

World Journal of *Clinical Cases*

World J Clin Cases 2022 December 26; 10(36): 13148-13469



MINIREVIEWS

- 13148** Liver injury in COVID-19: Holds ferritinophagy-mediated ferroptosis accountable
Jia FJ, Han J
- 13157** Amebic liver abscess by *Entamoeba histolytica*
Usuda D, Tsuge S, Sakurai R, Kawai K, Matsubara S, Tanaka R, Suzuki M, Takano H, Shimozawa S, Hotchi Y, Tokunaga S, Osugi I, Katou R, Ito S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Oba J, Nomura T, Sugita M
- 13167** Living with liver disease in the era of COVID-19-the impact of the epidemic and the threat to high-risk populations
Barve P, Choday P, Nguyen A, Ly T, Samreen I, Jhooty S, Umeh CA, Chaudhuri S
- 13179** Cortical bone trajectory screws in the treatment of lumbar degenerative disc disease in patients with osteoporosis
Guo S, Zhu K, Yan MJ, Li XH, Tan J
- 13189** Probiotics for preventing gestational diabetes in overweight or obese pregnant women: A review
Deng YF, Wu LP, Liu YP

ORIGINAL ARTICLE

Retrospective Cohort Study

- 13200** Effectiveness of microwave endometrial ablation combined with hysteroscopic transcervical resection in treating submucous uterine myomas
Kakinuma T, Kakinuma K, Shimizu A, Kaneko A, Kagimoto M, Okusa T, Suizu E, Saito K, Matsuda Y, Yanagida K, Takeshima N, Ohwada M
- 13208** Antibody and complement levels in patients with hypersplenism associated with cirrhotic portal hypertension and therapeutic principles
Zhang K, Zeng M, Li YJ, Wu HF, Wu JC, Zhang ZS, Zheng JF, Lv YF

Retrospective Study

- 13216** Case series in Indonesia: B.1.617.2 (delta) variant of SARS-CoV-2 infection after a second dose of vaccine
Karuniawati A, Syam AF, Achmadasyah A, Ibrahim F, Rosa Y, Sudarmono P, Fadilah F, Rasmin M
- 13227** Endobronchial ultrasound-guided transbronchial needle aspiration in intrathoracic lymphadenopathy with extrathoracic malignancy
Li SJ, Wu Q
- 13239** Analysis of the clinical efficacy of two-stage revision surgery in the treatment of periprosthetic joint infection in the knee: A retrospective study
Qiao YJ, Li F, Zhang LD, Yu XY, Zhang HQ, Yang WB, Song XY, Xu RL, Zhou SH

- 13250** Prognostic factors for disease-free survival in postoperative patients with hepatocellular carcinoma and construction of a nomogram model
Luo PQ, Ye ZH, Zhang LX, Song ED, Wei ZJ, Xu AM, Lu Z
- 13264** Oral higher dose prednisolone to prevent stenosis after endoscopic submucosal dissection for early esophageal cancer
Zhan SG, Wu BH, Li DF, Yao J, Xu ZL, Zhang DG, Shi RY, Tian YH, Wang LS
- 13274** Predictive value of the unplanned extubation risk assessment scale in hospitalized patients with tubes
Liu K, Liu Z, Li LQ, Zhang M, Deng XX, Zhu H
- 13284** Classification of rectal cancer according to recurrence types - comparison of Japanese guidelines and Western guidelines
Miyakita H, Kamei Y, Chan LF, Okada K, Kayano H, Yamamoto S
- 13293** Risk of critical limb ischemia in long-term uterine cancer survivors: A population-based study
Chen MC, Chang JJ, Chen MF, Wang TY, Huang CE, Lee KD, Chen CY
- 13304** Serum Spondin-2 expression, tumor invasion, and antitumor immune response in patients with cervical cancer
Zhang LL, Lin S, Zhang Y, Yao DM, Du X
- 13313** Thoracic para-aortic lymph node recurrence in patients with esophageal squamous cell carcinoma: A propensity score-matching analysis
Li XY, Huang LS, Yu SH, Xie D
- 13321** Anastomotic leakage in rectal cancer surgery: Retrospective analysis of risk factors
Brisinda G, Chiarello MM, Pepe G, Cariati M, Fico V, Mirco P, Bianchi V

