浜,2012.12

H. 知的財産権の出願・登録状況（予定を含む。）

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　金光幸秀　国立がん研究センター中央病院　大腸外科長

研究要旨：術前の側方リンパ節転移予測診断の可能性と転移例に対する手術および補助療法の治療効果を検証する。1975年から2009年までに系統的側方郭清を施行した根治度Aの下部直腸癌は517例であり、側方転移陽性は78例(15.1%)に認められた。この78例を対象として、術前に評価できる因子のみを用いて、側方リンパ節転移を予測する多変量モデル（ノモグラム）の作成を試み、術後化学療法施行群(n=51)と非施行群(n=27)、術後放射線照射群(n=27)と非照射群(n=51)に分けて遠隔成績について比較検討した。結果は、側方転移陽性例を術前に高精度に抽出することは難しい一方で、側方郭清と補助化学療法には一定の治療効果が認められた。

A．研究目的

術前の側方リンパ節転移予測診断の可能性と転移例に対する手術および補助療法の治療効果を検証する。

B．研究方法

当科における側方郭清の適応は、腹膜翻転部以下に腫瘍下縁を有し、深達度が固有筋層に達する下部直腸癌として、側方郭清は必ず両側行う。1975年から2009年までに系統的側方郭清を施行した根治度Aの下部直腸癌は517例であり、側方転移陽性は78例(15.1%)に認められた。この78例を対象として、術前に評価できる因子のみを用いて、側方リンパ節転移を予測する多変量モデル（ノモグラム）の作成を試みた。また、術後化学療法施行群(n=51)と非施行群(n=27)、術後放射線照射群(n=27)と非照射群(n=51)に分けて遠隔成績について比較検討した。

（倫理面への配慮）

本試験に関係するすべての研究者はヘルシンキ宣言および「臨床研究に関する倫理指針」（平成16年厚生労働省告示第459号）に従って本試験を実施する。

C．研究結果

ロジスティック回帰分析にて、女性(P=0.035)、腫瘍下縁からAVまでの短い距離(p＜0.0001)、術前CA19-9高値(p=0.043)が側方リンパ節転移の危険因子として抽出された。これら3因子を用いた側方転移予測ノモグラムを作成すると、ROC曲線下面積(AUC)=0.622(0.5=worthless test、1.0=perfect test)であった。側方転移陽性78例の5年生存率(5生率)は45.6%であった。深達度別の側方リンパ節転移率はpTis-SM=0%、pMP=7.5%、pA=19.7%、pAi=27.3%で、転移陽性例の5生率はpMP=51.3%、pA=48.5%、pAi=24.2%であった。補助療法の有無別でみた場合に術後化学療法施行群が非施行群より有意に5生率が良好であった(58.0% vs 25.9%, p=0.020)。一方、術後照射群と非照射群との間には5生率で有意な差を認めなかった(40.1% vs 48.9%, p=0.303)。多変量解析では術後補助化学療法が独立した予後因子であった。

D．考察

術前に判明する3因子を用いた側方転移予測ノモグラムを作成したが、その転移予測能は不良であった。

深達度MP以深の下部直腸癌では、側方転移陽性であっても長期生存する症例が見込めることから、側方郭清には一定の治療効果があると考えられる反面、その限界も明らかになった。

E.結論

側方転移陽性例を高精度に抽出し、有効性が認められた化学療法を含めて、各種補助療法の最適な投与時期を明らかにすることが今後の課題であると思われた。

F．研究発表

1. 論文発表

一覧表に記載

2．学会発表

金光幸秀　小森康司　木村賢哉ほか: 下部直腸癌側方リンパ節転移の予測と治療効果. 第10回消化器外科学会大会、2012. (神戸)「

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　山口高史　　独立行政法人国立病院機構　京都医療センター外科

研究要旨：臨床病期 II,III の下部直腸癌に対する神経温存 D3 郭清術の意義に関するランダム化比較試験(JCOG0212)の参加 1 施設として研究を継続している。平成 18 年 5 月から平成 22 年 6 月までに 31 例の症例登録を行った。そのうち D3 郭清群が 15 例、ME 単独群が 16 例であった。最終診断は Stage1 が 5 例(16%)、Stage2 が 11 例(35%)、Stage3 が 15 例(48%)であった。術式は LAR が 23 例、APR が 8 例であった。全例プロトコール治療を終了し、現在外来フォロー中である。

A．研究目的

臨床病期 II,III の下部直腸癌に対する神経温存 D3 郭清術の意義に関するランダム化比較試験(JCOG0212)の参加 1 施設として研究している。

B．研究方法

JCOG0212 研究実施計画書に基づき、適格症例に対して全例研究への参加を依頼し同意を得た方を登録した。

（倫理面への配慮）

患者さんには本研究の必要性、重要性を十分に説明して理解していただき、信頼関係を構築した上で同意を得た。

C．研究結果

平成 18 年 5 月から平成 22 年 6 月までに 31 例の登録を行った。そのうち D3 郭清群が 15 例、ME 単独群が 16 例であった。最終診断は Stage1 が 5 例(16%)、Stage2 が 11 例(35%)、Stage3 が 15 例(48%)であった。術式の内訳は LAR が 23 例、APR が 8 例であった。

D．考察

症例登録、プロトコール治療を問題なく完遂できた。

E.結論

全例プロトコール治療を終了し、現在外来フォロー中である。研究を順調に継続している。

F．研究発表

1．論文発表

Satoshi Ogiso　Takashi Yamaguchi ほか：Laparoscopic resection for sigmoid and rectosigmoid colon cancer performed by trainees: impact on short-term　outcomes and selection of suitable patients.　Int J Colorectal DisDOI 10.1007/s00384-012-1471-1.

山口高史　福田明輝ほか：原著　ステージ III 大腸癌に対する術後化学療法としてのカペシタビン（Xeloda）内服療法の検討．癌と化学療法 2012 年　第 39 巻　第 3 号　　389～393.

2．学会発表

長谷川傑　山口高史ほか：大学病院を中心とした内視鏡大腸手術手技教育の標準化とその効果．第112回日本外科学会定期学術集会．2012

山口高史　福田明輝ほか：ステージ３大腸癌術後補助化学療法としてのカペシタビン内服療法の検討．第67回日本消化器外科学会総会．2012

村上隆英　山口高史ほか：当院における5ポート法による腹腔鏡下結腸右半切除術のこだわり．第25回近畿内視鏡外科研究会．2012

山口高史　松末亮ほか：腹腔鏡下結腸切除における5ポート法による鋭的剥離へのこだわり．第74回　日本臨床外科学会総会．2012

山口高史　松末亮ほか：S状結腸切除後のDST吻合においてCircular Staplerの挿入を容易にするためのコツ．第25回日本内視鏡外科学会総会．2012

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　　赤在義浩　岡山済生会総合病院　消化器外科部長

研究要旨：多施設共同研究JCOG０２１２試験に参加、下部直腸がんに対する側方リンパ節郭清の意義を検討するため、症例登録し経過を追跡調査している。

A.研究目的

術前画像診断および術中開腹所見にて、明らかな側方骨盤リンパ節転移を認めない臨床病期 II・III の治癒切除可能な下部直腸がん患者を対象として、mesorectal excision（ME 単独）と自律神経温存 D3 郭清術（神経温存 D3 郭清）の臨床的有用性を比較評価する。

B.研究方法

術前画像診断にて登録適格規準を満たした症例に、インフォームドコンセントを行い同意取得後、術中開腹所見を確認し、中央割付法で２群にランダム化する。

（倫理面への配慮）

院内 IRB の承認を得た。

C.研究結果

症例の登録を完了した。当院より４２症例の登録を行った。男性が２９例と女性が１３例で、神経温存 D3 郭清が２０例と ME 単独が２２例であった。

登録４２症例のうちリンパ節転移を２０例に認めた。神経温存 D3 郭清２０例のうちリンパ節転移は９例で、側方リンパ節転移を認めたのは１例であった。

神経温存 D3 郭清２０例を含む登録４２症例全員に術後の排尿障害は認めなかった。術前の性機能アンケート調査は男性２９例全員に行い無回答が１例あった。術後１年経過後の性機能アンケート調査も２９例全員に行った。

