重要なことであり，海外からも注目されている．

大腸癌研究会のデータでは，側方郭清を行った下部直腸癌1427例中140例16.4%に側方リンパ節転移を認めている．その中で壁深達度が筋層を超える症例では19.9%に転移を認めており，郭清することによる生存への寄与率は9.2%と報告されている．一般的に，下部直腸癌で筋層を超えて浸潤している症例では側方郭清の適応と考えられている．側方郭清の効果については，この臨床試験で明らかにされるであろう．

E.結論

手術時間，出血量，術後合併症，排尿障害などの術後早期の治療成績においては側方郭清を行わない方が良好であったが，長期の予後に関しては今後の追跡調査による検討が必要である．

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G．知的所有権の取得状況

1．特許取得

なし

2．実用新案登録

なし

3.その他

なし

厚生労働科学研究費補助金（がん臨床研究事業）
研究分担者報告書
側方リンパ節郭清術の意義に関するランダム化比較試験に関する研究

研究分担者　白水　和雄　　久留米大学医学部外科教授

研究要旨：明らかな骨盤側方リンパ節転移を認めない治癒切除可能な下部直腸癌（stageII・III）の患者を対象とし、国内標準手術である自律神経温存 D3 郭清術（神経温存 D3 郭清）の臨床的有用性を、国際標準手術である mesorectal excision（ME 単独）を対照とした多施設共同臨床試験の、当教室からの登録症例について検討した。登録は 14 例で術後合併症は ME 単独群、D3 群それぞれ、縫合不全 1 例、イレウス 1 例づつであった。局所再発は認めていないが肝転移が 1 例あった。術後の排尿・排便機能障害は側方リンパ節郭清の有無に関わらず認められている。

A. 研究目的

本邦における下部直腸癌の進展の実態として、約 15%に側方骨盤リンパ節転移が存在することが言われている．このため，専門の施設を中心に自律神経機能を維持しつつ側方リンパ節郭清を施行している。しかし、側方リンパ節郭清の明らかなエビデンスはなく、その意義については不明である。一方，欧米では術前に放射線照射などを行い局所再発が減少したという報告もあり，側方リンパ節の予防的郭清には否定的な意見があるが、放射線照射の功罪についての検証はなされていない。われわれは自律神経温存 D3 郭清術（神経温存 D3 郭清）の臨床的有用性を、国際標準手術である mesorectal excision（ME 単独）を対照とした多施設共同ランダム化比較試験に参加し，その是非を検討する。

B. 研究方法（研究計画書より抜粋）

対象：臨床病期が II 期または III 期の腫瘍下縁が腹膜翻転部と肛門縁に存在する下部直腸癌。年齢が 20 歳から 75 歳までの PS 0-1 で、mesorectum 外にリンパ節転移および浸潤が無い症例。

＜エンドポイント＞

Primary endpoint: 無再発生存期間

Secondary endpoint: 生存期間、局所無再発生存期間、有害事象発生率、手術時間、出血量、性機能障害発生率、排尿機能障害発生率

＜治療方針＞

A 群：ME＋神経温存 D3 郭清

B 群：ME

p-stage III の場合、術後補助化学療法 5-FU+l-LV（8 週 1 コース×3 コース）施行

＜割付調整因子＞

術中リンパ節転移の有無、性別、施設

＜予定症例数、登録期間、追跡期間＞

我々の施設で対象となる症例にはインフォームドコンセントを行い参加を求めた。教室からは 2003 年 6 月より参加し、試験終了までに 14 例を登録した。

C. 倫理面への配慮（研究計画書より抜粋）

ヘルシンキ宣言に従い、十分なインフォームドコンセントをおこなって本試験を実施した。登録者の同定や照会は、登録時に発行される症例登録番号、患者イニシャル、生年月日、カルテ番号を用いて行われ，患者名など第三者が直接患者を識別できる情報はデータセンターのデータベースに登録していない。有害事象が発生した場合は保険診療の範囲で適切かつ迅速な対応をとるようにする。

D. 研究結果

登録症例の内訳は A 群（ME＋郭清）6 例 B 群（ME 単独）8 例であった。術後合併症は A,B 群それぞれに縫合不全 1 例，イレウス 1 例が認められた．しかしいずれも保存的に治療可能であった。

その他特記すべき有害事象の発生はなかった。また，再発は局所には認められていないが，肝転移をＢ群に１例認め，切除術を行い現在再々発は認められていない．機能障害についてはＡ，Ｂ群いずれにも程度の差はあるが排便異常がみられる。排尿障害は認められなかった。男性の性機能障害はＡ，Ｂ群それぞれに射精障害が２例ずつみられた．

E．考察

現在のところ，側方リンパ節郭清を施行したほうが術後の機能障害を惹起しやすいという確実な結果は得られていない。特に術後経過が長くなるとその差はないように思われる。また側方リンパ節郭清によるデメリットは手術時間の延長くらいである。しかし、男性の肥満や狭骨盤も手術時間の延長に大いにかかわっているので、結論には至らない。予後に関しては非郭清例に肝転移再発が見られている．局所再発はなく、郭清を抜いたことが原因とは考えられない。

F．結論

これまでに登録した少数の症例からは、予防的側方リンパ節郭清の意義は小さいように思われる。

G．健康危険情報

登録症例にはなし。

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G．知的所有権の取得状況

1．特許取得　：なし

２．実用新案登録　：なし

III. 研究成果の刊行に関する一覧表

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IV. 研究成果の刊行物・印刷

Int J Colorectal Dis (2010) 25:681–686
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ORIGINAL ARTICLE

Multi-institutional study of risk factors of liver metastasis from colorectal cancer: correlation with CD10 expression

