Pretreatment MRI in Primary Rectal Cancer as a Predictor for Oncological Outcomes After Surgery for Local Recurrence

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Abstract. *Background/Aim:* For patients with locally recurrent rectal cancer (LRRC) extensive surgery is often the only curative option and patient selection is crucial. This study aimed to investigate whether magnetic resonance imaging (MRI) characteristics of the primary tumour can predict oncological outcome after surgery for locally recurrent rectal cancer (LRRC). *Patients and Methods:* All patients undergoing surgery for LRRC with a curative intent at the Karolinska University Hospital 2003-2013 were included. MRI examinations of the primary tumour were re-evaluated. *Results:* In total, 54 patients were included. A tumour volume decrease of <70% after preoperative radiotherapy or chemoradiotherapy (C)RT for the primary tumour was correlated with a lower proportion of R0 resection of the LRRC (OR=0.07, 95% CI=0.01-0.84). No association between MRI characteristics of the primary tumour and prognosis after LRRC surgery was found. *Conclusion:* Long-term outcomes after surgery for LRRC were not significantly associated with MRI characteristics of the index tumour. However, factors associated with increased risk of R1 resection of LRRC were identified.

Local recurrence rates after rectal cancer surgery have been substantially reduced following the introduction of total

mesorectal excision (TME) surgery (1). Preoperative radiotherapy (RT) or chemoradiotherapy (CRT) for rectal cancer have further decreased the numbers of locally recurrent rectal cancer (LRRC) (2-4). Although improvement over time has occurred, patients undergoing surgery for LRRC have relatively poor survival outcomes, especially if an R0 resection is not accomplished (5-10).

Magnetic resonance imaging (MRI) has become standard for pretherapeutic staging and for the assessment of local tumour status after preoperative (C)RT in primary rectal cancer. Several tumour characteristics readily identifiable on pretherapeutic MRI of the primary tumour, predict for the later development of LRRC (11). Although with limited data available, a MRI-defined poor tumour regression grade (mrTRG) and a limited reduction of tumour volume on primary tumour MRI after preoperative (C)RT appear to correspond to a poor histopathological tumour response and are associated with inferior oncological outcomes (12-15).

Apart from patient factors such as advanced age and comorbidity, tumour factors such as disseminated disease and features of the LRRC on MRI play a key role for selection to surgery for LRRC (16). However, it is not fully explored if primary tumour characteristics may have a predictive value regarding long-term outcome after LRRC surgery. According to some recent reports, advanced histopathological T and N stage of the primary tumour corresponds to inferior prognosis after LRRC but there is limited data on the ability to predict long-term oncological outcomes after surgery for LRRC based on primary tumour MRI (7, 17).

Preoperative (C)RT in rectal cancer is associated with morbidity (18, 19). Furthermore, morbidity following surgery for LRRC is considerable (6, 20). Hence, all available information must be considered in treatment selection for both primary rectal cancer and LRRC to avoid over- and under-treatment.

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The aim was to investigate whether there are factors on pre-treatment and restaging MRI for primary rectal cancer of predictive importance regarding outcomes following surgery with a curative intent for LRRC. In addition effects of treatment selection for the primary tumour and outcomes with respect to the LRRC were explored.

Patients and Methods

Patients. Karolinska University Hospital is a tertiary referral centre for LRRC. All patients who underwent surgery for LRRC with a curative intent at the Karolinska University Hospital between January 2003 and December 2013 and had an MRI before surgery for the primary tumour were included. Information regarding age, sex, date and type of primary surgery, and preoperative and adjuvant treatment for the primary tumour was retrieved from patient records. For the LRRC, data collection included information on date and type of surgery, histopathology report, end of follow-up date, death and distant and/or local re-recurrence. For all patients, information was also retrieved concerning occurrence of and treatment for distant metastases. The study was approved by the regional Ethical Review Board at Karolinska Institutet (approval number: KI-00-135, 2008/1939-32, 2011/1481-32, 2012/1975-32, 2016/2487-32, 04-576/2, 2009/1468-32, 2014/1573-32) (Stockholm, Sweden).

