CHAPTER 1

Is the increasing role of transanal endoscopic microsurgery in curation for T1 rectal cancer justified?

A systematic review

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EPIDEMIOLOGY

Colorectal cancer is one of the leading causes of death and accounts for approximately 300,000 new cases in Europe and the USA.\(^1\) In the Netherlands in 2005 over 10,000 patients were diagnosed with colorectal carcinoma.\(^2\) Rectal cancer approximately constitutes 25% of all colorectal carcinomas. Almost half of all patients eventually die from the disease. Majority of rectal cancers develop from benign pre-neoplastic lesions: the adenomatous polyps or adenomas. Progression from a benign adenoma to a malignant carcinoma passes through a series of well-defined histological stages, which is referred to as the adenoma-carcinoma sequence.\(^3\) Because of the implementation of population-based screening programs, the number of patients with early staged rectal carcinomas is likely to increase in the near future.\(^4\)

There has been an impressive evolution in the therapy for rectal cancer. In 1826 Lisfranc was credited the first person to remove the cancer bearing segment of the rectum; he did so using a transanal approach.\(^5\) In that era, the only feasible treatment of rectal cancer consisted of a colostomy to relieve obstruction, as first described by Amussat in 1839.\(^6\) In 1885, Kraske and colleagues approached rectal cancer using a trans-sacral approach, which is removing the coccyx and distal sacrum, with preservation of the anus and muscles.\(^7\) In 1908 the abdomino-perineal resection (APR) was reported, which can be attributed largely to Ernest Miles.\(^8\) After observing a high incidence of cancer recurrence in patients undergoing local treatment for rectal cancer, he developed the concept of radical rectal excision. Miles postulated the lymphatic spread of rectal cancer was directed superiorly and that this surgery allowed complete resection of the anorectum and draining lymphatics. The APR procedure, which gained acceptance largely because it was oncologically sound and successful, has led to the cure of many patients with rectal tumors. Its feasibility was further enhanced by the availability of blood transfusion, allowing this radical surgery to become the most popular method of dealing with rectal cancer by 1947. In 1923 Hartmann described a two-stage procedure for upper rectal cancer.\(^9\) After an artificial anus was constructed, during the second operation the cancer bearing segment was excised and the closed upper rectum was peritonealized. Dixon established the safety of the anterior resection in the late 1940’s, but this approach was mainly limited to the treatment of upper rectal cancer until the 1970’s.\(^10\) At that time, the introduction of circular stapling devices facilitated the technical possibility of low rectal anastomosis and even colo-anal 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, to allow even ultralow resections with colo-anal anastomosis to be accepted as appropriate operations, resulting in survival rates comparable with APR, without the need for a permanent colostomy.\(^11\) 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.\textsuperscript{12} This however suffers from poor exposure and inadequate access to lesions, especially in the upper rectum, resulting in recurrence rates up to 60 percent.\textsuperscript{13, 14} Trans-sacral (Kraske) and trans-sphincteric (Mason) approaches are technically demanding and invasive, resulting in high morbidity (up to 40 percent), often severe and mortality rates of 1-5 percent.\textsuperscript{15-22} Moreover, recurrence rates range between 12 to 25 percent.

Transanal endoscopic microsurgery (TEM) is a recently introduced minimal invasive technique for local excision of rectal tumors.\textsuperscript{23} 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.\textsuperscript{24-27} In a recent report by You et al, from 1989 to 2003 the rate of LE for T1 rectal carcinomas in the USA increased from 26.6 to 43.7% and from 5.8 to 16.8% for T2 rectal carcinomas.\textsuperscript{28} This increasing role is ultimately reflected by several national guidelines, propagating selected tumors suitable for LE.\textsuperscript{29} 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 oncologic 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.

