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Original Article

Identification of the Risk Factors for Recurrence of Stage II Colorectal Cancer

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Abstract

Introduction: The use of adjuvant chemotherapy in stage II colorectal cancer patients remains controversial. However, patients with specific clinicopathological features are thought to have a high risk for recurrence. The aim of this study was to identify the subgroup of patients at the greatest risk by investigating the clinicopathological features associated with a poor survival in patients with stage II disease.

Patients & Methods: A total of 414 patients with stage II colorectal cancer who underwent curative resection between January 1990 and September 2007 at Kanagawa Cancer Center were enrolled. The clinicopathological data of the patients were retrospectively evaluated.

Results: The median follow-up period was 62.5 months. The 5-year disease-free survival rate was 89.6% in the study group as a whole. A univariate analysis of 5-year disease-free survival identified three factors: lymphatic invasion (p=0.001), the preoperative serum CEA level (>5 ng/ml) (p=0.005) and the CA19-9 level (>37 U/ml) (p=0.006). A multivariate analysis of 5-year disease-free survival identified one independent factor: lymphatic invasion (HR: 1.89; 95% CI: 1.02-3.50; p=0.044).

Conclusions: Patients with stage II colorectal cancer who exhibit lymphatic invasion are at a high risk for recurrence.

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Key words: colorectal cancer, stage II, high risk, disease free survival, adjuvant chemotherapy

Introduction

According to the colorectal cancer treatment guidelines[1], the administration of adjuvant chemotherapy following curative surgical resection in stage III colorectal cancer patients is recommended because it reduces the rate of tumor recurrence and improves disease-free and overall survival[2,3]. However, the usefulness of postoperative adjuvant chemotherapy for treating stage II disease has not been verified[4-7], and the administration of adjuvant chemotherapy in all patients with stage II disease has not been validated. In other guidelines, groups at a high risk for recurrence of stage II colorectal cancer have been defined, and the use of adjuvant chemotherapy in such groups is recommended. The American Society of Clinical Oncology (ASCO) guidelines[8] recommend considering the use of adjuvant chemotherapy in patients with stage II colon cancer, such as those with <12 regional lymph nodes examined, T4 lesions, perforation, poorly-differentiated adenocarcinoma, mucinous adenocarcinoma or signet-ring cell carcinoma. The European Society for Medical Oncology (ESMO) guidelines[9] recommend that adjuvant chemotherapy be considered in patients with the following high-risk factors: T4 lesions, poorly-differentiated adenocarcinoma/undifferentiated carcinoma, vascular invasion, lymphatic vessel invasion, perineural invasion, obstruction or perforation on initial presentation, <12 regional lymph nodes examined or a high carcinoembryonic antigen (CEA) level. The aim of this study was to

Table 1 Clinicopathological features of patients with stage II colorectal cancer

Factor	Category	Number of patients (n=414)
Gender	Male	267
	Female	147
Age	median	65 (23-91)
Colon or Rectum	Colon	302
	Rectum	112
T stage	T3	246
	T4	168
Number of lymph node examined	median	35
Adjuvant chemotherapy	Absent	269
	Present	142
Recurrence	—	369
	+	45

identify the subgroups of patients at the greatest risk by investigating the clinicopathological features associated with poor survival in patients with stage II disease.

Methods

Patients

Between January 1990 and September 2007, a total of 1,804 patients with colorectal cancer underwent curative resection at Kanagawa Cancer Center. We retrospectively reviewed the following clinicopathological data of 414 patients with stage II disease: clinical characteristics, preoperative tumor staging, details of surgery, postoperative histopathology and the results of follow-up. All patients were staged based on the findings of preoperative colonoscopy, imaging of the chest, abdomen and pelvis with computed tomography and radiographic contrast enemas. Patients with synchronous cancer of other organs or who died due to other causes were excluded.

Treatment and follow-up

All patients underwent standard curative resection at our department. The tumor location was classified into two categories: right colon (cecum, ascending colon and transverse colon) and left colon (descending colon, sigmoid colon, rectum and proctos). The patients received follow-up with computed tomography and measurement of the serum CEA and CA19-9 levels. The median follow-up period was 62.5 months. In each case, after curative surgery, the decision whether to administer adjuvant chemotherapy was left to the clinical discretion of the attending physician. A 5-fluorouracil (5-FU)-based regimen was used for adjuvant chemotherapy. The duration of treatment was at least six months.

Histopathological analysis

All resected specimens underwent standard histopathological analyses. After surgery, the disease was pathologically staged according to the 7th UICC TNM classification[10]. Complete tumor resection was performed in all patients. Well-differentiated, moderately-differentiated, poorly-differentiated and mucinous adenocarcinomas were evaluated histopathologically. The presence of local and distant recurrence was confirmed clinically, radiologically and/or histopathologically.

Statistical analysis

Disease-free survival rates were calculated using the Kaplan-Meier method, and survival curves were compared with the log-rank test. A Cox regression analysis was used for the univariate and multivariate analyses. The variables that reached statistical significance ($p<0.05$) were entered into a multivariate analysis. In all cases, p values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the Dr. SPSS II software program, version 11.0. 1J for Windows (SPSS, Inc., Chicago, IL).

Results

The clinicopathological features of the 414 patients with stage II colorectal cancer are shown in **Table 1**. Forty-five patients developed recurrence. Local recurrence was defined as intrapelvic recurrence and anastomotic recurrence. The recurrent sites includ-

Table 2 Univariate analysis of prognostic factors for 5-year disease-free survival

Factor	Category	Number of patients (n=414)	Hazard ratio	95% C.I.*	p-value
Gender	Male	267	1		
	Female	147	0.901	0.485-1.675	N.S.**
Age	≦65	208	1		
	>65	206	1.262	0.701-2.273	N.S.**
Colon or Rectum	Colon	302	1		
	Rectum	112	1.706	0.934-3.117	0.082
Tumor location	Right	126	1		
	Left	288	1.370	0.694-2.704	N.S.**
Tumor diameter(cm)	≦5	209	1		
	>5	204	0.606	0.331-1.106	N.S.**
Pathological type	Wel, Mod	363	1		
	Por, Muc	51	1.348	0.602-3.018	N.S.**
T stage	T3	246	1		
	T4	168	1.456	0.812-2.612	N.S.**
Lymphatic invasion	Absent	271	1		
	Present	143	2.460	1.366-4.429	0.001
Venous invasion	Absent	204	1		
	Present	210	1.030	0.574-1.848	N.S.**
Number of lymph node examined	<12	22	1		
	≧12	392	0.433	0.171-1.098	0.078
Preoperative serum CEA (ng/ml)	≦5	325	1		
	>5	81	2.450	1.303-4.606	0.005
Preoperative serum CA19-9 (U/ml)	≦37	347	1		
	>37	52	2.632	1.319-5.253	0.006
Adjuvant chemotherapy	Absent	269	1		
	Present	142	0.792	0.414-1.514	N.S.**

*C.I.: Confidence Interval **N.S.=Not Significant

Table 3 Multivariate analysis of prognostic factors for 5-year survival

Factor	Hazard ratio	95%C.I.*	p-value
Lymphatic invasion(Present/Absent)	1.887	1.018-3.496	0.044
CEA(>5/≦5)	1.951	0.979-3.889	0.057
CA19-9 (>37/≦37)	1.910	0.902-4.045	0.091

*C.I.: Confidence Interval

ed the liver (15 patients, 29.4%), lungs (14 patients, 27.5%), peritoneum (9 patients, 17.6%) and local sites (9 patients, 17.6%).

