Classification of rectal cancer according to recurrence types - Comparison of Japanese guidelines and Western guidelines-

Hiroshi Miyakita (mykt0124@tokai-u.jp)
Tokai University school of medicine

Research Article

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Abstract

Objectives

Local recurrence (LR) and lung metastasis are more common in rectal cancer than in colon cancer. However, the diagnosis of rectal cancer is not standardized as there is no global consensus on its definition and classification. The classification of rectal cancer differs between Japanese and Western guidelines. Thus, we aimed to elucidate how rectal cancer is classified by investigating the relationship between rectal cancer localization and recurrence in the patients

Methods

A total of 958 patients with cStage II and III colorectal cancer were included in the analysis: 323 with right-sided colon cancer (RC), 284 with left-sided colon cancer (LC), and 351 with rectal cancer. Localization of rectal cancers was assessed by enema examination and rigid endoscopy.

Results

There were no significant differences between rectal Rs, RC and LC in rates of liver and lung metastasis or LR . Lung metastasis or LR were significantly more common among Rab rectal cancers (in Japan) than among right-sided and left-sided colon cancers (p=0.0043, p=0.0002). Lung metastases and LR occurred at significantly higher rates in rectal cancers measuring ≤12 cm and ≤10 cm than in colon cancers (p=0.0117, p=0.0467, p=0.0036, p=0.0010 respectively). Finally, the liver and lung metastases and LR rates of rectal cancers measuring 11 to 15 cm were 6.9%, 2.8%, and 5.7%, respectively. This indicated Equivalent to colon cancer .

Conclusions

The upper rectum may have the same treatment strategies as the colon cancer. There was no difference in the classification of colorectal cancer between Japan and western countries

Introduction

Colorectal cancer is the third major cause of death in the United States and has the third highest rate of new cases [1]. Similar numbers can be observed in Japan, where it is the third major cause of mortality and the highest cause of morbidity among the cancers in Japan [2]. Rectal cancer has significantly higher rates of local recurrence, owing to to its anatomical characteristics, than colon cancer. However, the diagnostic criteria for rectal cancer have not been globally standardized. In Japan, the rectum is classified into Rs, Ra, and Rb, and the localization of the bulk of the tumor is determined by enema examination [3]. According to guidelines in Western countries, such as the National Comprehensive Cancer Network (NCCN) and the American Joint Committee on Cancer (AJCC), rectal cancers are defined as lesions within ≤ 12 cm of the anal verge assessed by rigid endoscopy [4, 5]. According to the European Society for Medical Oncology (ESMO), lesions ranging from 0 to 5 cm of the anal verge are defined as low rectal cancer, and those ranging from 5 to 10 cm of the anal verge are defined as mid-rectal cancer [6]; indeed, none of the definitions are standardized.

In Europe, according to ESMO guidelines, the standard therapy for patients with rectal cancer classified as mid or low is total mesorectal excision (TME) after surgical treatment [6]. Cancers located more orally to this

location are generally treated as colon cancer. Following the NCCN guidelines, in North America, patients with rectal cancer of ≤ 12 cm from the anal verge undergo surgical treatment, followed by TME surgery [4, 5]. In Japan, the standard therapy for rectal cancers located orally to Ra cancers is TME monotherapy. Moreover, rectal cancers located more anally than Rb cancers are treated by TME surgery and lateral lymph node dissection (LLND) [7, 8]. This presents a further lack of standardization in the treatment of rectal cancers.

Abdelsattar et al. have noted the inconsistencies in the guidelines for rectal cancer diagnosis and treatment [9]. Although similar comparisons of guidelines for colorectal cancer have been made, consensus on the topic has yet to be reached [10].

Although 80% of Ra and Rb rectal cancers are reported to correspond to mid and low rectal cancer, respectively, it is also noted that the diagnosis of Ra and Rb is not necessarily compatible with those of mid rectum and low rectal cancer [11].

Furthermore, it is possible that tumors diagnosed as Rs in Japan may also include tumors that correspond to cancers of the mid rectum.

This study thus aimed to elucidate how rectal cancer is managed by investigating the relationship between rectal cancer localization of patients treated with radical resection at our facility using the various guidelines and their recurrence type; and subsequently comparing them to colon cancer.