**LOCAL EXCISION OR RADICAL SURGERY**

Radical surgery (RS) for T1 rectal carcinomas leads to excellent results.\textsuperscript{30} Local recurrence rates are invariably low, ranging from zero to six percent. 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.\textsuperscript{14, 28, 31-34} (Table 1) The earlier mentioned study of You et al. reports upon outcome after LE according to Parks (LE) in comparison to radical surgery (RS). 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 were 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.\textsuperscript{34} 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 three centimeters and without lymph vascular invasion, 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.\textsuperscript{14} 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 versus zero percent; $p = 0.03$), as well as overall recurrence rates, although the latter not significantly (21 versus nine percent; $p = 0.54$). Five-year survival rates were comparable (LE 72%, RS 80%; $p = 0.50$). Another study was performed by Bentrem et al.\textsuperscript{32} 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% versus three percent after RS ($p = 0.0001$). Overall recurrence rates also differed significantly (LE 23%, RS six percent; $p < 0.001$).

### Table 1. Comparative series of local excision according to Parks (LE) versus radical surgery (RS) for T1 rectal carcinomas.

<table>
<thead>
<tr>
<th>Author</th>
<th>LE vs. RS (no.)</th>
<th>R0: LE vs. RS (5-yrs %)</th>
<th>LR: LE vs. RS (5-yrs %)</th>
<th>OR: LE vs. RS (5-yrs %)</th>
<th>OS: LE vs. RS (5-yrs %)</th>
<th>Other survival: LE vs. RS (5-yrs %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mellgren (2000)\textsuperscript{14}</td>
<td>69 vs 30</td>
<td>100 vs 100</td>
<td>18 vs 0\textsuperscript{f}</td>
<td>21 vs 9</td>
<td>72 vs 80</td>
<td>DSS: 95 vs. 95</td>
</tr>
<tr>
<td>Nascimbeni (2004)\textsuperscript{31}</td>
<td>70 vs 74</td>
<td>NS</td>
<td>6.6 vs 2.8\textsuperscript{f}</td>
<td>21 vs 10\textsuperscript{f}</td>
<td>72 vs 90\textsuperscript{f}</td>
<td>DSS: 89 vs. NS</td>
</tr>
<tr>
<td>Bentrem (2005)\textsuperscript{32}</td>
<td>151 vs 168</td>
<td>NS</td>
<td>15 vs 3\textsuperscript{f}</td>
<td>23 vs 6\textsuperscript{f}</td>
<td>89 vs. 93\textsuperscript{*}</td>
<td>DSS: 93 vs. 97\textsuperscript{*}</td>
</tr>
<tr>
<td>Endreseth (2005)\textsuperscript{33}</td>
<td>35 vs 256</td>
<td>83 vs 100\textsuperscript{f}</td>
<td>12 vs 6\textsuperscript{f}</td>
<td>12 vs 13</td>
<td>70 vs. 80\textsuperscript{f}</td>
<td>DSS: 64 vs. 77\textsuperscript{f}</td>
</tr>
<tr>
<td>Ptok (2007)\textsuperscript{34}</td>
<td>105 vs 312</td>
<td>100 vs 100</td>
<td>6 vs 2\textsuperscript{f}</td>
<td>10 vs 6</td>
<td>84 vs 92</td>
<td>DFS: 91 vs 92</td>
</tr>
<tr>
<td>You (2007)\textsuperscript{28}</td>
<td>601 vs 493</td>
<td>95 vs 99</td>
<td>12.5 vs 6.9\textsuperscript{f}</td>
<td>16 vs 10\textsuperscript{f}</td>
<td>77 vs. 82</td>
<td>DSS: 93 vs. 97\textsuperscript{f}</td>
</tr>
</tbody>
</table>

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; \textsuperscript{f} statistically significant ($p < 0.05$); NS= not stated; \textsuperscript{*} patients who received neoadjuvant and/or adjuvant therapy were not excluded.
and overall survival rates were similar for LE and RS. Of all recurrences after LE, 77% could be resected radically, compared to 50% of local recurrences after RS. A nationwide, prospective study was performed by Endreseth et al. They analyzed outcome of 291 T1M0 rectal carcinomas treated by LE according to Parks (n=35) or RS (n=256). In the LE group patients were older and tumors were smaller and located more distally and 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 versus six percent; p = 0.01). Overall survival (70 versus 80%; p = 0.04) and disease free survival (64 versus 77 percent; 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. 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 2 and 3)

Only one randomized controlled trial for clinical T1 rectal carcinomas has been performed. 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 percent (1/24). In the RS group no local recurrence occurred. Five-year procedure specific survival rates were 96 percent for both groups.