The 5-year disease-free survival rate was 89.6% and the overall survival rate was 96.1%. Clinicopathological features, including age, gender, tumor location, tumor diameter, pathological type, T stage, presence of lymphatic invasion, presence of venous invasion, number of lymph nodes examined, use of adjuvant chemotherapy and the preoperative serum levels of CEA and CA19-9, were analyzed. The Cox univariate regression analysis showed that the recurrence rate was significantly related to the presence of lymphatic invasion and the preoperative serum levels of CEA (>5 ng/ml) and CA19-9 (>37 U/ml) (**Table 2**). Features such as age, gender, tumor location, tumor diameter, pathological type, T stage, presence of venous invasion, number of lymph nodes examined and use of adjuvant chemotherapy were not found to be significant recurrent factors. The Cox multivariate analysis showed that the presence of lymphatic invasion (p=0.044) was the only independent prognostic factor significantly related to recurrence in patients with stage II colorectal cancer (**Table 3**).

The 5-year disease-free survival rates differed significantly between the patients without this prognostic factor (93.0%) and those with this prognostic factor (83.2%, p=0.0019; **Fig. 1**). Among the patients with this prognostic factor, the 5-year disease-free

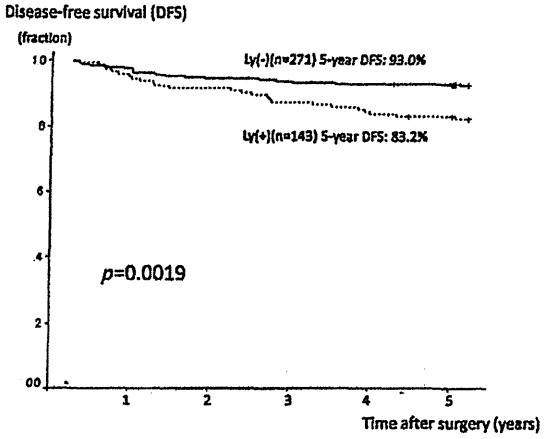

Fig. 1 Disease-free survival of patients with stage II colorectal cancer: 271 patients without lymphatic invasion, and 143 with it.

survival rates differed between the patients who received adjuvant chemotherapy (89.2%) and those who did not (77.6%, p=0.068), although the 5-year overall survival rates did not differ significantly (93.8% vs 89.5%, p=0.35).

Discussion

Many trials have shown that the administration of adjuvant chemotherapy in patients with stage III colorectal cancer is beneficial, whereas the benefits in patients with stage II disease remain controversial. In the QUASAR (Quick And Simple And Reliable) trial[5], chemotherapy with fluorouracil and folinic acid was found to improve the survival rates of patients with stage II colorectal cancer, although the absolute improvements were small. Sargent D. et al.[11] compared the use of surgery alone with surgery and FU-based adjuvant chemotherapy and found adjuvant chemotherapy to be associated with a significant improvement in 8-year overall survival (72.2% versus 66.8%; p=0.026). Lin BR et al.[12] compared the use of surgery alone with surgery and oral uracil and tegafur (UFT) adjuvant chemotherapy and found adjuvant chemotherapy to be associated with a significant improvement in 5-year overall survival (89.1% versus 84.2%; p=0.018).

On the other hand, a literature-based meta-analysis by an ASCO panel working in collaboration with the Cancer Care Ontario Practice Guideline Initiative[8] found no evidence of any statistically significant survival benefits for adjuvant chemotherapy in stage II patients. The authors concluded that the routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer is not recommended, although it can be considered in high-risk patients (those with inadequately sampled nodes, T4 lesions, perforation or poorly-differentiated histology). Using the Surveillance, Epidemiology and End Results (SEER) -Medicare database[13], either with or without poor prognostic features, adjuvant chemotherapy was not found to substantially improve overall survival among patients with stage II colon cancer.

In the American Joint Committee on Cancer study[14], T4aN0 and T4bN0 in stage II were found to be associated with a poorer prognosis than T1-2N1a and T1-2N1b in stage III in terms of 5-year relative survival rates. Therefore, administering adjuvant chemotherapy is thought to be necessary in groups at a high risk for recurrence of stage II colorectal cancer. The National Comprehensive Cancer Network (NCCN) guidelines[15] recommend that the use of adjuvant chemotherapy be considered in patients with stage II colorectal cancer, such as those with <12 regional lymph nodes examined, T4 lesions, perforation, peritumoral lymphovascular involvement, poorly-differentiated adenocarcinoma or perineural invasion.

In the MOSAIC trial[16], the use of LV5FU2 in addition to oxaliplatin (FOLFOX4) was compared with LV5FU2 alone in patients with stage II disease. The probabilities of surviving to six years were 86.9% and 86.8% in the FOLFOX4 and LV5FU2 groups, respectively (HR=1.00; 95% CI, 0.70 to 1.41; p=0.986). In an exploratory analysis, the probabilities of OS at six years in high-risk stage II patients (at least one of the following: T4 disease, tumor perforation, bowel obstruction, poorly-differentiated tumors, venous invasion or less than 10 lymph nodes examined) were 85.0% and 83.3% in the FOLFOX4 and LV5FU2 groups, respectively (HR=0.91; 95% CI, 0.61 to 1.36; p=0.648). This trial did not demonstrate any effectiveness of adding oxaliplatin.

Our study showed that the presence of lymphatic invasion was an independent prognostic factor in patients with stage II colorectal cancer. We evaluated lymphatic invasion using Hematoxylin-Eosin (HE) staining. Because evaluating lymphatic invasion is frequently difficult by means of HE staining alone, the additional use of D2-40 immunostaining, which is useful for evaluating lymphatic invasion, is

therefore considered to be essential in order to accurately evaluate colorectal cancer specimens. Developing objective criteria based H-E staining alone may therefore be difficult. However, the use of D2-40 staining is not standard for most general hospitals, and its high cost and the need for a pathological analysis make its use problematical. Yet, it is not necessary to use D2-40 staining for all patients. D2-40 staining should therefore be considered when lymphatic invasion cannot be fully evaluated by some pathologists.

We identified patients with stage II colorectal cancer with lymphatic invasion as being at high risk. Adjuvant chemotherapy might offer survival benefits in such patients. However, the administration of adjuvant chemotherapy in the patients with high risk factors did not improve the 5-year overall survival rates. In addition, our study is associated with some limitations. This study retrospectively examined the risk factors for recurrence of stage II colorectal cancer and the usefulness of adjuvant chemotherapy. The decision whether to administer adjuvant chemotherapy was not standardized in our department and was left to the clinical discretion of the attending physician. The drugs used for adjuvant chemotherapy and the duration of therapy differed. Various genetic and molecular biomarkers, including microsatellite instability (MSI), loss of heterozygosity at chromosome 18q (LOH18q) and thymidylate synthase[17], were not investigated. However, we identified the subgroup of patients at high risk by investigating the clinicopathological features of 414 patients who underwent standard curative resection at the same institution. Furthermore, this study examined many regional lymph nodes (median N=35); therefore, the results are credible. Considering the usefulness of various genetic and molecular biomarkers, adjuvant chemotherapy should be aggressively administered to stage II colorectal cancer patients with lymphatic invasion.

