ORIGINAL CONTRIBUTION

Predictive Factors for Pulmonary Metastases After Curative Resection of Rectal Cancer Without Preoperative Chemoradiotherapy

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OBJECTIVE: The aim of this study was to clarify the actuarial incidence of pulmonary metastases and risk factors for pulmonary metastases after curative resection of rectal cancer without preoperative chemoradiotherapy.

DESIGN: This study was a retrospective review.

PATIENTS: Data for 314 patients who underwent R0 resection for rectal cancer without preoperative chemoradiotherapy from 2000 to 2006 were reviewed. The mean duration of follow-up was 57.0 months.

RESULTS: Pulmonary metastases developed in 41 patients. Mean duration from rectal surgery to identification of pulmonary metastases was 21.1 months. Surgery for pulmonary metastases was performed first for 19 patients (46.3%), and all patients achieved R0 surgery. Multivariate analysis revealed that tumor depth (T3 to T4), lymph node ratio (>0.091), and tumor location (anal canal) were significant independent risk factors for pulmonary metastases. Five-year actuarial incidence of pulmonary metastasis increased significantly with increased numbers of risk factors (0 factors, 1.1%; 1 factor, 13.2%; ≥2 factors, 40.1%). In terms of lateral pelvic lymph node involvement, the number of lateral pelvic lymph node involvements (≥4) and the distribution of lateral pelvic lymph node metastases (bilateral) were significant risk factors for pulmonary metastases.

CONCLUSIONS: The present study clearly demonstrated predictive factors for pulmonary metastases after R0 resection of rectal cancer without preoperative chemoradiotherapy. Actuarial incidence of pulmonary metastases was significantly related to the number of risk factors present. The data from the present study should facilitate the establishment of novel algorithms for predicting pulmonary metastases after resection of rectal cancer, which may lead to the appropriate surveillance strategies after rectal surgery.

KEY WORDS: Rectal cancer; Pulmonary metastasis; Lymph node ratio; Lateral pelvic lymph node dissection.

Outcomes after surgery for rectal cancer are predominantly determined by local recurrence and distant metastases.[1] The lung is one of the most common sites of metastases from rectal cancer. To date, surgical resection has been the only radical treatment available for patients with pulmonary metastases, and several studies have focused on outcomes after the resection of a pulmonary tumor from rectal cancer. These studies reported overall 5-year survival rates after pulmonary metastasectomy of 32.4% to 67.8%, demonstrating acceptable long-term survival.[2–7] Conversely, the actuarial incidence of pulmonary metastasis, the predictive factors for pulmonary metastasis after complete (R0) resection of rectal cancer, and what proportion of patients with pulmonary metastases meet the indications for surgery remain unclear. Only a few studies have reviewed the incidence of pulmonary metastases in rectal cancer.[8–11] These studies estimated that approximately 1% to 12% of patients with rectal cancer would develop isolated pulmonary metastases.[8–11] Of patients with isolated pulmonary metastases, approximately 7% to 14% of patients would be considered candidates for pulmonary metastasectomy.[8–11] However, those data were relatively heterogeneous in terms of

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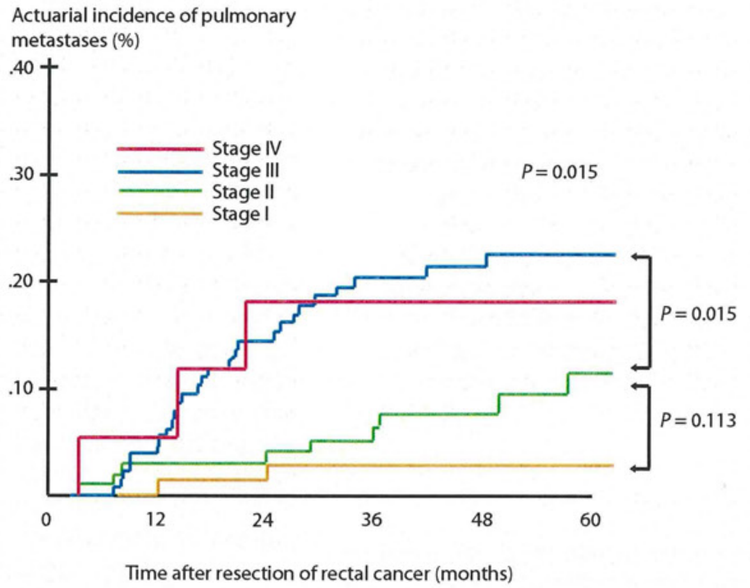
patients' backgrounds and diagnostic tools, and the reevaluation of the actuarial incidence of pulmonary metastasis after rectal surgery with the use of advanced diagnostic tools and therapies is essential.

The aim of the present study was to assess the actuarial incidence of pulmonary metastases as the first site of metastasis after R0 resection of rectal cancer, and to clarify the patterns of occurrence and predictive factors for pulmonary metastases.

METHODS

The present study was a retrospective review of the medical records of a total of 314 patients (219 men, 95 women) who underwent R0 resection for rectal cancer at the National Cancer Center Hospital East, Chiba, Japan from January 2000 to October 2006. Mean duration of follow-up for the 314 patients was 57.0 months (SD, 25.1 mo). Aside from the 314 patients, the following patients were excluded from the present study: patients with rectal cancer who underwent preoperative chemoradiotherapy (n = 47); patients with pulmonary metastases who had other metastases or local recurrence before pulmonary metastases after rectal surgery (n = 13) (liver, n = 7; local, n = 4; distant lymph node, n = 2); patients with rectal carcinoma in situ (n = 4); patients lost to follow-up (n = 8); patients with other concomitant cancer at rectal surgery (n = 16); patients with malignant carcinoid or melanoma (n = 3); patients showing preoperatively identified tiny indeterminate lesions in the lung and then confirmed pulmonary metastasis during follow-up (n = 5). Patients with preoperative chemoradiotherapy were excluded from the present study to avoid bias regarding pathological changes in surgical specimens. Each of the 47 patients with preoperative chemoradiotherapy who were excluded showed clinical T3 lower rectal cancer and had agreed to participate in clinical trials for preoperative adjuvant therapy, because preoperative chemoradiotherapy for resectable rectal cancer was not standard at that time in Japan.

Patients were staged using colonoscopy with biopsy, barium enema, and 5-mm section contrast-enhanced helical chest-abdomen-pelvis CT. Patients were subdivided into 3 groups according to the tumor location: upper rectum, lower rectum, and anal canal.[12] The definitions of the 3 groups were as follows: 1) upper rectum: the portion of large intestine that locates between the inferior border of the second sacral vertebra and the level of the peritoneal reflection, which is equivalent to 10 to 15 cm from the anal verge; 2) lower rectum: the portion of large intestine that locates between the peritoneal reflection and the superior border of the puborectal muscle, which is equivalent to 4 to 10 cm from the anal verge; and 3) anal canal: the tubular portion that extends from the superior border of the puborectal muscle to the anal verge, which is equivalent to 0 to 4 cm from the anal verge. The location of the rectal tumor was assessed by barium enema, CT, and digital rectal examination.



No. at risk						
Stage IV	18	16	12	7	2	1
Stage III	131	122	103	88	67	49
Stage II	97	92	91	80	62	44
Stage I	68	68	66	58	40	32

FIGURE 1. Kaplan-Meier curves for pulmonary metastases in 314 patients with rectal cancer according to UICC stage of rectal cancer. UICC = International Union Against Cancer.

TABLE 1. Characteristics of 41 patients with pulmonary metastases

Variables	*Results n (%)*
Sex (male/female)	30/11
Age at rectal surgery, y	59.5 ± 10.8
Site of primary tumor	
Upper rectum	17 (41.5)
Lower rectum	20 (48.8)
Anal canal	4 (9.8)
UICC stage	
I	2 (4.9)
II	9 (22.0)
III	27 (65.9)
IV	3 (7.3)
Adjuvant chemotherapy for rectal cancer	12 (29.3)
Simultaneous hepatectomy for liver metastases at rectal surgery	3 (7.3)
Concurrent metastases or local recurrence at diagnosis of pulmonary tumor	6 (14.6)
Pulmonary disease-free interval, months	21.1 ± 13.0
Pulmonary tumor size, mm	15.4 ± 6.5
No. of pulmonary tumors	
1	16 (39.0)
2	7 (17.1)
3	2 (4.9)
≥4	16 (39.0)
Distribution of pulmonary tumor	
Unilateral	22 (53.7)
Bilateral	19 (46.3)
Therapy for pulmonary metastases	
Operation	19 (46.3)
Chemotherapy	17 (41.5)
Best supportive care	5 (12.2)

UICC = International Union Against Cancer.

