The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer

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Abstract

Background

The importance of the circumferential resection margin (CRM) has been demonstrated in primary rectal cancer, but the role of the minimal tumor-free resection margin in locally recurrent rectal cancer (LRRC) is unknown.

Objective

To evaluate the prognostic importance of a minimal tumor-free resection margin in LRRC.

Design

This was a single-institution, retrospective study.

Setting

This study was conducted in a tertiary referral hospital

Patients and methods

Based on the final pathology report, surgically treated patients with LRRC between 1990 and 2013 were divided into 4 groups: 1) Tumor-free margins of >2mm; 2) tumor-free margins of >0-2mm; 3) microscopically involved margins and 4) macroscopically involved margins.

Main outcome measures

Local control and overall survival.

Results

A total of 174 patients with a median follow up of 27 months (range, 0-144) were eligible for analysis. There was a significant difference in 5-year local re-recurrence-free survival in favor of 41 patients with tumor-free margins of >2 mm compared to 34 patients with tumor-free margins of >0-2mm (80 vs. 62%,p=0.03) and a significant difference in 5-year overall survival (60 vs. 37%,p=0.01). The 5-years local re-recurrence-free and overall survival for 55 patients with microscopically involved margins were 28% and 16% and of 20 patients with macroscopically involved margins 0% and 5%, respectively. On multivariable analysis tumor-free margins of >0-2mm were independently associated with higher re-recurrence rates (HR 2.76 95%CI1.06 – 7.16) and poorer overall survival (HR 2.57 95%CI 1.27-5.21) compared to tumor-free margins of >2mm.

Limitations

This study was limited by its retrospective nature

Conclusion

Resection margin status is an independent prognostic factor for re-recurrences rate and overall survival in surgically treated LRRC. In complete resections, patients with tumor-free resection margins of >0-2mm have a higher re-recurrence rate and a poorer overall survival than patients with tumor-free resection margins of >2mm.

Introduction

Developments in the treatment of primary rectal cancer, such as total mesorectal excision (TME) and neoadjuvant (chemo-)radiotherapy, have significantly decreased the local recurrence rate. Unfortunately, locally recurrent rectal cancer (LRRC) still occurs in 6-13% of surgically treated patients.[1-4] LRRC is associated with a poor prognosis and treatment is challenging.

Multimodality treatment of LRRC, including neoadjuvant radiotherapy and surgical resection, can lead to long-term disease-free and overall survival. However, the outcome strongly depends on whether a complete surgical resection can be achieved. Recent studies have demonstrated that complete resections can result in 5-year overall survival rates of 30-57% and local control rates of 50-80%.[5-10] On the other hand, incomplete resections leads to drastically poorer survival rates and high re-recurrence rates.[11] The treatment options for re-recurrences are limited and overall survival is usually short when re-recurrence occurs. Moreover, the development of re-recurrences has a major impact on the patient's quality of life.

In primary rectal cancer, the optimal cut-off for defining an involved circumferential resection margin (CRM) is under debate. Some authors propose a tumor-free margin of 1mm, while others propose 2mm. Regardless of this debate, there is consensus that narrows CRMs, whether 1mm or 2mm, are associated with a poorer outcome.[12-14] It is likely that narrow resection margins in LRRC may lead to a poorer outcome as well. However, the association between the minimal distance of viable tumor to the nearest resection plane and long term outcome of LRRC has not been validated.[15] This is clinically relevant, because narrow resection margins in LRRC surgery are common. Moreover, when this holds true for LRRC, a more aggressive surgical approach may be warranted. The goal of this study was to evaluate the association between width of the tumor-free resection margin and the long term outcome after LRRC surgery with curative intent.

Patients and methods

All patients undergoing surgery for LRRC between January 1990 and March 2013 in our hospital, a tertiary referral center for the southwest region of the Netherlands, were retrospectively analyzed. LRRC was defined as a histopathologically proven local recurrence of colorectal cancer within the pelvic region. Demographic data, clinical characteristics, operative procedures and histopathology were examined.