登録４２症例のうち再発は１４例で、ステージ２の２２例のうち５例に、ステージ３の２０例のうち９例に認めた。神経温存 D3 郭清群２０例のうち再発は８例で、肝再発が５例、肺再発が２例、大動脈周囲リンパ節再発が１例で、骨盤内再発は

認めなかった。ME 単独２２例のうち再発は６例であるが、肝と肺の単独再発３例と骨盤内再発を３例認めた。

その他、登録４２症例のうち異時性多発がんを１例と異時性重複がんを３例に認めた。現在までに死亡は４例あり、原がん死３例と他病死が１例あった。

D.考察

登録は４２症例である。神経温存 D3 郭清２０例と ME 単独２２例の術後早期合併症に差はなく、排尿障害は両群とも認めなかった。術後経過は現在追跡中であるが、今後集積した両群の症例を比較し評価を行う。

E.結論

継続して研究を行う。

F.研究発表

なし。

G.知的所有権の取得状況

なし

III. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Fujita S, Akasu T, Mizusawa J, Saito N, Kinugasa Y, Kanemitsu Y, Ohue M, Fujii S, Shiozawa M, Yamaguchi T, Moriya Y; Colorectal Cancer Study Group of Japan Clinical Oncology Group.	Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): results from a multicentre, randomised controlled, non-inferiority trial	Lancet Oncol	13(6)	616-21	2012
Yamamoto S, Fujita S, Akasu T, Inada R, Moriya Y.	Risk factors for anastomotic leakage after laparoscopic surgery for rectal cancer using a stapling technique.	Surg Laparosc Endosc Percutan Tech.	22(3):	239-43	2012
Yamaguchi T, Taniguchi H, Fujita S, Sekine S, Yamamoto S, Akasu T, Kushima R, Tani T, Moriya Y, Shimoda T.	Clinicopathological characteristics and prognostic factors of advanced colorectal mucinous adenocarcinoma.	Histopathology.	61(2):	162-9	2012
Akagi Y, Shirouzu K, Fujita S, Ueno H, Takii Y, Komori K, Ito M, Sugihara K	Study Group of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) on the Clinical Significance of the Mesorectal Extension of Rectal Cancer. Predicting oncologic outcomes by stratifying mesorectal extension in patients with pT3 rectal cancer: a Japanese multi-institutional study.	Int J Cancer	131(5)	1220-7	2012
神山篤史、齋藤典男、杉藤正典、伊藤雅昭、小林昭広、西澤雄介、	進行直腸癌における肛門温存手術	手術	66(2)	179-184	2012
Nakajima K, Takahashi S, Saito N, Kotaka M, Konishi M, Gotohda N, Kato Y, Kinoshita T.	Predictive Factors for Anastomotic Leakage after Simultaneous Resection of Synchronous Colorectal Liver Metastasis	J Gastrointest Surg	16(4)	821-827	2012

Nishigori H, Ito M, Nishizawa Y, Koyama A, Koda T, Nakajima K, Minagawa N, Nishizawa Y, Kobayashi A, Sugito M, Saito N.	Postoperative chylous ascites after colorec tal cancer surgery	Surg Today	42	724-728	2012
Nishizawa Y, Fujii S, Saito N, Ito M, Nakajima K, Ochiai A, Sugito M, Kobayashi A, Nishizawa Y.	Differences in tissue degeneration between preoperative chemotherapy and preoperative chemoradiotherapy for colorectal cancer	Int J Colorectal Dis	27	1047-1053	2012
菅野伸洋、伊藤雅昭、中嶋健太郎、櫻庭　実、杉藤正典、小林昭広、西澤雄介、錦織英知、神山篤史、齋藤典男、	超低位前方切除あるいはISR術後の吻合部狭窄	消化器外科	35(11)	1647-1654	2012
Kanemitsu Y, Komori K, Ishiguro S, Watanabe T, Sugihara K	The Relationship of Lymph Node Evaluation and Colorectal Cancer Survival After Curative Resection	Ann Surg Oncol1	9	2169-2177	2012
Ogiso S,Yamaguchi T, Fukuda M, Murakami T, Okuchi Y,Hata H,Sakai Y, Ikai I.	Laparoscopic resection for sigmoid and rectosigmoid colon cancer performed by trainees: impact on short-term outcomes and selection of suitable patients.	Int J Colorectal Dis	DOI 10.1007/s00384-012-1471-1.		2012
山口高史、福田明輝、安井久晃、岡崎俊介、久保紀美代、田中雅子、畝佳子、瀬戸口由、花田圭太、森山沙也香、谷正樹、村上隆英、奥知慶久、小木曾聡、畑啓昭、坂田晋吾大谷哲之、大和俊夫、猪飼伊和夫	原著　ステージIII大腸癌に対する術後化学療法としてのカペシタビン（Xeloda）内服療法の検討.	癌と化学療法	39(3)	389-393	2012

IV. 研究成果の刊行物・印刷

Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): results from a multicentre, randomised controlled, non-inferiority trial

Shin Fujita, Takayuki Akasu, Junki Mizusawa, Norio Saito, Yusuke Kinugasa, Yukihide Kanemitsu, Masayuki Ohue, Shoichi Fujii, Manabu Shiozawa, Takashi Yamaguchi, Yoshihiro Moriya, on behalf of the Colorectal Cancer Study Group of Japan Clinical Oncology Group

Lancet Oncol 2012; 13: 616–21
Published Online
May 15, 2012
DOI:10.1016/S1470-2045(12)70158-4
See Comment page 565

Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, Japan (S Fujita MD, T Akasu MD, Y Moriya MD); **JCOG Data Center, Multi-Institutional Clinical Trial Support Center, National Cancer Center, Tokyo, Japan** (J Mizusawa MSc); **Department of Surgery, National Cancer Center Hospital East, Kashiwa, Japan** (N Saito MD); **Department of Surgery, Shizuoka Cancer Center, Shizuoka, Japan** (Y Kinugasa MD); **Department of Surgery, Aichi Cancer Center Hospital, Nagoya, Japan** (Y Kanemitsu MD); **Department of Surgery, Osaka Medical Center and Cardiovascular Diseases, Osaka, Japan** (M Ohue MD); **Department of Surgery, Yokohama City University Medical Center, Yokohama, Japan** (S Fujii MD); **Department of Surgery, Kanagawa Cancer Center, Yokohama, Japan** (M Shiozawa MD); **Department of Surgery, Kyoto Medical Center, Kyoto, Japan** (T Yamaguchi MD)

Correspondence to:
Dr Shin Fujita, Colorectal Surgery Division 1-1, Tukiji 5-chome, Chuo-ku, Tokyo, Japan
sfujita@ncc.go.jp

Summary

Background Mesorectal excision is the international standard surgical procedure for lower rectal cancer. However, lateral pelvic lymph node metastasis occasionally occurs in patients with clinical stage II or stage III rectal cancer, and therefore mesorectal excision with lateral lymph node dissection is the standard procedure in Japan. We did a randomised controlled trial to confirm that the results of mesorectal excision alone are not inferior to those of mesorectal excision with lateral lymph node dissection.

Methods This study was undertaken at 33 major hospitals in Japan. Eligibility criteria included histologically proven rectal cancer of clinical stage II or stage III, with the main lesion located in the rectum with the lower margin below the peritoneal reflection, and no lateral pelvic lymph node enlargement. After surgeons had confirmed macroscopic R0 resection by mesorectal excision, patients were intraoperatively randomised to mesorectal excision alone or with lateral lymph node dissection. The groups were balanced by a minimisation method according to clinical N staging (N0 or N1, 2), sex, and institution. Allocated procedure was not masked to investigators or patients. This study is now in the follow-up stage. The primary endpoint is relapse-free survival and will be reported after the primary analysis planned for 2015. Here, we compare operation time, blood loss, postoperative morbidity (grade 3 or 4), and hospital mortality between the two groups. Analysis was by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT00190541.

