Rectal cancers with microscopic circumferential resection margin involvement (R1 resections): survivals, patterns of recurrence and prognostic factors.

Gianpiero Gravante MD PhD¹, David Hemingway MD¹, James Andrew Stephenson MD², David Sharpe¹, Ahmed Osman MD³, Melissa Haines MD¹, Vafa Pirjamali MD¹, Roberto Sorge PhD⁴, Justin Yeung MD¹, Michael Norwood MD¹, Andrew Miller MD¹, Kirsten Boyle MD¹.

¹ Department of Colorectal Surgery, Leicester Royal Infirmary, Infirmary Square, Leicester, LE1 5WW – United Kingdom

² Department of Radiology, Leicester Royal Infirmary, Leicester - United Kingdom

³ Department of Oncology, Leicester Royal Infirmary, Infirmary Square, Leicester, LE1 5WW – United Kingdom

⁴ Department of Human Physiology, Laboratory of Biometry, University of Tor Vergata, Rome - Italy

Address for correspondence and reprints:

Dr. Gianpiero Gravante,
Department of Colorectal Surgery,
Leicester Royal Infirmary,
Infirmary Square,
Leicester, LE1 5WW
United Kingdom
Tel.: +4401162388244; Fax: +3906233216592
E-mail: ggravante@hotmail.com

Original article.

The Authors have no conflict of interests with the present manuscript and received no funding for the conduction of this study. The Authors thank the Leicester Colorectal Specialist Interest Group for permission to interrogate their database.

Running head: Prognosis of R1 rectal resections.

Abstract length: 209 words. Article length: 2895 words.

Synopsis: Rectal cancers with circumferential resection margin involvement (R1) are a heterogeneous group. Factors influencing systemic recurrences (lymph node ratio, adjuvant chemotherapy) are more associated with overall and disease-free survivals than those theoretically affecting locoregional pelvic recurrences (adjuvant radiotherapy).

Authors contributions

Gianpiero Gravante: acquisition of data, analysis and interpretation of data; drafting the article and final approval of the version to be published

David Hemingway: conception and design, interpretation of data; revising the article critically for important intellectual content; and final approval of the version to be published.

James Andrew Stephenson: radiological input re-reviewing all available MRI scans for assessment of threatened CRM, interpretation of data; revising the article critically for important intellectual content; and final approval of the version to be published.

Andrew Miller: conception and design, interpretation of data; revising the article critically for important intellectual content; and final approval of the version to be published.

Justin Yeung: conception and design, interpretation of data; revising the article critically for important intellectual content; and final approval of the version to be published.

Michael Norwood: conception and design, interpretation of data; revising the article critically for important intellectual content; and final approval of the version to be published.

Melissa Haines: acquisition of data, analysis and interpretation of data; drafting the article and final approval of the version to be published.

Justin Yeung: acquisition of data, analysis and interpretation of data; drafting the article and final approval of the version to be published.

Vafa Pirjamali: acquisition of data, analysis and interpretation of data; drafting the article and final approval of the version to be published.

David Sharpe, Roberto Sorge: acquisition of data, analysis and interpretation of data and final approval of the version to be published.

Kirsten Boyle: conception and design, interpretation of data; revising the article critically for important intellectual content; and final approval of the version to be published.

Abstract

Background and Objectives: We have reviewed our series of rectal cancer patients with circumferential resection margin involvement (R1) with particular regard to survival and prognostic factors. **Methods:** R1 rectal cancer patients undergoing surgery at the Leicester Royal Infirmary between 1998 and 2008. Age, gender, radiological and pathological tumor characteristics, neoadjuvant and adjuvant therapies were examined as prognostic factors on the overall survival (OS) and disease-free survival (DFS) at five-year follow-up. **Results:** A total of 885 rectal cancers were reviewed. 699 patients underwent a total mesorectal excision and 71 of them were R1 resections (12.9%). OS was 43.7% (CI95% 33.5%-53.8%; median survival 39 months). DFS was

57.4% (CI95% 43.0%-71.8%; median survival 31 months). Pelvic recurrence rate occurred in 16 patients (26.2%, CI95% 16.5%-36.0%), systemic recurrence rate in 23 patients (37.7%, CI95% 25.5%-49.9%). At Cox-regression LNR and adjuvant chemotherapy were associated with both OS and DFS. No significant association was found between OS or DFS and adjuvant radiotherapy.

Conclusions: In our series of R1 patients the rates of local recurrence and OS at 5 years were 26.2% and 43.7% respectively. Factors influencing systemic recurrences (LNR, adjuvant chemotherapy) are more associated with OS and DFS than those potentially affecting locoregional recurrences (adjuvant radiotherapy).

