ORIGINAL CONTRIBUTION

Selective Approach for Upper Rectal Cancer Treatment: Total Mesorectal Excision and Preoperative Chemoradiation Are Seldom Necessary

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BACKGROUND: The implementation of preoperative chemoradiation combined with total mesorectal excision has reduced local recurrence rates in rectal cancer. However, the use of both types of treatment in upper rectal cancer is controversial.

OBJECTIVE: The purpose of this work was to assess oncological results after radical resection of upper rectal cancers compared with sigmoid, middle, and lower rectal cancers and to determine risk factors for local recurrence in upper rectal cancer.

DESIGN: This was a retrospective analysis of prospectively collected data.

SETTINGS: This study was conducted in a tertiary care referral hospital in Valencia, Spain.

PATIENTS: Analysis included 1145 patients who underwent colorectal resection with primary curative intent for primary sigmoid (n = 450), rectosigmoid (n = 70), upper rectal (n = 178), middle rectal (n = 186), or lower rectal (n = 261) cancer.

MAIN OUTCOME MEASURES: Oncological results, including local recurrence, disease-free survival, and cancer-specific survival, were compared between the different tumor locations. Univariate and multivariate analyses were performed to identify risk factors for local recurrence in upper rectal cancer.

RESULTS: A total of 147 patients (82.6%) with upper rectal tumors underwent partial mesorectal excision, and only 10 patients (5.6%) of that group received preoperative chemoradiation. The 5-year actuarial local recurrence, disease-free survival, and cancer-specific survival rates for upper rectal tumors were 4.9%, 82.0%, and 91.6%. Local recurrence rates showed no differences when compared among all of the locations ($p = 0.20$), whereas disease-free survival and cancer-specific survival were shorter for lower rectal tumors ($p = 0.006$; $p = 0.003$). The only independent risk factor for local recurrence in upper rectal cancer was an involved circumferential resection margin at pathologic analysis (HR, 14.23 (95% CI, 2.75–73.71); $p = 0.002$).

LIMITATIONS: This was a single-institution, retrospective study.

CONCLUSIONS: Most upper rectal tumors can be treated with partial mesorectal excision without the systematic use of preoperative chemoradiation. Involvement of the mesorectal fascia was the only independent risk factor for local recurrence in these tumors.

KEY WORDS: Circumferential resection margin; Mesorectal excision; Neoadjuvant therapy; Oncological results; Upper rectal cancer.

Rectal cancer management requires a correct preoperative staging to select the most adequate treatment. Over the last 25 years, total mesorectal

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excision (TME) has become the criterion standard technique for surgical treatment of invasive tumors located at the middle and lower rectum.[1–3] However, there are controversies concerning the need for TME in upper rectal cancer.

Some authors have shown that tumors of the upper third of the rectum have similar oncological outcomes compared with sigmoid tumors, showing that TME would not be necessary for upper rectal cancer. Therefore, these tumors can be operated on a partial mesorectal excision (PME) with a very low local recurrence (LR) rate.[4,5] Nevertheless, other authors have published that upper-third tumors present high LR rates, such as those obtained in the middle third, suggesting that these tumors might need to be treated more aggressively with preoperative radiotherapy (PRT).[6] It has been reported that the audit of the surgical plane of the excised mesorectum may predict LR. In the upper rectum, the range of mesorectal complete resection varies between 57.8% and 89.0%.[7,8] This might partially account for the variability in LR rates in these tumors among surgeons and institutions.

An important controversy is the use of preoperative chemoradiation in upper rectal tumors. Most trials reporting the effectiveness of TME and neoadjuvant therapy consider the rectum as a single unit.[2,9] Consequently, there is a lack of specific evidence on this issue for upper rectal cancer.

In the last decade, the inclusion of MRI for tumor staging has allowed for more selective use of preoperative chemoradiation by identification of high-risk factors for disease recurrence.[10–13] Recently, the level of the peritoneal reflection assessment with MRI has gained importance in the upper rectum, because it divides tumors into intraperitoneal and extraperitoneal, which allows for specific treatment planning strategies.[11,14]

The aim of this study was to assess oncological outcomes after radical resection of tumors of the upper rectum compared with sigmoid, rectosigmoid junction, middle, and lower rectal cancers. The secondary aim was to determine any potential risk factors contributing to LR in upper-third rectal tumors.

PATIENTS AND METHODS

Study Population

Between 1992 and 2010, 1564 patients who were diagnosed with rectal and sigmoid cancers were prospectively registered in a specialized coloproctology unit database. Demographic, operative, pathologic, postoperative outcome, and follow-up data were recorded. For this study, we considered a consecutive series of patients who underwent primary radical resection for tumors located in the sigmoid, rectosigmoid junction, upper, middle, and lower third of the rectum. Exclusion criteria were nonsurgical treatment, operation not performed by a colorectal surgeon, metastatic disease at diagnosis, local excision, palliative resections, and in situ carcinoma at pathologic assessment (Fig. 1). Approval was obtained from the institutional ethics board to collect and review data.

