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ORIGINAL ARTICLE

Distinct Prognosis of High Versus Mid/Low Rectal Cancer: a Propensity Score–Matched Cohort Study

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Abstract

Background Rectal cancers have long been treated as a single-entity disease; however, whether the prognosis of high rectal cancer (inferior margin located 10.1 to 15.0 cm from the anal verge) differs from that of mid/low rectal cancer (0 to 10.0 cm) remains disputed.

Methods Patients with stages I–III rectal adenocarcinomas undergoing curative-intent surgery were enrolled between 2007 and 2013 in this retrospective analysis. Exclusion criteria were neoadjuvant therapy or concurrent cancers. Propensity score matching and Cox regression analysis were performed to compare a 5-year overall and cancer-specific survival between patients with high and mid/low rectal cancer.

Results Of 613 patients who met the inclusion criteria, 199 (32.5%) and 414 (67.5%) had high and mid/low rectal cancer, respectively. After propensity score matching (187 cases for each group), the high group showed a better overall survival (70.9 vs. 56.9%, $p = 0.042$) and cancer-specific survival (77.4 vs. 60.3%, $p = 0.028$) at 5 years compared with the mid/low group with stage III disease. However, high rectal cancer did not demonstrate prognostic superiority in stages I–II disease. Multivariate analysis identified high tumor location as an independent prognostic factor for cancer-specific survival (hazards ratio = 0.422, 95% confidence interval 0.226–0.786, $p = 0.007$) and overall survival (hazards ratio = 0.613, 95% confidence interval 0.379–0.991, $p = 0.046$).

Conclusions Patients with stage III high rectal adenocarcinoma demonstrated better overall and cancer-specific survival than those with mid/low type, and tumor location was an independent prognostic factor for patients with rectal carcinomas.

Keywords High rectal cancer · Mid/low rectal cancer · Propensity score matching · Survival

Introduction

In the last few decades, techniques such as total mesorectal excision (TME) and neoadjuvant radiotherapy have been proven to be milestones in the treatment of rectal cancer, significantly decreasing local recurrence.[1, 2] Moreover, preoperative magnetic resonance imaging (MRI) and multidisciplinary team (MDT) have enabled precise clinical stage and individualized therapy.[3,4] Currently, rectal cancers are categorized into three groups based on the inferior margin of the tumor with reference to the anal verge, as measured by rigid proctosigmoidoscopy (low 0 to 5.0 cm, middle 5.1 to 10.0 cm, high 10.1 to 15.0 cm).[5] In this study, we classified them into the high group (10.1 to 15.0 cm) and the mid/low group (0 to 10.0 cm).

Tumor location plays an important role in determining the treatment of rectal cancer, as elaborated by the European Society for Medical Oncology (ESMO) rectal guideline, namely, rectal cancer of different tumor location may have a distinct recurrent risk and therapeutic options.[5] However, the latest National Comprehensive Cancer Network (NCCN) rectal guideline does not consider the influence of tumor location on the treatment of rectal cancer.[6] The dispute regarding location-tailored treatment of rectal cancer among the guidelines may actually reflect whether high rectal cancer (HRC) shows survival superiority over the mid/low rectal cancer

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(MLRC). Several studies showed that without neoadjuvant therapy, non-metastatic carcinoma in the high rectum demonstrated lower local recurrence (LR, 2.8–3.5 vs. 8.6–11.1%), longer disease-free survival (DFS, 68.0–71.9 vs. 54.0–62.1%), and improved overall survival (OS, 73.9–79.0 vs. 59.3–73.9%) compared with those in the mid/low rectum, similar to sigmoid cancer (LR, 2.0–2.5%; DFS, 69.0–81.3%; OS, 77.0–88.8%).[7–9] Furthermore, some researchers established that high rectal tumors should be treated with partial mesorectal excision (PME) without the routine use of neoadjuvant chemoradiotherapy (nCRT), just like colon cancer.[8,10] Other studies, however, reported that HRC shared more survival similarity to MLRC than sigmoid cancer and PME for the high group increased local recurrence and cancer-specific mortality, suggesting that nCRT and TME should be warranted for HRC.[11,12]

Apart from these conflicting results, previous studies were mainly retrospective and inevitably had some confounders, including medical comorbidities, surgery-related complications, and so on, making it difficult to determine the unique effect of tumor location. In an international multi-institutional study ($n = 2102$) with the largest scale so far; Park JS, et al.[7] failed to allow such confounders and balance the baseline characteristics, like pathological details and adjuvant chemotherapy. To explore the possible prognostic distinction between HRC and MLRC more accurately, we utilized propensity score matching (PSM) in our study, which allowed patients in different cohorts to be matched based on select characteristics and reduced confounders in a retrospective analysis.

Materials and Methods

Study Population

From 2007 to 2013, 942 patients undergoing surgery for primary rectal adenocarcinoma, with pathological stages I to III, were prospectively registered in our center's database. Cases with neoadjuvant therapy (radiotherapy, chemotherapy, or both), palliative surgery, coexisting cancer, previous cancer history, or indefinite tumor location were excluded. We extracted data concerning demographics, comorbidity, operation, pathology, complication, and follow-up for further analysis.

