

Pulmonary Metastasis from Rectal Cancer on Chest CT Is Correlated with 3T MRI Primary Tumor Location

흉부단층촬영에서 발견되는 폐 전이의 빈도와 3T 직장자기공명영상에서의 종양의 위치 사이의 관련성

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Purpose: To evaluate the association between the incidence of pulmonary metastasis on chest CT and the location of the primary tumor on rectal MRI.

Materials and Methods: One hundred and nine consecutive patients with rectal adenocarcinoma underwent chest CT and 3T rectal MRI. Two radiologists classified the tumor on MRI as an upper (> 10 cm from the anal verge), mid (5-10 cm), or lower rectal tumor (< 5 cm) by consensus. All chest CT scans were retrospectively reviewed for the presence of metastasis. We used Fisher's exact test to evaluate the correlation between the incidence of pulmonary metastasis with the location of the rectal cancer and the Mantel-Haenszel test to control for local tumor stage.

Results: We only included the 60 patients with upper ($n = 26$) or lower ($n = 34$) rectal cancer, because of the complicated venous drainage system of the mid rectum. Among these, 9 (15%) showed evidence of pulmonary metastasis on chest CT and almost all (89%, 8/9) patients had lower rectal cancer. The incidence of pulmonary metastasis between the two groups was statistically different ($p < 0.05$) when local tumor stage was controlled.

Conclusion: The incidence of pulmonary metastasis was significantly higher for lower than upper rectal cancers when the T-stage of the tumor was accounted for.

Index terms

Rectal Neoplasm
Magnetic Resonance Imaging
Neoplasm Metastasis

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INTRODUCTION

Colorectal cancer is one of the most frequent neoplasms, with an incidence of 40 cases per 100,000 worldwide, and 45.8 per 100,000 in Korea (1). Pulmonary metastasis is the second most common site of metastasis from colorectal cancer after hepatic metastasis. In particular, pulmonary metastasis in rectal cancer has significance because rectal cancer is associated with pulmonary metastasis more than colon cancer (2). On CT, the incidence of pulmonary metastasis in patients with rectal cancer ranged from 10-18% and for colon cancer, 5-6% (3). In addition to hepatic metastasis from rectal cancer, complete resection of pulmonary metastasis helps to

prolong survival in selected patients (4). For this reason, accurate preoperative staging is essential.

The anatomy of the venous and lymphatic channels in the rectum is complex. Venous drainage occurs mainly through a portal route in the upper portion of the rectum and by a systemic route in the lower portion of the rectum (5) (Fig. 1). Although it is well known that different areas of the rectum are drained by different veins, few published studies have demonstrated an association between the location of rectal cancer and the incidence of pulmonary metastasis.

Consequently, the purpose of this study was to evaluate the correlation between the incidence of pulmonary metastasis and the location of the tumor within the rectum.

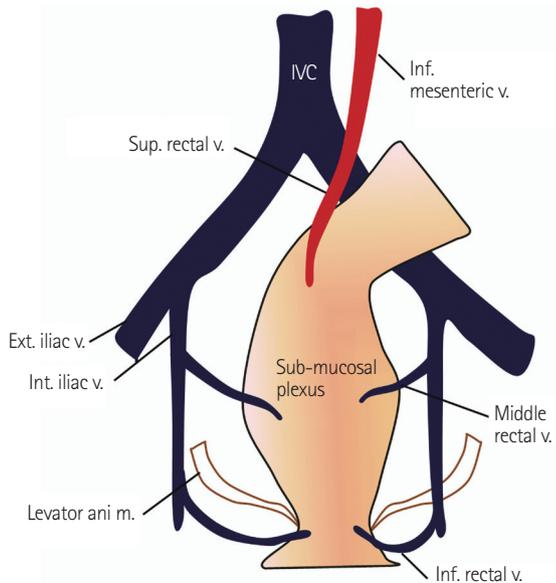


Fig. 1. Anatomy of the rectal venous plexus. The rectum has two drainage veins. The upper and middle thirds of the rectum drain primarily into the superior rectal vein and finally empty into the liver via the inferior mesenteric vein and portal vein. However, the lower third of the rectum drains into the middle rectal vein. The blood in the middle rectal vein skips the liver because it drains directly into the IVC. Note.—IVC = inferior vena cava

