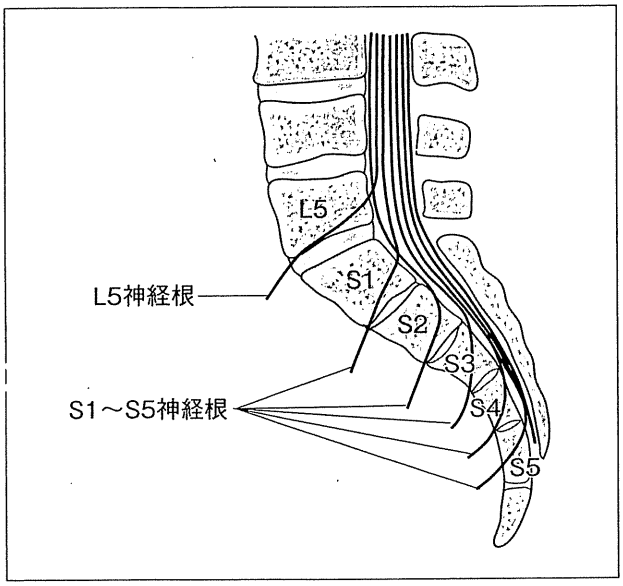

図4. 仙骨矢状断像
くも膜下腔は通常S1椎体下縁で終わる．脊柱管内で馬尾を形成した仙髄神経は，各椎体左右の前仙骨孔より神経根として前方へ出てくる．

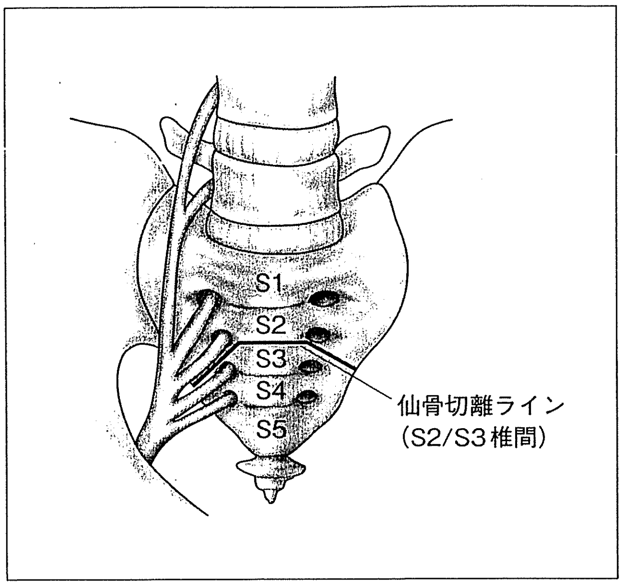

図5. 仙骨切断ライン（S2/S3椎間切断例）
温存予定の神経根を損傷しないように仙骨外側部をやや下方に彎曲させた逆U字状とする．

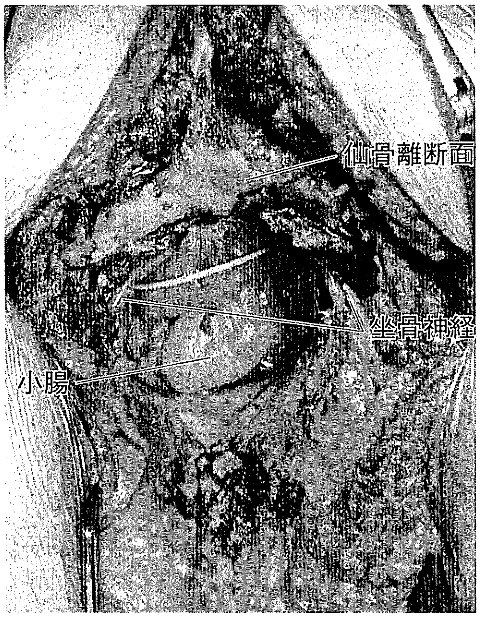

図6. 腫瘍摘出後
仙骨・腫瘍・骨盤内諸臓器は一塊として切除されている．仙骨離断面には骨蝋が塗られている．左右のS2神経根および坐骨神経は温存されている．

硬膜嚢が存在するのは，通常ほぼS1椎体下縁までであるので，S2神経根を温存する（S2/S3椎間あるいはS3椎体以下の仙骨切断）TPESでは，硬膜の結紮処理は必ずしも必要ない（図4）．S2以上の高位で仙骨切断を行う場合には，仙骨切断に先立って椎弓切除を行い，温存予定の神経根を同定して保護した後，切断レベルの硬膜および神経根を結紮・切離する．

腹腔側剥離面と仙骨切断レベルを再度確認した後，温存予定の神経根（S2/S3椎間あるいはS3椎体切断であればS2神経根，S3/S4椎間あるいはS4椎体切断であればS3神経根）を確実に温存しつつ，のみで仙骨切断を行う．切断は，神経根を損傷しないように，仙骨の両外側部をやや下方に彎曲させた逆U字状とする（図5）．仙骨離断面より出血するので，切断は手早く行い，不必要な出血を防ぐことが肝要である．骨離断面からの出血は骨蝋で止血する．仙骨切断により，腫瘍は骨盤内諸臓器・仙骨とともに一塊として切除される（図6）．大殿筋，皮下，および皮膚をwater-tightに縫合する．