Keywords: Colorectal cancer, circumferential margins, survival, prognostic factors.

Introduction:

Involvement of the surgical margins during rectal cancer resections is a major problem for oncologic surgery due to the high risk of local and distant disease recurrence [1]. Microscopic involvement of the surgical margins (R1 resections) is defined as tumor less than 1mm away from the cut margin. This implies that microscopic viable cells may have been left in the patient's pelvis and could give rise to local or systemic recurrences during postoperative follow-up. The potential involvement of the circumferential resection margins (CRM) is routinely assessed preoperatively on magnetic resonance imaging (MRI) in modern practice considering factors associated with the presence of an R1 status at the histological examination such as the proximity of the tumor to the mesorectal fascia [2,3], T4 staging following neoadjuvant therapy [4,5], tumor location in the low rectum [6] and bony pelvic dimensions [7]. Based on these factors neoadjuvant chemoradiotherapy is administered when margins are considered at risk in order to shrink the tumor and possibly prevent an R1 resection.

Despite these measures R1 resections are still present in 6.3%-13.0% of cases [4,8-14] and

demonstrate a significantly higher rate of local recurrence (25.8-38.2%) [1,15] and a lower overall survival (OS) at five-year follow-up (34.1%) [1] compared with R0 resections (microscopic tumor greater than 1mm away) [1,8,10]. In the current study we retrospectively reviewed our rectal R1 resections with two aims: first to present the survival of patients receiving an R1 resection, and secondly to investigate specific factors that could influence the prognosis in this high-risk group.

Materials and Methods:

A retrospective study on a prospectively-maintained database was performed on patients undergoing surgical resection of rectal cancer at the University Hospitals of Leicester between 1998 and 2008. All patients with R1 resected rectal adenocarcinoma confirmed on the post-surgical specimen were included. Excluded were patients with metastatic disease at presentation and where metastases could not be completely resected (R2 patients) [16], patients who did not undergo rectal resection (i.e. palliative defunctioning stomas only, transanal operations), R0 patients, and patients with incomplete data (surgical margin status or radiological TNM not reported).

The colorectal unit has a prospectively-maintained database which was interrogated; data collected included basic demographics, radiological staging, presence and type of neoadjuvant treatments, date of surgery, type of operation performed, surgeon performing the operation, pathologist performing the specimen evaluation, tumor characteristics such as histological staging, distance from the anal verge, distance from the closest longitudinal margin, relationship to the peritoneal reflection, appropriateness of the total mesorectal excision (TME), tumor length and width, differentiation, tumor perforation, presence of extramural vascular invasion lymph node status, lymph node ratio (LNR - defined as the number of positive nodes divided by the total number of nodes analysed), and use of adjuvant therapies. Histological and radiological reports were obtained from hospital electronic databases. Computed Tomography (CT) was used in all patients to diagnose distant metastases and, until September 2003, was the main radiological

modality for local staging; after September 2003 pelvic MRI was used unless contraindicated (i.e. patients with metallic prostheses). The radiological TNM staging was taken from the original radiology report. With regard to assessment of the CRM most cases had no formal documentation available from the time of the original multi-disciplinary team meeting (MDT) review, as such MRI images, when available, were retrospectively reviewed by a gastrointestinal radiologist (JAS). The CRM was defined as radiologically threatened if the tumor was lying within 1 mm of the mesorectal fascia (either main tumour, venous or lymph nodes) [17].

Appropriateness of the TME was assessed by the pathological examination of the surgical specimens and scored in three grades: grade 1 - mesorectal excision (smooth, complete), grade 2 - intramesorectal excision (moderately irregular, nearly complete), grade 3 – resection in the muscularis propria (severely irregular) [18,19]. The definition of the R status has taken into account both the clinical intraoperative judgment and the pathologic results [16,20]. With regards to the first factor, in our unit the surgeon has to report at the end of operation if this was considered curative, based on the absence of gross residual distant metastases or loco-regional tumor, otherwise the resection was considered non-curative (R2) [16]. With regards to the second factor, R1 was defined in potentially curative cases as microscopic tumor at or less than 1 mm from the cut surgical margin, and R0 where microscopic tumor was greater than 1 mm away from the cut surgical margin [20]. Survival data were also calculated from patients' follow-up. Overall survival (OS) was defined as patients who were alive as documented by the last clinic, date of the latest blood results conducted for any reasons and available in the hospital database, endoscopy or radiology visit. Disease free survival (DFS) was defined as the absence of local or recurrent metastases as identified via the surveillance program (colonoscopy and CT scan). OS and DFS were calculated at five-year follow-up.

The primary outcome of the study was to present DFS and OS at five-year follow-up for rectal patients receiving an R1 resection. The secondary outcome was to evaluate the influence of specific factors on survivals of such patients.