Patients were scheduled for neoadjuvant (chemo-)radiotherapy followed by surgery, either as a long course of 44.6-52Gy in 19-28 fractions of 1.8-2.3Gy or a short course of 25Gy in 5 fractions of 5Gy or were treated by surgery alone. Previously irradiated patients were scheduled for a re-irradiation dose of 27-30Gy, delivered in 15-18 fractions of 1.8-2.3Gy. After 2006, patients were treated with chemoradiotherapy with capecitabine administered orally at a dose of 825 mg/m2 twice a day during radiotherapy. Radiotherapy for LRRC was administered by a three field technique, using one posterior and two lateral portals, a four-field box or with five fields using intensity modulated radiotherapy.

Patients were locally staged by pelvic MRI or CT-scan and screened for distant metastases by a thoraco-abdominal CT-scan at the time of LRRC diagnosis. The majority of patients was restaged after (re-)irradiation to evaluate the response of the local recurrence to neo-adjuvant (chemo-)radiotherapy and to detect potential distant metastases.

LRRCs were treated by local recurrence excisions, low anterior resections (LARs), abdominoperineal resections (APRs), partial exenterations, total exenterations or abdominosacral resections. Patients were considered candidates for surgical treatment in case of no extensive distant metastases, no apparent lateral bone involvement, no sacral involvement above level S3, no extension through the greater sciatic notch, and no encasement of common or external iliac arteries.

Our multimodality approach for LRRC included intra-operative radiotherapy (IORT), which became available after 1996 for patients with tumor free margins of ≤2mm, evaluated during surgery on frozen sections.[16] Frozen section evaluation became a standard part of the surgical procedure after the introduction of IORT and was taken from sites that were potentially at risk for tumor involvement evaluated on pre-operative imaging or macroscopic evaluation by surgeon and pathologist.

All resection specimens were assessed by experienced gastrointestinal pathologists, inked following a standard procedure, formalin fixed and cutsectioned in slices. The minimal tumor-free resection margin was evaluated macroscopically and microscopically as the nearest distance of viable tumor cells to the inked resection plane. The minimal resection margin of the frozen section evaluation was confirmed by final pathology evaluation. For patients where a sampling error occurred (closer or involved margins at

another resection plane), the margin of the final pathology report was considered the definitive tumor-free resection margin. For patients with a more extended resection as a result of the frozen sections, the minimal tumor-free resection margin was measured in the additional resected tissue.

Based on the final pathology report, patients with viable tumor were divided into four groups: 1) tumor-free resection margins of >2 mm; 2) tumor-free margins of >0-2 mm; 3) microscopically involved resection margins and 4) macroscopically involved resection margins. In these subgroups, we compared the local re-recurrence-free survival and overall survival.

Follow up consisted of a program in which patients generally visited the outpatient clinic every 3 months during the first two years and biannually after 2 years. The first two years CEA determination was performed every 3 months and thoracic and abdominal imaging biannually. After 2 years of follow up, CEA determination was performed biannually and thoracic and abdominal imaging yearly. Re-recurrences were established by symptoms, CEA increase or imaging. All suspected re-recurrences were confirmed by CT/MR imaging or biopsies. Confirmation of the date of death was retrieved from the death registries of the municipal register. Some patients returned to the referring hospitals for follow up. In these patients follow up data was obtained by hospital notes and information of the general practitioner.

Statistical analysis was carried out using SPSS (version 20.0.0). Data was reported as median (interquartile range). Categorical data was reported as count (percentage). Univariate analyses for local re-recurrence-free survival and overall survival were performed by using the Kaplan-Meier method and a log-rank test. Univariate and multivariable analyses to determine the prognostic value of covariates regarding local re-recurrence-free and overall survival were performed by using Cox's proportional hazards model. In these analyses, we excluded patients with a pathological complete response or an indeterminable resection margin. Multivariable analysis was stratified for period of surgery (1990-1996, 1997-2005 and 2006-2013) to rule out the effect of non-measurable covariates. For the multivariate analysis, only parameters with P-values ≤0.05 in the univariate model were entered in the Cox regression model. Backward elimination was applied and variables were removed if P-values were >0.10. Local re-recurrence-free survival and overall survival were calculated from the date of LRRC surgery to last follow-up or death. P-values <0.05 were considered statistically significant.

Results

A total of 174 patients underwent surgery for LRRC. During surgery, 9 patients were considered incurable due to unresectable metastatic disease or unresectability of the local recurrence, leaving 165 patients (59 women and 106 men) eligible for analysis. The baseline characteristics are depicted in *table I*. The median age at LRRC surgery was 65 years (interquartile range, 56-70).