Shin Fujita · Hirokazu Taniguchi · Takashi Yao · Tadakazu Shimoda · Hideki Ueno · Takashi Hirai · Masayuki Ohue

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Abstract
Background The risk factors for liver metastasis from colorectal cancer are still unclear. We therefore evaluated the relationships between various clinicopathological factors, including CD10 expression, liver metastasis, and survival, in patients with colorectal cancer.
Methods Clinicopathological data for 1,025 patients with stage II or III colorectal cancer who underwent curative surgery in four participating hospitals were collected and evaluated. Three pathologists examined focal dedifferentiation, venous invasion, and CD10 expression without knowledge of the clinical outcome.
Results Univariate analysis showed that pathological T (pT), pathological N (pN), venous invasion, focal dedifferentiation, and CD10 expression were significantly associated with liver metastasis. Multivariate analysis selected pT, pN, and CD10 expression as significant risk factors for liver metastasis. pT, pN and CD10 were also shown by univariate and multivariate analyses to be significantly associated with disease-free survival. The incidence of liver metastasis was 3% in pN0 patients with CD10-negative or pT2 or pT3 tumors and 28% in pN2 patients with CD10-positive or pT4 tumors.
Conclusions CD10 expression is a significant risk factor for liver metastasis in patients with colorectal cancer and is correlated with prognosis. Patients with a high risk of liver metastasis can be selected on the basis of pT, pN, and CD10 expression.

Keywords CD10 · Venous invasion · Focal dedifferentiation · Liver metastasis · Colorectal cancer

S. Fujita (✉)
Colorectal Surgery Division, National Cancer Center Hospital,
1-1 Tsukiji 5-chome, Chuo-ku,
Tokyo 104-0045, Japan
e-mail: sfujita@ncc.go.jp

H. Taniguchi · T. Shimoda
Clinical Laboratory Division, National Cancer Center Hospital,
1-1 Tsukiji 5-chome, Chuo-ku,
Tokyo 104-0045, Japan

T. Yao
Department of Pathology,
Juntendo University School of Medicine,
1-1 Hongo 2-chome, Bunkyo-ku,
Tokyo 113-8421, Japan

H. Ueno
Department of Surgery, National Defense Medical College,
3-2 Namiki,
Tokorozawa, Saitama 359-8513, Japan

T. Hirai
Department of Gastroenterological Surgery, Aichi Cancer Center,
1-1 Kanokoden, Chikusa-ku,
Nagoya 464-8681, Japan

M. Ohue
Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Disease,
1-3-3 Nakamichi, Higashinari-ku,
Osaka 537-8511, Japan

Introduction

Approximately 50% of patients with colorectal cancer develop liver metastasis during the course of their disease, and liver metastasis is the cause of death in more than 50% of such patients. Therefore, prevention of liver metastasis would be expected to improve the prognosis of colorectal cancer patients. Recently, two randomized studies have demonstrated that hepatic arterial infusion (HAI) chemotherapy can reduce liver metastasis and improve the survival of patients with

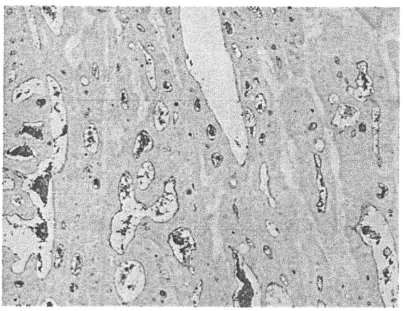

Fig. 1 Representative CD10 expression in colorectal cancer. CD10 is expressed on the luminal surface along the apical membrane of cancer glands

stage III colorectal cancer [1, 2]. Therefore, if it were possible to predict the occurrence of liver metastasis after curative resection of colorectal cancer, then adjuvant regional chemotherapy such as HAI chemotherapy would be more efficient and effective than adjuvant systemic chemotherapy for preventing liver metastasis. We have demonstrated that pathological T (pT), venous invasion, focal dedifferentiation, pathological N (pN), and CD10 expression are significantly associated with liver metastasis from colorectal cancer [3, 4]. Although another study has also demonstrated such an association [5], further proof is still required. In order to predict liver metastasis from colorectal cancer and evaluate the associated risk factors, including CD10 expression, we collected clinicopathological data from more than 1,000 patients with colorectal cancer who underwent curative resection at the four major hospitals offering cancer treatment, National Cancer Center Hospital, Tokyo (NCCH), National Defense Medical College, Tokorozawa (NDMC), Aichi Cancer Center, Nagoya (ACC), and Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka (OMC), and studied paraffin-embedded specimens obtained from them to evaluate the relationships between clinicopathological factors, liver metastasis, and survival.

Patients and methods

Patients

A total of 1,025 patients (524 treated at the NCCH between 1995 and 1998, 221 patients treated at the NDMC between

Table 1 Clinicopathological background, incidence of liver metastasis, and disease-free survival

	No. of patients (%)	Incidence of liver metastasis (%)	*P* value	5-year disease-free survival rate (%)	*P* value
Tumor site					
Colon	590 (57.6)	10.3	0.719	81.6	<0.001
Rectum	435 (42.4)	9.7		73.6	
Pathological T (pT)					
T2	141 (13.8)	5.7	0.006	87.7	<0.001
T3	748 (73.0)	9.6		78.8	
T4	136 (13.3)	16.9		65.2	
Pathological N (pN)					
N0	541 (52.8)	5.0	<0.001	89.5	<0.001
N1	333 (32.5)	12.3		71.9	
N2	151 (14.7)	23.2		51.3	
Tumor differentiation					
Well	331 (32.3)	9.4	0.614	82.2	0.027
Moderate	635 (62.0)	10.1		76.5	
Others	59 (5.8)	13.6		74.5	
Venous invasion					
Negative	430 (42.0)	7.0	0.005	86.7	<0.001
Positive	595 (58.0)	12.3		72.0	
Focal dedifferentiation					
Negative	451 (44.0)	6.7	0.001	88.3	<0.001
Positive	574 (56.0)	12.7		70.2	
CD10					
Negative	601 (58.6)	8.0	0.009	80.1	0.016
Positive	424 (41.4)	13.0		74.5	