4. 再建と閉腹

再び体位を仰臥位とし，腹腔側より完全な止血を確認し十分に洗浄した後，回腸導管による尿路

表2. 仙骨切断レベル

S2/S3椎間	14例(19.7%)
S3椎体	26例(36.6%)
S3/S4椎間	16例(22.5%)
S4椎体	10例(14.1%)
S4/S5椎間以下	5例(7.1%)
計	71例(100%)

再建，人工肛門作成を行う．術後の麻痺性イレウスや肺合併症予防のために胃瘻を作成する．太めのドレーンを1本骨盤底に挿入し閉腹する．

Ⅲ. 手術成績

当院では，1983～2005年に71例のTPESを行った[3~7]．全例の手術時間中央値は720分，出血量中央値は2,580 mlであった．合併症を58%で認め，仙骨創の離開52%，骨盤死腔炎39%などであった．手術侵襲，合併症を手術時期により比較すると，1983～1992年の前期例は平均出血量4,229 ml，骨盤死腔炎の発生頻度72%であったのに対し，1993～2005年の後期例では平均出血量2,500 ml，骨盤死腔炎の頻度23%と，出血量($p=0.002$)，骨盤死腔炎の発生頻度($p=0.046$)とも有意に減少しており，本術式に対するチームとしての理解，習熟度が上がった結果と考えられる[4]．R0手術は60例(84.5%)で達成され，R0手術例の5年生存率48.1%，10年生存率40.6%であった．

Ⅳ. 仙骨切断に関する考察

当院におけるTPES 71例の仙骨切断レベルを表2に示す．切断高位はS3椎体がもっとも多く26例(36.6%)，次いでS3/S4椎間16例(22.5%)，S2/S3椎間14例(19.7%)であった(図7)．

われわれは，TPESの適応として，仙骨切断レベルがS2/S3椎間以下のもの(S2神経根の温存が可能なもの)に限定し，S1やS2の高位仙骨切断が必要なものはTPESの適応外としている[3~5]．これは超拡大手術であるTPESの手術侵襲，合併症リスク，術後quality of life(QOL)と，TPESの根治性，メリットを天秤にかけた臨床的判断である．

Dozoisらは再発直腸癌に対してS2神経根以上の高位仙骨切断を伴う切除術を行った9例について検討し，多くは遠隔転移で死亡し3例で長期生存が得られたと報告している(生存期間中央値31ヵ月，5年生存率30%)[8]．手術時間中央値は13.7時間，術中輸血量は3,700 ml，術後歩行能力は歩行器歩行4例，杖歩行4例であった．仙骨切除による手術侵襲に関して，Tangらは仙骨切除173例の出血量について検討し，S2/S3椎間以上での切断は有意に($p<0.001$)出血量が多いことを報告している[9]．Devinらは，原発性あるいは転移性仙骨腫瘍27例の周術期合併症について検討し，S2椎体以上で仙骨切断を行った群(13例)は，それ以下で切断した群(14例)に比べて，出血量，合併症の頻度，入院期間などが有意に多い(長い)ことを報告し，S2以上の高位仙骨切断術の実施は，治癒可能性の高い限られた症例に限定されるべきであると述べている[10]．

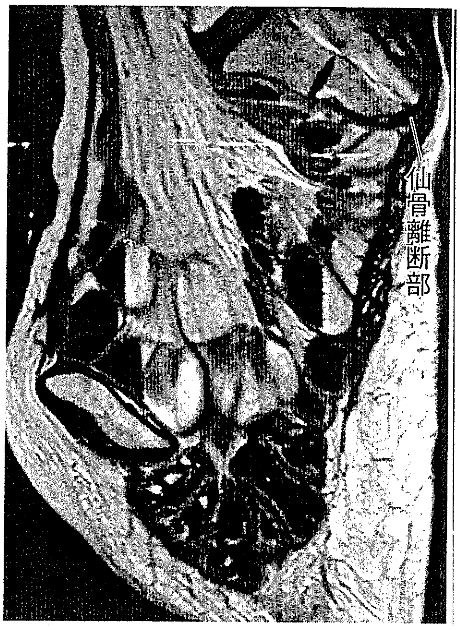

図7. 術後MRI矢状断像
仙骨はS2/S3椎間で切断されている．術後1年で再発・転移なく，下肢機能障害もない．

腫瘍による仙骨切除では，仙腸関節がどの程度温存されるかが術後の骨盤輪の安定，体幹の支持性に大きな影響を与える．仙骨を全切除するtotal sacrectomyは脊索腫などの原発性仙骨悪性腫瘍に対して適応となるが，骨盤輪の再建のためには金属インプラントによる強固な内固定が必要であり，術後合併症のリスクはきわめて高い[11,12]．

死体を用いた力学的な研究では，S1/S2椎間の切除で骨盤輪の強度は30％低下し，S1神経根を含む切除を行った場合には，なんらかの再建を考慮すべきと報告されている[13,14]．

TPESにおいては骨盤内臓器が合併切除されるため，仙骨神経の切除と膀胱直腸障害のリスクに関して考慮する必要はないが，陰部神経（S2～S4），後大腿皮神経（S2，S3）などの損傷により，肛門周囲～殿部の知覚障害や頑固な神経障害性疼痛を生じることが多い．S2神経根は大腿～足底の後内側，S1神経根は大腿～足底の後外側の知覚を支配しており，神経根の傷害によりこれらの部位の知覚脱失，知覚異常を生じる．

