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ORIGINAL ARTICLE

What is the significance of a microscopically positive resection margin in the curative-intent treatment of rectal adenocarcinoma? A retrospective study

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Summary

Purpose: *The aim of this study was to analyze the characteristics of patients with rectal cancer operated with a microscopic positive margin (R1) and thus avoid these situations or adapt treatment in these particular cases.*

Methods: *We reviewed all the pathology data of resected specimens from patients with rectal or recto-sigmoid cancer operated with curative intent at the Institute of Oncology "Prof. Dr. Ion Chiricuta" between 2000-2011 (763 patients in 12 years) and the pathology files of patients from other institutions referred for adjuvant treatment to our hospital (318 patients). We included patients with anterior resection, Hartmann's procedure and abdomino-perineal resection, but we excluded patients with local excision and patients with R2/R1 at first, but R0 after re-resection (56 patients). We have identified 31 patients with R1, but had to exclude one case from analysis because this patient was lost to follow-up.*

Results: *With surgery alone the local relapse (LR) was unavoidable. In the neoadjuvant chemoradiation (CRT) group 85.7% of the patients did not develop LR despite of R1. In the adjuvant CRT cohort 50% of the patients were LR-free at 2 years after conventional radiotherapy ($p<0.01$).*

Conclusion: *Based on these results it is concluded that a clear resection margin is extremely important for the local control of rectal cancer, because it cannot be always compensated by adjuvant CRT. In R1 cases neoadjuvant CRT seems to offer better prognosis than adjuvant CRT. To avoid R1 and its consequences a good quality control of total mesorectal excision (TME) is needed and CRT should be done before and not after surgery. R1 after primary surgery needs to be compensated by re-resection if possible, otherwise probably high dose radiotherapy with chemotherapy is needed.*

Key words: *circumferential resection margin, compensation with radiotherapy, microscopically positive resection margin, prognostic factor, rectal adenocarcinoma*

Introduction

According to GLOBOCAN, colorectal cancer is the third cancer type in incidence in men and second in women worldwide [1]. From all colorectal cancers, around 40% arise from the rectum [2]. In countries where screening for colorectal cancer is implemented, a large fraction of patients have only local or locoregional disease and are potentially curable. In the USA, where the screening rate is around 50% [3], 75% of colorectal cancer patients present with local disease or regionally advanced disease and only 25% of the patients have metastases at diagnosis [4].

LR rate and disease free survival (DFS) in rectal cancer are highly variable according to stage. In "good-prognosis" locally advanced rectal cancer (LARC), even using TME alone, the LR rate at 5 years is very low (3%) [5]. For "poor prognosis" LARC the rate of LR is higher, even when preoperative CRT is used. In the MERCURY study, "poor prognosis" cT1-T3a patients had 13% 5-year LR rate, cT3b-T4 patients had 19%, those who didn't respond well to CRT had 29% and in patients with

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predicted positive circumferential resection margin (CRM) the LR rate was 56% [6].

The current standard of treatment in T3-4, N0-2 rectal adenocarcinoma is neoadjuvant concomitant CRT or short-course radiotherapy (SRT) followed by surgical resection including TME. A selected patient group can undergo upfront surgery as an alternative. T1-T2N0 disease is treated by resection alone (including endoscopic) or by contact radiotherapy as an experimental alternative [7,8].

A positive microscopic margin (R1) is still an unsolved problem in curative-intent rectal resection. If a R1 patient has already been subjected to neoadjuvant radiotherapy (RT) or CRT, how can R1 be compensated for? Or do we need to compensate R1 at all in this situation (i.e. are these cells viable after RT/CRT)? On the other hand, in patients who underwent primary surgery, in what group or percentage of cases can the R1 be "corrected" with RT (with or without concurrent chemotherapy)?

The goal of this retrospective study was to analyze the prognostic factors of patients with R1 and to quantify the LR rate and local relapse free survival (LRFS) in relation to different treatment sequences and scenarios.

