Diseases of the Colon & Rectum

Original Contributions

The Influence of Histopathologic Criteria on the Long-Term Prognosis of Locally Excised pT1 Rectal Carcinomas: Results of Local Excision (Transanal Endoscopic Microsurgery) and Immediate Reoperation

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PURPOSE: Local excision of early rectal cancer is a controversial issue, which is in part because of differences in the evaluation of histopathologic criteria. This prospective study was designed to determine prognostic factors for recurrences and the need for reoperation. METHODS: In 105 of 118 patients with pT1 carcinomas and local excision, results of recurrence rates and ten-year cancer-free survival were studied separately according to different histologic criteria (R0, R1, Rx, R $\leq$ 1 mm, high-/low-risk situation), tumor localization (anterior, posterior, lateral wall and third of rectum), size, and degree of resection (full-thickness/partial wall). Patients were grouped into local excision (n = 89) and local excision followed by reoperation (n = 21). Risk classification was performed by division into "low-risk" carcinomas after local R0-resection (Group A) and unfavorable histologic results after local resection (R1, Rx, R $\leq$ 1 mm, high-risk situation; Group B). RESULTS: Local recurrence rates after local R0-resection of low-risk carcinomas were 6 percent, whereas patients in Group B with local resection were 39 percent. The recurrence risk in those patients was significantly reduced to 6 percent by reoperation (P = 0.015). In addition, ten-year, cancer-free survival was 93 percent in Group B after reoperation compared with 89 percent in patients of Group A after local excision alone. CONCLUSIONS: Local R0-resection in cases with low-risk pT1 carcinomas represents an oncologically adequate therapy, which results in similar survival rates compared with primary radical surgery of pT1N0M0 rectal carcinomas. High recurrence rates are observed in tumors with unfavorable histologic result (Group B) requiring further treatment. In these cases immediate reoperation reduces the recurrence rate to 6 percent. [Key words: Rectal cancer; Local excision; Recurrence risk; Survival rate]

The main advantage of transanal resection for early rectal carcinomas over former, more invasive local surgical techniques is the lower risk of intrasurgical and postsurgical complications.[1] However, there is significant variation in the recurrence rates reported by different studies,[2–4] which may be a consequence of differences in the histopathologic assessment for the locally excised specimen. In this study, data were collected in a prospective series of patients to determine the importance of both the technique of local excision and the histopathologic assessment of the extent of the resection for the risk of locoregional recurrence in T1 carcinomas. These measures were performed to establish the conditions under which immediate radical reoperation may be indicated.

PATIENTS AND METHODS

From 1984 to 2001, 561 patients underwent local excision of rectal tumors at the Clinic of General and

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Abdominal Surgery at the Johannes Gutenberg University Hospital, Mainz, Germany. Before surgery, a rigid rectoscopy with biopsy was performed in all patients to determine localization of the tumor and histologic classification. The localization of the tumor in the rectum was measured based on the distance from the anocutaneous line to the distal tumor margin. With respect to the anocutaneous line as point of reference the region below 4 cm represents the anal canal. The lower third of the rectum was defined as the area from 4 to <8 cm, the middle third was defined as 8 to <12 cm, and the upper third was defined as 12 to 16 cm. To judge the remaining colon, a coloscopy or a contrast enema was performed in the majority of patients. Ultrasound examination of the abdomen and a presurgical x-ray of the thorax were routine diagnostic measures. All patients had a rectal-digital examination, and clinical tumor staging was performed according to the categories described by Mason.[5] Since 1987, transanal endosonography was performed to determine the depth of tumor invasion, in addition to the assessment of tumor markers carcinoembryonic antigen and CA 19-9.

A pT1 carcinoma was identified in 120 patients. The tumor was excised in 64 patients (53 percent) by using a full-thickness technique, and a partial-wall excision was performed in 56 patients (47 percent). Full-thickness excisions were defined histologically as specimens in which the tumor basis was completely surrounded by a layer of perirectal fat. Apart from mucosectomies, all other specimens that did not meet the criteria of full-thickness excisions were grouped as partial-wall excision. The transanal endoscopic microsurgery (TEM) technique developed by Buess and colleagues[6] was applied in 111 patients. Another seven patients were treated by using the TEM technique in combination with the method according to Park, whereas an anal-retractor alone was used in two patients. The excised specimen was mounted on a cork plate by the surgeon and transferred to the Institute of Pathology for histologic assessment. The examination included an evaluation of the depth of tumor infiltration according to International Union Against Cancer (UICC) guidelines,[7] the degree of tumor differentiation (G1 = good, G2 = moderate, G3 = poor, and G4 = undifferentiated), in addition to the identification of tumors with lymphatic (L1) or venous invasion (V1). Poorly to undifferentiated carcinomas and/or tumors with lymphatic or venous invasion were classified as "high-risk" carcinomas, consistent with the criteria proposed by Hermanek and Gall.[8,9] Additional radical surgery within a period of four weeks was indicated in cases with R1 resection, high-risk carcinomas, tumor extending to the resection margin (≤1 mm), or in the presence of tumor fragmentation. These patients were combined in Group B; patients with "low-risk" cancer after clear R0 resection were designated as Group A.

During a period of two years, follow-up examinations were performed at six-month intervals, which included a rectal-digital investigation, rectoscopic, and abdominal ultrasound examination. In cases with preoperatively raised carcinoembryonic antigen or CA 19-9 levels, these also were determined at follow-up visits. Thereafter, supplementary examinations were performed annually for a period of up to five years. In addition, a coloscopy was scheduled after two years and repeated at five years, followed by further coloscopic examinations at three-year intervals. In all cases, local recurrences were diagnosed based on a histologic assessment of specimens excised during reoperation or by obtaining biopsies. When the tumor was limited to the rectal wall or to the perirectal fatty tissue, it was defined as a local recurrence. Additional recurrences limited to the small pelvis were classified as locoregional, and those occurring at other locations were defined as distant metastases.