All patients underwent resection of the primary tumor with lymph node dissection. Patients with rectal cancer underwent total mesorectal excision or tumor-specific mesorectal excision. Lateral pelvic lymph node (LPLN) dissection with autonomic nerve preservation was usually performed in patients with clinical T3 to T4 lower rectal cancer.[13,14] After manual dissection of lymph nodes in fresh specimens, all specimens were fixed in 10% phosphate-buffered formalin, embedded in paraffin, sectioned, and stained using hematoxylin and eosin. Each case was evaluated by at least 2 independent pathologists for histopathological type, depth of tumor invasion, number of lymph node involvements, vascular invasion, lymphatic invasion, and margin status. Histological diagnosis was performed according to the World Health Organization intestinal tumor classification.[15] Patients with lymph node involvement had undergone adjuvant chemotherapy since 2003, if the patients had good performance status and agreed to the adjuvant chemotherapy.

Routine follow-up consisted of physical examination, laboratory tests including estimation of serum CEA level, and 5-mm section contrast-enhanced helical chest-abdomen-pelvis CT or abdomen-pelvis CT with chest radiography (posteroanterior and lateral views). [^{18}F]Fluorodeoxyglucose positron emission tomography and CT was performed when routine imaging was normal despite the elevation of tumor marker or normal imaging was unable to distinguish the lesions from benign to malignant. After rectal operation, patients were followed up at 3-month intervals for the first 3 years, then at 6-month intervals for at least a total of 5 years.

Pulmonary metastasis was diagnosed by radiological evidence suggestive of lung metastases. Findings on CT or chest radiography were agreed on by 2 independent radiologists. Pathological confirmation by at least 2 independent pathologists was obtained for patients who underwent operation for pulmonary metastases. The criteria for pulmonary resection were as follows: metastatic lesions confined to the lung and technically resectable; no evidence of extrathoracic metastases, with the exception of resectable hepatic metastasis; and cardiorespiratory function capable of tolerating complete resection of all pulmonary tumors.[2,16] Contrast-enhanced helical CT (chest, 2-mm slice thickness; abdomen, 5-mm slice thickness) was routinely performed to exclude patients with extrapulmonary metastases or unresectable multiple pulmonary metastases before resection of pulmonary metastases.

Statistical Analysis

Actuarial incidence of pulmonary metastases and risk factors for each variable on pulmonary metastases were evaluated using the Kaplan-Meier method and the log-rank test. Factors related to occurrence of pulmonary metastases were analyzed with the Cox proportional hazards regression model for multivariate analysis. All statistical analyses were performed using SPSS version 13.0J software (SPSS Japan, Tokyo, Japan). Values of $P < .05$ were considered statistically significant.

TABLE 2. Kaplan-Meier analysis of risk factors for pulmonary metastases after R0 resection of rectal cancer in terms of the number of regional lymph node metastases

	Rectal cancer		
No. of involved regional LN	*n*	*5-y lung metastasis rate (%)*	*P*
≥1	145	23.8	<.001
0	169	7.6	
≥2	91	25.2	.521
1	54	21.2	
≥3	70	31.7	.046
1–2	75	16.9	
≥4	49	30.9	.112
1–3	96	20.3	

LN = lymph node.

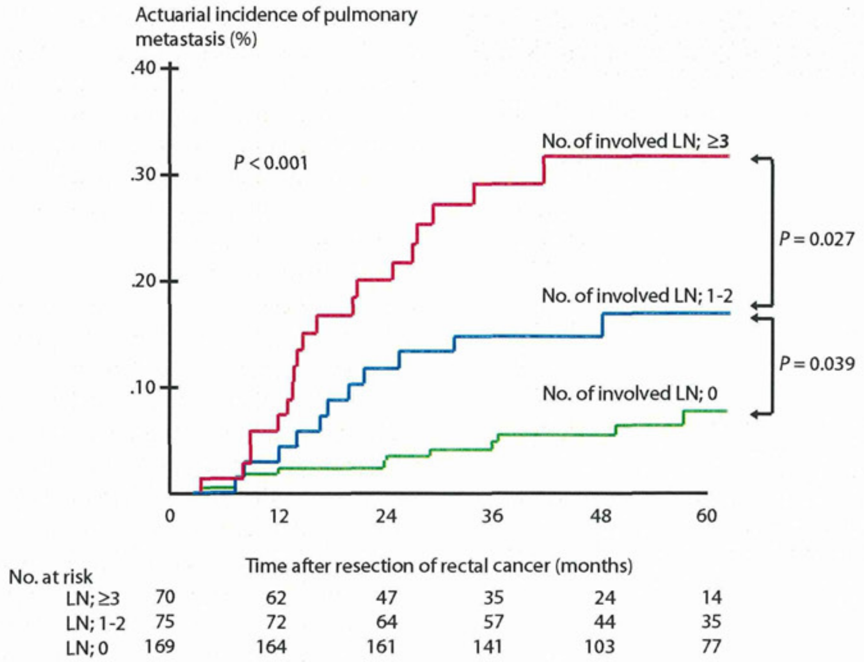


FIGURE 2. Kaplan-Meier curves for pulmonary metastases after R0 resection of rectal cancer according to the number of regional lymph node metastases. LN = lymph node.

RESULTS

Characteristics of 314 Patients With R0 Rectal Surgery

Mean age of the 314 patients with rectal cancer was 60.1 years (SD, 11.4 y). The primary tumor was located in the upper rectum in 116 patients, the lower rectum in 188 patients, and the anal canal in 10 patients. International Union Against Cancer staging was as follows: stage I, n = 68; stage II, n = 97; stage III, n = 131; and stage IV, n = 18.

A total of 131 patients with clinical T3 to T4 rectal cancer located in the lower rectum or anal canal underwent LPLN dissection in addition to total mesorectal excision with regional lymph node dissection.[13,14] Simultaneous hepatectomy for liver metastases was performed in 15 patients. Various adjuvant chemotherapy regimens were administered for 60 patients with rectal cancer (tegafur-uracil (UFT)/leucovorin (LV), n = 22; 5-fluorouracil (5-FU)/LV, n = 17; oxaliplatin combined with infusional 5-FU/LV (FOLFOX6), n = 8; UFT, n = 6; irinotecan combined with infusional 5-FU/LV (FOLFIRI), n = 2; irinotecan combined with bolus 5-FU/LV (IFL), n = 3; and 5-FU, n = 2).

Actuarial Incidence of Pulmonary Metastases

Of the 314 patients with rectal cancer, 41 developed pulmonary metastases during the study period. Mean duration from rectal surgery to identification of pulmonary metastases was 21.1 months. Pulmonary metastases were identified within 36 months after rectal surgery in 37 patients (90.2%). No patients developed pulmonary metastases >60 months after rectal surgery during the study period. There was no difference in the mean duration from rectal surgery to identification of pulmonary metastases in terms of imaging modalities (chest radiography (n = 16), 18.8 months; CT (n = 25), 22.5 months; $P = .377$). The overall occurrence rates of 5-year pulmonary metastasis according to International Union Against Cancer stage were as follows: stage I, 3.0%; stage II, 11.4%; stage III, 22.5%; and stage IV, 18.2% in patients with rectal cancer (Fig. 1).

TABLE 3. Kaplan-Meier analysis of risk factors for pulmonary metastases after R0 resection of colorectal cancer in terms of lateral pelvic lymph node metastases

	Rectal cancer		
	n	*5-y lung metastasis rate (%)*	*P*
No. of involved LPLN			
≥1	29	29.6	.152
0	102	17.2	
≥2	15	51.1	.125
1	14	14.3	
≥3	8	54.3	.067
1–2	21	22.7	
≥4	7	68.8	.011
1–3	22	21.4	
Distribution of involved LPLN			<.001
Bilateral	8	79.2	
Unilateral	21	17.1	

LPLN = lateral pelvic lymph node.

TABLE 4. Kaplan-Meier analysis of risk factors for pulmonary metastases after R0 resection of rectal cancer in terms of LNR

	Rectal cancer (n = 314)	5-y lung metastasis rate (%)	P
No. of retrieved regional LN (mean ± SD)	24.1 ± 16.3		
LNR (mean ± SD, median)	0.139 ± 0.137, 0.091		
0 < LNR ≤ 0.050	36	8.4	.024
0.050 < LNR ≤ 0.091	38	17.4	
0.091 < LNR ≤ 0.170	31	31.1	
0.170 < LNR ≤ 1.000	40	35.1	
(LNR = 0)	(169)	(7.8)	

LN = lymph node; LNR = lymph node ratio.

Characteristics of Patients With Pulmonary Metastases

The characteristics of the 41 patients with pulmonary metastases are shown in Table 1. Concurrent metastases or local recurrence were identified in 6 patients (liver, n = 3; local, n = 3; distant lymph node, n = 2; peritoneum, n = 1) at the time of diagnosis of pulmonary metastases. Surgery for pulmonary metastases was performed first for 19 patients (46.3%), and all patients achieved R0 surgery. Chemotherapy (IFL, n = 4; FOLFIRI, n = 4; 5-FU/LV, n = 3; FOLFIRI/bevacizumab, n = 2; FOLFOX6, n = 1; FOLFOX6/bevacizumab, n = 1; UFT/LV, n = 1; 5-FU/irinotecan, n = 1) was performed first for 17 patients (41.5%), and 5 patients (12.2%) received best supportive care.

