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Research Paper

Tumor location is an independent predictive factor for distant metastasis and metastatic sites of rectal adenocarcinoma in patients receiving total mesorectal excision

Chien-Hsin Chen[1], Mao-Chih Hsieh[2], Ping-Kun Hsiao[2], En-Kwang Lin[1], Yen-Jung Lu[1], Szu-Yuan Wu[3,4,5,6]✉

1. Department of Colorectal Surgery, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
2. Department of General Surgery, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
3. Institute of Toxicology, College of Medicine, NationalTaiwanUniversity, Taipei, Taiwan
4. Department of Radiation Oncology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
5. Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
6. Department of Biotechnology, Hungkuang University, Taichung, Taiwan

✉ Corresponding author: Szu-Yuan Wu, M.D., M.P.H., Ph.D., Attending Physician, Department of Radiation Oncology, Taipei Medical University - Wan Fang Medical Center, NO.111, Section 3, Hsing-Long Rd, Taipei 116, Taiwan, R.O.C. E-mail: szuyuanwu5399@gmail.com

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Abstract

Background and Objectives: To evaluate the predictive factor for and patterns of distant metastasis in patients with rectal adenocarcinoma receiving total mesorectal excision (TME).

Methods: We enrolled 217 consecutive patients who had histologically confirmed rectal adenocarcinoma and underwent surgery at Taipei Medical University– Wanfang Hospital between January 2000 and December 2014. TME was performed in all patients undergoing a sphincter-sparing procedure or abdominal perineal resection of rectal cancer. We performed univariate and multivariate Cox regression analyses of the distant metastasis rate in all patients to evaluate predictive factors. Overall survival (OS) rates were calculated using the Kaplan–Meier method, and Kaplan–Meier survival curves were compared using the log-rank test.

Results: A multivariate Cox regression analysis of the distant metastasis rate in patients with rectal adenocarcinoma identified tumor locations and American Joint Committee on Cancer (AJCC) stages as prognostic risk factors. The adjusted hazard ratios (aHRs) of distant metastasis for the upper-third, middle-third, and AJCC stage I–II cancers were 0.08 (95% CI, 0.01–0.69; p = 0.021), 0.41 (95% CI, 0.15–0.99; p = 0.047), and 0.20 (95% CI, 0.10–0.66; p = 0.008), respectively. The 5-year lung metastasis rates among patients with upper-, middle-, and lower-third rectal cancers were 0%, 3.37%, and 13.33%, respectively (log-rank, p = 0.001), and the 5-year liver metastasis rates among patients with upper-, middle-, and lower-third rectal cancers were 2.12%, 9.10%, and 11.76%, respectively (log-rank, p = 0.096). The 5-year OS rates also differed with different rectal adenocarcinoma locations. The 5-year OS rates for upper, middle, and lower rectal cancers were 96%, 86%, and 64%, respectively (log-rank, p < 0.001).

Conclusion: A poor OS rate and high lung or liver metastasis rate were observed in distal rectal adenocarcinoma. Longer intensive surveillance of the chest, abdomen, and pelvis after TME in distal rectal adenocarcinoma could be necessary.

Key words: Rectal adenocarcinoma; total mesorectal excision; distant metastasis

Introduction

Approximately 4256 Taiwanese people are diagnosed as having rectal cancer annually.[1] Adenocarcinomas constitute the vast majority of these cancers.[1] Primary rectal squamous cell carcinomas,

which are very rare, can be difficult to distinguish from anal cancers and are treated using the same approach as that for anal cancer, with initial chemoradiotherapy (CCRT) rather than surgery.[2] The optimal approach to treating rectal adenocarcinoma depends upon numerous factors, of which the location in the rectum and the local disease extent are most important.[3] The treatment of distal rectal cancer is still a challenge in terms of reducing permanent stoma, reducing local recurrence, and improving survival.[3] The improvements in the surgical technique total mesorectal excision (TME), described by Healed et al. in 1982,[4-6] have resulted in a local recurrence rate of 4%–10%.[3-5, 7, 8]

Although local recurrence appeared to considerably decrease because of the TME technique, the 5-year overall survival (OS) stratified by tumor stage at diagnosis for rectal cancer by using the 2010 staging criteria remains less than 50% in advanced stages.[9] Understanding the failure patterns of distant metastasis is very important, in addition to local recurrence in the era of TME. However, no strong predictive factor for distant metastasis exists, and the existing predictive factors have been used for determining outcomes of OS or local recurrence rather than those of distant metastasis.[9-12] Moreover, these predictive factors have been used for determining colon and rectal cancers, but are not specific for rectal adenocarcinoma.[9-12]

In the current study, our objective was to evaluate the predictive factors for distant metastasis in patients with rectal adenocarcinoma receiving TME. The patterns of distant metastasis including metastatic sites and metastatic interval were estimated in our study. Moreover, we evaluated whether the predictive factors for distant metastasis could be used for estimating the OS.