Statistical Analysis

All data were entered into an Excel database (Microsoft, Redmond, Washington – United States) and analyzed with the Statistical Package for the Social Sciences Windows version 15.0 (SPSS, Chicago, Illinois, USA). Descriptive statistics used were the mean and standard deviation for continuous parametric variables, the median and range (median and 1st-3rd interquartile for survivals) for non-parametric variables, and frequencies for categorical variables. Normality assumptions were tested with histograms and the Kolmogorov/Smirnov test.

All calculations of DFS and OS at five year follow-up were performed using time-to-event analysis (Kaplan-Meier) and curves presented. Factors potentially influencing OS and DFS at five-year follow-up were initially screened with the univariate analysis. Tests adopted for the univariate analysis were the ANOVA one-way test for parametric variables, Mann-Whitney test for non-parametric variables and Chi-Square test for frequencies (Fisher's exact test if counts in cells were less than 5). Factors examined were age, sex, type of operation performed, surgeon performing the operation, pathologist performing the specimen evaluation, neoadjuvant or adjuvant therapies, tumor location (distance from the anal verge, distance from the closest margin, relationship to the peritoneal reflection), radiological and pathological TNM staging, histological tumor characteristics (length, width, differentiation, perforation, extramural vascular invasion), appropriateness of the TME, and LNR. Those factors that were found significant associated with DFS and OS at five years follow-up at the univariate analysis were evaluated with the Cox-regression analysis (multivariate analysis) using the method enter. A *P* value less than 0.05 was considered statistically significant.

Results:

During the study period, 885 rectal cancers were treated in our institution. Included and excluded patients are presented in Table 1. Patients that received a Total Mesorectal Excision (TME) were 699 (Table 1), of which ninety patients (12.9%) had histological CRM involvement

(tumor less than 1 mm from the surgical resection margin). Nineteen patients with metastases (liver and lung) at the time of presentation underwent rectal surgery either because the metastases were deemed resectable at the preoperative multidisciplinary meeting but could not be completely excised intraoperatively, or because of palliative purposes. These patients were excluded because these were classified as R2 by definition [16]. Seventy-one non-metastatic patients underwent potentially curative surgery (no gross loco-regional or metastatic tumor left at the end of surgery) and had CRM involvement, therefore were classified as R1 resections [16,20]. This constituted the group considered for further analysis (Table 1).

R1 patients

Descriptive statistics for R1 patients are presented in Table 2, and the correlation between radiological and histological staging in Table 3. Thirty-eight patients received a pelvic MRI for local staging: until September 2003 MRI was used in only 17.6% of patients (6/34), from September 2003 to December 2008 in 86.5% (32/37). In both groups the remaining patients were staged locally with a pelvic CT. The radiological staging correctly matched the histological findings in forty-four patients (62.0%), while in 14 patients (19.7%) there was a radiological understaging and in 12 patients (16.9%) an overstaging compared to the histology. One patient was a complete responder to neoadjuvant chemoradiotherapy but an anterior defect was present in the specimen, therefore CRM were considered involved. Unexpected nodal disease was the most common reason for understaging (10/14, 71.4%) while T mismatch was responsible in the remaining patients (4/14, 28.6%). Similarly, non confirmed nodal disease was the most common reason for overstaging (11/12, 91.7%) while T mismatch was responsible in the remaining patient (1/12, 8.3%). Retrospective review of MRI images for CRM involvement was not possible in 5 patients as the images could not be downloaded from the PACS system (Picture Archiving and Communication Server). At retrospective review twenty three of patients had their circumferential margins

radiologically threatened (23/33; 69.7%). Of these, 5 patients were T2 and 7 T3 all of them with nodal involvement, 11 patients were T4 of which 8 had nodal involvement. Among the patients with non-threatened margins, 1 was a T1 (no nodal involvement), 5 were T2 (1 with nodal involvement), 4 were T3 (3 with nodal involvement).

No significant differences were present over the years for the use of neoadjuvant therapy or the types of regimens used (short course radiotherapy vs. long course chemoradiotherapy) (Fisher's exact test $p=0.407$; Table 4). In 2011 one patient had long course radiotherapy only because he was unfit to receive chemotherapy (Tab.4). All but one patient underwent elective resection ($n=70$, 98.6%); operations were performed by eight surgeons and included 35 abdominoperineal resections (APR; 49.3%), 21 low anterior resections (LAR; 29.6%), 14 Hartmann's resections (19.7%) and one panproctocolectomy ($n=1$, 1.4%). No extralevator abdominoperineal resections (ELAPE) were present. All operations were performed with an open approach either by consultants or by registrars assisted by consultants. Intraoperatively, five patients were found to have intraperitoneal metastases which were excised; in three cases in the omentum, one in the pouch of Douglas invading the vaginal wall (separate from the main tumour), and one in the right ovary (Table 3). In most cases the tumor was below the peritoneal reflection ($n=49$, 69.0%) followed by the tumor at the level of the peritoneal reflection ($n=15$, 21.1%) and above it ($n=4$, 5.6%). In three cases (4.2%) this information was not recorded.

