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Location of rectal cancer as determined using rectal magnetic resonance imaging, and its relationship with pulmonary metastasis

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Original Article

ABSTRACT

Background/Aims: The aim of this study was to evaluate the accuracy of 3-T magnetic resonance imaging (MRI) in locating rectal cancer, and to determine whether tumor location correlates with the incidence of pulmonary metastasis.

Materials and Methods: A total of 146 patients with confirmed rectal adenocarcinoma underwent 3-T rectal MRI, and abdominal and chest computed tomography (CT) within 2 weeks of the endoscopic examination. We reviewed the distance between the mass and the anal verge recorded in the endoscopic reports of these patients. Two radiologists evaluated the same distance on MRI scans by using picture archiving and communications systems. Multiple factors including the tumor location, primary tumor and lymph node stage, lung and liver metastasis, pathologic differentiation, and the carcinoembryonic antigen level were evaluated. The correlation between tumor location on MRI and endoscopy was assessed, and significant factors influencing pulmonary metastasis were identified using multivariate logistic regression analysis.

Results: There was a statistically significant correlation between the tumor location established using MRI and the actual location recorded during endoscopy. The incidence of pulmonary metastasis was significantly higher in patients with lower rectal cancer (11/17, 65%) compared to those with upper rectal cancer (6/17, 35%; $p<0.05$). Factors associated with pulmonary metastasis were tumor location and the presence of liver metastasis.

Conclusion: The accurate tumor location could be indicated using 3-T rectal MRI. Pulmonary metastasis occurred more frequently in patients with lower rectal cancer than in those with upper rectal cancer.

Keywords: Rectal cancer, magnetic resonance imaging, pulmonary metastasis, tumor location

INTRODUCTION

Colorectal cancer is a common neoplasm, with a global incidence of approximately 40/100,000 people. Metastases are present at the time of diagnosis in up to 30% of patients with colorectal cancer (1). Hematogenous spread is known to be one of the principal mechanisms of systemic metastasis in colorectal malignancy. The most common metastatic site is the liver, with an overall prevalence of approximately 40-50% over the course of the disease (2), while the second most common site is the lungs, with a prevalence of approximately 10-15% (1,3). However, the likelihood of cancer spreading to a particular site might be influenced by the location of the tumor within the colorectum. Previous studies have found that the incidence of pulmonary metastasis ranges from 10% to 18% for rectal cancer, but from only 5% to 6% for colon cancer (4). In addition, rectal cancer is known to be more strongly associated with the presence of isolated pulmonary metastases than colon cancer (1). It has been suggested that this difference reflects the different routes of venous drainage in the colon and rectum, as venous drainage is thought to be the decisive determinant for distant hematogenous spread (5). Generally, blood from the colon is directed toward the liver via the portal vein, while blood from the rectum drains into the systemic circulation (5). This anatomic feature has been known for more than 50 years, and is thought to be the basis for the different patterns of metastatic spread from these two sites.

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There are also differences in venous drainage within the rectum. Usually, the superior rectal veins drain the upper portion of the rectum and empty mainly into the portal system via the inferior mesenteric vein. In contrast, the middle rectal veins drain the lower portion of the rectum into the systemic circulation via the internal iliac veins (6), and thus, venous drainage from the lower portion of the rectum occurs directly into the systemic circulation, bypassing the liver. Therefore, theoretically, tumors arising in the lower rectum may be more likely to metastasize to the lungs rather than the liver. However, there have been no previous clinical studies to determine whether the incidence of pulmonary metastasis actually differs according to the venous drainage pattern. Currently, rectal magnetic resonance imaging (MRI) is widely used for preoperative evaluation of the location and stage of rectal cancer. From a surgical viewpoint, knowledge of the exact location of a tumor is very important because it guides decision-making regarding the choice of surgical techniques, and rectal MRI can help to provide this information (7).

The purpose of our study was to evaluate the accuracy of 3-T MRI in locating rectal cancer, and to determine whether tumor location correlates with the incidence of pulmonary metastasis.