Preoperative Assessment

All patients underwent physical and ancillary examinations such as digital rectal examination, serum carcinoembryonic antigen (CEA), full colonoscopy with biopsy, and thoracoabdominal computed tomography (CT) scanning. For those with suspicious distant metastasis, positron emission tomography (PET) was performed as a consideration. Rectal tumors were divided into two groups based on the location of inferior margin in reference to the anal verge, as measured with colonoscopy or rigid sigmoidoscopy, which were verified using pelvic CT or MRI. Comorbidity was another important factor to take into consideration because of its possibility to affect the patient's long-term survival and was evaluated by the Charlson comorbidity index (CCI), classified as mild (≤ 4 scores) and severe (> 4 scores) comorbidity burden.[13]

Surgical Approach and Pathological Evaluation

For lesions in the upper rectum, low anterior resection (LAR) extending 5 cm below the distal edge of the tumor using partial mesorectal excision (PME), followed by colorectal anastomosis, was performed. Some patients in this group received protective diverting stomas. TME through LAR or abdominoperineal resection (APR) was implemented for MLRC depending on the distal extent of the carcinoma. En bloc resections included a nerve-preserving technique with high ligation of the inferior mesenteric artery.

Surgical specimens were examined and details including the gross appearance of the specimen, histological grade, pTNM categories, number of resected and tumor-involved lymph node, the status of resection margins, lymphovascular invasion (LVI), perineural invasion (PNI), and number of tumor deposits were described in the pathologic reports.

Postoperative Therapy and Surveillance

Comprehensive pathologic assessment ensured precise recommendations for adjuvant chemotherapy. Indications for adjuvant chemotherapy were stage III disease and a subgroup of stage II disease with high-risk features (i.e., poor differentiation, pathologic T4 stage, number of harvested lymph nodes < 12, perforation, positive LVI or PNI, and resection margin involvement).[14] Preferred options were oxaliplatin-containing regimens, i.e., capecitabine-oxaliplatin and folinic acid–fluorouracil-oxaliplatin. Oral capecitabine was advised for the elderly with limited stage III disease or stage II disease with high-risk features. The duration of this perioperative therapy was 6 months. Patients with poor physical status did not receive adjuvant therapy. None of the patients included in this study received adjuvant radiotherapy.

Patients were followed up at the outpatient clinic, where they underwent physical examinations, thoracoabdominal contrast CT scanning, full colonoscopy, and determination of serum CEA level every 3 months for 2 years, then every 6 months for 3 years, and annually thereafter. PET-CT was not routinely performed unless a distant recurrence (DR) was suspected. Patients were also followed-up over the telephone by a dedicated medical secretary every 3 months until death. Primary end-points were overall survival (OS) and cancer-specific survival (CSS), and secondary end-point was disease-free survival (DFS) including local recurrence (LR) and DR. The index date of survival was when the patient underwent primary surgery.

Besides oncological outcomes, we also adopted the Clavien–Dindo classification (CDC) to evaluate complications within 30 days after the surgery, which were classified as mild (CDC < IV) and severe (CDC ≥ IV).[15]

Statistical Analysis

SPSS version 22.0 (IBM, Armonk, NY, USA) with REssentials_22.0-FP1, R-2.15.3, and PSMATCHING3.04 plugins was utilized for data analysis. Unmatched and matched characteristics were compared using standard tests for continuous variables (Kruskal-Wallis and Wilcoxon signed rank tests) and categorical variables (chi-squared test and McNemar tests). To manage the imbalance of potential confounders between two groups in the unmatched data, we applied a propensity score matching (PSM), which is based on the propensity score (PS), the conditional probability of the assignment to a particular treatment given a vector of observed covariates.[16,17] The more similar the PS is, the more balanced confounders are between two groups, which makes survival analysis more accurate.

In our work, the PS was estimated including six variables: preoperative serum albumin (ALB) concentration, preoperative obstruction, surgical technique, pathological T (pT) stage, pathological N (pN) stage, and histological grade. The high and mid/low rectal cancer cases were then pair-matched, via one-to-one nearest-neighbor caliper width of 0.1, which means the maximum allowable difference in PS. The balance was evaluated again via standardized differences (< 10% signifies well-balanced matching) before and after matching, and the baseline data were compared.[17]

All time-to-event outcomes, taking time zero as the date of primary surgery, were analyzed using the Kaplan–Meier method and the log-rank test. Both univariate and multivariate Cox proportional hazards models, with backward variable selection procedure, were performed to identify the prognostic factors for OS and CSS. A p value < 0.05 was considered statistically significant.

Results

Patient Characteristics

Between December 18, 2007, and December 26, 2013, 942 patients underwent surgery for rectal cancer. A total of 613 patients were included and underwent propensity score matching (PSM), including 199 (32.5%) cases with high rectal cancer (HRC) and 414 (67.5%) cases with mid/low rectal cancer (MLRC) (Fig. 1). Compared with MLRC, patients with HRC were more likely to have preoperative obstruction (p = 0.023), higher serum ALB concentration (p = 0.036), pT4 stage (p = 0.006), and also demonstrated a trend toward well/moderate differentiation (p = 0.055), but were less likely to have nodal involvement (p < 0.001). Regarding surgical details, patients diagnosed with HRC underwent more PME and LAR, whereas patients with MLRC underwent more TME and APR (all p values < 0.001). Using 1:1 PS matching, 219 patients were excluded, with 187 pairs selected in each group. No statistical differences were observed between the two groups in terms of ALB, preoperative obstruction, pT stage, pN stage, and histological grade, except in expected location-associated surgical details (i.e., mesorectal excision and surgical procedure) as described in Table 1.

For the balance test, Fig. 2a shows that the histograms before matching on the left differed substantially, whereas, on the right, the groups were similar. Additionally, the standardized difference of the unmatched group was > 40%, however, it decreased to < 10% in the matched cohort (Fig. 2b). In summary, both visual and numerical data demonstrated that PSM was successful in appropriately matching patients.