Ten pathologists analysed the specimens. All cases were adenocarcinomas; in one patient no tumor was identified following neoadjuvant therapy and so was deemed to have had a complete pathological response (Table 3). The quality of the TME was reported in the pathological analysis for 50 patients (70.4%; Tab.2). Following surgery 49 patients received adjuvant therapy (69.0%) in the form of chemotherapy ($n=23$, 32.4%), radiotherapy ($n=6$, 8.5%) or combination ($n=20$, 28.3%; Tab.2). No significant differences were present for the LNR between patients that received neoadjuvant treatments (median 20.2%, range 0%-74.2%) and those that did not (9.6%, range 0%-

94.4%; Mann-Whitney test $p=0.755$).

Overall and disease-free survivals

Thirty-one patients (43.7%, CI95% 33.5%-53.8%) are alive and 40 (56.3%, CI95% 44.8%-67.9%) are dead at five-year follow-up. Median OS is 39 months (range 0–60 months; Fig 1). Of the 31 patients alive at five years, 26 were disease-free and five had recurrent disease (two pelvic, two systemic and one both); among dead patients ten were disease-free at the time of death whilst 30 had recurrent disease (10 pelvic, 17 systemic, 3 both). In total thirty-six patients were disease-free (50.7%, CI95% 38.9%-62.5%) and 35 had recurrent disease (49.3%, CI95% 37.7%-60.9%) at five-year follow-up: 12 patients had pelvic recurrences, 19 patients had systemic recurrences, and four patients both. After exclusion of patients that died before the five-year follow-up without recurrence ($n=10$), DFS was 57.4% (35/61; CI95% 43.0%-71.8%), local recurrence rate 26.2% (16/61; CI95% 16.5%-36.0%) and systemic recurrence rate 37.7% (23/61; CI95% 25.5%-49.9%). Median DFS was 31 months (range 0-60 months).

Univariate and multivariate analysis

Among all the factors analysed, only a few of them were significantly associated with OS and DFS at five-year follow-up. In the univariate analysis OS was associated with the type of operation performed, the appropriateness of the TME, LNR and adjuvant chemotherapy. DFS was associated with LNR and adjuvant chemotherapy (Tab.2; Fig.1, 2). The significance of the TME for OS was present when comparing TME grade 1 vs. 3 and not for TME grade 1 vs. 2 or grade 2 vs. 3. TME grade 1 had longer OS compared to grade 3. With regards to the type of operation performed, a significant difference for OS was present between Hartmann's resections vs. APRs ($p=0.012$) and between Hartmann's resections vs. LARs ($p=0.033$). No significant differences for OS were observed between APR vs. LAR ($p=1.000$). Hartmann's resections had shorter OS compared to

APR and LAR.

The type of operation performed, the quality of the TME, LNR and adjuvant chemotherapy were entered in the multivariate Cox-regression analysis for OS. Two factors maintained their significant association with OS: LNR (Wald 5.045, $p=0.025$) and adjuvant chemotherapy (Wald 11.263, $p=0.001$). For DFS, the two significant factors at the univariate analysis (LNR and adjuvant chemotherapy) were entered in the multivariate Cox-regression analysis. Both remained significant associated with DFS (LNR: Wald 12.699, $p<0.001$; adjuvant chemotherapy: Wald 5.924, $p=0.015$).

Discussion

So far two types of studies are present in the literature on R1 resections. The first group focused on the ability of preoperative factors to predict an R1 resection; the second group analyzed the prognostic implications of the R1 status in terms of disease recurrences and survivals compared to R0. No study specifically investigated survivals in this peculiar high-risk category of patients or analyzed specific factors that could influence it, especially the effects of adjuvant therapies, which are the basis of our study.