Patients and Methods

Study Patients

We enrolled 217 consecutive patients who had histologically confirmed rectal adenocarcinoma and underwent surgery at Taipei Medical University–Wanfang Hospital between January 2000 and December 2014. All enrolled patients were Taiwanese (Asian population). After rectal surgery, the mean number of total harvested lymph nodes was 18.3 (standard deviation [SD], 9.6). The mean follow-up period was 80 months (SD, 37 months). Clinical and pathological data were reviewed to evaluate prognostic factors for the distant metastasis of rectal adenocarcinoma. Adjuvant radiotherapy (RT) and chemotherapy (CT) are indicated for pT3, pT4, or lymph node-positive rectal cancers in our hospital.[3] Upper-, middle-, and lower-third rectal adenocarcinomas were defined as tumor margins 11.1–15 cm from, 7.1–11 cm from, and within 7 cm of the anal verge, respectively, as measured through rigid sigmoidoscopy.[13] Our protocols were reviewed and approved by the institutional review board of our hospital.

Surgery and Follow-Up

TME was performed in all patients undergoing a sphincter-sparing procedure or an abdominal perineal resection (APR) of rectal cancer. TME included high ligation of the inferior mesentery artery and vein; mobilization of the sigmoid colon, descending colon, or splenic flexure; and mobilization of the rectum through sharp dissection with diathermy or scissors under direct vision in the avascular plane between the visceral fascia of the mesorectum and the parietal fascia of the pelvis, as described by Heald et al.[5]

Pathological staging of the disease was performed according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 6th edition. After the surgery, all patients were enrolled in a surveillance program designed to detect disease status including local recurrence or distant metastasis. Clinic visits were scheduled every 3 months for the first 2 years and then at 6-month intervals for 3 years. During each visit, pelvic examination was performed, and the carcinoembryonic antigen level was measured. Abdominal ultrasound or computed tomography was performed every 6 months. Colonoscopy was performed after 1 and 3 years. If the patients missed the follow-up session at our outpatient department, we contacted them by telephone or mail. Any symptom potentially related to local tumor recurrence or distant metastasis was investigated through digital rectal examination, colonoscopy, and computed tomography or magnetic resonance imaging. Distant metastasis was confirmed through biopsy.

Statistical Analysis

The primary endpoint of the study was confirmation of distant metastasis. Patients lost to follow-up were censored from the time of last follow-up. Patients with confirmed distant metastasis (confirmed through pathological findings) were compared with those without confirmed distant metastasis. Continuous variables (expressed as medians (ranges)) were compared using the Mann–Whitney U test or analysis of variance (ANOVA; two or more independent groups), whereas categorical variables (percentages) were compared using the chi-squared test or Fisher exact test, when indicated. Multivariate analysis was performed using Cox

regression analysis for long-term follow-up (different time, censored data), and the analysis included only model variables having the highest or lowest ($p < 0.05$) univariate risk. Statistical significance was defined as $p < 0.05$. Results are presented with a hazard ratio (HR) and 95% confidence interval (CI). All p values were two-tailed. Significant independent predictors for distant metastasis such as pathologic AJCC stages and locations of the rectum were determined using a multivariate Cox regression analysis to determine the HR; the independent predictors were controlled for or stratified in the analysis, and the endpoint was the distant metastasis rate among the rectal adenocarcinoma locations. The cumulative proportion of the distant metastasis rate was calculated using the Kaplan–Meier method. Kaplan–Meier survival curves were compared using the log-rank test. Statistical analyses were performed using SPSS, Version 13.0, for Windows (SPSS Inc., Chicago, IL, USA).