Histopathological evaluation

Thirteen patients (8%) had a pathological complete response without viable tumor in the resected specimen after neoadjuvant therapy. Forty-one patients (24%) had a tumor-free resection margin of >2 mm (median 5mm, range, 2.1-25mm), 34 patients (21%) a tumor-free margin of >0-2mm (median 1mm, range, 0.1-2), 55 patients (33%) a microscopically involved resection margin and 20 patients (12%) a macroscopically involved resection margin. In 2 patients (1%) the resection margin could not be determined accurately. Tumor-free resection margins of >2mm were most commonly achieved in central LRRCs (14/20=70%), followed by anterior LRRCs (10/30=33%), lateral LRRCs (10/45=22%) and posterior LRRCs (6/42=14%). Six patients (4%) had a well differentiated, 102 patients (62%) a moderately differentiated and 20 (12%) patients a poorly differentiated adenocarcinoma. In 36 patients (21%) tumor differentiation was not specified. Vaso-invasion was found in 30 patients (18%).

Follow up

The median length of follow up was 27 months (range, 0-144). At last follow up, 57 patients were alive with a median follow up of 43 months (range, 3-144). The estimated 1-, 3-, 5-year overall survival was 82%, 46%, 32%, respectively. A total of 66 patients suffered a re-recurrence during follow up, while 51 patients died without a known re-recurrence.

Results of univariate and multivariable analyses of 150 patients for local re-recurrence-free survival are provided in *table II.* Univariate and multivariable analyses for overall survival are provided in *table III.* Fifteen patients with a pathological complete response or an undeterminable margin were excluded from this analysis. Multivariate analyses demonstrated that the resection margin status was an independent prognostic factor for local re-recurrence-free survival and overall survival. In addition, interval between primary tumor resection and diagnosis of LRRC and vasoinvasion were independent prognostic factors for overall survival.

Table I. Baseline patients and LRRC characteristics

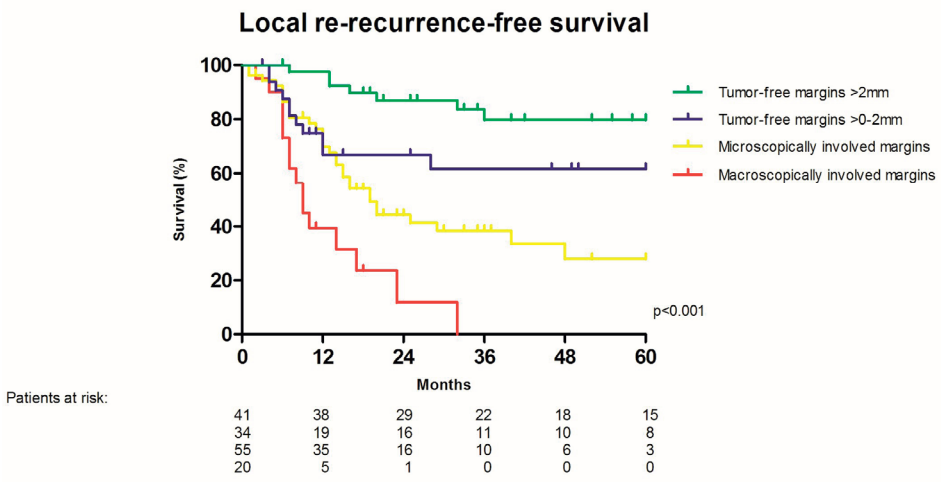
	Number of patients (%)
Total patients	165
Primary tumor resection	
Sphincter saving	127 (77)
Non-sphincter saving	38 (23)
Previous pelvic radiotherapy	
None	134 (81)
(CTx)RTx	31 (19)
Primary tumor resection	
Non-TME	65 (39)
TME	100 (61)
Interval primary tumor – LRRC*	24 (12-38)
Neoadjuvant treatment LRRC	
None	22 (13)
RTx	81 (49)
CTxRTx	62 (38)
Tumour location	
Central	20 (13)
Lateral	45 (30
Anterior	30 (20
Posterior	42 (28)
Unknown	13 (9)
LRRC surgery	
LAR	20 (12)
APR	29 (18)
Partial exenteration	61 (37)
Total exenteration	29 (18)
Abdominosacral resection	19 (12)
Recurrence resection	7 (4)
Distant metastases at diagnosis	7 (4)
Metastases-first treatment	2 (1)
Synchronous treatment	1 (1)
Delayed metastases treatment	3 (2)
Adjuvant chemotherapy	3 (2)
Blood loss***	3.000 (1.750-5.250)
IORT	76 (46)
Operation time	403 (281-499)

