The influence of circumferential resection margins on survival following rectal cancer surgery

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BACKGROUND AND AIMS: *A negative (R0) circumferential resection margin (CRM) is described as one of the most important factor that decrease the rate of local recurrence in rectal cancer. The primary outcome of the study was the status of the CRM, while the secondary outcomes were local recurrence and overall survival.*
METHODS: *Study includes 192 patients with rectal cancer operated between January 2012 and December 2013 in our Institute. The incidence of positive CRM and its impact on the survival rates after oncologic surgical resection were investigated along with factors that determine positive CRM. R1 was defined as a distance of ≤ 1 mm between the tumor and the resection margin.*
RESULTS: *The R1 rate was 3.6 % (7 cases). Nine patients (4.68%) developed local recurrence during a median follow-up period of 720 days. A positive CRM was found to be a risk factor of local recurrence (p-value = 0.031) and it decreased the overall survival (p-value=0.001). pT4 stage (p-value=0.008) and vascular invasion (p-value=0.005) are factors that play significant roles in determining CRM positivity. In case of inferior rectal tumours abdomino-perineal resection (APR) determines significantly higher (p-value=0.048) rates of positive CRM than anterior resection (AR) of the rectum.*
CONCLUSIONS: *Positive CRM affects overall survival and local recurrence in rectal cancer. pT4 stage and vascular invasion play determinant roles in determine CRM status. APR is a risk factor for positive CRM in inferior rectal tumors.*

KEY WORDS: Abdomino-perineal resection, Circumferential resection margins, Local recurrence, Rectal cancer, Overall survival

Introduction

In the mid-80s the concept of circumferential resection margin (CRM) raised the interest in the medical field [1]. Since then numerous researchers studied its prognostic significance in patients with various types and stages of rectal tumors. The microscopic CRM is defined as the minimal distance between the tumor and the resection plane. A positive CRM, termed as R1, is when that distance (described earlier) is ≤ 1mm [2]. A negative (R0) CRM is genuinely described as the most important determinant to minimize the rate of local recurrence in multiple cancers and more particularly in rectal cancers[3, 4]. One of the most important factors affecting the CRM positivity is the extent of surgical resection, in particular the introduction total mesorectal excision (TME). Moreover, higher rates of positive CRM were reported after abdominoperineal resection (APR) (10.2% to

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13.9%) compared to anterior resection (AR) (3.6% to 8.7%) [5,6], although it still a controversy whether the reason of this discrepancy is the surgical technique. There are theories that try to demonstrate that low rectal tumors are more aggressive [7] or that the anatomical limitations around the rearmost part of the rectum is that mesorectum tapers considerably [8-10].

TME is the current standard technique in rectal cancer surgeries. Since the standardization of this technique rates of local recurrence were markedly decreased from around 40% to less than 10% [11,12]. This was more evident in patients who underwent AR, including low rectal tumors, than APR [13-15].

Poor outcomes of APR raised the doubt in the standard APR technique therefore more radical excision was proposed. More recent studies reported reduced R1 rates after the modified, more radical APR with extralevator resection, which is indeed comparable to the one formerly described by Miles. Several studies reported diminished R1rates after APR in regards to the "en bloc" extralevator excision technique(41% to 14.8-20%) [16].

The local invasion of the tumor (T stage) and local lymph node involvement (N) play an essential role in CRM positivity as well. The more locally advanced the tumor is, the higher the R1 rate and the same applies to lymphovascular involvement as well [17-21].

MRI predicted CRM is one of the major determinants that guide the treatment plan, including the type and extent of surgical resection and the need for neoadjuvant and adjuvant chemoradiotherapy (CRT) [22]. The concept was demonstrated by various researchers and it is particularly of greater value in low rectal tumors in which a standard APR is proposed to be sufficient if the CRM is >1mm, especially in case when we are dealing with non-mucinous tumors [23,24]. CRM is repeatedly described as the major independent determinant of local recurrence, distant metastasis and overall survival in patients with rectal cancer [2,3,6,8,17,18,23,25].

The purpose of our study is to determine the main factors that play vital roles in CRM positivity in patients with rectal cancer, in particular the surgical technique and the extent of resection, the pathological stage of the tumor (T and N stages) and the tumor location. Furthermore, we intended to evaluate the magnitude of correlation between CRM and local recurrence and overall survival.