MATERIALS AND METHODS

Study population

We enrolled 146 consecutive patients referred to our institution for preoperative rectal cancer staging, over a period of 4 years. The institutional review board approved this study, and informed consent was waived because of its retrospective nature. All patients were confirmed to have rectal adenocarcinomas, based on histological analysis of endoscopy-guided biopsies. The median patient age was 60.7 years (range, 30-97 years), and 69% of patients were men. We established the distance from lowest portion of the mass to the anal verge on the basis of the endoscopy report. For all patients, rectal MRI and abdominal and chest computed tomography (CT) had been performed within 2 weeks of the endoscopic examination.

Imaging technique

Preparation of the bowel included the administration of rectal suppository (bisacodyl, Dulcolax, Boehringer Ingelheim, Ingelheim, Germany) approximately 3 hours prior to MRI. An intravenous or intramuscular antiperistaltic agent (ALGIRON® Boehringer Ingelheim, Ingelheim, Germany) was injected in order to minimize motion artifacts, and the patient was administered 150-250 mL warm saline into the rectum via a rectal tube for luminal distension immediately prior to MRI.

All patients were examined while breathing normally in the supine position by using a 3-T MRI unit (Siemens Trio Tim, Erlangen, Germany). An 8-channel surface flexible coil (Flex Large Siemens Medical Systems, Germany) was used for signal reception, and an initial 3-plane localizer view, covering the entire pelvis, was obtained. Subsequent sequences included axial, coronal, sagittal T2-weighted images (repetition time/echo time=3560/113 ms, echo train length of 14, 3-mm slice thickness, 0.3-mm gap, 320×320 matrix, 25 cm field of view, with 1 signal acquired, and a sequence duration of 2 min), and axial T1-weighted images (repetition time/echo time=538/11 ms, echo train length of 60, 5-mm slice thickness, 0.8-mm gap, 448×358 matrix, 30-cm field of view, SENSE factor of 2, with 2 signals acquired, and a sequence duration of 3-4 min).

Abdominal and chest CT were performed using a 64-slice scanner (Brilliance 64, Philips Medical Systems, Cleveland, OH, USA). CT was performed using a 1.5-mm collimator, with a slice thickness of 5 mm and a construction interval of 5 mm. Approximately 100-140 mL of a nonionic contrast agent (iopromide [Ultravist, Bayer HealthCare, Berlin, Germany]; Iopamidol [Pamiray, Dongkook Pharmaceutical, Seoul, Korea]; or iomeprol [Iomeron, Bracco, Milan, Italy]) was used as an intravenous contrast agent, administered at a rate of 2.5-3.0 mL/s, with image acquisition after a 40-60-s delay. The contrast material used differed according to the purpose of the image.

Image analysis

Rectal MRI, abdominal CT, and chest CT scans were retrospectively reviewed by two abdominal imaging radiologists (with 11 and 8 years of abdominal imaging experience, respectively). The reviewers were blinded to all clinical information, and they analyzed the images by consensus. The images were reviewed using a picture archiving and communication system (PACS) workstation (pi-viewer, INFINITT, Seoul, Korea).

The location, as well as the primary tumor (T) and lymph node (N) stage of the tumor, was evaluated on the rectal MRI scan. A line was drawn along the midline of the rectal lumen, and the distance from the lower margin of the rectal tumor to the anal verge was measured in a zigzag pattern on a sagittal T2-weighted image (Fig. 1). The anal verge was defined as the point at which the levator ani muscle was attached to the rectum, as observed on the MRI scan (7). Sagittal T2-weighted images were primarily used to measure this distance; axial and coronal T2-weighted images were used secondarily to determine the upper and lower margins of the tumors when required. All these processes were performed manually using the PACS. The radiologists also evaluated the local tumor stage and nodal stage by using the Tumor-Node-Metastasis (TNM) staging system. The TNM classification of the tumors observed on MRI scans was performed as described previously (8).

