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REVIEW ARTICLE

Is the increasing role of Transanal Endoscopic Microsurgery in curation for T1 rectal cancer justified? A systematic review

PASCAL G. DOORNEBOSCH[1], ROB A. E. M. TOLLENAAR[1] & EELCO J. R. DE GRAAF[2]

[1]*Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands and* [2]*Department of Surgery, IJsselland Hospital, Capelle aan den Ijssel, The Netherlands*

Abstract

Driven by the aim to avoid a permanent colostomy and also the morbidity and mortality of major radical surgery for rectal cancer, the proportion of patients with rectal cancer treated by local excision has increased the last ten years or so. In T1 carcinomas local excision is considered a curative option in selected tumors. However, the scientific base upon which this treatment regimen is built remains controversial. In this systematic review we try to elucidate current literature regarding local excision for T1 rectal carcinomas. Several questions are addressed. First, is there enough evidence to propagate LE as a curative option in selected (T1) rectal carcinomas? Second, if LE is justified, which technique should be the method of choice? Third, can we adequately identify, pre- and postoperatively, tumors suitable for LE? Finally, future perspectives are discussed.

There has been an impressive evolution in the therapy for rectal cancer. From the description of local techniques by Lisfranc (1826) and Kraske (1885), to the radical abdomino-perineal resection according to Ernest Miles (1908) [1–3]. This APR procedure, which gained acceptance largely because it was oncologically sound and successful, has led to the cure of many patients with rectal tumors. Dixon established the safety of the anterior resection in the late 1940s, but this approach was mainly limited to the treatment of upper rectal cancer until the 1970s [4]. The introduction of circular stapling devices facilitated the technical possibility of low rectal anastomosis and even coloanal anastomosis. This technological advance, along with the recognition that distal margins of <2 cm did not compromise outcome, dramatically changed the approach to many patients.

The most recent advance was the introduction of the concept of total mesorectal excision (TME). This technique has meanwhile shown, by Heald et al. and many others, to minimize local recurrence [5]. Nonetheless, these reconstructive operations are associated with a relatively high rate of complications, including anastomotic leakage, genito-urinary dysfunction, defecation disorders and up to 4% mortality.

More or less parallel with the advent of TME, others focused on the improved possibilities of local excision (LE) for rectal cancer, initially as a palliative procedure, but now even with curative intent in selected tumors. The technique most commonly used is the transanal approach, according to Parks [6]. This however suffers from poor exposure and inadequate access to lesions, especially in the upper rectum, resulting in recurrence rates up to 60% [6–8]. Transsacral (Kraske) and transsphincteric (Mason) approaches are technically demanding and invasive, resulting in high morbidity (up to 40%), often severe and mortality rates of 1–5% [9–16]. Moreover, recurrence rates range between 12 to 25%.

Transanal endoscopic microsurgery (TEM) is a recently introduced minimal invasive technique for local excision of rectal tumors [17]. In adenomas TEM is superior in safety and local control and tumors in the entire rectum can be treated and therefore TEM is the method of choice [18–21].

In a recent report by You et al., from 1989 to 2003 the rate of LE for T1 rectal carcinomas in the USA

Correspondence: Pascal G. Doornebosch, Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands. E-mail: p.g.doornebosch@lumc.nl

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increased from 26.6 to 43.7% and from 5.8 to 16.8% for T2 rectal carcinomas [22]. This increasing role is ultimately reflected by several national guidelines, propagating selected tumors suitable for LE [23]. In many studies it is emphasized LE is safe regarding morbidity and mortality, especially compared to (conventional) radical surgery. The main question to be answered however is whether LE is justified from an oncological point of view. The safety of a local procedure has to be balanced against the higher risk of local recurrences and/or worsened survival. In T2 rectal carcinomas, both local recurrence rates and survival rates after LE are worse compared to radical surgery, and therefore LE is considered a valid option only in palliative procedures.

In this review several issues regarding LE of rectal carcinomas are discussed. First, is there enough evidence to propagate LE as a curative option in selected (T1) rectal carcinomas? Second, if LE is justified, which technique should be the method of choice? Third, can we adequately identify, pre- and postoperatively, tumors suitable for LE? Finally, future perspectives are discussed.