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手術のtips and pitfalls

直腸癌に対する腹腔鏡下手術
—安全で確実な手術を行うために必要な解剖と術中ランドマーク—

静岡県立静岡がんセンター大腸外科

絹笠　祐介

キーワード　直腸癌，解剖，腹腔鏡手術，筋膜，側方靱帯

I. はじめに

直腸癌手術においては，根治性を担保しつつ，肛門温存および泌尿生殖器機能温存をはかる手術手技が要求される．近年の直腸癌手術においても，局所再発率および術後泌尿生殖器機能障害発生頻度[1)5)]は，共に決して満足出来る成績でないことを知る必要がある．誤った解剖の理解は術中・術後の合併症を増加させるだけでなく，癌の根治性を損なう恐れがある．正しい解剖の理解と共に，癌の進展/進行度により適切な剝離層を選択し，根治性を保持する必要がある．

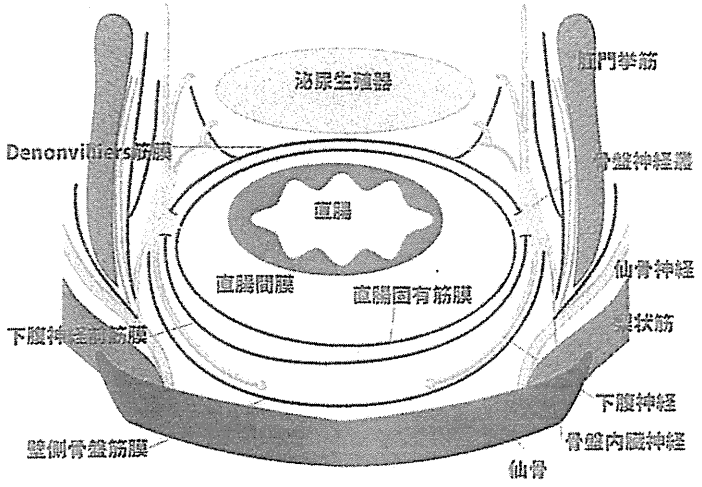

図1　直腸周囲の筋膜構成
直腸固有筋膜の前方ではDenonvilliers筋膜の外側が，後方では下腹神経前筋膜が温存すべき神経との境界を形成している[1)2)]．側方靱帯（直腸枝上群）において骨盤神経叢からこれら筋膜を貫く神経線維があり，剝離層が失われる手術のキーポイントとなる[3)]．

LAPAROSCOPIC RECTAL CANCER SURGERY BASED ON ANATOMY
Yusuke Kinugasa
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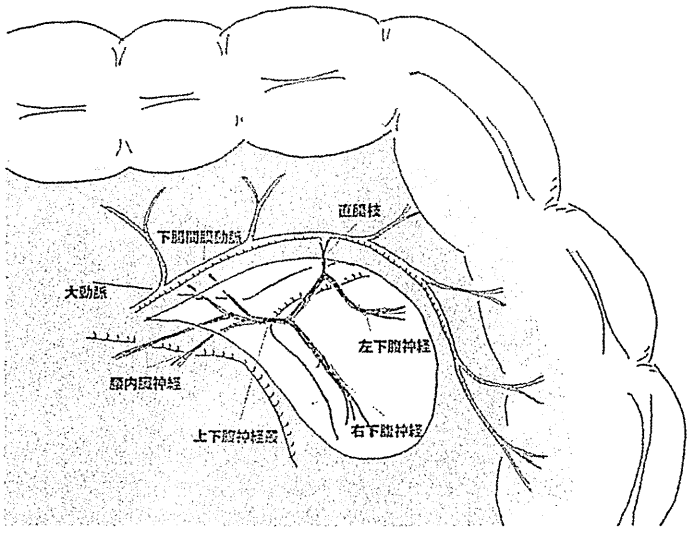

図2　直腸授動の開始時の注意点
下腹神経から下腸間膜動脈周囲へ細い直腸枝が流入しており，これによって下腹神経本幹が直腸に牽引される．岬角近傍で直腸の展開が不良のまま剝離を進めると下腹神経を損傷するリスクが高いので，IMA の処理を先行させると良い．

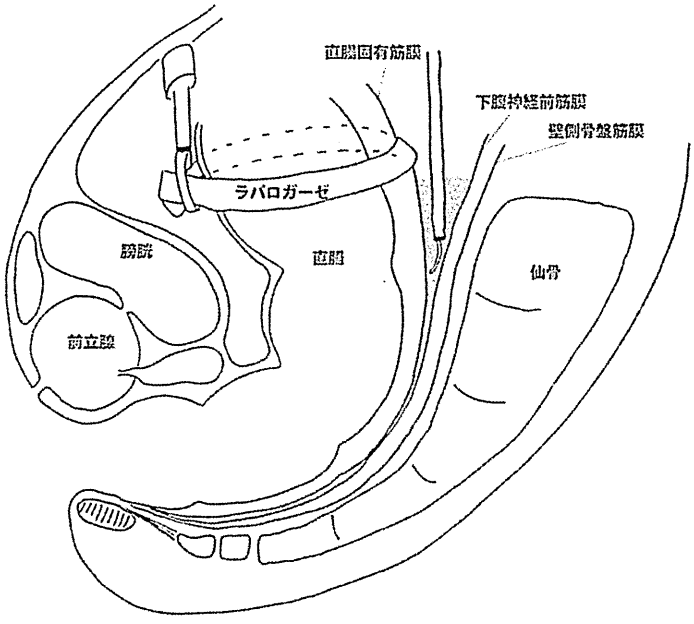

図3　直腸後方の剝離層
直腸を授動する際は，十分なテンションのもと，直腸固有筋膜に沿って剝離する．徐々に変化する剝離ラインに従って，はじめは肛門側へ押すように展開し，徐々に腹側・頭側へと向きを変えていく．その為には把持する場所を適宜肛門側へ移動させることも必要で，ラパロガーゼが有用である．

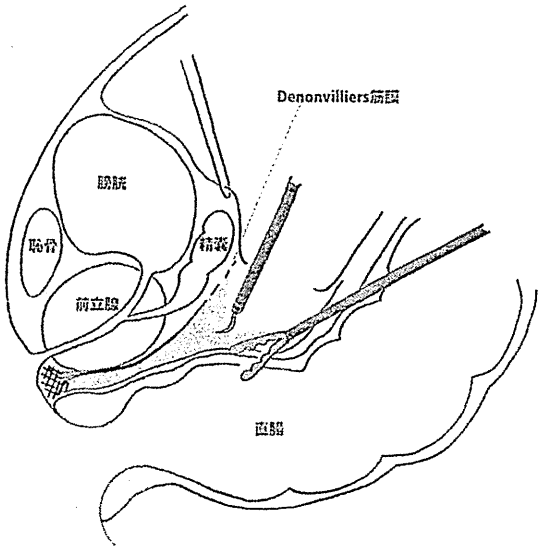

図4　直腸前方の剝離層
子宮や腹膜を糸で腹壁外より牽引し，助手による前方の展開を容易にする．直腸を，先端が鈍な鉗子もしくはガーゼなどで背側へ押し下げ，Denonvilliers 筋膜の背側で剝離を行う．