Methods

This study was approved by the institutional review board of our university (20R-238), and all patients provided written informed consent.

Patients

A total of 958 patients with cStage II and III colorectal cancer who underwent radical surgery between January 2005 and December 2014 were included in the analysis. A total 323 of patients had right side colon (RC) cancer, 284 had left-sided colon (LC) cancer and 351 had rectal (R) cancer. A total of 217 patients with rectal cancer underwent preoperative chemoradiotherapy (CRT). The rectal cancer was treated surgically by TME monotherapy and none of the patients underwent LLND.

Classification

The segment to the splenic flexure (cecum, ascending colon, transverse colon) was classified as the RC, and the descending colon and sigmoid colon as the LC. Rectal cancers were classified into Rs, Ra, and Rb according to the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (JCCRC) [3]. Localization of rectal cancers was assessed by enema examination and rigid endoscopy. The types of recurrences were studied by comparing the rates of liver and lung metastasis as well as local recurrence. Local recurrence included intrapelvic recurrences.

Enema examination

Double-contrast barium enema [12, 13] was performed by radiologists in all patients in order to determine the rectal division in which the main part of the tumor was located in accordance with the JCCRC (second English

edition translated from the 7th Japanese edition of the general rules) [3]. Tumors that involved two divisions, such as “Rb-Ra,” were assigned to the major division, i.e., the one in which the bulk of the tumor was located. The tumor size was measured as the vertical extension in the lateral view of the barium enema. The location of the tumor in the bowel wall was described as involving the anterior, lateral, and posterior quadrants.

Statistical analysis

Fisher’s exact test or χ^2 test were used to analyze categorical variables, and the Mann-Whitney U test or the Kruskal-Wallis test and Wilcoxon signed rank sum test were used for continuous variables. In all analyses, $p < 0.05$ was considered statistically significant. The software package JMP10 (SAS Institute Inc., NC, USA) was used for statistical analysis.

Results

Patients’ Characteristics (Table 1)

Of the 958 patients, 580 were men and 378 were women, with a median age of 68 years. Of these, 323 had RC, 284 had LC, 351 were rectal cancer patients, and 281 underwent CRT. Overall, 482 patients were at stage II and 379 were at stage III; 38 were at ypStage 0 and 59 were at ypStageI. These were patients with rectal cancer who underwent CRT and for whom down staging was achieved.

Distance to the lower border of the tumor according to localization by rigid endoscopy and enema examination (Table 2)

Rigid endoscopy was performed on 104 of the 351 patients with rectal cancer, and enema examination was performed on all patients, the results are displayed in Table 2. The mean (SD) distance for Rs, Ra, and Rb on rigid endoscopy and enema examination were 10.3, 7.7, 3.5, 12.3, 7.2, and 3.2 cm respectively. There was almost no difference between the distances measured by rigid endoscopy and enema examination for Ra and Rb tumors, but there was a 2 cm difference for rectal cancers in the Rs segment.

Table 2 presents the distances from the anal verge to the lower border of the tumor in various segments measured by enema examination. The tumor was located ≥ 11 cm of the anal verge in 77 patients (73.2%) of Rs cancer, and ≤ 10 cm of the anal verge in 28 (26.6%) patients. For Ra and Rb cancers, tumors were located ≤ 10 cm of the anal verge in 84 (93.2%) and 156 (100%) patients, respectively.

Tumor localization and recurrence type

Recurrence types were classified according to RC, LC, and rectal cancers. Rectal cancers were distinguished by CRT administration as it is associated with the local recurrence rate, and classified according to JCCRC, NCCN, AJCC, and ESMO guidelines. Since local recurrence is affected markedly by CRT, it was compared to patients who did not undergo CRT.

The rates of RC and LC with liver metastasis, lung metastasis and local recurrence were 11.4%, 5.8%, and 2.4%, for RC, respectively; and 14.0%, 4.9%, and 4.5%, for LC, respectively. The rates of liver and lung metastasis in

patients with rectal cancer who underwent CRT were 8.7% and 10.1%, respectively. The rate of local recurrence was 5.5% among patients who underwent CRT and 8.2% in patients who were treated with surgery alone.