Methods

A literature search was conducted for the period until December 2007, using PubMed and Embase databases. Search terms used were "early rectal cancer", "transanal endoscopic microsurgery", "TEM", "TEMS", "local excision", "rectal cancer", "CRC" and "T1 rectal carcinomas". One author (PGD) retrieved all available abstracts and bibliographies of extracted articles were further cross-referenced. Comparative and individual studies reporting on TEM and/or local excision for T1 rectal carcinomas were reviewed. All studies had to report at least one of the following outcome measures: local recurrence rate, overall/disease free survival or probability of survival. All included articles were further reviewed by a second author (EdG) and consensus upon interpretation was mandatory.

Local excision or radical surgery

Radical surgery (RS) for T1 rectal carcinomas leads to excellent results [24]. Local recurrence rates are invariably low, ranging from 0 to 6%. Five and 10-year survival rates are as high as 82 and 68%, respectively. Can similar results be achieved by applying LE according to Parks for T1 rectal carcinomas? No randomized study has been performed, but several comparative studies have been published upon this issue (Table I). The earlier mentioned study of You et al. reports upon outcome after LE according to Parks (LE) in comparison to radical surgery (RS) [22]. In the LE group patients were older and tumors were smaller and located more distal. LE was significantly safer, as expressed by the lower morbidity rate (5.6 vs. 14.6%, $p < 0.001$). The vast majority of tumors was excised microscopic radical (R0) in both groups (95 vs. 99%). Regarding oncologic outcomes, 5-years local recurrence rates after R0 excision were 12.5% after LE and 6.9% after RS ($p = 0.003$). Overall survival rates were comparable (LE 77.4%, RS 81.7%, $p = 0.09$), however disease specific survival rates were significantly lower after LE (93.2 vs. 97.2%, $p = 0.004$).

A prospective multicenter observational study was performed by Ptok et al. [25]. In their study, selection was made based on histopathological criteria. In case of a low-risk T1 rectal carcinoma, that is well or moderately differentiated, radically excised, smaller than 3 cm and without lymphangioinvasion, LE is presumed curative. Both LE according to Parks and TEM were performed and not analyzed separately. After LE local recurrence rate was higher (LE 6%, RS 2%; $p = 0.049$), although tumor-free survival was comparable (LE 91%, RS 92%; $p = 0.39$).

Mellgren et al. reported upon outcome after LE for 69 T1 rectal carcinomas, in comparison to 30 T1N0 rectal carcinomas treated by RS [8]. Neither group received neoadjuvant chemoradiation. In the LE group, tumors were significantly smaller and located more distally. After LE local recurrence rates were higher (18 vs. 0%; $p = 0.03$), as well as overall recurrence rates, although the latter not significantly (21 vs. 9%; $p = 0.54$). Five year survival rates were comparable (LE 72%, RS 80%; $p = 0.50$). Another study was performed by Bentrem et al. [26]. In their study 319 consecutive patients with T1 rectal carcinomas were treated by LE according to Parks ($n = 151$) or RS ($n = 168$) over a 17-year period. In the RS group 18% of tumors were node-positive; no tumor selection regarding differentiation grade and/or lymph vascular invasion was applied. Again, in the LE group tumors were smaller and located more distally. After LE adjuvant radiotherapy was given in case of close margins ($n = 11$) or high-risk pathology ($n = 5$). None of the patients received adjuvant systemic chemotherapy. After RS, in case of positive lymph nodes adjuvant radiotherapy ($n = 16$) or chemotherapy ($n = 29$) was given. At five years, local recurrence rate after LE was 15 vs. 3% after RS ($p = 0.0001$). Overall recurrence rates also differed significantly (LE 23%, RS 6%; $p < 0.001$). Disease-specific and overall survival rates were similar for LE and RS. Of all recurrences after LE, 77% could

Table I. Comparative series of local excision according to Parks (LE) versus radical surgery (RS) for T1 rectal carcinomas.