In our series the incidence of R1 patients (12.9%) is similar to those previously reported (12.0%-13.3%) [5,13,21,22]. After September 2003 most patients had preoperative MRI and the overall low use of neoadjuvant chemoradiation therapy (45.1%) is explained by the dates of recruitment for the study. In fact, this period of time (1998-2008) corresponds to years in which indications and type of neoadjuvant treatments were not as standardized as they are at present. All patients having an APR had their perineum dissected and reconstructed with a standard APR and primary closure. No ELAPE cases were performed as this technique was introduced in September 2010 in our unit. Furthermore no flap or mesh reconstructions, laparoscopic, robotic surgery or transanal TMEs were performed, therefore all patients were homogeneous for the surgical technique adopted. APRs were more frequent than LAR because we selected patients that

experienced R1 resections, and APR is known to have an increased risk of margin involvement compared to LAR [23,24]. The reasons for the discrepancies observed between baseline radiological findings and final histopathologic staging of the resection specimen are beyond the scope of this study, however various factors could have contributed. These include i) a large number of patients pre-September 2003 did not have baseline MRI staging, ii) rectal MRI was a relatively new technique in the study period, iii) assessment of lymph node involvement on MRI (the most frequent cause for mismatch) is reported to have a sensitivity and specificity as low as 66% and 76% respectively [25], iv) many patients had neoadjuvant chemoradiation without repeat pre-operative imaging, v) neoadjuvant therapy protocols themselves contributed to considerable delays between the baseline scan and surgery in a small number of patients.

Although specific data of our R0 resections were not presented as it was outside the scope of the study, the comparison of R1 results with those gathered from our R0 resections presented, as expected, worse figures. Our local recurrence rate at five-year follow-up was 26.2% for R1 resections compared to 2.9% for R0, and the OS at five years was 43.7% for R1 compared to 73.0% for R0 resections. Not surprisingly adjuvant chemotherapy was associated with improved OS and DFS at the Cox-regression analysis, but adjuvant radiotherapy showed no association with them. The addition of postoperative radiotherapy to chemotherapy does not reduce the recurrence or mortality in node-positive rectal cancers when compared with chemotherapy alone, including those with positive histological margins [26]. Our data confirm that in this specific subgroup of patients postoperative therapies directed systemically to prevent distant metastases, and not locally to avoid pelvic recurrences, impact more on OS and DFS. This suggestion is further corroborated by the association of DFS and OS with the second factor found significant at the Cox-regression analysis, the LNR.

Node-positive rectal cancers are nowadays considered heterogeneous for their prognosis, which is highly dependent on the amount of cancer spread to the nodes and is reflected in the

subcategories of N1 vs. N2 for the TNM or Stage III-A, III-B and III-C for the AJCC staging [27]. LNR is a similar measure of the tumor burden present in the locoregional lymph nodes that directly correlates with the potential for systemic spread. Numerous articles have found significant associations of the LNR with recurrences in rectal cancers and various cut-offs have divided node-positive disease into different prognostic groups, among the others 20%, 40% and 60% [28-34]. Results from our R1 series showed that the LNR was significant associated with the OS and DFS at the Cox-regression analysis, possibly explaining why adjuvant systemic chemotherapy, but not locoregional radiotherapy, was significant associated with the OS and DFS in our series. It has to be considered that our study covers a long period of time, during which the importance of harvesting and identifying higher numbers of lymph nodes was progressively uncovered. However, we have retrospectively checked that the harvested number of lymph nodes did not change over the years (median 12, range 3-44), and this hypothesis was confirmed by the analysis.

Significant limitations of our article consist in the retrospective nature of the study and in a selection bias introduced with the inclusion of R1 patients only. The initial database contained 855 rectal operations, of which 71 patients were R1 rectal resections. The retrospective nature of the study did not allow control for the heterogeneity of the various variables involved. These have been tested with the multivariate analysis, however the relatively small sample size could have influenced the results for factors different from the LNR. Similarly, the selection of patients experiencing a R1 resection increased the proportion of Hartmann's and APR's compared to LAR. These operations are likely to have been conducted for advanced disease. Although the type of operation has been tested with the multivariate analysis, the small sample size again could have masked any eventual specific association with OS. For both these reasons, future larger prospective studies are now required recruiting R1 patients and following them up with various protocols or applying different adjuvant treatments.

Conclusions

In our series R1 patients corresponded to 12.9% of the total rectal resections receiving TME. Although generally considered a high risk group of patients, they presented a rate of local recurrence and OS at 5 years of 26.2% and 43.7% respectively. LNR and adjuvant chemotherapy were associated with OS and DFS but not radiotherapy, suggesting the prognostic importance of systemic, and not locoregional, adjuvant treatments. Our results provide a better understanding of the patterns of recurrences and survivals in R1 patients, and show the prognostic importance of adjuvant systemic therapies possibly linked to the tumour lymph node burden in this peculiar subgroup of patients.

