厚生労働科学研究費補助金

がん臨床研究事業

臨床病期II・IIIの下部直腸がんに対する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

（H23-がん臨床-一般- 005）

平成23-25年度　総合研究報告書

研究代表者　　藤田　伸

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I. 総括報告書

厚生労働科学研究費補助金（がん臨床研究事業）

総合研究報告書

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

研究代表者　　藤田　伸　　栃木県立がんセンター　外来部副部長兼臨床管理部副部長

研究要旨

下部進行直腸がんの術式として我が国独自に発達してきた自律神経温存側方郭清術（側方郭清群）と世界標準術式 mesorectal excision（ME群）の治療成績を比較検討する目的で，2003年6月よりJCOG大腸がんグループの多施設共同臨床試験（参加34施設）として登録（目標登録数700例，追跡期間5年）を開始した．登録開始から7年2か月経過した2010年8月2日に701例目が登録され，登録を終了した．側方郭清群に351例、ME群に350例が登録された．この3年間で登録データ解析ならびにフォローアップを行った．短期成績では，ME群に比し側方郭清群で有意に手術時間が長く，出血量が多かった．術後早期合併症も有意差はないものの，側方郭清群に多く認められた．この結果を2011年米国臨床腫瘍学（ASCO2011）で発表し，Lancet Oncologyに論文発表した（2012. 13: 616-621）．性機能障害発生割合は，側方郭清群79.3%（23/29），ME群68.0%（17/25）と有意差はなかった．多変量解析では年齢が有意に関連する因子であった．排尿障害発生割合は，側方郭清群59.0%（207/351），ME群57.7%（202/350）と有意差はなかった．単変量ならびに多変量解析では，腫瘍部位と出血が有意に関連する因子であった．この結果をECC2013（欧州癌学会2013）で発表した．　現在，論文作成中である．

分担研究者氏名・ 所属機関名及び職名

齋藤典男・国立がんセンター東病院　病棟部長

藤井正一・横浜市立大学附属市民総合医療センター　准教授 (H23-24)

大田貢由・横浜市立大学附属市民総合医療センター　准教授　（H24-H25）

伴登宏行・石川県立中央病院　診療部長

絹笠祐介・静岡県立静岡がんセンター　部長

金光幸秀・愛知県がんセンター中央病院　医長（H23）

国立がんセンター中央病院　科長（H24-25）

小森康司・愛知県がんセンター中央病院　医長（H25）

山口高史・京都医療センター　外科医長

大植雅之・大阪府立成人病センター副部長（H23）

赤在義浩・岡山済生会総合病院　診療部長

塩澤　学・神奈川県立がんセンター　部長（H25）

A．研究目的

あき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癌の患者を対象として，国際標準手術であるmesorectal excisionの臨床的有用性を，国内標準手術である自律神経温存側方骨盤リンパ節郭清術を対照として比較評価する．

B．研究方法

JCOG大腸がん外科研究グループ48施設のうち本研究計画が各施設の倫理審査の承認が得られた34施設による多施設共同試験である．

術前画像診断および術中開腹所見にて，あきらかな遠隔転移を認めない臨床病期IIまたはIIIの下部進行癌と診断された症例をmesorectal excisionを行った後，自律神経温存側方郭清を行う群と行わない群に，術中ランダム割付し，それぞれの手術終了時に手術の妥当性評価の目的で，術中写真撮

影を行う.

Primary endpointを無再発生存期間，Secondary endpointを生存期間，局所無再発生存期間，有害事象発生割合，重篤な有害事象発生割合，手術時間，出血量，性機能障害発生割合（性機能調査票使用），排尿機能障害発生割合（術後残尿測定）とし，登録期間7年，追跡期間5年，予定登録数700例.

（倫理面への配慮）

本臨床試験計画は，研究班内で十分な検討を行い，さらに他領域の専門家の委員から構成されるJCOG臨床試験検審査委員会で審査承認を経て完成された．さらに各施設での倫理審査委員会において試験実施の妥当性について科学的，倫理的審査を受け承認されたことを確認した後，症例登録を行った.

C．研究結果

登録は2003年6月より開始し，登録開始から7年2か月経過した2010年8月2日に701例目の登録があり，登録を終了した.

側方郭清群に351例，ME群に350例登録された．性別，年齢，臨床病期，病理学的病期，占居部位に両群間に差はなかった．側方転移は，側方郭清群に26例（7.4%）に認められた．手術時間中央値は，側方郭清群360分、ME群236分で有意に側方郭清群が長かった．出血時間中央値は，側方郭清群576ml、ME群336mlで有意に側方郭清群に多かった．術後早期合併症のGrade 3, 4合併症は，側方郭清群76例（21.7%），ME群56例（16.1%）で有意差はないものの側方郭清群に多く認められた．縫合不全は，側方郭清群31例（8.9%），ME群37例（10.6%）で差は認められなかった.