Results

We enrolled 217 patients with rectal adenocarcinoma status post-surgery. The characteristics of these patients with and without distant metastasis following surgery are presented in Table 1. Of the 217 patients, 127 were men and 90 were women. The mean age of the patients was 67 years (SD, 12 years; range, 30–95 years). No significant difference was observed in age, sex, pathological AJCC stages, surgical procedures, APR receipt or nonreceipt, and pathological tumor size between the two groups (Table 1). Moreover, all distal surgical margins in the study were free, and the mean margin distance from the distal edge of the tumor was 2.27 cm (SD, 1.52 cm). Distant metastasis was significantly higher in patients with advanced pathologic AJCC stages (stages II–III compared with stage I); those receiving adjuvant RT, CT, or CCRT; and those with lower-third rectal cancers (Table 1). Specifically, the distant metastasis rates observed in patients with middle- and lower-third rectal cancers were 9.47% and 21.21%, respectively, compared with those in patients with upper-third rectal cancers (1.79%). The characteristics of patients with rectal adenocarcinoma at different tumor locations are presented in Table 2. The proportions of patients undergoing APR (100.00%), adjuvant CCRT (73.33%), and adjuvant RT (50.00%) were significantly higher among those having tumors in the lower third rectum (Table 2). To examine prognostic factors for distant metastasis, we performed univariate and multivariate Cox regression analyses of the distant metastasis rate in patients with rectal adenocarcinoma (Table 3). After including only model variables of distant metastasis with the highest or lowest univariate risk, we observed that middle- and lower-third rectal cancers, pathological AJCC stage III, APR receipt, adjuvant RT receipt, and adjuvant CT receipt were poor prognostic factors. However, after the execution of a multivariate Cox regression analysis of the distant metastasis rate in patients with rectal adenocarcinoma, tumor locations and AJCC stages were identified as prognostic risk factors (Table 3). The adjusted HRs (aHRs) of distant metastasis for the upper-third, middle-third, and AJCC stage I–II rectal cancers were 0.08 (95% CI, 0.01–0.69; $p = 0.021$), 0.41 (95% CI, 0.15–0.99; $p = 0.047$), and 0.20 (95% CI, 0.10–0.66; $p = 0.008$), respectively.

Table 1. Characteristics of patients with rectal adenocarcinoma with and without distant metastasis.

	Distant metastasis, *n* (%)	No metastasis, *n* (%)	*P* value
Sex			1.000
Male	13 (10.24)	114 (89.76)	
Female	11 (12.22)	79 (87.78)	
Age (years)			0.190
> 65	17 (16.35)	87 (83.65)	
≤ 65	7 (6.19)	106 (93.81)	
Pathological AJCC stage			<0.0001
I	0 (0.00)	48 (100)	
II	4 (5.63)	67 (94.37)	
III	20 (20.41)	78 (79.59)	
Surgical procedure			0.386
Open surgery	22 (12.29)	157 (87.71)	
Laparoscopic surgery	2 (5.41)	35 (94.59)	
Pathological tumor size			1.000
≥ 5 cm	4 (10.81)	33 (89.19)	
< 5 cm	20 (11.11)	160 (88.89)	
Pathological T stage			0.002
pT1	0 (0.00)	20 (100)	
pT2	1 (1.69)	58 (98.31)	
pT3	22 (17.32)	105 (82.68)	
pT4	1 (9.09)	10 (90.91)	
Pathological N stages			<0.0001
pN0	5 (3.97)	121 (96.03)	
pN1	6 (10.71)	50 (89.29)	
pN2	13 (37.14)	22 (62.86)	
Adjuvant CCRT			0.030
Yes	7 (23.33)	23 (76.67)	
No	17 (9.94)	154 (90.06)	
Adjuvant RT			0.009
Yes	11 (27.50)	39 (72.50)	
No	13 (7.78)	154 (92.22)	
Adjuvant CT			0.002
Yes	19 (18.10)	86 (81.90)	
No	5 (4.46)	107 (95.54)	
APR			0.239
Yes	4 (21.05)	15 (78.95)	
No	20 (5.05)	178 (94.95)	
Tumor location			0.001
Upper third	1 (1.79)	55 (98.21)	
Middle third	9 (9.47)	86 (90.53)	
Lower third	14 (21.21)	52 (78.79)	
Total	24	193	

RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; APR, abdominal perineal resection; AJCC, American Joint Committee on Cancer.

Table 2. Characteristics of patients with rectal adenocarcinoma at different locations.

	Upper third, *n* (%)	Middle third, *n* (%)	Lower third, *n* (%)	*P* value
Sex				0.292
Male	29 (23.97)	61 (48.03)	37 (29.13)	
Female	27 (30.00)	34 (37.78)	29 (32.22)	
Age (years)				0.649
> 65	31 (25.20)	57 (46.34)	35 (28.46)	
≤ 65	25 (26.60)	38 (40.43)	31 (32.98)	
Pathological AJCC stage				0.594
I	16 (33.33)	20 (41.67)	12 (25.00)	
II	19 (23.46)	29 (35.80)	23 (28.40)	
III	21 (21.43)	46 (46.94)	31 (31.63)	
Adjuvant CCRT				<0.0001
Yes	1 (3.33)	8 (26.67)	21 (73.33)	
No	55 (29.41)	87 (46.52)	45 (24.06)	
Adjuvant RT				0.002
Yes	7 (14.00)	18 (36.00)	25 (50.00)	
No	49 (29.34)	77 (46.11)	41 (24.55)	
Adjuvant CT				0.753
Yes	25 (23.81)	46 (43.81)	34 (32.28)	
No	31 (27.68)	49 (43.75)	32 (28.57)	
APR				<0.0001
Yes	0 (0.00)	0 (0.00)	19 (100)	
No	56 (28.28)	95 (47.98)	47 (23.74)	

RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; APR, abdominal perineal resection; AJCC, American Joint Committee on Cancer.