Author	LE vs. RS (no.)	R0: LE vs. RS (%)	LR: LE vs. RS (5-year [%])	OR: LE vs. RS (5-year [%])	OS: LE vs. RS (5-year [%])	Other survival: LE vs. RS (5-year [%])
Mellgren et al. [8] (2000)	69 vs. 30	100 vs.100	18 vs. 0‡	21 vs. 9	72 vs. 80	DSS: 95 vs. 95
Nascimbeni et al. [68] (2004)	70 vs. 74	NS	6.6 vs. 2.8‡	21 vs. 10‡	72 vs. 90‡	DSS: 89 vs. NS DFS: 67 vs. 84‡
Bentrem et al. [26] (2005)	151 vs. 168	NS	15 vs. 3‡	23 vs. 6‡	89 vs. 93*	DSS: 93 vs. 97*
Endreseth et al. [27] (2005)	35 vs. 256	83 vs. 100‡	12 vs. 6‡	12 vs. 13	70 vs. 80*‡	DFS: 64 vs. 77*‡
Ptok et al. [25] (2007)	105 vs. 312	100 vs. 100	6 vs. 2‡	10 vs. 6	84 vs. 92	DFS: 91 vs. 92
You et al. [22] (2007)	601 vs. 493	95 vs. 99	12.5 vs. 6.9‡	16 vs. 10‡	77 vs. 82	DSS: 93 vs. 97‡

R0 = microscopic radical excision
LR = local recurrence
OR = overall recurrence
DSS = disease specific survival
DFS = disease free survival
OS = overall survival
Survival rates are 5-years, unless otherwise specified
‡Statistically significant ($p < 0.05$)
*Patients who received neoadjuvant and/or adjuvant therapy were not excluded
NS = not stated

be resected radically, compared to 50% of local recurrences after RS. A nationwide, prospective study was performed by Endreseth et al. [27]. They analyzed outcome of 291 T1M0 rectal carcinomas treated by LE according to Parks (n = 35) or RS (n = 256). They found in the LE group patients were older and tumors were smaller and located more distally. In this study only in the minority of tumors with LE a R0 (microscopic negative) excision margin could be obtained. After excluding R2 (macroscopic irradical) procedures, local recurrence rate after LE was still significantly higher compared to RS (12 vs. 6%; $p = 0.01$). Overall survival (70 vs. 80%; $p = 0.04$) and disease free survival (64 vs. 77%; $p = 0.01$) were significantly worse after LE.

Interpretation of all above mentioned studies remains difficult, as a selection bias may have been introduced, as expressed by the smaller, more distal located tumors treated by LE. Nevertheless, in all studies a significant proportion of tumors recurred, although in majority of studies this seems not to influence survival rates.

TEM or Parks

Can results be improved by using another technique for local excision? In rectal adenomas it was shown that application of Transanal Endoscopic Microsurgery (TEM) results in lower recurrence rates compared to LE according to Parks [20,21]. Can these results be extrapolated for T1 rectal carcinomas? Four studies were retrieved in which TEM was compared with another type of surgery (LE according to Parks and/or RS) (Tables II and III).

Only one randomized controlled trial for clinical T1 rectal carcinomas has been performed [28]. This trial included 52 patients with presumed T1 rectal carcinomas, well or moderately differentiated, during an eight-year period. Patients were randomized to TEM or RS. Post-inclusion two patients were excluded because of a later pTNM staging. Twenty-four patients were treated using the TEM technique and 26 patients underwent anterior resection. Both groups were comparable in age and gender distribution. TEM proved to be the safest technique in the early postoperative period and patients required less postoperative analgesics. With median follow-up more than 40 months, local recurrence rate after TEM was 4.1% (1/24). In the RS group no local recurrence occurred. Five-year procedure specific survival rates were 96% for both groups.

Langer et al. reported (retrospectively) upon outcome after TEM in comparison to LE according to Parks and RS [20]. Overall 182 tumors (58 pT1 rectal carcinomas (G1/2) and 124 benign rectal tumors) were identified. Both local techniques proved to be faster in comparison to RS, resulting in less blood loss and shorter time of hospitalization. Also, complication rates after TEM and LE according to Parks were significantly lower compared to RS. An important outcome in this study was a significant higher rate of irradical excisions after LE according to Parks (TEM R1 = 19%, Rx = 5%;

Table II. Comparative series of TEM versus LE according to Parks and/or radical surgery (RS).