Findings 351 patients were randomly assigned to mesoretcal excision with lateral lymph node dissection and 350 to mesorectal excision alone, between June 11, 2003, and Aug 6, 2010. One patient in the mesorectal excision alone group underwent lateral lymph node dissection, but was analysed in their assigned group. Operation time was significantly longer in the mesorectal excision with lateral lymph node dissection group (median 360 min, IQR 296–429) than in the mesorectal excision alone group (254 min, 210–307, p<0·0001). Blood loss was significantly higher in the mesorectal excision with lateral lymph node dissection group (576 mL, IQR 352–900) than in the mesorectal excision alone group (337 mL, 170–566; p<0·0001). 26 (7%) patients in the mesorectal excision with lateral lymph node dissection group had lateral pelvic lymph node metastasis. Grade 3–4 postoperative complications occurred in 76 (22%) patients in the mesorectal excision with lateral lymph node dissection group and 56 (16%) patients in the mesorectal excision alone group. The most common grade 3 or 4 postoperative complication was anastomotic leakage (18 [6%] patients in the mesorectal excision with lateral lymph node dissection group *vs* 13 [5%] in the mesorectal excision alone group; p=0·46). One patient in the mesorectal excision with lateral lymph node dissection group died of anastomotic leakage followed by sepsis.

Interpretation Mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than mesorectal excision alone. The primary analysis will help to show whether or not mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection.

Funding National Cancer Center, Ministry of Health, Labour and Welfare of Japan.

Introduction

Total mesorectal excision or mesorectal excision, in which at least a clear margin of 4 cm of the attached mesorectum distal to the tumour is resected, is the international standard surgical procedure for rectal cancer because it has a lower rate of associated local recurrence and higher rate of patient survival than conventional surgery.[1–3] However, metastasis to lateral pelvic lymph nodes occasionally occurs in patients with clinical stage II or stage III lower rectal cancer, the lower margin of which is located at or below the peritoneal reflection.

The incidence of lateral pelvic lymph node metastasis from lower rectal cancer is about 15%, and mesorectal excision with lateral lymph node dissection has been the

standard procedure for patients with lower rectal cancer in Japan[4-6] since it was introduced in the 1970s. Pelvic autonomic nerve-sparing lateral lymph node dissection has been developed and refined since in the mid-1980s.[7] If metastatic lymph node metastases are not dissected, local or systemic recurrence can develop.[8,9] However, the incidence of local recurrence in patients with rectal cancer who undergo total mesorectal excision or mesorectal excision without lateral lymph node dissection at major hospitals in Europe and North America is reported to be less than 10%.[10-13] Although this incidence is much the same as the rate for patients undergoing standard treatment in major hospitals in Japan,[4-6] comparison is difficult because of differences in the backgrounds of patients.

The difficulty of comparison between different procedures in distinct populations prompted us to assess the survival benefit, local control, operative complications, and sexual and urinary function of patients with rectal cancer undergoing mesorectal excision alone or with lateral lymph node dissection in a randomised controlled trial in major hospitals in Japan. The study aims to determine whether or not mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection in terms of efficacy. The primary analysis is planned for 2015, and this study is now in the follow-up stage. In this report, we present the data obtained so far for operation time, blood loss, and postoperative morbidity (grade 3 or 4) and mortality. Further analyses of urinary and sexual function are underway and will be reported at a later date.

Methods

Study design and participants

Preoperative inclusion criteria were histologically confirmed adenocarcinoma of clinical stage II or III (as determined by digital rectal examination, CT or MRI, and endoscopy); main lesion of tumour located in the rectum, with the lower tumour margin below peritoneal reflection; no extramesorectal lymph node enlargement (ie, lymph nodes with a short-axis diameter of less than 10 mm shown by CT scan or MRI is not regarded as lymph node enlargement); and no invasion to other organs. Eligible patients were aged between 20 and 75 years with performance status 0 or 1 and no history of chemotherapy, pelvic surgery, or radiation. Intraoperative inclusion criteria were completed mesorectal excision, confirmation that the main lesion of the tumour was located in the rectum, with the lower tumour margin below peritoneal reflection, and macroscopic R0 (ie, no residual tumour) after the mesorectal excision. Exclusion criteria were synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ or mucosal carcinoma, pregnancy or breastfeeding in women, or a psychological disorder or severe mental illness. Patients undergoing treatment with systemic steroids, or with a history of myocardial infarction or unstable angina pectoris within 6 months, or with severe pulmonary emphysema or pulmonary fibrosis were also excluded. The attending physician had the final decision for exclusion.

Clinical stage was based on the results of digital rectal examination, imaging (CT or MRI), and endoscopy. Clinical stage I rectal tumours and tumours in which the lower margin was located above the peritoneal reflection were not included, because the incidence of lateral pelvic lymph node metastasis in such cases is very low. If lateral pelvic lymph node enlargement was detected by CT or MRI with 5 mm thick sections and the short-axis diameter of the nodes exceeded 10 mm, which is the minimum measurable size in such sections, patients were not included in this study and underwent mesorectal excision with lateral lymph node dissection.

Only surgeons specialising in both procedures from 33 Japanese institutions (listed in the appendix) participated in the study. We obtained written informed consent from all patients before surgery and the protocol was approved by institutional review boards.

See Online for appendix

Randomisation and masking

Randomisation and data handling were done by the JCOG Data Center. After surgeons had confirmed macroscopic R0 resection (ie, no residual tumour) by mesorectal excision and macroscopic absence of lymph node metastasis in the lateral pelvic lymph area, patients were randomised intraoperatively to mesorectal excision alone or with lateral lymph node dissection by phone call to the JCOG Data Center. The groups were balanced by a minimisation method with biased-coin assignment according to clinical N staging by imaging (CT or MRI) and surgical exploration (N0 or N1, 2), sex, and institution. Allocated procedure was not masked to investigators or patients.

Procedures

Mesorectal excision was done by open surgery in accordance with reported methods.[1] Under direct vision with sharp dissection, the rectum was mobilised keeping the plane around the mesorectum, and the attached mesorectum with at least a 4 cm clearance margin distal to the tumour was resected. If the length of the attached mesorectum distal to the tumour was less than 4 cm, the mesorectum was totally resected. The inferior mesenteric artery was ligated at its root. If the blood supply to the distal colon was deemed inadequate as a result of this procedure, preservation of the left colonic artery after lymph node dissection at its root was allowed.

Lateral lymph node dissection was done in accordance with reported methods.[4,5,14] Lateral pelvic lymph nodes include the common iliac node, internal iliac node, external iliac node, obturator node, and middle sacral node. Because metastasis to the external iliac node and middle sacral node in the patients eligible for this study without clinical lateral pelvic lymph node metastasis is rare,[15] dissection of those nodes was not deemed necessary. The other lateral pelvic lymph nodes in the fatty and

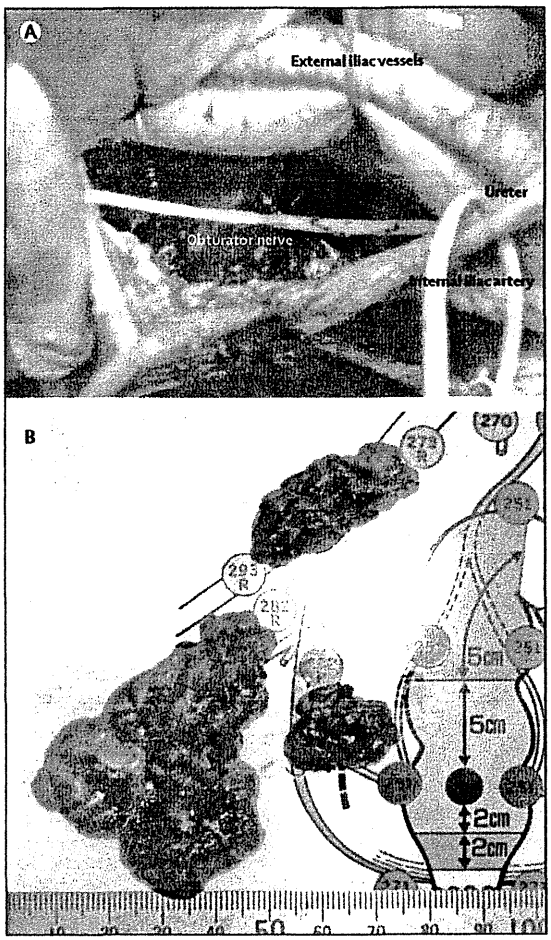

Figure 1: **Lateral lymph node dissection**
(A) The obturator fossa after lateral lymph node dissection, with the dissected fatty and connective tissues (right side). (B) Dissected fatty and connective tissues including lymph nodes.

connective tissues outside the pelvic plexus, around the common, internal, and oburator fossa were dissected after mesorectal excision (figure 1). All the autonomic nerves were preserved because lymph node metastasis around these nerves is rare in patients without clinical lateral pelvic lymph node metastasis.