S3神経根以下の傷害では通常下肢に明らかな運動障害を生じることはない．しかし，S2神経根以上を犠牲にする場合には下肢運動障害が問題となる．S1，S2神経支配を受ける下腿三頭筋（腓腹筋，ヒラメ筋）の麻痺により足関節の底屈力が障害され，さらに高位のL5，S1傷害では足関節の背屈力が障害される．Fourneyらは仙骨切除後の歩行能力に関して，S2神経根以下の切除で14％，S1以下の切除では40％の患者で術後歩行のためになんらかの支持装具が必要であったと報告している[12]．

TPESにより期待される利益と，仙骨切除に伴うこれらさまざまなリスク・障害を勘案すると，TPESの適応として仙骨切断レベルがS2/S3椎間以下のもの（S2神経根の温存が可能なもの）に限定している現在のわれわれの手術適応は，ほぼ妥当なものであると考えている．これ以上の高位仙骨切除が必要となる症例に対しては，術前化学放射線療法などを用いた集学的治療により，仙骨切除範囲を安全に縮小することが可能か検討することも必要である[15]．

おわりに

本稿では，整形外科医からみたTPESについて，特に仙骨切除の実際と問題点について述べた．TPESはFRTに対して唯一の根治可能性を有する術式であるが，その手術侵襲は大きく，厳密な手術適応と術前計画に基づいて経験豊富な外科チームによって実施されることによって，はじめて患者にとっての大きな福音となりうる．

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ORIGINAL ARTICLE

Diverting stoma in rectal cancer surgery. A retrospective study of 329 patients from Japanese cancer centers

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Abstract
Background A diverting stoma (DS) has been constructed for many patients with low anterior resection (LAR), but it is still controversial whether DS can prevent anastomotic leakages. The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for anastomotic leakage.

Patients and methods This was a retrospective analysis of 329 middle or lower rectal cancer patients who underwent LAR with mechanical reconstruction using circular staplers. Clinical data were collected from five cancer centers in Japan.
Results The overall anastomotic leakage rate was 10.0% (33 of 329). We experienced one mortality in this series (0.3%; 1/329). Clinical factors associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection, simultaneous resection of other organs, and the level of anastomosis, respectively.

On univariate analysis, high ligation of the inferior mesenteric artery had a significantly high leakage rate, but not on multivariate analysis. DS construction had no connection with the overall leakage rate. Concerning the clinical course affected by DS, the frequency of urgent reoperation was significantly increased in patients without DS compared with those with DS, 11.1% and 54.2%, respectively ($p=0.04$).
Conclusions LAR was the safe and preferred option for rectal cancer patients with very low mortality and an acceptable leakage rate. DS did not have a relationship with overall anastomotic leakage, but did seem to mitigate its consequences and reduce the requirement for urgent abdominal reoperation.

Keywords Rectal cancer · Anastomotic leakage · Diverting stoma · Defunctioning stoma · Low anterior resection

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Introduction

Anastomotic leakage is a major problem in rectal cancer surgery, because a sphincter-preserving operation has become standard for many rectal cancer patients. A temporary diverting stoma (DS) has been constructed for many patients in low anterior resection (LAR). But the indication of DS construction for patients without intraoperative adverse events has not been clarified for a long time. Theoretically, DS was constructed to divert the fecal stream from anastomotic sites, and to protect fragile anastomotic sites. But it remains unproven whether diverting the fecal stream in itself directly prevents leakage. Several retrospective studies showed that the absence of DS was a risk factor for leakage in LAR, whereas others did not. Therefore, it is controversial whether DS can prevent anastomotic leakage. Although recent randomized studies [1, 2] and meta-analyses [3, 4] have shown that DS reduced the incidence of symptomatic leakage in LAR for rectal cancer, there is still limited evidence as to the impact of DS on leakage. Moreover, there have been few analyses about this issue in multicenter studies with a large number of patients from Japan.

The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for such leakage using data collected from five cancer centers in Japan.

Patients and method

Patients

We reviewed the clinical data from five cancer centers in Japan which participated in the "Studies on the standardization for diagnosis, treatment, and follow-up of colorectal cancer patients", sponsored by Grant-in-Aid 18-2 for Cancer Research from the Ministry of Health, Welfare and Labor of Japan. All data on patient demographics, comorbidities, and the histological results were investigated retrospectively from the clinical records of each hospital.

From 2002 to 2004, a total of 329 consecutive patients with primary rectal cancer underwent LAR, and were investigated in this series. LAR was performed on patients with middle or lower rectal cancer, and reconstructions were done using circular staplers. Coloanal anastomosis using the hand-sewn technique was excluded from this study. Patients with subtotal colectomy, total proctocolectomy, abdominoperineal resection, Hartmann's procedure, or with pull-through procedures were also excluded.

Surgical procedure

The inferior mesenteric artery (IMA) was divided either at its origin or below the origin of the left colic artery (LCA). High ligation of IMA was defined as dividing IMA at its origin, while low ligation was defined as dividing IMA below the origin of LCA. For oncological lymph node dissection, we classify regional lymph nodes into three groups: perirectal, intermediate, and main lymph nodes. Perirectal nodes are lymph nodes in the mesorectum along the superior rectal artery. Intermediate nodes are lymph nodes along IMA between the origin of the left colic artery and the origin of the terminal sigmoid artery. Main nodes mean the lymph nodes along the IMA proximal to the origin of the LCA [5]. Lymph node dissection for UICC stage I is complete dissection of perirectal and intermediate lymph nodes, that is, low ligation without lymph node dissection around the root of IMA. Lymph node dissection for stage II, III, and IV is complete dissection of all regional lymph nodes, that is, high or low ligation with lymph node dissection around the root of IMA [6].