1995 and 1999, 169 treated at the ACC between 1998 and 2000, and 111 treated at the OMC between 1995 and 1998) with stage II or III colorectal cancer who underwent curative surgery (R0) were retrospectively examined. All the surviving patients were followed for more than 5 years (median follow-up period, 6.4 years). Pathological stage III patients with colon and rectal cancer were given adjuvant chemotherapy; none of the patients with rectal cancer received pre- or postoperative adjuvant radiotherapy.

Pathological examination

Histological sections were cut from samples, fixed with formalin, and embedded in paraffin containing the deepest site of cancer invasion. One section was stained with hematoxylin–eosin (HE) at each institution and sent to the NCCH. Two unstained sections were also sent to the NCCH: One of these was used for CD10 immunostaining and the other for Victoria blue-HE staining for evaluation of venous invasion. The avidin–biotin–peroxidase complex immunohistochemical method was used for all immunostaining in accordance with a previously described protocol [6]. 56C6 (Novocastra, Newcastle-upon-Tyne, UK; diluted 1:200) was used to detect CD10 expression. Patient age, sex, date of surgery, tumor site, tumor differentiation, pT, pN, number of lymph node metastases, stage, recurrence (sites, date of recurrence), survival (dead or alive), and date of death were collected from the clinical charts and pathological report forms at each institution using case report forms. Three pathologists (H.T., T.S., and T.Y.) examined focal dedifferentiation in HE sections, venous invasion in Victoria blue-HE sections, and CD10 expression in CD10-immunostained sections without knowledge of the clinical outcome. Any discrepancies in the results were resolved by joint consensus. Focal dedifferentiation was defined as positive when there were tumor cells with a single or a solitary trabecular form with indistinct polarity at the invasive front [3]. Venous invasion was defined as positive when tumor cells were present in veins stained with Victoria blue. CD10 expression was defined as positive when more than 5% of tumor cells were stained by CD10 antibody (Fig. 1).

Statistical analysis

Differences in the incidence of liver metastasis were compared statistically by Chi-squared test. Disease-free survival rates were calculated by the Kaplan–Meier method, and differences were compared statistically by the log-rank test. The logistic regression model was used for multivariate analysis of liver metastasis, and Cox's proportional hazards model was used for multivariate analysis of survival. Data differences between groups were considered statistically significant at $P<0.05$.

Results

Clinicopathological background

A total of 229 patients (22.3%) had recurrences. Incidences of liver, lung, peritoneal metastasis, and local recurrence were

Table 2 Multivariate analysis of factors affecting liver metastasis and disease-free survival

	Odds ratio (95% CI)	Hazard ratio (95% CI)	*P* value
Liver metastasis[a]			
pN (Positive/Negative)	3.19 (1.98–5.25)		<0.001
CD10 (Positive/Negative)	1.81 (1.19–2.78)		0.006
pT (pT2, pT3/pT4)	1.77 (1.00–3.07)		0.045
Disease-free survival[b]			
pN (Positive/Negative)		1.72 (1.48–2.02)	<0.001
pT (T2, T3/T4)		1.42 (1.18–1.69)	<0.001
Focal dedifferentiation (Positive/Negative)		1.29 (1.10–1.53)	0.002
Venous invasion (Positive/Negative)		1.28 (1.10–1.50)	0.001
Tumor site (Colon/Rectum)		1.28 (1.11–1.48)	<0.001
CD10 (Positive/Negative)		1.19 (1.05–1.48)	0.008

[a] Tumor differentiation, venous invasion, focal dedifferentiation, and tumor site were not selected as significant liver metastasis-related factors

[b] Tumor differentiation was not selected as a significant survival-related factor

Table 3 Incidence of liver metastasis in relation to risk factors

	CD10-negative and pT2, pT3	CD10 positive or pT4	*P* value
pN0	3% (9/275)	7% (18/266)	0.062
pN1	8% (14/167)	16% (27/166)	0.029
pN2	18/% (13/71)	28% (22/80)	0.182

10.0% (n=103), 7.1% (n=73), 2.9% (n=30), and 2.0% (n=21). The clinicopathological background, incidence of liver metastasis, and disease-free survival rate of the examined patients are shown in Table 1. The positivity rates for venous invasion, focal dedifferentiation, and CD10 expression were 58.0%, 56.0%, and 41.4%, respectively. Univariate analysis demonstrated that pT, pN, venous invasion, focal dedifferentiation, and CD10 expression were significantly associated with liver metastasis. All of the examined variables were significantly associated with disease-free survival. Multivariate analysis showed that pT, pN, and CD10 expression were significantly associated with liver metastasis (Table 2). All of the examined variables except tumor differentiation were still significantly associated with disease-free survival.

Incidence of liver metastasis in relation to significant liver metastasis risk factors

Incidences of liver metastasis in relation to significant risk factors of liver metastasis are shown in Table 3. The incidence of liver metastasis in pN0 patients with CD10-negative and pT2 or pT3 tumors was 3%, which was the lowest among the classified groups. On the other hand, that in pN2 patients with CD10-positive or pT4 tumors was 28%, which was the highest.