Recurrence pattern according to JCCRC guidelines (Table 3)

The rates of liver metastasis, lung metastasis and local recurrence in Rs cancers according to the JCCRC guidelines were 7.5%, 4.7%, and 5.7%, respectively. Ra and Rb cancers, including patients who underwent CRT, had liver metastasis, lung metastasis, and local recurrence rates of 9.3%, 10.5%, and 6.9%, respectively. The rate of local recurrence was 17.2% among patients who underwent surgery alone and 5.5% among patients who also underwent CRT. There were no significant differences between the rates of liver and lung metastasis and local recurrence between Rs cancer, RC and LC colon cancer ($p = 0.1491$, $p = 0.7737$, $p = 0.2657$).

Compared to RC and LC colon cancers, Rab rectal cancer patients had significantly higher rates of lung metastasis ($p = 0.0043$). Rab cancer treated by surgery alone had significantly higher rates of local recurrence compared to RC and LC colon cancer ($p = 0.0002$).

Recurrence pattern according to NCCN and AJCC guidelines (Table 4)

According to NCCN and AJCC guidelines, rectal cancers located ≤ 12 cm of the anal verge showed rates of liver and lung metastasis of 8.3% and 10.7%, respectively. The rates of lung metastasis were significantly higher in rectal cancers at ≤ 12 cm of the anal verge compared to colon cancers ($p = 0.0631$, $p = 0.0117$). The rate of local recurrence was 8.5% in rectal cancer located at ≤ 12 cm of the anal verge, which were treated with surgical monotherapy. Therefore, the local recurrence rate was significantly higher than in colorectal cancers located orally less than 12 cm of the anal verge ($p = 0.0467$).

Recurrence pattern according to ESMO guidelines (Table 5)

According to ESMO guidelines, tumors that are ≤ 15 cm of the anal verge are classified as rectal cancer. Mid or low rectal cancers are treated surgically, whereas lesions located more orally than ≥ 10 cm of the anal verge are generally administered the same treatment as colon cancer. Consequently, comparisons were made based on rectal cancers located ≤ 10 cm of the anal verge. The rates of liver and lung metastasis of rectal cancers located ≤ 10 cm of the anal verge were 8.9% and 10.4%, respectively. Rectal cancers located ≤ 10 cm of the anal verge had significantly higher rates of lung metastasis than colon cancer ($p = 0.1752$, $p = 0.0036$). The rate of local recurrence in rectal cancers located ≤ 10 cm of the anal verge and treated by surgical monotherapy was 13.2%. This was significantly higher than the rate of colorectal cancers located more than 10 cm orally of the anal verge. ($p = 0.0010$)

The rates of liver metastasis, lung metastasis, and local recurrence in rectal cancers located 11 to 15 cm of the anal verge were 6.9%, 2.8%, and 5.7%, respectively. This indicated no significant associations with recurrence rates of RC and LC cancers ($p = 0.1714$, $p = 0.3357$, $p = 0.3400$).

Discussion

Lung metastases and local recurrences were more common in rectal cancer than in colon cancer, and TME is performed for rectal cancer as a common operative method to reduce local recurrence [14–16]. Furthermore,

although therapeutic strategies for colon cancer are standardized worldwide, those for rectal cancer vary from nCRT and LLND to post-CRT watch and wait. Among these treatments, the indications for nCRT are notably different between classification systems, whereas the NCCN and AJCC guidelines recommend this procedure for advanced rectal cancer located ≤ 12 cm of the anal verge; the ESMO guidelines recommend it for advanced rectal cancer ≤ 10 cm of the anal verge; whereas the JCCR guidelines only make a weak recommendation in cancers that are T3 or deeper, or are cN + with a high risk of local recurrence. Additionally, the localization of the lesion for this recommendation is not specified [3–6].

This study compared the recurrence types of rectal cancer diagnosis according to various diagnostic criteria.