*LRRC, locally recurrent rectal cancer, RTx, radiotherapy; LAR, Low Anterior Resection; APR, abdominoperineal resection; CTxRTx, chemoradiotherapy.; TME, total mesorectal excision, *, Months (interquartile range)**, Weeks (interquartile range); ***, millilitres (interquartile range); IORT, intraoperative radiotherapy*

Local re-recurrence-free survival

The estimated 3- and 5-year local re-recurrence-free survival of patients with tumor-free margins of >2mm were 80% and 80% respectively, compared to 62% and 62% for patients with tumor-free margins of >0-2mm, 38% and 28% for patients with microscopically involved margins and 0% and 0% for patients with macroscopically involved resection margins. The re-recurrence-free survival of patients with tumor-free margins of >2mm was significantly longer than in patients with tumor-free margins of >0-2mm (p=0.03), microscopically involved margins (p<0.001) and macroscopically involved margins (p<0.001) (*figure I)*. In a subgroup analysis of the patients with a tumor-free resection margin of >0-2mm, there was no significant difference in local re-recurrence-free survival of patients with a tumor-free margin of <1mm (n=15) and patients with tumor-free margins of 1-2mm (n=19) (66 vs. 59%,p=0.61).

Figure I. Local re-recurrence-free survival of surgically treated LRRC patients



Overall survival

The estimated 3- and 5-year overall survival of patients with tumor-free margins of >2mm was 78% and 60% respectively, compared to 45% and 37% for patients with tumor-free margins >0-2mm, 32% and 16% for patients with microscopically involved margins and 16% and 5% for patients with macroscopically resection margins. The overall survival of patients with tumor-free margins of >2mm was significantly longer compared to patients with tumor-free margins of >0-2mm (p=0.01), microscopically involved margins (p<0.001) and macroscopically involved margins (p<0.001) (*figure II).* In a subgroup analysis of the patients with a tumor-free resection margin of >0-2mm, there was no significant difference in overall survival of patients with a tumor-free margin of <1mm and patients with tumor-free margins of 1-2mm (38 vs. 36%,p=0.57).

Table II. Univariate analysis of covariates regarding the local re-recurrence-free survival and multivariable analysis stratified for period of surgery

	Number of patients	Univariate Hazard ratio (95%CI)	p-value	Multivariable Hazard ratio (95%CI)	p-value
Gender					
Male	94	1			
Female	56	1.04 (0.63 – 1.72)	0.88	-	
Primary tumor resection					
Non TME	58	1			
TME	92	1.04 (0.62 – 1.73)	0.89	-	
Previous pelvic radiotherapy					
No RTx	121	1			
(CTx)RTx	29	1.26 (0.68 – 2.32)	0.46	-	
Age at surgery					
<65 year	74	1			
≥65 year	76	1.17 (0.72 – 1.92)	0.53	-	
Primary tumor resection					
Sphincter saving	114	1		1	
Non sphincter saving	36	1.89 (1.13 – 3.16)	**0.015**	1.48 (0.84 - 2.61)	0.16
Interval primary tumor and diagnosis of LRRC					
<2 years	72	1			
≥2 years	78	0.71 (0.43 – 1.16)	0.17	-	
LRRC neoadjuvant treatment					
No RTx	21	1			
(CTx)RTx	129	0.56 (0.30 – 1.05)	0.07	-	
LRRC surgery					
Non sphincter saving	97	1		1	
Sphincter saving	53	1.77 (1.00 – 3.12)	**0.05**	1.48 (0.84 – 2.61)	0.17
Total exenteration					
No	122	1			
Yes	28	0.92 (0.46 – 1.80)	0.80	-	
Partial sacrectomy					
No	132	1			
Yes	18	1.80 (0.98 – 3.32)	0.06	-	
Resection margin status					
>2mm	41	1		1	
>0-2mm	34	2.82 (1.09 – 7.27)	**0.033**	2.76 (1.06 – 7.16)	**0.037**
Microscopically involved	55	5.22 (2.28 – 11.95)	**<0.001**	4.92 (2.15 – 11.26)	**<0.001**
Macroscopically involved	20	12.52 (4.97 – 31.53)	**<0.001**	11.06 (4.20 – 29.12)	**<0.001**
IORT					
No	74	1			
Yes	76	1.38 (0.84 – 2.27)	0.20	-	
Tumor differentiation grade					
Well/moderate	105	1			
Poor	18	0.92 (0.42 – 2.03)	0.83	-	
Vasoinvasion					
No	121	1			
Yes	29	2.40 (1.38 – 4.16)	**0.002**	1.60 (0.89 – 2.89)	0.12