The SSPS® software package was used for statistical analysis of the data (SSPS® 11.0 for Windows®, SPSS Inc., Chicago, IL). An univariate analysis using the log-rank test was used for the evaluation of local recurrences in dependence on tumor stage, size, localization (anterior, posterior, or lateral wall) and distance from the anocutaneous line (upper, middle, lower rectum), extent of resection (full-thickness/partial wall), as well as the quality of the resection margin. In addition, cancer-free survival was calculated for patients after TEM resection compared with those undergoing reoperation using a Kaplan-Meier analysis. The performance of multivariate analysis was not allowed because of small sample sizes within subgroups.

Patients

After surgery, pT1 carcinomas were identified in 120 patients (64 males; median age, 68 (39–89) years). A high-risk tumor was found in 15 patients (13 percent). In 41 patients the carcinoma was

known preoperatively, whereas 79 patients underwent surgery after the diagnosis of an adenoma. Two patients with high-risk tumors that were not eligible for additional radical resection received adjuvant radiochemotherapy and were excluded from further evaluation. A total of 13 patients were lost in follow-up, among these were three tumors with high-risk situation. Data are available for 105 (89 percent) of the remaining 118 patients for a median period of 74 (range, 6–211) months. The tumors were localized in the lower third of the rectum in 45 (38 percent), in the middle in 47 (40 percent), and in the upper third in 26 (22 percent) patients. In 39 (33 percent) patients, the carcinoma was located at the anterior, in 44 (37 percent) at the posterior, and in 35 (30 percent) patients at the lateral wall of the rectum. The mean tumor size was 3 (1–10) cm, and a high-risk situation was found in 10 of these 105 patients. The tumor was operated on in 63 patients (53 percent) by using a full-thickness excision, and a partial-wall excision was performed in 55 patients (47 percent). Reoperation after local excision using the same technique (TEM) was necessary because of bleeding complications in two patients (2 percent). Five patients (5 percent) showed minor complications that did not require reintervention (perirectal abscess, n = 1; pneumoperitoneum with suture during primary TEM, n = 4). In none of our patients was there a reason to change to conventional technique and no patient died perioperatively. Temporary bowel incontinence because of sphincter weakness was observed in three cases, and after a period of three months these problems were self-limited. Local excision alone was performed in 84 patients with pT1 carcinomas. Twenty-one patients underwent additional radical reoperation: four of these after R0 resection, six after R1 resection, five with high-risk tumors, two because of a carcinoma extending to the resection wall (≤1 mm), and four patients with an Rx resection because of tumor fragmentation. Both patient collectives (TEM *vs.* TEM + reoperation) were similar. The mean age of 43 males and 41 females receiving TEM alone was 66 (range, 41–86) years. The group with TEM and reoperation included 13 males and 8 females, and the mean age was 60 (range, 39–81) years.

RESULTS

Local Recurrence After TEM Resection Alone

A R0 situation after sole TEM resection was found in 66 patients with low-risk and in 5 patients with high-risk carcinoma. One patient exhibited a R1 resection, in eight patients the resection margin (Rx) was not clear, and in four patients the carcinoma extended to the resection border (≤1 mm; Table 1).

Four of 66 patients (6 percent) with low-risk carcinomas undergoing R0 resection (Group A) had a recurrence, which developed after a mean period of 14 (range, 4–18) months. One of five patients with a high-risk tumor, which had been completely excised according to histopathology, developed a

Table 1.
Local Recurrence After Local Resection of pT1 Rectal Carcinoma Using Transanal Endoscopic Microsurgery Technique

Local Recurrence	R0 Low-Risk	R0 High-Risk	R1	R ≤ 1 mm	Rx	Total	α
Third of rectum (cm)							$P = 0.47$
4–8	2/26 (8)	1/1 (100)	–	2/3 (66)	1/3 (33)	6/33 (18)	
8–12	1/24 (4)	0/3 (0)	1/1 (100)	–	–	2/28 (7)	
>12	1/16 (6)	0/1 (0)	–	0/1 (0)	2/5 (40)	3/23 (13)	
Location							$P = 0.97$
Anterior wall	2/23 (9)	–	–	0/1 (0)	2/3 (67)	4/27 (15)	
Posterior wall	1/25 (4)	1/2 (50)	1/1 (100)	1/2 (50)	0/2 (0)	4/32 (13)	
Lateral wall	1/18 (6)	0/3 (0)	–	1/1 (100)	1/3 (33)	3/25 (12)	
Resection							$P = 0.15$
Full-thickness	2/44 (4)	1/4 (25)	–	1/1 (100)	0/1 (0)	4/50 (8)	
Partial wall	2/22 (9)	0/1 (0)	1/1 (100)	1/3 (33)	3/7 (43)	7/34 (21)	
Tumor size							$P = 0.27$
≤3 cm	2/40 (5)	1/5 (20)	–	1/2 (50)	0/1 (0)	4/48 (8)	
>3 – ≤6 cm	1/23 (4)	–	1/1 (100)	1/2 (50)	3/6 (50)	6/32 (19)	
>6 cm	1/3 (33)	–	–	–	0/1 (0)	1/4 (25)	
Total	4/66 (6)	1/5 (20)	1/1 (100)	2/4 (50)	3/8 (38)	11/84 (13)	

Data are numbers with percentages in parentheses unless otherwise indicated.

recurrence after seven months. The patient with R1 resection developed a local recurrence after six months. Two of four patients with a carcinoma extending to the resection margin showed tumor recurrence after 6 and 38 months, respectively. A local tumor progression was observed in three of eight patients (38 percent) with Rx resection after a median period of 16 (range, 7–22) months (Group B).