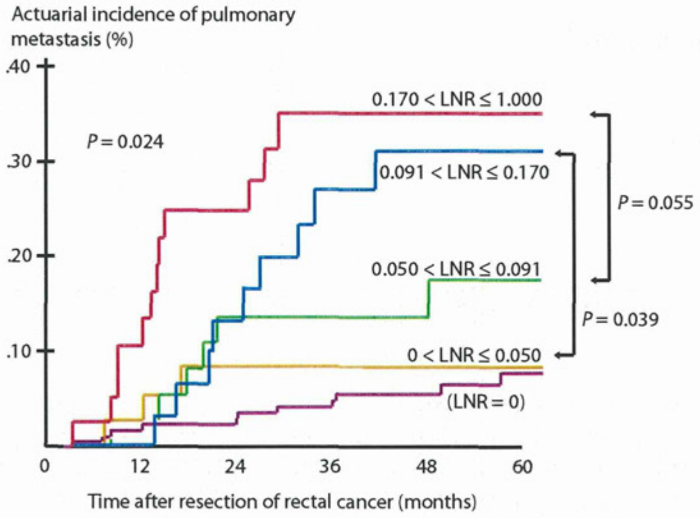
Risk Factors for Pulmonary Metastases According to Number of Lymph Node Involvements

Both the presence of regional lymph node involvement (0 vs ≥1) and the number of regional lymph node involvements (≥3 vs 1–2) were significant risk factors for pulmonary metastases (Table 2, Fig. 2).

In terms of LPLN involvement, the presence of LPLN involvement (0 vs ≥1) was not a significant risk factor for pulmonary metastases, but the number of LPLN involvements (≥4 vs 1–3) and the distribution of LPLN metastases (bilateral vs unilateral) were related to the significant risk factors for pulmonary metastases (Table 3). Six patients had both risk factors (the number of LPLN involvements, ≥4; the distribution of LPLN metastases, bilateral) and the 5-year actuarial incidence of pulmonary metastasis was 73.3%.

Risk Factors for Pulmonary Metastases According to LNR

Lymph node ratio (LNR) was determined by dividing the total number of involved regional lymph nodes by the total number of regional lymph nodes retrieved. Patients were assigned to 4 groups based on quartile (LNR with cutoff values based on 25% (LNR = 0.050), median (LNR =0.091), and 75% (LNR = 0.170)). Incidence rates of pulmonary metastases were increased with increasing LNR (P = .024) (Table 4, Fig. 3).



No. at risk

	0	12	24	36	48	60
0.170 < LNR ≤ 1.000	40	32	24	16	9	4
0.091 < LNR ≤ 0.170	31	31	26	20	14	10
0.050 < LNR ≤ 0.091	38	36	30	27	23	14
0 < LNR ≤ 0.050	36	35	31	29	22	21
(LNR = 0)	(169)	(164)	(161)	(141)	(103)	(77)

FIGURE 3. Kaplan-Meier curves for pulmonary metastases after R0 resection of rectal cancer according to lymph node ratio. LNR = lymph node ratio.

TABLE 5. Uni- and multivariate analysis of risk factors for pulmonary metastases after R0 resection of rectal tumor

	Rectal cancer				
	Univariate			Multivariate	
	n	*5-y lung metastasis rate (%)*	*P*	*Hazard ratio (95% CI)*	*P*
Overall	314	14.6			
Age at colorectal resection			.818		
≥60 (median) y	169	14.6			
<60 y	145	14.8			
Preoperative CEA level			.036		NS
<5 ng/mL	167	10.7			
≥5 ng/mL	147	19.3			
Simultaneous liver resection			.030		NS
No	299	13.9			
Yes	15	30.0			
Site of primary tumor (upper and lower rectum vs anal canal)			.006	3.289	.003
Upper rectum	116	11.7		(1.160–9.320)	
Lower rectum	188	14.5			
Anal canal	10	44.0			
Tumor size			.019		NS
<4 cm	108	7.6			
≥4 cm	206	18.6			
Depth of tumor invasion (T1/2 vs T3/4)			<.001	5.729	.004
T1	32	0		(1.749–18.765)	
T2	72	4.2			
T3	184	20.6			
T4	26	21.9			
LN involvements			<.001		NS
No	169	7.8			
Yes	145	22.9			
Lymphatic invasion			.001		NS
ly0/1	276	12.4			
ly2/3	38	35.2			
Vascular invasion			.001		NS
v0/1	183	9.2			
v2/3	131	22.4			
Histological type of adenocarcinoma			.093		
Well	50	6.2			
Moderate or poor	263	16.4			
(Other)	(1)				
No. of involved regional LN			<.001		NS
0–2	244	10.2			
≥3	70	31.7			
LNR			<.001	3.439	<.001
0 ≤ LNR ≤ 0.091	243	9.4		(1.841–6.423)	
0.091 < LNR ≤ 1	71	34.1			

LN = lymph node; LNR = lymph node ratio; NS = not significant.

Overall Risk Factors for Pulmonary Metastases

Multivariate analysis showed that depth of tumor invasion (T3–T4), LNR (>0.091), and tumor location (anal canal) were independent risk factors for pulmonary metastases in patients with rectal cancer (Table 5). Only 2 patients had all 3 risk factors. When patients were divided into 3 groups based on the presence of these 3 risk factors, the 5-year actuarial incidence of pulmonary metastasis increased significantly according to the number of risk factors present (0 factors, 1.1%; 1 factor, 13.2%; ≥2 factors, 40.1%) (Fig. 4).

We also analyzed the risk factors for pulmonary metastases, excluding 29 patients with LPLN involvement. Multivariate analysis showed that tumor location (anal canal), depth of tumor invasion (T3–T4), LNR (>0.091), and vascular invasion (v2–v3) were independent risk factors for pulmonary metastases (Table 6). No patients had all 4 risk factors. When patients were divided into 4 groups based on the presence of these 4 risk factors, the 5-year actuarial incidence of pulmonary metastasis increased significantly according to the number of risk factors present (0 factors, 0%; 1 factor, 8.3%; 2 factors, 19.2%; 3 factors, 51.8%) (Fig. 5).

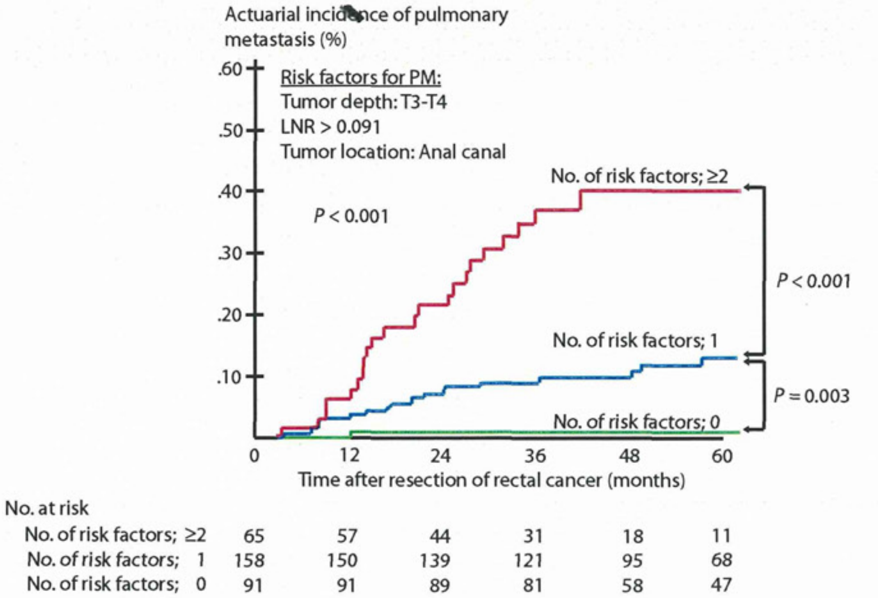


FIGURE 4. Kaplan-Meier curves for pulmonary metastases after R0 resection of rectal cancer according to the risk factors for pulmonary metastases. PM = pulmonary metastases; LNR = lymph node ratio.

DISCUSSION

The present study determined the actuarial incidence of pulmonary metastases and predictive factors for pulmonary metastases after R0 resection of rectal cancer without preoperative chemotherapy or radiotherapy. To the best of our best knowledge, this is the first study to describe the risk factors for pulmonary metastases after R0 resection of rectal cancer without preoperative chemotherapy or radiotherapy.