For surgical quality control and assurance, intraoperative photographs were taken. In the mesorectal excision alone group, five photos were taken: the site of inferior mesenteric artery ligation, the preserved right and left hypogastric nerves, and the anterior and posterior sides of the resected specimen. In the mesorectal excision with lateral lymph node dissection group, 11 photos were taken: the site of inferior mesenteric artery ligation, the preserved right and left hypogastric nerves, the right and left internal iliac artery, the right and left obturator fossa, the anterior and posterior sides of the resected specimen, and the right and left dissected fatty and connective tissues in the lateral

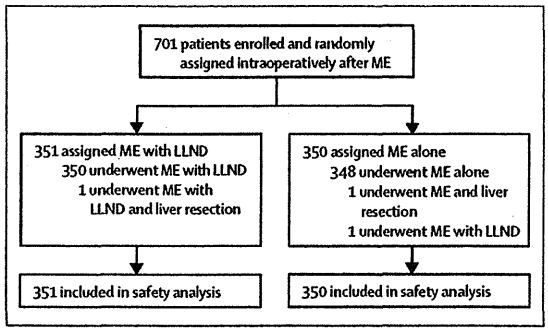

Figure 2: **Trial profile**
We did not collect data for the number of eligible patients before enrolment. ME=mesorectal excision. LLND=lateral lymph node dissection.

pelvic lymph node area. These photographs were assessed and scored by the committee for quality control and assessment of surgery, and the surgical procedure was discussed and assured according to the score at meetings held twice a year.

Adjuvant chemotherapy with the Roswell Park regimen of intravenous fluorouracil (500 mg/m^2) and L-leucovorin (250 mg/m^2) was given to patients with pathological stage III tumours in both groups. Patients who were stage II did not receive adjuvant chemotherapy.[16] This regimen consisted of three courses of six doses of weekly chemotherapy followed by a 2-week rest. Adjuvant radiotherapy was not used.

Operative methods and pathology results were recorded according to the Japanese Classification of Colon and Rectal Carcinoma (sixth edition)[17] and TNM classification (fifth edition).[18] The primary endpoint was relapse-free survival, and the secondary endpoints were overall survival, local recurrence-free survival, incidence of adverse events, incidence of major adverse events, operation time, blood loss, and incidence of sexual and urinary dysfunction. Operation time, blood loss, and all postoperative morbidities during hospital stay were recorded prospectively on case report forms. Postoperative morbidity was described according to the National Cancer Institute-Common Toxicity Criteria version 2·0. Hospital mortality was defined as postoperative death from any cause within 30 days.

Statistical analysis

We originally estimated that 5-year relapse-free survival after mesorectal excision with lateral lymph node dissection and mesorectal excision alone would be 65%, and the initial sample size was 600 patients, which was determined with one-sided alpha of 0·05, a power of 0·75, and a non-inferiority margin for a hazard ratio (HR) of 1·34. However, we calculated the 5-year relapse-free survival for all randomised patients 5 years after the start of registration, and recorded that it was about 75%. Therefore, the sample size was increased to 700 patients to maintain the required statistical power. Planned accrual and

follow-up were 7 years and 5 years, respectively. Incidences of operative morbidity and mortality were expressed as the number of cases divided by the total number of registered patients. Differences in proportions between groups were assessed with Fisher's exact test. Differences in operation time and blood loss were compared with the Wilcoxon rank sum test. All p values were two-sided, and statistical analysis was done with SAS version 9·1. The data presented in this paper were as of June 12, 2011. Analysis was by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT00190541, and UMIN-CTR, number C000000034.

Role of the funding source

The funding sources had no role in the design of the study, collection, analysis, interpretation of the data, writing of the report, or in the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the report for publication.

Results

701 patients were randomly assigned to the mesorectal excision alone group (n=350) or the mesorectal excision with lateral lymph node dissection group (n=351) between June 11, 2003, and Aug 6, 2010 (figure 2). All but three patients received the allocated surgery. Liver metastasis was identified after randomisation in one patient in each group and they underwent hepatic resection after rectal cancer surgery. Lateral lymph node metastasis was strongly suspected after randomisation in one patient allocated to the mesorectal excision alone group and the patient underwent lateral lymph node dissection. These three patients were eligible and included in this analysis. Two patients assigned to the mesorectal excision with lateral lymph node dissection group were found to have clinical stage I disease, despite being reported as clinical stage II or III at enrolment. Two other patients assigned to the same group had synchronous multiple cancers. Three patients (one in the mesorectal excision with lateral lymph node dissection group and two in the mesorectal excision alone group) were judged to have residual tumours before randomisation. We included these seven patients in this analysis, but their data will be excluded from the final survival analysis.

Table 1 shows the characteristics of all patients. Low anterior resection was done in 568 (81%) of 701 patients. Mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than did mesorectal excision alone (table 2). Of the 26 patients in the mesorectal excision with lateral lymph node dissection group who had lateral pelvic lymph node metastasis, 11 (42%) were clinical stage II and 15 (58%) were clinical stage III. 19 (73%) had pathological mesorectal lymph node metastasis and seven (27%) had no pathological mesorectal lymph node metastasis. Although more common in the mesorectal excision with lateral lymph node dissection group than with mesorectal excision alone, differences between groups in grade 3 and 4 postoperative complications were not significant (table 3). Anastomotic leakage of all grades,

	ME with LLND (n=351)	ME (n=350)
Sex		
Male	236 (67%)	236 (67%)
Female	115 (33%)	114 (33%)
Age (years)		
Median (IQR)	61 (54-67)	62 (55-68)
Clinical stage		
II	188 (54%)	197 (56%)
III	163 (46%)	153 (44%)
Tumour location*		
Ra	81 (23%)	80 (23%)
Rb	270 (77%)	270 (77%)
Tumour distance from anal verge (cm)†		
Median (IQR)	5·0 (4·0-6·0)	5·0 (3·7-6·0)

ME=mesorectal excision. LLND=lateral lymph node dissection. *Ra=tumour centre located above the peritoneal reflection, Rb=tumour centre located below the peritoneal reflection. †Data for five patients are missing.

Table 1: **Characteristics of patients**

	ME with LLND (n=351)	ME (n=350)	p value*
Type of surgery			..
Low anterior resection	284 (81%)	284 (81%)	
Abdominoperineal resection	66 (19%)	64 (18%)	
Hartmann's procedure	1 (<1%)	2 (<1%)	
Time (min)			
Median (IQR)	360 (296-429)	254 (210-307)	<0·0001
Blood loss (mL)			
Median (IQR)	576 (352-900)	337 (170-566)	<0·0001
Lateral lymph node metastasis			
Number (%)	26 (7%)	..	..

ME=mesorectal excision. LLND=lateral lymph node dissection. *Wilcoxon rank sum test, two-sided.

Table 2: **Operative details**

	ME with LLND (n=351)	ME (n=350)	p value*
Any grade 3-4 complication†	76 (22%)	56 (16%)	0·07
Anastomotic leakage‡	18 (6%)	13 (5%)	0·46
Urinary retention	18 (5%)	10 (3%)	0·18
Infection with normal absolute neutrophil count	16 (5%)	17 (5%)	0·86
Haemorrhage with surgery	13 (4%)	5 (1%)	0·09
Wound infection	10 (3%)	8 (2%)	0·81
Pelvic abscess	6 (2%)	2 (<1%)	0·29
Bowel obstruction	4 (1%)	3 (<1%)	1·00
Other§	12 (3%)	9 (3%)	0·66

ME=mesorectal excision. LLND=lateral lymph node dissection. *Fisher's exact test, two-sided. †National Cancer Institute-Common Toxicity Criteria Version 2·0. ‡Denominator is patients with anastomosis (ME with LLND=284, ME=284). §Other=fever, melaena, fistula, thrombosis, urinary frequency.

Table 3: **Grade 3-4 postoperative morbidity**

which is the major complication after low anterior resection, occurred in 37 (13%) of 284 patients in the mesorectal excision alone group and 32 (11%) of 284 patients in the mesorectal excision with lateral lymph node dissection group (p=0·61). One patient in the mesorectal excision with lateral lymph node dissection group died of anastomotic leakage followed by sepsis. All other patients recovered from surgery and were discharged from hospital.