After total mesorectal excision or tumor-specific mesorectal excision [7], we performed rectal irrigation, while clamping the anal side of the tumor. The rectum was then divided transversely or vertically [8]. After that, we usually added lateral lymph node dissection for patients diagnosed with stage II, III, and IV [9]. Although the extent of lymphadenectomy for stage IV is still debatable, in the case that every distant metastasis (stage IV) was resectable, we perform full lymph node dissection.

Reconstruction was done using a circular stapler. Most anastomoses were straight, and colonic J pouch or transverse coloplasty pouch was sometimes used at the discretion of the operating surgeon. Intraoperative leakage test by transanal instillation of fluid or air was performed depending on the surgeon. Pelvic drain was used routinely.

Indication of DS construction

No clear applicable criteria for DS construction were stipulated in the present study. The DS construction decision was made by the individual surgeon in each case.

Definition of anastomotic leakage

Anastomotic leakage was defined clinically by the presence of the following: discharge of gas, pus, or feces from the drain or wound; discharge of pus per rectum; or rectovaginal fistula. All clinically suspicious anastomotic leakages were confirmed by one or more of the following image diagnoses: contrast study; CT scan; rectoscopy. If these cases were proven not to show anastomotic insufficiency by these imaging studies, they were defined as pelvic abscess and not as anastomotic leakage. We did not perform routine diagnostic imaging after LAR to detect anastomotic dehiscence in clinically stable patients.

Variables analyzed

Variables included in this analysis were age, gender, body mass index (BMI), bowel obstruction, tumor location, tumor invasion, adjuvant therapy, level of IMA ligation, lateral lymph node dissection, type of anastomosis (single stapling technique, SST; or double stapling technique, DST), pouch surgery, intraoperative blood loss, operating time, DS construction, synchronous resections of other organs (hepatectomies for simultaneous liver metastasis or extended surgery to adherent organs, or additional cancer resections for double cancers), tumor size, and distal resection margin of specimen.

Bowel obstruction was defined as stenosis preventing the passage of a colon fiberscope. Tumor location was classified into middle or lower rectum according to the main part of the tumor. Tumors in the lower rectum were defined as those in which the main part was located below the peritoneal reflection. Tumor location in relation to the anal verge was preoperatively measured using rigid scope or digital examination. Tumor invasion was classified according to the UICC-TNM classification (6th edition [10]) preoperatively. Tumor size and distal resection margin were measured on the specimen before fixation with formalin. The level of anastomosis from the anal verge was measured with a digital examination. But due to the retrospective nature of this study, when the data were not available, the distance was calculated from the tumor location and distal resection margin.

Statistical analysis

In the univariate analysis, the chi-squared test and Mann–Whitney test were used. After univariate analysis, variables with a p value≤0.1 were selected for multivariate analysis. A multivariate analysis was performed using a binary logistic regression model. All p values <0.05 were considered statistically significant.

Table 1 Patient characteristics

Gender	
Male	215
Female	114
Age(years)	59.0±10.5 (23–87)
Tumor location (cm)	6.1±1.7 (4.0–12.0)
Bowel obstruction	
No	305
Yes	18
Missing	6
Tumor invasion	
T1,T2	108
T3,T4	215
Missing	6
Neoadjuvant chemo Tx	
No	324
Yes	5
Anastomosis	
SST	15
DST	314
High ligation	
No	142
Yes	183
Missing	4
LLND	
No	197
Yes	132
Level of anastomosis (cm)	4.1±1.4 (1.0–9.5)
Intraoperative bleeding (ml)	598±590 (10–3723)
Operating time (min)	240±104.1 (90–620)
BMI (k/m^2)	22.6±3.1 (14.1–31.2)
Tumor size (cm)	4.4±2.3 (0–12.0)
Simultaneous resection	
No	292
Yes	37
DS construction	
No	209
Yes	120

Values are number or mean±standard deviation (ranges)

DS diverting stoma, *BMI* body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Results

Patient characteristics

From 2002 to 2004, a total of 329 consecutive patients underwent LAR. Patient characteristics were shown in Table 1. One hundred and eighteen middle rectal cancer patients and 211 low rectal cancer patients were investigated in this series. Average distance from the lower edge of the tumor to the anal verge was 6.1 cm (4.0–12.0 cm). Average distance from anastomosis to the anal verge was 4.1 cm (1.0–9.5 cm).

Neoadjuvant chemotherapy was performed for five patients, but others were treated by surgery alone. Neoadjuvant radiotherapy or chemoradiotherapy was not performed in this series, because preoperative therapy for resectable rectal cancer was not standard in Japan.

Synchronous resections included 20 extended resections for direct invasion of adjacent organs, 13 hepatectomies for liver metastasis, and five resections of double primary cancers.

Morbidity and mortality

The overall rate of anastomotic leakage was 10.0% (33 of 329). We experienced only one mortality in this series (0.3%; 1/329). This patient died from a septic complication caused by anastomotic leakage in the case of LAR with DS 6 days after initial surgery.