性機能障害発生割合は，側方郭清群79.3%（23/29），ME群68.0%（17/25）と有意差はなかった．多変量解析では年齢が有意に関連する因子であった．排尿障害発生割合は，側方郭清群59.0%（207/351），ME群57.7%（202/350）と有意差はなかった．単変量ならびに多変量解析では，腫瘍部位と出血が有意に関連する因子であった.

D．考察

ME群に比し側方郭清群で手術時間が長く，出血量が多く，grade 3，4合併症頻度も有意差はないものの，側方郭清群に多く認められたが，側方郭清により障害されると考えられていた性機能，排尿機能は，自律神経温存側方郭清により，側方郭清非郭清と同等の機能温存が可能であることが示された.

E.結論

Secondary endpointである有害事象発生割合，手術時間，出血量においてME群の優越性がしめされたが，性機能、排尿機能は両群に有意差は認められなかった．ME群の非劣性が証明されるためには，Primary endpointである無再発生存期間が劣っていないことが実証されなければならない.

F.健康危険情報

なし

II. 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

III. 研究成果の刊行物・印刷

研究計画書（英文）

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

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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

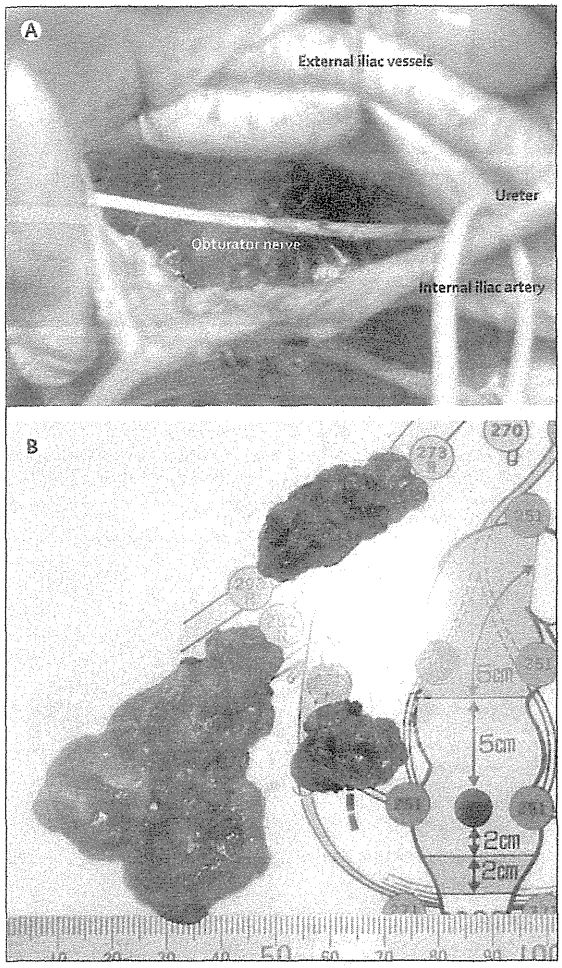

Figure 1: **Lateral lymph node dissection**
(A) The obturator fossa after lateral lymph node dissection, with the dissected fatty and connective tissues (right side). (B) Dissected fatty and connective tissues including lymph nodes.

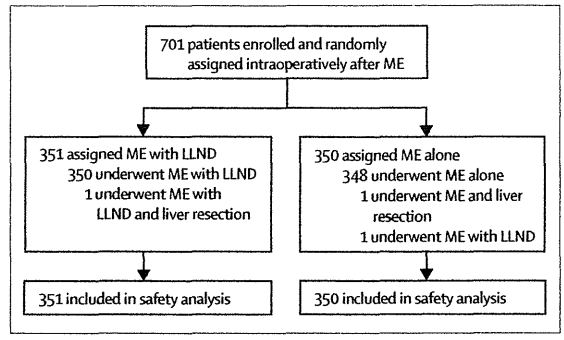

Figure 2: **Trial profile**
We did not collect data for the number of eligible patients before enrolment. ME=mesorectal excision. LLND=lateral lymph node dissection.

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 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/m²) and L-leucovorin (250 mg/m²) 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 excision 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.

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JCOG 0212

Mesorectal excision with lateral lymph node dissection versus without lateral lymph node dissection for clinical stage II, III lower rectal cancer. (JCOG0212) Protocol ver 1.6

Study Chair/ Study Coordinator
Shin Fujita
Colorectal Surgery Division, National Cancer Center.
5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
TEL 03-3542-2511 (ext) 2284
FAX 03-3542-3815
E-mail sfujita@ncc.go.jp