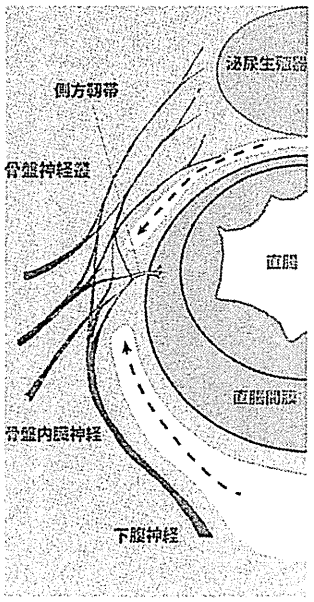

図5　側方靭帯の処理
側方では，細い直腸枝によって骨盤神経叢が直腸方向へ牽引されるので，これの損傷に注意する．剝離層も失われるため，前後の剝離を終えた後に側方の処理を行う．

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利益相反：なし

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原著

da Vinci S Surgical System®を用いた直腸癌に対するtotal mesorectal excision（TME）の短期成績

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Key words ◆ 直腸癌，ロボット手術，短期成績

◆要旨：【目的】当科のロボット支援下直腸癌手術の短期成績を明らかにすること．【対象および方法】2011年12月～2012年7月に，原発性直腸癌23例に対しロボット支援下手術を行った．そのうち，total mesorectal excision（TME）またはtumor-specific mesorectal excision（TSME）を施行した14例を対象に，その安全性と術後早期経過を解析した．【結果】患者の平均年齢は67.5歳．男性7例，女性7例であった．術式は高位前方切除術1例，低位前方切除術10例，ISR 3例であった．手術時間中央値は322分（156～415分），コンソール操作時間中央値は222分（86～302分）であった．開腹手術への移行例はなく，縫合不全などの合併症もなかった．全例根治度Aの手術が施行されていた．【結論】ロボット支援下直腸癌手術は，安全性と術後早期経過において良好であった．

はじめに

腹腔鏡下手術は，①拡大視効果によって微細構造の把握が可能，②術者と助手が同一の術野情報を同時に共有しつつ手術を進行できる，③術後の疼痛が少ない，などの利点があり，急速に普及している．

一方，問題点として，①視野展開や手術操作（鉗子の可動性）の制限，②空間認識の困難さ，などがある．視野展開や手術操作の制限に関しては鉗子の形状（ストレートタイプ）によるところが大きく，空間認識の困難さはモニター上に映し出された2次元の画像情報を見ながらの手術操作であることに起因する．骨盤腔という狭くて限られたworking spaceの中では，直線的な鉗子の可動性では，手術操作に制限が生じる局面があるため，腹腔鏡下直腸癌手術は結腸癌手術に比べてより手術難易度が高いものとなる．これに対しては，術者の豊富な経験によって補っているのが現状である．

ロボット支援手術システムda Vinci S Surgical System®は，鮮明な3次元ハイビジョン画像を見ながら，先端が人間の手指や手首の動きを模倣する高い自由度を持った多関節鉗子で手術操作ができるため，従来の腹腔鏡下手術では難易度の高い直腸癌手術においても，解剖学的構造にそった

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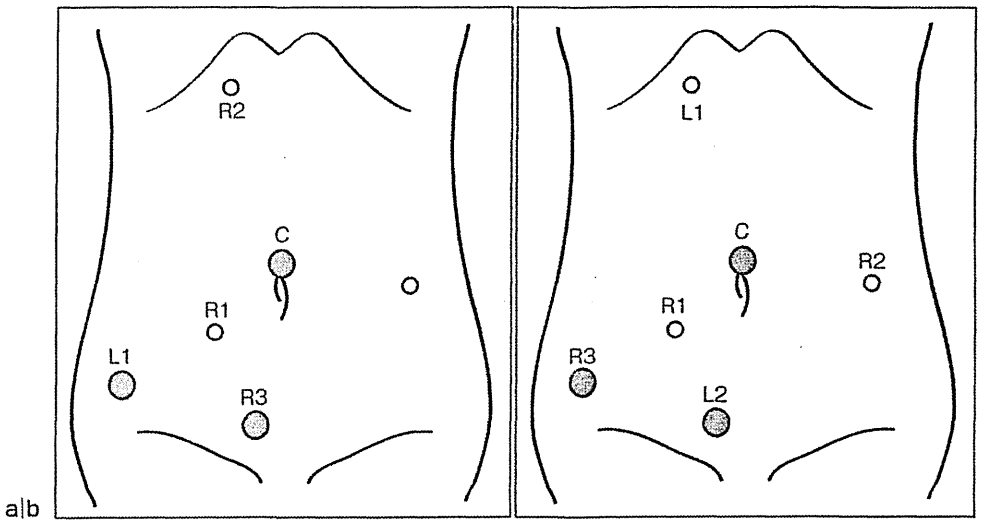

図1 ポート位置

a：中枢側リンパ節郭清～脾彎曲授動操作時の配置.
b：骨盤内操作時の配置.
● 12 mm ポート，○ 8 mm ポート，C：カメラ，R1：1st Arm，R2：2nd Arm，R3：3rd Arm，L1：助手用，L2：助手用.

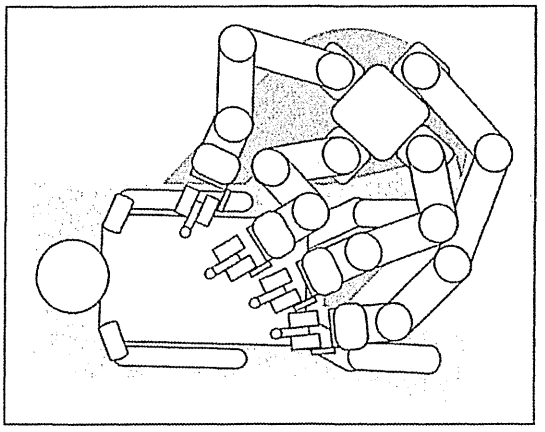

図2 ロボットのレイアウト

砕石位をとった患者の左斜め尾側からロボットを進入する.

繊細で正確な手術がよりスムーズに実行可能となり，有望なデバイスであると期待されている.

しかし，現時点では，このロボット支援下直腸癌手術の安全性と有効性を証明した報告は少ない．よって，今回筆者らのロボット支援下直腸癌手術の安全性と術後早期経過を検討し報告する.

対象および方法

2011年12月～2012年7月に，静岡県立静岡がんセンター大腸外科（以下，当科）で，原発性直腸癌患者23例に対しロボット支援下手術を行った．そのうち，側方リンパ節郭清を行わずtotal mesorectal excision（以下，TME）またはtumor-specific mesorectal excision（以下，TSME）を施行した14例を対象に検討した.

