Received:
04 February 2018

Revised:
18 June 2018

Accepted:
14 August 2018

<https://doi.org/10.1259/bjr.20180143>

Cite this article as:

Kim Y, Kim DY, Kim TH, Kim SY, Baek JY, Kim MJ, et al. Patterns of failure in rectal cancer with positive circumferential resection margin after surgery following preoperative chemoradiation: a propensity score matching analysis. *Br J Radiol* 2018; **91**: 20180143.

FULL PAPER

Patterns of failure in rectal cancer with positive circumferential resection margin after surgery following preoperative chemoradiation: a propensity score matching analysis

¹YOUNGKYONG KIM, MD, ^{1,2}DAE YONG KIM, MD, ¹TAE HYUN KIM, MD, ³SUN YOUNG KIM, MD, ²JI YEON BAEK, MD, ²MIN JU KIM, MD, ²HEE JIN CHANG, MD, ²YONGJUN CHA, MD, ²SUNG CHAN PARK, MD and ²JAE HWAN OH, MD

¹Proton Therapy Center, National Cancer Center, Goyang, Republic of Korea

²Center for Colorectal Cancer, National Cancer Center, Goyang, Republic of Korea

³Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Address correspondence to: Dr Dae Yong Kim

E-mail: radiopia@ncc.re.kr

Objective: To compare the patterns of failure between rectal cancer patients with negative and positive circumferential resection margin (CRM) after surgery following preoperative chemoradiation.

Methods: Of 944 stage II–III rectal cancer patients treated with radical surgery following preoperative chemoradiation, 74 patients (7.8%) showed positive CRM. Each 72 patients from negative and positive CRM groups were identified by propensity score matching and compared in terms of survival outcomes and patterns of failure. Local failure was defined as recurrence at the anastomosis site or adjacent to the mesorectal fascia.

Results: The median follow-up was 46 months (range, 4–155). No difference was observed in 5-year local recurrence-free survival (93.4% vs 89.6%, $p = 0.442$) in the negative and positive CRM groups. There was statistically significant difference in relapse-free survival (57.1% vs 39.1%, $p = 0.042$). Negative CRM group showed favorable outcomes than positive CRM in distant metastasis-free

survival (59.4% vs 43.3%, $p = 0.069$) and overall survival (67.5% vs 55.8%, $p = 0.186$), but the difference was not statistically significant. As the initial failure pattern, there were 30 and 43 recurrences in the negative and positive CRM groups (local 6.6 and 7.3%, regional 12.8 and 14.4%, and distant 38.5 and 54.9%). Isolated local recurrence was identified in two with negative CRM and in none with positive CRM ($p = 0.497$).

Conclusion: Distant metastasis was the major pattern of failure regardless of CRM involvement in rectal cancer patients treated with surgery following preoperative chemoradiation. It would be taken account of our finding on adjuvant treatment for the patient with positive CRM.

Advances in knowledge: Investigation of the patterns of failure in patients with CRM involvement after preoperative chemoradiation followed by surgery can be conducive to selecting the appropriate approach to additional treatment for them.

INTRODUCTION

Since the initial report that local recurrence is strongly associated with circumferential resection margin (CRM) status,¹ several studies have demonstrated the importance of the CRM as a predictor of local recurrence in rectal cancer.^{2–5} The widespread use of total mesorectal excision (TME) and the addition of radiotherapy (RT) for multimodal treatment have contributed to decreasing local recurrence.^{6–8} Even in the era of preoperative chemoradiation followed by TME, the reported CRM involvement rates are 4–9%.^{4,9,10}

A recent study reported that patients at high risk of CRM involvement after surgery could be identified by

preoperative MRI.¹¹ Local recurrence was significantly associated with the risk of CRM involvement in preoperative MRI which made it possible to predict the involvement of resection margin before surgery.^{12,13} Hence, more intensive treatment has been considered to increase local control in high-risk patients with CRM involvement. While there were studies suggesting increasing trend of distant recurrence with or without local recurrence in patient with CRM involvement.^{5,14} The appropriate approach to additional treatment has not been established in a patient with CRM involvement after preoperative chemoradiation followed by surgery. According to major pattern of failure, more aggressive local treatment might be considered for dominant local

recurrence, otherwise more intensified chemotherapy for dominant distant recurrence.