Disease-free survival rates in relation to significant prognostic factors

Five-year disease-free survival rates in relation to significant prognostic factors are shown in Table 4. Even in pN1 patients with three or four risk factors, the 5-year disease-free survival rate was 62% and 47% in patients with colon and rectal tumors, respectively, being comparable with that of pN2 patients. On the other hand, in pN2 patients with none or one risk factors, the 5-year survival rate was 88% and 71% in patients with colon and rectal tumors, respectively, being comparable with that of pN1 patients.

Discussion

This study clearly demonstrated the risk factors of liver metastasis in patients with colorectal cancer who underwent curative resection. The incidence of liver metastasis was more than 15% in pN1 patients with CD10-positive or pT4 tumors, and in pN2 patients, and was nearly 30% in pN2 patients with CD10-positive or pT4 tumors. In these patients, adjuvant chemotherapy such as HAI chemotherapy may be considered for prevention of liver metastasis. HAI chemotherapy for resectable or unresectable liver metastasis from colorectal cancer is reportedly effective for control of liver metastasis [7, 8]. Sadahiro et al. reported that adjuvant HAI chemotherapy for stage III colorectal cancer patients significantly inhibited liver metastasis and improved survival [1]. Xu et al. also demonstrated that preoperative HAI reduced and delayed the occurrence of liver metastasis and improved survival in patients with stage III colorectal cancer [2]. Because of technical issues related to the placement and management of hepatic artery catheters and the high cost of HAI, HAI chemotherapy should be given to only selected patients with risk factors for liver metastasis, and our results will be useful for selection of such patients.

Table 4 Five-year disease-free survival rates in relation to prognostic factors

	Focal dedifferentiation, venous invasion, CD10, pT4			
	0 or 1 factor positive	2 factors positive	3 or 4 factors positive	*P* value
Colon				
pN0	94% (n=171)	89% (n=102)	78% (n=60)	0.002
pN1	81% (n=65)	77% (n=67)	62% (n=58)	0.042
pN2	88% (n=17)	52% (n=21)	54% (n=29)	0.105
Rectum				
pN0	91% (n=107)	89% (n=76)	80% (n=25)	0.310
pN1	85% (n=49)	68% (n=61)	47% (n=33)	<0.001
pN2	71% (n=14)	43% (n=44)	27% (n=26)	0.043

The incidence of liver recurrence after liver resection of liver metastasis from colorectal cancer is higher than that after curative resection of colorectal cancer, and several randomized studies have evaluated adjuvant HAI chemotherapy after hepatic resection of liver metastasis [7, 9]. Although adjuvant HAI chemotherapy reduces the incidence of recurrence in the remaining liver, the survival benefit is still controversial. The incidence of extrahepatic recurrence after adjuvant HAI chemotherapy is reportedly higher than that after systemic adjuvant chemotherapy [10], and this is considered to be the reason why adjuvant HAI chemotherapy confers no survival benefit. Therefore, systemic chemotherapy should be added in any future study of adjuvant HAI [11]. This rationale also applies to patients with risk factors for liver metastasis and poor survival.

Survival of pN0 patients with three or four risk factors was almost the same as that of pN1 patients with two or less risk factors. Therefore, adjuvant chemotherapy might be indicated for pN0 patients with three or four risk factors. On the other hand, survival of pN1or pN2 patients without risk factors was nearly the same as that of pN0 patients, suggesting that for the former group, adjuvant chemotherapy might be unnecessary, or that mild adjuvant chemotherapy, i.e., without oxaliplatin or CPT-11, might be sufficient. Patients with factors related to poor survival or liver metastasis may be considered to receive strong chemotherapy combined with HAI chemotherapy. Although further randomized studies will be necessary, indications for adjuvant chemotherapy should be determined according to the potential survival benefits and risks of liver metastasis, as adjuvant chemotherapy has adverse effects and treatment costs are high. Patient selection will become an important consideration for adjuvant therapy in the future.

In this study, CD10 expression was selected as a significant risk factor for liver metastasis by multivariate analysis. Some previous studies have demonstrated that CD10 expression is associated with liver metastasis from colorectal cancer [4, 12], and the present multi-institutional study confirmed this. Therefore, it is suggested that CD10 may play an important role in the process of metastatic spread of colorectal cancer to the liver. CD10 is a 100-kDa cell surface zinc metalloendopeptidase that is commonly expressed on hematopoietic cells and tumor tissues. Several studies have shown an association between CD10 expression and progression of various kinds of tumors [13-19]. Although the actual function of CD10 in tumors is still unknown, the molecule shows structural similarity to matrix metalloprotease and is capable of degrading a number of bioactive peptides and cytokines. Therefore, CD10 is considered to activate or inactivate tumor-related substances and to facilitate tumor progression.

Although a number of biological markers are reportedly associated with prognosis and liver metastasis from colorectal cancer [20-22], few are used clinically because many have not been validated. CD10 has also been reported to be a factor associated with liver metastasis, and the association had not been validated prior to the present study. Because CD10 expression can be easily detected by immunohistochemistry, we recommend that it should be examined on a routine pathological basis.

Focal dedifferentiation and venous invasion were also examined as risk factors of liver metastasis because our colleagues had previously demonstrated such an association [3, 4]. However, in the present study, these were not selected as risk factors. Although focal dedifferentiation is defined as the presence of cancer cells with a single or a solitary trabecular form showing indistinct polarity at the invasive front, this definition is approximately similar to the definition of tumor budding. Tumor budding is defined as a single cancer cell or small clusters of undifferentiated cancer cells at the invasive front [23]. Several studies have demonstrated that tumor budding is a risk factor for survival in patients with colorectal cancer [21, 22]. Venous invasion has also been reported to be a prognostic factor of colorectal cancer [22]. Although tumor budding (or focal dedifferentiation) and venous invasion are considered to be useful prognostic markers, they need to be defined clearly before clinical use because there are no widely accepted standards or guidelines for their pathological evaluation.