MATERIALS AND METHODS

Study Population

From July 2007 to March 2009, 137 consecutive patients were referred to our institute to undergo an MRI of the rectum for preoperative rectal cancer staging. The institutional review board approved this study, and informed consent was waived because of the retrospective nature of the study. All patients were confirmed to have a rectal adenocarcinoma based on the histological analysis of an endoscopic biopsy. High-resolution rectal MRI was performed using a 3T scanner within 2 weeks before treatment. Among the patients, 28 were excluded because of no available chest CT scan within 2 weeks of performing the rectal MRI examination. A total of 109 patients were therefore included in this study. Clinical manifestations seen in these 109 patients (76 men, 33 women; mean age, 62.3 years; range, 30-97 years) included abnormal findings on screening endoscopy ($n = 84$), proven rectal cancer in another hospital ($n = 10$), bowel habit changes ($n = 6$), hematochezia ($n = 5$), positive stool occult blood ($n = 3$), and abdominal pain related to a large bowel mechanical obstruction ($n = 1$).

Histopathologic tumor grading revealed that of 109 adenocarcinomas, 57 were well-differentiated, 49 were moderately-differentiated, and 2 were poorly-differentiated. No pathology was available for one patient who initially presented with mechanical obstruction because of chemoradiotherapy performed before a biopsy specimen was taken.

Imaging Techniques

For bowel preparation, the patients were asked to perform rectal cleansing within 3 hours before the study using 133 mL of sodium phosphate (Fleet enema®; CB Fleet, Lynchburg, VA, USA). In the MR room, an intravenous or intramuscular anti-peristaltic agent (ALGIRON®; Boehringer Ingelheim, Ingelheim, Germany) was injected to minimize motion artifacts and 150-250 mL of warm saline was administered into the rectum via a rectal tube for luminal distension.

All patients were examined when they were breathing freely in the supine position on a 3T MRI unit (Magnetom Tim Trio, Siemens Medical Solutions, Erlangen, Germany). A 4-channel flexible surface coil (Flex Large; Siemens Medical Systems, Germany) was used. Standard two-dimensional (2D) T2-weighted fast spin-echo sequences were used in three planes to image the entire pelvis. The sagittal plane was used as a reference image to obtain the axial and coronal planes so that they would be exactly perpendicular and parallel to the primary tumor, respectively. For axial, coronal, sagittal T2-weighted images, the following settings were used: repetition time/echo time = of 3,560/113 ms, echo train length = 14, slice thickness = of 3 mm, gap = 0.3 mm, matrix = 320 × 320, and a field-of-view = 5 cm. One signal was acquired, and the sequence duration was 2 min. For the axial T1-weighted images, the settings were as follows: repetition time/echo time = 538/11, echo train length = 60, slice thickness = 5-mm, gap = 0.8-mm, matrix = 448 × 358, and field-of-view = 25-cm. A SENSE factor of two was used, accompanied by the acquisition of two signals with a sequence duration was 3-4 min.

Chest CT scans were performed using either a 4-slice scanner (Volume Zoom; Siemens Medical Solutions, Iselin, NJ, USA) ($n = 46$) or a 64-slice scanner (Brilliance 64, Philips Medical Systems, Cleveland, Ohio, USA) ($n = 63$). The scan was performed using a 1.5-mm collimator with a slice thickness of 5-mm and a construction interval of 5-mm, as well as 100 mL

of nonionic contrast media [iopromide (Ultravist, Bayer HealthCare, Berlin, Germany), (Pamiray, Dongkook Pharmaceutical, Seoul, Korea)]. Iomeprol (Iomeron, Bracco, Milan, Italy) was used as an intravenous contrast material and was injected at a rate of 2.5 mL/sec with image acquisition starting after a 40-second delay.

Image Analysis

Rectal MRIs and chest CT scans were examined retrospectively by two abdominal imaging specialists (8 and 5 years experience in abdominal imaging experience, respectively). The reviewers were blinded to all clinical information and analyzed the images by consensus. The images were reviewed using a picture archiving and communication system workstation (piviewer, INFINITT, Seoul, Korea).