Impact of Tumor Location on Prognosis

The mean follow-up period was 52 months (IQR, 36–68 months) in the unmatched data with a similar 5-year OS (high, 79.6% vs. mid/low, 73.6%, p = 0.110). However, the 5-year CSS was 87.2% in the HRC group, which was significantly better than that of the MLRC (81.7%, p = 0.029). After PSM procedures, the 5-year CSS of the MLRC remained superior for all stages (87.7 vs. 81.5%, p = 0.021) and OS displayed a favorable trend toward the high group without significance (81.0 vs. 73.9%, p = 0.082) (Fig. 3). There was no statistical difference in the DFS between the two groups after PSM (85.3 vs. 77.7%, p = 0.146) (Table. 2).

Stratified by tumor stage, the 5-year OS for HRC in the matched cohort was 95.7% in stage I, 81.3% in stage II, and 70.9% in stage III, compared with 87.3%, 82.7%, and 56.9%, respectively for MLRC; however, this was only significant in stage III (p = 0.042) (Fig. 4a–c). The 5-year CSS was 100%, 89.5%, and 77.4%, respectively for HRC staging I–III, whereas the outcome for mid/low rectal cancer was 97.8%, 87.0%, and 60.3%, respectively. Notably, CSS was also significantly different between the mentioned groups only in stage III (p = 0.028) (Fig. 4d–f).

For the 5-year DFS in the matched cohort, we identified a similar result for stages I–II disease (HRC vs. MLRC: 95.6 vs. 95.2%, p = 0.986; 86.9 vs. 87.7%, p = 0.871), but the results were significantly different in stage III (75.9 vs. 54.2%, p = 0.043). Regarding the recurrence patterns, as depicted in Table 2, HRC displayed non-significant trend toward a lower

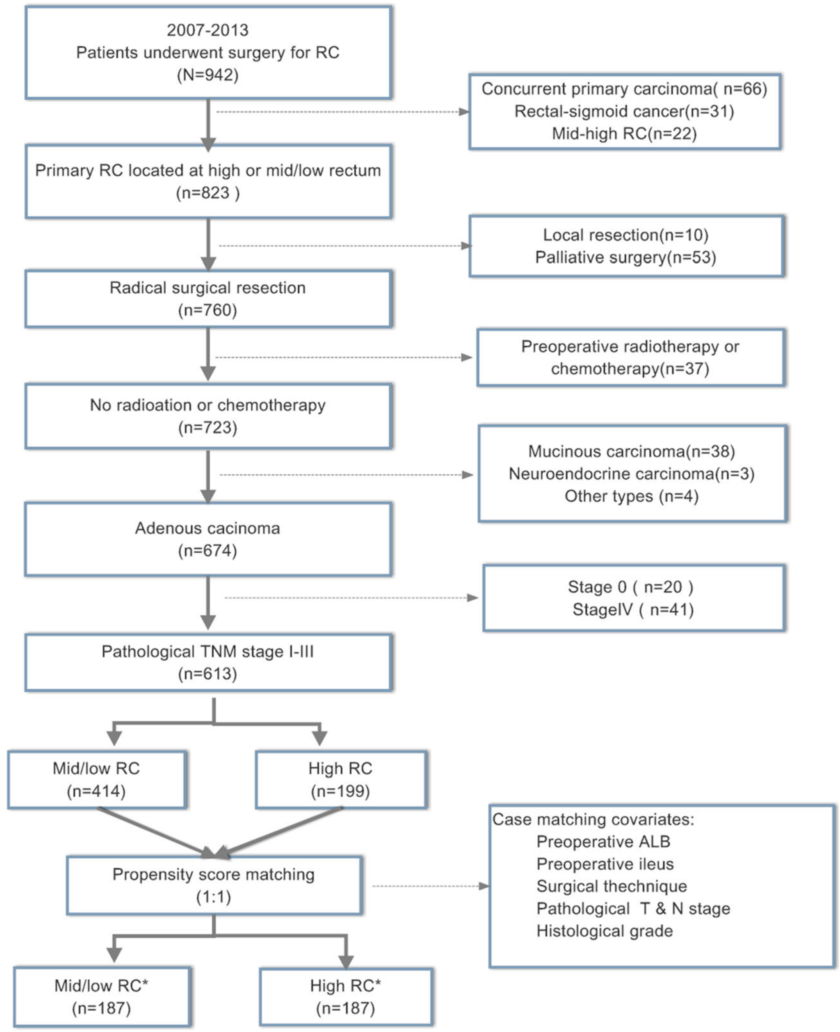

Fig. 1 The flowchart displays the selection of patients for analysis. RC, rectal cancer of the unmatched data, RC*, rectal cancer of the matched data

5-year rate of local and distant recurrence compared with MLRC regardless of tumor stage. Table 3 depicts that DR played a leading role in postoperative recurrence, and high rectal cancer showed a relatively lower percentage of local recurrence ($p = 0.169$) and lung recurrence ($p = 0.068$), which, however, did not reach statistical significance, either.

Prognostic Factors

In the multivariate analysis, HRC was associated with a better OS (HR = 0.613, 95% CI 0.379–0.991, $p = 0.046$) than the MLRC, and Table 4 lists other independent prognostic factors including CCI, preoperative CEA level, stage III disease, LVI, and CDC. For CSS, the high group remained to have a better survival (HR = 0.422, 95% CI 0.226–0.786, $p = 0.007$) compared to mid/low group, and other independent prognostic factors were preoperative CEA level, stage III disease, LVI, and CDC as shown in Table 5. Surprisingly, preoperative obstruction and advanced histologic grade were related to worse OS and CSS only in the univariate analysis.