Diverting stoma

A DS was constructed in 120 patients (36.5%; 120 of 329) in initial LAR, respectively. Among the colorectal surgeons participating in this study, ileostomy was major and chosen for 92 (76.7%) patients, while transverse colostomy was done for 28 (23.3%) patients.

The DS construction rate had a significant association with tumor location. DS was constructed in only 12.7% of middle rectal cancer patients, but in 48.3% of low rectal cancer patients who experienced temporary stoma at initial LAR, respectively.

Other factors found to be significantly associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection,

Table 2 Univariate analysis of factors related with DS construction

	Diverting stoma		Rate	*p*-value
	DS(−)	DS(+)		
Gender				
Male	130	85	39.5	0.11
Female	79	35	30.7	
Age (years)	58.8±10.7 (23–87)	59.4±10.2 (29–75)		0.42
Tumor location (cm)	6.4±1.6 (4.0–12.0)	5.9±1.7 (4.0–12.0)		0.001
Bowel obstruction				
No	195	110	36.1	0.76
Yes	11	7	38.9	
Tumor invasion				
T1,T2	71	37	34.6	0.50
T3,T4	133	82	38.1	
Neoadjuvant chemo Tx				
No	204	120	37.0	0.10
Yes	5	0	0.0	
Anastomosis				
SST	8	7	46.7	0.40
DST	201	113	36.0	
High ligation				
No	125	58	31.7	0.12
Yes	82	60	42.3	
LLND				
No	146	51	25.9	<0.0001
Yes	63	69	52.3	
Level of anastomosis (cm)	4.2±1.4 (1.0–9.0)	3.8±1.4 (1.0–9.5)		0.002
Intraoperative bleeding (ml)	505±524 (10–2985)	760±662 (17–3723)		<0.0001
Operating time (min)	231±90.6 (90–559)	318±102.7 (130–620)		<0.0001
BMI (k/m^2)	22.9±3.0 (14.1–31.2)	22.3±3.2 (15.8–30.8)		0.07
Tumor size (cm)	4.4±2. (0–12.0)	4.4±2.3 (1.0–10.0)		0.97
Simultaneous resection				
No	192	100	34.2	0.02
Yes	17	20	54.1	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection simultaneous resection of other organs, and level of anastomosis (Table 2).

Risk factors of anastomotic leakage

Clinical variables were analyzed to investigate the risk factors for anastomotic leakage (Table 3). On univariate analysis, LAR with high ligation of IMA had a significantly high leakage rate ($p<0.05$). There were increased but statistically insignificant impacts on leakage in males, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs.

Nine (7.5%) of 120 patients with DS had leakage, compared with 24 (11.5%) of 209 patients without DS ($p=0.25$). DS construction also had no relevance to the overall anastomotic leakage.

Risk factors of leakage limited to the LAR without DS were also investigated. As shown in Table 4, no obvious statistical significance was found with any clinical factor.

A multivariate analysis of risk factors for anastomotic leakage showed every factor including high ligation of IMA construction as not statistically significant (Table 5).

Table 3 Univariate analysis of leakage risk factors

	Leakage		Rate	*p*-value
	No leakage	Leakage		
Gender				
Male	190	25	11.6	0.19
Female	106	8	0.7	
Age(years)	58.8±10.6 (23–87)	61.1±10.0 (40–76)		0.20
Tumor location (cm)	6.2±1.7 (4.0–12.0)	6.5±1.7 (4.0–10.0)		0.31
Bowel obstruction				
No	276	29	9.5	0.16
Yes	14	4	22.2	
Tumor invasion				
T1,T2	101	7	6.5	0.12
T3,T4	189	26	12.1	
Neoadjuvant chemo Tx				
No	291	33	10.2	0.59
Yes	5	0	0.0	
Anastomosis				
SST	13	2	13.3	0.66
DST	283	31	9.9	
High ligation				
No	135	7	4.9	0.02
Yes	157	26	14.2	
LLND				
No	177	20	10.1	0.93
Yes	119	13	9.8	
Level of anastomosis (cm)	4.1±1.4 (1.0–9.5)	4.4±1.3 (1.9–7.0)		0.13
Intraoperative bleeding (ml)	573±559 (10–3365)	817±791 (40–3723)		0.06
Operating time (min)	261±102 (90–616)	273±118 (113–620)		0.70
BMI (k/m^2)	22.7±3.1 (14.1–31.2)	22.5±3.2 (16.1–27.0)		0.87
Tumor size (cm)	4.4±2.3 (0–12.0)	5.0±2.3 (2.0–11.0)		0.18
Simultaneous resection				
No	266	26	8.9	0.06
Yes	30	7	18.9	
DS construction				
No	185	24	11.5	0.25
Yes	111	9	7.5	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Table 4 Univariate analysis of leakage risk factors (without DS patients)

