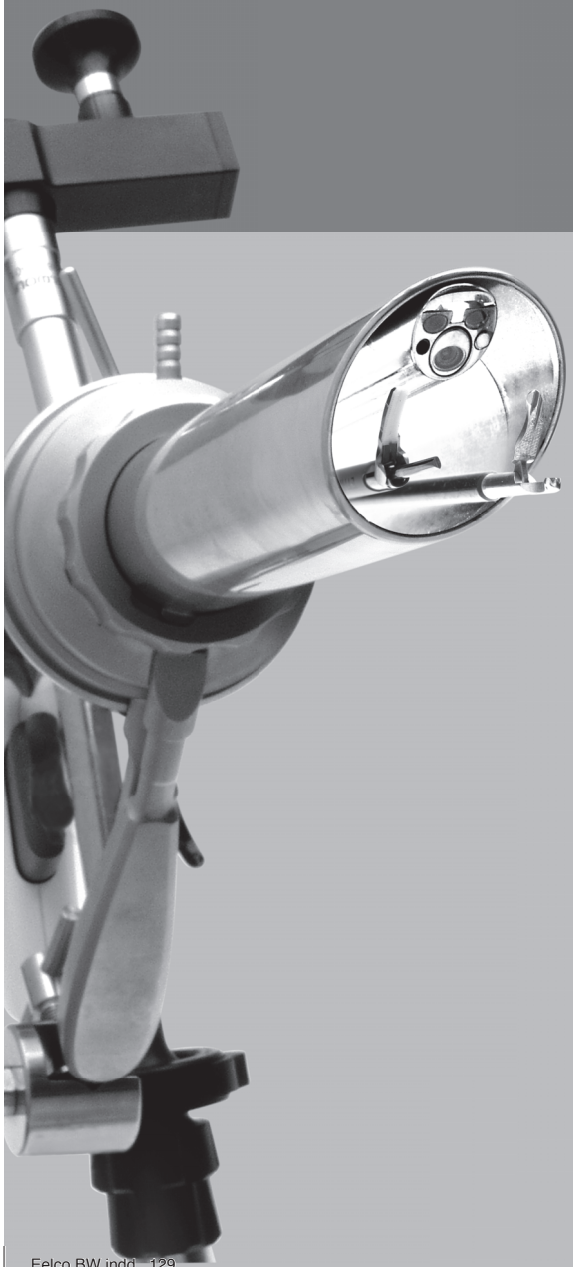
Acknowledgements/ Dankwoord



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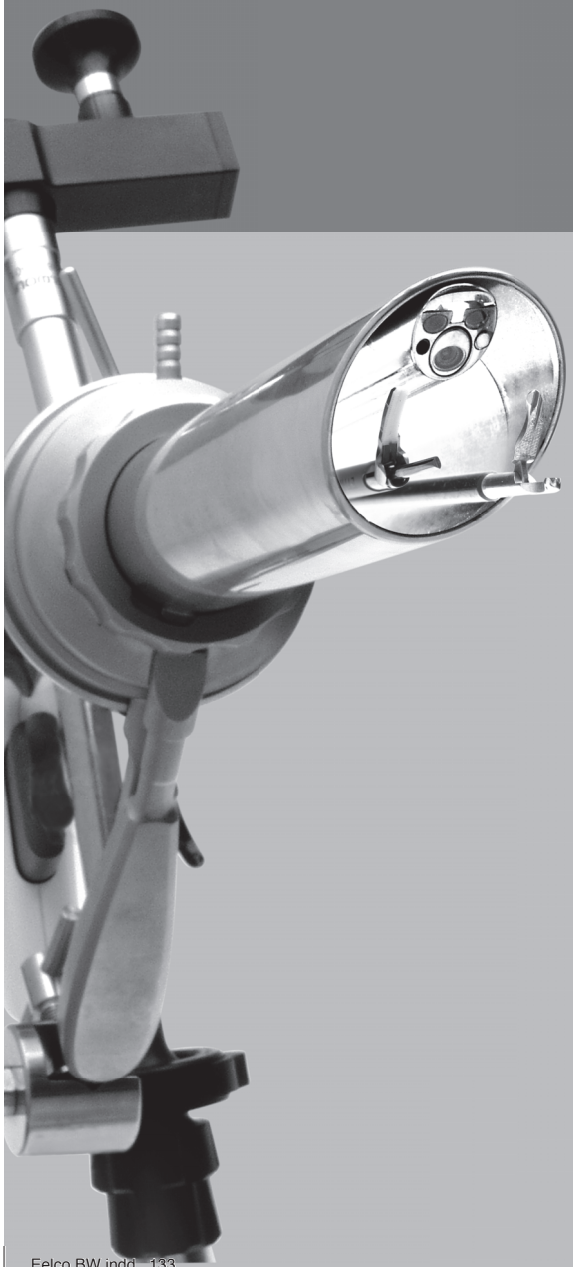
Curriculum vitae auctoris



Curriculum vitae auctoris

Eelco Jan Rade de Graaf was born March 5, 1959 in Groningen, the Netherlands.
He attended secondary school at the Willem Lodewijk Gymnasium in Groningen and he completed his medical studies at the University of Groningen in 1987.
In 1988, he worked as a surgical house officer at the Erasmus Medical Centre in Rotterdam, the Netherlands (Chief of Training: Prof. dr. H.A. Bruining). Thereafter, he commenced his formal surgical training at this same hospital in January 1989. In 1991, he continued his training in the Sint Franciscus Hospital in Rotterdam, the Netherlands (Chief of Training: Dr. W.C.J. Wereldsma). He finished his training in December 1994 and has been registered as a general surgeon since January 1995. In April 1, 1995, he started his practise as a consultant surgeon at IJsselland Hospital, Capelle aan den IJssel, the Netherlands. His fields of interest are gastro-intestinal, oncological and endoscopic surgery.
He performed his first TEM operation on January 30, 1996 at IJsselland Hospital. This marked the starting point for this doctoral reseach.