Discussion

In this study, patients with stage III HRC demonstrated a better 5-year OS and CSS compared to those with stage III MLRC. Additionally, long-term risk of all-cause and tumor-associated mortality of the upper third rectal cancer generally decreased by 38.7% and 57.8%, respectively, which was in line with the previous studies.[8,10] However, in contrast to the findings by Park, J. S, et al,[7] the present analysis displayed that stages I–II disease favored two groups similarly but stage III only favored the high group. The inconsistency may possibly result from an incomprehensive evaluation of the patients' characteristic in the previous study, for instance, preoperative comorbidities and postoperative complications, which were both justified as prognostic factors in our research. Furthermore, high tumor location was associated with superior overall and cancer-specific survival, independent of pTNM stage, histological grade, LVI status, CCI, and CDC. Similar prognostic superiority of HRC concerning DFS provided more evidence that tumor location might influence survival outcome mainly through tumor recurrence, including the LR and DR,

Table 1 Baseline characteristics of mid/low and high rectal cancer in the unmatched and matched data

Variable	Unmatched ($n = 613$)		p value	Matched($n = 374$)		p value
	Mid/low RC $n = 414$ (67.5%)	High RC $n = 199$ (32.5%)		Mid/low RC $n = 187$ (50%)	High RC $n = 187$ (50%)	
Gender			1.000			1.000
Male	249 (60.1)	119 (59.8)		112 (59.9)	112 (59.9)	
Female	165 (39.9)	80 (40.2)		75 (40.1)	75 (40.1)	
Age (year)	56.5 ± 11.6	58 ± 11.6	0.131	59.6 ± 12.2	60.7 ± 12.2	0.329
BMI (kg/m^2)	22.2 ± 2.9	22.6 ± 3.2	0.388	22.3 ± 3.1	22.5 ± 3.2	0.552
ALB (g/L)	41.0 ± 4.3	39.7 ± 4.9	0.036	40.1 ± 4.8	40.0 ± 4.8	0.910
CEA			0.855			0.193
≤ 5.0 μg/L	278 (67.1.)	132 (66.3)		115 (61.5)	128 (68.4)	
> 5.0 μg/L	136 (32.9)	67 (33.7)		72 (38.5)	59 (31.6)	
Follow-up (month)	53.1 ± 24.3	52.5 ± 20.9	0.709	49.7 ± 23.8	52.5 ± 22.5	0.231
Smoking history			0.425			1.000
Yes	98 (23.7)	53 (26.6)		48 (25.7)	47 (25.1)	
No	316 (76.3)	146 (73.4)		139 (74.3)	140 (74.9)	
Preoperative obstruction			0.023			1.000
Yes	8 (1.9)	11 (5.5)		4 (2.1)	5 (2.7)	
No	406 (98.1)	188 (94.5)		183 (97.9)	182 (97.3)	
CCI			1.000			0.887
≤ 4	353 (85.3)	170 (85.4)		157 (84.0)	159 (85.0)	
>4	61 (14.7)	29(14.6)		30 (16.0)	28 (15.0)	
pTNM stage (AJCC 7th ed.)			0.827			0.943
I	118 (28.5)	47 (23.6)		47 (25.1)	47 (25.1)	
II	116 (28.0)	76 (38.2)		68 (36.4)	69 (36.9)	
III	180 (43.5)	76 (38.2)		72 (38.5)	71 (38.0)	
T stage			0.006			0.929
T1	25 (6.0)	11 (5.5)		10 (5.3)	11 (5.9)	
T2	124 (30.0)	43 (21.6)		46 (24.6)	43 (23.0)	
T3	165 (39.9)	76 (38.2)		70 (37.4)	72 (38.5)	
T4	100 (24.2)	69 (34.7)		61 (32.6)	61 (32.6)	
N stage			< 0.001			0.748
N0	237 (57.2)	126 (63.3)		116 (62.0)	119 (63.6)	
N1	124 (30.0)	54 (27.1)		52 (27.8)	50 (26.7)	
N2	53 (12.8)	19 (9.5)		19 (10.2)	18 (9.6)	
Nodes retrieved			0.427			0.457
< 12	167 (40.3)	73 (36.7)		76 (40.6)	68 (36.4)	
≥ 12	247 (59.7)	126 (63.3)		111 (59.4)	119 (63.6)	
Grade			0.055			1.000
Low	360 (87.0)	184 (92.5)		173 (92.5)	172 (92.0)	
Advanced	54 (13.0)	15 (7.5)		14 (7.5)	15 (8.0)	
LVI			0.670			0.799
Positive	19 (4.6)	7 (3.5)		9 (4.8)	7 (3.7)	
Negative	395 (95.4)	192 (96.5)		178 (95.2)	180 (96.3)	
Surgical technique			0.147			0.916
Laparoscopic	128 (30.9)	77 (38.7)		71 (38.0)	69 (36.9)	
Open	274 (66.2)	118 (59.3)		113 (60.4)	114 (61.0)	
Conversion	12 (2.9)	4 (2.0)		3 (1.6)	4 (2.1)	
Mesorectal excision			< 0.001			< 0.001

Table 1 (continued)

Variable	Unmatched ($n = 613$)		p value	Matched($n = 374$)		p value
	Mid/low RC $n = 414$ (67.5%)	High RC $n = 199$ (32.5%)		Mid/low RC $n = 187$ (50%)	High RC $n = 187$ (50%)	
PME	61 (14.7)	129 (64.8)		23 (12.3)	119 (63.6)	
TME	353 (85.3)	70 (35.2)		164 (87.7)	68 (36.4)	
Surgical procedure			< 0.001			< 0.001
APR	89 (21.5)	1 (0.5)		45 (24.1)	1 (0.5)	
LAR	321 (77.5)	195 (98.0)		141 (75.4)	184 (98.4)	
Hartmann	4 (1.0)	3 (1.5)		1 (0.5)	2 (1.1)	
CDC			0.251			0.511
I–III	395 (95.4)	185 (93.0)		178 (95.2)	174 (93.0)	
≥ IV	19 (4.6)	14 (7.0)		9 (4.8)	13 (7.0)	
Adjuvant therapy			0.258			0.916
Yes	185 (44.7)	79 (39.7)		75 (40.1)	73 (39.0)	
No	229 (55.3)	120 (60.3)		112 (59.9)	114 (61.0)	

Data presented by frequency (n) and percentages (%) for categorical covariates, and mean ± SD for continuous covariates, unless indicated otherwise
SD, standard deviation

especially in the lung and primary surgical site (Tables 2 and 3), which was proved by Chiang JM, et al.[9] These findings suggest that, compared with their mid/low counterparts, stage III HRC may be oncologically less aggressive.