Preoperative Staging

The preoperative staging protocol for all of the patients included clinical examination, full preoperative/intraoperative colonoscopy, histopathologic examination of tumor biopsy, CEA level, and thoracoabdominal CT scanning. The preoperative protocol for rectal tumors has included rectal ultrasound since 1997 and pelvic MRI since 2000. All of the patients were discussed in a multidisciplinary session before treatment. At our unit, administration of preoperative chemoradiotherapy (CRT) started in May 1998. Recommendations for neoadjuvant CRT in middle and lower rectal cancers include middle advanced cT3 and cT4 cancers with high-risk factors for recurrence, such as involved or threatened mesorectal fascia on preoperative staging, extramural venous invasion, or evident lymph node involvement. For upper rectal cancer, the use of PRT was considered for bulky pelvic tumors, invasion to other structures, and involved or threatened mesorectal fascia when the tumor has an extraperitoneal extension.

Rectal tumors were subdivided according to their location from the anal verge on rigid rectoscopy into thirds, composed of the lower third (0–6 cm), middle third (7–10 cm), and upper third (11–15 cm). Tumors located from 16 to 18 cm were defined as rectosigmoid junction (RSJ) tumors. All of the tumors ranging from 18 to 40 cm from the anal verge measured by flexible endoscopy were classified as sigmoid tumors.

Surgery and Pathologic Assessment

All of the patients were operated on or supervised by 7 colorectal surgeons. For sigmoid cancer, a left hemicolectomy, sigmoidectomy, Hartmann procedure, or anterior resection was performed depending on the location of the tumor and the patient characteristics. In some patients, a total colectomy was performed because of synchronic polyps. If the tumor invaded adjacent organs, an en bloc resection with adequate margins was performed.

For rectal cancer, a TME technique was performed for all of the tumors located <10 cm from the anal verge. A PME was performed in rectal tumors >10 cm, including RSJ tumors. In these patients, 5 cm of mesorectum below the tumor was excised. TME and PME have been uniformly used in our unit since its inception in 1992, according to a standard technique described previously.[15] In the case of tumor infiltration of the sphincteric muscles, an abdominoperineal resection was performed. Our policy was to avoid the routine use of diverting stomas in upper rectal tumors when PME had been performed.

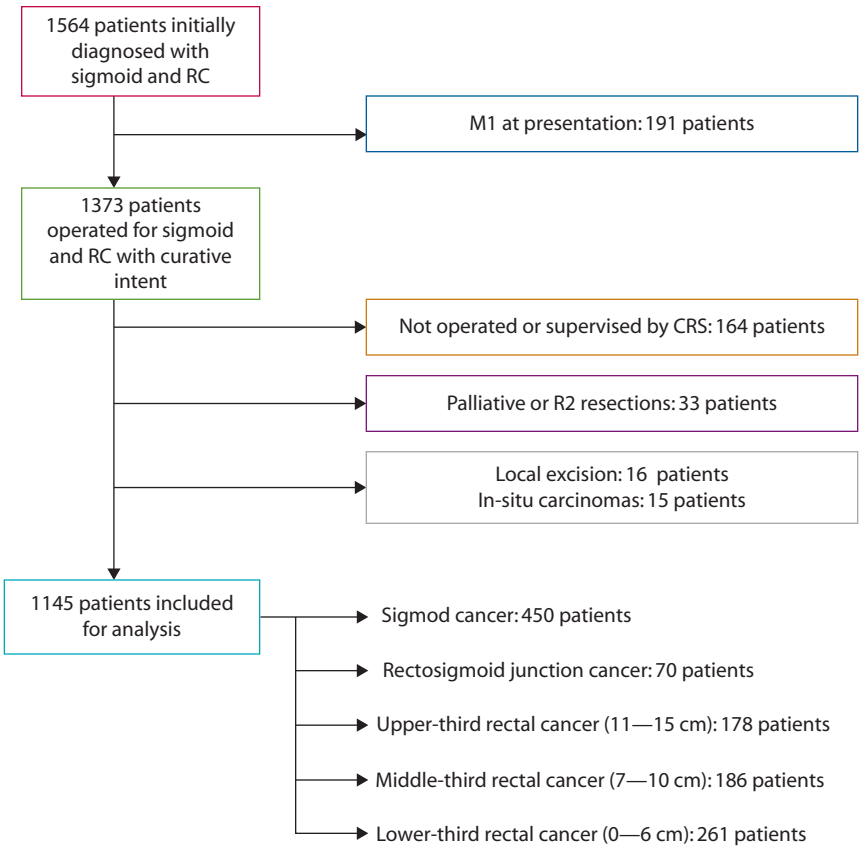

Figure 1. This flow chart illustrates the selection of patients for the current study. RC = rectal cancer; M1 = distant metastasis; CRS = colorectal surgeon; R2 = gross residual disease.