All the chest and abdominal CT scans were reviewed retrospectively for the presence of metastasis by the two radiologists. On chest CT scans, the presence of a parenchymal lung nodule (≥1 cm if solitary or >0.5 cm if multiple) with a soft-tissue component without calcification, was considered positive for the

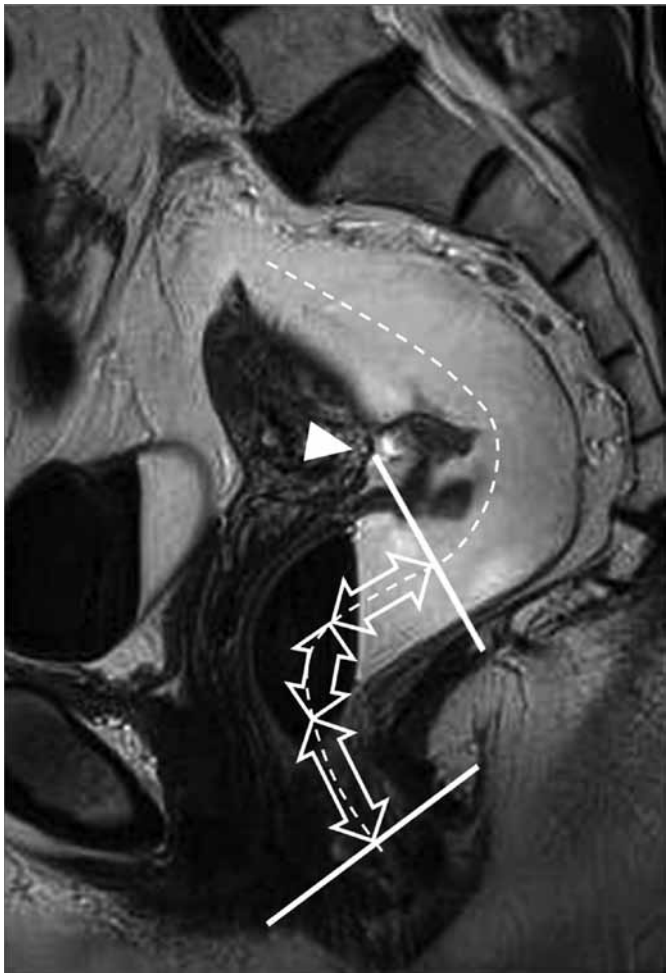

Figure 1. Determining tumor location using rectal magnetic resonance imaging (MRI). A line (dotted white line) was drawn along the midline of the rectal lumen, and the distance (double-headed arrows) from the lower margin (upper white line) of the rectal tumor (arrowhead) to the anal verge (lower white line) was measured in a zigzag pattern on a sagittal T2-weighted image. The anal verge was defined as the point at which the levator ani muscle (lower white line) was attached to the rectum, as seen on an MRI scan.

presence of metastasis (9). The sizes of the lung nodules were measured using a lung window setting (window level, -649 Hounsfield unit [HU]; window width, 1400 HU), and then the setting was changed to a mediastinal window (window level, 45 HU; window width, 440 HU) to exclude calcified granulomas. On abdominal CT scans, a definite hepatic metastasis was defined as a hypo-attenuating or heterogeneous mass in the liver that was >15 mm in diameter, without imaging features suggestive of a cyst, hemangioma, focal fatty infiltration, abscess, or focal eosinophilic necrosis (10,11). A cyst was defined as a circumscribed lesion without a perceptible wall, and with an attenuation value of -20 to +20 HU. A hemangioma was defined as a lesion with peripheral nodular or homogenous enhancement. Focal fat deposition was defined as a non-mass-like area of reduced attenuation at a specific location. An abscess was defined as a low-attenuating lesion with a thick enhancing wall, and eosinophilic necrosis was defined as a homogenous, hypo-attenuating lesion with indistinct margins on a portal phase image that could not be detected on an arterial or delayed phase image.