For this reason, we compared the treatment outcomes and patterns of failure between rectal cancer patients with a negative and positive CRM after surgery following preoperative chemoradiation.

METHODS AND MATERIALS

Patients

Between October 2001 and June 2012, preoperative concurrent chemoradiation was administered to 1138 patients with locally advanced rectal cancer (cT3–4 or N+) at the National Cancer Center in Korea. The patient eligibility for this study was histologically confirmed adenocarcinoma of the rectum with no evidence of distant metastasis at the initial workup. Patients were excluded from the analysis for the following reasons: (1) 66 patients had no surgery for any reason; (2) 37 had distant metastasis at diagnosis; (3) 27 received chemoradiation for palliation or recurrent disease; (4) 25 had a history of other malignancies, except thyroid cancer and carcinoma *in situ*; (5) 23 visited other hospitals for surgery; and (6) 16 underwent local excision. The remaining 944 patients were included in the analysis. Each 72 patients from negative and positive CRM groups were identified by propensity score matching (PSM) based on their age, sex, distance from anal verge, histological grade, pretreatment carcinoembryonic antigen (CEA), surgery type, ypStage, and the presence of vascular, angiolymphatic, and perineural invasion.

All patients underwent pretreatment workups that included a physical examination with a digital rectal examination, routine laboratory testing (complete blood count, liver function tests), serum CEA, chest radiography, colonoscopy, CT with or without transrectal ultrasonography, and pelvic MRI. ^{18}F -deoxyfluoroglucose positron emission tomography-CT was performed when MRI showed the equivocal finding of pelvic lymph node metastasis which could be the indication for preoperative chemoradiation. Pelvic MRI was performed for all patients as an initial workup tool to be staged clearly, such as perirectal fat invasion and lymph node metastasis. The patients were staged using the American Joint Committee on Cancer Staging System, seventh edition.¹⁵

Treatment

Preoperative RT was delivered to the entire pelvis with 45 Gy in 25 fractions, followed by a boost to the primary tumor with 5.4 Gy in three fractions. All patients underwent CT simulation for three-dimensional conformal RT planning, and the treatment was given as a three-field box technique using 6 MV posteroanterior and 15 MV opposed lateral beams. The radiation field for the pelvis encompassed the primary tumor, mesorectum, presacral space, entire sacral hollow, and regional lymphatics, including the perirectal, internal iliac, presacral, and distal common iliac node areas. The superior border of the pelvic field was placed at L5/S1 and the inferior border at least 3 cm caudal to the gross tumor. For the boost field, margins of at least 2 cm were added to the primary tumor with mesorectum in all directions.

Preoperative chemotherapy was given to all patients concurrently during RT with either a fluoropyrimidine-, irinotecan-, or oxaliplatin-based regimen. A radical proctectomy was performed 4–8 weeks after the end of the preoperative concurrent chemoradiation. Postoperative chemotherapy with a fluoropyrimidine- or oxaliplatin-based regimen was started 3–6 weeks after surgery.

Patients were scheduled for follow-up every 3 months for the first 2 years, then every 6 months for up to 5 years and yearly thereafter. The follow-up examination included a physical examination, complete blood count, liver function tests, serum CEA, and chest radiography; abdominopelvic CT was included every 6 months for the first 5 years and yearly thereafter. Colonoscopy was performed 1 year after surgery and then every other year.

Statistical analysis

The patients were divided into negative and positive groups based on the postoperative CRM status. A CRM ≤ 1 mm was defined as positive. For patient and treatment characteristics, the chi-square test or Fisher's exact test was used to compare the two groups. PSM was conducted by modeling the probability of the patients in negative and positive CRM groups. The probability of each patient was estimated using a logistic regression model based on their age, sex, distance from anal verge, histological grade, pretreatment CEA, surgery type, ypStage, and the presence of vascular, angiolymphatic, and perineural invasion.