Author	Type of study	Inclusion criteria	Type of surgery	Number of T1 carcinomas	Level of evidence‡
Winde et al [28] (1996)	Randomized controlled trial	uT1, G1/2	TEM	26	IIb
			RS	26	
Heintz et al. [29] (1998)	Retrospective	pT1	TEM	58	IIIb
			RS	45	
Lee et al. [30] (2003)	Retrospective	cT1N0, G1/2	TEM	52	IIIb
			RS	17	
Langer et al. [20] (2003)	Retrospective	pT1,G1/2	TEM	20	IIIb
			Parks	20	
			RS	18	

cT/N = clinical T/N-staging, uT/N = presumed, T/N-stage based on endorectal ultrasound, pT = T-stage based on histopathological investigation, G1 = well differentiated, G2 = moderately differentiated, G3 = poorly differentiated, LVI = lymfvascular invasion, TEM = transanal endoscopic microsurgery, RS = radical surgery ‡ = level of evidence according to Oxford Centre for Evidence-based Medicine Levels of Evidence.

Parks R1 = 37%, Rx = 16%; p = 0.001). Local recurrence rates after RS were only 3.7%, which was no different after TEM (8.9%). Following LE according to Parks local recurrence rate was 26.3% (p = 0.0055 vs. TEM). Statistical analysis of risk-factors for development of a recurrence, detected only tumor-size (p = 0.0236) and recurrent tumor at the time of operation (p = 0.0231) to be significant. Tumor grading, tumor dignity (adenoma/carcinoma), distance from the anal verge and residual status (R0, R1, Rx) proved to be non-significant factors. Disease specific survival rates between the three treatment groups were comparable.

Two retrospective studies could be identified comparing TEM to RS. Heintz et al. found in case of a T1 low-risk carcinoma, meaning well to moderately differentiated without lymph vascular-invasion, TEM resulted in 78% radical excisions (R0) [29]. In this subgroup of 46 tumors, after TEM local recurrence rate was 4% compared to 3% after RS for T1 low-risk carcinomas; this difference was not significant. Overall survival rates between both treatment groups were comparable (TEM 79%, RS 81%). In case of a T1 high-risk carcinoma, that is poorly differentiated and/or lymph vascular-invasion, using TEM only 58% of tumors could be excised radically (R0). Local recurrence rate after TEM was 33%, compare to 18% after RS. Overall survival rate after TEM was 62%, compared to 69% after RS.

Lee et al. compared TEM with RS for cT1N0 rectal carcinomas, well or moderately differentiated [30]. Local recurrence rates were comparable (TEM 4%, RS 0%; p = 0.95). Also overall and disease-free survival rates were comparable.

There is an abundance of published case series reporting on outcome after TEM for T1 rectal carcinomas [31–46] (Table IV). Inclusion criteria in these studies are not always clear, and immediate salvage procedures were sometimes performed, thereby possibly introducing a selection bias. In all series TEM is a safe procedure with complication rates varying between 5–26%. These complications are almost always minor with re-operation rates between 0–7%. Mortality is rare after TEM. All studies have a follow-up duration of more than 24 months and recurrence rates vary between 0–26%. If calculated, five years disease specific survival rates after TEM vary between 81–100% and overall survival rates range from 73 to100%.

Preoperative tumor selection

Although TEM seems to be the method of choice in local excision of T1 rectal carcinomas, local recurrence rates remain high. Can results be further improved by proper tumor selection?

One of the problems encountered is the unexpected finding of a carcinoma in presumed adenomas. This rate can be as high as 34%. A possible solution might be identifying genomic events within the adenoma fraction of a carcinoma, as recently reported by Lips et al. [47,48]. They found specific chromosomal events, gain of 8q22-24, 13q and 20q, and loss of 17p and 18q12-22, to be far more abundant in carcinomas than in adenomas. In adenoma fractions from cases with a carcinoma (infiltrating at least in the submucosa), twice the amount of such 'malignant aberrations' was observed, compared to pure adenomas. Furthermore,

Table III. Comparative series of TEM versus LE according to Parks and/or radical surgery (RS).

Authors	TEM vs. other (no.)	R0: (%)	LR: (5-years [%])	OR: (5-years [%])	OS (5-years [%])	Other survival: (5-years [%])
Winde et al. [28] (1996)	TEM 24	NS	4	4	NS	DSS: 96
	RS 26		0	4		DSS: 96
Heintz et al. [29] (1998)	TEM low risk 46	78	4	4	79	NS
	RS low risk 34	100	3	6	81	
	TEM high risk 12	58	33	33	68	NS
	RS high risk 11	100	18	18	69	
Lee et al. [30] (2003)	TEM 52	100	4	NS	100	
	RS 17	100	0		93	DFS: 96
	100					DFS: 94
Langer et al. [20] (2003)	TEM 20	76	10	NS	NS	100 (2-years)
	Parks 20	47‡	15			100 (2-years)
	RS 18	100	0			93 (2-years)