META-ANALYSIS

- 13337** Successful outcomes of unilateral *vs* bilateral pedicle screw fixation for lumbar interbody fusion: A meta-analysis with evidence grading
Sun L, Tian AX, Ma JX, Ma XL

CASE REPORT

- 13349** Pregnancy-induced leukocytosis: A case report
Wang X, Zhang YY, Xu Y
- 13356** Acute moderate to severe ulcerative colitis treated by traditional Chinese medicine: A case report
Wu B
- 13364** Solitary hyoid plasmacytoma with unicentric Castleman disease: A case report and review of literature
Zhang YH, He YF, Yue H, Zhang YN, Shi L, Jin B, Dong P
- 13373** Recurrence of intratendinous ganglion due to incomplete excision of satellite lesion in the extensor digitorum brevis tendon: A case report
Park JJ, Seok HG, Yan H, Park CH

- 13381** Two methods of lung biopsy for histological confirmation of acute fibrinous and organizing pneumonia: A case report
Liu WJ, Zhou S, Li YX
- 13388** Application of 3D-printed prosthesis in revision surgery with large inflammatory pseudotumour and extensive bone defect: A case report
Wang HP, Wang MY, Lan YP, Tang ZD, Tao QF, Chen CY
- 13396** Undetected traumatic cardiac herniation like playing hide-and-seek-delayed incidental findings during surgical stabilization of flail chest: A case report
Yoon SY, Ye JB, Seok J
- 13402** Laparoscopic treatment of pyogenic liver abscess caused by fishbone puncture through the stomach wall and into the liver: A case report
Kadi A, Tuergan T, Abulaiti Y, Shalayiadang P, Tayier B, Abulizi A, Tuohuti M, Ahan A
- 13408** Hepatic sinusoidal obstruction syndrome induced by tacrolimus following liver transplantation: Three case reports
Jiang JY, Fu Y, Ou YJ, Zhang LD
- 13418** *Staphylococcus aureus* bacteremia and infective endocarditis in a patient with epidermolytic hyperkeratosis: A case report
Chen Y, Chen D, Liu H, Zhang CG, Song LL
- 13426** Compound heterozygous p.L483P and p.S310G mutations in GBA1 cause type 1 adult Gaucher disease: A case report
Wen XL, Wang YZ, Zhang XL, Tu JQ, Zhang ZJ, Liu XX, Lu HY, Hao GP, Wang XH, Yang LH, Zhang RJ
- 13435** Short-term prone positioning for severe acute respiratory distress syndrome after cardiopulmonary bypass: A case report and literature review
Yang JH, Wang S, Gan YX, Feng XY, Niu BL
- 13443** Congenital nephrogenic diabetes insipidus arginine vasopressin receptor 2 gene mutation at new site: A case report
Yang LL, Xu Y, Qiu JL, Zhao QY, Li MM, Shi H
- 13451** Development of dilated cardiomyopathy with a long latent period followed by viral fulminant myocarditis: A case report
Lee SD, Lee HJ, Kim HR, Kang MG, Kim K, Park JR
- 13458** Hoffa's fracture in a five-year-old child diagnosed and treated with the assistance of arthroscopy: A case report
Chen ZH, Wang HF, Wang HY, Li F, Bai XF, Ni JL, Shi ZB

LETTER TO THE EDITOR

- 13467** Precautions before starting tofacitinib in persons with rheumatoid arthritis
Swarnakar R, Yadav SL

ABOUT COVER

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Retrospective Study

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

Hiroshi Miyakita, Yutaro Kamei, Lin Fung Chan, Kazutake Okada, Hajime Kayano, Seiichiro Yamamoto

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Abstract

BACKGROUND

Rectal cancer is characterized by more local recurrence (LR) and lung metastasis than 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.

AIM

To clarify the characteristics of rectal cancer by comparing the tumor location and characteristics of rectal cancer with those of colon cancer according to each set of guidelines.