The tumor was classified based on location (one of three locations) and rectal MRI results. 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. The anal verge was defined as the point at which the levator ani muscle attached to the rectum on MRI (Fig. 2) (6). Sagittal T2-weighted images were primarily used to measure the distance; axial and oblique coronal T2-weighted images were used secondarily to determine the upper and lower margins of the tumors when required. All of these processes were performed manually. Tumor locations were defined as the upper (10-15 cm from anal verge), mid (5-10 cm), and lower (< 5 cm) rectum by consensus (7).

The radiologists also evaluated rectal MRI scans for local tumor staging using the tumor-node-metastasis (TNM) staging system. The radiologists were blinded to the original reports and pathologic results. The TNM classification of MRI images was performed as described on previous reports (7).

All of the chest CT scans were reviewed retrospectively for the presence of metastasis by the two radiologists. The presence of a parenchymal lung nodule (≥ 1 cm if single and > 0.5 cm if multiple) with a soft tissue component without calcification was considered positive for the presence of metastasis (Fig. 3) (8). The size of the lung nodules were measured on a lung window setting (window level, -649; window width, 1,400) and then the setting was changed to a mediastinal win-

dow (window level, 45; window width, 440) to exclude calcified granulomas.

Statistical Analysis

We applied Fisher's exact test to evaluate the correlation between the incidence of pulmonary metastasis with the location of the rectal cancer in the entire group and in each local tumor stage group. We also used the Mantel-Haenszel test to verify this correlation while controlling for the effect of local tumor stage. A p -value < 0.05 was considered statistically significant. Statistical analyses were performed using the statistical software package SPSS, version 15.0, for Windows (SPSS



Fig. 2. The method used to determine the location of the tumor. A patient with a mid rectal tumor (arrowhead). On the sagittal T2-weighted image, a line (dotted line) was drawn along the midline of the rectal lumen and then another two lines (solid lines) were drawn vertically at the level of the lower margin of the tumor and the anal verge. The distance from the lower margin of the tumor to the anal verge was measured in a zigzag pattern (double-headed arrows).