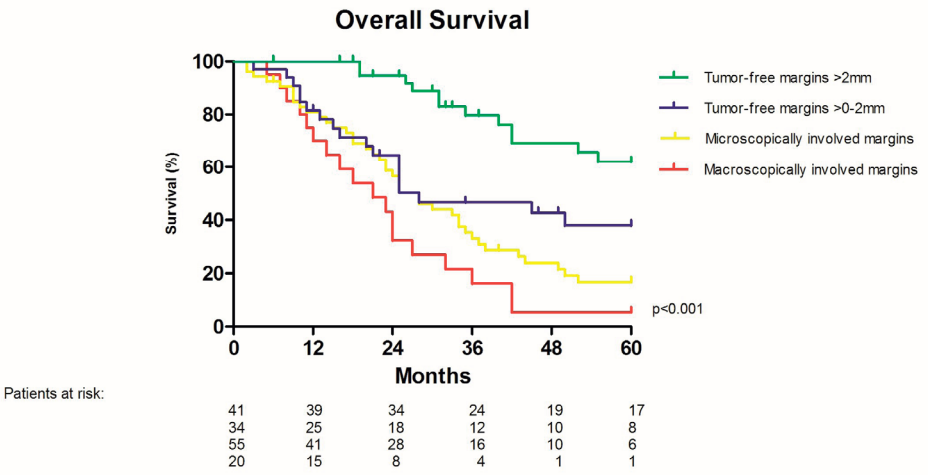
LRRC, locally recurrent rectal cancer; TME, total mesorectal excision, RTx, radiotherapy; CTxRTx, chemoradiotherapy; IORT, intraoperative radiotherapy

Table III. Univariate analysis of covariates regarding the overall survival and multivariable analysis stratified for period of surgery

	Number of patients	Univariate Hazard ratio (95%CI)	p-value	Multivariable Hazard ratio (95%CI)	p-value
Gender					
Male	94	1			
Female	56	0.86 (0.56 – 1.32)	0.50	-	
Primary tumor resection					
Non-TME	58	1			
TME	92	0.83 (0.55 – 1.26)	0.38	-	
Previous pelvic radiotherapy					
No RTx	121	1			
(CTx)RTx	29	0.75 (0.43 – 1.33)	0.33	-	
Age at LRRC surgery					
<65 year	74	1			
≥65 year	76	1.21 (0.80 – 1.83)	0.36	-	
Primary tumor resection					
Sphincter saving	114	1			
Non sphincter saving	36	1.17 (0.74 – 1.85)	0.51	-	
Interval primary tumor and diagnosis of LRRC					
<2 years	72	1		1	
≥2 years	78	0.60 (0.40 – 0.90)	**0.015**	0.55 (0.36 – 0.83)	**0.006**
LRRC neoadjuvant treatment					
No RTx	21	1			
(CTx)RTx	129	0.89 (0.51 – 1.58)	0.69	-	
LRRC surgery					
Non sphincter saving	97	1			
Sphincter saving	53	1.52 (0.97-2.38)	0.07	-	
Total exenteration					
No	122	1			
Yes	28	1.17 (0.69 – 1.98)	0.56	-	
Partial sacrectomy					
No	132	1			
Yes	18	1.25 (0.70-2.25)	0.45	-	
Resection margin status					
>2mm	41	1		1	
>0-2mm	34	2.56 (1.26 – 5.20)	**0.009**	2.58 (1.26 – 5.26)	**0.009**
Microscopically involved	55	3.91 (2.09 – 7.31)	**<0.001**	3.64 (1.89 – 7.00)	**<0.001**
Macroscopically involved	20	5.95 (2.89 – 12.28)	**<0.001**	4.89 (2.29 – 10.45)	**<0.001**
IORT					
No	74	1			
Yes	76	1.37 (0.91 – 2.07)	0.14	-	
Tumor differentiation grade					
Well/moderate	105	1			
Poor	18	1.29 (0.70 – 2.39)	0.41	-	
Vasoinvasion					
No	121	1		1	
Yes	29	2.38 (1.50 – 3.81)	**0.001**	1.78 (1.06 – 2.98)	**0.029**