When all patients with high-risk tumors, R1 or Rx resection, and carcinomas extending to the resection margin are combined in one evaluation group with unfavorable histologic classification (Group B), the development of local recurrence is observed in 7 of 18 patients (39 percent). All patients with positive or suspicious margins (R1, Rx, and R ≤ 1 mm) did not exhibit high-risk situations. After subdivision of Group B into patients with high-risk tumors and R0 resection, the recurrence rate was 1 of 5 (20 percent), whereas patients with R1, Rx, and R ≤ 1 mm resections showed local recurrence rates of 6 of 13 (46 percent; Table 1). A further separation in R1 (n = 1), Rx (n = 8), or R ≤ 1 mm (n = 4) was not feasible because of the small patient numbers without demographic comparability. Univariate analysis using the log-rank test did not demonstrate significant differences in the development of recurrence on division into the following categories: low-risk or high-risk tumors, dependence of upper, middle, or lower rectum involvement, rectal wall localization, extent of resection, or safety margin.

The lowest local recurrence rates after TEM-R0 resection were noted for low-risk pT1 carcinomas, ranging at 4 percent for tumors in the middle third of the rectum (1/24), location at the posterior wall (1/25), after full-thickness excision (2/44), and occurred in 5 percent (3/63) of patients with tumors ≤6 cm in size (Table 1).

Local Recurrence After TEM Followed by Conventional Reoperation

TEM resection was followed by additional radical reoperation in 21 patients (3 anterior, 16 low anterior resection, 2 abdominoperineal extirpations). Four patients with preoperatively diagnosed adenoma, who were diagnosed with low-risk carcinomas after TEM-R0 resection (Group A), wished radical reoperation and did not develop local recurrence (Table 2).

After combining five patients with high-risk carcinomas, six with R1 resection, four with Rx resection, and two patients with carcinomas extending to the resection margin (<1 mm) in one (Group B), development of local recurrences was observed in 6 percent (1/17) of the patients nine months after reoperation with the tumor extending to the resection margin (Table 2). In aggregate, in both groups (A+B) the rate for development of systemic metastasis after local excision after immediate reoperation was 5 percent (1/21).

Table 2.
Local Recurrence After TEM Resection and Reoperation of pT1 Rectal Carcinoma

pT1 TEM Histology	TEM + Reoperation	Local Recurrence
Group A	4	0 (0)
Group B	17	1 (6)

TEM = transanal endoscopic microsurgery.
Data are numbers of patients with percentages in parentheses.

Cancer-Free Survival

Kaplan-Meier analysis showed that in patients with TEM-R0 resection and pT1 low-risk carcinomas (n = 66) the cancer-free survival was 94 percent after five years and 89 percent after ten years (Table 3; Fig. 1). One of four patients with local recurrence developed liver metastasis after 12 months. Pulmo-

Table 3.
Cancer-Free Survival After TEM Resection Alone and After TEM With Reoperation

Histology	Surgical Procedure	No. of Patients	Mean Age (yr)	CFS (%)		α
				Five-Year	Ten-Year	
Group A	TEM resection	66	66 (41–81)	94	89	$P = 0.162$
	TEM + reoperation	4	60 (47–67)	75	75	
Group B	TEM resection	18	68 (49–86)	57	49	$P = 0.015$
	TEM + reoperation	17	60 (39–81)	93	93	

TEM = transanal endoscopic microsurgery; CFS = cancer-free survival.
Data are numbers with ranges in parentheses unless otherwise indicated.

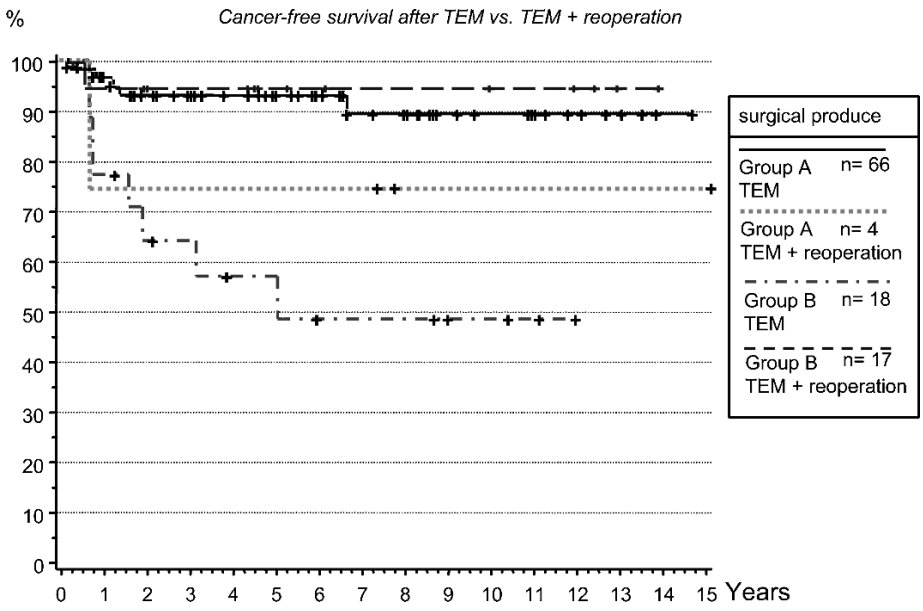

Figure 1. University Hospital Mainz: TEM excision of pT1 rectal carcinoma. Kaplan-Meier analyses: cancer-free survival after TEM alone and TEM + reoperation in patients with favorable (Group A) and unfavorable (Group B) histologic results. TEM = transanal endoscopic microsurgery.

nary metastasis was diagnosed in an additional patient after 87 months. In patients after R0 resection of low-risk tumors, the total metastasis rate was 3 percent (2/66).