Several reasons may support the assumption. First, in contrast with the almost extra-peritoneal mid/low rectum, the upper rectum is covered by the peritoneum anteriorly and laterally, thus leaving a natural barrier to block tumor from invading surrounding organs or structures, just like the colon cancer, and many scholars held this opinion.[7,8,10] However, it was surprising that the high group had more cases with pT4 stage than the mid/low group in these studies, as seen in Table 1 before PSM (34.7 vs. 24.2%, $p = 0.006$). This may partly be explained by possible delays in the diagnosis of upper rectal cancer, which tended to be more asymptomatic because of the distal location from the anus. Second, the lymphatic drainage of the high rectum proceeds mostly along the superior rectal artery to the inferior mesenteric vessels, leading to a typical upward spread of cancers and better local control, similar to colon carcinomas, whereas the mid/low rectum may

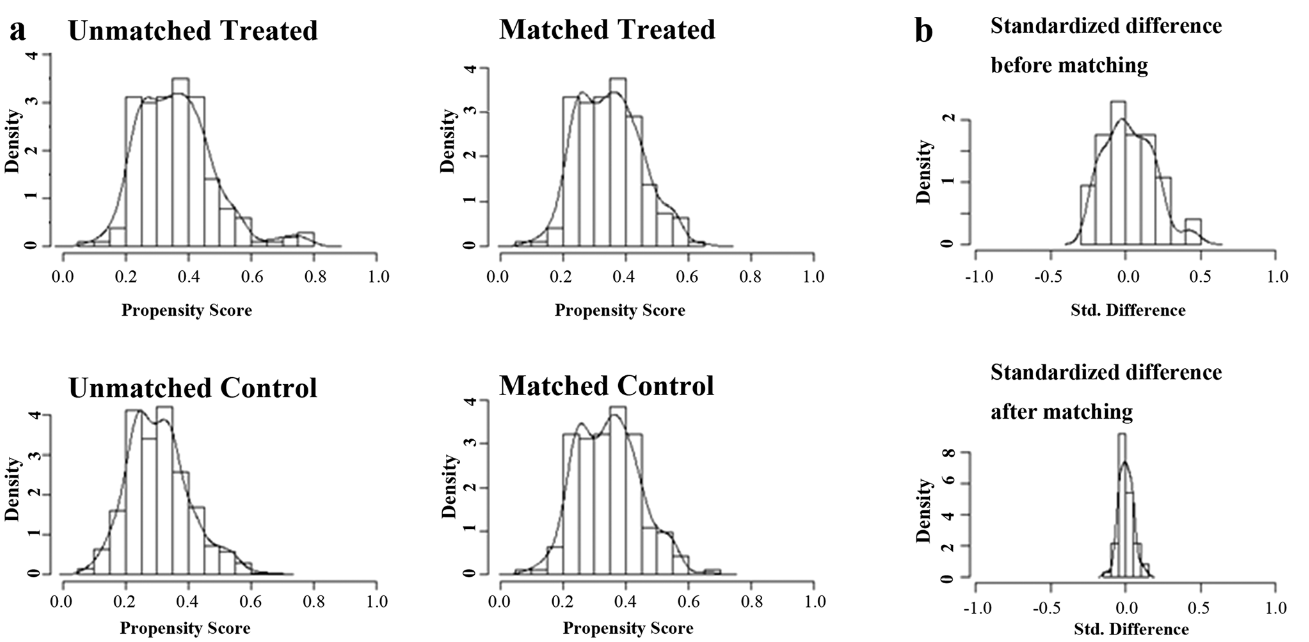

Fig. 2 Overall balance of six variables in the PS model, indicating the matching procedure is successful. **a** Histograms of the unmatched and matched groups. **b** Standardized difference of PS before and after matching