Material and methods

A retrospective review of patients who underwent surgery for rectal cancer between January 2012 and December 2013 at our Institute was performed. Data was collected retrospectively from our Institute's electronic database.Of a total of 408 patients with rectal cancer who underwent surgery at our department, 192 were included in our study. Patients with distant metastasis at the time of the surgery, those who underwent palliative surgery and patients whose CRM status could not be determined were excluded. Pathologic staging of the disease was performed according to The American Joint Committee on Cancer (AJCC) 7xth edition.

The database included age, gender, surgery type, location, histological tumor type, the number and the site of lymph node involvement, vascular and lymphatic status, stage, tumor grade, the distance from the anal margin and whether they received neoadjuvant CRT. A positive CRM was consider if cancer cells were found at or within 1 mm of the radial resection margin. The primary outcome of the study was the status of the CRM, while the secondary outcomes were local recurrence and overall survival.

Patient follow-up included endoscopy and computed tomography once a year after surgery. Overall survival was defined as the time from the date of surgery to the date of death or the date of the last follow-up of patients who were still alive.

Statistical analysis

Results were analysed using SPSS 19. The Chi-square test was used for qualitative data, together with the contingency and the uncertainty coefficients. Comparison between the groups was performed and the p-value was computed in the adjusted form according to Bonferroni. Ordinal variables were evaluated with the help of the Spearman and Kendall coefficients. For quantitative data, comparisons between groups were conducted in two forms –parametric (t Student) or non-parametric tests. Kaplan–Meier curves were constructed for the analysis of survival based on CRM status. Three statistic tests were used to assess the validity of the results (Log Rank, Breslow and Tarone-Ware). Multivariate analysis was carried out using the Binary Logistic regression to assess the factors that influence the appearance of CRT positive margins and the recurrence. The best fitting model was obtained in the Forward Conditional variant. p-values of <0.05 were considered statistically significant

Results

Clinical Data

A total of 192 patients, including 109 men and 83 women, between 21 and 91 years old, were included in a cohort study. Regarding surgery, 107 (55.72%) patients underwent anterior resection (AR) of the rectum, 10 (5.2%) of them were done laparoscopically (LAR). Sixty-seven (34.89%) patients underwent abdominoperineal resection (APR), 13 (6.77%) of them were done laparoscopically [26]. Hartmann's procedure was performed in 17 (8.85%) patients and a laparoscopic total procto-colectomy with an ileo-anal anastomosis was performed in one patient (Table I). TME was performed in all of the cases.

Fifty-four (28.12%) patients had inferior rectal tumours, 77 (40.1%) middle and 61 (31.77%) a superior rectal tumour. Thirty-one (16.14%) patients recevied neoadjuvant CRT (Table I).

TABLE I - *Patient and tumor characteristics according to CRM.*

Variable	R0	R1	p-value
Age	62.96 ± 10.33	60.29 ± 11.31	0.503
Gender			0.984
Male	105 (96.3%)	4 (3.7%)	
Female	80 (96.4%)	3 (3.6%)	
Surgery type*			0.148
AR	96 (99%)	1 (1%)	
LAR	10 (100%)	0 (0%)	
APR	50 (92.6%)	4 (7.4%)	
LAPR	13 (100%)	0 (0%)	
Hartmann procedure	15 (88.2%)	2 (11.8%)	
LTPC	1 (100%)	0 (0%)	
Laparoscopy			0.308
No	161 (95.8%)	7 (4.2%)	
Yes	24 (100%)	0 (0%)	
Localization			0.360
Inferior	50 (92.6%)	4 (7.4%)	
Middle	76 (98.7%)	1 (1.3%)	
Superior	59 (96.7%)	2 (3.3%)	
AM distance*	8.45 ± 3.52	6.86 ± 4.95	0.249
T stage**			0.043
1	12 (100%)	0 (0%)	
2	53 (98.1%)	1 (1.9%)	
3	97 (99%)	1 (1%)	
4	21 (80.8%)	5 (19.2%)	
N stage**			0.551
0	118 (96.7%)	4 (3.3%)	
1	50 (98%)	1 (2%)	
2	16 (88.9%)	2 (11.1%)	
Tumor stage**			0.180
I	58 (98.3%)	1 (1.7%)	
IIA	53 (98.1%)	1 (1.9%)	
IIB	8 (80%)	2 (20%)	
IIIA	9 (100%)	0 (0%)	
IIIB	38 (97.4%)	1 (2.6%)	
IIIC	17 (89.5%)	2 (10.5%)	
IVA	1 (100%)	0 (0%)	
L**			0.695
0	119 (96.7%)	4 (3.3%)	
1	65 (95.6%)	3 (4.4%)	
V**			0.116
0	171 (97.71%)	4 (2.29%)	
1	13 (81.3%)	3 (18.8%)	
G**			0.207
1	46 (97.9%)	1 (2.1%)	
2	131 (77.8%)	4 (3%)	
3	7 (77.8%)	2 (22.2%)	
Neoadjuvant CRT			0.886
No	155(96.3%)	6 (3.7%)	
Yes	30 (96.8%)	1 (3.2%)	