Cancer-free survival without reoperation was 57 percent (5 years) and 49 percent (10 years) in Group B (high-risk tumors, n = 5; R1, n = 1; Rx, n = 8; R ≤ 1 mm, n = 4). One of seven patients with locoregional recurrences developed liver metastases after 62 months. This patient was diagnosed with high-risk carcinoma. Overall, the metastasis rate of patients with high-risk tumors was 20 percent (1/5). Among the remaining 13 patients with unfavorable resection margin, 1 patient (8 percent) with tumor extending to the resection margin developed hepatic metastases 38 months after TEM surgery. In aggregate, the observed rate for systemic metastasis of patients in Group B after local excision alone was 11 percent (2/18).

After 26 months, peritoneal carcinomatosis occurred in one of the reoperated patients with low-risk carcinomas and no further local or distant recurrences were observed during a follow-up period of 10 years (Group A, n = 4). Cancer-free survival after five and ten years was 93 percent in Group B (n = 17) with reoperation. One patient from this group had local recurrence, but no patient developed metastases. In a total number of 21 patients with immediate reoperation (Group A+B), systemic metastasis were observed in 5 percent (1/21).

Log-rank analysis identified a significant improvement (P = 0.015) in the ten-year cancer-free survival rate of patients with histologically proven unfavorable result (Group B) after TEM who underwent radical reoperation immediately after diagnosis (Table 3).

DISCUSSION

The value of local excision for the treatment of rectal carcinoma is a controversially debated issue, arising from significant differences in the recurrence rates cited by numerous studies.[1–4,10–23] The assessment of the reported data is limited because of large variations in the histologic evaluation in each study regarding the type of cancer, extent of local excision, and duration of follow-up.

In this prospective follow-up study, 120 patients underwent local excision for rectal carcinoma. The postoperative course is known in 105 of these patients, who were followed for a median period of 74 months. The histopathologic examination was performed according to a standardized procedure. The histologic results of the resection were classified as R0 or R1. In addition, patients with unclear (Rx) and tumors extending to the resection margin (≤1 mm) were analyzed separately. Carcinomas of the categories G1/2, L0, and V0 were described as low-risk, and those of the categories G3/4 and/or V1/L1 as high-risk tumors. A correlation was established between the locoregional recurrence rate and tumor localization, the degree of excision (full-thickness, or partial wall), and the result of the histopathologic

examination. The goal was to determine the importance of critical histopathologic evaluation after local excision of early rectal carcinomas for long-term outcome and identify selection criteria for patients who require oncologic radical reoperation.

Differences in the local excision technique were shown to have an influence on the recurrence rate. Additional to mucosectomies, TEM specimens that did not meet the criteria for full-thickness excisions (covered by a layer of perirectal fat) were classified as partial-wall excisions. As expected, the lowest recurrence rate (4 percent; 2/44) was achieved after full-thickness excision compared with a rate of 9 percent (2/22) after partial-wall excision. Our different histologic classification may be the reason why our data were not statistically significant. There was no definite correlation between the risk of recurrence and tumor localization or tumor size, although tumors with a diameter of ≥6 cm were associated with higher recurrence rates (25 percent). In a literature analysis performed by Graham *et al.*,[14] the authors found a recurrence rate of 11 percent for tumors ≤ 3 cm in size and 33 percent for larger tumors. However, none of the studies included in the analysis described used the transanal endoscopic microsurgical technique that was used in the present patient population.[14] Baron and colleagues[24] and Faivre and colleagues[25] did not find a relationship between tumor size and recurrence rate.

The locoregional recurrence rate after a histologically proven complete excision (R0 resection) was 6 percent (4/66) for low-risk pT1 carcinomas. Therefore, the recurrence rate for low-risk tumors in this study is within the lower range of rates reported by other researchers (0–25 percent).[2–4] Kim and Madoff[18] determined a recurrence rate of 5 percent for low-grade (G1/2) pT1 carcinomas after R0 resection, whereas Mentges and colleagues[19] and Winde and colleagues[23] calculated a rate of 4 percent for low-risk pT1 tumors. In the present analysis, the high recurrence rate of 39 percent (7/18) for Group B, shown separately as 20 percent (1/5) for high-risk tumors and 46 percent (6/13) for critical resection margins (R1, Rx R ≤ 1 mm), is in accordance with rates reported in the literature.[2–4,14,15,26] In contrast, with regard to local recurrences rates, patients with critical resection margin and high-risk carcinomas benefited from immediate reoperation, leading to a significant improvement (P = 0.015) of the ten-year cancer-free survival rate. Of our 21 immediately reoperated patients, 12 showed a questionable TEM resection result (R1, Rx, R ≤ 1 mm) and 5 patients had a high-risk carcinoma. One of these patients (5 percent), who was reoperated because of a doubtful resection margin (R ≤ 1 mm), developed a local recurrence.