Histopathologic reports of the study population include pathologic TNM staging, cell differentiation, and other prognostic factors, such as mucinous component, venous, perineural, or lymphatic invasion. Tumor infiltration of all resection margins and invasion to other viscera was also evaluated. When neoadjuvant therapy was used, posttreatment pathologic TNM staging was applied for study analysis.

Circumferential resection margin (CRM) has been analyzed at the unit since 1996 for rectal tumors at the extraperitoneal level.[16,17] A rectal tumor was considered involved when it was within 1 mm of the resected circumferential margin. Lymph node involvement at CRM was classified in this study as positive. For intraperitoneal tumors, CRM was not evaluated, and tumors with serosa infiltration were staged as pathologic T4a. Macroscopic standardized assessment of the quality of the mesorectum was introduced in 1998 according to criteria initially described by García-Granero et al [8,15] and then formally defined by Nagtegaal et al.[18] The mesorectal quality assessment was reported as complete (mesorectal plane), nearly complete (intramesorectal plane), or incomplete (muscularis propria plane).[8] In case of abdominoperineal resection, the anal canal and sphincteric complex were also assessed to detect a potential waist effect of the specimen.

Postoperative Treatment and Follow-up

Our institutional policy during this study was that all of the patients who had stage III disease and those who had stage II with high-risk features (such as pathologic T4 tumors, lymph node metastasis, perforation, vascular invasion, or perineural invasion) and CRM involvement should receive adjuvant chemotherapy. From November 1997 to June 2004, the standard treatment was 5-fluorouracil and leucovorin according to the Mayo Clinic schedule.[19] After June 2004, postoperative chemotherapy was based on oxaliplatin-containing regimens. Patients aged >70 years who had comorbidities or who did not fully recover 6 weeks after surgery were not considered candidates for adjuvant treatment with oxaliplatin. None of the patients included in this study received postoperative radiotherapy. Recommendations for adjuvant chemotherapy were always discussed in the multidisciplinary group by the oncologist and the surgeon after reviewing the pathology report. The discussion also assessed patient general status by both clinical and laboratory parameters.

Patients were followed-up at the outpatient clinic by serial clinical examination and CEA assessment every 3 months during the first year, every 6 months during the second year, and annually thereafter. Thoracoabdominal CT scanning was performed every 6 months for the first

2 years. Colonoscopy was performed after 1 year and 3 to 5 years thereafter, depending on individual patient risk. If recurrence was suspected, further diagnostic methods were used as required. LR was defined as the presence of any anastomotic, peritoneal, pelvic, or perineal tumor documented by proctoscopic, imaging, or histopathologic examination. Peritoneal carcinomatosis was also considered as LR. Distant recurrence was defined as evidence of disease in any other location.

For this study, LR, disease-free survival (DFS), and cancer-specific survival (CSS) rates were assessed for each group. The calculation of LR rates included patients who developed LR alone or combined with distant recurrence.

Statistical Analysis

SPSS software (IBM SPSS Statistics for Macintosh, version 21.0, IBM Corp, Armonk, NY) was used for data management and statistical analyses. Categorical variables were compared among groups using χ^2 and Fisher exact tests. Continuous variables were compared by ANOVA. All time-to-event variables were calculated from the date of surgery. The univariate influence of prognostic factors on LR, DFS, and CSS was analyzed for all of the groups with the Kaplan-Meier method and the log-rank (Mantel-Cox) test. To investigate independent predictors of LR in upper rectal tumors, a Cox multivariate regression model was constructed including variables with $p < 0.10$ at univariate analysis. Proportional hazards assumption of the Cox model was assessed.[20] Statistical significance for all of the results was defined as $p < 0.05$.

RESULTS

A total of 1564 patients were included in the study. After exclusion criteria were applied, 1145 patients remained for analysis. The sigmoid cancer group included 450 patients, the upper rectal cancer group 178 patients, the RSJ group 70 patients, the middle rectal cancer group 186 patients, and the lower rectal cancer group 261 patients (Fig. 1). Patient, tumor, and treatment characteristics of the study population and histopathologic data are listed in Table 1.

Regarding upper third rectal tumors, 147 patients (82.6%) underwent PME, required fewer diverting stomas with lower morbidity, including anastomotic leak rates, when compared with middle and lower rectal cancers (Table 1). The quality assessment of the mesorectal surgical plane was considered complete in 88.3% of specimens of this group. The use of preoperative chemoradiation was higher in tumors of the middle and lower thirds of the rectum (28.5% and 40.6%), whereas in tumors of the upper rectum it was only used in 5.6% (10 patients). CRM involvement was 10.8% for tumors of the upper rectum, 10.9% for tumors of the middle rectum, and 14.5% for tumors of the lower rectum.