The identification and classification of treatment failure was described in elsewhere.¹⁶ In brief, pelvic CT was used as the initial tool for detecting the treatment failure. MRI or positron emission tomography-CT was considered in the case of equivocal finding of the follow-up CT. Recurrence was confirmed by surgical resection, biopsy, or cytology, and/or radiological finding of increasing size over time. Tumor recurrence within the pelvic cavity was defined as locoregional failure and that without the pelvic cavity as distant failure. Local failure was defined as recurrence in the tumor bed, anastomosis site, anterior pelvic organs, and within the pelvic nerve plexus and perineum. Regional failure was defined as recurrence in the lateral lymph node-bearing area outside the pelvic nerve plexus, along the obturator, internal, external, and common iliac vessels. The local recurrence-free survival (LRFS), relapse-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS) were calculated from the initial date of chemoradiation to the date of local recurrence, any recurrence, distant metastasis, and any death, respectively. Considering that the analysis for patterns of failure was the aim of the current study, any death was not counted as an event for LRFS, RFS, and DMFS, except OS. The 5-year actuarial rates of LRFS, RFS, DMFS, and OS were compared between the negative and positive CRM groups using Kaplan–Meier methods with the log-rank test. *P*-values < 0.05 were considered significant.

RESULTS

Survival outcome and patterns of failure

Table 1 summarizes the patient characteristics and intergroup comparison. The baseline characteristics were unfavorable for

Table 1. Patient characteristics according to the circumferential resection margin status before and after propensity score matching (n = 144)

Parameter		Total population		p^a	Propensity score-matched population		
		CRM- (n = 870)	CRM+ (n = 74)		CRM- (n = 72)	CRM+ (n = 72)	p^a
Age	≥ 60	424 (48.7)	31 (41.9)	0.258	38 (52.8)	29 (40.3)	0.133
	< 60	446 (51.3)	43 (58.1)		34 (47.2)	43 (59.7)	
Sex	Male	596 (68.5)	51 (68.9)	0.941	52 (72.2)	49 (68.1)	0.585
	Female	274 (31.5)	23 (31.1)		20 (27.8)	23 (31.9)	
Distance from AV (cm)	≥ 5 cm	604 (69.4)	30 (40.5)	< 0.001	25 (34.7)	30 (41.7)	0.391
	< 5 cm	266 (30.6)	44 (59.5)		47 (65.3)	42 (58.3)	
Histological grade	Low	848 (97.5)	66 (89.2)	0.001	68 (94.4)	66 (91.7)	0.512
	High	22 (2.5)	8 (10.8)		4 (5.6)	6 (8.3)	
Pre-treatment CEA (ng/mL)	> 5	279 (32.1)	48 (64.9)	< 0.001	48 (66.7)	46 (63.9)	0.726
	≤ 5	591 (67.9)	26 (35.1)		24 (33.3)	26 (36.1)	
Surgery	Sphincter-preserving	756 (86.9)	44 (59.5)	< 0.001	44 (61.1)	43 (59.7)	0.865
	APR	114 (13.1)	30 (40.5)		28 (38.9)	29 (40.3)	
cN classification	0	161 (18.5)	9 (12.2)	< 0.001	12 (16.7)	9 (12.5)	0.624
	1	528 (60.7)	34 (45.9)		35 (48.6)	33 (45.8)	
	2	181 (20.8)	31 (41.9)		25 (34.7)	30 (41.7)	
cStage	I-II	162 (18.6)	9 (12.2)	0.166	12 (16.7)	9 (12.5)	0.479
	III-IV	708 (81.4)	65 (87.8)		60 (83.3)	63 (87.5)	
	0-I	369 (42.4)	0 (0.0)	< 0.001	0 (0.0)	0 (0.0)	.
ypStage	II-IV	501 (57.6)	74 (100.0)		72 (100.0)	72 (100.0)	
Vascular invasion	Yes	148 (17.0)	37 (50.0)	< 0.001	37 (51.4)	36 (50.0)	0.868
	No	722 (83.0)	37 (50.0)		35 (48.6)	36 (50.0)	
Angiolymphatic invasion	Yes	206 (23.7)	41 (55.4)	< 0.001	37 (51.4)	39 (54.2)	0.738
	No	664 (76.3)	33 (44.6)		35 (48.6)	33 (45.8)	
Perineural invasion	Yes	164 (18.9)	49 (66.2)	< 0.001	45 (62.5)	47 (65.3)	0.729
	No	704 (81.1)	25 (33.8)		27 (37.5)	25 (34.7)	

AV, anal verge; CEA, carcinoembryonic antigen; APR, abdominoperineal resection; CRM, circumferential resection margin.