Table 3. Cox proportional hazards model for the risk of distant metastasis among patients with rectal adenocarcinoma.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	aHR*	95% CI	*P* value
Tumor locations						
Lower third (ref)	1			1		
Middle third	0.37	(0.16– 0.86)	0.021	0.41	(0.15– 0.99)	0.047
Upper third	0.06	(0.01– 0.48)	0.007	0.08	(0.01– 0.69)	0.021
Pathological AJCC stage						
III (ref)	1			1		
I–II	0.14	(0.05– 0.40)	0.001	0.20	(0.10– 0.66)	0.008
Surgical procedure						
APR (ref)	1			1		
LAR	0.34	(0.12– 0.99)	0.049	0.74	(0.20– 2.76)	0.658
Adjuvant CCRT						
Yes (ref)	1			1		
No	0.94	(0.32– 2.74)	0.906	0.73	(0.26– 2.10)	0.731
Adjuvant RT						
Yes (ref)	1			1		
No	0.32	(0.14– 0.72)	0.006	1.03	(0.42– 2.54)	0.948
Adjuvant CT						
Yes (ref)	1			1		
No	0.23	(0.08– 0.60)	0.003	0.55	(0.18– 1.72)	0.305

*aHRs were adjusted for age, sex, stages, tumor locations, surgical procedures, adjuvant CCRT, adjuvant CT, and adjuvant RT.

CCRT, concurrent chemoradiotherapy; CCI, Charlson comorbidity index; CI, confidence interval; aHR, adjusted hazard ratio; RT, radiotherapy; AJCC, American Joint Committee on Cancer; Ref, reference group.

The 5-year distant metastasis rates among patients with rectal cancers at different locations were 22.71% (lower third), 12.47% (middle third), and 1.82% (upper third; Supplemental Table 1). The cumulative curve of distant metastasis among patients with tumors in the lower third rectum was steep within the first 5 years after surgery, almost reached a plateau after 6.25 years, and remained unchanged after 10 years (Figure 1). We also evaluated the metastatic sites by different locations of rectal cancers by using ANOVA (Table 4). A statistically significant trend of lung metastasis was observed in lower-third rectal cancer (p = 0.008), but no statistically significant trend of liver metastasis was observed in different locations of rectal cancers. The 5-year lung distant metastasis rate in lower-third rectal adenocarcinoma was also significantly high, with a metastasis rate of 13.33% in the lungs (P = 0.001; Supplemental Table 2). In addition, the different metastatic sites at different locations of rectal adenocarcinoma were determined using the Kaplan–Meier method, and Kaplan–Meier survival curves were compared using the log-rank test (Figures 2 and 3). The 5-year lung metastasis rates among patients with different tumor locations such as the upper, middle, and lower third rectum were 0%, 3.37%, and 13.33%, respectively (log-rank, p = 0.001), and the 5-year liver metastasis rates among patients with upper-, middle-, and lower-third rectal cancers were 2.12%, 9.10%, and 11.76%, respectively (log-rank, p = 0.096; Figure 2). The 5-year OS rates were also very different with different locations of rectal adenocarcinoma. . The 5-year OS rates for upper, middle, and lower rectal cancers were 96%, 86%, and 64%, respectively (log-rank, p < 0.001; Figure 4).

Table 4. Different metastatic sites at different locations of rectal adenocarcinoma.

	Upper third, *n* (%)	Middle third, *n* (%)	Lower third, *n* (%)	*P* value
Lung metastasis				0.008
Yes	0 (0.00)	2 (2.11)	7 (10.61)	
No	56 (100)	93 (97.89)	59 (89.39)	
Liver metastasis				0.140
Yes	1 (1.79)	7 (7.37)	7 (10.61)	
No	55 (98.21)	88 (92.63)	59 (89.39)	

Discussion

Patients with rectal adenocarcinoma receiving TME have a local recurrence of approximately 4%–10%,[7, 14] but they still have a high distant metastasis rate.[15, 16] The most common metastatic sites are the liver and lungs.[17] The metastasis could shorten the life spans of patients with rectal adenocarcinoma, and retreatment such as salvage surgery, CT, or RT might be necessary.[18] When patients with rectal adenocarcinoma receiving TME developed distant metastasis, the 5-year OS was dismal.[16] Till now, no clear predictive risk factor for distant metastasis in patients with rectal adenocarcinoma receiving TME is available. Data

elucidating the patterns of distant metastasis, including the required duration of follow-up, whether the metastasis rate could reach a plateau, the most common metastatic sites (the liver or lungs), and whether a close monitoring of the liver, lung, or both metastases is sufficient, are limited.