Discussion

As expected, mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than did mesorectal excision alone. Although the incidence of grade 3 or grade 4 complications was higher in the mesorectal excision with lateral lymph node dissection group than in the mesorectal excision alone group, these differences were not significant.

In previous reports, the mean difference in intraoperative blood loss between surgical procedures with and without lateral lymph node dissection was more than 500 mL.[19–22] Blood loss might have been less in our study because none of the eligible patients had clinical evidence of lateral pelvic lymph node metastasis. In these patients, lateral lymph node dissection is easier than it is in those with clinical evidence of such metastasis. Also, because expertise with the lateral lymph node procedure is improving, blood loss might have been minimised compared with earlier studies.

The median operation time needed for mesorectal excison with lateral lymph node dissection was longer than that for mesorectal excision alone. This result is attributable to the time needed for lateral lymph node dissection, which is a meticulous procedure, and confirms previous results with regard to the difference in operation time.[20–22]

The incidence of all grade 3 or 4 postoperative complications, apart from infection with a normal absolute neutrophil count, was higher in the mesorectal excision with lateral lymph node dissection group than in the mesorectal excision alone group, but differences were not significant. Results of a previous meta-analysis[19] comparing extended lymphadenectomy including lateral lymph node dissection and conventional surgery for rectal cancer showed that the incidence of perioperative morbidity was higher for extended lymphadenectomy than for conventional surgery. However, one of the major complications, anastomotic leakage of all grades, showed no difference in incidence between the groups. Although we did not collect data for defunctioning stoma, the incidences of anastomotic leakage of all grades in patients who underwent low anterior resection in the mesorectal excision with lateral lymph node dissection group and mesorectal excision alone group were much the same, which suggests that lateral lymph node dissection was not a highly invasive surgical procedure.

Only one patient died from sepsis after anastomotic leakage. The reported mortality after mesorectal excision for rectal cancer surgery in Europe and North America is 1–3%,[11–13,23] and that after mesorectal excision with lateral lymph node dissection in Japan is 1%,[19] which is in line with our results (panel). The low mortality in our study can be attributed to several factors. Only surgeons specialising in both mesorectal excision and lateral lymph node dissection participated in this trial. Second, only patients who were judged to be capable of tolerating lateral lymph node dissection were selected and only high-volume centres for cancer treatment were allowed to enrol patients by the Colorectal Cancer Study Group.

Neoadjuvant chemoradiotherapy for rectal cancer is used worldwide. However, patients undergoing such treatment were not included and adjuvant radiotherapy was not used in our study for two reasons. First, the effectiveness and safety of adjuvant or neoadjuvant chemoradiotherapy for rectal cancer had not been clearly shown when we designed the protocol of this study. Second, adjuvant radiotherapy is not commonly used in Japan because of the lower local recurrence rate and better prognosis for patients in Japan than for those in Europe and North America.

Kim and colleagues[8] showed that lateral pelvic lymph node metastasis is a major cause of local recurrence of rectal cancer. With serial sections from human fetuses and three-dimensional reconstruction, Kusters and colleagues[24] showed that tumour recurrence might arise from lateral pelvic lymph nodes. However, other reports from Europe and North America have not supported these results. Syk and colleagues[25] examined the pattern of local recurrence after total mesorectal excision and concluded that lateral pelvic lymph node metastases are not a major cause of local recurrence. The results of a Dutch trial of total mesorectal excision showed that the rate of lateral site

Panel: Research in context

Systematic review

Total mesorectal excision or mesorectal excision is the international standard surgical procedure for lower rectal cancer.[1] However, lateral pelvic lymph node metastasis occasionally occurs in patients with clinical stage II or stage III rectal cancer, and therefore mesorectal excision with lateral lymph node dissection is the standard procedure in Japan. When metastatic lateral pelvic lymph nodes are not dissected, the patients can have local or systemic recurrence. Although we did not do a systematic search of published work before starting this trial, the reported incidence of local recurrence in rectal cancer patients undergoing mesorectal excision without lateral lymph node dissection at major hospitals in Europe and North America is less than 10%,[10–13] which is much the same as the incidence in patients who undergo mesorectal excision with lateral lymph node dissection at major hospitals in Japan.[4–6] Therefore, we did a randomised controlled trial to determine whether mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection.

Interpretation

7% of the patients with lower rectal cancer without lateral pelvic lymph node enlargement had lateral pelvic lymph node metastasis. Mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than mesorectal excision alone. The primary analysis will help to determine whether or not mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection.

recurrence was only 3% in patients with lower rectal cancer, being much the same as results for patients who underwent lateral lymph node dissection at the National Cancer Center, Tokyo.[26] Analysis of the pattern of local recurrence in our study is very important, and should give a reliable indication of the incidence of lateral pelvic lymph node metastasis. The incidence of such metastasis was 7%, which was lower than the 15% reported in a retrospective multicentre study in Japan,[6] because only patients who had no clinical evidence of lateral pelvic lymph node enlargement were eligible for our study. This result shows that even in patients without clinically evident lateral pelvic lymph node metastasis, such metastasis is sometimes present pathologically.

Our patient population was defined as being lateral pelvic lymph node negative by CT or MRI. Nonetheless, the 7% of patients in the mesorectal excision with lateral lymph node dissection group were found to have lateral pelvic lymph node metastasis after lymph node dissection. Therefore, a similar proportion of patients undergoing mesorectal excision alone probably have such metastasis. If all patients with lateral pelvic lymph node metastasis have local or systemic recurrence, then the relapse rate will be about 7% higher in patients who undergo mesorectal excision alone than in those who also have lateral lymph node dissection. If the results for the primary analysis planned for 2015 show that the upper confidence limit of the HR is less than 1·34, which corresponds to an 8% difference in 5-year relapse-free survival between the groups, then the non-inferiority of mesorectal exicision alone will be confirmed in terms of outcome. If not, mesorectal excision with lateral lymph node dissection should be considered the standard surgical procedure for lower rectal cancer.

Contributors

SFujita, TA, NS, and YM contributed to study design. SFujita, TA, NS, YKi, YKa, MO, SFujii, MS, TY, and YM contributed to data collection, data analysis, and interpretation. JM contributed to statistical analyses. All the authors contributed to writing or review of the report and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

We thank the members of the JCOG Data Center and JCOG Operations Office for their support in preparing the report (Kenichi Nakamura, Hiroshi Katayama, Atsuo Takashima), data management (Harumi Kaba, Ayaka Nakano), and overseeing of study management (Haruhiko Fukuda). This study was supported in part by the National Cancer Center Research and Development Fund (23-A-16, 23-A-19) and Grants-in-Aid for Cancer Research (14S-4, 17S-3, 17S-5, 20S-3, 20S-6), Health Sciences Research Grants for Medical Frontier Strategy Research, Health and Labour Sciences Research Grants for Clinical Research for Evidence-based Medicine and Health, and a Labour Sciences Research Grant for Clinical Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