Clinical analysis

Endoscopy specialists recorded the distance between the anal verge and the nearest tumor border during endoscopy. Endoscopic tumor location could not be determined in 18 cases (18/146, 12%). All enrolled patients were tested for the level of carcinoembryonic antigen (CEA) before treatment, and a CEA level >4.5 µg/L was considered abnormal.

Pathologic analysis

Information regarding both pathologic tumor-node (TN) staging and tumor differentiation was available for 113 patients who underwent surgical resection. For the remaining 33 patients, only tumor-cell differentiation was included in the statistical analysis. To confirm the diagnosis of rectal adenocarcinoma, a pathologist performed a detailed retrospective histopathologic examination of biopsy or surgical specimens. Tumors were graded, according to the percentage of glandular structures in the tumor, as well differentiated (>95%), moderately differentiated (50-95%) poorly differentiated (5-50%) and undifferentiated (<5%) carcinoma. Pathologic T-staging was performed according to the TNM staging system of the American Joint Committee on Cancer.

Statistical analysis

The data were analyzed using SPSS version 12.0 (SPSS, Chicago, IL, USA). The correlation between endoscopic tumor location and the distance of the tumor from the anal verge, measured on rectal MRI scans, was evaluated using the Wilcoxon signed-rank test and Spearman's rho test. For the comparison of patient characteristics, the Mann-Whitney test was used. Receiver operating characteristic (ROC) analysis was then performed to identify the cut-off level of distance from the anal verge for maximizing its sensitivity and specificity in predicting the presence of a lung metastasis. Conventionally, the rectum is divided into three parts based on the anatomic distance from the anal verge: the upper third (10-15 cm), middle third (5-10 cm), and lower third (0-5 cm). However, in this study, the location of the tumor on rectal MRI scans was recorded as being in either the upper or the lower rectum, as this reflects the position of the two distinct pathways of venous drainage. This cut-off value was determined to be within the middle third of the rectum (5-10 cm from the anal verge). Within these two groups, potential factors that might be associated with lung metastasis were analyzed using a logistic regression method.

RESULTS

Patient characteristics

Patient characteristics are summarized in Table 1. Of the 146 patients, 113 had undergone primary tumor resection without any preoperative treatment. Twenty-eight patients did not undergo primary tumor resection as they were treated using

Table 1. The characteristics of the patients

Characteristics		Total, n=146 (n,%)	Tumor location		p value*
			Upper, n=86 (n)	Lower, n=60 (n)	
Age (years)		61±12	70	76	0.434
Gender					0.590
	Male	101 (69)	61	40	
	Female	45 (31)	25	20	
Primary treatment					
	Surgical resection	113	38	75	
	Neoadjuvnat treatment	28	19	9	
	Follow up loss	5	3	2	
Depth of invasion	Radiologic T stage				0.033
	T1	3	0	3	
	T2	17	7	10	
	T3	115	74	41	
	T4	11	5	6	
	Pathologic T stage				0.391
	T1	6	3	3	
	T2	19	10	9	
	T3	86	61	25	
	T4	2	1	1	
Node	Radiologic N stage				0.687
	N0	40	23	17	
	N1	49	27	22	
	N2	57	36	21	
	Pathologic N stage				0.347
	N0	69	49	20	
	N1	22	12	10	
	N2	22	14	8	
Metastasis	Lung metastasis				
	positive	17	6	11	
	negative	129	80	49	
	Liver metastsis				1.000
	positive	16	9	7	
	negative	130	77	53	
Pathologic differentiation					0.495
	Mild	66	37	29	
	Moderate	77	48	29	
	poorly	3	1	2	
Level of CEA					0.366
	Normal	96	59	37	
	Elevated	6	24	21	

T stage: primary tumor stage; N stage: lymph node stage
*Mann-Whitney test was applied (p<0.05 is significant)