Table 1. Patient characteristics (N=30)

Characteristics	*Patients N (%)*
Age, years, median (range)	55 (24-78)
Distance from anal verge (cm)	
≤5	14 (46.7)
5-10	13 (43.3)
>10	3 (10)
Type of surgery	
Abdomino-perineal resection	12 (40)
Anterior resection	13 (43.3) (1 with combined total hysterectomy)
Hartmann's operation	5 (16.7) (1 with combined partial cystectomy)
Pathological stage (pTN)	
pT1	2 (6.7)
pT2	4 (13.3)
pT3	21 (70)
pT4a	2 (6.7)
pT4b	1 (3.3)
pN1/N2	20 (66.7)
Liver metastases at diagnosis	7 (23.3)
Location of R1	
Circumferential only	24 (70)
Circumferential plus distal	3 (10)
Distal only	4 (13.3)
Proximal only	1 (3.3)
Nodal	1 (3.3)

Methods

Patient selection criteria

We reviewed all the pathology data of resected specimens from all patients with rectal or recto-sigmoid cancer operated with curative intent at the Institute of Oncology "Prof. Dr. Ion Chiricuta" between 2000-2011 (763 patients) and the pathology files of patients from other institutions who were referred to our hospital for adjuvant treatment (318 patients). From these patients we selected only those who had R1 operation; patients with clear resection margin (R0) or macroscopically incomplete resection (R2) were excluded. Furthermore, we excluded tumors resected by a transanal procedure and those cases with R2/R1 at first, but R0 after re-resection (56 from 763 patients).

We used the definition of a microscopically positive resection (R1) margin as described in the TNM staging system for rectal cancer, i.e. a margin of ≤ 1 mm [9].

Thus, respecting the above criteria, from 763 patients with curative rectal resection in our institution, 30 (3.9%) patients had R1. From the 318 patients who applied only for adjuvant treatment, one patient had R1. Only one patient was completely lost to follow-up, leaving 30 patients to study the patterns of relapse. From the analysis of LR we excluded patients who were followed less than 2 years or died of metastases in the first 2 years without having a LR, since there should be a minimum of 2 years follow-up to correctly quantify the LR rate (around 80% of LRs are diagnosed in the first 2 years after treatment of the primary disease) [10].

Patient and disease characteristics

Fourteen out of 30 (46.7%) patients had lower rectal cancer (≤5 cm from the anal verge), 13 patients middle (5-10 cm) and 3 upper (>10 cm) or recto-sigmoid disease (Table 1).

Twelve (40%) patients underwent abdomino-perineal resection and 18 (60%) a sphincter-saving procedure, all operations being carried out with TME. Twenty-one (70%) patients had stage pT3 disease, 4 pT2, 2 pT1, 2 pT4a and one pT4b (vaginal invasion). In 20 (66.7%) patients involved lymph nodes were found and 7 (23.3%) patients had liver metastases at diagnosis.

In 24 of 30 patients (80%) R1 was detected at the circumferential margin, in 3 patients involving both the circumferential and the distal margin. Four (13.3%) patients had only distal R1 and one a purely proximal positive margin. In 3 patients with positive circumferential margin, R1 was detected towards the vagina. In one patient R1 was located at the level of a perirectal lymph node.

Statistics

Patient data were acquired from the electronic database of the Ion Chiricuta Institute of Oncology and individual case notes. Follow-up was updated when the last known information about a patient was older than 3 months at the time of data collection. Kaplan-Meier method with log-rank test were used for survival analysis. ANOVA test was used to compare the rate of R1 resection in different treatment scenarios. The distributions of the categorical variables related to local control were compared by the chi-square test and if the number of patients in categories was low, Yate's correction was applied. Confidence intervals were estimated at a threshold of 95%. Statistical significance was set at $p<0.05$.

Results

With a median follow-up of 21.6 months (range 7.7-136) 11 (36.7%) patients developed LR and a further 4 were diagnosed simultaneously with both LR and distant metastasis (2 liver, 1 lung, 1 peritoneal); these latter 4 patients died during follow-up. Two of 11 patients developed metastases after the local failure and died. One of 11 patients was salvaged with abdomino-perineal resection and 3 patients died during follow-up due to LR without developing metastases. Overall, all patients who developed LR died of the disease, except one, whose relapse was at the level of the anastomosis and was successfully salvaged by abdomino-perineal resection.

Patients were further stratified into 3 categories according to the therapeutic modalities used: (1) surgery only; (2) neoadjuvant RT or CRT; and (3) adjuvant RT or CRT.

Surgery-only patients

From the 30 patients 11 underwent only surgical excision without RT. Six of them had a follow-up < 2 years due to death caused by M1 disease present from the start of treatment and were excluded from analysis of the LR. From the 5 patients with sufficient follow-up, all experienced LR. All these 5 patients had a tangential resection margin (no normal cell layers between the tumor and margin).