TEM = Transanal Endoscopic Microsurgery, Parks = LE according to Parks, RS = radical surgery, R0 = microscopic radical excision, LR = local recurrence, OR = overall recurrence, OS = overall survival, DFS = disease free survival, DSS = disease specific survival, ‡ = statistically significant ($p < 0.05$).

combined aberrations such as gain of 13q and loss of 18q were only found in adenomatous fractions of carcinomas and not in benign lesions. Based on these five genomic events associated with carcinoma, a clear distinction between adenoma and carcinoma tissue could be made. Whether these results are clinically relevant or not remains to be seen. It seems more relevant to identify tumors suitable for TEM, that is rectal adenomas and T1 rectal carcinomas, which have to be discriminated from T2 or more invasive carcinomas, as these latter have to be treated by radical surgery. Most studies focusing on T-stage, found endorectal ultrasound (ERUS) to be more accurate than conventional computerized tomography (CT) scanning and magnetic resonance imaging (MRI) [49]. We recently performed a large study upon the feasibility of ERUS in rectal tumors, and found in 78% of presumed rectal adenomas proper investigation of the tumor was possible [50]. The rate of missed carcinomas could be reduced from 21 to 3% by using ERUS; furthermore if rectal adenomas and T1 rectal carcinomas are considered one clinical entity, ERUS results in sensitivity of 95%, however overstaging frequently occurs. In conclusion, ERUS has a substantial additional value in the preoperative staging of rectal tumors, especially in identifying tumors possibly suitable for TEM.

Depth of invasion is not the only criterion in identifying tumors suitable for TEM. Main difference between TEM and radical surgery is the omission of lymph node dissection. In general in T1 rectal carcinomas it is assumed lymph node metastases are present in 4–14% of cases [51]. A more recent study performed by Nascimbeni et al. found depth of invasion in submucosal level 3 (Sm3), lymph vascular invasion and distal rectal carcinomas to be significant contributors to lymph node metastases [52].

Can we identify, preoperative, tumors already harboring lymph node metastasis? Using single nucleotide polymorphism array analysis of chromosomal instability patterns in rectal tumors, the finding of gain on chromosome 1q might correlate with lymph node metastasis, however validation studies have to be awaited [47]. None of the conventional pre-operative staging methods, ERUS/CT-scan/MRI has yielded satisfactory results upon identifying lymph node metastases [53]. A recent break through was the introduction of MRI-USPIO [54,55]. Preliminary data show an increased accuracy for nodal status prediction as compared to non-enhanced MRI. However, again further studies have to be awaited.

Postoperative tumor selection

In most cases based on definite histopathological staging after LE a decision has to be made upon the necessity for immediate salvage surgery. In case additional salvage surgery is performed after LE according to Parks, controversy remains upon outcome [53,56]. Accepted low-risk criteria in T1 rectal carcinomas, are well to moderate differentiation, carcinomas smaller than three centimeters, without lymph vascular-invasion. Above these features, probably excision margin (microscopic radical (R0)

Table IV. Case series of TEM in T1 rectal carcinomas.

