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Local excision for more advanced rectal tumors

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Abstract

Over the past 20 years, local excision (LE) of T1 rectal cancer was increasingly established and represents an oncologically established technique. In contrast, the situation for T2 tumors is less clear and has only been investigated in small patient collectives. LE for T2 tumors is thus discussed controversially. *Materials and methods.* In addition to our own patients with T2 rectal cancer treated locally (n=40), we have analysed the local recurrence (LR) rates after LE alone (n=124), after immediate conventional radical reoperation (n=29), after adjuvant (chemo)-radiotherapy (n=294) and those after neoadjuvant chemoradiotherapy (nCRT) (n=269) using a PubMed search. *Results.* LR rates of low-grade T2 tumors after R0 resection by LE alone was 19%. If additional prognostically unfavorable findings were present, the LR rate rose to 52%. By immediate radical reoperation the LR rate was decreased to 7%, whereas that after adjuvant therapy was 16%. In contrast, LE of more advanced tumors after nCRT resulted in LR rates of 9%. *Discussion.* LE alone of T2 rectal cancer should not be performed, and after adjuvant chemoradiotherapy the risk of developing LR was also high. In cases with unexpected T2 finding after LE, immediate conventional reoperation can represent an adequate oncological therapy, because it reveals comparable results to those obtained by primary radical resection. First results after nCRT followed by LE showed favorable results with low LR rates. If the indication for LE of T2 cancers can be extended to patients after nCRT in the future will have to be determined in prospective mutlticentre studies.

The surgical approach is still the gold standard in the therapy of rectal cancer. Since the implementation of an optimized surgery using partial and total mesorectal excisions (TME), the local recurrence (LR) rates were decreased to below 10% [1–5]. The addition of combined neoadjuvant chemoradiotherapy (nCRT) signficantly reduced the recurrence rates especially of more advanced (T3/T4) tumors [6–11]. So called "low risk" T1 tumors showing well to moderate differentiation (G1-2) with absence of lymph (L0) and blood vessel invasion (V0) represent a special situation. These tumors can be excised locally, because they have an only remote potential for lymphogenic metastasis [12]. Several series of long-term investigations showed LR rates of 5% for this procedure [13–25].

Among local surgical procedures, the transanal endoscopic microsurgery (TEM) technique exhibits the largest surgical flexibility. More radical local techniques, i.e. transsphincter resection (Mason) or the rectotomia posterior (Kraske), have been abandoned because of higher complication rates despite similar oncological results [14,20,23,24].

Local excision (LE) used for T2 tumors restricted to the rectal wall and without lymph node metastases (N0) is controversially discussed [14,20,23,24,26, 27]. In addition, further therapeutic approaches are not uniformly defined if after initial LE of primarily as adenoma or T1 carcinoma staged tumors the postoperative histology reveals an unexpected T2 carcinoma. LE as sole procedure can be considered as definitive therapy or an adjuvant (chemo)-radiotherapy as well as an immediate radical reoperation can be performed as additional regimes. In contrast to these procedures, a further minimally invasive therapeutic concept for T2 tumors is nCRT before LE. The aim of this study was to evaluate the results obtained after LE of T2 carcinomas by analysing our own results together with the results of the literature as far as possible.

Material and methods

In addition to 40 patients with pT2 rectal cancer, who received TEM resection of their tumors in the Clinic for General- and Abdominal Surgery (Johannes Gutenberg-University Hospital), we identified several

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studies reporting results after LE of T2 tumors between 1990 and 2006 using a PubMed search. The median follow-up period in our patient collective was 61 (14–189) months. Quality characteristics for the analyzed studies were a follow-up of a minimum of 24 months (median), that with regard to radicality the data could be devided in a group including complete or adequate resctions (R0), and inadequate results. The latter findings combine incomplete resections (R1), doubtful resection margins or tumor fragmentation (RX), and a close distance from the cancer to the resection margin (Rclose). In our collective, we definded Rclose as a distance of less than 1 mm ($R \leq 1$mm). Furthermore, we considered tumor gradings (G1 = well; G2 = moderate; G3 = poorly differentiated; G4 = undifferentiated), lymph (L1) or blood vessel tumor invasion (V1).