Patients with neoadjuvant RT/CRT

Nine out of 30 patients (30%) underwent neoadjuvant RT or CRT followed by curative-intent rectal resection. The delivered RT dose ranged from 25 Gy in 5 fractions to 50.4 Gy in 28 fractions. Two patients were excluded because of death from metastasis (liver and soft tissue) in the first 2 years of follow-up. From 7 R1 patients analyzed for relapse, only one (14.3%) developed LR, and the remaining 6 (85.7%) were alive, with no signs of LR at a minimum of 2 years follow-up. In conclusion, 85.7% of the patients did not develop LR despite of a R1 after neoadjuvant RT or CRT.

Patients with adjuvant RT/CRT

Ten out of 30 patients (33.3%) underwent surgery first and then adjuvant RT or CRT. The delivered RT dose was 50 Gy in 25 fractions in 6 patients, 45 Gy in 25 fractions in 3 and 39.6 Gy in 22 fractions in one patient.

At a minimum follow-up of 2 years, 5 (50%) experienced LR and 5 (50%) were recurrence free. From the 5 LRs one was salvaged by abdomino-perineal resection. Three patients presented with both local and distant relapse and died of the disease, while 1 patient developed metastases after LR and died.

Comparison and summary of the three treatment groups

A trend for better LRFS was noted in patients with neoadjuvant RT/CRT, compared to patients with adjuvant RT/CRT or no RT ($p=0.09$) (Figure 1). When the LR rate was compared between treatment modalities, patients with neoadjuvant RT/CRT had a recurrence rate of only 14.3% (1 out of 7), compared to 100% in the surgery-only arm

Table 2. The local relapse rate in different categories

	Total number of patients	*Died of M1 present from the diagnosis in the first 2 years without LR*	*Died of M1 occurring in the evolution in the first 2 years without LR*	*Patients selected to study the LR rate (at least 2 years of follow-up)*	*LR rate in selected cases (at least 2 years of follow up) N (%)*
Surgery only	11	6	0	5	5/5 (100)
Adjuvant EBRT (±CT)	10	0	0	10	5/10 (50)
Neoadjuvant EBRT (±CT)	9	0	2	7	1/7 (14.3)

LR: local relapse, EBRT: external beam radiotherapy, CT: chemotherapy

(5 out of 5) and 50% in the adjuvant CRT arm (5 out of 10) (ANOVA, p=0.009; 14.3% significantly different from 100% and 50%). (Table 2).

There was also a trend for higher LR rate in patients with tumor cells present at the margin or < 1 mm from the margin, compared to patients with a 1 mm resection margin. After exclusion of patients deceased from metastases in the first 2 years, 11 out of 18 (61.1 %) of the patients with very close resection margin relapsed locally, while from those with exactly 1 mm margin, none developed LR (0/4 patients, p=0.17).

In general, the median time from surgery to LR was 15.2 months (range 3.5-20). The median time from LR to death due to cancer was 8.4 months (range 1.6-24.4).

Discussion

In mixed patient groups presented in the literature the rate of R1 varies from 3 to 20% in rectal cancer treated by curative intent resection. In the MRC CR07 and NCIC-CTG CO16 randomized clinical trials the rate of R1 was 11% [11]. In a large retrospective Dutch study the rate of R1 was nearly 19% [12]. In the CLASICC trial of laparoscopic vs open surgery the authors reported a R1 rate of 13% [13]. A study from the Yonsei University College of Medicine, Republic of Korea, reported a large series of TME patients (876 subjects) from which 55 had R1 (5.5 %), 48 patients a circumferential R1, and 7 patients distal R1 [14]. In a prospective randomized trial comparing neoadjuvant CRT with SRT, R1 was more frequent in the SRT arm (13%) than in the CRT arm (4%, p=0.017) (Table 3) [15].

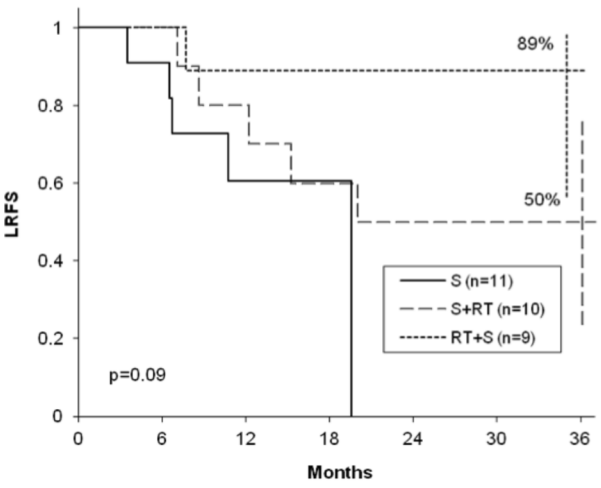

Figure 1. Local relapse-free survival for different treatment sequences. S: surgery only, S+RT: surgery plus adjuvant radiotherapy (± chemotherapy), RT+S: neoadjuvant radiotherapy (± chemotherapy) plus surgery.