References

1. Tilney HS, Rasheed S, Northover JM, Tekkis PP: The influence of circumferential resection margins on long-term outcomes following rectal cancer surgery. *Dis Colon Rectum* 2009;52:1723-1729.
2. Wieder HA, Rosenberg R, Lordick F, Geinitz H, Beer A, Becker K, Woertler K, Dobritz M, Siewert JR, Rummeny EJ, Stollfuss JC: Rectal cancer: MR imaging before neoadjuvant chemotherapy and radiation therapy for prediction of tumor-free circumferential resection margins and long-term survival. *Radiology* 2007;243:744-751.
3. Taylor FG, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, St Rose S, Sebag-Montefiore DJ, Tekkis P, Brown G: One millimetre is the safe cut-off for magnetic resonance imaging prediction of surgical margin status in rectal cancer. *Br J Surg* 2011;98:872-879.
4. Debove C, Maggiori L, Chau A, Kanso F, Ferron M, Panis Y: Risk factors for circumferential R1 resection after neoadjuvant radiochemotherapy and laparoscopic total mesorectal excision: a study in 233 consecutive patients with mid or low rectal cancer. *Int J Colorectal Dis* 2015;30:197-203.
5. Homan J, Bokkerink GM, Aarts MJ, Lemmens VE, van Lijnschoten G, Rutten HJ, Wijsman

JH, Nagtegaal ID, de Wilt JH: Variation in circumferential resection margin: Reporting and involvement in the South-Netherlands. *Eur J Surg Oncol* 2015.

6. Salerno G, Daniels IR, Brown G, Norman AR, Moran BJ, Heald RJ: Variations in pelvic dimensions do not predict the risk of circumferential resection margin (CRM) involvement in rectal cancer. *World J Surg* 2007;31:1313-1320.
7. Boyle KM, Petty D, Chalmers AG, Quirke P, Cairns A, Finan PJ, Sagar PM, Burke D: MRI assessment of the bony pelvis may help predict resectability of rectal cancer. *Colorectal Dis* 2005;7:232-240.
8. Tilly C, Lefevre JH, Svrcek M, Shields C, Flejou JF, Tiret E, Parc Y: R1 rectal resection: look up and don't look down. *Ann Surg* 2014;260:794-799; discussion 799-800.
9. Chambers W, Collins G, Warren B, Cunningham C, Mortensen N, Lindsey I: Benchmarking circumferential resection margin (R1) resection rate for rectal cancer in the neoadjuvant era. *Colorectal Dis* 2010;12:909-913.
10. Debove C, Maggiori L, Chau A, Kanso F, Ferron M, Panis Y: What happens after R1 resection in patients undergoing laparoscopic total mesorectal excision for rectal cancer? A study in 333 consecutive patients. *Colorectal Dis* 2015;17:197-204.
11. Shihab OC, Quirke P, Heald RJ, Moran BJ, Brown G: Magnetic resonance imaging-detected lymph nodes close to the mesorectal fascia are rarely a cause of margin involvement after total mesorectal excision. *Br J Surg* 2010;97:1431-1436.
12. Pettersson D, Lorinc E, Holm T, Iversen H, Cedermark B, Glimelius B, Martling A: Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer. *Br J Surg* 2015;102:972-978; discussion 978.
13. Klein M, Fischer A, Rosenberg J, Gogenur I: Extralevatory abdominoperineal excision (ELAPE) does not result in reduced rate of tumor perforation or rate of positive circumferential resection margin: a nationwide database study. *Ann Surg* 2015;261:933-938.
14. Simpson GS, Eardley N, McNicol F, Healey P, Hughes M, Rooney PS: Circumferential resection margin (CRM) positivity after MRI assessment and adjuvant treatment in 189 patients undergoing rectal cancer resection. *Int J Colorectal Dis* 2014;29:585-590.
15. Birbeck KF, Macklin CP, Tiffin NJ, Parsons W, Dixon MF, Mapstone NP, Abbott CR, Scott

N, Finan PJ, Johnston D, Quirke P: Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg* 2002;235:449-457.