	Leakage		Rate	p-value
	No leakage	Leakage		
Gender				
Male	114	16	12.3	0.63
Female	71	8	10.1	
Age(years)	58.7±10.8 (23–87)	59.7±10.1 (40–76)		0.65
Tumor location (cm)	6.4±1.6(4.0–12.0)	6.3±1.6 (4.0–10.0)		0.61
Bowel obstruction				
No	173	22	11.3	0.64
Yes	9	2	18.2	
Tumor invasion				
T1,T2	65	6	8.5	0.28
T3,T4	115	18	13.5	
Neoadjuvant chemo Tx				
No	180	24	11.8	0.54
Yes	5	0	0.0	
Anastomosis				
SST	7	1	12.5	0.63
DST	178	23	11.4	
High ligation				
No	108	17	13.6	0.47
Yes	75	7	8.5	
LLND				
No	130	16	11.0	0.72
Yes	55	8	12.7	
Level of anastomosis (cm)	4.2±1.4 (1.0–9.0)	4.2±1.1(2.2–7.0)		0.89
Intraoperative bleeding (cm)	480±502 (10–2985)	703±650 (40–2720)		0.07
Operating time (cm)	228±88 (90–552)	248±108(113–559)		0.60
BMI (k/m^2)	22.9±3.0 (14.1–31.2)	22.7±3.1 (16.1–27.0)		0.82
Tumor size (cm)	4.3±2.3 (0–12.0)	5.0±2.4 (2.0–11.0)		0.26
Simultaneous resection				
No	171	21	10.9	0.31
Yes	14	3	17.6	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Clinical course affected by DS construction

The clinical course affected by DS was also investigated, focusing on the necessity of urgent abdominal reoperation for anastomotic leakage. Nine of 120 (7.5%) patients who underwent LAR with DS experienced leakage. Of these nine, only one patient (11.1%) needed urgent reoperation for peritonitis, and eight patients were treated conservatively. Twenty-four of 209 (11.5%) patients who underwent LAR without DS experienced leakage, and 13 (54.2%) of them needed urgent reoperation, while 11 patients were treated conservatively (Table 6). The need for reoperation was significantly increased in patients without DS compared to those with DS, 54.2% and 11.1%, respectively (p=0.04).

Table 5 Multivariate analysis of leakage risk factors

	p-value	Odds ratio (95% CI)
High ligation	0.17	1.9 (0.77–4.54)
Intraoperative bleeding	0.78	1.0 (0.99–1.00)
Simultaneous resection	0.12	2.2 (0.82–6.09)

Discussion

LAR was the safe and preferred option for middle or low rectal cancer patients with very low mortality and an acceptable leakage rate among the institutes participating in this study. DS did not have a statistically significant

Table 6 Clinical course affected by diverting stoma

DS in initial LAR		Leakage		Conservative therapy	Urgent operation	Rate of urgent operation	
			%			%	
DS(+)	120	9	7.5	8	1	11.1	$p=0.04$
DS(−)	209	24	11.5	11	13	54.2	

relationship with the overall leakage rate. Although we cannot conclude the value of DS in terms of leakage prevention from this retrospective study, DS did seem to mitigate the consequences of leakage and reduce the need for urgent abdominal reoperation for leakage. There have been few reports about this issue in multicenter studies with a large number of patients from Japan.

With the advances in surgical procedures and devices in recent decades, sphincter-preserving surgery has become the treatment of choice for rectal cancer patients. In addition, simple and easy reconstruction has become possible thanks to circular stapling devices, even in low-level anastomosis within a narrow pelvis.

However, anastomotic leakage is still a major problem in rectal cancer surgery, sometimes resulting in severe morbidity or mortality. Since stapled anastomosis developed in the 1970s, the mortality of sphincter-preserving operations has decreased. In 1975, Fain et al. [11] reported their experience of mechanical suturing in 165 rectal cancer patients with a mortality of 2.4%. Now, symptomatic anastomotic leakage has been reported to occur in 5% to 20% of cases [12–20], and when present, the associated risk of postoperative mortality is increased to between 6% and 22% [15]. The present study encountered very low mortality (1/329; 0.3%), which is not inferior to the 0.8% recently described [2]. Our result shows the obviously improved safety of LAR using mechanical anastomosis in the Japanese cancer centers participating in this study.

Several risk factors for anastomotic leakage have been reported [12–20], and the relationship between DS and leakage was discussed in many retrospective or non-randomized prospective studies. Wong et al. [21] reported no statistical difference between patients who were defunctioned (3.8%; 28/742) and those who were not (4%; 13/324). So, they concluded that DS did not reduce the postoperative leak rate. They also concluded that a stoma carried a certain morbidity and also added to the cost of the entire operation, so it should not be performed routinely. On the other hand, Peeters et al. [18] reported that the absence of DS was significantly associated with a higher leakage rate: 43 (8.2%) of 523 patients with DS had leakage, compared with 64 (16.0%) of 401 patients without DS ($p<0.001$). In the present study, DS construction had no association with the overall anastomotic leakage rate. This reflects our low leakage rate in cases without DS (11.5%; 24 of 209). This rate is comparable to the leakage rate in cases with DS in a randomized controlled trial by Matthiessen et al. (10.3%; 12 of 116) [1].

Although absence of DS was not a risk factor of leakage in this study, because of a general selection bias of nonrandomized study including ours, we cannot conclude whether or not DS can prevent the leakage. This bias results from the selective creation of DS for the patients anticipated to undergo "risky" anastomosis by each surgeon as shown in this investigation. We can also point out another bias, namely that clinically unapparent leakages might have been missed in either group because no systematic assessment of the anastomosis for clinically stable patients was performed in the present study.