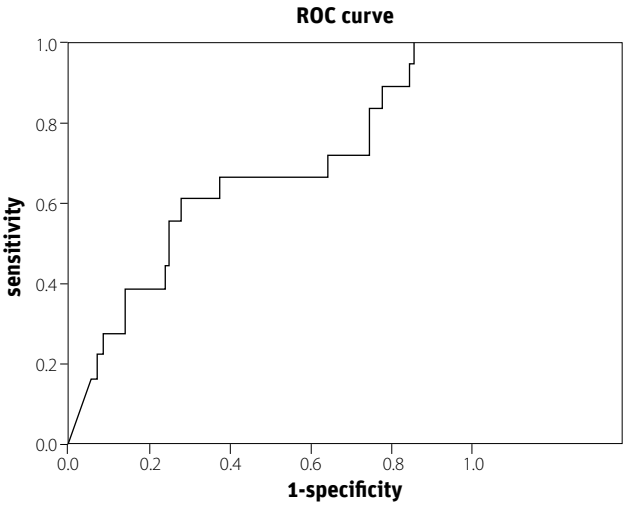

Figure 2. Receiver operator characteristics (ROC) curve for tumor location. The ROC curve was used to determine the optimal cut-off value between the upper and lower rectum. The cut-off value for upper and lower rectal cancer was 5.3 cm from the anal verge (sensitivity, 0.667; specificity, 0.723).

concurrent chemoradiotherapy (CCRT), and the remaining 5 patients were lost to follow-up before treatment initiation. Seventeen patients (11.6%; 11 with lower rectal cancer and 6 with upper rectal cancer) were considered to have a pulmonary metastasis on the basis of the observations on chest CT scans, and there was evidence of liver metastasis in 16 patients (11%; 7 with lower rectal cancer and 9 with upper rectal cancer). There were no significant differences in the baseline characteristics between patients with upper rectal cancer (n=86) and lower rectal cancer (n=60; p>0.05), except for the radiologic T stage (p=0.033).

Tumor location determined using endoscopy and MRI

The distance from the anal verge to the tumor measured using endoscopy (mean, 6.24 cm; range, 0-16 cm) or rectal MRI (mean, 6.23 cm; range, 0-15 cm) was not significantly different (Wilcoxon signed-rank test, p 0.05). There was also a significant correlation between the two sets of results (Spearman's rho test, p<0.05, r=0.862).

Location of rectal cancer

The cut-off value between the upper and lower rectum that optimized the sensitivity and specificity was 5.3 cm (sensitivity, 0.667; specificity, 0.723; Figure 2). Based on this cut-off value, 86 (58.9%) patients had upper rectal cancer and 60 (41.1%) had lower rectal cancer.

Significant factors associated with lung metastasis

We performed multivariate analysis of factors that might be associated with lung metastasis by using a logistic regression method, the results of which are summarized in Table 2. These factors included tumor location, radiologic and pathologic depth of invasion, radiologic and pathologic nodal involvement, level of pretreatment CEA, pathologic grade, and liver metastasis. The incidence of pulmonary metastasis was significantly higher in the group with lower rectal cancer (11/60, 18.3%) than in the group with upper rectal cancer (6/86, 7%; p<0.05; likelihood ratio, 3.43; 95% confidence interval [CI], 1.09-10.82). The incidence of pulmonary metastasis was also significantly higher in the group with liver metastasis (7/16, 43.8%) than in the group with upper rectal cancer (10/130, 7.7%; p<0.05; likelihood ratio, 0.103; 95% CI, 0.03-0.36). There were no significant differences in the radiologic and pathologic TN stages, CEA level, and grade of tumor differentiation between the two groups with or without pulmonary metastasis (p>0.05).

DISCUSSION

In this study, we found no significant difference in the distances between the anal verge and the tumor measured using rectal MRI or endoscopy. On the basis of this result, we used MRI and a ROC analysis to determine a cut-off distance from the anal verge of 5.3 cm for subdividing upper and lower rectal cancer. Further analysis then showed that the incidence of lung metastasis was higher in patients with lower rectal cancer and in patients with liver metastasis.