^aChi-square test or Fisher's exact test.

Figure 1. 5-year rates of LRFS (A), RFS (B), DMFS (C), and OS (D) between negative and positive CRM groups defined by propensity score matching. CRM, circumferential resection margin; LRFS, local recurrence-free survival; RFS, relapse-free survival; DMFS, distant metastasis-free survival; OS, overall survival.

prognosis in a positive CRM group, but they were comparable in the patients of each group after PSM.

The median follow-up duration was 46 months (range, 4–155), and those for negative and positive CRM groups were 49 months (range, 4–153) and 41 months (range, 8–155), respectively ($p = 0.125$). The median interval between chemoradiation and surgery was 48.5 days (range, 32–62) for negative CRM and 48 days (range, 27–196) for positive CRM, respectively ($p = 0.813$ by Mann-Whitney U test). No statistically significant difference was observed in the 5-year LRFS between the negative and positive CRM groups (93.4 vs 89.6%, $p = 0.442$) (Figure 1A). There was a significant difference in the 5-year RFS rate (57.1% vs 39.1%, $p = 0.042$) and a borderline significant difference in the DMFS (59.4% vs 43.3%, $p = 0.069$) between the negative and positive CRM groups (Figure 1B and C). A negative CRM group showed more favorable OS than a positive CRM group, but there was no statistical significance (67.5 vs 55.8%, $p = 0.186$) (Figure 1D). The patterns of failure are shown in Figure 2. There were 30

recurrences with a negative CRM and 43 with a positive CRM. Regarding the initial recurrence pattern, two patients with a negative CRM experienced isolated local recurrence vs none with a positive CRM ($p = 0.497$). The 5-year cumulative incidence of local recurrence was 6.9% in PSM population. For the comparison of negative and positive CRM, those of local, regional, and distant recurrence were 6.6% vs 7.3% ($p = 0.896$), 12.8% vs 14.4% ($p = 0.749$), and 38.5% vs 54.9% ($p = 0.090$), respectively.

Salvage outcome of patients with local recurrence

Salvage therapy was given to the eight patients with local recurrence. Isolated local recurrence occurred in two patients. One patient received concurrent chemoradiation with capecitabine and further chemotherapy for local recurrence. He showed a partial response with salvage treatment and died of disease 19 months after recurrence. The other patient underwent pelvic exenteration for the recurrent lesion at anastomosis site, but he died of disease from another recurrence identified 3 months after the exenteration. In addition, six patients experienced

Figure 2. Comparison of the initial recurrence pattern between negative and positive CRM groups defined by propensity score matching. CRM, circumferential resection margin.

local recurrence with regional or distant recurrence. All but one patients eventually died of progressive disease under palliative treatment.

DISCUSSION

Despite the well-known adverse effects of CRM involvement in rectal cancer, there are no follow-up treatment guidelines for patients who have a positive CRM after surgery following preoperative chemoradiation. A multicenter randomized trial¹⁷ reported that the risk of local recurrence was not compensated by postoperative RT in rectal cancer with a CRM ≤ 1 mm (2-year rate: TME alone 17.3% vs TME+ adjuvant RT 15.7%, $p = 0.98$). In that study, however, postoperative RT was not indicated for those patients who had already received preoperative chemoradiation, and the effect of additional radiation was still unknown in patients after preoperative chemoradiation followed by surgery. To identify the uncertain effect of additional radiation to the primary tumor bed in a rectal cancer patient with CRM involvement after surgery treated with preoperative chemoradiation, we compared the patterns of failure between negative and positive CRM groups, instead of a direct comparison between the patients with and without additional RT. Most previous studies defined local failure as intrapelvic recurrence and reported local recurrence rates of 4.2–10.6% after surgery with preoperative chemoradiation,^{18–21} while we classified local and regional recurrence separately, considering the need for an additional tumor bed boost. The 5-year cumulative rate for local recurrence in our study was 6.9% (8/144), which was consistent with previous data.