In conclusion, CD10 expression is a significant risk factor of liver metastasis and prognosis in patients with colorectal cancer. On the basis of pT, pN, and CD10 expression, patients with a high risk of liver metastasis can be selected.

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ORIGINAL ARTICLE

Risk Factors for Anastomotic Leakage Following Intersphincteric Resection for Very Low Rectal Adenocarcinoma

Takayuki Akasu · Masashi Takawa · Seiichiro Yamamoto · Tomohiro Yamaguchi · Shin Fujita · Yoshihiro Moriya

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Abstract
Background The aim of this study was to perform a retrospective analysis of the risk factors for anastomotic leakage following intersphincteric resection (ISR) for very low rectal cancer.
Methods Between 1993 and 2007, 120 patients with T1–T3 rectal adenocarcinomas located 1 to 5 cm (median 3 cm) from the anal verge underwent ISR without radiotherapy. Univariate and multivariate analyses of 47 prospectively recorded parameters were conducted.
Results All patients had total mesorectal excision after complete bowel preparation. Of them, 103 underwent partial resection, and 17 underwent complete resection of the internal sphincter. Some 108 patients had a defunctioning stoma. Morbidity and mortality rates were 33% and 0.8%, respectively. Fifteen patients (13%) developed clinical leakage, and six (5%) had severe leakage causing relaparotomy, permanent stoma, or death. Univariate analysis of risk factors for clinical leakage revealed tumor annularity, intraoperative blood transfusion, and pulmonary disease to be significant. Multivariate analysis showed transfusion (hazard ratio, 6.5 [95% confidence interval, 1.4 to 30]; $p=0.018$) and pulmonary disease (6.3 [1.6 to 26]; $p=0.009$) to be independently significant. Moreover, transfusion (71 [3.0 to 1000]; $p=0.008$), colonic J-pouch (32 [1.8 to 500]; $p=0.018$), and pulmonary disease (32 [1.1 to 1000]; $p=0.044$) were independently associated with severe leakage.
Conclusions This study suggests intraoperative blood transfusion and pulmonary disease as independent risk factors for clinical and severe leakage following ISR and colonic J-pouch as that for severe leakage. By considering these factors, we may be able to stratify high-risk patients and prepare countermeasures.

Keywords Rectal cancer · Surgery · Intersphincteric resection · Anastomotic leakage · Risk factor

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T. Akasu (✉) · M. Takawa · S. Yamamoto · T. Yamaguchi · S. Fujita · Y. Moriya
Colorectal Surgery Division, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: takasu@ncc.go.jp

Introduction

Although abdominoperineal resection is standard surgery for patients with massively invasive rectal adenocarcinomas located within 5 cm from the anal verge,[1] intersphincteric resection (ISR) has recently been considered as an alternative option to avoid permanent colostomy for selected patients.[2–4] ISR is defined as a procedure obtaining sufficient margins by removing part or whole of the internal sphincter and restoring bowel continuity for patients with rectal cancers involving or neighboring the anal canal.

Careful performance of ISR has been reported to allow satisfactory results both in the short and long term.[4–11] Furthermore, reported rates of anastomotic leakage follow-

ing ISR have been as comparatively low as 5% to 16% in experienced hands.[7–11] However, anastomotic leakage after rectal cancer surgery can result in reoperation, morbidity, mortality, permanent stoma, prolonged hospitalization, anal stenosis, and anal dysfunction and may be associated with a higher local recurrence rate.[12,13] To reduce such complications, clarification of the risk factors for anastomotic leakage should help in identifying high-risk patients and planning countermeasures. The aim of this study was, therefore, to perform a retrospective exploratory analysis of risk factors for anastomotic leakage following ISR for very low rectal adenocarcinomas.

Patients and Methods

Between October 1993 and February 2007, 122 patients with T1 to T3 rectal adenocarcinomas located within 5 cm from the anal verge underwent ISR at the National Cancer Center Hospital, Tokyo. All of the T1 tumors were accompanied by massive submucosal invasion. Selection criteria for ISR were as follows: (1) sufficient medical fitness; (2) normal sphincter function; (3) distance between the tumor and the anorectal junction (upper edge of the surgical anal canal) less than 2 cm; (4) no involvement of the external sphincter; and (5) no signs of disseminated disease. Preoperatively, the patients were assessed with chest and abdominal computed tomography (CT), digital anorectal examination, and radiological studies, including endorectal ultrasonography, thin-section helical CT, or high-resolution magnetic resonance imaging.

Univariate and multivariate analyses of 47 prospectively recorded clinicopathologic variables were conducted for the 120 consecutive patients who did not receive neoadjuvant radiotherapy. Data from the remaining two given radiotherapy were excluded from the present analysis. Approval by the institutional review board was not required for the observational study. All patients gave informed consent for usage of their data for analysis.