The median follow-up time was 60 months (range, 6–236 months) for the overall study group. Seventy-nine patients of the series developed LR, and 8 corresponded with upper rectal tumors. Of them, 6 patients developed pelvic recurrence, whereas 2 patients developed peritoneal carcinomatosis.

After the introduction of MRI in preoperative staging, mesorectal fascia involvement was detected in 8 patients with upper rectal tumors. Five of them received neoadjuvant therapy, and after pathologic examination, CRMs were not involved. No LR was detected during follow-up. Three patients with preoperative mesorectal involvement did not receive neoadjuvant therapy. An en bloc resection was performed in these patients. After pathologic examination, only 1 patient showed CRM involvement and developed pelvic recurrence after 2 years of follow-up.

Five-year actuarial rates of LR, DFS, and CSS for upper rectal cancer were 4.9%, 82.0% and 91.6%. For sigmoid tumors these rates were 7.0%, 81.2%, and 88.2%, and for RSJ tumors they were 7.8%, 83.0%, and 89.4%. There were no significant statistical differences when upper-third tumors were compared with sigmoid and RSJ tumors. Middle rectal tumors showed an LR rate of 5.9% and a DFS rate of 77.2%. CSS was the only statistically significant parameter obtained when middle rectal tumors were compared with upper rectal tumors (5-year value, 83.4% vs 91.6%; $p = 0.002$). All of the oncological survival parameters obtained in lower rectal tumors were significantly worse than those described for upper rectal tumors (LR, 10.9% vs 4.9%, $p = 0.05$; DFS, 69.7% vs 82%, $p = 0.006$; CSS, 79.8% vs 91.6%, $p = 0.001$). The 5-year actuarial rates and oncological outcome comparisons between groups are shown in Table 2. After Kaplan-Meier analyses (Fig. 2A), significant statistical differences among groups were not observed regarding LR rates ($p = 0.20$). However, DFS and CSS analyses (Figs. 2B and C) showed significant differences when comparing different tumor locations ($p = 0.006$; $p = 0.003$).

Factors associated with LR in upper rectal cancer at the univariate analysis included tumor perforation ($p = 0.012$), T3 or T4 stage ($p = 0.03$), CRM involvement ($p < 0.001$), and perioperative transfusion ($p = 0.03$). On multivariate Cox regression analysis (Table 3), involvement of CRM was identified as an independent predictor for LR in tumors of the upper rectum (HR, 14.23 (95% CI, 2.75–73.71); $p = 0.002$). The subgroup of patients with free CRM showed an actuarial LR rate of 1.9% at 5 years (data not shown).

DISCUSSION

The specific literature on the multidisciplinary approach of upper rectal cancer is scarce. Our data show that cancer of the upper third of the rectum has similar incidence

Table 1. Patient, tumor, and treatment characteristics; postoperative outcomes; and histopathologic features of the study groups