MRI re-evaluation. Pelvic MR examinations of the primary rectal cancer were retrieved for all patients. In patients in whom a restaging MRI had been performed after preoperative therapy, these examinations were also collected. All MR images were re-evaluated a first time by a body radiologist specialised in rectal cancer MRI (NB) and, if judged necessary by the first radiologist, a second time together with a second radiologist specialised in rectal cancer MRI (either LB or CS). When re-evaluating the primary tumour MRIs, the radiologists were blinded for the original MRI report. Re-evaluation of the pretherapeutic MRI included tumour level above anal verge, tumour volume, mrT stage, mrN stage, presence of suspicious lateral lymph nodes, extramural vascular invasion (mrEMVI) status and involvement of the mesorectal fascia (mrMRF). Lateral lymph nodes were defined as anatomically located along the internal iliac artery and in the obturator fossae. Morphological criteria on pretherapeutic T2-weighted images were used to define presence of lymph node metastases (21, 22). Restaging MR images were re-evaluated with respect to tumour volume and mrTRG. A 70% decrease in tumour volume between the pre-treatment staging MRI and the restaging MRI was considered as a significant response based on previous studies (13, 23). mrTRG was assessed using a five-graded scale according to experiences from the MERCURY study group (24, 25). An mrTRG of 1, 2 and 3 represents a complete, near complete and moderate response, respectively, while an mrTRG of 4 and 5 a slight and no response with a predominance of tumour, respectively.

Preoperative treatment. After re-evaluation of the pre-treatment MRI before primary surgery, all primary tumours were classified as early, intermediate or locally advanced according to a previous publication and related to the selected preoperative treatment regimen in each patient (26). According to the Swedish guidelines, early, intermediate, and locally advanced tumours should be selected for no preoperative treatment, preoperative short-course RT and preoperative CRT, respectively (26).

Outcomes. The outcome measures included overall survival (OS), disease-free survival (DFS) and local re-recurrence. OS was defined as time from LRRC surgery to death from any cause and DFS as time from LRRC surgery to local or systemic re-recurrence or death from any cause.

Statistical analysis. For comparison of categorical variables the chi-square test was used. The Kaplan-Meier method was used to estimate rates of DFS, OS and local re-recurrence. Differences were assessed by the log-rank test. All *p*-values <0.050 were considered statistically significant. To identify risk factors for outcome measures, OS, DFS, and local re-recurrence after surgery for LRRC present at the time of primary surgery, univariable Cox regression analyses were used. Predictors for non-radical LRRC surgery were identified with univariable logistic regression analyses. Wald test was used to test for trends. Data were analysed using Stata® version 12.0 statistical software package (Stata Corp LP, College Station, Texas, USA).

Results

Patients. During the study period, a total of 76 patients underwent surgery for LRRC. Two patients were excluded as surgery was indicated by re-recurrence. Because of unavailability of MRI before primary surgery, another 20 patients were excluded, leaving 54 patients for analyses. Table I summarizes descriptive data on these 54 patients.

Primary tumour. Prior to surgery for the primary tumour, 42 (78%) patients received preoperative (C)RT. Among those patients, 14 had direct surgery and 20 had a restaging MRI after preoperative therapy. In the remaining 8 patients, a restaging MRI was not available.

Of all patients, 15 (28%) were treated with adjuvant chemotherapy for the primary tumour. Two patients had synchronous metastases at primary surgery and 9 patients were treated for metachronous metastases before LRRC surgery.

Of all primary tumours at re-evaluation, 10 (19%) were classified as early, 14 (26%) as intermediate and 30 (56%) as locally advanced (Table II). Among the 30 patients with locally advanced tumours according to MRI, 20 (67%) patients did not receive preoperative CRT. Out of these 20 patients, 12 were 65 years or younger. In total, preoperative treatment of a lower intensity than that recommended by the Swedish guidelines was delivered to 24 (45%) patients.