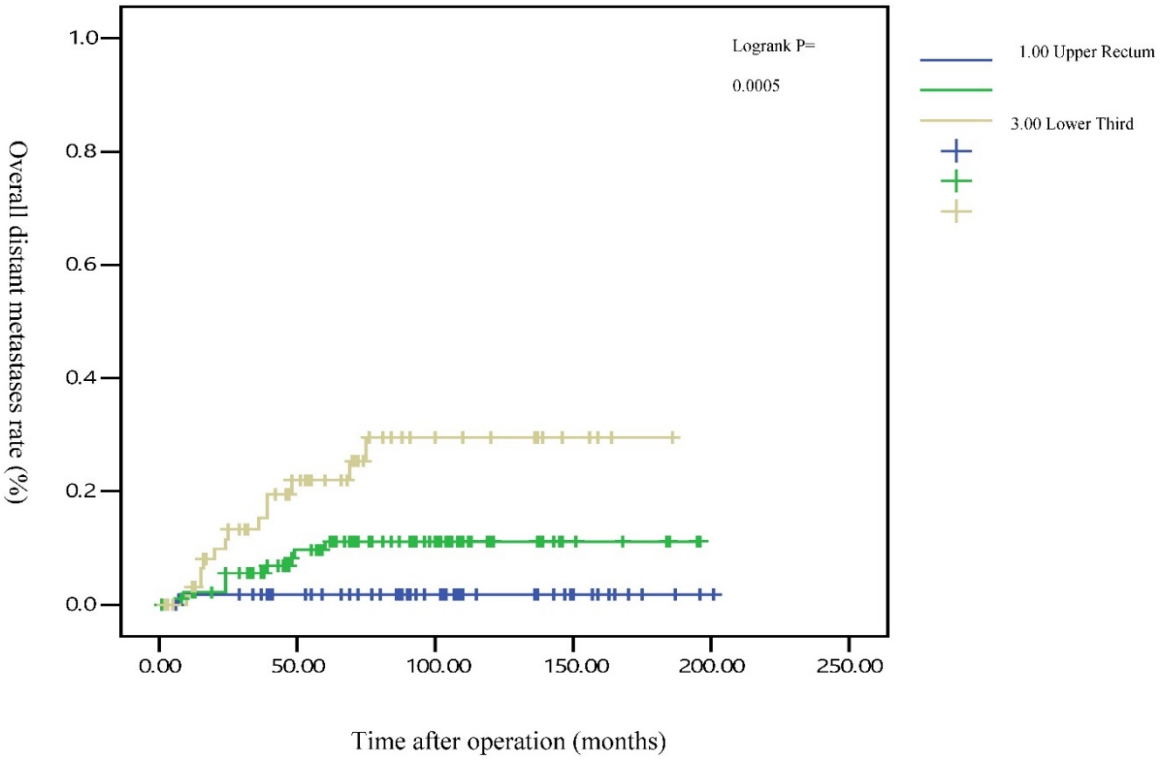

Figure 1. Five-year overall distant metastasis rates by different locations of rectal adenocarcinoma