当科のロボット支援下手術の適応は，臨床病期Ⅰ～Ⅲの原発性大腸癌患者で，年齢20歳以上80歳以下，BMI（body mass index）が30未満，腸管切除の既往がない，術前腸閉塞がない症例としている．深達度T4b症例は適応外としている.

術前・術中・術後のデータはすべて前向きに用意したデータベースに登録し，今回はその内容から検討した.

術後合併症は術後30日以内に発生したすべての有害事象として，Clavien Dindo分類に従って評価した.

すべての手術は，日本内視鏡外科学会技術認定医であり，Intutive Surgical社の推奨する研修プ

表1 患者背景

年齢（歳）	67.5（36～79）	cT stage（例）		術式（例）	
性別（例）		Tis	1	HAR	1
男性	7	T1	9	LAR	10
女性	7	T2	2	ISR	3
主占居部位（例）		T3	2	中枢側郭清程度（例）	
RS	3	T4	0	D2	8
Ra	2	cN stage（例）		D3	6
Rb	9	N0	10	脾彎曲授動（例）	
BMI	23.3（19.6～26.1）	N1	4	なし	10
ASA score（例）		N2	0	あり	4
1	5	cM stage（例）		TME/TSME（例）	
2	9	M0	14	TME	8
3	0	M1	0	TSME	6
		術前化学放射線療法（例）		吻合部AV距離（cm）	4.9（0.5～6.0）（平均±標準偏差＝2.9±2.2）
		なし	14		
		あり	0		

HAR：高位前方切除術，LAR：低位前方切除術，ISR：intersphincteric resection，TME：total mesorectal excision，TSME：tumor-spesific mesorectal excision.

ログラムを終了した2名の大腸専門医が執刀した．

なお，対象症例にはデータベース登録前に臨床研究としてのインフォームド・コンセントを得ている．

手術手技

砕石位で左高位のTrendelenburg体位としている．ポート位置を図1に示す．

まず，腹腔鏡下に横行結腸・小腸を頭側に排除し，大動脈前面と骨盤内の視野を展開する．次にpatient cartを患者左尾側からdockingし（図2），図1aのようにロボットアームを装着し，ロボット手術操作を開始する．

腹腔鏡下手術と同様に下腸間膜動脈根部近傍から内側アプローチを開始し，尿管・性腺血管を背側に落とし，下行結腸外側まで至る．次いで結腸外側の授動を行う．脾彎曲結腸の授動は症例に応じて施行する．

その後，骨盤内操作に移行するためにロボットアームをいったんポートから取り外し，図1bのように再装着する．

骨盤内操作では直腸に腹腔鏡用ガーゼを巻き，助手が腹腔鏡鉗子で把持牽引し，視野展開の補助を行う．Denonvilliers' fasciaや下腹神経前筋膜をメルクマールにしながら，直腸固有筋膜に沿った鋭的な切離操作を行う．

腫瘍肛門側まで十分に剝離した後に，前方切除術症例ではロボットの1番のアームを外し，図1bのL2ポートからlinear staplerを挿入して直腸を切離する．その後patient cartを患者からundockingし，カメラポート部で小開腹して標本を摘出する．再建は腹腔鏡操作にてdouble stapling technique（DST）で行う．

一方，intersphincteric resection（ISR）症例ではロボット支援下に肛門管内まで直腸を授動した後，undockingし経肛門操作によって標本を摘出する．再建は手縫いの結腸肛門吻合を行う．

結　果

患者背景は表1に示す．術式は，高位前方切除術1例，低位前方切除術10例，ISR 3例であった．

手術時間中央値は322分，コンソール操作時間中央値は222分であった．出血量中央値は17 g（5～62 g）で，全例に周術期輸血は行わなかった（表2）．術中他臓器損傷を含む有害事象はなく，腹腔鏡下手術や開腹手術への移行もなかった．一

表2　手術成績

手術時間（分）	
全手術時間	322（156～415）
コンソール操作時間	222（86～302）
出血量（g）	17（5～62）
合併症（例）	
縫合不全	0
創感染	0
イレウス	0
尿路感染	1（Clavien Dindo 分類 II）
末梢静脈炎	1（Clavien Dindo 分類 II）
術後入院期間（日）	7（7～10）

表3　病理組織所見

pTNM stage（例）	
0	1
I	7
II	0
III	6
IV	0
郭清リンパ節個数（個）	23（11～35）
腫瘍サイズ（cm）	3.0（1.0～15.0）
口側切離断端（例）	
陰性	14
陽性	0
肛門側切離断端（例）	
陰性	14
陽性	0
外科剝離面（例）	
陰性	14
陽性	0

時的人工肛門は前方切除術の2/11例（18.2%），ISRの3/3例（100%）に造設した．縫合不全などの重篤な合併症は認めなかった．術後入院期間の中央値は7日（7～10日）であった．

病理組織所見では，腫瘍径中央値は3.0cm（1.0～15.0cm），郭清リンパ節個数中央値は23個（11～35個）で，全例に直腸固有間膜損傷はなく，口側・肛門側・外科的切離面ともに陰性の根治術が施行された（表3）．

考　察

近年，ロボット支援下直腸癌手術の短期成績が韓国や欧米を中心に報告されており，安全性に関するエビデンスが構築されつつある[1-3]．

Kwakら[4]は，腹腔鏡下手術とロボット支援下直腸癌手術，各59例の症例対照研究において，ロボット支援下手術は手術時間が長いものの，郭清リンパ節個数，手術根治度，開腹移行率，術後合併症の点で差がなく，安全に施行可能であると報告している．Bianchiら[5]は，腹腔鏡下手術とロボット支援下直腸癌手術，各25例の比較において，手術時間，入院期間，郭清リンパ節個数，手術根治度に有意差はなく，術後合併症に関して有意差はないもののロボット手術に少ない傾向があると報告している．

このように，近年，ロボット支援下手術の安全性を示す報告は散見されるものの，腹腔鏡下手術に対するアドバンテージを証明するには至っていない．これは，現時点ではまだ各施設のロボット支援下手術導入初期段階での成績のためと考える．ロボット支援下直腸癌手術の有用性に関するエビデンスの構築には時間を要し，今後の課題であると考える．

国内からは勝野ら[6]の報告があるが，これは対象に結腸癌も含んだ報告であり，国内からの直腸癌に関するエビデンスは，まだ少数例の報告である．

直腸癌の手術においては，直腸周囲の解剖を正確に認識し，適切な剝離層で直腸を授動し[7,8]，適切な肛門側距離を確保して切離する[9,10]ことがきわめて重要である．直腸固有間膜損傷や外科剝離面陽性の手術は，局所再発につながり[11]，たとえ低侵襲であっても許容されない．今回の筆者らの対象では，摘出標本の肉眼的・病理組織学的検索にて全例に直腸固有間膜損傷はなく，口側・肛門側・外科剝離面ともに陰性の根治術が施行され，本術式が安全に高い成功率で遂行できることを示している．

一般に直腸癌術後の縫合不全率は5～20%と報告されており[12-14]，ロボット支援下手術では1.8～13.6%と報告されている[4,15]．今回の筆者らの縫合不全率は0%であり，十分に良好なものであった．縫合不全の危険因子は様々だが，吻合部の位置が多くの報告で共通する[16,17]．自験例は吻