LRRC, locally recurrent rectal cancer; TME, total mesorectal excision, RTx, radiotherapy; CTxRTx, chemoradiotherapy; IORT, intraoperative radiotherapy

Figure II. Overall survival of the surgically treated LRRC patients



Distant metastases

Sixty-two patients (41%) developed distant metastases during follow up. The most common location was pulmonary (58%), followed by hepatic (31%) and other (20%). The 5-year distant metastases-free survival was 62% for patients with tumor-free margins of >2mm followed by 42% for tumor-free margins of 0-2mm, 28% for microscopically involved margins and 0% for macroscopically involved margins.

Discussion

The current study demonstrates that resection margins are the key to successful curative surgery for LRRC. Patients with resection margins of more than 2mm suffer less local re-recurrences and have an improved overall survival compared to patients with narrow resection margins (>0-2mm). Subsequently, patients with narrow resection margins (>0-2mm) have a more favorable outcome compared to patients with microscopically involved margins. Accurate determination of the minimal tumor-free resection margin leads to a more accurate assessment of the risk of local re-recurrence and overall survival. These data suggest that all efforts should be made to achieve resection margins more than 2 mm by downstaging with neoadjuvant treatment and by aggressive, multivisceral surgery when needed.

The association between the width of the tumor-free resection margin of LRRC and the re-recurrence rate is in line with the association of the CRM and recurrence rates in primary rectal cancer. However, re-recurrence rates after LRRC surgery are high compared to primary rectal cancer, which suggests a more aggressive local tumor

behavior of LRRC.[12] In primary rectal cancer, recurrences rates after CRMs of >2mm are reported in 2-12% of the patients compared to a re-recurrence rate of 20% after LRRC surgery. In patients with CRMs of >0-2mm, local recurrence rates of 5-28% are reported in primary rectal cancer compared to a re-recurrence rate of 38% in this study. Microscopically involved CRMs lead to a recurrence rate of 35-55% in primary rectal cancer compared to a re-recurrence rate of 72% after LRRC surgery in this study.[12-14,17]

The majority of published studies considers any microscopically uninvolved margin after LRRC surgery as a R0-resection. The local re-recurrence rates after such R0-resections are 25-50%.[6,10,18,19] These high re-recurrence rates can be explained by the fact these R0-resections probably contain a high proportion of patients with tumor-free resection margins of >0-2mm. In our series, tumor-free margins of >0-2mm were present in 46% of the patients with complete resections. In line with our results, authors who consider tumor-free margins of ≥1mm as R0-resections reported lower re-recurrence rates of 13-16%.[11,20] In the current study, re-recurrence rate and overall survival rates of patients with tumor-free margins of <1mm or tumor-free margins of 1-2mm were similar. We therefore suggest that tumor-free resection margins of >2mm should be the goal of curative surgery for LRRC.

The high frequency of narrow and involved resection margins in rectal surgery is caused by the anatomy of the pelvis. Moreover, local recurrences in the TME era are usually not confined to an anatomical compartment, since the anatomical compartment (mesorectum) was resected completely during resection of the primary rectal tumor. Consequently, local recurrences usually involve structures such as the pelvic fatty tissue and sidewalls, the bony sacrum, iliac and sacral vessels and nerves, ureters, bladder and the internal genitalia (prostate, uterus and vagina). Few patients have true intraluminal recurrences. These are the recurrences that may result in wide tumor-free resection margins as compared to recurrences that occur anterior, lateral and dorsal in the pelvis.[21] In not-centrally located LRRCs wide tumor-free resection margins can only be achieved by performing aggressive surgery, such as posterior exenterations, total exenterations or abdominosacral resections.[11,22,23]