References

1 Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *Br J Surg* 1982; 69: 613–16.
2 MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; 341: 457–60.
3 Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst* 2001; 93: 583–96.
4 Moriya Y, Sugihara K, Akasu T, Fujita S. Importance of extended lymphadenectomy with lateral node dissection for advanced lower rectal cancer. *World J Surg* 1997; 21: 728–32.
5 Takahashi T, Ueno M, Azekura K, Ohta H. Lateral node dissection and total mesorectal excision for rectal cancer. *Dis Colon Rectum* 2000; 43: S59–68.
6 Sugihara K, Kobayashi H, Kato T, et al. Indication and benefit of pelvic sidewall dissection for rectal cancer. *Dis Colon Rectum* 2006; 49: 1663–72.
7 Moriya Y, Sugihara K, Akasu T, Fujita S. Nerve-sparing surgery with lateral node dissection for advanced lower rectal cancer. *Eur J Cancer* 1995; 31A: 1229–32.
8 Kim TH, Jeong SY, Choi DH, et al. Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. *Ann Surg Oncol* 2008; 15: 729–37.
9 MERCURY Study Group. Relevance of magnetic resonance imaging-detected pelvic sidewall lymph node involvement in rectal cancer. *Br J Surg* 2011; 98: 1798–804.
10 Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. *J Am Coll Surg* 1995; 181: 335–46.
11 Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. *Arch Surg* 1998; 133: 894–99.
12 Lopez-Kostner F, Lavery IC, Hool GR, Rybicki LA, Fazio VW. Total mesorectal excision is not necessary for cancers of the upper rectum. *Surgery* 1998; 124: 612–17.
13 Zaheer S, Pemberton JH, Farouk R, Dozois RR, Wolff BG, Ilstrup D. Surgical treatment of adenocarcinoma of the rectum. *Ann Surg* 1998; 227: 800–11.
14 Akasu T, Moriya Y. Abdominopelvic lymphadenectomy with autonomic preservation for carcinoma of the rectum: Japanese experience. In: Wanebo HJ, ed, Surgery for gastrointestinal cancer: a multidisciplinary approach. Philadelphia: Lippincott-Raven, 1997: 667–80.
15 Kobayashi H, Mochizuki H, Kato T, et al. Outcomes of surgery alone for lower rectal cancer with and without pelvic sidewall dissection. *Dis Colon Rectum* 2009; 52: 567–76.
16 Haller DG, Catalano PJ, Macdonald JS, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. *J Clin Oncol* 2005; 23: 8671–78.
17 Japanese Society of Cancer of the Colon and Rectum. General rules for clinical and pathological studies on cancer of the colon, rectum and anus, 6th edn. Tokyo: Kanehara, 1998.
18 Sobin LH, Wittekind C. TNM classification of malignant tumours, 5th edn. New York: Wiley-Liss, 1997.
19 Georgiou P, Tan E, Gouvas N, et al. Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis. *Lancet Oncol* 2009; 10: 1053–62.
20 Hojo K, Sawada T, Moriya Y. An analysis of survival and voiding, sexual function after wide iliopelvic lymphadenectomy in patients with carcinoma of the rectum, compared with conventional lymphadenectomy. *Dis Colon Rectum* 1989; 32: 128–33.
21 Nagawa H, Muto T, Sunouchi K, et al. Randomized, controlled trial of lateral node dissection vs. nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. *Dis Colon Rectum* 2001; 44: 1274–80.
22 Fujita S, Yamamoto S, Akasu T, Moriya Y. Lateral pelvic lymph node dissection for advanced lower rectal cancer. *Br J Surg* 2003; 90: 1580–85.
23 Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; 345: 638–46.
24 Kusters M, Wallner C, Lange MM, et al. Origin of presacral local recurrence after rectal cancer treatment. *Br J Surg* 2010; 97: 1582–87.
25 Syk E, Torkzad MR, Blomqvist L, Ljungqvist O, Glimelius B. Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer. *Br J Surg* 2006; 93: 113–19.
26 Kusters M, Beets GL, van de Velde CJ, et al. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. *Ann Surg* 2009; 249: 229–35.

Risk Factors for Anastomotic Leakage After Laparoscopic Surgery for Rectal Cancer Using a Stapling Technique

Seiichiro Yamamoto, MD, Shin Fujita, MD,* Takayuki Akasu, MD,* Ryo Inada, MD,* Yoshihiro Moriya, MD,* and Seiichiro Yamamoto, PhD†*

Purpose: This study evaluated the risk factors for anastomotic leakage after laparoscopic surgery for rectal cancer using a stapling technique.

Methods: The total prospective registry of 111 patients with rectal cancer who initially underwent laparoscopic low anterior resection using a stapling technique was reviewed. Univariate and multivariate analyses were carried out to identify relevant risk factors.

Results: Overall anastomotic leakage rate was 5.4% (6/111). Univariate analysis demonstrated that body mass index (BMI) ($P = 0.0377$) was significantly associated with anastomotic leakage. After univariate analysis, the variables of BMI and the size of the circular stapler ($P = 0.0923$) were selected for multivariate analysis, as their P values were < 0.2, and multivariate analysis demonstrated that BMI was independently predictive of developing anastomotic leakage ($P = 0.0458$).

Conclusions: Laparoscopic surgery for rectal cancer using a stapling technique can be performed safely without increasing the risk of anastomotic leakage, and increased BMI might be a potential risk factor for anastomotic leakage.

Key Words: laparoscopic anterior resection, risk factor, anastomotic leakage, obesity, multifiring technique

(*Surg Laparosc Endosc Percutan Tech* 2012;22:239–243)

Controversy still persists regarding the appropriateness of laparoscopic surgery (LS) for patients with rectal cancer because of concerns over the safety of the procedure and the uncertainty of the long-term outcome compared with open surgery (OS). An increase in the number of patients who would benefit from the low invasiveness of LS is desirable, but the laparoscopic procedure is technically demanding in patients with rectal cancer. Although many studies of LS and OS for rectal cancer have reported no statistical difference in terms of anastomotic leakage, some authors still recommend covering ileostomy as a routine procedure in laparoscopic low anterior resection (Lap-LAR), a step that may not be required in open low anterior resection (Op-LAR) cases.[1–6] Because of the high conversion and complication rate, it is unclear whether Lap-LAR for rectal cancer should be regarded as a minimally invasive surgery.

Anastomotic leakage is the most important complication after low anterior resection for rectal cancer. This complication contributes not only to postoperative morbidity and mortality, but also to local recurrence and poor functional prognosis.[7,8] In Op-LAR, many studies have evaluated the risk factors for anastomotic leakage, with age, sex, preoperative medical disease, obesity, preoperative chemoradiotherapy, bowel obstruction, tumor location, pelvic drainage, and the level of anastomosis identified as risk factors.[8–12] However, the devices and techniques used for Lap-LAR differ from those used for Op-LAR, which suggests that the risk factors for anastomotic leakage may also differ between Lap-LAR and Op-LAR.

Several studies have evaluated the risk factors for anastomotic leakage in Lap-LAR, and it has been reported that the number of stapler firings used for rectal transection has been associated with subsequent leakage.[6,13] In the present study, risk factors for anastomotic leakage after Lap-LAR for rectal cancer using the stapling technique in our institution were analyzed, with an assessment of the association between the number of linear stapler firings and anastomotic leakage.

MATERIAL AND METHODS

The study took the form of a single-center, prospective, observational, case-series analysis. Between July 2001 and February 2011, we performed 111 continuous Lap-LAR for selected patients with rectal cancer. Because the safety of LS in cancer patients remains to be established, candidates for radical surgery were basically patients who were preoperatively diagnosed with T1 or T2. LS was also performed in patients who were preoperatively diagnosed with T3/4 but wished to undergo LS and in those for which palliative resection was considered necessary. Eighteen patients registered for the clinical trial (Phase II Trial to Evaluate Laparoscopic Surgery for Stage 0/I Rectal Carcinoma) are included in the present study.[14] We excluded the following groups of patients from laparoscopic resection, because performing LS in these patients was expected to require advanced skills, and technical safety has not been achieved: patients with tumors > 8 cm, patients with a prior history of extensive adhesions, patients with severe obesity (body mass index [BMI] $> 30\,kg/m^2$), patients with intestinal obstruction, patients who required lateral pelvic lymph node dissection, patients who have undergone preoperative chemoradiotherapy, and patients who did not consent to LS.

All patients were evaluated before operation by clinical investigation, including barium enema or computed

Received for publication July 6, 2011; accepted February 9, 2012.
From the *Division of Colorectal Surgery, National Cancer Center Hospital; and †Epidemiology and Statistics section, Cancer Information Services and Surveillance Division, National Cancer Center, Tokyo, Japan.
The authors declare no conflicts of interest.
Reprints: Seiichiro Yamamoto, MD, Division of Colorectal Surgery, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan (e-mail: seyamamo@ncc.go.jp).

tomographic (CT) colonography, total colonoscopy, chest x-ray, abdominal ultrasonography, and CT. Tumor location was defined according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus published by the Japanese Society for Cancer of the Colon and Rectum.[15] Tumors located between the inferior margin of the second sacral vertebra and the peritoneal reflection were classified as present in the upper rectum, and tumors located below the peritoneal reflection were classified as present in the lower rectum. The location of the tumor was determined by a pelvic CT scan, colonoscopy, barium enema, and/or CT colonography, preoperatively, and confirmed during surgery.