Only four randomized control studies sought to investigate the association between DS and leakage [1, 2, 22, 23]. Matthiessen et al. [1] reported the result of intraoperative randomization of a patient undergoing LAR for rectal cancer within 15 cm from the anal verge, and anastomosed within 7 cm. 10.3% (12 of 116) of patients with defunctioning stoma ($n=116$) had symptomatic leakage, against 28.8% (33 of 118) of those without stoma ($n=118$). They concluded that defunctioning stoma significantly decreased the rate of symptomatic leakage and was therefore recommended in LAR for rectal cancer. Pakkastie et al. [22] and Graffner et al. [23], on the other hand, could not find any statistical difference between the two groups in their randomized studies comprising 50 and 38 patients, respectively. But due to the small sample, no firm conclusion could be made. So, it is still controversial whether DS can prevent anastomotic leakage. The problem is the limited evidence about this issue. The value of DS in preventing leakage should be evaluated by more prospective studies in the future. And prospective, randomized studies are also warranted to address this issue.

Other reported risk factors include male gender [13–16], level of anastomosis [12–15], previous radiation therapy [13, 14], absence of pelvic drainage [18], poor bowel preparation [12], blood transfusion [12], immunosuppression, and underlying vascular insufficiency. Among these risk factors, male gender and level of anastomosis were widely accepted as significant for leakage. In the present study, there were increased impacts on leakage in male gender, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs. Although statistical significance was not reached, these factors were comparable to those in previous reports. In the present investigation, due to the retrospective nature of the study design, the level of anastomosis was calculated from the tumor location and distal resection margin when data were not available. And in some patients, tumor location was measured only by digital examination and not by rectoscopy, these might introduce bias. Although the anastomotic level was not associated with leakage, this data should be evaluated with caution.

High ligation of IMA was the only leakage risk factor on univariate analysis in the present study. Lange et al. [24] systematically reviewed the literature concerning the level of ligation and concluded that preserving IMA and left colic artery was anatomically less invasive with respect to circulation and autonomous innervations of the proximal limb of anastomosis. Seike et al. [25] measured the colonic blood flow at the proximal site of the anastomosis by laser Doppler flowmetry to evaluate the influence of high ligation. They proved a significant reduction of colonic blood flow at the proximal site after clamping IMA. Our result also suggested the possibility that blood flow reduction on anastomotic sites leads to more leakage.

In the present study, we reported our low leakage rate in cases without DS (11.5%; 24 of 209). This rate is comparable to the leakage rate in cases with DS in a randomized controlled trial by Matthiessen et al. (10.3%; 12 of 116) [1]. This may have some association with our patient population that neoadjuvant radiotherapy or chemoradiotherapy was not performed in this series. Neoadjuvant radiation therapy is considered to be a risk factor by some authors [13, 14]. Although randomized multicenter trials have shown that neoadjuvant radiation does not increase postoperative morbidity [26–28], Peeters et al. [18] retrospectively analyzed risk factors from the database of the Dutch Colorectal Cancer Group, and reported that a defunctioning stoma was constructed more often in patients who had received radiation, and that the absence of a DS was significantly associated with a higher leakage rate.

We also reported our low mortality. This reflects our low leakage rate in cases without DS and our appropriate decision of reoperation for peritonitis in cases without DS. We considered that our appropriate decision lead to low mortality rate and high reoperation rate (54.2%). In the present study, a DS constructed at the time of initial surgery obviously reduced the necessity of an urgent reoperation after overt leakage, proving the clinical benefits of DS in this regard. The important objective of DS was not to eliminate leakage but to decrease the risk of reoperation. However, DS construction did not guarantee the complete safety of LAR. In fact, we experienced one mortality in a patient with DS in this series, so complete elimination of leakage and severe septic complications was not feasible.

In conclusion, we clearly demonstrated the outstanding safety of LAR with very low mortality and acceptable leakage rate in our group. Although this retrospective study could not prove whether DS can prevent leakage itself, we found that it could mitigate the need for urgent abdominal reoperation for leakage. To define clear criteria for DS construction, a well-designed randomized control study is genuinely needed in the future.

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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.

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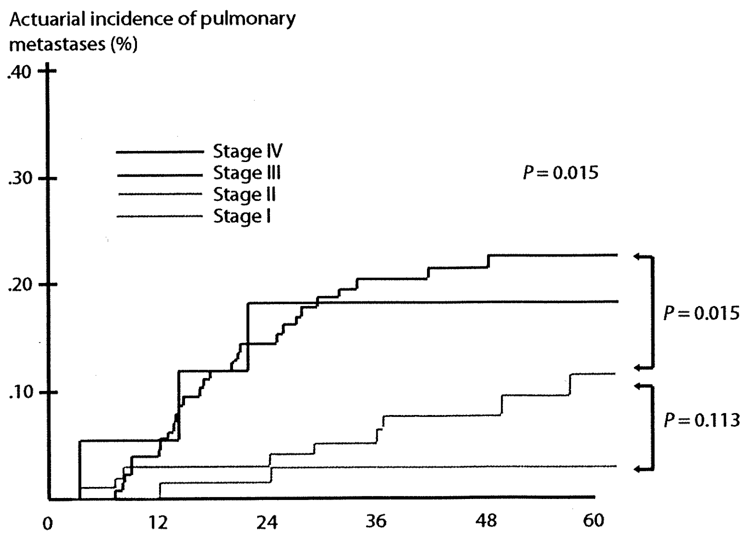
Outcomes after surgery for rectal cancer are predominantly determined by local recurrence and distant metastases.[1] The lung is one of the most common sites of metastases from rectal cancer. To date, surgical resection has been the only radical treatment available for patients with pulmonary metastases, 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 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.