Local recurrence. Median age at surgery for the LRRC was 65 years (range=42-82). The median time interval between primary surgery and LRRC surgery was 28 months (range=5-146). There were no in-hospital deaths. Among the 42 patients initially treated with preoperative (C)RT, re-irradiation for the LRRC was given to 13 (31%) patients. In the group of 12 patients previously non-irradiated, 6 patients received RT before LRRC surgery, 2 patients received intra-operative RT and 4 patients were never irradiated. Eight

Table I. Clinical and radiological characteristics of the primary rectal cancer (n=54).

	n (%)
Age at primary surgery*, years	63 (41-82)
<65	32 (59)
≥65	22 (41)
Gender	
Male	33 (61)
Female	21 (39)
Tumour height, MRI (cm)	
0-5	16 (30)
6-10	23 (43)
10-15	14 (26)
mrT stage	
T0-T2	11 (20)
T3	23 (43)
T4	20 (37)
mrN stage	
N0	11 (20)
N1	26 (48)
N2	17 (32)
mrMRF status	
Positive	25 (46)
Negative	29 (54)
mrEMVI	
Yes	28 (52)
No	26 (48)
Involved lateral nodes, MRI	
Yes	13 (24)
No	41 (76)
Tumour volume decrease, MRI**	
>70%	10 (50)
≤70%	10 (50)
mrTRG**	
1-3	14 (70)
4-5	6 (30)

MRI, Magnetic resonance imaging; mr, MRI-defined; MRF, mesorectal fascia; EMVI, extramural vascular invasion; TRG, tumour regression grade. *Data presented as median (range); **n=20.

patients received adjuvant chemotherapy after LRRC surgery and in 3 of those patients adjuvant chemotherapy had been delivered also after primary surgery.

Outcomes. R0 resection of the LRRC was achieved in 35 (65%) patients and the remaining 19 patients had R1 resections. In Table III, the univariable logistic regression analyses of associations between radiological factors on pre-treatment MRI of the primary tumour and R0 surgery of the LRRC are shown. No statistically significant associations could be detected except among the 20 patients with a available restaging MRI after preoperative (C)RT. In those patients in whom primary tumour volume decrease was less than 70% after (C)RT, R0 surgery for the LRRC was less likely to occur (OR=0.07, 95% CI=0.01-0.84). Also an

Table II. Pre-treatment stage according to magnetic resonance imaging (MRI) re-evaluation related to preoperative treatment of the primary rectal cancer (n=54).

Tumour stage	Total n	Preoperative treatment		
		No	RT	CRT
Early	10	4 (40)	6 (60)	0 (0)
Intermediate	14	4 (29)	9 (64)	1 (7)
Locally advanced	30	4 (13)	16 (53)	10 (33)

RT, Radiotherapy; CRT, chemoradiotherapy. Values in parentheses are percentages.

mrTRG of 4-5 was associated with a decreased chance of R0 resection of the LRRC (OR=0.14, 95% CI=0.02-1.14), however without statistical significance.

The 3-year OS, DFS and local re-recurrence rate after LRRC surgery were 57%, 26% and 41%, respectively. One patient had synchronous liver metastases at the time of LRRC surgery and was therefore excluded from the analyses of DFS. There were no statistically significant differences between women and men in terms of OS and DFS. R0 resection of the local recurrence was a strong predictor for 3-year OS (R0 66% vs. R1 42%, $p=0.005$) and DFS (R0 31% vs. R1 7%, $p=0.024$). Patients 65 years or older had local re-recurrence to a lesser extent than younger patients (HR=0.30, 95%CI=0.10-0.91). Patients who received preoperative (C)RT for the primary tumour had inferior OS following LRRC surgery compared to those without primary preoperative treatment ($p=0.028$). MRI characteristics of the primary tumour with potential predictive value for the LRRC surgery are displayed in Table IV. There were no statistically significant associations between pretherapeutic primary tumour MRI variables such as mrT stage, mrN stage, mrMRF or mrEMVI and OS, DFS or local re-recurrence in the univariable Cox regression analyses.

Discussion

In this retrospective study, 54 patients who underwent surgery for LRRC were analysed and possible associations between primary tumour MRI characteristics and surgical outcomes were investigated. The results showed that no characteristics of the pre-treatment MRI could predict outcomes, whereas an evident response to preoperative (C)RT in the primary tumour, measured as decreased tumour volume, was associated with an increased chance of obtaining an R0 resection of the LRRC. Although not statistically significant, the result on mrTRG pointed in the same direction. It is conceivable that biological properties of a tumour influencing response to neoadjuvant therapy may

Table III. Univariable logistic regression analyses of association between MRI characteristics of the primary tumour and R0 surgery of the locally recurrent rectal cancer (n=54).