*AR = anterior resection; LAP = Laparoscopically anterior resection; APR = abdominoperineal resection; LAPR = laparoscopically abdominoperineal resection; LTPC = laparoscopic total procto-colectomy; AM = anal margin. ** One patient had squamos cell carcinoma and one had complete response after neoadjuvant CRT.

Pathological Data

One patient had squamos cell carcinoma and one had complete response after neoadjuvant CRT. The rest 190 (98.95%) patients had adenocarcinoma of the rectum. Twenty-six (13.54%) cases were pT4, 98 (51.04%) cases were pT3, 54 (28.12%) cases were pT2 and 12 (6.25%) cases were pT1. Staging according to AJCC 7th ed., 2010 is presented in Table I. Fifty-one (26.56%) were pN1, 18 (9.37%) were pN2 moreover 68 (35.41%) displayed lymphatic and 16 (8.33%) vascular invasion.

Resection Margin Status

Seven (3.6%) patients had microscopically positive margins (R1). All 7 were CRMs. Out of all the factors analysed at the univariate analysis, only one proved to be significant – the T stage (p-value = 0.043). Five of the 7 patients with positive CRM were pT4. Therefore, significant differences were found between the two R groups when analysed against these two factors (Table I). Furthermore, multivariate binary logistic regression was applied to compare the two groups, R0 and R1, and to evaluate the factors that could influence the probability of developing R1 margins. The best fitting model proved to be in the Forward Conditional variant. Out of all the aspects considered, pT4 stage (p-value=0.008) and Vascular invasion (p-value=0.005) were found to significantly influence the probability to have R1 margins (Table II). The anal margin (AM) distance also influences in a significant manner the probability of having R1 margins, although the relation between them was negative in our study. Thusly, the lower the distance from AM, the higher the probability of having R1 (Table II).

Overall, 9 (4.68%) patients with local recurrences were identified during a median follow-up period of 720 days, 7 of them belonged to the R0 group, while the other 2 to the R1 type. Local recurrence rates in patients with positive CRM were 28.57%, significantly higher (p=0.031, at the multivariate logistic regression analysis) than in those with negative CRM 3.64%. Results showed that recurrence is significantly influenced by two of the factors considered – the G stage and the R type. Table III shows that the probability of having recurrence is lower in patients with advanced G stage and higher in those with R1 margins.

TABLE II - *Multivariate binary logistic regression analysis of factors that determine positive CRM - Forward Conditional form*

Variables in the equation	Coef. B	Exp (B)	P-value
pT4	4,68	107,4	0,008
V	5,55	257,48	0,005
AM distance	-0,91	0,401	0,082
Constant	-30,38	0	0,996

TABLE III - *Multivariate binary logistic regression analysis of factors affecting local recurrence after rectal cancer surgery - Forward Conditional form*

	Coef. B	Exp (B)	P-value
G	-1,96	0,141	0,019
R	2,74	15,404	0,031
Constant	-19,24	0	1

TABLE IV - *The overall survival comparison tests*

	Chi-Square	df	p-value
Log Rank (Mantel-Cox)	11,934	1	0,001
Breslow (Generalized Wilcoxon)	9,475	1	0,002
Tarone-Ware	10,658	1	0,001