These findings are in support of the need for reoperation not only in patients with high-risk carcinoma or tumor invasion of the resection margin (R1), but also in those with an extremely narrow resection margin (≤1 mm) or with tumor fragmentation. Adherence to the principle of ensuring an

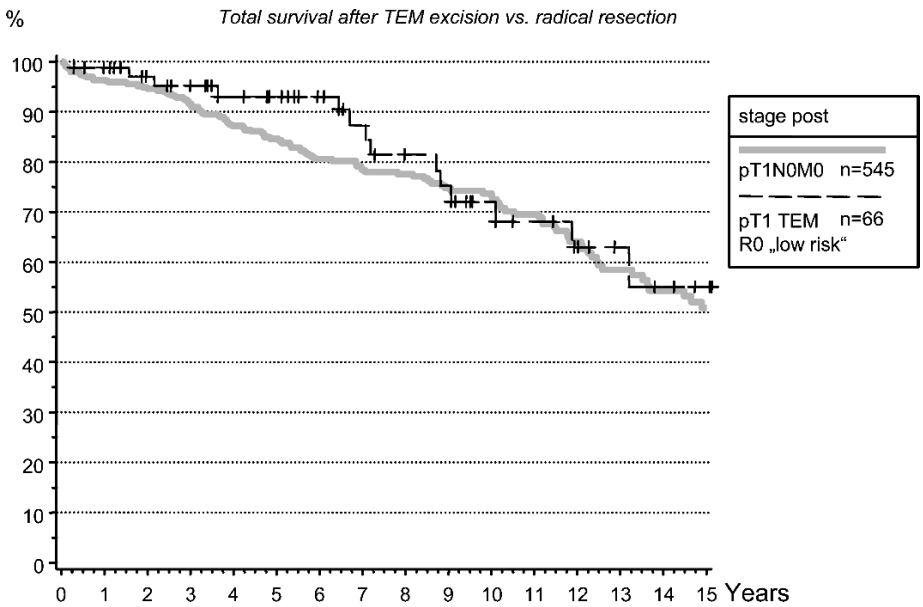

Figure 2. University Hospital Mainz/Tumor Register Munich: pT1 rectal carcinoma. Kaplan-Meier analyses: influence of type of operation (TEM excision *vs.* radical operation) on total survival. TEM = transanal endoscopic microsurgery.

adequate safety margin (1 cm) is a prerequisite for averting the risk of tumor recurrence. This is consistent with experiences of Baron *et al.*[24] For patients after local resection of rectal cancer, they demonstrated that the five-year, disease-free survival was significantly improved after immediate reoperation (94 percent) *vs.* salvage surgery (56 percent). In addition, the studies by Mellgren *et al.*[26] and Friel *et al.*[27] have proven that patients with local excisions of pT1 carcinomas awaiting reoperation of recurrences have a shortened disease-free survival compared to patients with conventional therapy.

Despite the achievement of complete tumor resection, patients with high-risk tumors had a high-risk of recurrence. One reason is the increased chance for high-risk pT1 carcinomas to develop lymph node metastasis. A series of studies investigating the lymph node status of pT1 tumors found constant results.[28–46] A review of this literature by Deinlein and colleagues[46] revealed that high-risk carcinomas exhibit an overall chance of 14 percent to develop lymph node metastasis, whereas the risk for the appearance of lymph node metastasis is minimal (1–2 percent) for low-risk cancers. In no patient of this study did the preoperative biopsy detect the presence of a high-risk status. This is consistent with experiences reported by other authors.[15,26]

Systemic metastasis were detected in 20 percent (1/5) of our patient collective with high-risk carcinomas and in 8 percent (1/13) with unfavorable resection results (R1, Rx, R $\leq$ 1 mm) after local excision alone. In aggregate, the rate for development of systemic metastasis after TEM excision alone was 11 percent (2/18) for tumors with critical histologic results. However, after R0 resection, patients with low-risk carcinomas developed distant metastasis in 3 percent (2/66).

In our patients with pT1 tumors, which have been treated by local excision alone, distant metastasis was found in 5 percent (4/84). For comparison, patients who received immediate reoperation developed local or distant recurrences in 5 percent (1/21). These findings are consistent with the observations by Deinlein and colleagues,[46] who calculated a systemic metastasis rate of 7 percent for pT1 rectal carcinomas, and by Cecil and colleagues,[47] who reported a total of 8 percent distant recurrences after total mesorectal excision of Dukes A tumors.

Compared with long-term follow-up of patients with T1N0M0 tumors who underwent primary conventional surgery,[48] our data suggest that local R0 resection of low-risk pT1 carcinomas offers similar chances for cure. The 15-year survival rates observed in our patient population are consistent with those of the IBE Tumor Register Munich (Ludwig Maximilian University, Munich, Germany) for patients after radical surgical therapy (Fig. 2).

CONCLUSIONS

Local excision for pT1 carcinoma may be considered as an adequate surgical treatment, with the advantage of low rates of associated perioperative complications, urogenital dysfunctions, and short periods of hospitalization. Decisive factors for the outcome are differences in the histopathologic assessment for the locally excised specimen. To be avoided are both an incomplete resection (R1) and an extremely narrow resection margin ($\leq$1 mm), in addition to fragmentation of the tumor, which renders an accurate assessment of the resection margin impossible. In these circumstances, there is an increased risk of locoregional recurrence after local excision when performed as the sole procedure. However, the risk of recurrence is significantly reduced after immediate radical reoperation. The critical determinant for successful surgery is a narrow time frame for reoperation. It should take place within the first few weeks after TEM and not after local recurrences have previously developed. Further data are needed to answer the question of whether adjuvant radiochemotherapy may lead to similar results compared with those obtained after radical reoperation. In this regard, a critical histologic assessment is required to judge whether radiochemotherapy is an adequate oncologic therapy or whether, depending on the histologic classification, division into different treatment arms is necessary. Previous studies showed beneficial results after adjuvant radio-(chemo)-therapy.[49,50] A prospective, randomized study may serve to provide the data from which future conclusions can be drawn.