Approximately 26.6% of the tumors diagnosed as Rs are located between 6 and 10 cm of the anal verge. They likely include more mid and lower rectal cancers that should be indications for nCRT, rather than tumors classified according to other guidelines. However, according to our current findings, the local recurrence rates of Rs cancers (i.e., tumors located more orally than 12 cm from the anal verge) and rectal cancers considered “high rectum” cancers (i.e., those located more orally than 10 cm from the anal verge) after surgical monotherapy were 5.7%, 8.3% and 5.7%, respectively. These results were similar to the results of colon cancer. There was no significant difference in the recurrence types between Rs and colon cancers. In light of its characteristic recurrence types (i.e., local recurrence and lung metastasis), rectal cancer can be treated similarly to high rectal and colon cancers as presented by other guidelines. This suggests that the Japanese convention is as reliable as its western counterparts.

The local recurrence rates of rectal cancers (of which 97.5% are tumors located ≤ 10 cm of the anal verge) and tumors located ≤ 12 cm and ≤ 10 cm of the anal verge after surgical monotherapy were 17.2%, 8.3%, and 13.2%, respectively. These results were significantly higher compared to colon cancer ($p = 0.0002$, $p = 0.0467$, $p = 0.0010$). However, the local recurrence rate of rectal cancers dropped to 5.5% when CRT was added. This value is equivalent to the recurrence rate of colon cancer. Unlike other guidelines, the JCCRC criteria classify rectal cancers according to the location between the tumor and the sacrum and the peritoneal reflection [3]. A large proportion of Rb rectal cancers are defined as tumors located below the peritoneal reflection. Measurements performed in this study according to these guidelines showed that 84.6% of Rb cancers were located within 0 to 5 cm. However, Najarian et al. reported that the mean distance between the anal verge and the peritoneal reflection was 9.7 cm in men and 9.0 cm in women [17]. Although differences in the relationships between peritoneal reflection locations and RaRb cancers are possible, the findings of our investigation on recurrence types generally seemed to suggest that RaRb cancers had higher local recurrence rates according to the JCCRC guidelines compared to other guidelines. Additionally, the study found that this diagnosis should be considered valid for caution in rectal cancer. In terms of therapeutic modalities, the findings of this study showed that in Western countries, nCRT is administered for the majority of tumors below the peritoneal reflection, whereas in Japan, LLND is only performed for tumors diagnosed with Rb. This suggests that tumors diagnosed as Ra may include tumors for which LLND should be performed, assuming that CRT and LLND are treatments for local control.

In conclusion, on the basis of recurrence types, rectal cancers diagnosed as Rs according to the JCCRC guidelines can be treated as colon cancer in terms of therapeutic strategies, similar to other guidelines. Rectal cancers diagnosed as Ra and Rb generally correspond to rectal cancer as defined by the NCCN and AJCC guideline, and to mid rectum and lower rectal cancer, as defined by the ESMO guidelines. However, the

retrospective, single-center design is a limitation of this study and warrants further research of patients in a multi-center study for more detailed investigations.

Limitations

This study was limited because it was a retrospective study in a single institution. Prospective multi-institutional study is needed to confirm the strict treatment of rectal cancer.

Conclusions

Our findings suggest that rectal cancers classified as Rs under the JCCRC guidelines and rectal cancers classified as high rectal rectal cancer under ESMO guidelines can be treated in the same way as colon cancer. The recurrence types of various lesions that require treatment as rectal cancer under the various guidelines were generally consistent; no major differences were found between them.

Declarations

Conflict of interest

All authors have no conflict of interest to declare in association with this study.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Hiroshi Miyakita. The first draft of the manuscript was written by Hiroshi Miyakita and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table.1 Patients' Characteristics

Variable		n (%)
Sex	Male	579 (60)
	Female	379 (40)
Age	Range	22-93
	Median	68
Location of the tumor	RC	323 (33.7)
	LC	284 (29.6)
	R	351 (36.6)
Neoadjuvant CRT	Yes	217 (61.8)
	No	134 (38.2)
Histological type	wel-mod	868 (90.6)
	muc	37 (3.8)
	por or sig	21 (2.2)
	pCR	26 (2.7)
	unknown	6 (0.6)
T factor	0	37 (3.8)
	1	40 (4.2)
	2	83 (8.6)
	3	610 (63.6)
	4	188 (19.6)
N factor	positive	379 (39.5)
	negative	579 (60.4)
Lymphatic invasion	positive	655 (68.3)
	negative	302 (31.5)
	unknown	1 (0.1)
Venous invasion	positive	647 (67.5)
	negative	310 (32.3)
	unknown	1 (0.1)
Pathological Stage	0	38 (4)
	I	59 (6.1)
	II	482 (50.3)
	III	379 (39.5)