A limited number of studies have reviewed the incidence of pulmonary metastases after resection of rectal cancer, and have estimated that approximately 1% to 12% of patients with rectal cancer would develop isolated pulmonary metastases.[8–11] Of those patients with isolated pulmonary metastases, approximately 7% to 14% of patients would be considered as candidates for pulmonary metastasectomy.[8–11]

In the present study, 41 patients developed pulmonary metastases after rectal surgery and 19 of these 41 patients (46.3%) underwent surgery for pulmonary metastases first. The rate of surgery was much higher than previously reported.[8–11] The higher rate of patients indicated for surgery in the present study may be due to widened indications for surgery with the aid of advanced diagnostic tools. For example, 2-mm section contrast-enhanced helical chest CT provides accurate images of the location, size, and extent of the tumor, which have extended the surgical indications for pulmonary metastases to patients with multiple resectable pulmonary tumors.[2]

The present study clearly demonstrated predictive factors for pulmonary metastases after R0 resection of rectal cancer without preoperative chemoradiotherapy. Actuarial incidence of pulmonary metastases was significantly related to the number of risk factors present. Tumor depth (T2–T3), LNR (>0.091), and tumor location (anal canal) were the independent risk factors for pulmonary metastases in patients with rectal cancer.

Because lateral pelvic lymph node dissection is not performed by many Western countries, we also analyzed the risk factors for pulmonary metastases, excluding 29 patients with LPLN involvement. Multivariate analysis showed that tumor location (anal canal), depth of tumor invasion (T2–T3), LNR (>0.091), and vascular invasion (v2–v3) were independent risk factors for pulmonary metastases. Surprisingly, the 5-year actuarial incidence of pulmonary metastasis was 51.8% in the group of patients who had 3 risk factors.

The present study is the first to reveal LNR as a significant risk factor for pulmonary metastases after R0 resection of rectal cancer. Preoperative chemoradiotherapy is known to significantly reduce the number of lymph nodes in the tumor specimen.[17–19] Unlike the situation in Western countries, preoperative chemoradiotherapy for resectable rectal cancer is not standard therapy in Japan, so the present study was able to assess the native number of lymph nodes and LNR without the influence of chemoradiotherapy. Some recent studies have reported LNR as a possible prognostic factor for overall survival after resection of rectal cancer, although those studies included patients with preoperative chemoradiotherapy.[20,21]

Previous studies reported that pulmonary metastases were more frequent in rectal cancer than colon cancer.[8,9]

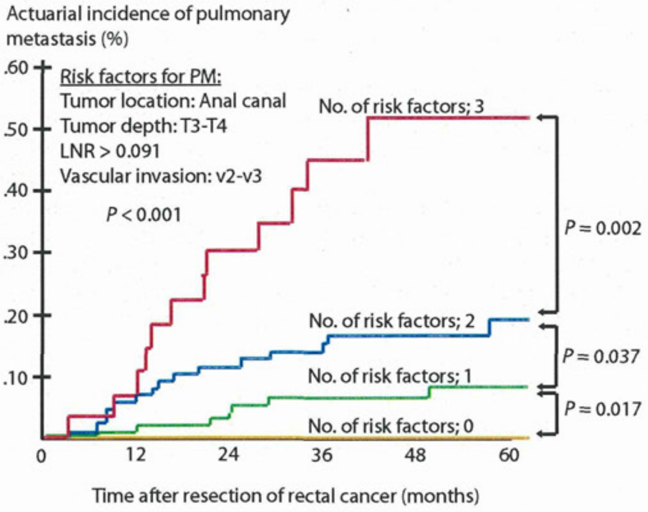
TABLE 6. Uni- and multivariate analysis of risk factors for pulmonary metastases after R0 resection of rectal tumor (excluded 29 patients with LPLN involvement)

	Rectal cancer				
	Univariate			Multivariate	
	n	*5-y lung metastasis rate (%)*	*P*	*Hazard ratio (95% CI)*	*P*
Overall	285	13.2			
Age at colorectal resection			.636		
≥60 (median) y	159	14.7			
<60 y	126	11.4			
Preoperative CEA level			.023		NS
<5 ng/mL	159	8.9			
≥5 ng/mL	126	18.8			
Simultaneous liver resection			.078		
No	272	12.6			
Yes	13	26.2			
Site of primary tumor (upper and lower rectum vs anal canal)			.022	8.444	.002
Upper rectum	110	14.7		(2.218–32.145)	
Lower rectum	167	10.8			
Anal canal	8	43.8			
Tumor size			.046		NS
<4 cm	108	7.6			
≥4 cm	177	16.9			
Depth of tumor invasion (T1/2 vs T3/4)			<.001	4.148	.022
T1	32	0		(1.227–14.021)	
T2	71	4.3			
T3	163	29.0			
T4	19	22.8			
LN involvements			<.001		NS
No	169	7.8			
Yes	116	21.4			
Lymphatic invasion			.044		NS
ly0/1	256	12.1			
ly2/3	29	22.6			
Vascular invasion			.001	3.197	.006
v0/1	174	7.0		(1.405–7.272)	
v2/3	111	23.2			
Histological type of adenocarcinoma			.198		
Well	46	6.7			
Moderate or poor	238	14.6			
(Other)	(1)				
No. of involved regional LN			<.001		NS
0–2	232	9.7			
≥3	53	30.3			
LNR			<.001	3.262	.001
0 ≤ LNR ≤ 0.091	230	8.8		(1.647–6.459)	
0.091 < LNR ≤ 1	55	32.6			

LN = lymph node; LNR = lymph node ratio; LPLN = lateral pelvic lymph node; NS = not significant.

The present study revealed that the lowest rectal cancer (anal canal) had a higher risk of developing pulmonary metastases compared with upper and lower rectal cancer. These findings may be attributed to anatomical difference. The lowest rectal cancer cells may be likely to show direct spread to the lung tissue via the vena cava from the inferior and middle rectal veins.

Finally, we should mention the limitations of the present study. We excluded patients who had other metastases or local recurrence before pulmonary metastases to avoid bias, so interactions between pulmonary metastases and other metastases or local recurrence remain unclear. Further investigation is needed to clarify interactions among distant metastases or local recurrence.



No. at risk						
No. of risk factors; 3	28	25	17	12	7	4
No. of risk factors; 2	88	81	73	63	45	33
No. of risk factors; 1	96	93	89	77	58	42
No. of risk factors; 0	73	73	72	65	48	40

FIGURE 5. Kaplan-Meier curves for pulmonary metastases after R0 resection of rectal cancer according to the risk factors for pulmonary metastases, excluded 29 patients with lateral pelvic lymph node involvement. PM = pulmonary metastases; LNR = lymph node ratio.

CONCLUSION

The present study clearly demonstrated predictive factors for pulmonary metastases after R0 resection of rectal cancer without preoperative chemoradiotherapy. Actuarial incidence of pulmonary metastases was significantly related to the number of risk factors present. The data from the present study should facilitate the establishment of novel algorithms for predicting pulmonary metastases after resection of rectal cancer, which may lead to the appropriate surveillance strategies after rectal surgery.

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Original Article

Association Between Incisional Surgical Site Infection and the Type of Skin Closure After Stoma Closure

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Abstract

Purpose. This study was performed to investigate the effect of subcuticular sutures on the incidence of incisional surgical site infection (SSI) after closure of a diverting stoma.

Methods. The study was carried out as a retrospective analysis of prospectively collected data from 51 patients who underwent closure of diverting stoma following resections of lower rectal cancer between January 2008 and December 2008. This study attempted to determine whether there was an association between the type of skin closure and the incidence of incisional SSI. Moreover, risk factors for incisional SSI after closure of diverting stoma were identified using a multivariate analysis.

Results. An incisional SSI occurred in 12 of the 51 patients (23.5%). The rate of incisional SSI with subcuticular sutures was 11.1% (3/27) in comparison to 37.5% (9/24) with transdermal suture and skin stapler. A subcuticular skin closure was the only favorable factor that was significantly associated with a lower incidence of incisional SSI (odds ratio: 0.19; 95% confidence interval: 0.04–0.92).

Conclusions. A subcuticular skin closure has a protective effect against incisional SSI after closure of diverting stoma. A larger study is necessary to further define the role of subcuticular suture on the prevention of incisional SSI in cases of gastrointestinal surgery.

Key words Subcuticular skin closure · Stoma · Surgical site infection

Introduction

Incisional surgical site infection (SSI) is one of the most frequent complications observed after stoma closure,[1] and previous studies have reported that the rate of occurrence of such complications is as high as 40%.[2] Delayed primary closure or healing by secondary intention is recommended to reduce the occurrence rate of this type of infection.[2,3] However, the wounds take several days to be closed with delayed primary closures. Furthermore, they are accompanied by painful dressing changes. Moreover, healing by secondary intention requires a minimum of several weeks for epithelialization.[4] Several recent reports have suggested that subcuticular suturing is associated with a lower incidence of incisional SSI in cardiovascular, orthopedic, and gynecological surgeries.[5–8] Although previous studies have previously reported that subcuticular sutures are preferred from an aesthetic viewpoint,[9] the protective effect of these sutures against incisional SSI has never been reported in gastrointestinal surgery. In particular, the procedures used for stoma closure are potentially at high risk for the occurrence of incisional SSI.

The aims of this study were to describe the association between incisional SSI and the type of skin closure after diverting stoma closure and to examine the protective effect of subcuticular suture against incisional SSI. Moreover, clinicopathological factors were analyzed to identify the risk factors for incisional SSI after closure of diverting stoma using a multivariate analysis.