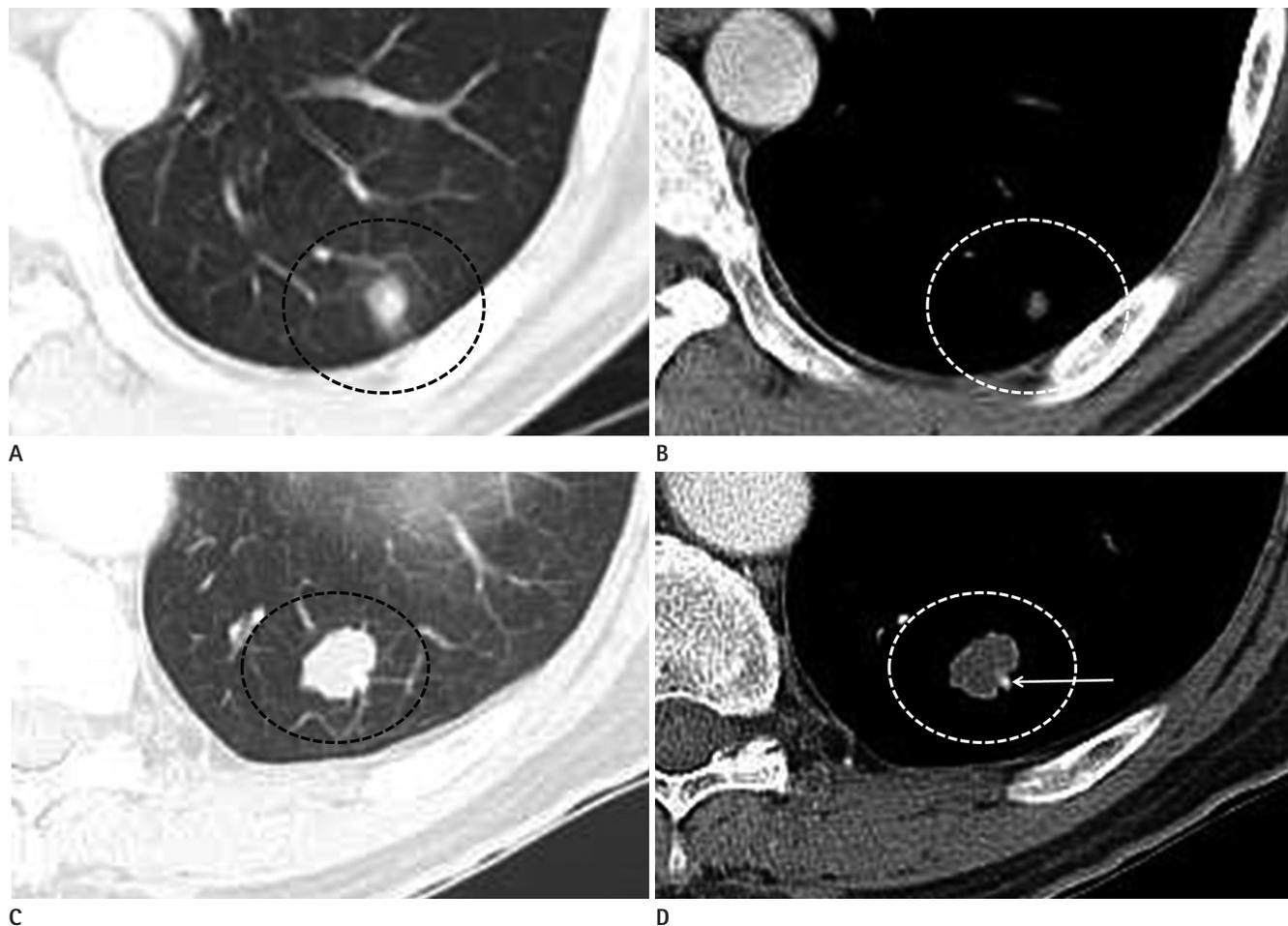


Fig. 3. Chest CT scans of two patients who were considered to have pulmonary metastases. Chest CT scans with the lung **(A)** and mediastinum **(B)** setting of a 37-year-old man with rectal adenocarcinoma. A nodule (dotted circles) measuring about 0.9 cm in size without calcification was detected. Another nodule larger than 0.5 cm in diameter was also detected (not shown), and therefore, this patient was considered to have pulmonary metastasis. Chest CT scans with the lung **(C)** and mediastinum **(D)** setting of a 69-year-old man with rectal adenocarcinoma. A nodule (dotted circle) measuring about 1.9 cm in size without calcification in diameter is visible. The nodule was determined to be a metastatic lesion. The hyperdense dot beside the nodule (arrow) is a nearby enhanced pulmonary artery.

Inc., Chicago, IL, USA).

RESULTS

Of the 109 patients, 2 were excluded from the statistical analysis because the measured distance of the tumor from the anal verge was greater than 15 cm and therefore regarded to be a rectosigmoid colon cancer. Among 107 patients included (74 men, 33 women; mean age, 62.3 years; range, 30-97 years), 34 had a tumor of the lower rectum, 47 had a tumor of the mid rectum, and 26 had a tumor of the upper rectum. Evidence of pulmonary metastasis was identified in 15/109 (14%) patients on chest CT scans (Fig. 4). Of these 15 patients who

had CT evidence of lung metastasis, 8 had a lower rectal tumor, 6 had a mid rectal tumor, and 1 had an upper rectal tumor. Furthermore, 47 of the 107 patients with a mid-rectal primary were excluded from the statistical analyses to minimize confusion regarding venous drainage from the mid rectum and the presence of the submucosal plexus.

In the 60 patients with upper and lower rectal cancer, 9 patients (15%) showed pulmonary metastasis on chest CT scan. Clinical parameters of these 9 patients with pulmonary metastasis are shown in Table 1. The incidence of pulmonary metastasis in patients with lower rectal cancer (8/34, 23.5%) was higher than in patients with upper rectal cancer (1/26, 3.8%), but this difference was not statistically significant ($p >$

0.05) (Table 2). Patients with lower or upper rectal cancer ($n = 60$) were subdivided into four sub-groups based on radiologic T-staging results, and Fisher's exact test was applied to each group (Table 3). Of the 8 patients with pulmonary metastasis, 7 had T3 rectal cancer based on the presence of signal intensity extending into the perirectal fat on rectal MRI (7), while 1 patient had T4 cancer due to vaginal invasion. For the T3 lesions, the incidence of pulmonary metastasis in lower rectal cancer (7/34, 20.6%) was higher than in upper rectal cancer (1/23, 4.3%), and the difference was statistically significant ($p = 0.048$).