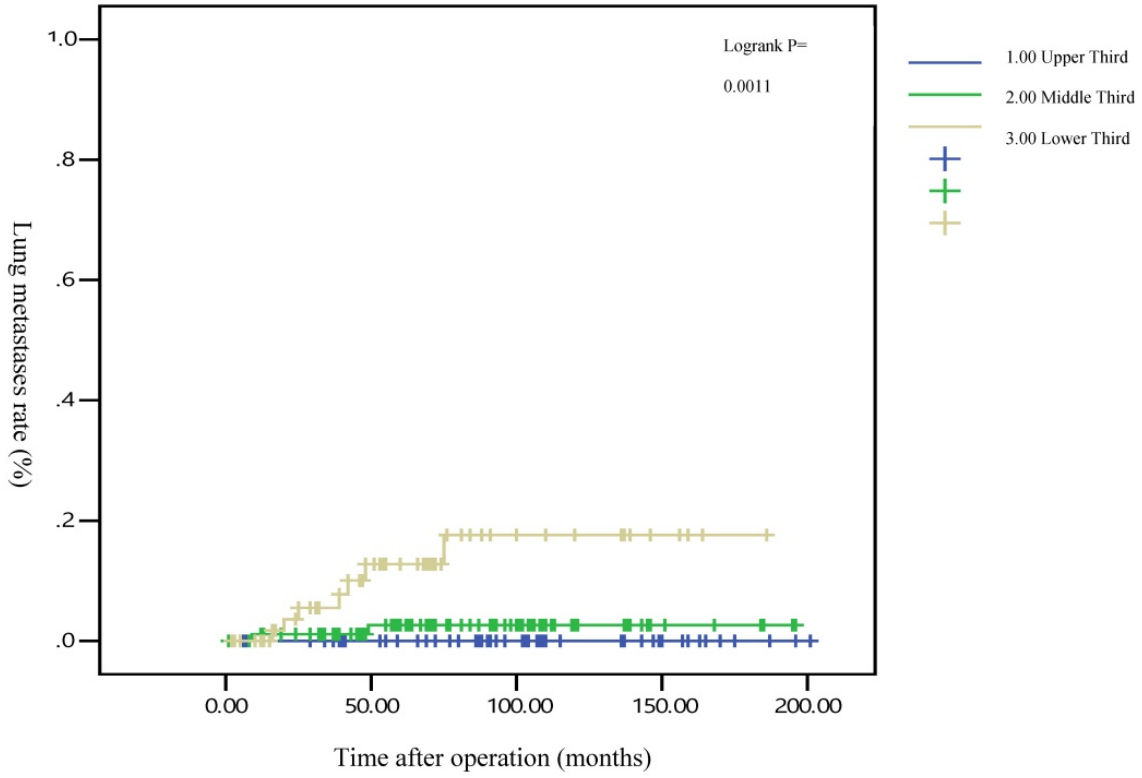

Figure 2. Five-year lung metastasis rates by different locations of rectal adenocarcinoma

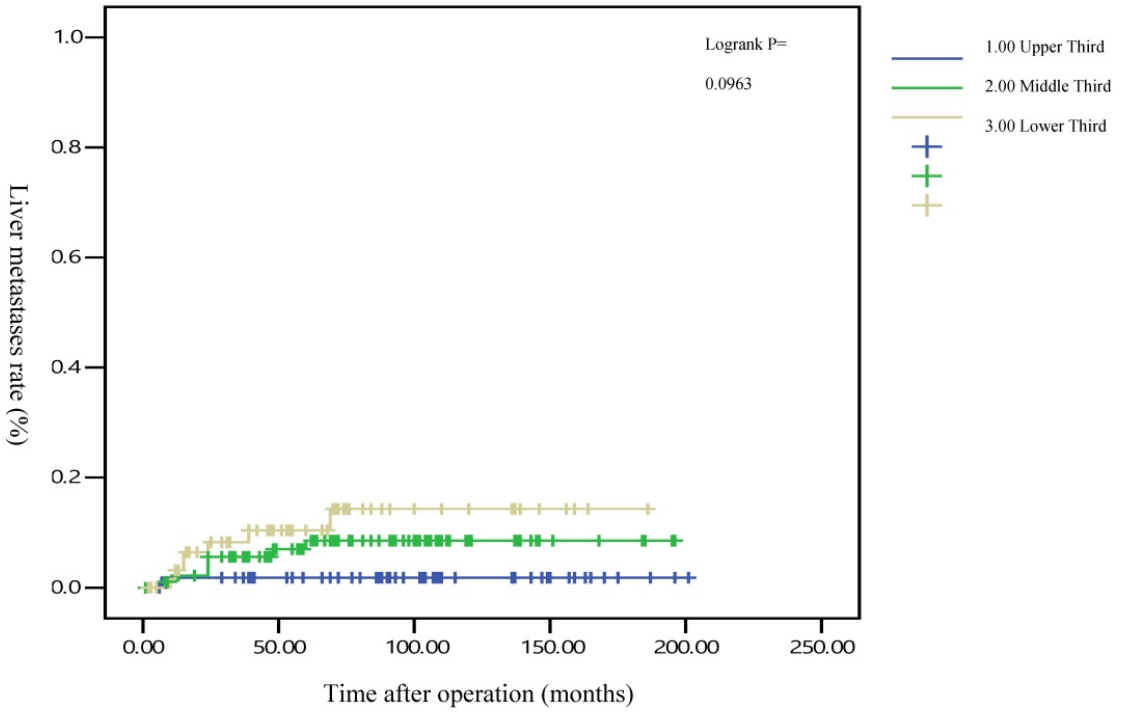

Figure 3. Five-year liver metastasis rates by different locations of rectal adenocarcinoma