Surgical Procedures

The day before surgery, bowel lavage with 2 L of polyethylene glycol was carried out, and all patients received parenteral antibiotic prophylaxis no more than 30 min before skin incision. The surgical procedures were as described previously[11] and basically similar to those originally documented by Schiessel et al.[4,7] The intersphincteric plane between the puborectalis and the internal sphincter was dissected cautiously as caudad as possible under direct vision, using long right-angle retractors and electrocautery. When the lower edge of the tumor was reached, the anal canal was closed just below the tumor and then irrigated with povidone iodine followed by saline. After retractors were applied to the anal canal, the anal canal mucosa and internal sphincter were circumferentially incised, and the intersphincteric plane was dissected cephalad. A resection margin of at least 1 cm was always attempted. If the rectum was not closed in the abdominal phase, it was closed using sutures during per-anal dissection. After removal of the rectum, the pelvic cavity and anal canal were washed, and then a coloanal anastomosis was made using 3-0 absorbable vertical mattress sutures. A pelvic drain was placed, and a defunctioning stoma was made.

Definition of Anastomotic Leakage

Clinical anastomotic leakage was defined as clinically apparent leakage including gas, pus, or fecal discharge from the pelvic drain or peritonitis. All anastomotic leakages were confirmed as extravasation of endoluminally administered water-soluble contrast material on radiography or computed tomography. An abscess around the anastomosis or a rectovaginal fistula was also considered as leakage. Radiological examination was performed by the surgeon and only when there was clinical suspicion of anastomotic leakage. Pouch fistula, pouch necrosis, and necrosis of neorectum were also regarded as evidence of a leakage. Severe leakage was defined as causing emergency relaparotomy, permanent stoma, or death.

Statistical Analysis

The chi-square test was used to compare proportions. The influence of each variable on the risk of clinical anastomotic leakage or severe leakage was calculated using the chi-square test. All variables associated with clinical leakage or severe leakage at $p<0.05$ were entered in a multivariate analysis using the multiple logistic regression model with the forward stepwise method (likelihood ratio). All statistical analyses were performed using SPSS for Windows, version 11.0J (SPSS-Japan Inc., Japan). A two-sided p value of less than 0.05 was considered significant.

Results

Of 39 patients (33%) who suffered complications, 30 were treated conservatively and nine received reoperations. Fifteen patients (13%) had clinical anastomotic leakage, and six underwent an emergency relaparotomy (Table 1). Five of those six had permanent stoma and one dying of

Table 1 Details of the Patients with Anastomotic Leakage

Severity	Reconstruction	Site of leakage	Treatment
Severe[a]	Colonic J-pouch (5)[a]	Pouch necrosis (2)[a] Anterior wall of pouch (1)	Pouch resection, colostomy and drainage (3)[a]
		Pouch anal anastomosis (1)	Ileostomy and drainage (1)
		Pouch-vaginal fistula (1)	Drainage and fistulectomy (1)
	Straight end to end (1)	Anovesical fistula (1)	Drain irrigation and fistulectomy (1)
Minor	Straight end to end (6)	Anastomosis (6)	Transanal drainage (3), Observation (2), Drain irrigation (1),
	Transverse coloplasty (3)	Anastomosis (3)	Drain irrigation (1), Transanal drainage (1), Observation (1)

Numbers in parentheses are numbers of patients

[a] One patient died

anastomotic leakage and sepsis (30-day mortality rate= 0.8%). Seven patients had permanent stoma due to complications (six patients) or local recurrence (one). Other complications included wound infection (nine patients), bowel obstruction (six), urinary tract infection (four), anal pain (two), cholecystitis (two), anastomotic stenosis (one), anal prolapse (one), peristomal hernia (one), and thrombocytopenia (one).

Of the 47 variables analyzed, 28 are summarized in Table 2. The remaining 19 variables were tumor size, pT, pN, pM, lateral pelvic lymph node metastasis, preoperative vital capacity, serum carcinoembryonic antigen, CA19-9, C-reactive protein, hemoglobin A1c levels, white blood cell count, hamatocrit, lymphocyte count, arterial blood oxygen tension, carbon dioxide tension, bicarbonate, base excess, liver disease, and drinking habit.

There were 92 male and 28 female patients with a median age of 57 years (range 26 to 75 years). Thirteen had pulmonary disease including chronic obstructive pulmonary disease in eight patients and restrictive respiratory disease in five. The median distance from the anal verge to the tumor was 3 cm (range 1 to 5 cm).

All patients underwent total mesorectal excision. In addition, 46 patients received extended lateral pelvic lymph node dissection. Sixty-seven patients underwent high ligation of the inferior mesenteric artery. A total of 103 patients underwent partial resection of the internal sphincter, and 17 underwent complete resection. A small part of the external sphincter was resected in six patients to obtain sufficient surgical margins. Combined resection of adjacent organs was performed for 12 patients. Two patients with solitary liver metastases and one with a solitary lung metastasis underwent complete resection of their metastases. Mobilization of the splenic flexure was performed for 35 patients. A colonic J-pouch was constructed for 24 patients, a transverse-coloplasty pouch for 38, and a straight anastomosis for 58. Some 108 patients had a defunctioning stoma which was closed 3 months after ISR. Median operating time was 339 min (range 200 to 590 min). Median blood loss was 462 mL (range 45 to 3,644 mL), and nine patients received intraoperative blood transfusions (Table 2).

The median tumor diameter was 3.7 cm (range 1 to 12 cm). Pathologic findings are shown in Table 2. Resection margins were macroscopically negative in all patients but microscopically positive in four. The median number of lymph nodes removed at surgery was 29 (range 4 to 88), and 108 patients (90%) underwent dissection of 12 or more.

Univariate Analysis

Clinical anastomotic leakage was statistically significantly associated with tumor annularity, intraoperative blood transfusion, and pulmonary disease (Table 2). Severe leakage was significantly associated with tumor annularity, extended lateral pelvic lymph node dissection, a colonic J-pouch, intraoperative transfusion, preoperative serum total protein and albumin levels, the preoperative platelet count, and pulmonary disease (Table 2). Neither overall clinical leakage nor severe leakage showed significant association with the 19 variables not shown in Table 2.