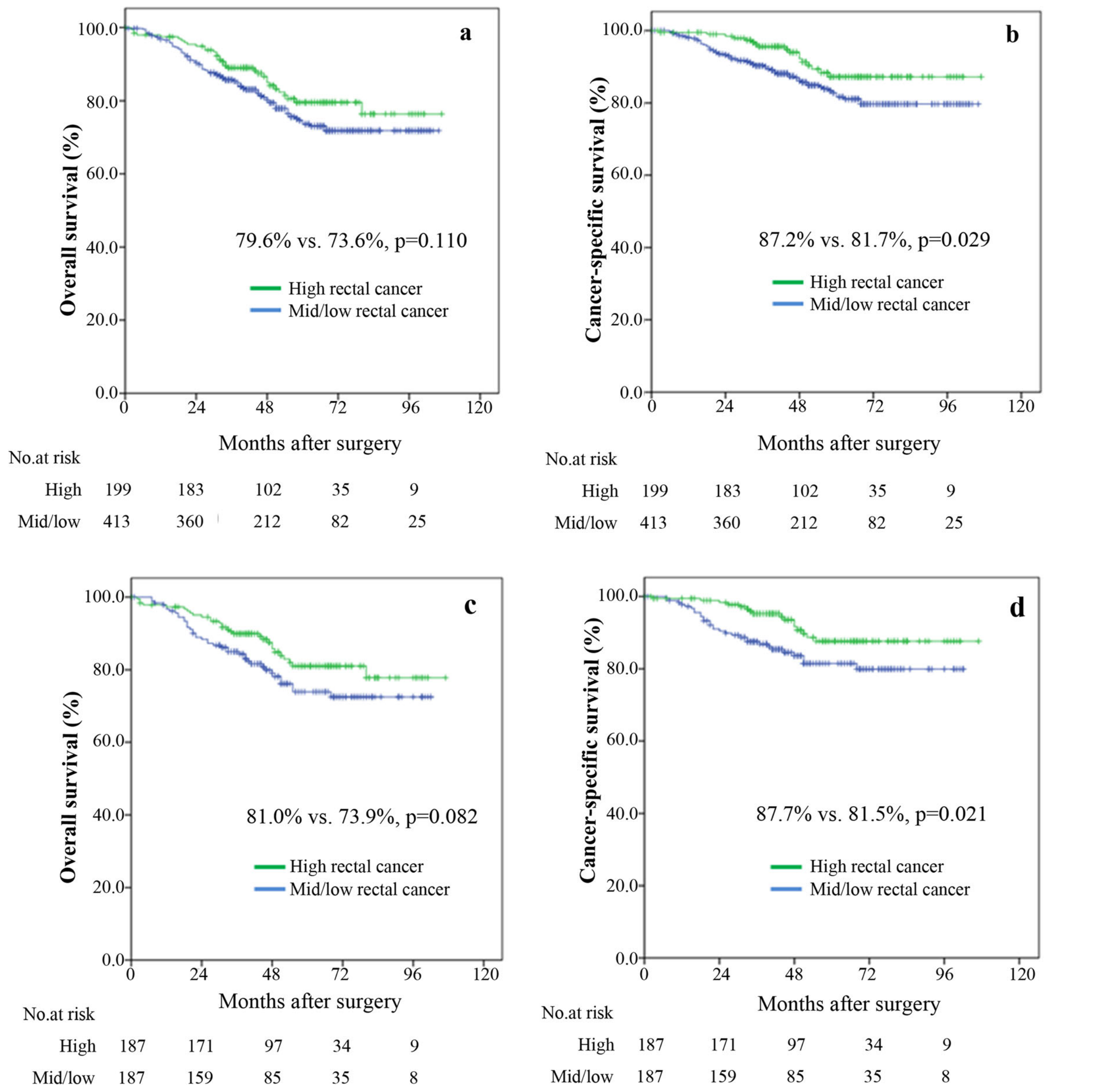

Fig. 3 Kaplan-Meier curves for OS and CSS of high and mid/low rectal cancer. **a** and **b** depict the OS and CSS in the unmatched cohort, while **c** and **d** depict the OS and CSS in the matched cohort. The 5-year survival rate and the number of rectal cancer patients at risk are given in each plot

additionally drain laterally through the internal iliac system to the lateral pelvic sidewall, and such nodes are the major cause of LR.[18, 19] The distinct lymphatic drainage may explain why OS and CSS only favored the high group rather than the mid/low group in stage III disease, what is more, lymphatic metastasis was relatively infrequent for HRC, just as showed in Table 1. Third, HRC was better differentiated compared to mid/low RC with low histological grade of 92.5 vs. 87.0% ($p = 0.055$), respectively. It is widely acknowledged that poor differentiation serves a predictive factor of inferior prognosis

Table 2 Five-year cumulative incidence of different recurrence patterns between high and mid/low groups in the matched cohort

High vs. mid/low	DFS	LR	DR
Overall	85.3 vs. 77.7%, $p = 0.146$	4.6 vs. 10.3%, $p = 0.265$	11.1 vs. 15.1%, $p = 0.212$
Stage I	95.6 vs. 95.2%, $p = 0.986$	0.0 vs. 2.7%, $p = 0.324$	4.4 vs. 4.8%, $p = 0.986$
Stage II	86.9 vs. 87.7%, $p = 0.871$	5.8 vs. 6.3%, $p = 0.756$	7.7 vs. 7.9%, $p = 0.669$
Stage III	75.9 vs. 54.2%, $p = 0.043$	6.7 vs. 22.7%, $p = 0.129$	20.2 vs. 30.8%, $p = 0.173$