Author	Type of study	Inclusion criteria	No. of T1 carcinomas	Comments	LR	OS	DSS	Level of evidence‡
Smith et al. [43] (1996)	retrospective	NS	30	No pre-/postoperative adjuvant therapy	3/30 (10%)	NS	NS	IV
Mentges et al. [35] (1997)	prospective	G1/2 curative intent (N = 60) G3 in selected patients (N = 4)	64	No pre-/postoperative adjuvant therapy	2/52 (4%)	NS	NS	IV
Demartines et al. [33] (2001)	prospective	G1/2, LVI -	9	One patient adjuvant therapy, type not mentioned	1/7 (14%)	NS	NS	IV
De Graaf et al. [46] (2002)	retrospective	NS	21	No pre-/postoperative adjuvant therapy	2/19 (11%)	NS	NS	IV
Dafnis et al. [44] (2004)	retrospective	NS	10	No pre-/postoperative adjuvant therapy	1/10 (10%)	NS	NS	IV
Stipa et al. [38] (2004)	retrospective	uT1-T3, <3 cm	39	Overall 43% of patients pre-/postoperative RT	5/39 (13%)	92%	92%	IV
Duek et al. [45] (2005)	retrospective	G1/2, <3 cm, <10 cm from dentate line, cN0	25	No pre-/postoperative adjuvant therapy	0/25 (0%)	NS	NS	IV
Endreseth et al. [40] (2005)	retrospective	NS	8	No pre-/postoperative adjuvant therapy	0/8 (0%)	NS	NS	IV
Floyd et al. [39] (2005)	retrospective	NS	53	No pre-/postoperative adjuvant therapy	4/53 (8%)	100%	100%	IV
Ganai et al. [42] (2006)	retrospective	NS	21	One patient postoperative CRT	4/21 (19%)	73%	89%	IV
Borschitz et al. [34] (2006)	prospective	pT1	105	21 patients immediate radical surgery No pre-/postoperative adjuvant therapy	11/84 (13%)	93% (low-risk, R0)	94% (low-risk, R0)	IV
Stipa et al. [37] (1996)	retrospective	uT1/T2, uN0	23	2 patients preoperative CRT 2 patients postoperative RT	2/23 (9%)	91%	91%	IV
Bretagnol et al.[36] (2007)	retrospective	G1/2, <3 cm	31	3 patients immediate radical surgery	3/28 (11%)	79%	81%	IV
Whitehouse et al. [41] (2007)	retrospective	NS	25	2 patients immediate radical surgery Pre-/postoperative CRT not clear	6/23 (26%)	NS	NS	IV
Lezoche et al. [31] (2007)	prospective	uT1N0	51	Pre-/postoperative CRT not mentioned	0/51 (0%)	94%	100%	IV
Maslekar et al. [32] (2007)	prospective	G1/2 en 3	27	No pre-/postoperative adjuvant therapy	0/27 (0%)	NS	NS	IV

uT/N = presumed T/N-stage based on endorectal ultrasound
pT = T-stage based on histopathological investigation
G1 = well differentiated, G2 = moderately differentiated, G3 = poorly differentiated
NS = not stated
LR = local recurrence
OS = overall survival
DSS = disease specific survival
‡ = level of evidence according to Oxford Centre for Evidence-based Medicine Levels of Evidence
CRT = chemoradiotherapy
RT = radiotherapy

versus microscopic irradical (R1)) may be of major importance [27]. Only three studies specifically addressed the outcome after TEM for low-versus high risk carcinomas. Mentges et al. found recurrence rates after TEM for low-risk carcinomas (n = 52) to be only 3.8%; however recurrence rates for high risk carcinomas (n = 4) were not given, thereby prohibiting adequate comparison [35]. A retrospective, comparative study was performed by Heintz et al. [29]. In low-risk carcinomas (n = 46) in 78% a R0 excision margin with TEM was obtained, whereas in high-risk carcinomas (n = 12) only 58% of tumors was microscopically radical. Regarding local recurrences, in the low-risk group two carcinomas recurred (4%) and in the high-risk group four carcinomas (33%). All recurrences were after a microscopic irradical (R1) excision. Overall survival rates after TEM for low- and high-risk carcinomas were 79 and 62% respectively (p-value not given).

A meticulous evaluation was performed by Borschitz et al., with emphasis on margin of excision [34]. In 105 tumors TEM was performed. Immediate salvage was performed in 21 tumors, for varying reasons. In case a R0 excision was obtained, that is an excision margin of > 1 mm, in low-risk carcinomas recurrence rate was only 4%. In high-risk carcinomas with R0 status, the local recurrence rate was already 20%. If the excision margin was < 1 mm, unknown (Rx) or positive (R1), the local recurrence rate after TEM was 46%. Immediate radical surgery in case of margin < 1 mm, unknown margin status (Rx) or positive margin (R1), results in local recurrence rates of 6%. Survival rates in low-risk carcinomas, microscopic radically excised are 94% and if microscopically irradically excised 57%. Immediate radical surgery in irradical excised T1 carcinomas results in survival rates of 93%.

In contrast to the above studies, Langer et al. found 24% of all TEM specimens to be R1 or Rx, but excisional margin status was not of significant influence on developing local recurrences [20]. This unexpected finding was thought to be reflected by inadequate follow up and/or limited patient numbers. All above findings warrant a larger study, specifically addressing the role of histopathological staging in predicting high probability for a local recurrence after TEM for T1 rectal carcinomas.