Langer et al. reported (retrospectively) upon outcome after TEM in comparison to LE according to Parks and RS. 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%; 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 versus 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). In this subgroup of 46 tumors, after TEM local recurrence rate was four percent compared to three percent 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-) vessel 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. Local recurrence rates were comparable (TEM four percent, RS zero percent; 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. 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 percent. These complications are almost always minor with re-operation rates between 0-7 percent. Mortality is rare after TEM. All studies have a follow-up duration of more than 24 months and recurrence rates vary between 0-26 percent. If calculated, five years disease specific survival rates after TEM vary between 81-100 percent and overall survival rates range from 73 to 100 percent.

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. 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, 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, 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
### Table 4. Case series of TEM in T1 rectal carcinomas.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Inclusion criteria</th>
<th>No.</th>
<th>Comments</th>
<th>LR</th>
<th>OS</th>
<th>DSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith</td>
<td>retrospective</td>
<td>NS</td>
<td>30</td>
<td>No adjuvant therapy</td>
<td>3/30 (10%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mentges</td>
<td>prospective</td>
<td>G1/2 curative intent (N=60) G3 in selected patients (N=4)</td>
<td>64</td>
<td>No adjuvant therapy</td>
<td>2/52 (4%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Demartines</td>
<td>prospective</td>
<td>G1/2, LVI -</td>
<td>9</td>
<td>One pt adjuvant therapy, type NS</td>
<td>1/7 (14%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>De Graaf</td>
<td>retrospective</td>
<td>NS</td>
<td>21</td>
<td>No adjuvant therapy</td>
<td>2/19 (11%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Dafnis</td>
<td>retrospective</td>
<td>NS</td>
<td>10</td>
<td>No adjuvant therapy</td>
<td>1/10 (10%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Stipa</td>
<td>retrospective</td>
<td>uT1-T3, &lt; 3 cm G1/2, &lt; 3 cm, &lt;10 cm from dentate line, cN0</td>
<td>39</td>
<td>Overall 43% of pts pre-/postoperative RT</td>
<td>5/39 (13%)</td>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>Duek</td>
<td>retrospective</td>
<td>NS</td>
<td>25</td>
<td>No adjuvant therapy</td>
<td>0/25 (0%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Endreseth</td>
<td>retrospective</td>
<td>NS</td>
<td>8</td>
<td>No adjuvant therapy</td>
<td>0/8 (0%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Floyd</td>
<td>retrospective</td>
<td>NS</td>
<td>53</td>
<td>No adjuvant therapy</td>
<td>4/53 (8%)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Ganai</td>
<td>retrospective</td>
<td>NS</td>
<td>21</td>
<td>One pt postoperative CRT</td>
<td>4/21 (19%)</td>
<td>73%</td>
<td>89%</td>
</tr>
<tr>
<td>Borschitz</td>
<td>prospective</td>
<td>pT1</td>
<td>105</td>
<td>21 pts immediate RS</td>
<td>11/84 (13%)</td>
<td>93%</td>
<td>94%</td>
</tr>
<tr>
<td>Stipa</td>
<td>retrospective</td>
<td>uT1/T2, uN0</td>
<td>23</td>
<td>2 pts preoperative CRT</td>
<td>2/23 (9%)</td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td>Bontanigol</td>
<td>retrospective</td>
<td>G1/2, &lt; 3 cm</td>
<td>31</td>
<td>3 pts immediate RS</td>
<td>3/28 (11%)</td>
<td>79%</td>
<td>81%</td>
</tr>
<tr>
<td>Whitehouse</td>
<td>retrospective</td>
<td>NS</td>
<td>25</td>
<td>2 pts immediate RS Pre-/postoperative CRT not clear</td>
<td>6/23 (26%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Lezocche</td>
<td>prospective</td>
<td>uT1N0</td>
<td>51</td>
<td>Pre-/postoperative CRT not mentioned</td>
<td>0/51 (0%)</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>Maslekar</td>
<td>prospective</td>
<td>G1/2 en 3</td>
<td>27</td>
<td>No adjuvant therapy</td>
<td>0/27 (0%)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

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, RS= radical surgery, OS= overall survival, DSS= disease specific survival, CRT= chemoradiotherapy, RT= radiotherapy.
computerized tomography (CT) scanning and magnetic resonance imaging (MRI). Whether ERUS has additional value in the preoperative staging of rectal tumors, especially in identifying tumors possibly suitable for TEM, should be addressed properly.