Multivariate Analysis

In a multivariate analysis for clinical leakage, the significant variables in the univariate analysis were entered. Pulmonary disease (hazard ratio, 6.3 [95% confidence interval, 1.6 to 26]; $p=0.009$) and intraoperative transfusion (6.5 [1.4 to 30]; $p=0.018$) were found to be independently significant. The incidences of clinical leakage for patients with 0, 1, and 2 positive risk factors were estimated to be 8%, 28%, and 100%, respectively.

In a multivariate analysis for severe leakage, the eight significant variables in the univariate analysis were used.

Table 2 Univariate Analyses of 28 Clinicopathologic Variables Related to Clinical Anastomotic Leakage and Severe Leakage

	Number of patients	Clinical leak (%)	*p* Value	Severe leak (%)	*p* Value
Gender					
Male	92	12 (13)	1	5 (5)	1
Female	28	3 (11)		1 (4)	
Age					
<60 years	71	6 (8)	0.16	2 (3)	0.22
≥60 years	49	9 (18)		4 (8)	
Distance of the tumor from the anal verge					
<2.5 cm	21	1 (5)	0.47	0 (0)	0.59
≥2.5 cm	99	14 (14)		6 (6)	
Tumor annularity					
<3/4	101	10 (10)	0.033	3 (3)	0.033
≥3/4	16	5 (31)		3 (19)	
Unknown	3				
Histopathologic grade					
Well-differentiated	59	9 (15)	0.62	3 (5)	1
Moderately differentiated	53	6 (11)		3 (6)	
Poorly differentiated	8	0 (0)		0 (0)	
Pathological UICC TNM stage					
Stage I	50	7 (14)	0.91	1 (2)	0.23
Stage II	21	3 (14)		3 (14)	
Stage III	46	5 (11)		2 (4)	
Stage VI	3	0 (0)		0 (0)	
Microscopic resection margins					
Negative	116	15 (13)	1	6 (5)	1
Positive	4	0 (0)		0 (0)	
Internal sphincter resection					
Partial	103	15 (15)	0.13	6 (6)	0.59
Complete	17	0 (0)		0 (0)	
Combined resection					
No	108	15 (14)	0.36	6 (6)	1
Yes	12	0 (0)		0 (0)	
Extended lateral pelvic lymph node dissection					
No	74	8 (11)	0.57	1 (1)	0.03
Yes	46	7 (15)		5 (11)	
High ligation of the inferior mesenteric artery					
No	50	6 (12)	1	3 (3)	1
Yes	67	9 (13)		3 (4)	
Mobilization of the splenic flexure					
No	63	8 (13)	1	1 (2)	0.129
Yes	35	5 (14)		3 (9)	
Reconstruction					
Straight anastomosis	58	7 (12)	0.18	1 (2)	0.001
Transverse coloplasty	38	3 (8)		0 (0)	
Colonic J-pouch	24	5 (21)		5 (21)	
Defunctioning stoma					
No	14	1 (7)	1	0 (0)	1
Yes	106	14 (13)		6 (6)	
Anastomosis height from the anal verge					
<2.0 cm	57	5 (9)	0.28	1 (2)	0.21
≥2.0 cm	63	10 (16)		5 (8)	

Table 2 (continued)

	Number of patients	Clinical leak (%)	*p* Value	Severe leak (%)	*p* Value
Operating time					
<6 h	68	8 (12)	0.79	1 (1)	0.084
≥6 h	52	7 (13)		5 (10)	
Blood loss					
<500 mL	64	6 (9)	0.29	2 (3)	0.42
≥500 mL	56	9 (16)		4 (7)	
Intraoperative blood transfusion					
No	111	11 (10)	0.014	2 (2)	<0.001
Yes	9	4 (44)		4 (44)	
Preoperative body mass index					
<25	89	10 (11)	0.53	4 (4)	0.65
≥25	31	5 (16)		2 (6)	
Preoperative FEV_1 (%)					
<70%	8	3 (38)	0.061	2 (25)	0.051
≥70%	112	12 (11)		4 (4)	
Preoperative serum total protein level					
Normal (6.3–8.3 g/dL)	113	13 (12)	0.21	4 (4)	0.039
Abnormal	7	2 (29)		2 (29)	
Preoperative serum albumin level					
Normal (3.7–5.2 g/dL)	110	12 (11)	0.11	3 (3)	0.007
Abnormal	10	3 (30)		3 (30)	
Preoperative blood hemoglobin level					
Normal (11.3–14.9 g/dL)	85	8 (9)	0.13	2 (2)	0.059
Abnormal	35	7 (29)		4 (11)	
Preoperative platelet count					
Normal (125,000–375,000/μL)	115	13 (11)	0.12	4 (3)	0.02
Abnormal	5	2 (40)		2 (40)	
Diabetes mellitus					
No	106	12 (11)	0.38	6 (7)	1
Yes	14	3 (21)		0 (0)	
Cardiovascular disease					
No	98	10 (10)	0.15	4 (4)	0.30
Yes	22	5 (23)		2 (9)	
Pulmonary disease					
No	107	10 (9)	0.011	3 (3)	0.017
Yes	13	5 (38)		3 (23)	
Smoking habit					
No	79	11 (14)	0.58	6 (8)	0.094
Yes	41	4 (10)		0 (0)	

The remaining 19 variables not shown here did not demonstrate any significant association

FEV_1 forced expiratory volume in the first second of expiration

Intraoperative transfusion (hazard ratio, 71 [95% confidence interval, 3.0 to 1,000]; $p=0.008$), a colonic J-pouch (32 [1.8 to 500]; $p=0.018$), and pulmonary disease (32 [1.1 to 1,000]; $p=0.044$) were independently associated with adverse outcomes. The incidences of severe leakage for patients with 0, 1, 2, and 3 positive risk factors were estimated to be 0%, 6%, 67%, and 100%, respectively.