Salvage surgery for local recurrences after TEM

Local recurrences in rectal cancer after radical surgery (TME) are considered incurable, with only few patients amenable to salvage surgery. Recurrences after LE seem to be more related to the rectum than to the pelvic wall, as is seen in recurrences after RS. In the literature most series on salvage surgery for local recurrences after LE lack both an adequate number of patients undergoing salvage procedures and adequate follow-up to allow proper analysis. Disease free survival rates following salvage procedures for local recurrences after local excision range between 30–58% [57–59]. Moreover, to obtain a R0 resection, extended resections are required, often involving multivisceral excision. Results after salvage surgery were significantly worse compared to immediate radical surgery in case of adverse histopathological features [53]. One must realize however that the above series and data are based on local recurrences after LE according to Parks.

In T1 rectal carcinomas local recurrence rates after TEM vary between 0–26%. Salvage surgery in case of a local recurrence after TEM seems amenable to most patients, with often a possible R0 resection [37]. However, because of the low number of patients and short duration of follow up, reliable long-term results have to be awaited.

Future perspectives

Preoperative chemoradiation in rectal carcinomas results in significant downstaging with complete pathological response in approximately 15% of advanced rectal carcinomas [60–64]. These figures might even be improved in earlier stages of rectal cancer [65]. If local control is improved by preoperative radiotherapy and preoperative chemoradiotherapy results in sterilizing lymph node metastases, local excision following preoperative chemoradiotherapy might be a logical step. One randomized controlled trial investigating this treatment strategy was performed [66]. Forty patients with histological proven adenocarcinomas, staged as uT2-N0-M0, G1/2, within 6 cm from the anal verge, were randomized to TEM or laparoscopic TME. Preoperative chemoradiotherapy was given by means of 5 040 cGy in 28 fractions with concomitant 5-fluorouracil infusion (2 000 mg/m^2/day). Restaging was performed and patients went on to the planned operation. Surgery was not influenced by preoperative treatment. Local and distant recurrence rates were 10% following TEM and 12% following laparoscopic TME. Overall survival rates were 95 and 83% respectively. All differences were not significant. Because this study has several major methodological shortcomings, one has to be cautious to draw any conclusions from this single study.

Another proposed regimen is a rectal sparing treatment after neoadjuvant treatment with clinical complete response [67]. Definite evidence, ideally by means of a randomized controlled trial, has to be

awaited and until then this treatment should be considered experimental.

Discussion

Local excision (LE) for rectal cancer is being applied increasingly [22]. Originally only as a palliative treatment, but nowadays also with curative intent in selected tumors. Several national guidelines have implemented this treatment as a valid option [23]. What is the basis for this treatment shift?

Several large studies have reported upon outcome after LE according to Parks for T1 rectal carcinomas [8,27,68]. Invariably, local recurrence rates after LE are significantly higher compared to radical surgery (RS). Overall and disease specific survival rates are comparable, although several methodological shortcomings have to be discussed. None of the studies was a randomized trial, and therefore a selection bias may have been introduced. This biasing is expressed by the higher number of smaller and more distal located tumors in the LE group. A preselection has been adopted in most studies, as only low-risk tumors were analyzed. Also, (neo-) adjuvant treatment strategies were not always clear, thereby introducing a possible confounding factor. Nevertheless, LE is judged justified by many in case of a T1 rectal carcinoma.

Transanal Endoscopic Microsurgery (TEM) was introduced by Buess in the 1980s [17]. Originally the procedure was introduced for the local excision of rectal adenomas, achieving excellent results regarding safety and local control, which were superior to other LE techniques. These results have been confirmed by others [20,21]. Early reports also claim feasibility of the technique in rectal cancer, but oncologic outcome should be the main focus [46]. The single randomized trial, comparing TEM with RS (anterior resection) for T1 rectal carcinomas, is a small study with difficult accrual, as expressed by the 8-year span of the study. Primary endpoints studied were safety of the procedure and survival rates. Although methodological shortcomings are obvious, local recurrence rates (4%) and overall survival rates (96%) were comparable between treatment groups. A further three retrospective studies, comparing TEM to RS, found overall- and disease specific survival to be comparable [20,29,30]. Nevertheless, local recurrence rates were higher after TEM, which is confirmed in almost all case series reporting on TEM for T1 rectal carcinomas.