合部距離が肛門縁から平均2.9 cmと低い対象だが，縫合不全率は低率であった．これは骨盤深部までの直腸授動において，先に述べたロボットの利点が有効に発揮され，肛門側腸管を愛護的に十分に授動でき，安全に再建できたのが理由の1つと考える．

腹腔鏡下直腸癌手術において，開腹移行率は10～20%と報告されている[18,19]．開腹移行の危険因子は，進行度・性別・肥満などが報告されている．開腹移行は術後合併症の増加や腫瘍学的長期成績の悪化との関連が示唆されているため，これを減らすことは重要である．当科のロボット支援下手術の適応条件はBMI 30未満としているが，今後は肥満症例にも段階的に適応拡大していくつもりである．開腹手術でも腹腔鏡下手術でも難渋するような症例こそ，ロボット支援下手術の恩恵を受けるのではないかと考える．

ダ・ヴィンチS手術システムにはいくつかの課題がある．1つ目は，ロボットの個々のアームが大きく太いため，体腔外でのアーム同士の干渉が起こりうる．欧米人に比べ体格が小さな日本人に対しては，十分なポート間距離を保つことは困難な場合が多い．その場合でも，カメラポートを臍部よりやや頭側に置くことで，その他のポートとの距離を確保するなどの工夫をしている．また，ロボットの患者への進入角度によってもアームの干渉が生じる．正しいsettingが手術時間のみならず，手術全体の成否を決定する重要な因子である．アームの干渉が少ない最適なポート位置，アーム配置を術式ごとにさらに検討していく必要がある．

2つ目はコストの問題である．現在，ロボット支援下大腸癌手術は高額自費診療である．より多くの患者に治療法の選択肢として提示し，本術式に関するより多くのエビデンスを構築するためにも，先進医療として承認されることを期待する．

今回の検討は依然として少数例の報告である．今後は，症例を重ねて本術式の安全性・治療成績を検証する必要がある．

おわりに

当科のロボット支援下直腸癌手術は，安全性と術後早期経過において良好であった．

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Robotic-assisted total mesorectal excision for rectal cancer

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[Aim] The aim of this study was to evaluate the short term outcome of robotic-assisted surgery for rectal cancer. **[Method]** Fourteen patients undergoing robotic-assisted total mesorectal excision or tumor-specific mesorectal excision for rectal cancer between December 2011 and July 2012 were investigated in this study. **[Result]** One patient had high anterior resection, 10 patients had low anterior resection, and 3 patients had intersphincteric resection. The median operation time was 322 (156-415) minutes, and console time was 222 (86-302) minutes. Conversion rate was 0% and complication rate was 0% respectively. The circumferential margin and distal resection margin were negative for all patients. **[Conclusion]** Robotic-assisted surgery for rectal cancer was safe and effective.

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Feasibility of Laparoscopic Intersphincteric Resection for Patients with cT1-T2 Low Rectal Cancer

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Key Words
Rectal cancer · Intersphincteric resection · Laparoscopic surgery · Morbidity · Survival · Functional result

Abstract
Aims: The purpose of this study was to assess the feasibility of laparoscopic intersphincteric resection (LAP-ISR) for rectal cancer in terms of morbidity, oncological outcomes, and functional results. ***Methods:*** Thirty-seven patients with primary low rectal cancer cT1-T2 underwent LAP-ISR. Surgical outcomes, pathological results, postoperative complications, oncological outcomes, and functional results were analyzed retrospectively. ***Results:*** Three patients (8.1%) had carcinoma in situ, 22 (59.5%) had pT1 tumor, and 11 (29.7%) had pT2 tumor. Eleven patients (29.7%) were diagnosed as being node positive, while 26 (70.3%) had node-negative disease. The median operative time was 315 min (range: 195–502). The median blood loss was 37 ml (range: 0–745). One case was converted to open surgery. Pathological complete resection was achieved in all cases. There was no surgical mortality. Postoperative complications of grade III-IV on the Clavien-Dindo classification were observed in 16.2% of the patients. The median follow-up period was 2.8 years (range: 187–2,241 days), and 3-year disease-free survival was 93.1%. No patient developed local recurrence. The functional result was objectively good. ***Conclusion:*** LAP-ISR can be recommended as a feasible, ultimate sphincter-preserving procedure with acceptable functional and intermediate-term oncological outcomes in patients with cT1-T2 very low rectal cancer.

Background/Aims

Intersphincteric resection (ISR), the ultimate sphincter-saving procedure, has experienced much progress in the investigation of its short- and long-term results, and as a result has been adopted as a promising procedure for selected patients with very low rectal cancer to avoid permanent colostomy at a number of specialized institutions [1, 2]. In addition, laparoscopic surgery is increasingly being used and is becoming the standard procedure for colorectal cancer treatment.

In performing a total mesorectal excision (TME), meticulous and precise dissection of the mesorectum is extremely important for good short-term outcomes and satisfactory oncological results [3]. In our view, the good view of the surgical field achieved with the high-vision

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scope during the laparoscopic procedure provides definite advantages in low rectal cancer surgery, especially in laparoscopic ISR (LAP-ISR). Evaluation of LAP-ISR to determine whether it is an appropriate procedure should be based on achieving acceptable results in terms of morbidity, oncological safety, and functional results. However, the evidence for LAP-ISR is still limited [4, 5]. Therefore, the purpose of this study was to assess the feasibility of LAP-ISR in terms of early and late complications, oncological outcomes, and functional results.

Patients and Methods

Patients

Between September 2003 and April 2012, 37 consecutive patients with primary low rectal cancer underwent LAP-ISR, and these patients' medical charts were reviewed retrospectively. The inclusion criterion for LAP-ISR was cT1-T2 low rectal cancer. The exclusion criteria were poorly differentiated adenocarcinoma diagnosed by biopsy, macroscopic infiltrating type, or impaired fecal continence. Patients with cT3 or T4 tumors were also excluded from this procedure because they were candidates for conventional open surgery at our institute. The operations were performed by 5 experienced colorectal surgeons in this period. Preoperative tumor staging was done by digital examination, CT, MRI, barium enema, or colonoscopy examination. Endorectal ultrasonography was not performed routinely. Neither preoperative radiotherapy nor chemoradiotherapy was performed in this series.

Surgical Technique

The surgical technique included both laparoscopic abdominal approaches and per-anal approaches. Medial-to-lateral retroperitoneal dissection of the mesocolon and ligature of inferior mesenteric blood vessels close to their origin were performed. Mobilization of the splenic flexure was performed in most cases. Next, the posterior side of the rectum was mobilized in the avascular plane between the fascia propria of the rectum and the prehypogastric nerve fascia [6]. The anterior side of the rectum was dissected preserving Denonvilliers' fascia (the rectovaginal septum in women). The lateral side dissection was completed by preserving the hypogastric nerve and pelvic plexus.

Meticulous and precise sharp dissection was needed to avoid injuring the neurovascular bundle in the anterolateral dissection. As the final step of the laparoscopic abdominal approach, the anococcygeal ligament [7] was dissected, followed by sufficient dissection into the intersphincteric space.