Patients and Methods

Fifty-one patients underwent closure of diverting stoma at the National Cancer Centre Hospital East (NCCHE), Kashiwa, Japan, between January 2008 and December 2008. Forty-eight of the 51 patients underwent reconstruction during resections for primary rectal cancer, and 3 were emergently constructed after the occurrence of anastomotic leakage. The stomas were usually closed several months following the previous surgery. The surgeon determined whether ileostomy or colostomy had been constructed.

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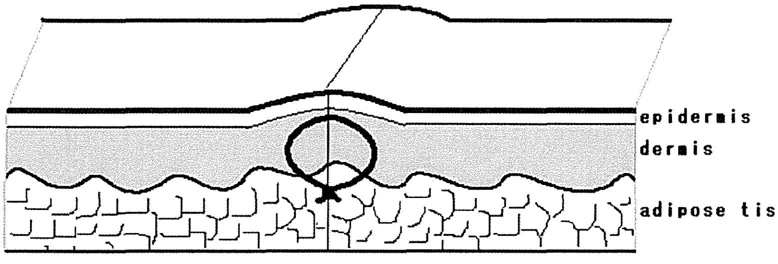

Fig. 1. Schematic illustration of subcuticular sutures. The dermal layer on each edge is properly attached by subcuticular sutures

Stoma Closure Procedures

The skin around the rim of the stoma was excised with 2–3-mm margins, the intestine was mobilized from the abdominal wall, and the stoma was tightly closed with the intestinal mucosa inverted by suturing the skin rim. Intra-abdominal dissections were performed in order to enable complete mobilization of the stomas. The bowels were transected on either side of the stomas, and either stapled functional end-to-end anastomosis or hand-sewn anastomosis was performed.[3] Abdominal fascia was closed with interrupted suturing with a gradually absorbable monofilament material (polydioxanone; Johnson & Johnson, Tokyo, Japan; or Glycomer 631; Covidien, Tokyo, Japan). The wounds were thoroughly irrigated with 300–500 ml of warm saline. Thereafter, the skin was closed by subcuticular suturing with slowly absorbable monofilament material (polydioxanone, or polytrimethylene carbonate; Covidien) as illustrated in Fig. 1, interrupted transdermal suturing using 4-0 nylon, or a skin stapler (Visistat; Teleflex Medical, Durham, NC, USA). No drains were placed in the abdominal cavity.

Perioperative Care

Patients received mechanical bowel lavage treatment with 180 ml of magnesium citrate (Magcorol P; Horii-Yakuhin, Osaka, Japan) for 2 days before the surgery. No chemical bowel preparation was applied. Patients were administered two doses of cefmetazole sodium (CMZ) — a second-generation cephalosporin — as a prophylactic antibiotic. One gram of CMZ was administered to patients within 30 min prior to the skin incision; thereafter, the same dose of the drug was administered 3 h later. Clear liquid intake was allowed in patients on postoperative day (POD) 2, soft food intake was allowed on POD 4, and the patients were discharged from the hospital after removal of nonabsorbable sutures or staples on POD 7 or 8.

SSI Surveillance

Incisional SSI was defined, according to the guidelines issued by the Centers for Disease Control and Prevention, as any infection that involved the skin and subcutaneous soft tissue around incisions within 30 days after the operation,[10] and it included at least one of the following: (1) an infection accompanied by apparently purulent discharge with or without laboratory evidence; (2) culture-positive drainage fluid or soft tissue from the incision; (3) the incision had signs of inflammation, was deliberately opened by a surgeon, and the culture was positive. The wounds were inspected for any problem twice a day during admission and at the outpatient clinic at least once, 30 days after surgery. Incisional SSI was identified retrospectively by an infection-control team that thoroughly reviewed clinical records of patients who underwent stoma closure. All data regarding SSI were prospectively recorded in a database and were analyzed as a retrospective cohort study.

Statistical Analysis

The data were collected in a database for analysis (SPSS 11.0 J for Windows; SPSS, Chicago, IL, USA). Differences between numerical variables were tested using the Mann–Whitney *U*-test and those between categorical variables were tested using chi-square statistics. The multivariate analysis was performed using a logistic regression model. A P value of less than 0.05 was considered to be significant.

Results

Fifty-one patients underwent stoma closure at NCCHE, Kashiwa, Japan during the period of study. The procedures followed for the primary operation included abdominoanal resection ($n = 29$), low anterior resection ($n = 20$), total colectomy ($n = 1$), and pelvic exenteration ($n = 1$). Twelve of the 51 patients (23.5%) developed incisional SSI. Bacteria identified from the incisions with positive SSIs included methicillin-resistant *Staphylococcus aureus* ($n = 2$), *Escherichia coli* ($n = 1$), *Enterococcus faecium* ($n = 1$), *Enterococcus faecalis* ($n = 1$), *Enterococcus raffinosus* ($n = 1$), and *Enterococcus avium* ($n = 1$). The median postoperative day on which patients

Table 1. Clinical background of patients according to the type of skin closure

Factor		Subcuticular (n = 27)	Staple and transdermal (n = 24)	P value
Age (years)	Mean ± SEM	60.2 ± 2.5	63.5 ± 2.1	0.30
Sex (n)	Male/Female	23/4	15/9	0.06
ASA score (n)	1/2	14/12	12/12	0.50
Total protein (g/dl)	Mean ± SEM	6.9 ± 0.1	6.9 ± 0.1	0.62
Albumin (g/dl)	Mean ± SEM	4.1 ± 0.0	4.0 ± 0.1	0.97
DM	+/–	3/24	4/20	0.43
BMI (kg/m^2)	Mean ± SEM	22.4 ± 0.5	22.0 ± 0.7	0.52
Type of stoma (n)	Colostomy/Ileostomy	3/24	12/12	<0.01
Type of anastomosis (n)	FEEA/hand-sewn	26/1	24/0	0.53
Blood loss (g)	Mean ± SEM	56.8 ± 10.5	60.0 ± 7.8	0.29
Operation time (min)	Mean ± SEM	81.2 ± 6.8	72.7 ± 9.7	0.68
Body temperature[a] (°C)	Mean ± SEM	36.4 ± 0.1	36.3 ± 0.1	0.63

There were no statistical differences in the background except for the type of stoma
SEM, standard error of the mean, ASA, American Society of Anesthesiology, DM, diabetes mellitus; BMI, body mass index; FEEA, functional end-to-end anastomosis
[a] Body temperature is demonstrated as the lowest value recorded during operation

Table 2. Analysis of variables associated with incisional surgical site infection (SSI)

Factor		SSI(+) (n = 12)	SSI(–) (n = 39)	P value
Age (years)	Mean ± SEM	65.7 ± 2.9	60.5 ± 1.9	0.20
Age ≥70 (n)	+/–	6/6	10/29	0.11
Sex (n)	Male/Female	10/2	28/11	0.35
ASA score (n)	1/2	6/6	21/18	0.57
Total protein (g/dl)	Mean ± SEM	6.9 ± 0.1	6.9 ± 0.1	0.51
Albumin (g/dl)	Mean ± SEM	4.1 ± 0.1	4.1 ± 0.0	0.51
DM	+/–	2/10	5/34	0.53
BMI (kg/m^2)	Mean ± SEM	21.7 ± 0.8	22.3 ± 0.5	0.63
Type of stoma (n)	Colostomy/Ileostomy	5/7	10/29	0.24
Type of anastomosis (n)	FEEA/hand-sewn	11/1	39/0	0.24
Type of skin closure	Subcuticular/Staple or transdermal	3/9	24/15	0.03
Blood loss (g)	Mean ± SEM	69.8 ± 16.3	54.7 ± 7.0	0.56
Operation time (min)	Mean ± SEM	85.2 ± 14.6	74.7 ± 6.1	0.59
Body temperature[a] (°C)	Mean ± SEM	36.2 ± 0.2	36.4 ± 0.1	0.51

A lower rate of incisional SSI was observed with subcuticular skin closure than with stapler or transdermal closure. All other factors were insignificant
[a] Body temperature is demonstrated as the lowest value recorded during operation.

were diagnosed with incisional SSI was day 5. Eleven patients were diagnosed with incisional SSI during admission and the remaining patient was diagnosed after discharge. All incisional SSIs were treated by wound opening, drainage, and irrigation with normal saline.

Table 1 presents the clinical background of patients on the basis of the type of skin closure. The subcuticular suture group underwent a greater number of ileostomy procedures than the stapler/transdermal suture group. No statistical differences of background between the two groups were found in other clinical factors. Table 2 presents the associations between clinical factors and incidence of incisional SSI. A lower rate of incisional SSI was observed with subcuticular skin closure than with stapler or transdermal closure (P = 0.03). There was a trend toward a higher rate of incisional SSI in patients older than 70 years (P = 0.11).