These findings support our hypothesis that different venous drainage patterns from upper and lower rectal cancers determine the site of metastasis. Although several reports have described skip metastasis from colon cancer bypassing the liver and spreading to the lungs and/or thyroid gland (1), the precise mechanism for this is unclear, and they are regarded as exceptional cases. In general, venous drainage is thought to be the decisive determinant for distant hematogenous tumor spread (5). There are several references to the anatomy of venous drainage in the rectum. Some textbooks and reports state that the upper and middle third of the rectum drain into the superior rectal vein and hence into portal circulation (6), while other sources state that the middle and lower third of the rectum drain into the middle rectal vein and hence into the systemic circulation (5). However, we could find no previous reports that clarified the exact anatomy or variation in the venous drainage system of the rectum through dissection or imaging studies. Therefore, in this study, we used a cut-off value of 5.3 cm from the anal verge, derived from an ROC analysis, in order to divide the rectum into upper and lower compartments. There have been several reports in which the incidence of pulmonary metastasis was found to be significantly different between cases involving rectal or colon tumors (1,4,12). However, to our knowledge, there has been no published report about the incidence of pulmonary metastasis arising from tumors in different parts of the rectum.

We used MRI to determine the location of the tumor. MRI has increasingly been used to determine the best treatment strategy for rectal cancer patients. Rectal MRI provides information about the TN stage, as well as the relationship between a tumor and the mesorectal fascia, which allows tumor resectability to be evaluated, and helps to determine whether patients

Table 2. Multiple factors influencing on the lung metastasis

		Lung metastasis		Multivariate analysis		
		negative (n (%))	positive (n (%))	p-value*	Likelihood ratio	95% Confidence interval
Tumor location				0.035	3.43	1.09~10.82
	Upper	80 (54.8)	6 (4.1)			
	Lower	49 (33.6)	11 (7.5)			
Depth of invasion	Radiologic T stage			0.811		
	T1	3 (2.1)	0 (0.0)			
	T2	16 (11.0)	1 (0.7)			
	T3	101 (69.2)	14 (9.6)			
	T4	9 (6.2)	2 (1.4)			
	Pathologic T stage			0.106		
	T1	6 (5.3)	0 (0.0)			
	T2	19 (16.8)	0 (0.0)			
	T3	77 (68.1)	9 (8.0)			
	T4	1 (0.9)	1 (0.9)			
Node	Radiologic N stage			0.222		
	N0	38 (26.0)	2 (1.4)			
	N1	44 (30.1)	5 (3.4)			
	N2	47 (32.2)	10 (6.8)			
	Pathologic N stage			0.368		
	N0	65 (57.5)	4 (3.5)			
	N1	18 (15.9)	4 (3.5)			
	N2	20 (17.7)	2 (1.8)			
Metastasis	Liver metastasis			0.000	0.103	0.03~0.36
	Negative	120 (82.2)	10 (6.8)			
	Positive	9 (6.2)	7 (4.8)			
Level of CEA				0.954		
	Normal	88 (62.4)	8 (5.7)			
	Elevated	36 (25.5)	9 (6.4)			
Pathologic grade				0.539		
	Mild	61 (41.8)	5 (3.4)			
	Moderate	65 (44.5)	12 (8.2)			
	Poor	3 (2.1)	0 (0.0)			

T stage: primary tumor stage; N stage: lymph node stage; CEA: carcinoembryonic antigen
*p value less than 0.05 is significant

can be treated with surgery alone or require radiation therapy. Furthermore, its multiplanar capability means that rectal MRI can provide relatively accurate information on the size and location of the tumor. Our results show no statistical difference between tumor locations measured using MRI and those measured using endoscopy.

