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　久保義郎　四国がんセンター　消化器外科医長

研究要旨　直腸癌に対する側方郭清の有用性を証明するために，ランダム化第II相比較臨床試験（JCOG0212）に参加して症例の登録を行った．当院より登録した９例の有害事象や予後について検討した．

A．研究目的

臨床的に側方リンパ節転移が疑われない下部直腸癌に対する側方郭清の意義について明らかにすること．

B．研究方法

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clinical stageII・IIIの治癒切除可能な下部直腸癌症例に対して，JCOG0212のプロトコールに定められた適格基準に従い，患者同意の上，試験登録を行った．当院より登録した９例について検討した．

（倫理面への配慮）

IRBで審査承認された文書で十分な説明を行い，文書で同意を得て登録を行った．

C．研究結果

９例の内訳は，年齢が57±11（51～75）歳，男性７例，女性２例．いずれも主占居部位はRbで腫瘍径は4.8±1.1（3.4～6.5）cmであった．手術は低位前方切除を6例，腹会陰式直腸切断術を3例に行い，リンパ節郭清は側方郭清あり（A群）が5例，側方郭清なし（B群）が4例であった．手術時間は235±57（130～296）分で，A群の方が平均で約80分長かった．出血量は727±509（100～1710）ｇで，やはりA群の方が平均で約500ml多かった．

術後入院期間は18±6（12～29）日で，A群の方が平均で約5日長かった．

組織型は，高分化型:4例，中分化型:4例，粘液癌:1例で，壁深達度はmp:2例，a1:5例，a2:2例で，リンパ節転移は4例に認め，n1:3例，n2:1例であったが，A群において側方リンパ節に転移を認めた症例はなかった．

術後10日目の残尿量が50mlを超えたのはA群の1例のみであった．術後合併症は3例に認め，骨盤内感染2例（Grade3とGrade2）と創感染1例（Grade2）で，いずれもA群であった．観察期間33±20（3～66）か月で，B群の1例に肺転移を認め，化学療法を施行中であるが，全例生存している．

D．考察

骨盤内リンパ節郭清は，我が国では側方リンパ節郭清と称され，直腸癌の手術では欠かせない手技のように行われてきた．しかし，欧米では排尿障害や性機能障害などの合併症や後遺症が多いことや骨盤リンパ節に転移があれば予後不良であるという理由で，必ずしも支持されていない．確かに，側方リンパ節郭清を行うことにより，手術時間は延長し，出血量は増え，排尿障害や性機能障害が出現しやすい傾向にある．予防的に側方郭清を行わず，術後に側方リンパ節転移が出現した際に，他に遠隔転移がなければ，手術（側方郭清）を行うのも一つの治療方針と思われる．一方，郭清することにより骨盤内局所制御および生存率改善が期待される．そこで，側方リンパ節を郭清することが，局所再発の減少や生存率の向上にどれだけ有効であるかを証明することは非常に重要なことであり，海外からも注目されている．

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

E.結論

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

F．研究発表

1．論文発表

1) Nozaki I, Kubo Y, et al: Long-term outcome after laparoscopic wedge resection for early gastric cancer. Surg Endosc. 2008. 22 : 2665-2669
2) 大田耕司,久保義郎, 他 ： 幽門側胃切除術後過食を契機とした胃破裂の1例　日本消化器外科学会雑誌　2009.　42(3) : 253-256
3) Dote H, Kubo Y, et al : Primary extranodal non-Hodgkin's lymphoma of the common bile duct manifesting as obstructive jaundice: report of a case.　Surg Today. 2009. 39(5) : 448-451.
4) 小畠誉也, 久保義郎, 他 ： 神経性摂食障害を併存した直腸癌穿孔性腹膜炎の１例.　日本外科系連合学会雑誌　2009. 34(2) : 268-271
5) 小畠誉也, 久保義郎, 他 ： ベバシズマブ療法中に発症した結腸間膜内への穿通に対し右結腸切除・１期的吻合を施行した１例.　日本消化器外科学会雑誌　2009. 42(9) : 1528-1533

2．学会発表

1) 久保義郎, 小畠誉也, 他 : 上行結腸癌に対する Surgical trunk 周辺のリンパ節郭清．第23回 四国内視鏡外科研究会（平成21年02月 徳島）
2) 久保義郎,小畠誉也,他 : 腹腔鏡補助下大腸切除術の長期予後．第109回日本外科学会（平成21年04月　福岡）
3) 久保義郎,小畠誉也,他 : 高齢者に対する大腸癌治癒切除後のサーベイランスについての検討．第64回日本消化器外科学会総会（平成21年07月　大阪）
4) 小畠誉也,久保義郎, 他 : 結腸癌切除後，ベバシズマブ投与中に来した結腸間膜内への穿通に対し，結腸切除・一期的吻合を施行した1例．第63回日本大腸肛門病学会（平成20年10月　東京）
5) 小畠誉也,久保義郎,他 : 当院における大腸癌術後SSIサーベイランスと効果　－特にIncisional SSI発生率について-．第64回日本消化器外科学会総会
(平成21年07月　大阪)
6) 土手秀昭,久保義郎,他 : 腹腔鏡大腸癌手術における合併症危険因子に関する検討．第64回日本消化器外科学会総会（平成21年07月　大阪）
7) 枝園和彦,久保義郎,他 : Stage 大腸癌に対する腹腔鏡下手術と開腹術の比較検討．第63回愛媛外科集談会（平成21年08月　松山）