We defined conversion to OS as any incision >8 cm, excluding cases in which the incision was enlarged due to a large specimen size that could not be removed from an 8-cm incision.

Our Institutional Review Board does not mandate obtaining their approval for the collection of patient clinical records prospectively and for publication as an institutional case-series study, and written consent was obtained from all patients for the use of their clinical data in the future.

The techniques of laparoscopic resections have been thoroughly described previously, and tumors were treated by total mesorectal excision.[16,17] After mobilization of the left colon and splenic flexure, if necessary, intracorporeal high ligation of the inferior mesenteric vessels followed by mobilization of the rectum was performed. Recently, the laparoscopic median-to-lateral approach has been indicated. In this approach, medial-to-lateral retroperitoneal dissection of the mesocolon and early division of the inferior mesenteric vessels were performed, which preserved the inferior mesenteric plexus and superior hypogastric plexus. Immediately before rectal transection, laparoscopic rectal clamping was performed just above the anticipated point of rectal transection, using a bowel clamping device introduced through the 12-mm midlower port. Rectal washout was routinely performed using 1000 mL of 5% povidone-iodine solution. Rectal transection was then performed either by the multiple firing technique, using endolinear staplers introduced through the 12-mm right midabdominal port or through a small laparotomy using rectal clamping devices for OS, with this decision made by the surgeon. The bowel was exteriorized under wound protection through a small incision made over the midlower port site. In patients with rectal transection using endolinear staplers, after inserting the anvil head of the circular stapler into the end of the proximal colon, the proximal colon was internalized and the incision was closed. Intracorporeal end-to-end anastomosis under laparoscopic view was performed by the stapling technique, using a circular stapler. In patients with rectal transection by rectal clamping devices for OS, anastomosis was completed through a small incision by direct vision. The anastomotic air leakage test was performed if the "doughnuts" were incomplete, and if the air leak test was positive, either reanastomosis by stapling technique or protective ileostomy was performed. Patients with low anastomosis within 2 cm from the dentate line and incomplete doughnuts underwent covering ileostomy. In all cases, the retroperitoneum was not repaired.

Data on combined surgical techniques were all included in the analyses of cancer surgeries. In the present study, clinical anastomotic leakage was defined as the presence of leakage signs (pelvic abscess, fecal or purulent discharge from a drainage tube or wound, peritonitis) and confirmed by radiographic work-up or by operative findings within 30 days from the initial operation.

In univariate analysis, patients were divided into those with or without anastomotic leakage and compared. Parameters analyzed included sex, age, BMI, prior abdominal surgery, location of the tumor, size of the tumor, preceding endoscopic resection, the American Society of Anesthesiologists classification, pathologic stage, operative time, operative blood loss, combined surgery, protective stoma, colonic pouch, anastomotic procedure, conversion, number of stapler cartridges fired for rectal transection, size of the circular stapler, and year of operation. Pathologic staging was performed according to the TNM stage.

Statistical analysis was performed using SPSS ver. 11.0 software (SPSS, Chicago, IL). In univariate analysis, Student *t*-test and Fisher exact test were used as appropriate. Multivariate analysis was performed by logistical regression using independent variables with a $P < 0.2$ in univariate analysis. A P value of < 0.05 was considered significant.

RESULTS

Patient demographics are summarized in Table 1. There were no perioperative mortalities, and the overall anastomotic leakage rate was 5.4% (6/111). In univariate analysis, BMI was significantly higher ($P = 0.0377$) in

TABLE 1. Patient's Characteristics

	Leakage (n = 6)	No. Leakage (n = 105)	P
Sex (male:female)	5:1	61:44	0.3981
Age (y)	63.0 (42-75)	60.7 (28-86)	0.6334
Body mass index (kg/m^2)	24.7 (23.8-29.0)	22.3 (17.1-30.4)	0.0377
Prior abdominal surgery	2 (33%)	28 (27%)	0.3226
Location			
Upper rectum	3	63	
Lower rectum	3	42	0.6849
Size of tumor (mm)	26 (11-50)	29 (6-80)	0.7071
Preceding endoscopic resection	3 (50%)	30 (29%)	0.3597
ASA (I:II)	3:3	60:45	1.0000
Pathologic T stage			
T0,1	5	54	
T2	1	24	
T3	0	26	
T4	0	1	
T0,1:T2,3,4	5:1	54:51	0.2116
Pathologic N stage			
N0	5	70	
N1	1	33	
N2	0	2	
N0:N1,2	5:1	70:35	0.6618
pTNM stage			
0, I	5	58	
II	0	11	
III	1	33	
IV	0	3	
0, I:II + III + IV	5:1	58:47	0.2321

Data are numbers or means with ranges in parentheses.
ASA indicates American Society of Anesthesiologists.

patients with anastomotic leakage, and it was selected for multivariate analysis.

Operative parameters are shown in Table 2. In univariate analysis, there were no significant differences in operative parameters among groups, including the number of stapler cartridges fired for rectal transection ($P = 0.6788$). The variable of the size of the circular stapler was selected for multivariate analysis, as their P values were < 0.2.

Regarding the postoperative outcomes of the 6 patients with anastomotic leakage, 3 patients required emergency operation of diverting ileostomy, and these 3 patients did not have protective stoma at the initial surgery. Remaining 3 patients with anastomotic leakage were treated conservatively, and 2 of 3 did not have protective stoma at the initial surgery. The air leakage test was performed in 4 patients, and 2 patients did not have air leakage sign; however, protective ileostomy was indicated in these 2 patients, because the anastomosis was low. In other 2 patients, reanastomosis was indicated in success. One patient required conversion to OS, because of an intraoperative bleeding. Fortunately, that patient did not develop anastomotic leakage. We did not experience anastomotic stricture in this series.

Table 3 summarizes the results of multivariate analysis, and BMI was independently predictive of developing anastomotic leakage ($P = 0.0458$).

DISCUSSION

This study demonstrated that increased BMI might be a potential risk factor for anastomotic leakage after Lap-LAR for rectal cancer using the stapling technique, and the anastomotic leakage rates in Lap-LAR was 5.4% (6/111) in cases of rectal cancer. In contrast, the number of linear stapler firings for rectal transection was not associated with anastomotic leakage. These findings demonstrate the technical feasibility and safety of Lap-LAR for selected patients with rectal cancer.

Obesity, age, sex, preoperative medical disease, preoperative chemoradiotherapy, bowel obstruction, tumor location, pelvic drainage, and the level of anastomosis have been reported to be risk factors for anastomotic leakage in Op-LAR.[9–12] In contrast, only a few studies have examined risk factors for anastomotic leakage in Lap-LAR. A unique aspect of these reports is the association of the number of stapler firings used for rectal division with a high anastomotic leakage rate.[13] The differences in surgical techniques between Op-LAR and Lap-LAR may contribute to this finding. LS is performed under pneumoperitoneum, and the limited performance of laparoscopic linear staplers may cause difficulty with a single cartridge firing. In multiple firings, especially when the number of stapler cartridges used for rectal transection increases, there is a concern that an increased number of stapler firings will lead to an incomplete rectal stump and, in turn, to anastomotic leakage; however, in the present study, the number of stapler firings was not significantly associated with anastomotic leakage. We believe that Lap-LAR can be performed without increasing the anastomotic leakage rate by maintaining the surgical principles of rectal transection in Lap-LAR.[16,17]

The result of the current study demonstrated that BMI was significantly associated with an increased anastomotic leakage rate. Many studies have shown that the difficulty of LS increases in obese patients, and some reports have found increased complication rates in obese patients; however, other studies have reported similar complication rates in obese and nonobese patients.[18–21] Therefore, studies with larger populations are required to determine whether obesity is a risk factor for morbidities such as anastomotic leakage in Lap-LAR.