A clear distinction between results after LE alone and after LE with additional treatments was required. We analysed studies, which divided their recurrence rates separately for T2 tumors and which allowed creating different groups (LE only/LE and immediate reoperation/LE and adjuvant (chemo)-radiotherapy). Studies about LE after nCRT reporting only cT2 tumors were not found, thus, we included cumulative results for cT(1)2–3 tumors treated in a neoadjuvant regimen which were locally excised afterwards.

We were unable to differentiate if the various local surgical techiques revealed differing results. Even within the single studies, different operation techniques were considered to various degrees. However, the majority of studies used transanal resections.

Using this approach, we identified seven studies fulfilling these criteria and – together with our own data – we analysed 124 patients, in whom their T2 carcinoma was locally excised as sole procedure [18,19,25,28–30]. Results of immediate reoperation were found in one additional study [17], and thus – together with our own data – they were analysed in a total of 29 cases. Results about adjuvant (chemo)-radiotherapy after LE of T2 tumors were presented in 13 studies (n = 294) [29,31–42]. A calculation of recurrence rates after nCRT and LE of rectal cancer was performed from a total of nine studies including ours (n = 269) [43–51].

A statistical comparison between different therapeutic concepts with the aim of identifying superior results was impossible, since the respective collectives differed in their composition.

Results

Local excision of T2 carcinomas as sole procedure

In our own patient collective, follow-up information about 20 patients with only TEM excision of T2 tumors was available for a median of 59 (15–181) months. These patients experienced a LR rate of 35% (n = 7) and systemic metastases in 30% (n = 6) of the cases. Separated by R0 resection of low-risk (G1-2/L0/V0) (n = 14) and high-risk (G3-4/L1/V1) T2 carcinomas and/or inadequate resection (R1/RX/$R \leq 1$mm), the LR-free survivals in the entire follow-up period were 70% and 50%, respectively.

T2 carcinomas with "low grade" situation after complete resection (R0). In addition to our patients, we were able to analyse data from four other studies, which presented their results for low-grade (G1-2) T2 tumors after R0 resection separately (Table I) [18,19,25,28]. The mean of all medians of the different follow-up durations was 51 (29–62) months and the LR rate of all 99 patients was 19% (0–37%). An extended analyses of the results of low-risk (G1-2/L0/V0) carcinomas only was impossible due to the cumulative presentation of this information together with high-risk rates [38,43,49,53].

T2 tumors with prognostically unfavorable resection results (G3-4/L1/V1/R1/RX/Rclose). An evaluation of results of T2 tumors with high grade (G3-4) situation and inadequate resection margins (R1/RX/Rclose) was possible in two additional studies (Table II) [29,30]. Thus, together with our patients, we analysed results from 25 patients with a mean follow-up median of 51 (47–72) months. In cases with prognostically unfavorable resection results or if these results were not excluded, the LR rate of T2 tumors after LE as sole procedure rose to 52% (46–63%) as compared to 19% after local R0 excision of "low grade" (G1-2) tumors.

Immediate reoperation after LE of T2 carcinomas

In our collective, 20 patients after LE of a T2 carcinoma were reoperated immediately, i.e. within four weeks, by conventional radical surgery

Table I. Results after complete (R0) LE of "low grade" (G1-2) T2 rectal carcinomas.

	Local recurrences		
Author	n =	%	Follow-up (months)
Borschitz[§]	14	29% (4/14)	62[*] (15–181)
Garcia-Aguilar[#] [28]	27	37% (10/27)	54[*] (n.s.)
Kim[#] [18]	18	11% (2/18)	50[*] (n.s.)
Slisow[#] [25]	27	11% (3/27)	60[*] (n.s.)
Mentges[§] [19]	13	0% (0/13)	29[*] (3–65)
Total	**99**	**19% (19/99)**	**47 (29–62)**

[*]Median, [§]TEM technique, [#]other technique.