DFS, disease-free survival; LR, local recurrence; DR, distant recurrence

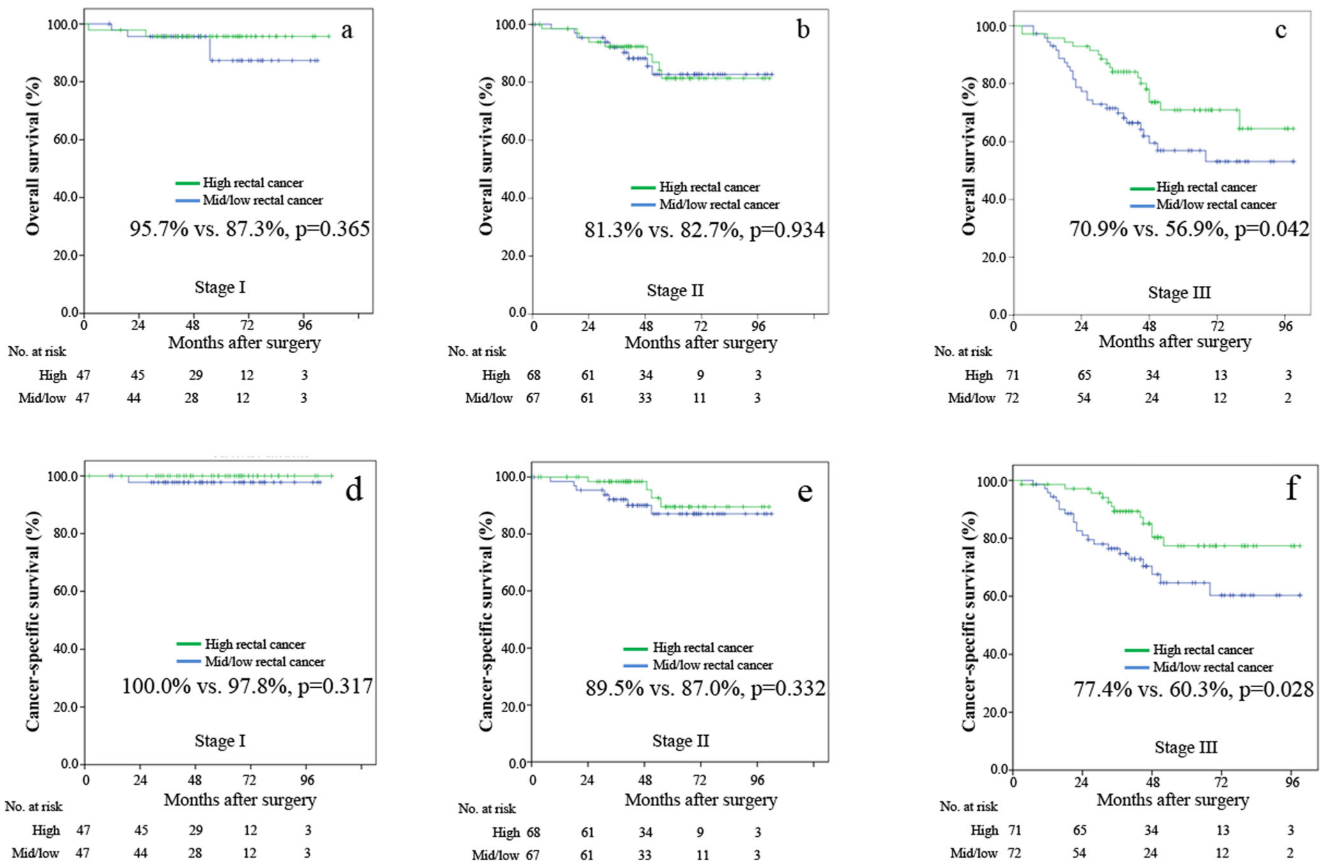

Fig. 4 Kaplan–Meier curves for OS and CSS of mid/low and high rectal cancer in the matched cohort. Panels **a**, **b**, and **c** depict OS with stages I–III, respectively. Panels **d**, **e**, and **f** depict the CSS with stages I–III, respectively. The 5-year survival rate and the number of rectal cancer patients at risk are given in each plot

though not included as an independent prognostic factor in our study.[6] A similar distribution of tumor differentiation between groups was reported by other researchers.[10] Finally, of course, there were operating factors, as surgical procedures of high rectal cancer were commonly less destructive concerning mesorectal excision and anastomosis. Table 1 shows that the high group received less APR compared to mid/low group (0.5 vs. 21.5%, $p < 0.001$), which was correlated with long-term autonomic dysfunction and inferior survival justified as seen in a meta-analysis.[20]

As illustrated above, there were considerable pathological distinctions between the two groups. It is thought-provoking whether there is a genetic or epigenetic effect beneath these findings. Colorectal cancer is a heterogeneous disease, as the CRC Subtyping Consortium stated, and has been coalesced into four consensus molecular subtypes (CMS), i.e., CMS1 (MSI immune), CMS2 (canonical), CMS3 (metabolic), and CMS4 (mesenchymal), in which CMS1 primary cancer displayed superior prognosis while CMS4 displayed the worst survival.[21] Though this system is not yet clinically

Table 3 The first recurrent pattern of patients with stage III disease in the matched cohort ($n = 139$)

Recurrent pattern	Mid/low group ($n = 71$)	High group ($n = 68$)	p value
Local	5.9% (4)	12.7% (9)	0.169
$^{\psi}$Distant	16.2% (11)	23.9% (17)	0.254
Liver	7.4% (5)	7.0% (5)	1.000
Lung	5.9% (4)	15.5% (11)	0.068
Bone	0.0% (0)	1.4% (1)	1.000
Adrenal	1.5% (1)	1.4% (1)	1.000
Other	2.9% (2)	5.6% (4)	0.681

$^{\psi}$ Five cases had two or more distant organs involved in this recurrent pattern, with 4 cases and 1 case for mid/low group and high group, respectively

Table 4 Prognostic factors for overall survival in the matched data ($n = 374$)

Variable		Univariate analysis		ψMultivariate analysis	
		HR (95%CI)	*p* value	HR (95%CI)	*p* value
Tumor location	Mid/low	0.658 (0.409–1.059)	0.085	0.613 (0.379–0.991)	0.046
	High				
CCI	≤ 4	–	0.011	–	0.005
	> 4	2.028 (1.173–3.504)		2.186 (1.259–3.796)	
Smoking history	No	–	0.095	–	0.094
	Yes	1.529 (0.928–2.519)		1.548 (0.929–1.076)	
Preoperative obstruction	No	–	0.014	–	0.436
	Yes	3.532 (1.285–9.708)		1.545 (0.518–4.609)	
CEA	≤ 5.0 μg/L	–	0.013	–	0.036
	> 5.0 μg/L	1.816 (1.136–2.905)		1.678 (1.035–2.719)	
TNM stage (AJCC 7th ed.)	I	–	< 0.001	–	< 0.001
	II	2.303 (0.914–5.804)	0.077	1.196 (0.769–4.994)	0.158
	III	6.124 (2.613–14.353)	< 0.001	5.257 (2.206–12.527)	< 0.001
Grade	Low	–	0.001	–	0.507
	Advanced	2.866 (1.537–5.342)		1.279 (0.618–2.647)	
LVI	Negative	–	< 0.001	–	< 0.001
	Positive	4.719 (2.338–9.522)		4.236 (2.043–8.781)	
CDC	I-III	–	0.078	–	0.007
	≥IV	2.018 (0.924–4.409)		3.038 (1.353–6.820)	