16. Wittekind C, Compton CC, Greene FL, Sobin LH: TNM residual tumor classification revisited. *Cancer* 2002;94:2511-2516.
17. Nougaret S, Reinhold C, Mikhael HW, Rouanet P, Bibeau F, Brown G: The use of MR imaging in treatment planning for patients with rectal carcinoma: have you checked the "DISTANCE"? *Radiology* 2013;268:330-344.
18. Leonard D, Penninckx F, Laenen A, Kartheuser A: Scoring the quality of total mesorectal excision for the prediction of cancer-specific outcome. *Colorectal Dis* 2015;17:O115-122.
19. Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture J, O'Callaghan C, Myint AS, Bessell E, Thompson LC, Parmar M, Stephens RJ, Sebag-Montefiore D: Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet* 2009;373:821-828.
20. Wittekind C, Compton C, Quirke P, Nagtegaal I, Merkel S, Hermanek P, Sobin LH: A uniform residual tumor (R) classification: integration of the R classification and the circumferential margin status. *Cancer* 2009;115:3483-3488.
21. Tekkis PP, Heriot AG, Smith J, Thompson MR, Finan P, Stamatakis JD: Comparison of circumferential margin involvement between restorative and nonrestorative resections for rectal cancer. *Colorectal Dis* 2005;7:369-374.
22. Khan MA, Hakeem AR, Scott N, Saunders RN: Significance of R1 resection margin in Colon Cancer Resections in the Modern Era. *Colorectal Dis* 2015.
23. Anderin C, Martling A, Hellborg H, Holm T: A population-based study on outcome in relation to the type of resection in low rectal cancer. *Dis Colon Rectum* 2010;53:753-760.
24. Shihab OC, Brown G, Daniels IR, Heald RJ, Quirke P, Moran BJ: Patients with low rectal cancer treated by abdominoperineal excision have worse tumors and higher involved margin rates compared with patients treated by anterior resection. *Dis Colon Rectum* 2010;53:53-56.

25. Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J: Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. *Radiology* 2004;232:773-783.
26. Huh JW, Lim SW, Kim HR, Kim YJ: Effects of postoperative adjuvant radiotherapy on recurrence and survival in stage III rectal cancer. *J Gastrointest Surg* 2011;15:963-970.
27. Edge SB, Byrd DR, Compton CC: AJCC (American Joint Committee on Cancer) Cancer Staging Manual. ed 7th, New York, 2010.
28. Shimomura M, Ikeda S, Takakura Y, Kawaguchi Y, Tokunaga M, Egi H, Hinoi T, Okajima M, Ohdan H: Adequate lymph node examination is essential to ensure the prognostic value of the lymph node ratio in patients with stage III colorectal cancer. *Surg Today* 2011;41:1370-1379.
29. Park YH, Lee JI, Park JK, Jo HJ, Kang WK, An CH: Clinical Significance of Lymph Node Ratio in Stage III Colorectal Cancer. *J Korean Soc Coloproctol* 2011;27:260-265.
30. Kim YS, Kim JH, Yoon SM, Choi EK, Ahn SD, Lee SW, Kim JC, Yu CS, Kim HC, Kim TW, Chang HM: lymph node ratio as a prognostic factor in patients with stage III rectal cancer treated with total mesorectal excision followed by chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2009;74:796-802.
31. Zhang J, Lv L, Ye Y, Jiang K, Shen Z, Wang S: Comparison of metastatic lymph node ratio staging system with the 7th AJCC system for colorectal cancer. *J Cancer Res Clin Oncol* 2013;139:1947-1953.
32. Kobayashi H, Mochizuki H, Kato T, Mori T, Kameoka S, Shirouzu K, Saito Y, Watanabe M, Morita T, Hida J, Ueno M, Ono M, Yasuno M, Sugihara K: Lymph node ratio is a powerful prognostic index in patients with stage III distal rectal cancer: a Japanese multicenter study. *Int J Colorectal Dis* 2011;26:891-896.
33. Ceelen W, Van Nieuwenhove Y, Pattyn P: Prognostic value of the lymph node ratio in stage III colorectal cancer: a systematic review. *Ann Surg Oncol* 2010;17:2847-2855.
34. Noura S, Ohue M, Kano S, Shingai T, Yamada T, Miyashiro I, Ohigashi H, Yano M, Ishikawa O: Impact of metastatic lymph node ratio in node-positive colorectal cancer. *World J Gastrointest Surg* 2010;2:70-77.

Legend:

Table 1: Inclusion and exclusion criteria with the corresponding number of patients.

Table 2: Descriptive statistics and associations of factors with Overall Survival (OS) and Disease Free Survival (DFS) at 5 years of follow-up at the univariate analysis. LNR = lymph node ratio. RTx = radiotherapy. CTx = chemotherapy. TME = Total Mesorectal Excision. Reported in cells are *p* values. * = significant differences. - = see Table 3. ° = see text.

Table 3: TNM staging achieved through the radiological imaging and histological analysis.

Table 4: Distribution of the use of neoadjuvant chemoradiation over the years in R1 resections.

Figure 1: Kaplan-Meyer survival curves showing overall survival (*left panels*) and disease-free survival (*right panels*) at 5 years of follow-up according to the presence (Y) or absence (N) of adjuvant chemotherapy (*upper panels*) and radiotherapy (*lower panels*).

Figure 2: Box-plots showing the lymph node ratio (LNR) values for dead vs. alive patients (*left panel*) and patient with or without recurrences (*right panel*). The ends of the boxes are quartiles (25 and 75), the horizontal line is the median value and the vertical line represents the range.