Table II. Results after LE of T2 carcinomas with prognostically unfavorable findings.

Author	Local recurrences		R1/Rx/Rclose G3-4/L1/V1	Follow-up (months)
	n =	%		
Borschitz[§]	6	50% (3/6)	R1 20% Rx/Rclose 55% G3-4/L1/V1 40%	47* (14–151)
Chakravarti[#] [29]	8	75% (6/8)	R1 11% Rx/Rclose n.s. G3-4/L1/V1 n.s.	51* (4–162)
Varma[#] [30]	11	46% (5/11)	R1 12% Rx/Rclose 36% G3-4 10%/L1 9%/V1 6%	72* (0–198)
Total	**12/25**	**52% (13/25)**	–	**61 (47–72)**

*Median, [§]TEM technique, [#]other technique.

(Table III). A prognostically unfavorable local resection result (R1/RX/R ≤ 1mm/G3-4/L1/V1) was found in 55% (11/20). After a follow-up of 63 (14–189) months, we observed LR in two cases (10%) and systemic metastases in two other cases (10%). A separate analysis of tumor-free lymph nodes (N0; n = 9) as compared to patients with lymph node filiae (N+; n = 11) showed that patients with N0 findings did not develop LR (0%) or metastases (0%). In contrast, patients with N+ situation showed in 18% LR and metastases each and none of them received an adjuvant therapy.

Hahnloser et al. reported about the results obtained with patients with T2 carcinomas, who were immediately reoperated (n = 9) using conventional surgery after primary LE (Table III) [17]. The time point for reoperation was also chosen to be within four weeks after LE. Eight patients revealed a N0 finding and did not receive adjuvant therapy, whereas one patient with N+ finding was treated postoperatively with chemoradiotherapy. None of the patients developed a LR (0%; 0/9) and a systemic metastasis (11%; 1/9) was found in one patient with N0 resection result.

Altogether, for T2 tumors, a LR rate of 7% (2/29) and a metastasis rate of 10% (3/29) was observed after a mean follow-up time of 57 (51–62) months. Separated for N0 and N+ situations, the LR rates were 0% and 17% (2/12) and the metastasis rates were 6% (1/17) and 17% (2/12), respectively (Table III).

Adjuvant chemoradiotherapy after LE of T2 carcinomas

A total of 13 studies allowed for an analyses of their results after adjuvant (chemo)-radiotherapy after LE of T2 carcinomas (Table IV) [29,31–42]. In eight investigations a combined chemoradiotherapy was performed, but only four of these studies used this combined approach in all (100%) of their patients [32,36,39,40], whereas in the other four studies ~50% of the patients with radiation received additional chemotherapy [29,33,35,42]. Adjuvant radiation only was used in the remaining five studies [31,34,37,38,41].

Two investigators did not provide information about the tumor grading (G1-4) or lymph/blood vessel invasion (L1/V1) [29,40], and one of them did also not specify the number of inadequate resection results [29]. In the remaining studies the rate of R1 resections was between 4–29%, of RX or Rclose resections between 0–57% and the proportions of high-risk or high-grade carcinomas showed a range of 5–44%.

The mean of all median follow-up durations was 47 (33–73) months. In addition, for the entire collective of 294 patients, a local recurrence rate of 16% (46/294) was calculated. Information about systemic metastases was provided by three investigators, which together resulted in a metastasis rate of 11% (10/88) [34,39,40]. A separation of these results for the various therapeutic concepts revealed differences: The LR rate after complete adjuvant therapy, i.e. all patients received combined chemoradiotherapy postoperatively, was 12%. If ~50% of the patients additionally received chemotherapy, the results were similar to those obtained with adjuvant radiation alone. For these groups, the LR rate was 18% each.

Not considered were the single adjuvant radiation or chemoradiation protocols (total radiation dose, fractionation, chemotherapeutic agent used, way of

Table III. Results after LE of T2 rectal carcinomas and immediate reoperation.