METHODS

A total of 958 patients with Stage II and III colorectal cancer were included in the analysis: 607 with colon cancer and 351 with rectal cancer. Localization of rectal cancers was assessed by enema examination and rigid endoscopy. According to Japan guidelines, rectal cancer is classified as Rb (below the peritoneal inversion), Ra (between the inferior margin of second sacral vertebrae and Rb) or RS (between Ra and sacral promontory).

RESULTS

There were no significant differences between RS rectal cancer and colon cancer in the rates of liver and lung metastasis or LR. Lung metastasis and LR were significantly more common among Rb rectal cancer (in Japan) than in colon cancer ($P = 0.0043$ and $P = 0.0002$, respectively). Lung metastases and LR occurred at significantly higher rates in rectal cancer measuring ≤ 12 cm and ≤ 10 cm than in colon cancers ($P = 0.0117$, $P = 0.0467$, $P = 0.0036$, $P = 0.0010$). Finally, the rates of liver metastasis, lung metastasis, and LR in rectal cancers measuring 11 cm to 15 cm were 6.9%, 2.8%, and 5.7%, respectively. These were equivalent to the rates in colon cancer.

CONCLUSION

High rectal cancer may be treated with the same treatment strategies as colon cancer. There was no difference in the classification of colorectal cancer between Japan and Western countries.

Key Words: Colon cancer; Metastasis; Local recurrence; Classification of rectal cancer; Western guidelines; Japanese guideline

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Core Tip: Local recurrence 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. High rectal cancer may be treated with the same treatment strategies as colon cancer. There was no difference in the classification of colorectal cancer between Japan and Western countries.

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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 are observed in Japan, where colorectal cancer is the third major cause of mortality and the highest cause of morbidity among cancers[2]. Due to its anatomical characteristics, rectal cancer has significantly higher rates of local recurrence (LR) than colon cancer. However, the diagnostic criteria for rectal cancer have not been globally standardized. In Japan, rectal cancer is classified into Rb (below the peritoneal inversion), Ra (between the inferior margin of second sacral vertebrae and Rb) and RS (between Ra and sacral promontory) categories, 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 American Joint Committee on Cancer (AJCC) guidelines, rectal cancers are defined as lesions within ≤ 12 cm of the anal verge and are assessed by rigid endoscopy[4,5]. According to the European Society for Medical Oncology (ESMO), lesions from 0 cm to 5 cm of the anal verge are defined as low rectal cancer, and those from 5 cm to 10 cm of the anal verge are defined as mid-rectal cancer; indeed, none of the definitions are standardized[6].

In Europe, according to the ESMO guidelines, the standard therapy for patients with mid- or low rectal cancer is total mesorectal excision (TME) after chemoradiotherapy[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 ≤ 12 cm from the anal verge undergo chemoradiotherapy 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 cancer. Abdelsattar *et al*[9] noted inconsistencies in the guidelines for rectal cancer diagnosis and treatment. Although similar comparisons of guidelines for colorectal cancer have been made, a 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, the diagnoses of Ra and Rb rectal cancers are not necessarily compatible with those of mid-rectal and low rectal cancer, respectively[11]. Furthermore, tumors diagnosed as RS rectal cancer 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 in patients treated with radical resection at our facility using the various guidelines and their recurrence type and by subsequently comparing them with patients with colon cancer.

MATERIALS AND METHODS

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

Patients

A total of 958 patients with Stage II and III colorectal cancer who underwent radical surgery between January 2005 and December 2014 were included in the analysis. A total of 607 patients that had colon cancer and 351 patients that had rectal cancer. A total of 217 patients with rectal cancer underwent preoperative chemoradiotherapy (CRT). Rectal cancer was treated surgically by TME monotherapy and none of the patients underwent LLND.

Classification

The segments of the colon including the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon can all be involved in colon cancer. Rectal cancer was classified into RS, Ra, and Rb categories according to the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (JCCRC)[3]. The localization of rectal cancer was assessed by enema examination and rigid endoscopy. The type of recurrence was evaluated by comparing the rates of liver and lung metastasis as well as LR. LR included intrapelvic recurrences.