Characteristic	*Sigmoid colon (N = 450 [39.3%])*	*Rectosigmoid junction (N = 70 (6.1%))*	*Upper-third rectum (N = 178 [15.5%])*	*Middle-third rectum (N = 186 [16.3%])*	*Lower-third rectum (N = 261 [22.8%])*
Sex					
Male, n (%)	233 (51.8)	37 (52.9)	95 (53.4)	110 (59.1)	163 (62.5)
Female, n (%)	217 (48.2)	33 (47.1)	83 (46.6)	76 (40.9)	98 (37.5)
Age, mean (SD), y	69.8 (10.5)	69.9 (9.9)	67.5 (10.2)	66.3 (12.6)	66.9 (11.7)
Preoperative chemoradiation, n (%)	0 (0)	0 (0)	10 (5.6)	53 (28.5)	106 (40.6)
Tumor obstruction, n (%)	53 (11.8)	2 (2.9)	1 (0.6)	2 (1.1)	3 (1.1)
Surgical procedure					
Left hemicolectomy, n (%)	14 (3.1)	1 (1.4)	1 (0.6)	0 (0)	0 (0)
High anterior resection, n (%)	345 (76.7)	58 (82.9)	130 (73)	14 (7.5)	0 (0)
Hartmann procedure, n (%)	62 (13.8)	7 (10.0)	14 (7.9)	26 (14.0)	8 (3.0)
Abdominoperineal resection, n (%)	1 (0.2)	1 (1.4)	1 (0.6)	4 (2.2)	130 (49.8)
Low/ultralow anterior resection, n (%)	1 (0.2)	2 (2.9)	31 (17.4)	141 (75.8)	121 (46.3)
Subtotal colectomy, n (%)	6 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)
Total colectomy, n (%)	21 (4.7)	1 (1.4)	1 (0.6)	1 (0.5)	2 (0.8)
Extended resection, n (%)	68 (15.1)	8 (11.4)	16 (9.0)	18 (9.7)	34 (13)
Mesorectum excision					
Not available or analyzed, n (%)	–	22 (31.4)	–	3 (1.6)	7 (2.4)
Partial excision, n (%)	–	48 (68.6)	147 (82.6)	18 (9.7)	0 (0)
Total excision, n (%)	–	–	31 (17.4)	165 (88.7)	254 (97.6)
Tumor perforation					
Spontaneous, n (%)	35 (7.8)	6 (8.6)	6 (3.5)	4 (2.2)	8 (3.1)
Iatrogenic, n (%)	1 (0.2)	0 (0)	2 (1.2)	1 (0.6)	6 (2.3)
Diverting ileostomy, n (%)	8 (1.8)	3 (4.3)	21 (11.8)	89 (47.8)	120 (46.0)
Morbidity					
Ileus, n (%)	15 (3.3)	1 (1.4)	5 (2.8)	13 (7.0)	15 (5.7)
Wound infection, n (%)	61 (13.6)	6 (8.6)	28 (15.7)	26 (14)	60 (23)
Anastomotic leak, n (%)	23 (6.0)	2 (2.9)	11 (6.2)	12 (7.7)	17 (14.2)
Abdominal abscess, n (%)	16 (3.6)	1 (1.4)	4 (2.2)	14 (7.5)	7 (2.7)
Perioperative transfusion, n (%)	129 (28.7)	13 (18.6)	52 (29.2)	75 (40.3)	125 (47.9)
Perioperative mortality, n (%)	16 (3.6)	2 (2.9)	6 (3.4)	11 (5.9)	9 (3.4)
Differentiation grade					
Not available, n (%)	56 (12.4)	11 (15.7)	30 (16.9)	9 (4.8)	18 (6.9)
Low grade, n (%)	71 (15.8)	6 (8.6)	30 (16.9)	41 (22.0)	35 (13.4)
Intermediate grade, n (%)	315 (70.0)	52 (74.3)	116 (65.2)	131 (70.4)	195 (74.7)
High grade, n (%)	8 (1.8)	1 (1.4)	2 (1.1)	5 (2.7)	12 (4.6)
T (includes pT + ypT)					
0, n (%)	0 (0)	0 (0)	4 (2.2)	6 (3.2)	17 (6.5)
1, n (%)	55 (12.2)	7 (10.0)	24 (13.5)	14 (7.5)	18 (6.9)
2, n (%)	71 (15.7)	9 (12.9)	35 (19.7)	58 (31.2)	79 (30.3)
3, n (%)	266 (59.1)	44 (62.9)	99 (55.6)	101 (54.3)	123 (47.1)
4, n (%)	58 (12.9)	10 (14.3)	16 (9.0)	7 (3.8)	24 (9.2)
4a, n (%)	20 (4.4)	6 (8.6)	6 (3.4)	1 (0.6)	0 (0)
4b, n (%)	38 (8.5)	4 (5.7)	10 (5.6)	6 (3.2)	24 (9.2)
N (includes pN + ypN)					
0, n (%)	327 (72.6)	44 (62.9)	119 (66.9)	123 (66.1)	182 (69.7)
1, n (%)	87 (19.4)	16 (22.9)	36 (20.2)	43 (23.1)	48 (18.4)
2, n (%)	36 (8.0)	10 (14.3)	23 (12.9)	20 (10.8)	31 (10.8)
Mesorectal surgical plane assessment					
Not assessed or analyzed n (%)	–	54 (77.1)	75 (42.1)	60 (32.3)	72 (27.6)
Analyzed		16 (22.9)	103 (57.9)	126 (67.7)	189 (72.4)
Incomplete, n (%)	–	0 (0)	2 (1.9)	10 (7.9)	18 (9.5)
Nearly complete, n (%)	–	1 (6.2)	10 (9.7)	12 (9.5)	35 (18.5)
Complete, n (%)	–	15 (93.8)	91 (88.3)	104 (82.6)	136 (72)
Circumferential resection margin					
Not assessed or analyzed, n (%)	–	–	39 (21.9)	31 (16.7)	27 (10.4)
Analyzed, n (%)	–	–	139 (78.1)	155 (83.3)	234 (89.6)
Involved, n (%)	–	–	15 (10.8)	17 (10.9)	34 (14.5)
Lymphatic infiltration, n (%)	68 (15.1)	16 (22.9)	35 (19.7)	30 (16.1)	42 (16.1)
Venous infiltration, n (%)	69 (15.3)	16 (22.9)	27 (15.2)	36 (19.4)	38 (14.6)
Perineural infiltration, n (%)	61 (13.6)	13 (18.6)	28 (15.7)	33 (17.7)	29 (14.9)
Mucinous component >50%, n (%)	29 (6.4)	4 (5.7)	8 (4.5)	20 (10.8)	24 (9.2)
Follow-up, median (range), mo	65 (6–236)	53 (6–217)	58 (6–150)	59 (6–190)	58 (6–179)

p = pathologic; yp = posttreatment pathologic.

of LR and oncological survival outcomes when compared with sigmoid and RSJ cancers. In addition, CRM involvement was the only identified independent risk factor for LR.