One of the problems encountered in daily practice is the high rate of unexpected findings of a carcinoma within a presumed adenoma. This can be as high as 34%, and outcome after immediate salvage surgery is still under debate [53,56]. Efforts have been made to diagnose a carcinoma within an adenoma. Several genomic events were identified, even within adenoma fractions of the tumor, possibly predicting the presence of a carcinoma [47,48]. Whether preoperative identification of a carcinoma within a presumed adenoma is a prerequisite, remains to be seen, as T1 rectal carcinomas are still considered suitable for TEM. Improvement in preoperative tumor selection might be found in proper T-staging of rectal tumors. Of all staging modalities, endorectal ultrasound (ERUS) is considered most accurate [49]. If rectal adenomas and T1 carcinomas are considered suitable candidates for TEM, ERUS has a substantial additional value in the preoperative staging of rectal tumors [50].

Main difference between TEM and RS is the omission of a lymph node dissection in TEM. This residual cancer bearing lymph node may give rise to local recurrence. Conventional staging modalities, up till now have failed to deal with this problem. A recent study from Memorial Sloan Kettering Cancer Center concluded that early rectal cancers (T1 and T2) are more likely to have small lymph node metastases not easily identified by ERUS, which may explain the relatively high rates of recurrence seen after local excision [69]. Preliminary data of a novel, contrast enhanced MRI (MRI-USPIO) show an increased accuracy for nodal status prediction as compared to non-enhanced MRI [54,55]. However, further studies are still lacking.

Ideally tumor biopsy would reveal the presence of lymph node metastases upfront. In a recent study by Lips et al., using single nucleotide polymorphism array analysis of chromosomal instability patterns in rectal tumors, the finding of gain on chromosome 1q might correlate with lymph node metastasis, however validation studies have to be awaited [47].

Traditional accepted low-risk criteria in rectal carcinomas are tumors smaller than three centimetres, well or moderately differentiated without lymphangio-invasion. In these cases additional lymph node dissection seems unnecessary as only 4% harbour lymfnode metastases [51]. However, no randomized trial has been performed comparing TEM for presumed low- versus high-risk tumors. Only one study compared results for low- and high-risk tumors [29]. Both for TEM and RS, local recurrence rates were lower for low-risk tumors (TEM low-risk 4%, TEM high-risk 33%; RS low-risk 3%, RS high-risk 18%). All local recurrences occurred in microscopic irradical excised (R1) tumors. In low-risk tumors, disease specific survival rates after TEM and radical surgery were comparable.

After TEM proper histopathological evaluation of the specimen, specifically addressing excisional margin is possible. Borschitz et al. performed a meticulous evaluation upon the role of excisional margin after TEM procedures [34]. A microscopic radical excision (>1 mm margin) seems mandatory in obtaining optimal results.

In contrast to the above series, Langer et al. found residual status (R0 vs.R1 or Rx) to be a non-significant factor ($p=0.071$) [20]. They mitigated their conclusions, as follow-up might have been inadequate, as well as the limited number of patients.

Local recurrences after local excision seem more related to the rectum than to the pelvic wall. However, several authors have raised concern regarding outcome because of the higher rate of local recurrences. Most series report on outcome of salvage surgery after local excision according to Parks, without discriminating between T1 and/or T2 rectal carcinomas [53,57]. Literature on salvage surgery for local recurrences after TEM is sparse, but most authors claims curative salvage surgery to be feasible after TEM [37]. Larger series with longer follow-up have to be awaited, before definite conclusions can be drawn.

In the near future, special focus of interest will be on non-surgical therapy or local excision of rectal carcinomas following neoadjuvant chemoradiotherapy. The only series on TEM following neoadjuvant chemoradiotherapy showed the procedure to be feasible with promising early results [66]. Again however, before definite conclusions can be drawn, larger, randomized studies have to be initiated.

In conclusion, based upon merely retrospective case series, TEM has been incorporated enthusiastically in the surgical armamentarium. Despite the lack of level I evidence, TEM seems justified in well selected T1 rectal carcinomas. To avoid unjustified use of TEM in T1 rectal carcinomas, using molecular profiling, combined with improved radiological staging modalities, node positive tumors have to be diagnosed preoperatively. Further area of investigation should be on neo-adjuvant therapies of rectal carcinomas combined with TEM in a randomized setting.

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