Discussion

In this study, the incidences of clinical anastomotic leakage and mortality after ISR were 13% and 0.8%, respectively. These are comparable to the respective incidences of 5% to 16% and 0 to 0.8% in recent ISR series.[7–11] Since these figures are even comparable to the 2.8% to 19.2% and 0%

to 2.5% observed with anterior resection,[14–26] appropriately administered ISR can be regarded as safe in terms of leakage and mortality. However, such figures should be interpreted cautiously because incidences of anastomotic leakage depend on the definition, patient selection, and treatment details. Patient factors like gender,[15,16,18,22,25] age,[25] American Society of Anesthesiology score,[25] heart disease,[26] malnutrition,[17] weight loss,[17] obesity,[15] smoking habit,[26] and alcohol abuse[17] have been reported to independently influence the incidences of leakage after anterior resection, and so have treatment factors such as neoadjuvant chemoradiotherapy,[18,22] bowel preparation,[19] timing of surgery,[25] surgeon caseload,[25] anastomotic level,[14,15,18,19,22] intraoperative contamination,[17,18] pelvic drainage,[21] defunctioning stoma,[16,20,21,24] operation time,[17] and blood transfusion.[17,19]

To our knowledge, there have only been few studies addressing risk factors for anastomotic leakage following ISR. Rullier et al.[15] investigated 272 anterior resections for rectal cancer, in which 131 anastomoses were situated 5 cm or less from the anal verge. Multivariate analysis of their overall population showed that male sex and the level of anastomosis were independent factors for leakage. In a second analysis of 131 very low anastomoses, obesity was an independent factor. The authors concluded that a protective stoma is suitable after anastomoses situated at or less than 5 cm from the anal verge, particularly for men and obese patients.

In the present study, all of the patients had undergone complete bowel preparation, elective surgery by high-volume colorectal specialists, and pelvic drainage, all of which have been reported to be independently beneficial for reducing leakage.[19,21,25] Most had a defunctioning stoma as well.[16,20,21,24] None had received neoadjuvant chemoradiotherapy considered to be an independent risk factor for leakage.[18,22] Therefore, these already known significant factors could not be evaluated in this study. Our multivariate analysis revealed intraoperative blood transfusion and pulmonary disease to be independently associated with overall clinical leakage and severe leakage, and a colonic J-pouch was associated with severe leakage. These results suggest that under the circumstances prevailing in our institution, we can stratify high-risk patients by using these factors and prepare countermeasures against them.

Although the exact mechanism whereby anastomotic leakage may be related to blood transfusion is unclear, it is known that allogeneic blood transfusion induces immunosuppression and predisposes to postoperative infection.[27] Allogeneic leukocytes have a critical role in the induction of transfusion-induced immunosuppression.[27] Tang et al.[27] reported that intra- or postoperative blood transfusion was an independent risk factor for overall surgical site infection, incisional infection, and organ/space infection with and without clinical anastomotic leakage in a prospective study of 2,809 consecutive patients undergoing elective colorectal resection. Therefore, susceptibility to infection induced by transfusion may promote development of anastomotic leakage.

To avoid intraoperative transfusion, it is preferable to treat anemia before surgery using oral and parenteral iron therapy. Transfusion should be reserved for patients with cardiovascular instability and continued and excessive blood loss. Furthermore, it should be given before the operation because deleterious effects appear to be more likely with intra- or postoperative transfusion.[27] Operative blood loss should be minimized by cautious procedures. If excessive blood loss is expected, autologous blood transfusion should be considered, especially in the presence of other risk factors.

In line with previous reports on intestinal anastomotic leakage, we found an independent association with pulmonary disease. Jonsson et al.[28] measured oxygen tension and collagen deposition in subcutaneous wounds in 33 postoperative patients and found that this and the resultant tensile strength are limited by perfusion and tissue oxygen tension. Hopf et al.[29] measured subcutaneous wound oxygen tension in 130 surgical patients and observed that this factor is a strong predictor of infection. Millan et al.[23] determined intramucosal pH at colorectal anastomoses, which reflects blood supply and oxygenation of the mucosa, and found that it can accurately predict the risk of anastomotic leakage. Smoking is a major cause of chronic obstructive pulmonary disease and is known as an independent risk factor for anastomotic leakage after anterior resection.[26] Therefore, although the exact pathophysiology remains to be clarified, it is reasonable to speculate that pulmonary disease predisposes to anastomotic hypoxia which in turn hinders wound healing, aggravates infection, and promotes anastomotic dehiscence.

Because of their chronic and irreversible nature, the chronic obstructive pulmonary disease and restrictive respiratory diseases seen in our series are difficult to treat. However, intensive respiratory management including continuous pulse oximetry monitoring, supplemental oxygen, appropriate analgesia, bronchoscopy when needed, and early mobilization, similar to the management applied after esophageal cancer surgery,[30] may prevent the respiratory complications and hypoxemia which can lead to anastomotic leakage.

Although the incidence of leakage with a colonic J-pouch was reported to be significantly lower than with straight coloanal anastomosis[31] and transverse coloplasty[32] in anterior resection, we paradoxically found a J-pouch to be an independent risk factor for severe leakage in our ISR series. Of the five patients who underwent J-pouch construction and suffered severe leakage, four were male, four received an intraoperative transfusion, and two had