ψ Factors with *p* value < 0.1 in the univariate analysis were included in the multivariate regression model

Table 5 Prognostic factors for cancer-specific survival in the matched data ($n = 374$)

Variable		Univariate analysis		ψMultivariate analysis	
		HR (95%CI)	*p* value	HR (95%CI)	*p* value
Tumor location	Mid/low	–	0.024	–	0.007
	high	0.498 (0.272–0.914)		0.422(0.226–0.786)	
CCI	≤ 4	–	0.440	Not included	–
	> 4	1.351 (0.630–2.897)			
Smoking history	No	–	0.189	Not included	–
	Yes	1.512 (0.816–2.802)			
Preoperative obstruction	No	–	0.019	–	0.385
	Yes	4.064 (1.258–13.125)		1.724 (0.504–5.894)	
CEA	≤ 5.0 μg/L	–	0.003	–	0.010
	> 5.0 μg/L	2.411 (1.350–4.308)		2.186 (1.206–3.965)	
TNM stage (AJCC 7th ed.)	I	–	< 0.001	–	< 0.001
	II	8.444 (1.090–65.416)	0.041	6.486 (0.828–50.792)	0.075
	III	27.292(3.734–199.478)	0.001	22.857 (3.083–169.460)	0.002
Grade	Low	–	0.006	–	0.680
	Advanced	2.936(1.367–6.303)		1.200 (0.504–2.858)	
LVI	Negative	–	< 0.001	–	< 0.001
	Positive	5.686 (2.539–12.731)		4.822 (2.083–11.164)	
CDC	I–III	–	0.094	–	0.003
	≥ IV	2.212(0.873–5.601)		4.384 (1.630–11.785)	

ψ Factors with *p* value < 0.1 in the univariate analysis were included in the multivariate regression model implemented, microsatellite instability (MSI) type, namely CMS1, has been well proved a superior factor for predicting better prognosis and response to the immunotherapy in rectal cancer.[22,23] To date, unfortunately, little is known about the possible variation of MSI status or other molecular types within the rectal cancers of different locations.[7,11,24–26]

Our study is of note because it may potentially help to make an optimal strategy to manage HRC. The NCCN guideline recommended that lesions in the upper rectum be treated with TME to facilitate adequate lymphadenectomy and achieve negative circumferential margins. In addition, neoadjuvant therapy is advocated for stage II (T3–4, a node-negative disease with tumor penetration through the muscle wall) or III (node-positive disease without distant metastasis) rectal cancer, regardless of tumor location.[6] In contrast, the ESMO guideline suggests risk stratification strategies on this issue: high or middle rectal cancers characterized as cT3a/b, N0 (or also cN1 if high), with clear mesorectal fascia, and no extramural vascular invasion were categorized as an early disease. In these patients, neoadjuvant therapy may be avoided, and PME is a possible alternative in HRC.[5] The favorable prognosis of stage III HRC over MLRC in our research might provide circumstantial evidence in favor of the ESMO guideline.

To our knowledge, this was the first PS-matched analysis that investigated the prognostic impact of tumor location in non-metastatic rectal cancer patients. Additionally, we had the unique opportunity to evaluate the relatively natural survival of the patients without nCRT, as our institution did not adopt neoadjuvant therapy until 2015, later than the widespread adoption of these modalities in western countries. Furthermore, unlike other studies, we took preoperative comorbidity and postoperative complication into consideration and measured them by two scales, i.e., CCI and CDC, which were overlooked by other researchers.[1,7–10] Unsurprisingly, it was shown that comorbidity mainly affected non-oncological outcomes, as previously demonstrated.[27] Meanwhile, higher CDC had a negative effect on oncological and overall survival, indicating that there might be an interaction between severe complication and relapse of carcinomas.[28] These results suggest the importance of close follow-up of patients with diminished physical function and severe postoperative complications.

There are limitations in our study. First of all, this is a single-institution study with a relatively small sample size, rendering some important factors such as circumferential resection margin and PNI too rare for appropriate analysis. Then, as in all retrospective studies, there may be selection bias among the patients included. Hence, we attempted to reduce the bias using PSM, which, however, cannot balance all potential confounders and may introduce new selection bias due to poor PSM procedure. In addition, the study population includes patients treated about 10 years ago and may not fully reflect the current medical practice. Finally, genetic information is not available in our research, hence, the heterogeneity of genetics/epigenetics and even molecular subtypes within rectal cancer remains to be determined, just as lively debated in right-sided and left-sided colon cancer.[29,30]

Conclusion

This study provides evidence that patients with high rectal adenocarcinoma demonstrate better survival than those with mid/low rectal adenocarcinoma in stage III disease. Further studies about the special mechanisms of anatomical location in the biological behavior of tumors are needed, which may facilitate the patient-tailored treatment of rectal cancer.

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Compliance with Ethical Standards

Ethical Standards An ethical subcommittee of the First Affiliated Hospital of Sun Yat-sen University approved this retrospective study. Written consent was obtained from the patients for their information to be stored in the hospital database and used for research.

Conflict of Interest The authors declare that they have no competing interests.

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