Inclusion criteria:	R1	71
Exclusion criteria:	R0	609
	No TME resection:	186
	o Defunctioning stoma only (palliation)	82
	o Transanal operation	77
	o Endoscopic polypectomy (incidental findings)	5
	o No TME resection	6
	o No surgery	22
	Metastases at presentation	19
TOTAL		885

Table 1

Factor analysed	R1 patients (n=71)	Five year OS	Five year DFS
Age (years)	67 ± 11	0.466	0.856
Gender (males)	49 (69.0%)	0.801	1.000
T (radiological)	-	0.294	0.326
N (radiological)	-	0.941	0.832
Neoadjuvant treatment	32 (45.1%)		
• Shour course RTx	19 (26.8%)	0.348	0.637
• Long course RTx (no CTx)	1 (1.4%)		
• Long course RTx+CTx	12 (16.9%)		
Type of operation performed	-	0.021 *	0.168
Surgeon performing the operation	-	0.573	0.826
Pathologist analysing the specimen	-	0.102	0.092
T (histological)	-	0.767	0.386
N (histological)	-	0.072	0.165
Tumor distance from the anal verge (mm)	40 (0-120)	0.871	0.722
Tumor distance from the closest margin (mm)	29 (0-55)	0.092	0.443
Tumor relationship with the peritoneal reflection	°	0.350	0.486
TME appropriateness	19/50 (38.0%)		
• Grade 1	15/50 (30.0%)	0.047 *	0.175
• Grade 2	16/50 (32.0%)		
• Grade 3			
Tumor length (mm)	42 (18-140)	0.971	0.214
Tumor width (mm)	35 (4-80)	0.785	0.785
Tumor grading/differentiation	55 (77.5%)	0.096	0.836
○ well/moderate	16 (22.5%)		
○ poor			
Tumor perforation	11 (15.5%)	0.547	0.128
Extramural vascular invasion	38 (53.5%)	0.067	0.125
LNR (%)	12.1 (0-94.4)	0.001 *	0.016 *
Adjuvant treatment (overall)	49 (69.0%)	<0.001 *	<0.001 *
○ CTx (alone or with RTx)	43 (60.6%)	<0.001 *	<0.001 *
○ RTX (alone or with CTx)	26 (36.6%)	0.094	0.113

Table 2

Staging		Radiological (CT/MRI)	Histological
T		1 (1.4%)	-
	○ T1	16 (22.5%)	4 (5.6%)
	○ T2	29 (40.8%)	48 (67.6%)
	○ T3	23 (32.4%)	18 (25.4%)
	○ T4	2 (2.8%)	1 (1.4%)
	○ Tx		
N		20 (28.2%)	22 (31.0%)
	○ N0	43 (60.6%)	24 (33.8%)
	○ N1	8 (11.3%)	25 (35.2%)
	○ N2		
M		71 (100%)	-
	○ M0	-	5 (7.0%)
	○ M1	-	66 (93.0%)
	○ Mx		

Table 3

Year	Overall n=32	Short course n=19	Long course RTx n=1	Long course RTx/CTx n=12
1998-2000	3 (9.4%)	1 (5.3%)	0	2 (16.7%)
2001	6 (18.8%)	4 (21.1%)	1 (100%)	1 (8.3%)
2002	4 (12.5%)	3 (15.8%)	0	1 (8.3%)
2003	3 (9.4%)	0	0	3 (25.0%)
2004	2 (6.2%)	2 (10.5%)	0	0
2005	8 (25.0%)	4 (21.1%)	0	4 (33.3%)
2006	3 (9.4%)	2 (10.5%)	0	1 (8.3%)
2007-2008	3 (9.4%)	3 (15.8%)	0	0

Table 4

Fig1 .

Fig2 .

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Gravante, G;Hemingway, D;Stephenson, JA;Sharpe, D;Osman, A;Haines, M;Pirjamali, V;Sorge, R;Yeung, JM;Norwood, M;Miller, A;Boyle, K

Title:

Rectal cancers with microscopic circumferential resection margin involvement (R1 resections): Survivals, patterns of recurrence, and prognostic factors.

Date:

2016-10

Citation:

Gravante, G., Hemingway, D., Stephenson, J. A., Sharpe, D., Osman, A., Haines, M., Pirjamali, V., Sorge, R., Yeung, J. M., Norwood, M., Miller, A. & Boyle, K. (2016). Rectal cancers with microscopic circumferential resection margin involvement (R1 resections): Survivals, patterns of recurrence, and prognostic factors.. J Surg Oncol, 114 (5), pp.642-648. <https://doi.org/10.1002/jso.24360>.

Persistent Link:

<http://hdl.handle.net/11343/291937>