The multivariate analysis showed that the type of skin closure was the only independent factor associated with incidence of incisional SSI (Table 3). The rate of the incisional SSI decreased from 37.5% in cases closed by transdermal sutures or staples to 11.1% in those closed with subcuticular sutures (odds ratio: 0.19; 95% confidence interval: 0.04–0.92). No statistically significant difference was observed in the postoperative length of the hospital stay between patients with or without subcuticular sutures (the median postoperative hospital stay in both groups was 8 days; P = 0.96). A postoperative reoperation was required in 3 (5.9%) of 51 patients due

Table 3. Multivariate analysis of the risk factors of incisional SSI after closure of diverting stoma

Factor		Odds ratio	(95% CI)	*P* value
Type of stoma	Ileostomy	1		
	Colostomy	1.26	(0.26–6.1)	0.78
Age	<70	1		
	≥70	3.25	(0.73–14.4)	0.12
Type of skin closure	Staple or transdermal suture	1		
	Subcuticular suture	0.19	(0.04–0.92)	0.04

The multivariate analysis demonstrated that the type of skin closure was the only independent factor associated with incidence of incisional SSI
CI, confidence interval

to associated complications, i.e., anastomotic leakage in one case, and intestinal obstruction in the other two patients. No mortalities were observed in this series.

Discussion

Several randomized controlled trials have indicated the protective effects of subcuticular skin closure against incisional SSI in cases of clean surgery.[5,6] Furthermore, some retrospective studies showed that subcuticular suturing is associated with a significantly lower rate of incisional SSI in clean-contaminated wounds following gynecological surgery.[7,8] However, there is no available evidence to support the protective effects of subcuticular suturing against incisional SSI in gastrointestinal surgery, in which the incidence of incisional SSI is rather high. This study is the first to clearly demonstrate that subcuticular suturing reduces the rate of incisional SSI in gastrointestinal surgery.

Although several reports noted the protective impact of subcuticular suturing against incisional SSI,[5–8] none of them clearly explained the mechanism underlying the effect. Subcuticular skin closure approximates the skin by tightly connecting both edges at the level of the dermis; thereafter, suture strings are buried beneath the surface of the skin. This prevents subcutaneous dead space and excessive tissue inflammation, both of which are risk factors of incisional SSI.[11] On the contrary, improper placement of skin staples disturbs the normal contact between the dermis and adipose tissues, which causes subcutaneous dead space and prevents proper wound healing.[12,13] Transdermal suturing with nonabsorbable material might also prevent the formation of subcutaneous dead space, but it is likely to cause excessive inflammation because it penetrates the dermal barrier with foreign material. Transdermal suturing is also likely to damage fragile adipose tissue, because it holds the dermis and subcutaneous tissue together with the same tensile strength.[14] Therefore, subcuticular suturing is superior to skin staples and transdermal suturing because it helps the wound-healing process. Subcuticular skin closure also supports the reconstruction of the dermis. Capillary vessel loops in the dermis provide the main blood supply to cutaneous wound healing while collagen formation in the dermis offers tensile strength to the wound.[15–17] Therefore, proper reconstruction of the dermis is the critical process in the restoration of cutaneous function. The appropriate contact of dermis achieved by subcuticular suturing may promote proper wound healing and restoration of cutaneous function, which, in turn, enhances host defense against infection.[11]

A univariate analysis showed that subcuticular suturing was the only factor that was associated with the incidence of incisional SSI. Although the elderly had an increased likelihood of developing incisional SSI, as seen in previous studies,[18,19] the results did not show statistical significance. In addition, contrary to previous reports,[20] colostomy closure was not associated with a higher incidence of incisional SSI. A multivariate analysis was performed to exclude the possible confounding effect among these three factors. The results clearly demonstrated that subcuticular suturing had the greatest effect in preventing incisional SSI among clinical factors previously reported to be associated with incisional SSI.

The current study has several limitations. First, SSI was identified retrospectively by daily chart review of the infection control doctor. Detection by chart review is suggested to be a less accurate method than direct observation of surgical sites.[10] However, chart review is the most widely employed method of SSI surveillance in the medical literature.[2,7,18,19,21] The reported sensitivity of this method is as high as 83.8%–92.3% in comparison to prospective direct SSI surveillance.[22] Therefore, the surveillance method did not preclude the importance of the findings in the current series. Second, this study was a single-center study, and it involved a relatively small number of cases. Although a multivariate analysis revealed an association between subcuticular suturing and the incidence of incisional SSI, a larger, more scientific study is warranted. A multicenter, randomized controlled trial is currently under way to confirm the effect of subcuticular suturing on the incidence of incisional SSI in gastrointestinal surgery.

In conclusion, subcuticular suturing was found to have a protective effect against incisional SSI after diverting stoma closure. This study was the first to report the effect of subcuticular suturing on the prevention of incisional SSI in gastrointestinal surgery. A large multicenter randomized controlled trial is ongoing to confirm the role of subcuticular suturing in preventing incisional SSI in gastrointestinal surgery.

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The Association Between Anal Function and Neural Degeneration After Preoperative Chemoradiotherapy Followed by Intersphincteric Resection

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BACKGROUND: Preoperative chemoradiotherapy for rectal cancer is administered to improve local control, but it can also induce severe anal dysfunction after surgery.

OBJECTIVE: The goals of the study were to assess the influence of preoperative chemoradiotherapy on pathological findings and to examine the correlation of these findings with the cause of severe anal dysfunction after intersphincteric resection.

DESIGN: Peripheral nerve degeneration was evaluated histopathologically with the use of hematoxylin and eosin-stained sections of surgical specimens after intersphincteric resection, based on karyopyknosis, vacuolar degeneration, acidophilic degeneration of cytoplasm, denucleation, and adventitial neuronal changes. Each item was scored to quantify the level of neural degeneration, and the relationship between degeneration and anal function was examined at 12 months after closure of the stoma. Anal function was assessed by questionnaire, and incontinence was evaluated based on the Wexner score.

SETTING: This study was conducted at the National Cancer Center Hospital East from 2001 to 2006.

PATIENTS: The subjects were 68 patients with lower rectal cancer who underwent intersphincteric resection with (n = 47) or without (n = 21) preoperative chemoradiotherapy.

MAIN OUTCOME MEASURES: The findings in the 2 groups were compared to clarify the association between the degree of histological degeneration and postoperative anal function.

RESULTS: Neural degeneration was significantly higher in the chemoradiotherapy group, and the neural degeneration and Wexner scores had a significant correlation ($P = .003$, $r = 0.477$).

CONCLUSION: Preoperative chemoradiotherapy induced marked neural degeneration around the rectal tumor. The significant correlation between the degeneration score and postoperative anal function suggests that this score may be a useful marker to predict the influence of preoperative chemoradiotherapy on anal function after surgery.

KEY WORDS: Chemoradiotherapy; Internal sphincteric resection; Neural degeneration; Rectal cancer; Anal function.

Innovative treatment for lower rectal cancer has recently tended toward preservation of the anus. Low anterior resection with coloanal anastomosis[1] and intersphincteric resection (ISR)[2] are advanced anus-preserving operations for the treatment of low rectal cancer with avoidance of a colostomy. Anastomoses are made near to or under the dentate line in the anal canal, and the procedures have a tolerable and clinically acceptable local recurrence rate.[3,4] Preoperative chemoradiotherapy (CRT) or

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radiotherapy is also thought to be necessary to decrease local recurrence following ISR.[5–7]

Investigations of functional outcome after ISR[6,8–11] have shown that satisfactory anal function is preserved in most patients, but some have severe dysfunction[11,12] and conversion to colostomy may be necessary as an additional treatment.[8,12] Preoperative CRT has been found to be most strongly associated with poor anal function after ISR, suggesting that patients with rectal cancer who undergo ISR after preoperative CRT are likely to experience incontinence.[13,14] Lim et al[15] reported that a conventionally fractionated 45-Gy dose of preoperative CRT caused poor anorectal function because of damage to the pudendal nerve. Rectal function may also be worsened by radiation-induced proctitis and induction of rectal compliance due to fibrosis of the rectal wall,[16,17] and direct radiation injury to the internal anal sphincter muscles can also cause anal sphincter dysfunction.[18]

Given this background, it is likely that pathological analysis of the anal sphincter muscle area may show an association with anal sphincter dysfunction. However, the relationship between histopathological findings and CRT in the anal sphincter muscle area has not been studied. Therefore, we examined the degree of tissue degeneration, with a particular focus on neural degeneration and tissue fibrosis, in surgical specimens resected from patients who underwent surgery with or without preoperative CRT. In previous reports[19,20] on esophageal carcinoma, toxicities such as neuropathy have been observed during CRT, suggesting that neuropathy may be based on neural degeneration. The aim of this study was to investigate neural degeneration pathologically, because this may cause anal dysfunction. Findings in patients with or without preoperative CRT were compared to clarify the association between the degree of histological degeneration and postoperative anal function.