The incidence of pulmonary metastasis was significantly higher in patients with lower rectal cancer when excluding the effect of T-stage of the tumor ($p = 0.041$).

DISCUSSION

The results of our study indicate that the incidence of lung metastasis in patients with lower rectal cancer is significantly higher than that in patients with upper rectal cancer when the effect of T-stage of the tumor is excluded. In other words, the location of the rectal cancer influences the incidence of pulmonary metastasis.

The upper and lower rectum is drained by different venous

drainage systems (5). 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 rectum and the upper anal canal into the systemic system via the internal iliac veins. He-

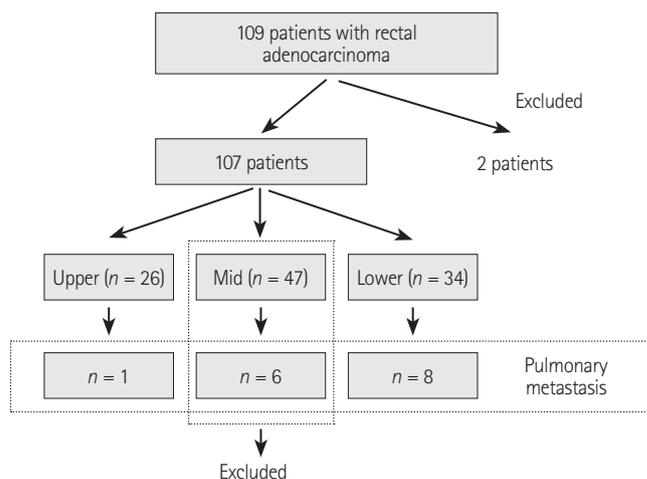


Fig. 4. Selection of patients for the study. Of the 109 patients considered, 2 were excluded because the measured distance to the anal verge was over 15 cm. Of the 107 patients, 34 patients had a lower rectal tumor, 47 had a mid rectal tumor, and 26 had an upper rectal tumor. Of the 15 patients who had chest CT scans suspicious for lung metastasis, 8 had a primary rectal tumor, 6 had a mid rectal tumor, while 1 had an upper rectal tumor. The patients with a mid rectal tumor were excluded from the statistical analyses because of the complexity of the venous drainage of the mid rectum.

Table 1. Clinical Parameters of Patients with Pulmonary Metastasis

Patient No.	Sex	Age	Location	CEA*	Liver Metastasis	Radiologic T Stage on MRI	Pathologic Differentiation
1	M	60	Lower	4.5	-	3	Moderate
2	M	53	Lower	5.7	-	3	Well
3	M	60	Lower	7.5	-	3	Moderate
4	M	61	Lower	2.4	-	4	Well
5	F	61	Lower	2.3	-	3	Moderate
6	M	66	Lower	3.3	-	3	Moderate
7	M	69	Lower	2.2	-	3	Well
8	M	66	Lower	2601	+	3	Moderate
9	F	61	Upper	6.1	+	3	Moderate

Note. — *normal range, 0–5 ng/mL.
CEA = carcinoembryonic antigen (ng/mL)

Table 2. Incidence of Pulmonary Metastasis according to the Tumor Location of the Rectum at 3T MRI

		Metastasis		<i>p</i> -value
		+ (9/60, 15%)	- (51/60, 85%)	
Tumor location	Upper ($n = 26$)	1 (4%)	25 (96%)	$> 0.05^*$
	Lower ($n = 34$)	8 (24%)	26 (76%)	

Note. — *Fisher's exact test was applied.

Table 3. Statistical Result in Four Sub-Groups Subdivided according to Radiologic T Staging

	T stage	Tumor Location	Pulmonary Metastasis		p-value*
			-	+	
1		upper	0	0	> 0.05
		lower	2	0	
2		upper	0	0	> 0.05
		lower	4	0	
3		upper	22	1	< 0.05
		lower	17	7	
4		upper	3	0	> 0.05
		lower	3	1	

Note.—*Fisher’s exact test was applied.

patic or pulmonary metastases occur when the primary tumor invades the venous structure and tumor cells are carried as an embolus along veins to a target organ. Most of the venous system of the rectum drains via the portal system, which explains why the first site of hematogenous dissemination is usually the liver. However, venous drainage from the lower rectum occurs primarily via middle rectal veins to the systemic circulation, skipping the liver. Therefore, tumors arising in the lower rectum may theoretically initially metastasize to the lungs. In our study, 89% (8/9) of pulmonary metastases were found in patients with lower rectal cancer, while only one pulmonary metastasis was found in a patient with upper rectal cancer. However, the factors influencing the incidence of pulmonary metastasis are variable. The T-stage of tumors is known to be an important determinant of pulmonary metastasis. Kirke et al. (8) reported that the incidence of lung metastasis increased with higher T-stage in rectal tumors.