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INVITED COMMENTARY

To the Editor—During the past 20 years, there has been tremendous advances in all facets of the management of adenocarcinoma of the rectum. Potential treatment options have burgeoned to include modalities, such as chemotherapy, radiotherapy, and innovative surgical techniques, which often are brought together in a multidisciplinary approach. The surgeon, because of necessity, has now become the leader of this multispecialty team. Further advances include the recognition of advanced histopathologic features and improvement in preoperative assessment of tumor stage leading to the coordinated administration of chemoradiation in a neoadjuvant or adjuvant setting. Radiotherapy was initially considered only as a last resort for presumed terminal patients with far advanced, fixed, nonresectable tumors. The field of chemotherapeutics has grown from a single drug (5-fluorouracil) to an impressive and growing menu of complementary agents, often used in conjunction with radiotherapy to provide a synergistic effect. Even surgical techniques have been refined with confirmation of concepts, such as sharp, circumferential dissection preserving tissue planes, thus allowing oncologically sound *en bloc* removal of tumor-bearing tissue. In short, we now have the advantage of more therapeutic options and diagnostics, providing better prognostic information so that rectal cancer may be assessed and managed in a collegial, multidisciplinary fashion.

More recently, the widespread use of local excision techniques once described for all stages of rectal carcinoma has methodically and effectively been eliminated as a curative procedure. Other local, ablative-type procedures (electrodessication, intracavitary/Papillon radiotherapy) "have been abandoned in the potentially curative setting."[1] Furthermore, local excision techniques have been abandoned for T4, T3,[1–3] and T2[4–7] rectal cancer (except for patients unfit for abdominal surgery).

Recent reports from several high-profile tertiary care centers now provide evidence of high recurrence and low salvage rates for "favorable" or "low-risk" T1 rectal carcinoma, thus casting doubt on the propriety of local excision techniques for any invasive rectal carcinoma. These centers of excellence include Memorial Hospital and Sloan-Kettering Cancer Center (MHSKCC), Cleveland Clinic, University of Minnesota, Mayo Clinic, and Roswell Park Cancer Institute (RPCI). The Cleveland Clinic study,

for instance, excluded patients with poorly differentiated cancers, perineural or lymphovascular invasion, or cancers with a mucinous component.[8] Despite this highly select group of patients with T1 rectal cancer, the recurrence rate was still 29 percent with salvage surgery resulting in only 56 percent five-year survival. The University of Minnesota study also excluded patients with "adverse histologic features" (poor differentiation, lympovascular invasion or mucinous component) and reported an 18 percent recurrence rate with only 59 percent of patients free of disease after radical salvage surgery.[9] The stage of the recurrent cancer was more advanced than the primary tumor in 93 percent of patients, leading to the conclusion that salvage surgery cannot provide results equivalent to those of initial radical treatment. MHSKCC also excluded those with "adverse pathologic features" (poor differentiation) and noted a 17 percent recurrence rate.[10] The Mayo Clinic prefers a "more aggressive approach with primary radical surgery."[11] In their retrospective study of "highly selected" patients with locally excised T1 rectal cancers, who all had radical surgery within 30 days, 21 percent of these low-risk T1 rectal cancers were found to have lymph node metastases. The RPCI reported recurrence in 31 percent of T1 rectal cancers.[12] Recent studies with similar results originate from Australia,[6] Canada,[13] and the United Kingdom.[1] Given this background, it is not surprising that enthusiasm for local excision techniques for adenocarcinoma of the rectum has waned.

The current study by Borschitz *et al.* focuses on surgical technique. However, poor technique is not the reason for these high local recurrence rates and average salvage rates. The focus on T stage while low N stage is a recipe for disaster. The consternation about recent reports of high local recurrence after local excision is understandable given the previous understanding of the risk of nodal metastases for these T1 rectal cancers. Borschitz *et al.*, for instance, claim that "the appearance of lymph node metastasis is minimal (1–2 percent) in low-risk cancers." However, a Mayo Clinic study revealed that the lower one-third of the rectum is especially prone to lymphatic spread in their retrospective study of patients with T1 rectal carcinoma who underwent radical resection. Thirty-four percent of patients with lower third cancers had lymph node metastases compared with 10 percent with cancers in the rest of the rectum. Furthermore, MHSKCC reported a lymph node metastasis rate of "22 percent in the lower rectum compared with 8 percent in the left colon."[14] Clearly, misunderstanding of the actual risk of nodal spread for T1 carcinoma of the distal rectum may lead one to question these studies that report very high rates of tumor recurrence. Such misconception has led to accusations and disparaging remarks regarding the technical skills of the surgeons and institutions reporting this data.[15]

Further confounding the situation is our inability to accurately establish nodal spread in the preoperative setting. The most recent University of Minnesota experience with the use of endorectal ultrasound (ERUS) to stage rectal cancer is troubling.[7] The "accuracy was lower than previously reported" at 64 percent, with 25 percent of patients over-staged and 11 percent of patients under-staged. ERUS is limited in that it can only visualize enlarged lymph nodes (which may be benign) and not image small lymph nodes. We know that metastatic lymph nodes are most commonly < 5 mm.[16] In a Mayo Clinic study, the T-stage accuracy of ERUS for T1 rectal cancer was only 39 percent.[8]

Even the most precise technique of transanal excision will still violate tumor-bearing tissue planes in a significant number of patients with low-risk T1 rectal cancer containing unrecognized lymphatic spread. This scenario may result in up-staging of the tumor as cancer cells are spilled and scattered. This possibility has led Mellgren *et al.*[7] to conclude that "salvage surgery can be successful but cannot provide results equivalent to those of initial radical treatment." Given the massive amount of medical literature with discourse on proper techniques of radical rectal resection, including preservation of Heald's "holy plane,"[17] it does not make intuitive sense to blow a hole through this "holy plane" and then scramble to mop up the mess.