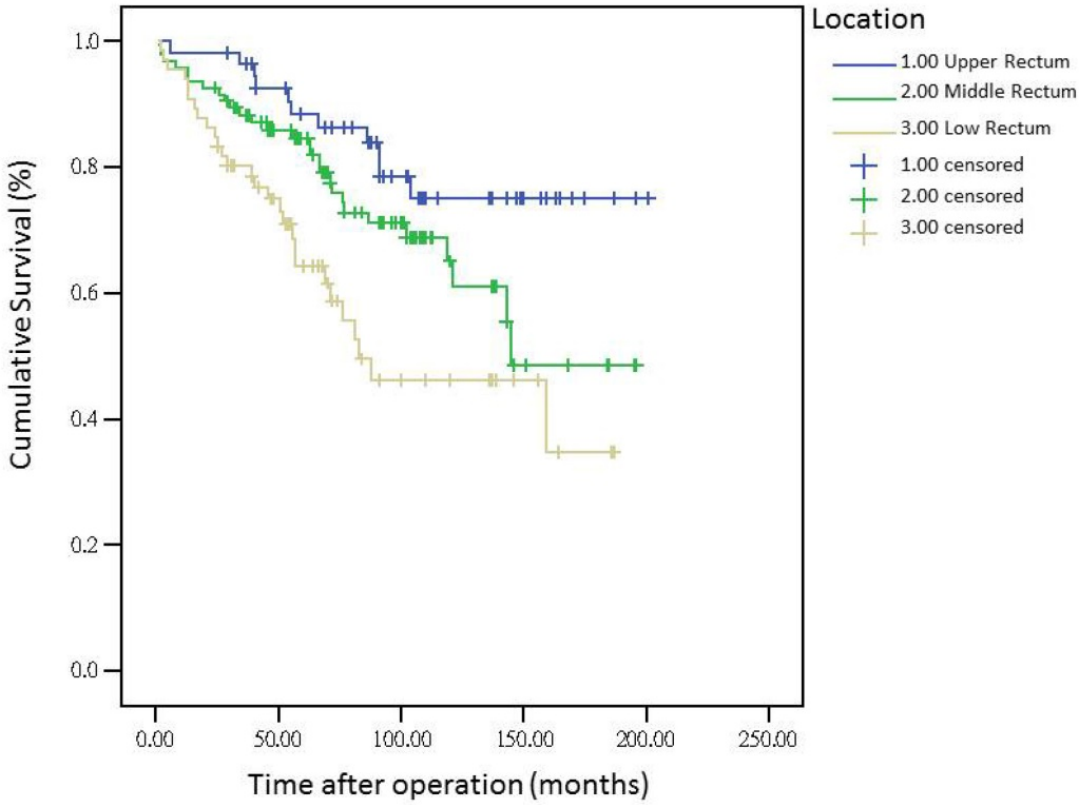

Figure 4. Five-year overall survival rates by different locations of rectal adenocarcinoma

The metastasis rate was higher in advanced pT, pN, and pathologic AJCC stages (Table 1). Our findings are comparable to those of previous studies[19-21]; nevertheless, although these predictive factors were used for determining colon and rectal cancers, they were not specific to rectal adenocarcinoma. However, the metastasis rate remained high in patients receiving adjuvant RT, CT, and CCRT in our study (Table 1), which is inconsistent with the findings of previous studies[16, 22, 23]; these results

might be masked by adverse pathologic risk factors such as close margin, perineural invasion, lymphatic vascular invasion, advanced pathologic AJCC stages, and surgeons' concerns during operation. A multivariate Cox regression analysis revealed that these findings were not statistically significant (Table 3). Another notable finding was the association between tumor locations and distant metastasis rates (Table 1). We separated different locations of rectal adenocarcinoma in our study, and no statistically significant difference was observed in sex, pathologic AJCC stages, and age between the upper-, middle-, and lower-third rectal adenocarcinomas (Table 2). Statistical significance was noted in adjuvant RT, adjuvant CCRT, and APR receipt. These findings indicate that more patients with lower-third rectal adenocarcinoma received adjuvant RT, adjuvant CCRT, and APR, which might be because of the difficulties in surgical approach due to anatomical structures[3, 24]; however, no statistical significance in pathologic AJCC stages was observed between the upper-, middle-, and lower-third rectal adenocarcinomas (Table 2). In the current study, all distal surgical margins were free, even in lower-third rectal adenocarcinoma, because we performed APR rather than the sphincter-sparing procedure, leading to positive margins. Therefore, more patients with lower-third rectal cancer received adjuvant RT and adjuvant CCRT; adjuvant RT or adjuvant CCRT exhibited more favorable outcomes in patients with rectal cancer when compared with nonadjuvant treatments.[22, 23, 25, 26] The current study findings demonstrate that although the number of patients with middle- and lower-third rectal adenocarcinomas receiving adjuvant CCRT or RT was higher, the distant metastasis rate remained higher in middle- and lower-third rectal cancers. According to our review of the relevant literature, this is the first study to demonstrate that the distant metastasis rate and metastatic sites differed with different locations of rectal adenocarcinoma. In addition, the OS rate was influenced by the different locations of rectal cancer. A trend of higher distant metastasis and mortality rates was observed in patients with middle and lower rectal adenocarcinoma compared with those with upper rectal adenocarcinoma (Figures 1 and 4).