After the laparoscopic abdominal approach, the per-anal approach was performed. Circumferential incision of the mucosa and internal sphincter was initiated 1–2 cm distal from the lower edge of the tumor. The anal orifice of the rectum was immediately closed and washed with povidone iodine to avoid scattering of tumor cells during the per-anal procedure.

The specimen was extracted through the anus. Reconstruction consisted of a hand-sewn coloanal straight anastomosis. A diverting ileostomy was created in all cases.

Adjuvant Therapy

Patients with pathological TNM stage III tumors received postoperative adjuvant systemic chemotherapy with 5-fluorouracil and leucovorin, capecitabine, or other drugs for 6 months.

Complications

Postoperative short-term complications were defined as all events that occurred within 30 days after operation and were classified according to the Clavien-Dindo classification [8]. Late complications were defined as all events after 31 days from the operation that were reported in the outpatient clinic.

Anastomotic leakage was defined by the emission of pus or feces from the drain or the vagina, or the discharge of pus per anum. All clinically suspicious leakages were confirmed by one or more of the following techniques: contrast enema radiography, CT scan, and endoscopy. When there was no abnormal communication of the intraluminal and extraluminal compartments due to a dehiscence of intestinal wall integrity, the patient was said to have a pelvic abscess and not anastomotic leakage.

Follow-Up

Follow-up examinations were performed every 3 months for 3 years postoperatively and every 6 months after this period, using clinical examinations, laboratory tests (including tumor markers CEA and CA19-9), radiologic examinations (liver and pelvic CT and pulmonary CT), digital examination, and colonoscopy. Defecatory function was clinically evaluated through personal interviews by surgeons about the frequency of bowel movements and continence (the classification of Kirwan et al. [9]) during this follow-up period.

Recurrence

Local recurrence was defined as every event in the pelvic cavity, including anastomotic, pelvic, or perineal tumor, and regional lymph node metastases documented by clinical, radiologic, and/or pathological examination, even if distant metastases were present.

Statistical Analysis

Disease-free survival (DFS) was calculated using the Kaplan-Meier method. The survival time was calculated as the duration from the time of resection until the last follow-up visit or death. All statistical analyses were performed using IBM SPSS Statistics software for Windows, version 18 (SPSS Inc., Chicago, Ill., USA).

Results

A total of 37 consecutive patients (17 males, 20 females) underwent LAP-ISR for very low rectal cancer. The median distance between the lower edge of the tumor and the anal verge was 4.0 cm (range: 1.0–5.0). The characteristics of the 37 patients are shown in table 1. With respect to pathological T stage distribution, 3 patients (8.1%) had carcinoma in situ, 22 (59.5%) had pT1 tumor, and 11 (29.7%) had pT2 tumor. Eleven (29.7%) patients were diagnosed as node positive, and 26 (70.3%) patients had node-negative disease.

Table 1. Patients' characteristics and operative results of LAP-ISR

	n = 37
Age, years	66 (39–75)
Gender	
Male	17
Female	20
Tumor size, cm	2.5 (0.8–6.0)
Tumor location from anal verge, cm	4.0 (1.0–5.0)
cT	
T1	26
T2	11
T3	0
T4	0
cN	
N0	35
N1	2
N2	0
cM	
M0	37
M1	0
History of abdominal surgery	
No	30
Yes	7
Neoadjuvant Tx	
No	37
Yes	0
Operation time, min	315 (195–502)
Blood loss, ml	37 (0–745)
Conversion to open surgery	1

Values are given as n or median (range).

Table 2. Pathological results after LAP-ISR

Lymph nodes harvested	22 (6–49)
Distal clearance margin, cm	1.2 (0.5–2.2)
R0 resection	
Distal margin	
Negative	37
Positive	0
Circumferential margin	
Negative	37
Positive	0
Differentiation on histology	
Well	36
Moderate	9
poor	2
pT	
Tis	3
T1	22
T2	11
T3	1
T4	0
pN	
N0	26
N1	9
N2	2
pStage	
Stage 0	3
Stage I	24
Stage II	0
Stage III	10
Stage IV	0

Values are given as n or median (range).

Operative Results

The median operative time was 315 min (range: 195–502), and 1 case was converted to open surgery. The reason for conversion was severe intra-abdominal adhesion. The median blood loss was 37 ml (range: 0–745). No patient required blood transfusion. Pelvic autonomic nerve preservation was achieved in every patient. All patients had a diverting ileostomy created in the right iliac fossa, all of which were reversed at the end of the study.

Pathological Results

Pathological complete resection (R0) was achieved in all cases. All patients had negative distal margin clearance, with a median distal margin clearance length of 1.2 cm (range: 0.5–2.2). The median number of harvested lymph nodes was 22 (range: 6–49). The objective TME quality assessment carried out by surgeons and pathologists was also perfect in all cases (table 2).

Postoperative Complications

There was no surgical mortality. The median postoperative hospital stay was 10 days (range: 7–19). The distribution of early and late complications is shown in table 3. One patient developed anastomotic leakage with a Clavien-Dindo classification of grade IIIB and was managed by per-anal debridement and reconstruction by hand-sewn anastomosis. One patient developed obstructive ileus caused by incisional hernia and was managed by surgical repair. Two patients developed neorectal mucosal prolapse and were treated by transanal mucosal resection. Two patients developed anastomotic stenosis that was treated by perianal dilatation.

Oncological Outcomes

The median follow-up period was 2.8 years (range: 187–2,241). No patient was lost to follow-up. The 3-year DFS for patients who underwent LAP-ISR was 93.1% (fig. 1). The 3-year DFS according to TNM stage was

88.7% for stage I and 100% for stage III. Recurrences included a liver metastasis in 1 patient with stage I and multiple lung metastases in 1 patient with stage I. Since no patient developed local recurrence, the 3-year cumulative local recurrence rate after LAP-ISR was 0%.

Functional Results

All 37 patients underwent diverting ileostomy closure at the end of this study. The median stool frequency after LAP-ISR was 4 times per day (range: 0.5–10). Frequent major soiling (Kirwan grade IV) occurred in 1 patient, and complete incontinence requiring colostomy (Kirwan grade V) developed in 1 patient (table 4).

Discussion

Schiessel et al. [1] first described ISR in 1994 as the ultimate sphincter-saving procedure for low rectal cancer patients. Since then, with progress in the investigation of the short-term and long-term results of this procedure, ISR has been adopted as a promising procedure for selected patients with very low rectal cancer to avoid permanent colostomy [10–13].

TME with autonomic nerve preservation and sharp dissection deep into the pelvic cavity is needed in low rectal cancer surgery, but this procedure is sometimes stressful even for specialized colorectal surgeons. These technical difficulties come from the poor view caused by the narrow working space of a narrow pelvis.

Laparoscopic colorectal surgery is becoming the new standard for colorectal cancer treatment [14–16]. The benefits of laparoscopic colorectal cancer surgery include less postoperative pain, earlier recovery of normal bowel movements, and shorter hospital stay, with an easier return to normal life. Adding to these benefits, we consider that laparoscopic surgery provides definite advantages for surgeons in visualizing the surgical dissection planes by using high-definition images even in a narrow pelvic space [17]. With this good view magnified by the laparoscope, surgeons can perform sufficient surgical dissection toward the intersphincteric space with more precise and easier complete autonomic nerve preservation than with conventional open surgery. Thus, we believe in the potential of laparoscopic surgery for the LAP-ISR procedure. However, the evidence about LAP-ISR is still limited [4, 5, 18]. Therefore, the purpose of this study was to evaluate the efficacy of LAP-ISR in terms of mortality, morbidity, oncological adequacy, and functional results.