The reality is that for low-risk T1 rectal cancers without any adverse histopathology, the surgeon will not be aware of these circumstances until the patient returns some time later with detectable recurrence. The pathologist can only comment on the tissue removed (bowel wall) and not on the tissue left inside the patient (lymph nodes). In the best-case scenario for a patient with lymph node metastases, the pathology report will establish high-risk or adverse histopathology (poor differentiation, mucin production, or lymphovascular invasion), prompting the surgeon to advise adjuvant therapy, radical surgery, or a combination of the two. In the worst-case scenario for a patient with undetectable lymph

node metastases, there will be no high-risk or "adverse" histopathology but only "favorable" or low-risk features of T1 rectal cancer. Postoperative discussion may veer away from further intervention, such as radical surgery (avoid a stoma) and perhaps adjuvant chemoradiation, toward observation alone. It is exactly this scenario that led to the recent studies revealing high rates of cancer recurrence for favorable T1 rectal cancer. Borschitz *et al.* suggest "immediate radical reoperation" and state, the "critical determinant for successful surgery is a narrow time frame for reoperation," and not wait for signs of recurrence.[14] How can they know which patients should have radical resection if there are no clues, no red flags: no adverse histopathology? That would only work for those who exhibit high-risk behavior on pathology. What about the rest?

I agree with the Mayo Clinic suggestion of chemoradiation for low-risk T1 rectal cancer of the lower one-third of the rectum.[11] Despite their reasoning, Borschitz *et al.* could find no difference in T1 rectal cancers treated by local excision alone *vs.* patients who had immediate reoperation (5-percent recurrence in both groups). Similarly, the Mayo Clinic reported "immediate radical surgery after attempted local excision did not compromise outcome, but it also did not significantly improve outcome compared with local excision only."[11] I agree with their conclusion that "the poor results of salvage surgery emphasize the importance of appropriate selection of the initial treatment of Stage 1 rectal cancers."[11] Such appropriate treatment may no longer include local excision alone. Rather than rushing the patient back to surgery for "immediate radical reoperation," given the likelihood of nodal metastases, preoperative neoadjuvant chemoradiation would seem to be an excellent alternative before any attempts at curative resection.

The full and frank discussion that we have with our rectal cancer patients in the postoperative period would be incomplete without recognition of the propensity of lymphatic spread even in these small, favorable T1 carcinomas of the distal rectum. So, what do we say to our patients? What advice do we give?

First, full disclosure is a must. Patients need to know the risks of recurrence, or more precisely, the odds of having left cancer behind in the surrounding lymphatics. Second, prompt referral to our colleagues in oncology (radiation and medical oncology) for further discussion and clarification of treatment options, including risks and benefits. I believe this is especially prudent for United States-based surgeons, considering the medicolegal climate in this country. Litigation over cancer recurrence and alleged "lack of informed consent" may wither if the medical record contains documentation from multiple specialist consultants reinforcing these various issues.

Above all else, we want to do the right thing for our patients, leading the way to recovery and well-being. We must not forget the patient's role in this decision-making process. Some patients seemingly make the decision process easy by saying, "Doc, I don't want a bag," or "I'll take my chances" when rejecting all options for further surgical or adjuvant treatment. Typically that sentiment will quickly change to, "Doc, I don't want to die!" if the unexpected happens and cancer recurrence is detected. Conversely, some patients have absolutely no qualms about life with a stoma, if it means an increased chance of survival.

These tough decisions will not go away. Even surgeons who reject local excision techniques for rectal cancer will still face the situation when the pathology report on that large villous adenoma reveals an invasive adenocarcinoma or the endoscopist sends over the patient after removal of a polyp containing invasive adenocarcinoma. Pandora's Box of issues, options, and headaches will be wide open.

Although studies continue to emerge regarding the role of adjuvant therapy and/or radical resection for these patients, many questions remain unanswered. Borschitz *et al.* recommend immediate radical surgery for those tumors that display adverse features on pathology or for those with local recurrence. I would favor the algorithm established at the University of Minnesota and initiate therapy with preoperative chemoradiation for those who have not previously received radiation.[9] Several studies similarly suggest postoperative radiation therapy after local excision in patients with favorable or low-risk T1 rectal cancer (negative prognostic factors).[13,18,19] One must recognize that in this case scenario, the time to local recurrence may be more than ten years.[10]

For a small subset of patients, transanal excision is acceptable and may be the only viable treatment option (patients unfit for abdominal surgery or chemoradiation). The vast majority of patients require a time investment for the decision-making

process to discuss treatment options along with their own individual wants and needs to come up with an acceptable plan on a case-by-case basis.

Expectations must be reasonable. We cannot save every patient. Bleday *et al.*[20] have stated that "a more fatalistic viewpoint is that some tumors have 'bad biology' and that no matter what operation one does (abdominoperineal resection, local excision, local excision plus adjuvant chemoradiation) they will recur and the patient will die of their disease." This is every surgeon's nightmare. Moreover, we have no way of knowing just who these "bad biology" patients are. Sadly, perusal of these recent studies suggests that there may be a lot more of these patients than any of us ever imagined.

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THE AUTHORS REPLY

To the Editor—We thank Dr. Cirocco for his controversial and complex commentary in which he highlights the huge variability of results obtained after local excision of T1 rectal cancer. In addition, he challenges local excision to be an adequate therapy for T1 rectal carcinoma even in low-risk situations because of the possible presence of lymph node metastases.