Performing more radical surgical approaches may be the key to increase the number of patients with wider resection margins and thus improving the long-term outcome. Several experienced LRRC centers have shown that more radical surgical approaches for LRRC can be carried out with good results. A recent study of Colibaseanu et al.[24] have demonstrated that extended sacropelvic resections, for example with high sacral involvement above the level of S2 or resections in combination with hemipelvectomies, can be carried out with acceptable morbidity and results in a high complete resection rate of 93% and an excellent 5-year survival rate of 46%. Others have demonstrated previously that extensive resections of pelvic sidewall recurrences or extensive resections including sacrectomy can be carried out with excellent results.[25,26]

The introduction of multidisciplinary tumor boards and the improvement of the quality of the imaging modalities can further increase the number of complete resections by more accurate determination of the required extent of the surgical approach. It should be kept in mind that surgical planning should be performed on the initial imaging before neoadjuvant (chemo-)radiotherapy to reduce the chance of incomplete resections. Restaging imaging is unreliable to differentiate between post-radiation fibrosis and malignant tissue.

In general, the type of surgical procedure for LRRC did not change during the study period. However, developments in the treatment of primary rectal cancer, such as TME and radiotherapy, did influence the surgical treatment of LRRC. Complete resections after TME for the primary rectal tumor are considered more difficult and may result in an increased number of patients with narrow or involved resection margins. At the same time, the introduction of neoadjuvant radiotherapy for primary rectal cancer has caused re-irradiation doses for the treatment of LRRC to be limited in those patients who received radiotherapy for the primary tumor. This may result in decreased downstaging and less complete resections for LRRC. Additionally, the use of re-irradiation is still controversial, because of the potential toxicity. To evaluate the possible influence of these variables, we performed uni- and multivariable analyses, but none of these factors proved significant.

Although others have suggested a beneficial effect of IORT, the univariate analysis did not show a similar result.[27,28] However, IORT was specifically administered to patients with a high risk of local re-recurrence (i.e. involved or narrow margins ≤2mm), thus creating a selection bias to the detriment of the value of IORT.

An interval of more than 2 years between primary tumor resection and the diagnosis of LRRC was a prognostic factor for overall survival after LRRC surgery. Due to the fact that only patients with minimally of non-metastasized LRRC were selected for surgery, patients diagnosed with LRRC after an interval of more than 2 years may have tumors with a more favorable biological behavior.

Due to the retrospective nature of this analysis, this study has drawbacks. Firstly, the number of patients included is low compared to the studies that evaluated the prognostic value of the CRM in primary rectal cancer. However, this may be compensated by a higher occurrence of patients with tumor-free margins of >0-2mm. Secondly, the current study applied no standardized pathological examination to the resected specimens as was conducted in primary rectal cancer. Standardized pathological examination of LRRC is difficult due to the heterogeneity of the resected specimens, varying from specimens of total exenterations to resections of relative small local recurrences. Furthermore, the number of pathologists involved was high. The resection specimens were always evaluated by a team of 4 designated GI pathologists. However, we found that the turnover in this team has been very high, resulting in approximately 20 pathologists

evaluating the specimens. Thirdly, the long time span of this study may have introduced non-measurable variables and inherent biases, such as the quality of imaging and the experience of different surgeons. Although at all times a team of three dedicated colorectal surgeons performed resections of LRRCs (total of 8 surgeons during the study period). By stratifying for period of surgery in multivariable analysis, the influence of these variables was reduced. Fourthly, the median follow up of all patients was relative short (27 months), which was caused by a relative short overall survival. A substantial proportion of local re-recurrences may develop after this follow up period. However, the median follow up of the surviving patients was 43 months and we therefore think these patients were followed for an adequate length of time to evaluate the local re-recurrence-free survival. Fifthly, this study only included patients that underwent surgery. Since 2002, approximately 40% of the patients referred to our hospital were considered candidates for a surgical resection (data not shown). This is a potential selection bias and implies that the findings of current study are only applicable for selected patients. This may also explain the high number of patients who were treated by sphincter-saving procedures for the primary tumor.

In conclusion, resection margin status is an independent prognostic factor for re-recurrence and overall survival after curative surgery for LRRC. Patients with tumor-free resection margins of less than or equal to 2mm have a significantly higher re-recurrence rate and a poorer overall survival than patients with tumor-free resection margins over 2mm. All efforts should be directed at achieving wide tumor-free resection margins of more than 2mm.

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