Preoperative investigations for staging of colon and rectal cancer are very important. However, an optimal strategy for distant staging of colorectal carcinomas has not yet been defined (9, 10). Abdominal and pelvis CT scans are currently widely accepted as suitable preoperative evaluation techniques. The value of chest CT scans as a routine requirement, however, is controversial. In a multicenter study, preoperative chest CT scans were performed in 37% of patients with colorectal tumors. Among those patients, a significant number (18%) of chest CT examinations revealed abnormalities suspicious for metastatic disease in the initial work-up (10). Several studies have investigated the necessity of preoperative chest CT scans for patients with colorectal cancer. Kronawitter et al. (11) questioned the use of chest CT scans as routine pre-

operative workups for potentially resectable liver metastasis from colorectal carcinoma. According to their study, indications of lung metastasis were found on CT scans in only 10 of 202 patients (5%) with negative chest radiographs. However, McIntosh et al. (12) reported that CT scans are more sensitive than radiography alone for the pulmonary staging of colorectal cancer.

Despite the high incidence of colorectal cancer and importance of initial staging, an optimal strategy for distant metastatic disease has yet to be defined. The European Society for Medical Oncology and the Dutch Working Group for Gastrointestinal Tumours recommend in their guidelines the use of routine chest X-rays or preferably chest CT scans to exclude pulmonary metastasis in patients with colorectal cancer during the initial staging (13). In the National Comprehensive Cancer Network guidelines, however, chest CT scans are mandatory during the preoperative workup for rectal cancer. These guidelines recommend that chest CT scans be performed as part of preoperative staging for all patients, followed by annual CT scans for the first 3 years in patients considered to be at high risk for recurrence and/or those with increased carcinoembryonic antigen levels (14).

Positron-emission tomography-computed tomography (PET-CT) is another method for evaluating the pulmonary metastasis. The value of PET-CT compared to CT has been studied in the preoperative evaluation of colorectal cancer (3). There is no previous report demonstrating the superiority of PET-CT to CT. Because of poor anatomic detail due to a minimum resolution of 5-6 mm, PET-CT is limited in the detection of small nodules. And for lesions larger than 5 mm, a negative 18F-fluorodeoxyglucose (FDG) uptake frequently

does not provide any information because of a high false-negative rate.

In our study, we investigated the incidence of pulmonary metastasis according to the location of the tumor using 3T rectal MRI. Our results show that the location of the tumor is another factor that may influence the incidence of pulmonary metastasis, and can potentially be used as a factor in deciding which patients should mandatorily undergo preoperative chest CT scans. When we controlled for the effect of T-stage using statistical analysis, we found that the incidence of pulmonary metastasis was significantly higher in patients with lower rectal tumors than in patients with upper rectal tumors. Elucidating the factors that influence the incidence of pulmonary metastasis from rectal cancer will help determine if preoperative chest imaging is required.

Similar to liver metastasis from rectal cancers, complete resection of metastatic lung nodules significantly improves long-term survival (15). Multiple series have reported 5-year survival rates after complete resection of lung metastasis ranging from 30 to 60% (10). Both solitary and multiple or bilateral metastasis are also candidates for complete resection. Moreover, recent studies have reported that surgical resection of both liver and lung metastases increases survival in a highly select group of patients (16). More dedicated evaluation of pulmonary metastasis is needed because in some studies, multiple lung metastasis and lesions of more than 3 cm have been shown to be associated with a poor outcome (17). In particular, we advise that chest imaging studies be performed for patients with rectal tumors of stage T3 or lower, because these lung metastases can be treated surgically without chemotherapy or radiation therapy.