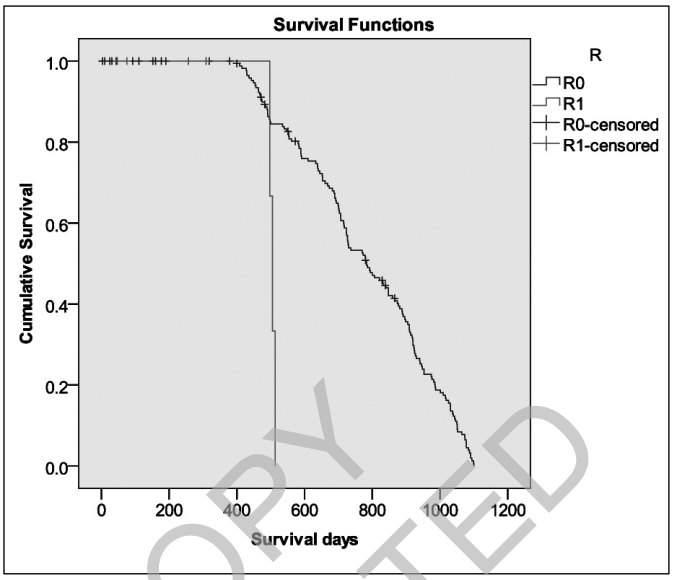

Fig. 1: Kaplan-Meier plot illustrating overall survival by CRM after rectal cancer surgery.

Regarding overall survival, out of the 183 patients with R0, 25 died during the analysed period. Among patients of R1 group, 3 of them survived while 4 of them died. In order to see whether important differences exist between patients with R0 and R1 in terms of survival probability, we applied the Kaplan-Meier survival analysis. Fig. 1 shows the Kaplan-Meier overall survival function for the two groups of patients. Additionally, all the three tests used in table IV had brought to light the significant differences between R0 and R1 patients regarding the survival time.

Among the 7 patients who reported positive CRM, four of them underwent APR. There is a significant correlation between APR and CRM in cases with inferior rectal tumors (less than 5 cm from de AM). The relationship is significant at the 5% critical level (p-value = 0.048 < 0.05). This means that when dealing with inferior rectal tumors, there is a higher probability to obtain positive CRMs when the APR is performed.

Discussions

Our study confirms the role of CRM in the overall survival and the local recurrence. Univariate analysis denoted that pT4 stage (p-value = 0.043) is an independent factors of CRM positivity. At the multivariate analysis vascular invasion (p-value=0.005) was found to play an important role to determine positive CRM. The AM distance also influences in a significant manner the probability of having positive CRM, but this time, the relationship was negative.

A huge deal of authorized studies estimated the rate of local recurrence after rectal cancer resection in correspondence with multiple variables. The strongest statistically significant factor affecting local recurrence was the CRM [2,17,18,20,21,27,28]. Local recurrence was reported to be around 22 % and 4% after R1 and R0 rectal cancer resections, respectively [8, 29].

Local recurrence after rectal surgery is associated with postoperative pain and impaired quality of life plus it is frequently incurable. Despite the fact that Nagtegaal et al[18]. in 2002 recommended a cut off margin of ≤ 2mm for positive CRM, all the other studies demonstrated and recommended that CRM margin to be ≤1 mm[2,17,28]. Along with these studies, we confirm that a CRM >1 mm leads to good oncologic outcomes.

Since the introduction of TME, outcomes following AR have become a major focus of surgical research [1]. Patients who were treated with AR have benefited from the standardization of the surgery subsequently their outcomes were uniformly improved [15], even in patients with very low tumours [14]. In contrast, little improvement was reported in the outcome of patients treated with APR [13]. Reported high CRM positivity rates following APR have prompted re-examination of the surgical technique.

As we refer to the higher rates of CRM after APR, our data seems to approve the theory that higher rates of positive CRM are reported after APR compare to the AR. Many studies reported higher R1 rates in patients who underwent APR compared to those who underwent low AR [13,19,21,30,31]. An Irish study applied multivariate analysis on the relation between CRM after APR and the T and N stages in low rectal tumors. Their figures were of statistical significance and they concluded that pT4 tumors (OR 19.92; 95% C.I. 6.48 to 68.61; P < 0.001)) and N+ (OR 3.04; 1.32 to 8.05; P = 0.004)) stages are independent determinants of R1 [32]. As we have mentioned before, it is still controversial which fac-

tors determine CRM positivity: the surgical technique, aggressive tumors or that the mesorectum tapers considerably.
Likewise, multivariate analysis of the same Irish study we mentioned earlier concluded that R1 is the single most eminent predictor of local recurrence after APR (OR 3.63; C.I. 1.42 to 9.75; P = 0.016)[32].

Conclusion

The CRM remains among the most important factors in what concerns the survival and local recurrence. pT4 stage and the presence of vascular invasion notably increase the probability of obtaining a positive CRM. APR is an essential element in the management of inferior rectal cancer (≤ 5 cm from de AM), being an important factor in determining CRM positivity.

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