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）
分担研究報告書

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

研究分担者　　白水　和雄　　久留米大学医学部外科教授

研究要旨：多施設共同臨床試験である本試験に参加し、これまでにME単独群７例、神経温存D3群5例の12例が登録された。合併症はME単独で縫合不全1例、イレウス1例を認めた．再発はME単独群に肝転移1例を認めている。局所再発はいずれの群にも認めていない。術後の機能障害では、性機能障害と一時的な排尿障害がME単独群、神経温存D3群に各1例ずつみられた。問題点は同意取得率が極めて低くなっていることである。

A．研究目的

下部直腸進行癌の約15%に側方骨盤リンパ節転移が存在する．このため，本邦において側方リンパ節郭清を予防的に施行している施設からその功罪についての報告がなされている。一方，欧米では術前放射線化学療法により局所再発が減少したとか、メタアナリシスでは側方リンパ節の予防的郭清には否定的な意見がみられる．しかしながら放射線照射による晩期合併症として、肛門機能の低下が問題となりつつある。しかし、側方リンパ節郭清の明らかなエビデンスはなく、その意義についてはいまだ不明といえる。

そこで国際標準手術のmesorectal excision（ME単独）を対照とした自律神経温存D3郭清術（神経温存D3郭清）の臨床的有用性を、多施設共同ランダム化比較試験に参加し，その有用性について検討する。

B．研究方法（研究計画書より抜粋）

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

＜エンドポイント＞

Primary endpoint: 無再発生存期間

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

＜治療方針＞

A群：ME＋神経温存D3郭清

B群：ME

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

C．倫理面への配慮（研究計画書より抜粋）

すべての研究者はヘルシンキ宣言に従って本試験を実施する。十分な説明と同意を得る（インフォームドコンセント）。登録患者の氏名は試験データセンターへ知らせることはなく、登録者の同定や照会は、登録時に発行される症例登録番号、患者イニシャル、生年月日、カルテ番号を用いて行われ，患者名など第三者が直接患者を識別できる情報がデータセンターのデータベースに登録されることはない。本試験に参加する研究者は，患者の安全と人権を損なわない限りにおいて本研究実施計画書を遵守する．有害事象の発生に対しては保険診療の範囲で適切かつ迅速な対応をとる。D．研究結果

現在までに、ME単独群７例、神経温存D3群5例の12例が登録された。ME単独群の1例に縫合不全，イレウスが1例合併症として認められた．しかしいずれも保存的に治療可能であった。その他特記すべき有害事象の発生はなかった。また，再発は局所には認められていないが，肝転移を1例認め，切除術を行った．術後の機能障害に

ついて、排便機能で頻回便が1例、一時的な排尿機能障害２例、性機能障害については術式に起因するものは例にみられた。

E. 考察

現在のところ，側方リンパ節郭清に伴う障害やデメリットは考えられず，予後に関しては両群で局所再発は認められていない。症例数の少なさから結論は導けないが，側方郭清を行うことによるデメリットはみられていない。しかし当施設における問題点
として、登録症例数が少数で予定登録数を大幅に下回っている。その理由として、比較臨床試験における患者さんの試験参加の同意が得にくいことがあげられる。また，施設の特異性もあり高度進行例や高齢者が多いことも挙げられる。

F. 結論

現時点では、我々の施設における症例からは、治療成績に関しては妥当であると思
われる。術後機能に関しても大きな差はないようであるが、もっと詳細な検討が必要
と考える。

G．知的所有権の取得状況

1．特許取得　　特記なし

２．実用新案登録　特記なし

H. 研究発表

１．論文発表

1) Ogata Y, Sasatomi T, Akagi Y, Ishibashi N, Mori S, Shirouzu K：Dosage escalation study of S-1 and irinotecan in metronomic chemotherapy against advanced colorectal cancer.Kurume Med J. 2009:56 1-7

2) Shirouzu K, Ogata Y:Histopathologic tumor spread in very low rectal cancer treated with abdominoperineal resection.Dis Colon Rectum. 2009 :52;1887-1894

3) Torigoe S, Ogata Y, Matono K, Shirouzu K :Molecular mechanisms of sequence-dependent antitumor effects of SN-38 and 5-fluorouracil combination therapy against colon cancer cells.Anticancer Res.2009.29:2083-2089

4) Ogata Y, Murakami H, Sasatomi T, Ishibashi N, Mori S, Ushijima M, Akagi Y, Shirouzu K. Elevated preoperative serum carcinoembrionic antigen level may be an effective indicator for needing adjuvant chemotherapy after potentially curative resection of stage II colon cancer. J Surg Oncol. 2009.99;65-70

5) 赤木由人、白水和雄、衣笠哲史、石橋生哉、白土一太郎.括約筋を伴う肛門温存手術（開腹）の術後成績　－遠隔成績とQOL－.消化器外科. 2009. 32(7).1187-1194

6) 赤木由人、白水和雄、衣笠哲史：下部直腸癌の治療：括約筋切除による肛門温存手術　－intersphincteric resection(ISR), external sphincteric resection(ESR). 外科.2009. 71(2)157-162.