Colon and rectal cancer are frequently described using the combined term "colorectal cancer," and thus, in most cases, integrated statistics and guideline recommendations are used. However, our findings suggest that even upper and lower rectal cancer might need to be considered separately. Based on the venous drainage of the upper rectum, this structure should actually be considered as part of the colon. The incidence of pulmonary metastasis in upper rectal cancer (6/86, 7%) in our study is closer to the known incidence of pulmonary metastasis from colon cancer (5-6%) than from rectal cancer (10-18%).

Similar to the case of liver metastasis from rectal cancers, complete resection of metastatic lung nodules also significantly improves long-term survival (13), and it has been reported that the 5-year survival rate of patients suitable for pulmonary metastasectomy is 38.3-63.7% (14). Advances in surgical techniques have resulted in the indication for pulmonary metastasectomy being extended beyond single isolated lung metastases, but the efficacy of this surgery is still unclear (15). As curative resection of pulmonary metastasis has become possible in a greater proportion of patients, preoperative investigations for metastatic staging of colon and rectal cancer are becoming increasingly important.

An optimal strategy for the distant metatstasis staging of colorectal carcinomas is yet to be defined (12,16). Abdominal CT and pelvic CT are currently widely accepted as suitable preoperative evaluation techniques; however, the value of routine chest CT is still debated. Recent guidelines for colorectal cancer often recommend chest CT as a routine preoperative evaluation modality, and the 2009 National Comprehensive Cancer Network guidelines for colon and rectal cancer recommend chest CT staging as a baseline evaluation (17,18). However, Grossmann et al. found that routine preoperative chest CT staging in colorectal cancer patients is of only limited clinical value (12). The incidence of lung metastasis was low (7%) and only a minority (16%) of the frequent indeterminate lesions were determined to be metastasis. They concluded that routine pulmonary staging of colorectal cancer patients by using chest CT should not be recommended. Several authors have suggested that pulmonary staging in colorectal cancer should be utilized for high-risk patients. Reported high-risk groups included rectal cancer patients with a higher T stage tumor or liver metastasis (4,9,12). In this study, we found that the incidence of pulmonary metastasis was higher among patients with lower rectal cancer and with liver metastasis, and this in turn has implications for its management. On this basis, chest CT could be an important preoperative evaluation for rectal cancer, especially in patients with lower rectal cancer and in those with liver metastasis. In addition, it is suggested that a more intensive evaluation may be needed to investigate indeterminate nodules, and CCRT may be recommended for these patients to reduce systemic relapse. However, additional studies are needed to support these recommendations.

On the basis of the results of our multivariate logistic regression analysis, the incidence of lung metastasis was higher in patients with liver metastasis than in patients without metastasis. This may be because cells from a liver metastasis can easily move into the systemic circulation. This is supported by findings of previous reports that the presence of liver metastasis is a risk factor for lung metastasis in colorectal cancer (4,9,12).

We found no correlation between the incidence of lung metastasis and the radiologic or pathologic TN stage, pathologic differentiation of the tumor, or the level of CEA, on multivariate analysis. Contrary to our finding, Kirke et al. (9) reported a higher incidence of lung metastases associated with a higher T stage. Therefore, further evaluation of the relationship between the incidence of lung metastasis and local tumor stage is needed. Our results also showed no association between the nodal stage of rectal cancer and the incidence of lung metastasis, which supports our hypothesis that venous drainage is a more important determinant of distant hematogenous spread than nodal involvement.

There were several limitations to the present study. First, this series of patients was enrolled from a single institution, and the data were retrospectively reviewed. Second, all patients with lung metastases in this series were diagnosed on the basis of radiologic findings rather than histology or cytology of the lung lesion. For this reason, some of the cases may have had primary lung tumors or other benign lesions. Finally, we were unable to obtain histological confirmation of the preoperative TN stage for 24 patients because they had undergone CCRT or were lost to follow-up. In conclusion, we found that the location of rectal tumors could be accurately determined using rectal MRI, and the incidence of pulmonary metastasis was higher among patients with lower rectal cancer compared to those with upper rectal cancer.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

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