PATIENTS AND METHODS

Patients

Between 2001 and 2006, 68 patients underwent ISR for very low rectal cancer at the National Cancer Center Hospital East, Chiba, Japan. Of these patients, 47 received CRT before surgery and 21 underwent surgery alone (control group). For ISR cases from 2002 to 2004, CRT was performed for all patients who gave consent. The subjects examined before and after this period and ISR cases in which patients did not consent to CRT were examined as the surgery-only group. Cases in which infiltration in the external sphincter muscle was shown by MRI in the preoperative diagnosis of tumor depth were excluded from our indication for ISR. A diverting stoma was constructed in each patient, and the stoma was finally closed in all the patients. Questionnaires on postoperative anal function[8] were collected from 59 of the 68 patients at 12 months after closure of the stoma. Our operative indications for ISR were a tumor edge 5 cm above the anal verge or 3 cm above the dentate line; adenocarcinoma confirmed histologically by preoperative biopsy; and age less than 76 years.[8] Preoperative stage was determined according to the International Union Against Cancer classification.[21]

Surgical Procedure

ISR was performed as described previously.[8] First, dissection was performed by the abdominal approach until total mesorectal excision was complete. The outside layer of the internal sphincter muscle was then exposed and circumferentially divided from the puborectal muscle and the external sphincter. After the abdominal approach was completed, perianal resection was performed. The mucosa and the internal sphincter muscle were incised 1 to 2 cm distal to the tumor. If the tumor had invaded the external sphincter, ISR plus partial resection of the external sphincter was performed with preservation of at least the subcutaneous part of the external sphincter. The decision of whether to create a pouch (either a J-pouch or a transverse coloplasty pouch) was left to the discretion of the surgeon.

Preoperative Therapy

Forty-seven patients with clinical T3 tumors agreed to undergo CRT. Over a 5-week period, a dose of 45 Gy was administered along with intravenous infusion of 5-fluorouracil (250 $mg \cdot m^{-2} \cdot d^{-1}$) to increase the efficacy of radiotherapy. Nerve-sparing resection surgery was performed 2 weeks after completion of preoperative CRT.[22]

Pathological Evaluation

Hematoxylin and eosin-stained sections of the surgical specimens were used for pathological evaluation. The sections were evaluated by 2 authors (S.F. and Y.N.) who were blinded to the clinical information for the patients.

Pathological Examination of Nerves Near the Internal Sphincter Muscle

Before pathological evaluation, the numbers of nerves in the hematoxylin and eosin-stained sections were counted in low-power magnification fields (10×10). Ten nerves around the primary lesion were selected and photographed, and the consistency of features of the nerves in each photograph was evaluated. In this manner, pathological neural degeneration was evaluated for 10 nerves near to the tumor in each patient, based on the following features: karyopyknosis, vacuolar degeneration, acidophilic degeneration of cytoplasm, denucleation, and adventitial neuronal changes. To obtain a total degeneration score, the presence of the first 4 features was scored as 1 point each. Adventitial neuronal changes were evaluated based on a 3-point scale, with 1, 2, and 3 defined as perineurial hypertrophy, perineurial fibrosis, and intraneural fibrosis.

Therefore, the degeneration score ranged from 0 to 7. The association between this score and anal function was examined at 12 months after surgery.

Fibrosis

The degree of fibrosis of the primary tumor was evaluated on a 4-point scale, with grades 0, 1, 2, and 3 reflecting <10%, 10% to 30%, 30% to 50% and ≥50% replacement of tumor tissue by fibrosis in the section with the maximum tumor diameter.[18]

Abscess Formation

The presence of an abscess in the tumor was examined based on aggregates of neutrophil infiltration (0, absence of abscess; 1, presence of abscess). An abscess was defined as an area of neutrophilic aggregation with a diameter larger than 500 μm observed microscopically.

Assessment of Anal Function

The functional outcome was assessed by the use of the continence score of Jorge and Wexner (Wexner score).[23] Questionnaires were collected from patients during consultation in the physician's office after the patient had filled out the questionnaire by themselves at home. Questionnaires to evaluate the Wexner score were given at 12 months after stoma closure. Thus, the relationship between the degree of degeneration and postoperative anal function was examined based on the Wexner score at 12 months after stoma closure. This score reflects the postoperative anal function, because gradual improvements in Wexner scores are seen from 3 to 6 months and further slight improvements occur between 6 and 24 months.[13]

Statistical Analysis

A Student *t* test and Fisher exact test were used to examine histological differences between the CRT and control groups. A Mann-Whitney *U* test was used to examine the relationship between CRT and Wexner scores. The Mann-Whitney *U* test was also used to examine the relationship between histological findings (karyopyknosis, vacuolar degeneration, acidophilic change, and denucleation) and Wexner scores. A Kruskal-Wallis test was used to examine the relationship between histological findings (adventitial neuronal changes, fibrosis, and abscess) and Wexner scores. Spearman analysis was used to examine the correlation between degeneration scores and Wexner scores. All statistical analyses were performed using SPSS for Windows, v.13.0 J (SPSS-Japan Inc., Tokyo, Japan). A *P* value of <.05 was considered to be significant.

RESULTS

The clinical characteristics of the 68 patients are shown in Table 1, including preoperative CRT, mean tumor distance from the anal verge, extent of excision of the internal sphincter muscle, resection of the external sphincter, and pathological stage. There were no significant differences between the CRT and control groups in age, sex ratio, and anal verge distance. Total ISR was used less frequently in the control group. Regarding the pathological stage, 66% of cases in the CRT group were stages I and II, whereas 58% of cases in the control group were stage III. There were no significant differences in clinical stage (P = .70) and pathology stage (P = .12) between the CRT and control groups. Many cases in the CRT group were stage I or II and total ISR was performed in some of these cases (Table 1).

TABLE 1. Clinical characteristics of the patients

	CRT group	Control group	P
Patients	47	21	
Median age (range)	56 (27–77)	60 (39–72)	.22
Sex, M:F	35:12:00	15:06	.79
Median AV (cm)	3.5 (0–5.0)	4.0 (2.5–5.5)	.66
Operative procedure (%)			
Total ISR	20 (43)	1 (5)	.03
Subtotal ISR	22 (47)	13 (62)	
Partial ISR	5 (11)	7 (33)	
PESR	13 (28)	7 (33)	.63
Clinical/pathology stage (%)			
I	9 (19)/25 (53)	4 (19)/4 (19)	.70/.12
II	16 (34)/6 (13)	8 (38)/5 (24)	
IIIa	9 (19)/5 (11)	5 (24)/6 (29)	
IIIb	11 (23)/8 (17)	3 (14)/6 (29)	
IV	2 (4)/2 (4)	1 (5)/0 (0)	
Postoperative complications (%)	14 (29)	9 (43)	.29
Anastomotic leakage	5 (11)	3 (14)	.67
Pelvic abscess	6 (12)	5 (24)	.25

AV = anal verge; ISR = intersphincteric resection; CRT = chemoradiotherapy; PESR = partial external sphincter resection.

Postoperative complications occurred in 14 subjects (29%) in the CRT group (anastomotic leakage in 5 (11%) and pelvic abscess in 6 (12)), and in 9 subjects (43%) in the control group (anastomotic leakage in 3 (14%) and pelvic abscess in 5 (24%)). There was no significant difference in the rate of postoperative complications between the 2 groups. The average time between the primary operation and closure of the stoma was 227 days (range, 80–665 days) in the CRT group and 247 days (range, 85–558 days) in the control group.

Tissue fibrosis of grade 2 or 3 was observed in 73% of cases in the CRT group, whereas fibrosis of grade 0 or 1 accounted for 86% of cases in the control group. The incidence of more severe fibrosis was significantly higher in the CRT group (P < .001). No intratumor abscess was present in 79% of cases in the CRT group, but abscesses were observed in 52% of cases in the control group, giving a significantly higher incidence of abscess formation in the control group (P = .010).

TABLE 2. Pathologic findings

	CRT group (n = 47)	Control group (n = 21)	P
Fibrosis grade: 0/1/2/3, n (%)	2/11/13/21 (4/23/28/45)	16/2/2/1 (76/10/10/5)	<.001
Abscess grade: 0/1, n (%)	37/10 (79/21)	10/11 (48/52)	.010
Karyopyknosis, n (%)	19 (40)	0 (0)	.001
Vacuolar degeneration, n (%)	32 (68)	4 (19)	<.001
Acidophilic degeneration of cytoplasm, n (%)	15 (32)	0 (0)	.002
Adventitial neuron change: 0/1/2/3, n (%)	2/25/7/13 (4/53/15/28)	17/4/0/0 (81/19/0/0)	<.001
Denucleation, n (%)	26 (55)	0 (0)	<.001

Karyopyknosis, vacuolar degeneration, acidophilic degeneration of cytoplasm, adventitial neuron change, and denucleation were evaluation items of neurodegeneration.
CRT = chemoradiotherapy.