We found that the incidence of pulmonary metastasis was significantly higher in patients with lower rectal cancer (20.6%) than those with upper rectal cancer (4.3%) for T3 stage tumors. On the basis of the anatomy of the rectum, the incidence of pulmonary metastasis is expected to be higher for rectal cancer than colon cancer. In addition, we found that 14% (15/109) of patients showed signs suspicious of pulmonary metastatic disease. Based on our results, the strategy used for preoperative evaluation of rectal cancers can be determined according to the location of the tumor. If the rectal cancer is located in the lower rectum and the local stage is T3

or greater, then a preoperative chest CT scan is absolutely required during the initial work up. Even if the exact local tumor staging is not known, we recommend that preoperative chest CT scans be performed in patients with lower rectal cancer.

Our study had several limitations. First, there was a selection bias because of the retrospective nature of the study. Second, only a small number of patients were enrolled and tumors of different TNM stages were included. Further, we were not able to analyze the data with respect to the T1, T2, and T4 stages because of low sample numbers. Nevertheless, we found that the incidence of pulmonary metastasis was significantly higher in patients with T3 lower rectal cancers than T3 upper rectal cancers. Third, we did not obtain histopathological confirmation or perform long term follow-up studies of patients with suspected pulmonary metastasis. Fourth, we used radiologic staging instead of pathologic staging for local tumor staging. However, it is known that preoperative 3-T MRI using a phase array coil accurately reflects the T-stage of



Fig. 5. A 34-year-old man with rectal adenocarcinoma. The sagittal T2-weighted image shows a pedunculated rectal mass (arrow). The shape of the mass and more uncommonly, the acute angled and dilated rectum makes it difficult to determine the location of the tumor.

rectal cancers (18). Finally, our method of determining tumor location was not objective because we used manual measurements (Fig. 5) and various degrees of distension and, angulations of the rectum can affect the location of the tumor. To control for this, we excluded patients with mid rectum tumors from the statistical analyses.

In patients with primary rectal cancer, accurate assessment of pulmonary metastasis is essential. The factors influencing the incidence of lung metastasis should be considered in the preoperative evaluation. We demonstrated that the incidence of pulmonary metastasis was significantly higher in patients with lower rectal cancer than in patients with upper rectal cancer after accounting for tumor stage. In conclusion, we consider preoperative chest CT scans to be essential in patients with lower rectal cancer.

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흉부단층촬영에서 발견되는 폐 전이의 빈도와 3T 직장자기공명영상에서의 종양의 위치 사이의 관련성

한나연 · 김민주 · 박범진 · 성득제 · 정규병 · 오유환

목적: 흉부단층촬영에서의 폐 전이 빈도와 3T 직장 자기공명영상에서 직장암의 위치간 상관관계를 연구하고자 하는 것이다.

대상과 방법: 선암으로 진단된 109명의 환자에서 치료시작 전 2주 이내에 3T 직장 자기공명촬영과 흉부단층촬영을 시행하였다. 두 명의 영상의학과 의사가 합의 하에 직장 자기공명촬영에서 종양의 위치를 항문면에서의 거리에 따라 상부(10~15 cm), 중부(5~10 cm), 하부(< 5 cm)의 세 부분으로 나누었다. 폐 전이 평가를 위해 흉부단층촬영을 후향적으로 검토하였다. 피셔의 정확검정을 이용하여 폐 전이의 빈도와 직장암의 위치 사이의 관련성에 대하여 평가하였으며, 맨틀-헨젤 검정을 통해 T-병기의 영향을 배제하였다.

결과: 109명의 환자 중, 15 cm 이상의 위치에 있는 2명의 종양은 S상 결장암으로 생각하여 제외하였고 나머지 107명 중에서 직장 중부의 종양은 직장의 정맥 해부학을 고려하여 볼 때, 정맥 배출이 다양하여 제외하였다. 상부($n = 26$)와 하부($n = 34$) 직장선암을 가진 60명의 환자를 연구에 포함하였다. 흉부단층촬영에서 9명의 환자(15%)가 폐 전이를 보였으며, 이 중 8명의 환자(24%, 8/24)는 하부 직장암을 가진 환자였다. T-병기의 영향을 배제하였을 때 두 군 간에 폐 전이의 빈도는 통계적으로 유의한 차이를 보였다($p < 0.05$).

결론: 직장암에서의 폐 전이는 T-병기의 영향이 제외되었을 때 하부직장암에서 더 높은 빈도를 보였다.

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