Enema examination

A double-contrast barium enema was performed by radiologists in all patients to determine the rectal division in which the main part of the tumor was located in accordance with the JCCRC guidelines (second English edition translated from the 7th Japanese edition of the general rules)[3,12,13]. 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 on the lateral view of the barium enema. The location of the tumor in the bowel wall was described as involving the anterior, lateral, or posterior quadrants.

Statistical analysis

Fisher's exact test or the χ^2 test was used to analyze categorical variables, and the Mann-Whitney U test or Kruskal-Wallis test and the 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, United States) was used for statistical analysis.

RESULTS

Patient characteristics

Of the 958 patients, 580 were men and 378 were women, with a median age of 68 years. Of these, 607 had colon cancer, 351 patients had rectal cancer, and 281 underwent CRT. Overall, 482 patients had Stage II disease, and 379 had Stage III disease; 38 had ypStage 0 disease, and 59 had ypStage I disease. These were patients with rectal cancer who underwent CRT and for whom down staging was achieved (Table 1).

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

Rigid endoscopy was performed on 104 of the 351 patients with rectal cancer, and an enema examination was performed on all patients; the results are displayed in Table 2. The mean (SD) distance for RS, Ra, and Rb rectal cancer on rigid endoscopy was 10.3 cm, 7.7 cm, and 3.5 cm, respectively; and that for RS, Ra, and Rb rectal cancer on enema examination was 12.3 cm, 7.2 cm, 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).

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 from the anal verge in 77 patients (73.2%) with RS cancer and ≤ 10 cm from the anal verge in 28 (26.6%) patients. For Ra and Rb cancers, tumors were located ≤ 10 cm from the anal verge in 84 (93.2%) patients and 156 (100%) patients, respectively.

Tumor localization and recurrence type

The recurrence type was classified according to colon cancer and rectal cancer. Rectal cancer was distinguished by CRT administration as it is associated with the LR rate, and they were classified according to the JCCRC, NCCN, AJCC, and ESMO guidelines. Since local recurrence is affected markedly by CRT, it

Table 1 Patients' characteristics

Variable	n (%)
Male	579 (60)
Female	379 (40)
Age	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 differentiated adenocarcinoma; Mod: moderated differentiated adenocarcinoma; muc: mucinous adenocarcinoma; Por: Poorly differentiated adenocarcinoma; Sig: Signet cell adenocarcinoma; PCR: Pathological complete response.

was compared to patients who did not undergo CRT.

The rates of colon cancer with liver metastasis, lung metastasis, and LR were 12.6%, 5.4% and 3.4%, respectively. The rates of liver and lung metastasis in patients with rectal cancer who underwent CRT were 8.7% and 10.1%, respectively. The LR rate was 5.5% among patients who underwent CRT and 8.2% in patients who were treated with surgery alone.

Recurrence pattern according to the JCCRC guidelines

The rates of liver metastasis, lung metastasis, and LR in RS cancers according to the JCCRC guidelines were 7.5%, 4.7% and 5.7%, respectively. In Ra and Rb cancers, including in patients who underwent CRT, the liver metastasis, lung metastasis, and LR rates were 9.3%, 10.5% and 6.9%, respectively. The LR

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

Classification	Rigid endoscope			Enema examination		
	mean \pm SD	Range	n	mean \pm SD	Range	n
RS	10.3 \pm 2.3	6-13.5	12 (11.8)	12.3 \pm 2.8	7-21	105 (29.9)
Ra	7.7 \pm 1.6	5-12	38 (37.6)	7.2 \pm 2.3	3-18	90
Rb	3.5 \pm 1.8	0-7	54 (53.4)	3.2 \pm 2.3	0-10	156
	0-5 cm	6-10 cm	11-15 cm	> 15 cm	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	

Classifications: Rb (below the peritoneal inversion), Ra (between the inferior margin of second sacral vertebrae and Rb) and RS (between Ra and sacral promontory). SD: Standard deviation.

rate 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 metastasis, lung metastasis, and local recurrence between RS cancer and colon cancer ($P = 0.1491$, $P = 0.7737$, and $P = 0.2657$, respectively) (Table 3).