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. A more recent study performed by Nascimbeni et al. found invasion in submucosa level 3 (Sm3), lymph vessel invasion and distal rectal carcinomas to be significant contributors to lymph node metastases.

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. None of the conventional pre-operative staging methods, ERUS/CT-scan/MRI has yielded satisfactory results upon identifying lymph node metastases. A recent break through was the introduction of MRI-USPIO. 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. Accepted, although not validated, low-risk criteria in T1 rectal carcinomas, are well to moderate differentiation, carcinomas smaller than three centimetres, without lymph vessel invasion. Above these features, probably excision margin (microscopic radical (R0) versus microscopic irradical (R1)) may be of major importance. 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 percent; however recurrence rates for high risk carcinomas (n= four) were not given, thereby prohibiting adequate comparison. A retrospective, comparative study was performed by Heintz et al. In low-risk carcinomas (n=46) in 78 percent an R0 excision margin with TEM was obtained, whereas in high-risk carcinomas (n=12) only 58 percent of tumors were excised microscopic radical. Regarding local recurrences, in the low-risk group two carcinomas recurred (four percent) and in the high-risk group four carcinomas (33 percent). All recurrences were after a microscopic irradical (R1) excision. Overall survival rates after TEM for low- and high-risk carcinomas were 79 and 62 percent respectively (p-value not given).
A meticulous evaluation was performed by Borschitz et al, with emphasis on margin of excision.\textsuperscript{38} 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 four percent. In high-risk carcinomas with R0 status, the local recurrence rate was already 20 percent. If the excision margin was < 1 mm, unknown (Rx) or positive (R1), the local recurrence rate after TEM was 46 percent. Immediate radical surgery in case of margin < 1 mm, unknown margin status (Rx) or positive margin (R1), results in local recurrence rates of six percent. Survival rates in low-risk carcinomas, microscopic radically excised are 94 percent and if microscopic irradical excised 57 percent. Immediate radical surgery in irradical excised T1 carcinomas results in survival rates of 93 percent.

In contrast to the above studies, Langer et al. found 24 percent of all TEM specimens to be R1 or Rx, but excision margin status was not of significant influence on developing local recurrences.\textsuperscript{26} 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 FOLLOWING 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 percent.\textsuperscript{63-66} Moreover, to obtain a R0 resection, extended resections are required, often involving multi-visceral excision. Results after salvage surgery were significantly worse compared to immediate radical surgery in case of adverse histopathological features.\textsuperscript{61} 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 percent. Salvage surgery in case of a local recurrence after TEM seems amenable to most patients, with often a possible R0 resection.\textsuperscript{51} 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 percent of advanced rectal carcinomas. These figures might even be improved in earlier stages of rectal cancer. 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. Forty patients with histologic proven adenocarcinomas, staged as uT2-N0-M0, G1/2, within six centimeters 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 (2000 mg/m²/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 percent following TEM and 12 percent following laparoscopic TME. Overall survival rates were 95 percent and 83 percent 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. Definite evidence, ideally by means of a randomized controlled trial, has to be awaited and until then this treatment should be considered experimental.

In the near future, special focus of interest will be on non-surgical therapy or local excision of rectal carcinomas following neo-adjuvant chemoradiotherapy. The only series on TEM following neo-adjuvant chemoradiotherapy showed the procedure to be feasible with promising early results. 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 rectal carcinomas, using molecular profiling, combined with improved radiological staging modalities, besides node positive tumors, also tumors with a high chance of a local recurrence 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.
REFERENCES