	Total LRRC		R0 resection	
	n	n (%)	OR (95% CI)	p-Value*
Tumour height, MRI (cm)**				0.653
0-5	16	12 (75)	1.00	
6-10	23	14 (61)	0.52 (0.13-2.12)	
11-15	14	9 (64)	0.60 (0.12-2.89)	
mrT stage				0.927
T0-T2	11	7 (64)	1.00	
T3-4	43	28 (65)	1.07 (0.27-4.24)	
mrN stage				0.168
N0	11	9 (82)	1.00	
N1-2	43	26 (60)	0.34 (0.07-1.77)	
mrEMVI				0.290
No	26	15 (58)	1.00	
Yes	28	20 (71)	1.83 (0.59-5.68)	
mrMRF status				0.907
Positive	29	19 (66)	1.00	
Negative	25	16 (64)	0.94 (0.31-2.87)	
mrTRG***	0.054			
0-3	14	11 (79)	1.00	
4-5	6	2 (33)	0.14 (0.02-1.14)	
Tumour volume decrease, MRI***				0.015
>70%	10	9 (90)	1.00	
≤70%	10	4 (40)	0.07 (0.01-0.84)	

LRRC, Locally recurrent rectal cancer; MRI, magnetic resonance imaging; mr, MRI-defined; MRF, mesorectal fascia; EMVI, extramural vascular invasion; TRG, tumour regression grade. *Wald test. **One missing patient because of primary tumour undetectable on MRI. ***n=20.

also have an impact on the LRRC and the possibilities to successfully treat the LRRC. The experience of pre- or post-operative re-irradiation is limited; however, some recent investigations demonstrated that re-irradiation of LRRC, possibly with the addition of induction chemotherapy, resulted in enhanced survival and local control, acceptable morbidity, as well as a possibility of complete pathological response (27, 28). There are indications that primary tumour response to neoadjuvant (C)RT predicts outcomes after rectal cancer surgery and possibly the response to preoperative (C)RT for the primary tumour could be helpful to guide in the selection of treatment of the LRRC (29).

In this series of patients, it appears as if a substantial proportion of patients were undertreated with respect to the primary tumour, since 2/3 of patients with a locally advanced tumour did not receive CRT as recommended. Previous studies have shown that advanced age and comorbidity are important factors and also that the selection strategy may have an impact on outcomes following treatment of primary rectal cancer (30, 31). In the present study, patients were relatively young (median age 63 years) and subsequently were considered fit for surgery of a LRRC. Therefore, neither advanced age nor significant co-morbidity appear as

reasonable explanations for this under-treatment. Since the patients in this study were included from 2003, the recommendations of preoperative treatment have changed throughout the study period and this could partly explain the under-treatment. Also, previous pelvic irradiation as a reason for omittance of preoperative RT of the rectal cancer was not possible to control for. However, given the relatively young median age among the studied patients, this explanation seems less likely.

The finding that patients who had received primarily neoadjuvant (C)RT had an inferior OS after LRRC surgery should not be interpreted so that (C)RT should be avoided when indicated; rather, tumours that are initially more aggressive produce more aggressive recurrences, resulting in poorer survival rates. Treatment for LRRC is demanding and results, although gradually improving, are still poor in comparison with treatment for primary rectal cancer (32). Thus, a main objective in rectal cancer treatment should be to avoid a LRRC and obtain sustained local control. The present series indicate that there may be room for improved treatment selection in primary rectal cancer management and, theoretically, some of the LRRCs in this series may have been avoided had (C)RT been given.