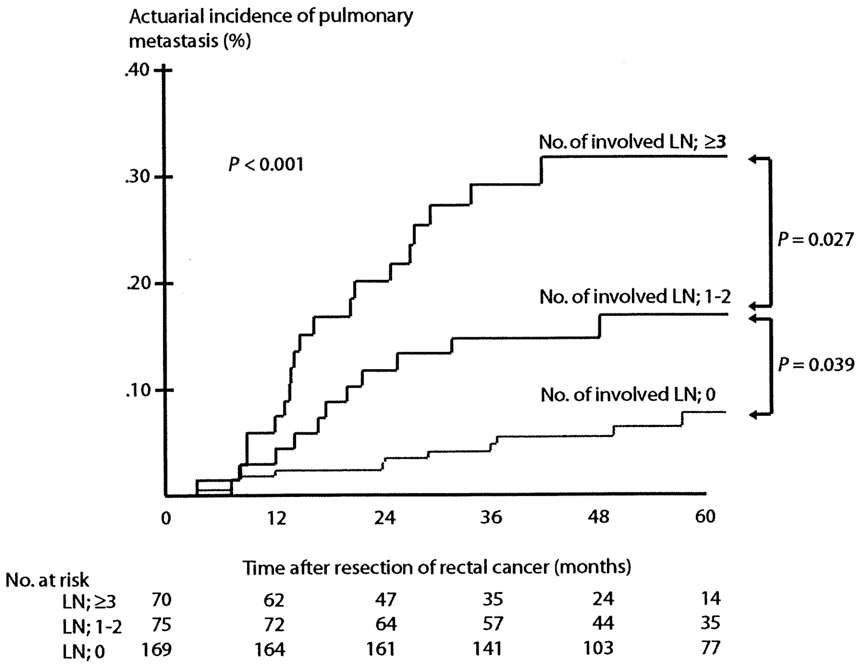


FIGURE 2. Kaplan-Meier curves for pulmonary metastases after R0 resection of rectal cancer according to the number of regional lymph node metastases. LN = lymph node.

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.

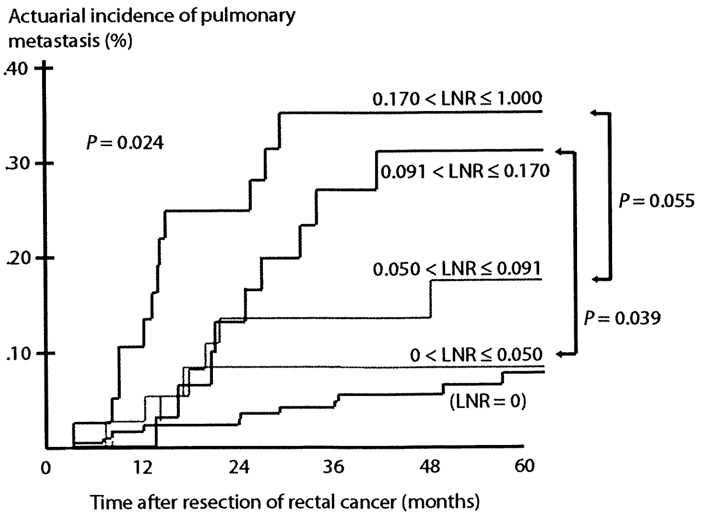
Risk Factors for Pulmonary Metastases According to Number of Lymph Node Involvements

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						
0.170 < 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

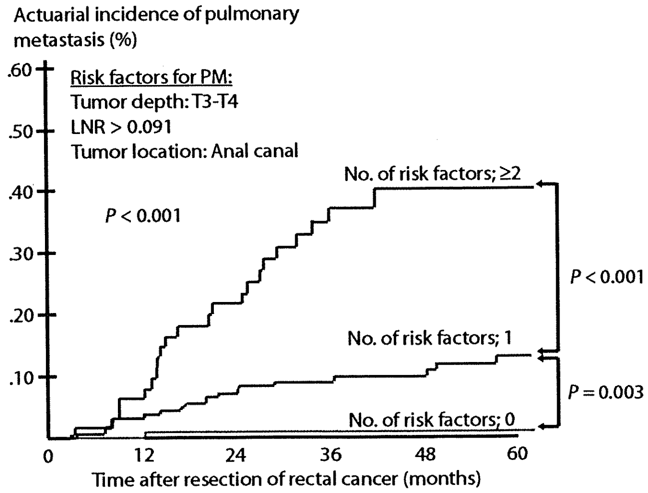
	Rectal cancer				
	Univariate			Multivariate	
	n	5-y lung metastasis rate (%)	*P*	Hazard ratio (95% CI)	*P*
Overall	314	14.6			
Age at colorectal resection			.818		
≥60 (median) y	169	14.6			
<60 y	145	14.8			
Preoperative CEA level			.036		NS
<5 ng/mL	167	10.7			
≥5 ng/mL	147	19.3			
Simultaneous liver 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).



No. at risk

No. of risk factors; ≥2	65	57	44	31	18	11
No. of risk factors; 1	158	150	139	121	95	68
No. of risk factors; 0	91	91	89	81	58	47

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.