Author	T2N0		T2N+		Follow-up (months)
	LR	M	LR	M	
Borschitz[§]	0% (0/9)	0% (0/9)	18% (2/11)	18% (2/11)	62* (14–189)
Hahnloser[#] [17]	0% (0/8)	13% (1/8)	0% (0/1)	0% (0/1)	51* (4–162)
Total	**0% (0/17)**	**6% (1/17)**	**17% (2/12)**	**17% (2/12)**	**57 (51–62)**

*Median, [§]TEM technique, [#]other technique.

Table IV. Results after LE of T2 rectal carcinomas and adjuvant radio- or chemoradiotherapy.

Author	n =	RT	CT	LR	M	R1/Rx/Rclose G3-4/L1/V1	Follow-up (months)
Bleday[#] [32]	21	100%	100%	0% (0/21)	n.s.	R1 4% Rx/Rclose 0% G3-4 n.s./L1 11%/V1 9%	41[**] (n.s.)
Russell[#] [39]	25	100%	100%	16% (4/25)	12% (3/25)	R1 14% Rx/Rclose 57% G3-4 11%/L1 n.s./V1 n.s.	73[*] (n.s.)
Steele[#] [40]	51	100%	100%	14% (7/51)	10% (5/51)	R1 0% Rx/Rclose 0% G3-4/L1/V1 n.s.	48[*] (22–92)
Lamont[#] [36]	10	100%	100%	20% (2/10)	n.s.	R1/Rx/Rclose 17% G3-4/L1/V1 44%	33[*] (2–102)
Total	**107**	**100%**	**100%**	**12% (13/107)**	**11% (8/76)**	–	**49 (33–73)**
Gopaul[#] [35]	11	100%	47%	9% (1/11)	n.s.	R1 16% Rx/Rclose 5% G3-4 14%/L1 14%/V1 19%	37[*] (9–125)
Wagmann[#] [42]	25	100%	56%	24% (6/25)	n.s.	R1 28% Rx/Rclose 5% G3-4 8%/L1 13%/V1 21%	41[*] (9–131)
Chakravarti[#] [29]	33	100%	55%	15% (5/33)	n.s.	R1 11% Rx/Rclose n.s. G3-4/L1/V1 n.s.	51[*] (4–162)
Bouvet[#] [33]	27	100%	partial	19% (5/27)	n.s.	R1 6% Rx/Rclose 13% G3-4 9%/L1 34%/V1 15%	51[*] (n.s.)
Total	**96**	**100%**	**~50%**	**18% (17/96)**	**n.s.**	–	**45 (37–51)**
Benson[#] [31]	36	99%	none	22% (8/36)	n.s.	R1 25% Rx/Rclose 25% G3-4 6%/L1 16%/V1 n.s.	48[*] (10–165)
Minsky[#] [38]	12	100%	none	17% (2/12)	n.s.	R1 5% Rx/Rclose 5% G3-4 5%/L1 n.s./V1 n.s.	37[*] (5–73)
Le Voyer[#] [37]	16	100%	none	13% (2/16)	n.s.	R1 20% Rx/Rclose 14% G3-4 11%/L1 11%/V1 29%	46[*] (8–120)
Valentini[#] [41]	12	100%	none	17% (2/12)	n.s.	R1 0% Rx/Rclose 9% G3-4 14%/L1 n.s./V1 n.s.	54[*] (18–128)
Fortunato[#] [34]	15	100%	none	13% (2/15)	17% (2/12)	R1 29% Rx/Rclose 14% G3-4 29%/L1 5%/V1 5%	56[*] (n.s.)
Total	**64**	**~100%**	**none**	**18% (16/91)**	**17% (2/12)**	–	**48 (37–56)**
OVERALL	267	~100%	partial	16% (46/294)	11% (10/88)	–	47 (33–73)

*Median, **Mean, RT = radiotherapy, CT = chemotherapy, LR = local recurrences; M = Metastases, [#]other surgical technique.

application), since the used protocols differed from patient to patient and from study to study.