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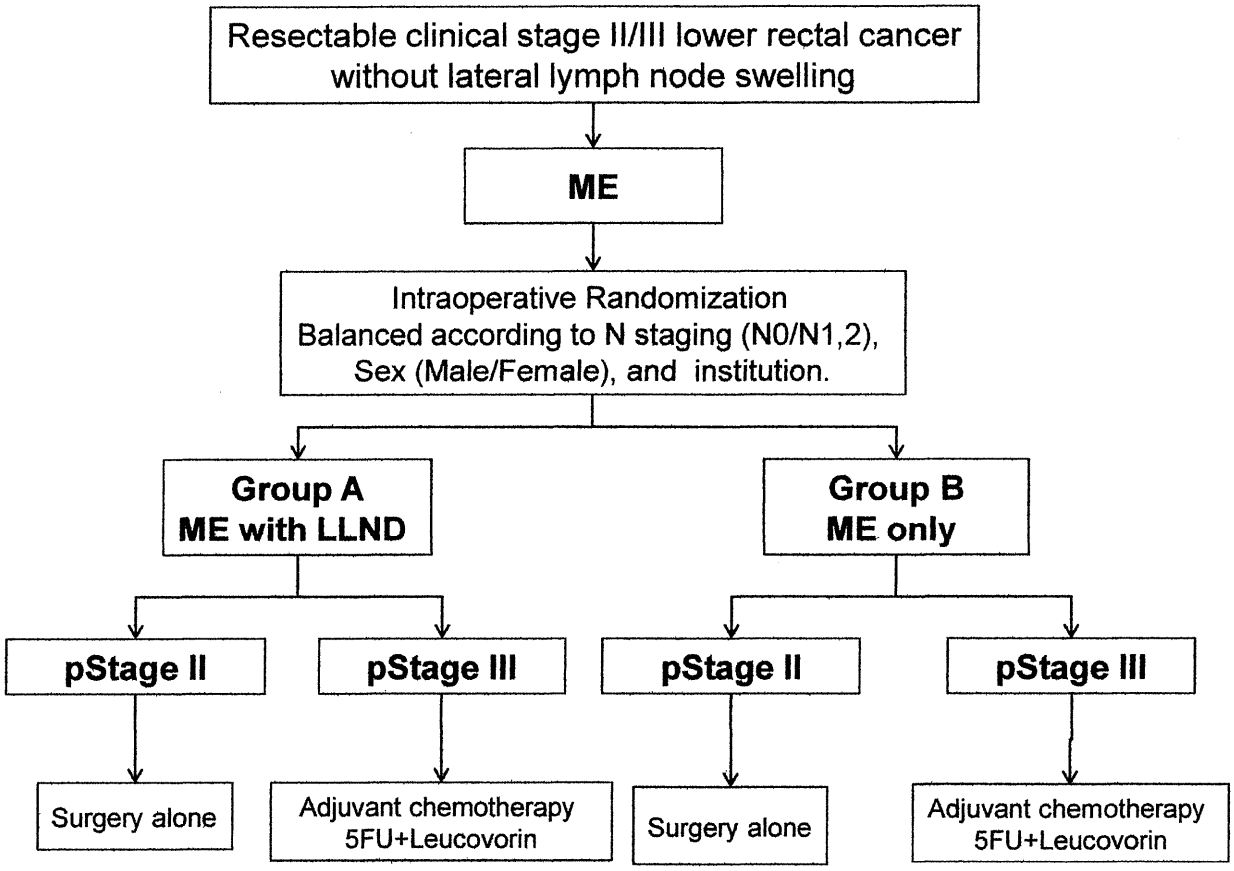
0. Summary

0.1. Shema



0.2. Objective

To evaluate the of international standard operation, mesorectal excision (ME alone) compared to Japanese standard operation, ME with lateral lymph node dissection (LLND) for clinical stage II, III lower rectal cancer without lateral lymph node swelling.

Primary endpoint: Relapse-free survival (RFS)
Secondary endpoints: Overall survival (OS), Local relapse-free survival, Incidence of adverse events, Incidence of major adverse events, Operative time, Blood loss, Incidence of sexual and urinary dysfunction

0.3. Subjects

Preoperative criteria

1. Histologically confirmed adenocarcinoma
2. Clinical stage II or III
3. Preoperative findings:
   i) Main lesion of the tumor is located at the rectum
   ii) Lower tumor margin is below the peritoneal reflection
   iii) No extramesorectal lymph node swelling:
   iv) Shorter diameter is less than 10 mm by CT scan or MRI
   v) No invasion to other organ (s)
4. Patient age is more than 20 and less than 75
5. PS: 0, 1
6. No past history of chemotherapy, pelvic surgery or radiation
7. Written informed consent

Operative criteria

8. ME is performed
9. Operative findings:
   i) Main lesion of the tumor is located at the rectum
   ii) Lower tumor margin is below the peritoneal reflection
10. R0 after the ME procedure

0.4. Treatment

After surgeons performed ME, the patients are randomized to Group A or Group B.

Group A : ME with LLND

LLND is performed preserving all the autonomic nerves. After LLND, surgical reconstruction is done.

Group B : ME only

Only surgical reconstruction is done.

Postoperative adjuvant chemotherapy

For pathological stage III (TNM classification) patients, adjuvant chemotherapy (5-FU+l-LV, RPMI regimen) is administered.

0.5. Study period and planned sample size

(1) Planned accrual period - 7years. Follow-up period - 5 years.
(2) Planned sample size - 700 cases.

Contents

1. Objective

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Primary endpoint: Relapse-free survival (RFS)
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2. Background

3.Drug Information