After the execution of a multivariate Cox regression analysis of the distant metastasis rate in patients with rectal adenocarcinoma, tumor locations and AJCC stages were identified as prognostic risk factors (Table 3). Although the distributions of pathological stages between the upper-, middle-, and lower-third rectal adenocarcinomas were balanced (Table 2), the location of the rectal adenocarcinoma was the independent predictive factor for distant metastasis (Table 3). The aHRs of distant metastasis for the upper- and middle-third rectal cancers were 0.08 (95% CI, 0.01–0.69; P = 0.021) and 0.41 (95% CI, 0.15–0.99; P = 0.047), respectively. The locations of rectal adenocarcinoma were closer to the anal verge, and the higher distant metastasis rates were significant (Figure 1). Rectal adenocarcinoma can spread through lymphatic and hematogenous dissemination, as well as through contiguous and transperitoneal routes.[27-29] The most common metastatic sites are the liver and lungs.[30, 31] Because the venous drainage of the intestinal tract passes through the portal system, the first site of hematogenous dissemination is usually the liver, followed by the lungs.[27, 31, 32] In addition, tumors arising from the distal rectum may initially metastasize to the lungs because the inferior rectal vein drains into the inferior vena cava rather than into the portal venous system.[6, 33, 34] Our clinical finding is compatible with previous theories.[6, 33, 34] A statistically significant trend of lung metastasis was observed in lower-third rectal cancers (p = 0.008), but no statistically significant trend of liver metastasis was observed in different locations of rectal cancers (Table 4). The 5-year lung distant metastasis rate in lower-third rectal adenocarcinoma was also significantly high, with a metastasis rate of 13.33% in the lungs (p = 0.001; Supplemental Table 2). The 5-year lung metastasis rates among patients with tumors at different locations such as the upper, middle, and lower third rectum were 0%, 3.37%, and 13.33%, respectively (log-rank, p = 0.001), and the 5-year liver metastasis rates among patients with upper-, middle-, and lower-third rectal cancers were 2.12%, 9.10%, and 11.76%, respectively (log-rank, p = 0.096) (Figure 2). This is the first clinical study to prove that lower-third rectal cancer has an equal metastatic trend toward the lungs and liver, whereas upper- and middle-third rectal cancers have a strong metastatic trend toward the liver (Table 4).

In all, 14 patients with lower-third rectal adenocarcinoma exhibited distant metastasis and 7 patients exhibited lung metastasis first rather than liver metastasis. Our results suggest that routine surveillance should include lung survey, particularly in lower-third rectal adenocarcinoma.

Several meta-analyses have supported a modest but significant survival benefit from an intensive surveillance strategy after resection of a colorectal cancer.[35-39] Our results reveal that no more distant metastasis occurred after 5 years in patients with upper and middle rectal cancers, and the distant metastasis might reach a plateau after 5 years (Figure 1). However, metastasis was still observed after 5 years in patients with lower-third rectal cancer, and a

metastatic plateau seemed to be reached after 6.25 years. These findings imply that annual surveillance of the chest, abdomen, and pelvis should be performed for at least 6.25 years for lower-third rectal cancers (Figure 1). After 5 years, the metastatic site in lower-third rectal cancer was the lungs instead of the liver (Figures 2 and 3). Therefore, chest surveillance should be performed for more than 6 years in patients with lower-third rectal cancer (Figure 2).

No clinical data are available to prove that patients with lower-third rectal cancer receiving TME still have an equal distant metastasis trend toward the lungs and liver, even after 6 years. Our data demonstrate the clinical findings in patients with rectal cancer receiving TME. Furthermore, this is the first study to demonstrate a poor OS rate and high metastasis rate in distal rectal adenocarcinoma, irrespective of adjuvant treatments such as CT, RT, or CCRT. Longer intensive surveillance of the chest, abdomen, and pelvis could be necessary after TME in distal rectal adenocarcinoma.

Conclusions

A poor OS rate and high lung or liver metastasis rate were observed in distal rectal adenocarcinoma. Therefore, longer intensive surveillance of the chest, abdomen, and pelvis could be necessary after TME in distal rectal adenocarcinoma.

Abbreviations

RT: radiotherapy; CT: chemotherapy; CCRT: concurrent chemoradiotherapy; LAR: low anterior resection; TME: total mesorectal excision; AJCC: American Joint Committee on Cancer; CI: confidence interval; aHR: adjusted hazard ratio; Ref: reference group; OS: Overall survival.

Supplementary Material

Supplementary tables.
http://www.jcancer.org/v09p0950s1.pdf

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Competing Interests

The authors have declared that no competing interest exists.

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