There are only a few publications regarding treatment of patients with R1/R2 with adjuvant RT or CRT. Such studies were performed at the Erasmus Medical Center [16] and at the University of Heidelberg [16,17]. Both teams based their treatment on single fraction intraoperative RT, a prescribed dose of 10-15 Gy corresponding practically to 20–30 Gy of classically fractionated external beam radiotherapy (EBRT) [15].

The authors from the Erasmus Medical Center used intraoperative brachytherapy (BT) or electron irradiation for patients with close R0 margins (≤ 2 mm) and R1, where R1 was defined as tangential margin. All patients underwent neoadjuvant RT, receiving 50.4 Gy in 28 fractions. Not only patients with primary treatment but also cases that received RT for recurrence were included in this study, making the patient group inhomogeneous. The dose administered was 10 Gy in one fraction. The local control rate was high for R1 patients (74%), but it was not corrected for patients who died from metastases sooner than 2 years of follow-up, and thus these patients had no sufficient follow-up to correctly quantify local relapses [15].

The authors from the University of Heidelberg report their results with intraoperative electron irradiation [16,17]. In both reports, a dose of 12 Gy in a single fraction was administered to R1 patients and 15 Gy to R2 patients. In addition, a median dose of 41.4 Gy in 23 fractions of EBRT was administered before or after surgery. The 5-year local control rate in the R1/R2 patients was 77% in the first report and 72% in the second report. When analyzing the local control rate the authors did not take into account a minimum of 2 years of follow-up, the same possible source of bias as in the previous study [15] (Table 4).

In the Yonsei University College of Medicine retrospective study [13] 3 out of 7 patients (42.9%) with distal R1 had a LR despite adjuvant or neoad-

Table 3. R1 rate in different studies for patients undergoing curative-intent rectal resection in cT2-T4, N0-2 rectal cancer

Study	*R1 rate %*
Hall et al. (1998) [20]	13
Nagtegaal et al. (2002) [12]	19
Guillou et al. (2005) [13]	13
Roeder et al. (2007) [18]	6.6
Kim et al. (2008) [28]	3.3
Quirke et al. (2009) [11]	11
Kim et al.(2009) [14]	5.5

Table 4. Results of neoadjuvant or adjuvant radiotherapy studies for R1/R2 comparing to our results

Study	*Resection margin*	*Radiotherapy*	*Local control N (%)*	*Alive without disease*
Nuyttens et al. (2004) [16]	Tangential R1, primary treatment or recurrence	Neoadjuvant EBRT + intraoperative HDR BT or electron irradiation	13/18 (74) (at 3 yrs) *	Not reported for this subgroup of patients
Krempien et al. (2006) [17]	R1 or R2	Neoadjuvant or adjuvant EBRT + intraoperative electron irradiation	14/18 (77) *	0/18 (0%)
Roeder et al. (2007) [18]	R1 or R2	Neoadjuvant or adjuvant EBRT + intraoperative electron irradiation	15/19 (72) *	Not reported for this subgroup of patients
Quirke et al. (2009) [11]	R1	Neoadjuvant SRT	52/56 (92.9) *	Not reported for these subgroup of patients
		Adjuvant CRT	62/72 (86.1) * p=0.27	
Kim et al. (2009) [14]	R1	Adjuvant or neoadjuvant EBRT	4/7 (57.1) *	Not reported for this subgroup of patients
Institute of Oncology Ion Chiricuta (current study)	R1	Neoadjuvant EBRT/CRT	6/7 (85.7) (at 2 years)	6/7 (85.7) (at 2 years)
		Adjuvant EBRT/CRT	5/10 (50) (at 2 years)	6/10** (60) (at 2 years)
		Total neoadjuvant or adjuvant EBRT	11/17 (64.7) (at 2 years)	12/17** (70.6) (at 2 years)

*not corrected for deaths (usually from metastases) occurring in less than 2 years after treatment
** after salvage resection in 1 patient
EBRT: external beam radiotherapy, HDR BT: high dose rate brachytherapy, SRT: short-course radiotherapy , CRT: chemoradiation

juvant RT at conventional EBRT doses, but the authors did not report neoadjuvant cases separately from adjuvant cases. In a second report from the same center [18], 13% of patients with positive circumferential resection margin treated with adjuvant CRT developed LR. The results of the two reports seem conflicting, but the numbers of patients with R1 were low and a proper follow-up for at least 2 or 3 years should be set for each patient to properly register LRs. All patients with independent systemic relapses and death in the first 2-3 years, patients dying from other causes in the first 2-3 years, or those lost to follow-up should be excluded.