Our data indicated unfavorable relapse rate (5-year RFS 57.1 vs 39.1%, $p = 0.042$) and distant metastasis (5-year DMFS 59.4 vs 43.3%, $p = 0.069$) in patients with a positive CRM, compared with a negative CRM (Figure 1). Local recurrence was not differed between negative and positive CRM groups (5-year LRFS 93.4% vs 89.6%, $p = 0.442$). Although there was a difference by about 12% in OS, but it was not within statistical significance. We inferred that factor other than local recurrence largely determined the difference in prognosis between negative and positive CRM.

Regarding the patterns of failure, local recurrence was not more frequent overall in the positive CRM than the negative CRM group (6.6% vs 7.3%, $p = 0.896$), although the patients with a negative CRM were associated with more isolated local recurrence. In rectal cancer treated with TME, the major pattern of failure was distant recurrence regardless of the sequence of chemoradiation.¹⁸ There were 3–11% of local recurrence and 21–36% of distant recurrence in patients received preoperative chemoradiation in randomized controlled trials.^{18,21,22} Our data showed similar finding for local recurrence (6.6% in negative and 7.3% in positive CRM) but more distant recurrence (38.5 and 54.9%). The inconsistent distant recurrence rate might be resulted from the proportion of CRM involvement (our data 50% vs others not available, maybe less than 10%) and inclusion of ypStage 0–I patients (our data 0% vs others 8–42%).

In our study, distant recurrence was dominant in both the negative and positive CRM groups, although the overall recurrence

rate was higher in positive CRM (Figure 2). This finding is consistent with studies that evaluated CRM involvement as a prognostic factor. Park et al.¹⁴ found that a positive CRM increased distant metastasis rather than local recurrence in rectal cancer treated with neoadjuvant chemoradiation. There were significant differences in overall recurrence (19.6% vs 53.8%, $p = 0.010$) and distant metastasis (13.1% vs 38.5%, $p = 0.028$) and a trend towards increased local recurrence (6.5% vs 15.4%, $p = 0.237$) in the negative vs positive CRM group, respectively. Bernstein et al.⁵ also suggested that distant metastasis (5-year rate 44%) occurred more frequently than did local recurrence (5-year rate 21%) in the patients who underwent preoperative RT and TME with a CRM ≤ 2 mm. However, it should be noted that, in that study, recurrences were divided into local recurrence and distant metastasis, and either of them was counted both in an isolated status and a combined status of having concomitant presence of the other. In comparison, the influence of CRM involvement was greater for local recurrence than distant metastasis in the review by Nagtegaal and Quirke,²³ who reported that a negative CRM was associated less with local recurrence (HR 0.16, 95% CI 0.06–0.27) than with distant metastases (HR 0.47, 95% CI 0.26–0.68) in rectal cancer treated with neoadjuvant therapy and curative surgery, compared with a positive CRM. However, the results of this review must be interpreted after considering the substantial differences in the numbers of cited articles and patients analyzed (2479 patients in nine articles on local recurrence vs 520 in six articles on distant metastasis). Consequently, it is more reasonable to consider CRM involvement as a surrogate of distant metastasis rather than directly affecting local recurrence.

Based on previously reported data and our finding of distant recurrence as major pattern of failure, additional RT boost is not considered for patient with positive CRM who received surgery following preoperative chemoradiation in our center. Intensified chemotherapy would be more appropriate for adjuvant treatment. Adjuvant chemotherapy or its regimen was not considered as a factor affecting treatment outcome in the current study. The role of adjuvant chemotherapy remains unclear in rectal cancer, unlike colon cancer. No difference was seen in cumulative incidence of distant metastases ($p = 0.52$) from the long-term results of the European Organisation for Research and Treatment of Cancer 22921 trial.²⁴ Systematic review and meta-analysis by