RC : Right sided colon

LC : Left sided colon

R : Rectum

CRT : Chemoradiotherapy

wel : well diffenciated Adenocarcionoma

mod : moderated diffenciated Adenocarcionoma

muc : mucinous Adenocarcionoma

por : poorly diffenciated Adenocarcionoma

sig : Signet cell Adenocarcionoma

pCR : Pathological complete response

Table. 2 Distance to the lower border of the tumor according to localization by rigid endoscopy and enema examination.

	Rigid endoscope			Enema examination		
	mean+/-SD	Range	n	mean+/-SD	Range	n
Rs	10.3+/-2.3	6-13.5	12 (11.8)	12.3+/-2.8	7-21	105 (29.9)
Ra	7.7+/-1.6	5-12	38 (37.6)	7.2+/-2.3	3-18	90
Rb	3.5+/-1.8	0-7	54 (53.4)	3.2+/-2.3	0-10	156

	0-5cm	6-10cm	11-15cm	15cm<	total
Rs	0	28(26.6)	66 (62.8)	11 (10.4)	105
Ra	17 (18.8)	67 (74.4)	5 (4.4)	1 (1.1)	90
Rb	132 (84.6)	24 (15.3)	0	0	156

Table.3 Reccurence pattern according to JCCRC guidelines

	Liver (%)			Lung (%)			Local (%)		
	metastasis	no	p-value	metastasis	no	p-value	metastasis	no	p-value
RC	37 (11.4)	286 (88.6)		19 (5.8)	304 (94.2)		8 (2.4)	315 (97.6)	
LC	40 (14.0)	244 (86)		14 (4.9)	270 (95.1)		13 (4.5)	271 (95.5)	
Rs	8 (7.5)	97 (92.5)	0.1491	5 (4.7)	100 (94.3)	0.7737	6 (5.7)	99 (94.3)	0.2657
Rab	23 (9.3)	223 (90.7)	0.3049	26 (10.5)	220 (89.5)	0.0043	5 (17.2)	24 (82.8)	0.0002
total		958			958			740	

Table.4 Recurrence pattern according to NCCN and AJCC guidelines

	Liver (%)			Lung (%)			Local (%)		
	metastasis	no	p-value	metastasis	no	p-value	metastasis	no	p-value
RC	37 (11.4)	286 (88.6)		19 (5.8)	304 (94.2)		8 (2.4)	315 (97.6)	
LC	40 (14.0)	244 (86)		14 (4.9)	270 (95.1)		13 (4.5)	271 (95.5)	
12cm<	6 (11.5)	46 (88.5)		2 (3.8)	50 (96.2)		4 (8.3)	48 (91.7)	
≦12cm	25 (8.3)	274 (91.4)	0.0631	29 (10.7)	270 (89.3)	0.0117	7 (8.5)	75 (91.5)	0.0467
total		958			958			740	

Table.5 Recurrence pattern according to ESMO guidelines

	Liver (%)			Lung (%)			Local (%)		
	metastasis	no	p-value	metastasis	no	p-value	metastasis	no	p-value
RC	37 (11.4)	286 (88.6)		19 (5.8)	304 (94.2)		8 (2.4)	315 (97.6)	
LC	40 (14.0)	244 (86)		14 (4.9)	270 (95.1)		13 (4.5)	271 (95.5)	
15cm<	2 (16.6)	10 (83.4)		1 (8.3)	11(91.7)		0 (0)	12 (100)	
11-15cm	5 (6.9)	66 (93.1)	0.1714	2 (2.8)	69 (97.2)	0.3357	4 (5.7)	65 (94.3)	0.3400
≦10cm	24 (8.9)	244 (91.1)	0.1752	28 (10.4)	240 (89.6)	0.0036	7(13.2)	46 (86.8)	0.0010
total		958			958			740	