Based on our results (only 50% "compensation" of R1 by conventional EBRT doses) probably higher doses should be investigated to properly compensate > 50% of R1 cases. In the second study from the Yonsei University College of Medicine [18], the authors found that patients with positive circumferential margin treated with adjuvant CRT with a dose of 50.4 Gy in 28 fractions didn't have LRs more frequently than patients with clear resection margin (13.0 and 13.5%, respectively, p=0.677), which seems to prove the compensatory effect of CRT, but the potential source of bias with short follow-up remains.

Another discussion is if R1 represents an independent prognostic factor for LRs or not. According to some studies, a positive margin might be not important if other risk factors are present. In the CR07 and NCIC-CTG CO16 randomized clinical trials [19] the circumferential resection margin positivity was associated, but not independently, with LR. In our series a tangential R1 made LR unavoidable if not compensated by adjuvant or neoadjuvant RT. A multivariate analysis could not been carried out in our study due to lack of comparison with R0 patients.

Is R1 an independent risk factor for both LR and metastasis? There is data supporting that this is the case, as there is an increased risk for distant metastases demonstrated in a study from the Netherlands (Dutch-Swedish short-course RT trial) [11]. In this RT trial, R1 was an independent prognostic factor not only for LR, but also for metastases, although the authors did not report the number of patients who developed metastases

independently from LR. When the total number of patients who developed metastases was taken into account, the difference was significant: 37.6% in R1 vs 12.7% in R0, p <0.0001. In our series 8 patients (from 26 subjects without M1 at diagnosis) developed metastasis at follow-up (30.8 %), but only 2 patients without prior or concomitant LR. A comparison with R0 cases has not been done.

A prospective observational study from the University of Leeds, UK [20] found no statistically significant higher LR rate for R1 patients compared to R0 cases (15 vs 11%, p=0.38), but there was a significant difference in DFS (50% in R1 and 24% in R0 after a median follow-up of 42 months, p=0.01). The authors hypothesized that in their patient group subjects with an involved margin had a more advanced or aggressive disease and died of distant metastasis before a LR could have been evident.

In our study the low LR rate in the neoadjuvant RT group (14.3%) might be due to the fact that, although these patients had a positive resection margin, often these cells were non-viable. This is in line with the results of the Dutch-Swedish SRT trial, which showed a low LR rate (16.4%) for patients with R1 undergoing neoadjuvant RT, although the results of this trial were not corrected for patients who died or were lost to follow-up in the first 2 years [21,22].

Another problem which needs to be discussed is the technique of pathologic examination. It should be worth noticing that probably a higher number of R1 cases would have been detected in our hospital records if serial sectioning of the rectum would have been a standard procedure in the studied patient group from 2000 to 2011. This method was described by Quirke et al. [23,24]. In our patient population the pathology data regarding circumferential R1 was obtained through two perpendicular sections through the deepest site of invasion.

Our methodology required a minimum of 2 years of follow-up for each patient for analysis of LRs, but a minimum of 3 years probably would have been more reliable, or at best a 5-year of follow-up would have been ideal and would have resulted of almost 100% registration of LRs [10]. In our study the longest time to LR was 20 months (in a patient who underwent adjuvant CRT).

A final note concerns the quality of surgery. It was shown [25,26], that a R1 status is not necessarily the result of poor surgery, but it could be attributed to more advanced disease. There are several determinants of a proper TME, the most important being an intact rectal adventitia and fascia on the resected specimen. No formal quality control was undertaken for our series of patients in the years studied.

We conclude that inside the category of R1 disease, patients with R1 who underwent neoadjuvant RT (with or without chemotherapy) seem to have the best prognosis. In patients who underwent surgery first, followed by RT, R1 could not be compensated in 50% of the cases by conventional RT doses. In this patient group re-excision would be indicated, if surgically feasible, and if not, high-dose RT should be employed. All patients with tangential R1 and without combined CRT (before or after surgery) experienced LR.

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