Patients with Ra and Rb rectal cancer had significantly higher rates of lung metastasis than those with colon cancer ($P = 0.0043$). Ra and Rb cancer treated by surgery alone had significantly higher rates of local recurrence than colon cancer ($P = 0.0002$).

Recurrence pattern according to the NCCN and AJCC guidelines

According to the NCCN and AJCC guidelines, rectal cancer located ≤ 12 cm from the anal verge showed rates of liver and lung metastasis of 8.3% and 10.7%, respectively. The rate of liver and lung metastasis was significantly higher in rectal cancer ≤ 12 cm from the anal verge than in colon cancer ($P = 0.0631$, $P = 0.0117$). The LR rate was 8.5% in rectal cancer located ≤ 12 cm from the anal verge treated with surgical monotherapy. Therefore, the LR rate was significantly higher than that in colon cancers located orally less than 12 cm from the anal verge ($P = 0.0467$) (Table 4).

Recurrence pattern according to the ESMO guidelines

According to the ESMO guidelines, tumors ≤ 15 cm from the anal verge are classified as rectal cancer. Mid- or low rectal cancers are treated surgically, whereas lesions located more orally than ≥ 10 cm from the anal verge are generally treated the same as colon cancer. Consequently, comparisons were made based on rectal cancers located ≤ 10 cm from the anal verge. The rates of liver and lung metastasis of rectal cancer located ≤ 10 cm from the anal verge were 8.9% and 10.4%, respectively. Rectal cancer located ≤ 10 cm from the anal verge had significantly higher rates of liver and lung metastasis than colon cancer ($P = 0.1752$, $P = 0.0036$). The LR rate in rectal cancer located ≤ 10 cm from the anal verge treated with surgical monotherapy was 13.2%. This was significantly higher than the LR rate of colorectal cancer located more than 10 cm oral to the anal verge ($P = 0.0010$) (Table 5).

The rates of liver metastasis, lung metastasis, and LR in rectal cancer located 11 cm to 15 cm from the anal verge were 6.9%, 2.8%, and 5.7%, respectively. There was no significant association with the liver metastasis, lung metastasis, and LR rates of colon cancer ($P = 0.1714$, $P = 0.3357$, and $P = 0.3400$, respectively).

DISCUSSION

Lung metastases and LR were more common in rectal cancer than in colon cancer, and TME is performed for rectal cancer as a common operative method to reduce LR[14-16]. Furthermore, although therapeutic strategies for colon cancer are standardized worldwide, those for rectal cancer vary from CRT and LLND to post-CRT watch and wait. Among these treatments, the indications for CRT are notably different between classification systems; while the NCCN and AJCC guidelines recommend this procedure for advanced rectal cancer located ≤ 12 cm from the anal verge, the ESMO guidelines recommend it for advanced rectal cancer ≤ 10 cm from the anal verge, and the JCCR guidelines only make a weak recommendation in cancers that are T3 or deeper or are cN+ with a high risk of LR. In addition, the localization of the lesion for this recommendation is not specified[3-6].

Table 3 Recurrence pattern according to Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma guidelines

	Liver (%)			Lung (%)			Local (%)		
	Metastasis	n	P value	Metastasis	n	P value	Metastasis	n	P value
Colon cancer	77 (12.6)	530 (87.4)		33 (5.4)	574 (94.6)		21 (3.4)	586 (96.6)	
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
Ra and Rb	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 National Comprehensive Cancer Network and American Joint Committee on Cancer guidelines

	Liver (%)			Lung (%)			Local (%)		
	Metastasis	n	P value	Metastasis	n	P value	Metastasis	n	P value
Colon cancer	77 (12.6)	530 (87.4)		33 (5.4)	574 (94.6)		21 (3.4)	586 (96.6)	
> 12 cm	6 (11.5)	46 (88.5)		2 (3.8)	50 (96.2)		4 (8.3)	48 (91.7)	
≤ 12 cm	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 European Society for Medical Oncology guidelines