The incidence of neural degeneration was significantly higher in the CRT group and the incidence of vacuolar degeneration (68%) was particularly high in the CRT group compared with the control group. In the adventitia and perineurium of neurons, only perineurial hypertrophy (grade 1) occurred in the control group, whereas perineurial and intraneural fibrosis (grades 2 and 3) was found in 43% of cases in the CRT group, indicating a significantly higher frequency of severe effects in the CRT group ($P \leq .001$ to $P = .01$) (Table 2). Representative histopathological findings for neurons are shown in Figure 1.

Association with Anal Function 12 Months After Surgery

No patient had a Wexner score of ≥2 preoperatively, and none had problems with preoperative anal function. The median values of the Wexner scores at 12 months after stoma closure in the CRT and control groups were 8.0 and 5.0, indicating that function was significantly poorer in the CRT group ($P = .018$ by Mann-Whitney *U* test) (Fig. 2).

In a comparison of Wexner scores based on background factors in the CRT group, sex, age, type of resection (partial, subtotal, total ISR), and partial resection of the external sphincter were not associated with poor anal function after ISR. Postoperative anal dysfunction did not show a significant association with each feature of neural degeneration or with Wexner score in the CRT group (karyopyknosis, $P = .05$; vacuolar degeneration, $P = .298$; acidophilic change, $P = .090$; denucleation, $P = .067$; and adventitial neuronal changes, $P = .081$). However, there was a significant correlation between the total degeneration score and the Wexner score ($P = .003$, $r = 0.477$ by Spearman analysis) (Fig. 3).

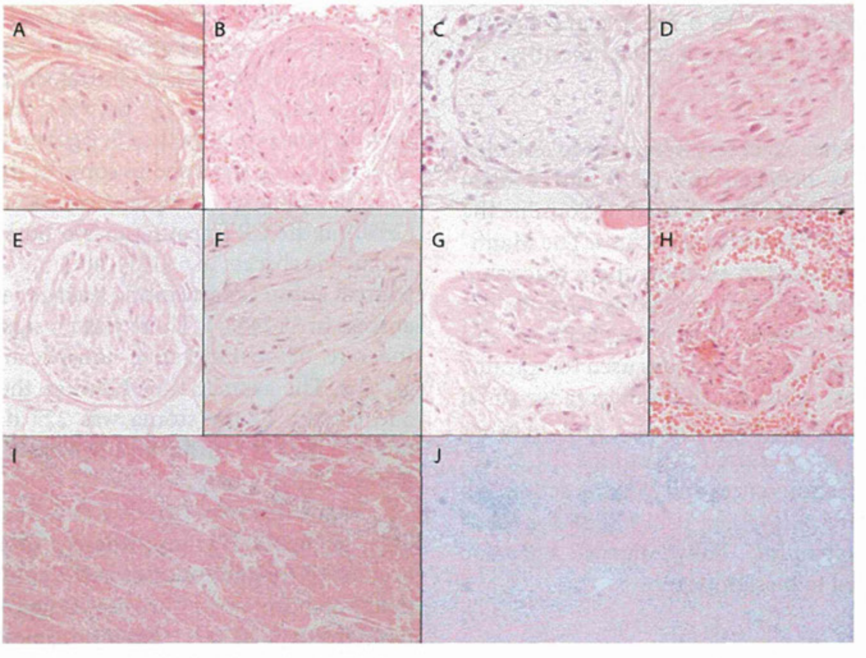

FIGURE 1. Pathological evaluation. The hematoxylin and eosin sections were assessed under a standard light microscope at low-power magnification (×100). The nerve evaluation items are (A–H): A, Normal. B, Karyopyknosis. C, Vacuolar degeneration. D, Acidophilic degeneration of cytoplasm. E, Denucleation. F, Adventitial neuron change grade 1. G, Adventitial neuron change grade 2. H, Adventitial neuron change grade 3. The degree of fibrosis was evaluated by grades: I, grade 1; J, grade 3.

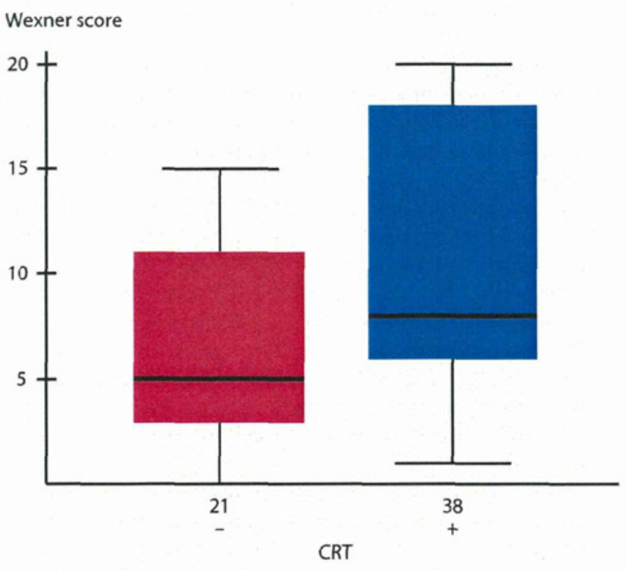

FIGURE 2. Relationship between CRT and Wexner score. Wexner score comparison at 12 months after stoma closure between the CRT and control groups resulted in median values of 8.0 and 5.0 (P = .018 by Mann-Whitney U test). CRT = chemoradiotherapy.

DISCUSSION

The results of the study showed that preoperative CRT had a negative effect on anal function regardless of the surgical method. This suggests that it is important to examine neural degeneration around the internal sphincter muscle for prediction of anal dysfunction. Many cases were of pathological stages I and II because of downstaging by CRT, but total ISR was performed in some of these cases. This approach was used because we were unable to judge the position of the tumor edge on the anal side before preoperative CRT, which prevented maintenance of a clear distal margin. However, this had no influence on the analysis of the Wexner score because the comparison of this score with anal dysfunction was performed only within the CRT group. Moreover, of the factors investigated, preoperative CRT had the greatest effect on anal dysfunction after ISR, and total ISR was more strongly associated with anal dysfunction than either subtotal or partial ISR. Therefore, a negative effect of preoperative CRT on anal function was found regardless of the extent of internal sphincter muscle preservation.[13]

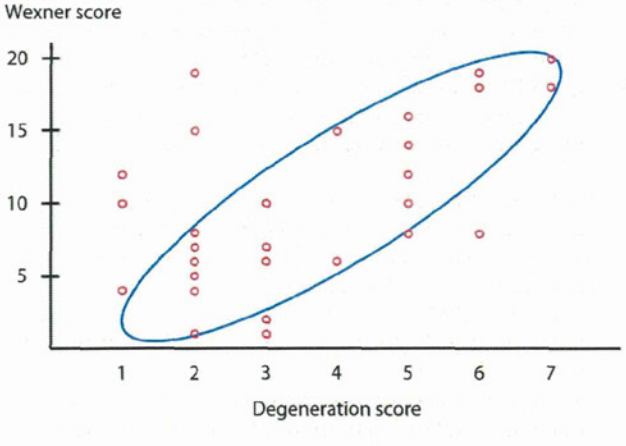

FIGURE 3. Association between the degeneration score and Wexner score. The correlation between the original score (range, 0–7) and the Wexner score was investigated. Correlation was significant with P = .003 and a correlation coefficient of r = 0.477 by Spearman analysis.

The cause of the negative effect of conventionally fractionated CRT on anorectal function is still unclear. Lim et al[15] suggested that poor anorectal function after preoperative CRT was due to damage to the pudendal nerve, and rectal function may also be worsened by radiation-induced proctitis and reduced rectal compliance.[16,17] Moreover, anal sphincter dysfunction may be caused by direct radiation injury to the internal anal sphincter muscles.[18] Our results showed a significantly higher incidence of neural degeneration and fibrosis in the CRT group. In this study, we did not include cases treated with radiation therapy only. However, in another series, we found that treatment with radiation alone caused tissue degeneration, including neural degeneration similar to that caused by CRT. We also evaluated another 8 patients with colorectal cancer who received preoperative folinic acid/fluorouracil/oxiliplatin (FOLFOX) treatment. The incidence of neural degeneration was significantly higher in the CRT group than in the FOLFOX cases. There were no differences in any items of neural degeneration between the FOLFOX cases and control groups, suggesting that radiation may exert a critical damage on tissue damage. In the pathological evaluation, patients treated with preoperative chemotherapy alone had no neural degeneration, with results similar to those in the control group. These results suggest that radiation plays a critical role in tissue damage.

The tissue and nerves were evaluated in surgical tissue specimens, but these specimens and the left internal and external sphincter muscles were similarly affected by CRT, which suggests that the histological changes in the analyzed specimens were also present in the body. The nerve examined in the study is an autonomic nerve that is distributed longitudinally in the intestine and innervates the internal sphincter muscle. After surgery, the somatic and pudendal nerves are involved in anal function and mainly innervate the external sphincter muscle of the anus. Although their origins are different, examination of these 2 nerves may be appropriate for assessment of neural degeneration, because neuronal failure of these nerves may cause anal dysfunction. In this study we evaluated tissue degeneration in the neural range affected by CRT, including the sphincter muscle, and these results are important for prediction of anal function after surgery.