Table IV. *Univariable Cox regression analyses of association between MRI characteristics of the primary tumour and outcome after surgery for locally recurrent rectal cancer (n=54).*

	Overall survival HR (95% CI)	Disease-free survival* HR (95% CI)	Local re-recurrence HR (95% CI)
Tumour height, MRI (cm)**			
0-5	1.00	1.00	1.00
6-10	0.78 (0.35-1.71)	1.10 (0.54-2.24)	0.77 (0.28-2.14)
10-15	1.31 (0.55-3.15)	1.25 (0.54-2.87)	0.85 (0.25-2.92)
mrT stage			
T0-2	1.00	1.00	1.00
T3-4	1.21 (0.53-2.77)	1.32 (0.63-2.76)	1.77 (0.52-6.06)
mrN stage			
N0	1.00	1.00	1.00
N1-2	1.53 (0.64-3.69)	1.70 (0.79-3.67)	3.02 (0.70-13.05)
mrMRF status			
Positive	1.00	1.00	1.00
Negative	1.20 (0.63-2.30)	1.52 (0.83-2.77)	1.26 (0.52-3.02)
mrEMVI			
No	1.00	1.00	1.00
Yes	1.21 (0.62-2.35)	1.18 (0.65-2.15)	1.69 (0.69-4.15)
Involved lateral nodes, MRI			
No	1.00	1.00	1.00
Yes	1.20 (0.56-2.57)	1.33 (0.67-2.65)	1.54 (0.59-4.02)
mrTRG***			
0-3	1.00	1.00	1.00
4-5	2.20 (0.71-6.84)	2.05 (0.74-5.72)	2.01 (0.58-6.98)
Tumour volume decrease, MRI***			
>70%	1.00	1.00	1.00
≤70%	1.07 (0.39-2.96)	0.76 (0.30-1.93)	1.69 (0.49-5.80)
Preoperative tumour stage, MRI			
Early	1.00	1.00	1.00
Intermediate	1.36 (0.48-3.84)	1.23 (0.49-3.14)	2.46 (0.48-12.70)
Locally advanced	1.32 (0.64-3.84)	1.48 (0.66-3.29)	2.70 (0.61-11.98)

MRI, Magnetic resonance imaging; mr, MRI-defined; MRF, mesorectal fascia; EMVI, extramural vascular invasion; TRG, tumour regression grade.
 *One patient excluded because of synchronous metastases by primary surgery. **One missing patient because of primary tumour undetectable on MRI. ***n=20.

The association between age and local re-recurrence where older patients had better local control after LRRC surgery is possibly due to the fact that younger patients are being selected for curatively intended surgery for LRRC to a higher extent, also with more advanced tumours, than older patients.

There are several limitations that need to be addressed. The retrospective approach and the small study population create obvious restrictions. Only 20 of 42 patients treated with preoperative (C)RT could be assessed regarding mrTRG and tumour volume decrease. Local recurrence rates in rectal cancer are low today (33). Furthermore, far from all patients with a LRRC can be offered surgery with a curative intent; therefore, few patients are available for inclusion into clinical investigations. Prospective studies on rare conditions are difficult to perform and implicate a long study inclusion period. An international registry of LRRC-patients with prospectively collected data could possibly

improve the possibilities to design investigations with sufficient quality. Secondly, the LRRC surgery of the patients was carried out over a relatively long time span. Treatment of both the primary tumour and the LRRC has evolved over time, especially regarding preoperative (C)RT, and this could naturally have an impact on prognosis. Thirdly, many factors other than the features of the primary tumour may influence the outcome after LRRC surgery. There is an obvious risk of confounding because of differences in, for example, comorbidity, oncological treatment before and after LRRC and the histopathological stage of the primary tumour and LRRC.

In conclusion, it is well established that preoperative (C)RT for rectal cancer reduces the risk of LRRC. Still, among the patients who undergo surgery for LRRC, this study revealed that the primary tumour may have been under-treated in a substantial proportion of the patients. However, prediction of long-term outcome after LRRC surgery based on the

radiological features on the pretherapeutic MRI for the primary tumour was not possible. Improved decisions on both surgical and preoperative oncological therapy in rectal cancer patients can reduce rates of LRRC and possibly also improve survival, as well. Multicentre investigations and international prospectively collected registries are warranted to increase knowledge about the management and prevention of LRRC in rectal cancer.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

Authors' Contributions

Study concepts and design: All Authors; Data acquisition: AE, BO, CS, LB and HI; Data analysis and interpretation: AE, LB, HJ, BG, PN and HI; Statistical analysis: AE and HJ; Manuscript preparation: AE and HI; Manuscript editing and approval of the final article: All Authors.

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