	Liver (%)			Lung (%)			Local (%)		
	Metastasis	n	P value	Metastasis	n	P value	Metastasis	n	P value
Colon cancer	77 (12.6)	530 (87.4)		33 (5.4)	574 (94.6)		21 (3.4)	586 (96.6)	
> 15 cm	2 (16.6)	10 (83.4)		1 (8.3)	11 (91.7)		0 (0)	12 (100)	
11-15 cm	5 (6.9)	66 (93.1)	0.1714	2 (2.8)	69 (97.2)	0.3357	4 (5.7)	65 (94.3)	0.3400
≤ 10 cm	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	

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

Approximately 26.6% of the tumors diagnosed as RS were located between 6 cm and 10 cm from the anal verge. They likely include more mid- and low rectal cancers that should be treated with CRT rather than tumors classified according to other guidelines. However, according to our current findings, the LR rates of RS cancers and rectal cancers considered “high rectal” cancers (*i.e.* those located more orally than 12 cm, 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 for colon cancer. There was no significant difference in the recurrence type between RS and colon cancers. In light of its characteristic recurrence types (*i.e.* LR 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 LR rates of RS cancers, tumors located ≤ 12 cm from the anal verge, and those located ≤ 10 cm from the anal verge after surgical monotherapy were 17.2%, 8.5% and 13.2%, respectively. These results were significantly higher than those for colon cancer ($P = 0.0002$, $P = 0.0467$, and $P = 0.0010$). However, the LR rate of rectal cancers decreased 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 of the tumor relative to 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 cm to 5 cm of the peritoneal reflection. However, Najarian *et al*[17] 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. Although differences in the relationships between peritoneal reflection locations and Ra cancer and Rb cancers are possible, the findings of our investigation on recurrence types generally seemed to suggest that Ra cancer and Rb cancers had higher local recurrence rates according to the JCCRC guidelines than according to other guidelines. In addition, this 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 located below the peritoneal reflection, whereas in Japan, LLND is only performed for tumors diagnosed as Rb. This suggests that tumors diagnosed as Ra may include tumors for which LLND should be performed, assuming that CRT and LLND are performed as treatments for local control.

In conclusion, based on 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 guidelines and to mid-rectal and low rectal cancer as defined by the ESMO guidelines. However, the retrospective, single-center design is a limitation of this study, and further research of patients in a multi-center study is warranted for more detailed investigations.

CONCLUSION

Our findings suggest that rectal cancers classified as RS under the JCCRC guidelines and rectal cancers classified as high 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 different guidelines were generally consistent; no major differences were found.

ARTICLE HIGHLIGHTS

Research background

Rectal cancer is characterized by more local recurrence and lung metastasis than 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.

Research motivation

To clarify the characteristics of rectal cancer by comparing the tumor location and characteristics of rectal cancer with those of colon cancer according to each set.

Research objectives

To make the management of rectal cancer a common understanding and to help determine the optimal treatment strategy. To that end, each guideline was compared.

Research methods

A total of 958 patients with Stage II and III colorectal cancer were included in the analysis: 607 with colon cancer and 351 with rectal cancer. Localization of rectal cancers was assessed by enema examination and rigid endoscopy.

Research results

Rectal cancer, which is indicated for chemoradiotherapy in the Western country, is consistent with middle-lower rectal cancer in Japan, and the recurrence rate was characterized by local recurrence and lung metastasis more than colon cancer.

Research conclusions

High rectal cancer may be treated with the same treatment strategies as colon cancer. There was no difference in the classification of colorectal cancer between Japan and Western countries.

Research perspectives

Chemoradiotherapy and lateral lymph node dissection are available for rectal cancer. Although many studies are being conducted around the world, clarifying the correct diagnosis will help in selecting the optimal treatment.

FOOTNOTES

Author contributions: Miyakita H designed the research; Miyakita H and Chan LF performed the research; Miyakita H and Kamei Y contributed new reagents/analytic tools; Miyakita H, Okada K and Kayano H analyzed the data; Miyakita H and Yamamoto S wrote the paper.

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