The concept of TME was introduced for tumors located throughout the rectum.[1,21] However, whether this technique is appropriate for tumors located in the upper rectum is unclear and associated with unnecessary morbidity.[5,22] In 1998, Lopez-Kostner et al[4] reported that the outcomes for tumors of the upper rectum were similar to those for sigmoid cancer, differing favorably from lower rectal tumors. The LR rate at 5 years for upper rectal cancer was 4.7%, similar to sigmoid cancer (3.9%), whereas in lower rectal cancer LR was higher (LR, 12.9%; $p < 0.001$). These results are similar to those obtained in the present study. Moreover, Law and Chu[22] reported that rectosigmoid and upper rectal tumors (>10 cm) operated with PME showed no statistical differences in LR rates at 5 years when compared with lower rectal tumors (<10 cm) operated with TME (7.4% vs 10.7%; $p = 0.20$).

In contrast, a recent institutional analysis of upper rectal cancer operated with PME and adjuvant radiochemotherapy revealed that tumors in the upper third showed similar oncological outcomes when compared with middle-third tumors. In that study, LR rates of 15.5% for upper rectum, 11.7% for middle rectum, and 6.3% for sigmoid cancer were observed ($p = 0.055$), suggesting that upper rectal cancer should be treated more aggressively.[6] These results might be explained by the learning curve of TME implementation, the wide variety of surgeons, and the concept of PME limited to 3 to 5 cm distal to the tumor. Moreover, the mesorectal excision quality assessment was not reported in that study. In the present series, 7 specialized colorectal surgeons performed all of the procedures, and the mesorectal plane quality assessment was considered complete in 88.3% of upper rectal cancer specimens, in line with a previous analysis.[8]

This study has accurately measured the different locations of the tumors in the sigmoid, RSJ, upper, middle, and lower rectum. The majority of patients with tumors of the upper rectum underwent PME with a 5-year LR rate of 4.9% with no statistical difference compared with sigmoid and rectosigmoid tumors. These results suggest that TME is not necessary to obtain low LR rates in tumors of the upper third of the rectum, according to the current recommendation of The American Society of Colon and Rectal Surgeons.[23]

Another important issue is the need for neoadjuvant CRT in upper rectal tumors. PRT associated with TME has been proven to enhance tumor response and reduce LR rates.[2,9,24] However, these studies include all rectum thirds and only differentiate anatomic cutoff points to express results. Also, the spatial relation of the rectum with the peritoneal reflection is not evaluated to recommend PRT. In this sense, the Dutch mesorectal excision trial reporting the effect of short-course PRT and TME showed no significant reduction in the LR rate in upper rectal tumors at 2 and 6 years of follow-up (3.8% and 6.2% after TME alone vs 1.3% and 3.7% after PRT and TME).[2,24] Moreover, the CR07 trial[25] (in which patients were randomly assigned to short-course radiotherapy versus the selective use of postoperative chemoradiation) included 15% of the tumors located >10 cm from the anal verge. Although the local relapse rate was 1.2 % for those receiving PRT versus 6.2% for the postoperatively treated group, this is based in a subset exploratory analysis, and no firm conclusion could be taken from it. Therefore, short-course PRT is not recommended for tumors of the upper rectum because of limited benefits.[23] In this study, the selective use of PRT in upper rectal cancer allowed for a reduction of diverting stomas (4.3%) with an anastomotic leak rate of 6.2% and an LR rate of 4.9%. This restrictive policy of PRT might have also avoided long-term functional problems related to radiation in these patients, such as fecal incontinence, urgency, and bowel frequency.[26]

Table 2. Univariate analysis of oncological results according to tumor location

				95% CI		
Location	*Parameter*	*Actuarial 5-y rate, %*	*HR*	*Lower*	*Higher*	*p*
Sigmoid vs upper third	LR	7.0 vs 4.9	0.64	0.29	1.39	0.26
	DFS	81.2 vs 82.0	0.95	0.62	1.44	0.81
	CSS	88.2 vs 91.6	0.64	0.35	1.17	0.15
Rectosigmoid vs upper third	LR	7.8 vs 4.9	0.59	0.19	1.82	0.36
	DFS	83.0 vs 82.0	1.01	0.51	2.02	0.97
	CSS	89.4 vs 91.6	0.64	0.25	1.62	0.35
Middle third vs upper third	LR	5.9 vs 4.9	0.99	0.37	2.64	0.98
	DFS	77.2 vs 82.0	0.79	0.48	1.27	0.33
	CSS	83.4 vs 91.6	0.46	0.24	0.88	0.02
Lower third vs upper third	LR	10.9 vs 4.9	0.45	0.21	0.99	0.05
	DFS	69.7 vs 82.0	0.55	0.36	0.84	0.006
	CSS	79.8 vs 91.6	0.36	0.19	0.66	0.001

P value was calculated by Cox method.
CSS = cancer-specific survival; DFS = disease-free survival; LR = local recurrence.