Brugom et al. also reported no beneficial effects of adjuvant chemotherapy on distant recurrences (HR 0.94, 95% CI 0.78–1.14; $p = 0.523$) and overall survival (HR 0.97, 95% CI 0.8–1.17; $p = 0.775$).²⁵ There were studies conducted by our institute that suggested consistent results. For patients with locally advanced rectal cancer, adjuvant chemotherapy and its regimen was not demonstrated as a significant factor in univariate analysis for disease-free survival ($p = 0.541$).²⁶ Another study showed that there were no differences in 5-year local control (91.7% vs 92.5%, $p = 0.875$), RFS (80.8% vs 77.2%, $p = 0.685$), and OS (88.4% vs 90.4%, $p = 0.723$) in the comparison with capecitabine alone and capecitabine plus irinotecan as adjuvant chemotherapy of patient treated with preoperative chemoradiation and curative surgery.²⁷ On the other hand, multicenter, randomized controlled trial (ADORE) reported superior disease-free survival with the addition of oxaliplatin to adjuvant fluorouracil and leucovorin regimen (3-year rate 71.6% vs 62.9%, $p = 0.047$) for patients with postoperative pathological Stage II–III rectal cancer.²⁸ In a retrospective study by Bhatti et al., patients who received induction chemotherapy showed a significantly low CRM involvement (9.2% vs 34%, $p = 0.002$) and more favorable OS (5-year rate 70% vs 47%, $p = 0.003$).²⁹ Given these results, intensified chemotherapy could lead to better treatment outcome in patient with positive CRM after surgery following preoperative chemoradiation.

CONCLUSION

Distant metastasis was the major pattern of failure regardless of CRM involvement in rectal cancer patients who underwent surgery following preoperative chemoradiation. A positive CRM was not associated with overall local recurrence compared with a negative CRM, but it showed the increasing trend of distant metastasis with or without local recurrence. Our finding would be useful for treatment strategy in rectal cancer patient with a positive CRM after surgery following preoperative chemoradiation.

ACKNOWLEDGMENT

This work was supported by a National Cancer Center Grant (NCC-1510160 & NCC-1610440). The present affiliation of Y. Kim is the Department of Radiation Oncology, Kyung Hee University Hospital, Seoul, Korea.

REFERENCES

1. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986; 2: 996–9.
2. Nagtegaal ID, Marijnen CA, Kranenburg EK, van de Velde CJ, van Krieken JH, et al Pathology Review Committee, et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 2002; 26: 350–7.
3. 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: 1723–9. doi: <https://doi.org/10.1007/DCR.0b013e3181b54fbd>
4. Trakarnsanga A, Gonen M, Shia J, Goodman KA, Nash GM, Temple LK, et al. What is the significance of the circumferential margin in locally advanced rectal cancer after neoadjuvant chemoradiotherapy? *Ann Surg Oncol* 2013; 20: 1179–84. doi: <https://doi.org/10.1245/s10434-012-2722-7>
5. Bernstein TE, Endreseth BH, Romundstad P, Wibe A, Norwegian Colorectal Cancer Group. Circumferential resection margin as a prognostic factor in rectal cancer. *Br J Surg* 2009; 96: 1348–57. doi: <https://doi.org/10.1002/bjs.6739>
6. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective

- postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009; **373**: 811–20. doi: [https://doi.org/10.1016/S0140-6736\(09\)60484-0](https://doi.org/10.1016/S0140-6736(09)60484-0)
7. Maurer CA, Renzulli P, Kull C, Käser SA, Mazzucchelli L, Ulrich A, et al. The impact of the introduction of total mesorectal excision on local recurrence rate and survival in rectal cancer: long-term results. *Ann Surg Oncol* 2011; **18**: 1899–906. doi: <https://doi.org/10.1245/s10434-011-1571-0>
 8. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; **12**: 575–82. doi: [https://doi.org/10.1016/S1470-2045\(11\)70097-3](https://doi.org/10.1016/S1470-2045(11)70097-3)
 9. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudelko M, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. *Radiother Oncol* 2004; **72**: 15–24. doi: <https://doi.org/10.1016/j.radonc.2003.12.006>
 10. Bosset JF, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results-EORTC 22921. *J Clin Oncol* 2005; **23**: 5620–7. doi: <https://doi.org/10.1200/JCO.2005.02.113>
 11. Kim KH, Park MJ, Lim JS, Kim NK, Min BS, Ahn JB, et al. Circumferential resection margin positivity after preoperative chemoradiotherapy based on magnetic resonance imaging for locally advanced rectal cancer: implication of boost radiotherapy to the involved mesorectal fascia. *Jpn J Clin Oncol* 2016; **46**: 316–22. doi: <https://doi.org/10.1093/jjco/hyv208>
 12. Taylor FG, Quirke P, Heald RJ, Moran BJ, Blomqvist L, Swift IR, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. *J Clin Oncol* 2014; **32**: 34–43. doi: <https://doi.org/10.1200/JCO.2012.45.3258>
 13. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 2006; **333**: 779. doi: <https://doi.org/10.1136/bmj.38937.646400.55>
 14. Park JS, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, et al. A circumferential resection margin of 1 mm is a negative prognostic factor in rectal cancer patients with and without neoadjuvant chemoradiotherapy. *Dis Colon & Rectum* 2014; **57**: 933–40. doi: <https://doi.org/10.1097/DCR.0000000000000171>
 15. AJCC Cancer Staging Manual. 7th edition. New York (NY): Springer. 2010.
 16. Kim TH, Jeong SY, Choi DH, Kim DY, Jung KH, Moon SH, et al. Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. *Ann Surg Oncol* 2008; **15**: 729–37. doi: <https://doi.org/10.1245/s10434-007-9696-x>
 17. Marijnen CA, Nagtegaal ID, Kapiteijn E, Kranenbarg EK, Noordijk EM, et al. Cooperative investigators of the Dutch Colorectal Cancer Group Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. *Int J Radiat Oncol Biol Phys* 2003; **55**: 1311–20. doi: [https://doi.org/10.1016/S0360-3016\(02\)04291-8](https://doi.org/10.1016/S0360-3016(02)04291-8)
 18. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, et al. German Rectal Cancer Study Group Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351**: 1731–40. doi: <https://doi.org/10.1056/NEJMoa040694>
 19. Gérard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006; **24**: 4620–5. doi: <https://doi.org/10.1200/JCO.2006.06.7629>
 20. Park JS, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, et al. A circumferential resection margin of 1 mm is a negative prognostic factor in rectal cancer patients with and without neoadjuvant chemoradiotherapy. *Dis Colon Rectum* 2014; **57**: 933–40. doi: <https://doi.org/10.1097/DCR.0000000000000171>
 21. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol* 2009; **27**: 5124–30. doi: <https://doi.org/10.1200/JCO.2009.22.0467>
 22. Park JH, Yoon SM, Yu CS, Kim JH, Kim TW, Kim JC. Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. *Cancer* 2011; **117**: 3703–12. doi: <https://doi.org/10.1002/cnccr.25943>
 23. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? *J Clin Oncol* 2008; **26**: 303–12. doi: <https://doi.org/10.1200/JCO.2007.12.7027>
 24. Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014; **15**: 184–90. doi: [https://doi.org/10.1016/S1470-2045\(13\)70599-0](https://doi.org/10.1016/S1470-2045(13)70599-0)
 25. Breugnot AJ, Swets M, Bosset J-F, Collette L, Sainato A, Cionini L, et al. Adjuvant chemotherapy after preoperative (chemo) radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol* 2015; **16**: 200–7. doi: [https://doi.org/10.1016/S1470-2045\(14\)71199-4](https://doi.org/10.1016/S1470-2045(14)71199-4)
 26. Kim TH, Chang HJ, Kim DY, Jung KH, Hong YS, Kim SY. Pathologic nodal classification in the Cancer Patients Treated With Preoperative Chemoradiotherapy and Curative Resection. *Int J Radiat Oncol Biol Phys* 2010; **77**: 1158–65. doi: <https://doi.org/10.1016/j.ijrobp.2009.06.019>
 27. Kim DY, Jung KH, Kim TH, Kim DW, Chang HJ, Jeong JY, et al. Comparison of 5-fluorouracil/leucovorin and capecitabine in preoperative chemoradiotherapy for locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2007; **67**: 378–84. doi: <https://doi.org/10.1016/j.ijrobp.2006.08.063>
 28. Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol* 2014; **15**: 1245–53. doi: [https://doi.org/10.1016/S1470-2045\(14\)70377-8](https://doi.org/10.1016/S1470-2045(14)70377-8)
 29. Bhatti AB, Waheed A, Hafeez A, Akbar A, Syed AA, Khattak S, et al. Can induction chemotherapy before concurrent chemoradiation impact circumferential resection margin positivity and survival in low rectal cancers? *Asian Pac J Cancer Prev* 2015; **16**: 2993–8. doi: <https://doi.org/10.7314/APJCP.2015.16.7.2993>