Neoadjuvant radio- and chemoradiotherapy of T2-3 rectal cancer

In our own collective, we have treated five patients with cT2-3 rectal cancer neoadjuvantly using chemoradiotherapy. During a follow-up period of a median of 30 (18–85) months, we did not observe LR (0%) in any of the patients. We detected systemic metastases in two patients (40%). Overall, we were able to analyse the results of eight additional studies after neoadjuvant therapy followed by LE with a total of 269 patients (Table V) [43,45–51]. Taken together, the clinical staging before neoadjuvant chemoradiotherapy revealed cT1-2 categories in 15% (n = 41), cT2 findings in 35% (n = 94) and cT3 tumors in 45% (n = 134). The mean of all median follow-up durations was 36 (24–55) months. Altogether, 9% LR (24/269) as well as 9% (23/243) systemic metastases were found.

A separation of recurrence rates for each initial cT category was impossible because of a lack of information provided. In addition, analysing the results with regard to an influence of radicality achieved during LE (R0/R1/RX/Rclose), tumor grading (G1-4) and tumor vessel invasion (L1/V1) on the oncological outcome was also not possible.

Discussion

The goal of this study was to determine if there is an indication for LE of T2 rectal cancer and, thus, if the indication for LE can be extended to tumors with higher T categories than pT1. In this context, we showed that even after LE of "low grade" or "low risk" T2 carcinomas, despite of complete resection (R0), one has to expect a high number of LR (19%). If an additional prognostically unfavorable resection result (G3-4/R1/RX/Rclose) is present, LR occur in >50% of cases. Thus, LE of T2 tumors alone does not represent a curative therapy.

To avoid unnecessary LE of T2 tumors, the preoperative staging is very important. For the differentiation of the tumor stages endorecal ultrasonography (EURS) shows the highest sensitivity, however, the experience of the investigator is critical [52–54]. Elastoendosonography may be one option to further increase the sensitivity [55].

Table V. Results after neoadjuvant chemoradiation and LE of rectal carcinomas.

Author	n =	LR	M	Follow up (months)
Borschitz[§]	cT3 = 3, cT2 = 2	0% (0/5)	40% (2/5)	30* (18–85)
Ruo[#] [49]	cT2 = 6, cT3 = 4	10% (1/10)	20% (2/10)	29* (2–89)
Schell[#] [50]	cT3 = 11	0% (0/11)	18% (2/11)	48* (18–105)
Hershman[§] [45]	cT1-2 = 33	12% (4/33)	6% (2/33)	33* (3–120)
Bonnen[#] [43]	cT3 = 26	8% (2/26)	15% (4/26)	42* (5–109)
Stipa[§] [51]	cT1 = 4, cT2 = 14, cT3 = 8	15% (4/26)	n.s.	37* (25–118)
Lezoche[§] [47]	cT2 = 54, cT3 = 46	5% (5/100)	5% (5/100)	55* (7–120)
Kim[#] [46]	cT2 = 6, cT3 = 20	4% (1/26)	4% (1/26)	24* (6–77)
Meadows[#] [48]	cT1 = 4, cT2 = 12, cT3 = 16	22% (7/32)	19% (6/32)	27* (2–123)
Total	**269**	**9% (24/269)**	**9% (23/243)**	**36 (24–55)**

*Median, [§]TEM technique, [#]other technique.

If after LE a T2 carcinoma is diagnosed, LE can only be regarded as diagnostic measure and additional therapeutic actions are necessary. In our patients together with the study by Hahnloser et al., we investigated the results of immediate reoperation [17]. In both studies, the time points of reoperation lay within four weeks after LE and despite of ~1/3 UICC stage III° the total LR rate was 7% and the metastasis rate was 10%. Similarly, immediate conventional reoperation was performed after four weeks in the studies presented by Nakagoe et al. and Baron et al [56,57]. In these, the results after LE of pT1-2 tumors (n = 11) or of pT1-3 rectal cancers (n = 16) were investigated, respectively. After immediate radical reoperation, the 5-year recurrence-free survival was 94% (Baron et al.) and 100% (Nakagoe et al.). These findings confirm that immediate conventional reoperation of rectal cancer represents an oncologically adequate therapy generating results comparable to primary conventional resection [1–5,17,28,56,57]. However, one limitation was the relatively small patient number.