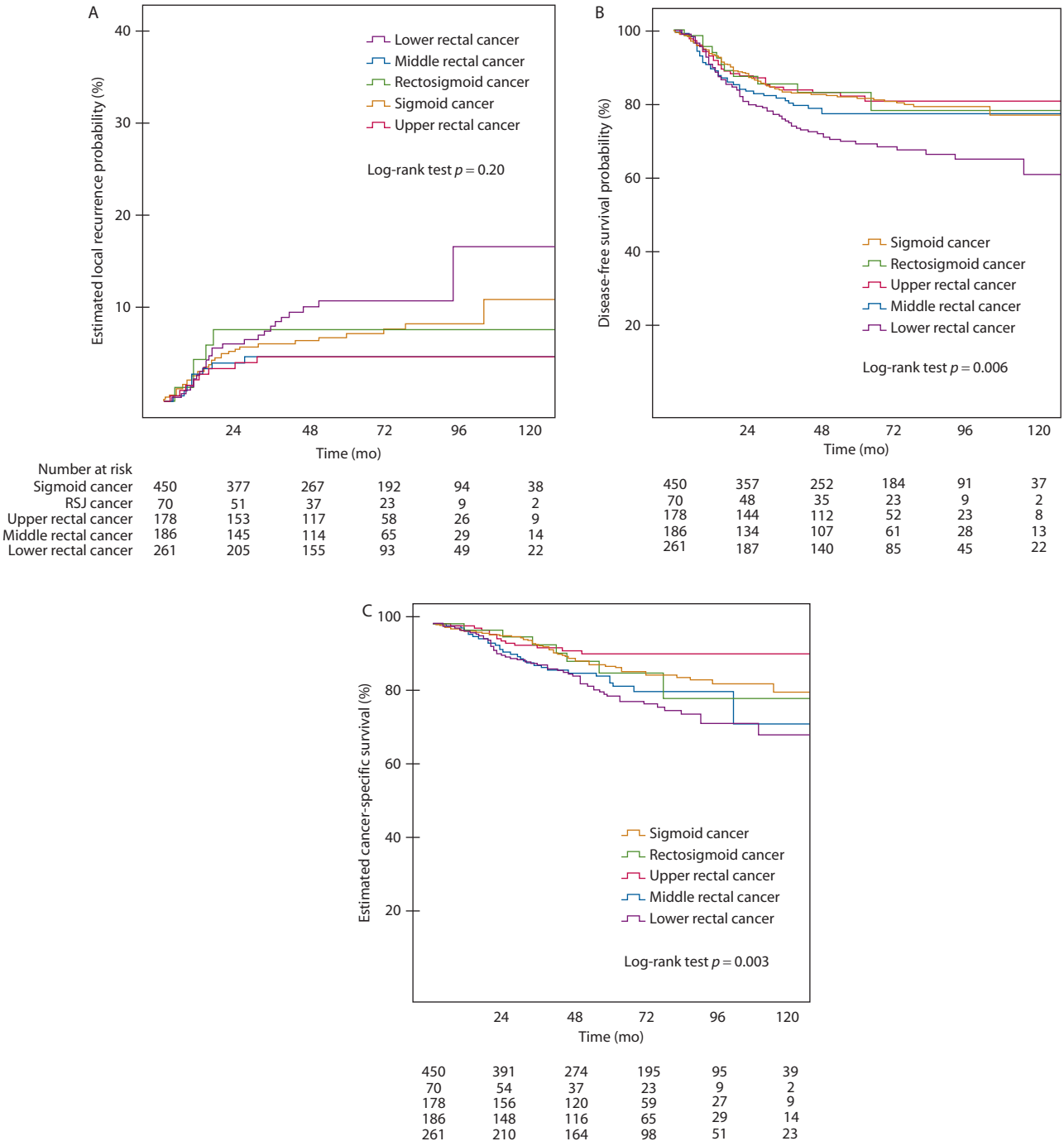

Figure 2. These Kaplan-Meier curves demonstrate the oncological outcomes for all of the patients according to tumor location. A, Time to local recurrence ($p = 0.20$). B, Disease-free survival rate ($p = 0.006$). C, Cancer-specific survival rate ($p = 0.003$). RSJ = rectosigmoid junction.