Recent literature analyses regarding the outcome of local excision of T1 rectal cancer report local recurrence rates as an average of 10 percent. For so-called low-risk carcinomas (G1-2/V0/L0) values of approximately 5 percent were determined, and the best results were obtained with the transanal endo-

scopic microsurgical technique (TEM).[1–3] Using this technique, tumors in the upper and lower third of the rectum can be reached alike. The low recurrence rate was confirmed in a hitherto single, prospective, randomized study (4 percent).[4] In contrast, other studies have shown noticeable higher local recurrence rates (23 percent) for low-risk carcinomas.[1,2,5]

While reviewing the literature, one notices that the terms "low risk" and "high risk" are not used uniformly. "Low-risk" and "low-grade" carcinomas often are equated, whereas the term "high risk" is extended to R1 resections.[1,2] This may be the reason for the discrepant results obtained from this "homogeneous" group, which does not exist in reality. Regarding the acquisition of histopathologic results, Dr. Rothenberger recently discussed with Dr. Paty, as senior author of the paper by Bentrem *et al.*, the difficulty of a retrospective assessment of histologic findings.[6] In addition to a general loss of data, information about tumor-associated vessel invasion, for example, may be missing. In the 1990s, the value of tumor differentiation in combination with vessel invasion was increasingly appreciated as prognostic factor and included into the documentation. However, to date the term "high-risk" situation suggested by Hermanek and Gall is not used uniformly.[7]

The goal of our study was to critically analyze our patient collective according to histologic criteria. Our total local recurrence rate after local resection of T1 carcinomas (13 percent) is consistent with prevailing results (Hahnloser 8 percent; Floyd 11 percent; Endreseth 12 percent; Bentrem 13 percent; Gopaul 13 percent).[6,8–11] In a detailed analysis of the histopathologic results, we noted clear differences in recurrence rates within our patient collective. Tumors excised with a clear safety margin (>1 mm) and low-risk tumors resected *in toto* showed significantly lower local recurrence rates (6 percent) than T1 carcinomas with prognostically unfavorable resection results (39 percent). Similar results were obtained by Kim and Madoff.[12] For histopathologic assessment it was of importance that the pathologist received the specimen *en bloc*. If the tumor was fragmented or the resection margin mechanically altered, no reliable statement about the radicality (R0/R $\leq$ 1 mm) or vessel involvement was possible. Dr. Paty discussed difficulties in the assessment of resection margins if the specimen and margins were artificially altered[6].

We were able to show that especially the resection result is of critical value. In our experience, this represents an independent unfavorable prognostic parameter for the development of local recurrences in addition to detection of a high-risk situation. Few authors present their results about recurrence rates separated for high-risk tumors, questionable or positive resections margins, but cumulative.[1,2,5,6,9–11] Often it remains unclear whether the recurrences arise from these unfavorable resection results. Others report only about patients after R0 resection of low-risk tumors.[1,2,5,11] In retrospect, it would be of interest to learn about the patients after R1 resection or those with high-risk tumors: how cases with fragmented tumors were proceeded, and how results, which were not classified as R1 by the pathologist, were included in further analysis.

In our patient collective, we achieved similar results (5 percent) by immediate reoperation of patients with prognostically unfavorable results compared with primary conventional surgery (Bentrem *et al.*[6] 2 percent; Hahnloser *et al.*[8] 5 percent; Endreseth *et al.*[10] 6 percent). Baron *et al.*[13] and Hahnloser *et al.*[8] confirmed these results obtained with immediate reoperation. In addition, in the annex to his recent study, Dr. Paty reported that patients with local R1 resection were immediately reoperated and analyzed together with patients with primary conventional surgery, thus equating these groups.[6] For the concept of delayed salvage surgery, *i.e.,* reoperation of patients after the development of recurrences, significantly inferior results have been reported.[14–16]

Dr. Cirocco mentions the central role that lymph node metastases have in the development of recurrences of T1 carcinomas. As well as the numbers of local recurrences, the rates of tumor-affected lymph nodes reported exhibit considerable variability: range is from 0 to 18 percent in low-risk carcinomas.[17–25] In various reports, tumor-associated factors, such as grading, vessel invasion, and budding, were identified as significant determinants for the development of lymph node metastasis. Poorly demarcated invasive fronts and the extent of submucosal invasion (sm1–3) may additionally be of importance. In comparison to the above-mentioned parameters, the influence of the latter two is less clear.

Bayar *et al.*[17] found lymph node metastases in 9 percent of T1 carcinomas, Nascimbeni *et al.*[18] detected 9 percent, and Steup *et al.*[19] found 7 percent. In these studies, prognostically unfavorable results were associated with significantly higher lymph node metastasis rates. Sitzler *et al.*[20] identified 6 percent lymph node metastases in T1 rectal

cancers, but tumors without lymph vessel invasion showed no metastases. Likewise, no positive lymph nodes were detected in patients with low-risk T1 tumors (Sugihara *et al.*[21]), whereas Blumberg *et al.*[22] found metastases in 7 percent. Although Brodsky *et al.*[23] described 12.5 percent positive lymph nodes in well-differentiated to moderately differentiated T1 rectal cancers, tumors without lymph or blood vessel invasion exhibited no (0 percent) lymph node metastasis.

The discrepant results highlight the necessity for prospective studies using uniform standards with a differentiated histologic assessment of the excised specimens. It can be assumed that in future studies increasing numbers of tumor-positive lymph nodes will be reported because of improved methods for detection of micrometastases. However, their prognostic value remain to be determined.

CONCLUSIONS

We agree with Dr. Cirocco that certain carcinomas have "bad biology" and are associated with poor prognosis independent of tumor stadium and kind of therapy. Unchanged, we believe that TEM surgery of early rectal cancer requires strict indication. In addition, subsequent to surgery, it is important to verify on the basis of the excised specimen whether local excision alone is sufficient or if immediate reoperation is necessary. Thus, the local surgical procedure can represent an oncologically adequate therapy with a resulting high quality of life for a distinct patient collective with T1 rectal cancer. For patients with prognostically unfavorable resection results, TEM serves as diagnostic measure without impairing the oncologic outcome.

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