Conversion to OS and sex have also been reported as potential risk factors for anastomotic leakage in Lap-LAR.[22–24] Unfortunately, we were unable to examine the relationship between conversion and leakage, as we experienced only 1 case that required conversion to OS; however, many studies have shown increased complication rates in converted cases. The major cause of conversion in Lap-LAR is a problem with rectal transection or the anastomotic process, and if the Lap-LAR is performed by an experienced laparoscopic team, there is a possibility that conversion to OS for recovery at these points may not decrease operative difficulties, and therefore, conversion does not decrease the anastomotic leakage rate. Sex is also thought to be a risk factor for anastomotic leakage. Surgery in males with a narrow pelvic cavity is demanding in OS and LS, because rectal clamping and transection are more difficult. Although sex was not a significant risk factor in univariate analyses in the present study, there is a

TABLE 2. Operative Parameters

	Leakagae (n = 6)	No. Leakage (n = 105)	P
Operative time (min)	284 (207-327)	270 (120-467)	0.6879
Blood loss (mL)	35 (8-131)	57 (1-2103)	0.5859
Combined surgery (Yes:no)	0:6	3:102	1.0000
Protective stoma (Yes:no)	1:5	22:83	1.0000
Colonic pouch (Yes:no)	0:6	4:101	1.0000
Anastomosis (Laparoscopic:direct vision)	4:2	72:33	1.0000
Conversion (Yes:no)	0:6	1:104	1.0000
No. stapler cartridges fired for rectal transection			
1	2	53	
2	3	37	
3	0	11	
4	1	4	
1:2-4	2:4	53:52	0.6788
Size of the circular stapler (mm)			
25	0	2	
29	1	57	
33	5	46	
25 + 29:33	1:5	59:46	0.0923
Year of operation			
~2007	3	44	
2008~	3	61	0.6967

Values are medians with ranges in parentheses.

TABLE 3. Multivariable Analysis of Factors Affecting Wound Infection

Independent Predictors	Odds Ratio	Confidence Intervals	P
Body mass index (kg/m^2)	1.479	1.008-2.165	0.0458
Size of the circular stapler	8.130	0.772-83.33	0.0809

possibility that this may be due to the selection bias. There is no doubt that larger multicenter studies are required to address these issues further.

Several surgical techniques for Lap-LAR have been proposed to decrease the anastomotic leakage rate. Ito et al[13] reported that vertical rectal division through a suprapubic site was useful for avoiding multiple stapler firings during laparoscopic total mesorectal excision and suggested that this method could decrease the anastomotic leakage rate. A prolapsing method using OS devices outside of the anus may also be useful to transect the rectum with a single firing under direct vision; however, a disadvantage of this method is that it is only indicated for relatively small tumors and early cancer.[25]

If an increased number of laparoscopic linear stapler firings for rectal transection is a risk factor for anastomotic leakage, multiple firings should be avoided to prevent this complication. For this purpose, transection of the rectum through a lower, miniabdominal incision using devices for OS under direct vision should be considered.[26] In our institution, this method is often used when rectal transection is technically difficult; that is, in cases of rectal retransection caused by problems with rectal anastomosis or when the surgeon is at an early stage of the learning curve. The anastomotic leakage rate in these cases compares favorably with that in cases of rectal transection under pneumoperitoneum. We note that LS is not an objective but a method and should be replaced by a more suitable method to avoid unnecessary complications.

The design of the present study was limited in that LS was not compared with OS, and the patients who had cancer at a relatively early stage, patients who have undergone preoperative chemoradiotherapy, and those who have had a bowel obstruction are not indicated for LS in our institution. Moreover, patients with severe obesity (BMI $>30\,kg/m^2$) were excluded from LS in our institution, determining risk factors for anastomotic leakage with only 6 patients might be difficult. However, considering the results of the present study, exclusion of patients with severe obesity for Lap-LAR is reasonable. The difference of BMI between the 2 groups is slight; however, we excluded patients with severe obesity (BMI $>30\,kg/m^2$) from laparoscopic resection, and if these patients had been included, the difference in BMI between the 2 groups would have been expected to be greater. It goes without saying that a prospective, multicenter, randomized clinical trial is required to demonstrate that the short-term and oncological outcomes of Lap-LAR are not inferior to those of Op-LAR; however, because of the lack of randomized clinical trial with a sufficient number of patients, we chose to analyze the safety of Lap-LAR in a single-center study, and confirmation the safety of the laparoscopic approach will require further accumulation of patients. Recently, a phase II trial to examine the technical and oncological feasibility of LS for rectal carcinoma in patients with a preoperative diagnosis of stage 0/I rectal carcinoma has been initiated under the direction of the Japan Society of Laparoscopic Colorectal Surgery, with the participation of leading hospitals in LS for colorectal carcinoma in Japan.[14] This trial represents an initial step in the evaluation of the safety of LS for rectal carcinoma.

In conclusion, LS for rectal cancer using the stapling technique can be performed safely without increasing the risk of anastomotic leakage; however, obesity was found to be a risk factor for anastomotic leakage. Appropriate patient selection is essential for LS for rectal cancer, particularly when considering Lap-LAR for an obese patient. Further analysis in a large series may facilitate the identification of further risk factors for anastomotic leakage in Lap-LAR.

REFERENCES

1. Guillou PJ, Quirke P, Thorpe H, et al. MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet*. 2005;365:1718–1726.
2. Aziz O, Constantinides V, Tekkis PP, et al. Laparoscopic versus open surgery for rectal cancer: a meta-analysis. *Ann Surg Oncol*. 2006;13:413–424.
3. Laurent C, Leblanc F, Gineste C, et al. Laparoscopic approach in surgical treatment of rectal cancer. *Br J Surg*. 2007;94:1555–1561.
4. Bianchi PP, Rosati R, Bona S, et al. Laparoscopic surgery in rectal cancer: a prospective analysis of patient survival and outcomes. *Dis Colon Rectum*. 2007;50:2047–2053.
5. Lujan J, Valero G, Hernandez Q, et al. Randomized clinical trial comparing laparoscopic and open surgery in patients with rectal cancer. *Br J Surg*. 2009;96:982–989.
6. Kim JS, Cho SY, Min BS, et al. Risk factors for anastomotic leakage after laparoscopic intracorporeal colorectal anastomosis with a double stapling technique. *J Am Coll Surg*. 2009;209:694–701.
7. Branagan G, Finnis D. Prognosis after anastomotic leakage in colorectal surgery. *Dis Colon Rectum*. 2005;2048:1021–1026.
8. Jung SH, Yu CS, Choi PW, et al. Risk factors and oncologic impact of anastomotic leakage after rectal cancer surgery. *Dis Colon Rectum*. 2008;51:902–908.
9. Peeters KC, Tollenaar RA, Marijnen CA, et al. Dutch Colorectal Cancer Group. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. *Br J Surg*. 2005;92:211–216.
10. Yeh CY, Changchien CR, Wang JY, et al. Pelvic drainage and other risk factors for leakage after elective anterior resection in rectal cancer patients: a prospective study of 978 patients. *Ann Surg*. 2005;241:9–13.
11. Lee WS, Yun SH, Roh YN, et al. Risk factors and clinical outcome for anastomotic leakage after total mesorectal excision for rectal cancer. *World J Surg*. 2008;32:1124–1129.
12. Buchs NC, Gervaz P, Secic M, et al. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. *Int J Colorectal Dis*. 2008;23:265–270.
13. Ito M, Sugito M, Kobayashi A, et al. Relationship between multiple numbers of stapler firings during rectal division and anastomotic leakage after laparoscopic rectal resection. *Int J Colorectal Dis*. 2008;23:703–707.
14. Yamamoto S, Yoshimura K, Konishi F, et al. Phase II trial to evaluate laparoscopic surgery for stage 0/I rectal carcinoma. *Jpn J Clin Oncol*. 2008;38:497–500.
15. Japanese Society for Cancer of the Colon and Rectum. *General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (in Japanese)*. Sixth Edition. Tokyo: Kanehira-Syuppan; 1998.
16. Yamamoto S, Fujita S, Akasu T, et al. A comparison of the complication rates between laparoscopic colectomy and laparoscopic low anterior resection. *Surg Endosc*. 2004;18:1447–1451.
17. Yamamoto S, Fujita S, Akasu T, et al. Safety of laparoscopic intracorporeal rectal transection with double-stapling technique anastomosis. *Surg Laparosc Endosc Percutan Tech*. 2005;15:70–74.
18. Schwandner O, Farke S, Schiedeck TH, et al. Laparoscopic colorectal surgery in obese and nonobese patients: do differences in body mass indices lead to different outcomes? *Surg Endosc*. 2004;18:1452–1456.
19. Leroy J, Ananian P, Rubino F, et al. The impact of obesity on technical feasibility and postoperative outcomes of laparoscopic left colectomy. *Ann Surg*. 2005;241:69–76.