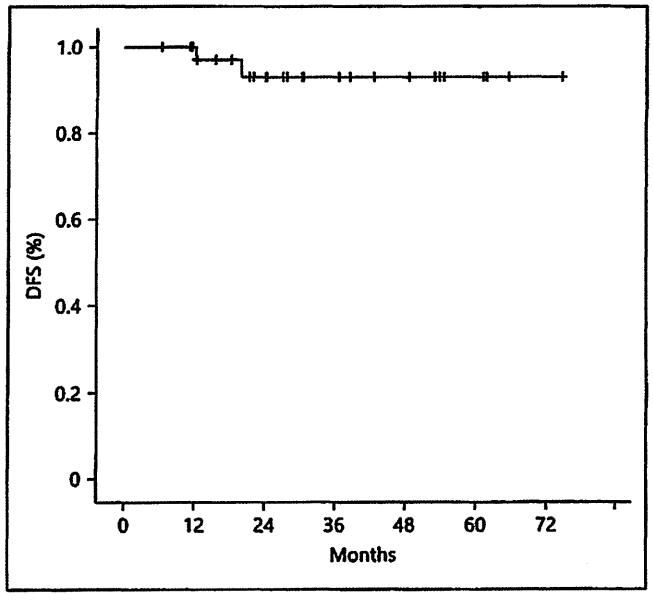

Fig. 1. DFS after LAP-ISR.

Table 3. Postoperative complications after LAP-ISR

Clavien-Dindo grade	I	II	IIIA	IIIB	IV	V
Early complications						
Wound infection	2	0	0	0	0	0
Anastomotic leakage	0	0	1	1	0	0
Urinary tract infection	0	2	0	0	0	0
Ileus	0	2	3	1	0	0
Late complications						
Ileus	2	1	0	0	0	0
Anastomotic stricture	2	0	0	0	0	0
Neorectal mucosal prolapse	0	0	0	2	0	0

Median postoperative hospital stay: 10 days (7–19).

Table 4. Functional results after LAP-ISR (n = 29)

Stool frequency, per day		4 (0.5–10)
Continence		
Kirwan grade		
Grade I	perfect	11
Grade II	incontinence of flatus	2
Grade III	occasional minor soiling	14
Grade IV	frequent major soiling	1
Grade V	incontinent (required colostomy)	1

Values are given as n or median (range).

Of particular importance in rectal cancer surgery is the performance of TME with clear surgical margins and adequate lymph node dissection. Injury of the mesorectum or a positive circumferential resection margin (CRM) or distal resection margin obviously leads to local recurrence [3]. In this framework, the quality of the resected specimen is a very important surrogate factor that shows the quality of the surgical procedure and the oncological outcome. The quality of the resected specimen can be judged from CRM, distal resection margin, and macroscopic completeness of the resected rectal specimen and so on. The macroscopic completeness of a resected rectal specimen has been proposed as 'the objective TME quality' by Quirke et al. [19]. In this series, pathological complete resection (R0) was performed in all cases, and 'the objective TME quality' assessment was also perfect in all cases. Involvement of the CRM is influenced by two factors: tumor location from the fascia propria of the rectum and the quality of the surgery. CRM positivity in this series was 0%, but this may be obvious given that our target criterion for this procedure was clinical T1-T2 tumor. However, the objective TME quality is influenced by only one factor: the quality of the surgical procedure. Our perfect TME quality reveals that ISR using the laparoscopic technology was feasible and acceptable.

In the present study, the conversion rate was 2.7%. In the recently reported LAP-ISR series, the conversion rate ranged from 0 to 12.0% [4, 20]. In the present study, the low rate of conversion was fundamentally the result of the surgeon's accumulated experience. Another reason may be appropriate selection of patients with tumors that were not bulky and did not invade neighboring major structures. Although the operative time seems rather long (median: 315 min), in the recent 11 cases operated after 2011, median time was 263 min (range: 195–372). There was a trend showing shorter operative time during the study period as the learning curve.

In the present study, no perioperative mortality occurred, and the overall short-term complication rate was comparable to that of other ISR series. Concerning the complications after ISR, Saito et al. [21] reported that postoperative morbidity was 24% (55 of 228 patients) in a retrospective review of 228 patients who received conventional open ISR. In this report, postoperative complications included anastomotic leakage (10.1%; n = 24), pelvic infection and abscess (4.4%; n = 10), and postoperative ileus (0.9%; n = 2); 9 of these 55 patients (4.0%) required additional surgery, such as abdominoperineal resection or Hartmann's operation because of their complications.

Laurent et al. [5] reported the complications of LAP-ISR (n = 110) in a retrospective comparative study with their open ISR. In their report, overall morbidity was 40.9%, including 25.5% with septic pelvic complications. Surgical morbidity graded Clavien-Dindo III-IV was 22.7%, and 18.2% required reintervention. In the present series, the most commonly encountered complication was anastomotic leakage, but the rate was 5.4% lower than in other reports, and none of the patients required surgical reintervention for this complication. Moreover, in this series, the diverting stoma was closed after LAP-ISR in every patient. Thus, the short-term results appear acceptable.

Yamada et al. [22] reported that neorectal mucosal prolapse in patients with total ISR and coloanal anastomotic stenosis in patients with subtotal or partial ISR were observed as characteristic late complications. Neorectal mucosal prolapse and anastomotic stenosis cause frequent defecation and incontinence. Thus, treatment by mucosal resection and perianal dilatation has been shown to be effective in improving fecal dysfunction.

The information on function after LAP-ISR is limited. In this study, the evaluation of continence status more than 6 months after diverting stoma closure showed an acceptable functional result in the majority of the patients. The median stool frequency in the present study was four times per day, which was more frequent than that reported by Schiessel et al. [23] (2.24 times per day). They reported that the frequent defecation episodes in the early postoperative period decreased gradually after stoma closure. A longer follow-up period is needed for the functional results.

With respect to local recurrence after rectal cancer surgery, Rich et al. [24] reported local recurrence rates of 8% for T1-2N0 and 25% for T1-2N+ rectal cancer patients after potentially curative surgery. Akasu et al. [25] reported their oncological results of ISR. The incidence rates of local failure for stages I, II, and III were 6, 19, and 7%, respectively, and for pathological T1, T2, and T3 tumors, the incidence rates were 4, 2, and 12%, respectively. In the present study, the local recurrence rate was 0%, which is an acceptable result taking into account that the inclusion criterion for the laparoscopic procedure was very low rectal cancer patients with cT1-T2.

With respect to overall survival or DFS, Lim et al. [18] reported the recurrence rate of LAP-ISR according to TNM stage: 7.1% for stage 0, 15.6% for stage I, 14.3% for stage II, and 50% for stage III. In the report by Yamada et al. [23] of ISR, the 5-year DFS was 100% for stage I, 83.5% for stage II, and 72.0% for stage III cases. However, in