The current recommendations for PRT in rectal cancer are adjusted to high-risk factors of recurrence determined mainly by preoperative staging using MRI. The most important factor in estimating the risk of LR in rectal cancer is the pathologic assessment of the CRM. The potential mesorectal fascial involvement assessed preoperatively by MRI has proven to be useful in selecting PRT to reduce positive CRM and LR.[10,12,13] Nonetheless, specific data about CRM are scarce regarding upper rectal cancer. The Norwegian Colorectal Cancer Group reported an LR rate of 7.6% in 918 patients after upper rectal tumor resection treated by TME without radiotherapy. In multivariate analysis, a CRM ≤2 mm and an N2 node status were independent predictor factors for LR in upper rectal tumors.[27] In the present series, an involved CRM was the only independent factor for LR in upper rectal cancer. In

Table 3. Univariate and adjusted multivariate analyses of risk factors for local recurrence in upper rectal cancer

	Univariate analysis (Cox method)			*Multivariate analysis (Cox regression)*		
Variable	*HR*	*95% CI for HR*	*p*	*HR*	*95% CI for HR*	*p*
Sex (male/female)	0.91	0.22–3.64	0.89	Not included	–	–
Age, y	1.12	0.8–1.22	0.11	Not included	–	–
Obstructed tumor (no/yes)	2.28	0.1–2.86	0.88	Not included	–	–
Perforated tumor (no/yes)	8.26	1.6–42.61	0.012*	2.02	0.19–20.86	0.56
Extended resection (no/yes)	3.54	0.71–17.49	0.12	Not included	–	–
Differentiation grade (low/high)	1.72	0.16–3.94	0.76	Not included	–	–
Mucinous component (no/yes)	3.06	0.38–24.92	0.29	Not included	–	–
T						
0–2 (r)	1		0.03*	1	–	0.24
3	3.47	0.41–29.66	0.26	1.33	0.12–15.07	0.82
4	14.58	1.51–140.82	0.02	1.74	0.08–36.73	0.72
N						
0 (r)	1		0.31	Not included	–	–
1	2.61	0.41–29.66	0.21	–	–	–
2	14.58	0.56–16.93	0.19	–	–	–
Circumferential resection margin (free/involved)	22.18	5.53–88.98	<0.001*	14.23	2.75–73.71	0.002*
Lymphatic infiltration (no/yes)	2.37	0.57–9.91	0.24	Not included	–	–
Venous infiltration (no/yes)	1.3	0.16–10.57	0.81	Not included	–	–
Perineural infiltration (no/yes)	1.33	0.16–10.87	0.79	Not included	–	–
Perioperative transfusion (no/yes)	4.84	1.16–20.25	0.03*	4.43	0.91–18.95	0.09
Postoperative sepsis (no/yes)	2.42	0.30–19.68	0.41	Not included	–	–
Neoadjuvant therapy (no/yes)	2.38	0.29–19.36	0.42	Not included	–	–

*p Value is significant.

fact, in patients with a free CRM, the LR rate at 5 years was 1.9%. Therefore, even in upper rectal tumors, preoperative mesorectal fascia involvement assessment appears to be essential in selecting PRT. However, this assessment in the upper rectum cannot be adequately measured when the tumors are intraperitoneal[17] because the serosa on the anterolateral surface is separated by a thin layer of connective tissue from the muscularis propria.[28] Thus, it would be more appropriate to classify intraperitoneal rectal tumors as T4a when the serosa is affected at or above the peritoneal reflection. These features are not specifically analyzed in studies referring to oncological results in upper rectal cancer.[2,4,9,22,27] The majority of studies consider rectal cancer as those tumors located within 15 or 16 cm from the anal verge and have been arbitrarily divided into thirds.[21,29,30] This standard division does not consider the position of the rectum in relation to the peritoneum. Currently, MRI provides an accurate spatial relation between the rectum and the peritoneal reflection with 90.7% accuracy and might help enhance tumor staging.[14,28] In this sense, the MERCURY experience highlighted that peritoneal reflection involvement should be reported on MRI and histopathology as being CRM negative, because CRM corresponds with the cut surgical resection margin and does not cover the anterior aspect of the upper rectum.[31]

A different approach might be considered for intraperitoneal rectal cancer staged as T4a when the tumor perforates the visceral peritoneum. Previous studies showed that serosal surface involvement was associated with pelvic recurrence in colorectal cancer, because these tumors are at high risk of cell spread into the peritoneal cavity.[32,33] In a recent meta-analysis, tumoral cell spread into the peritoneal cavity retrieved by peritoneal washings was an independent prognostic factor for poor survival.[34] The current European Society of Medical Oncology guidelines for the treatment of upper-third tumors (>10 cm) suggest that large tumors with extension to the adjacent structures or peritoneal reflection need preoperative CRT, whereas tumors that are at stage ≤T4a should be treated like colosigmoid cancer.[35] It should be reasonable to improve on preoperative staging for tumors of the upper rectal third and RSJ, because it has been performed for colon cancer essaying preoperative chemotherapy.[36]

Although this was a single-institution and retrospective study, these results suggest that the majority of upper rectal tumors can be operated on with adequate PME without the systematic use of PRT, achieving satisfactory oncological results. CRM involvement was the only independent risk factor for LR. Therefore, the involvement of mesorectal fascia should also be accurately assessed preoperatively in upper rectal tumors to selectively recommend neoadjuvant chemoradiation.

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