An additional therapeutic option is adjuvant radio- or chemoradiotherapy. For combined chemoradiotherapy we calculated a mean LR rate of 12% [32,36,39,40]. If this combined therapy was administered to only half of the patients [29,33,35,42], or if they were only treated by radiation after surgery [31,34,37,38,41], the LR rate increased to 18% each. However, these results afford only a crude estimation of the results of each adjuvant therapy and should therefore also be regarded with caution. The adjuvant treatment regimens were different [29,31–42], and each study showed a large variation with regard to inadequate resection results and/or the numbers of "high grade" or "high risk" carcinomas [29,31–35,37–42].

If upon reoperation tumor-free lymph nodes (N0) were found, no LR was observed independent of the radicality of initial local resection. A critical prognostic parameter for the development of recurrences are lymph node metastases. If a N+ finding after conventional reoperation is diagnosed, these patients should receive adjuvant chemoradiotherapy. Analogous to primary conventional resection of UICC stage IIIa findings, adjuvant therapy can significantly reduce the recurrence rates [58–62].

As compared to immediate reoperation, the adjuvant treatment regimens all resulted in less favorable outcomes. Neither an adjuvant radiation nor a combined chemoradiotherapy represent an adequate measure for patients with incomplete/inadequate LE. If adjuvant (chemo)-radiotherapy after R0 resection represents a sufficient therapy has not conclusively been addressed, since only one investigation is based on results of R0 resections [40]. Despite this selection and the unavailability of information regarding tumor grading and tumor-associated vessel invasion, the LR rate found in that study was 14%. Thus, no conclusion can be drawn about the therapeutic benefit of low-risk T2 carcinomas after R0 resection.

Neoadjuvant treatment followed by reoperation has to be discussed as additional option. If after LE a T2 carcinoma is found, a neoadjuvant therapy could be offered. However, no data exists yet that demonstrates if this procedure helps to reduce LR rates as compared to adjuvant therapy.

In contrast to the studies presenting data after adjuvant therapy, the reports showing data after LE as sole procedure and after LE followed by immediate reoperation used the TEM resection method to a similar degree. Studies showing results after adjuvant therapy of T2 tumors and surgery using the TEM technique were not found. Most favorable results were obtained for TEM resections of early (T1) rectal cancers as compared to other resection methods [20], however, similar studies for T2 tumors do not exist. Our patients with TEM R0 resection of "low risk" T2 tumors showed unacceptably high LR rates.

More clearly proven are the results obtained after LE of rectal cancer after neoadjuvant chemoradiotherapy. From a total of nine studies with a majority of cT2-3 carcinomas a mean LR rate of 9% was calculated. In these reports the distribution of TEM versus other transanal resection methods (rectractor) was almost similar. In addition, approx. half of the patients presented with initial cT3 tumors [43–51]. Similar to the assessment of the results after adjuvant therapy, the heterogeneity of the various therapeutic regimens is limiting [43–51]. How the results separated by preinterventional cT catergory are to be judged is still an open question, since differentiation of the results was impossible.

In summary, LE of T2 rectal cancer alone does not represent an oncologically adequate therapy, independent of the resection radicality achieved and high-grade or high-risk situations. As subsequent therapeutic measure immediate conventional reoperation provides the best oncological results, which are comparable to primary conventional resection [13,17,56,57]. Even if not conclusively proven yet, the results obtained with adjuvant chemoradiotherapy after LE showed that this therapeutic option does not serve as curative therapy. If the indication of LE can be extended to T2 rectal cancer after nRCT will have to be confirmed using prospective multicenter studies with high statistical power (>0.8), before one can recommend this treatment regimen for every day routine.

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