7)衣笠哲史，赤木由人、白水和雄，消化器癌の診断・治療　直腸癌　－診断と治療法の選択. 消化器外科，2009. 32(5):919-924

8) 森　眞二郎，石橋生哉，赤木由人，緒方裕，白水和雄.直腸癌治療　最近の進歩と動向　下部直腸癌に対する肛門機能温存手術としてのESRその理論的根拠.臨床外科.2009.64(3).339-343

9) 溝部智亮，白水和雄、赤木由人:大腸癌の病理診断の問題点　大腸癌の病理組織　診断の記載、その基準１）.大腸癌Frontier.2009.2(2);118－124

２．学会発表

１）赤木由人，白水和雄，衣笠哲史，ほか
下部直腸癌に対する肛門括約筋切除・肛門温存手術の術後成績と術中の留意点
第109回日本外科学会定期学術集会　シンポ

２）赤木由人,白水和雄、溝部智亮、ほか
第7版大腸癌取扱い規約における検討課題－大腸癌の壁外浸潤とリンパ節転移個数について

第5回日本消化管学会総会学術集会　(2/12-13．東京)コアシンポ

３）赤木由人, 白水和雄, 衣笠哲史,ほか
再発からみた下部直腸癌に対する括約筋切除・肛門温存手術の検討（パネル）
第64回日本大腸肛門病学会学術集会

４）吉田武史、赤木由人, 白水和雄,ほか
直腸癌における側方伸展の実態
第64回日本大腸肛門病学会学術集会

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, Yamamoto S, Akasu T, Moriya Y.	Risk factors of lateral pelvic lymph node metastasis in advanced rectal cancer.	Int J Colorectal Dis	24	1085-1090	2009
Kusters M, van de Velde CJ, Beets-Tan RG, Akasu T, Fujita S, Yamamoto S, Moriya,Y.	Patterns of Local Recurrence in Rectal Cancer: A Single-Center Experience.	Ann Surg Oncol	16	289-296	2009
Ishiguro S, Akasu T, Fujita S, Yamamoto S, Kusters M, Moriya Y	Pelvic exenteration for clinical T4 rectal cancer: oncologic outcome in 93 patients at a single institution over a 30-year period	Surgery	145(2)	189-195	2009
藤田伸	【直腸癌治療の新知見】JCOG0212(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).	大腸癌Frontier	2(3)	217-220	2009
藤田伸、山本聖一郎、赤須孝之、森谷宜皓	進行下部直腸癌の治療成績と補助放射線治療の必要性.	癌の臨床	55(2)	101-105	2009
Ito M, Saito N, Sugito M, Kobayashi A, Nishizawa Y, Tsunoda Y.	Analysis of Clinical Factors Associated with Anal Function after Intersphincteric Resection for Very Low Rectal Cancer.	Dis Colon & Rectum	52(1)	64-70	2009
Koda K, Yasuda H, Hirano A, Kosugi C, Suzuki M, Yamazaki M, Tezuka T, Higuchi R, Tsuchiya H, Saito N.	Evaluation of postoperative damage to anal sphincter/levator ani muscles with three-dimensional vector manometry after sphincter-preserving operation for rectal cancer.	J Am Coll Surg.	208(3)	362-367	2009

Saito N, Sugito M, Ito M, Kobayashi A, Nishizawa Y, Yoneyama Y, Nishizawa Y, Minagawa N.	Oncologic outcome of intersphincteric resection for very low rectal cancer.	Word J Surg	33(8)	1750-1756	2009
小林宏寿、榎本雅之、樋口哲郎、安野正道、植竹宏之、飯田聡、石川敏昭、石黒めぐみ、杉原健二	下部直腸癌：大腸癌治療ガイドラインの解説	外科	71(2)	115-119	2009
樋口哲郎、杉原健一	消化器癌：診断・治療のすべて下部消化管（結腸・直腸）癌	消化器外科	32(5)	546-551	2009
Shoichi Fujii, Hiroshi Shimada, Shigeru Yamagishi, Mitsuyoshi Ota, Yasushi Ichikawa, Chikara Kunisaki, Hideyuki Ike, Shigeo Ohki	Surgical Strategy for Local Recurrence after Resection of Rectal Cancer	Hepato-gastroenterology	56	667-671	2009
Noura S, Ohue M, Seki Y, Tanaka K, Motoori M, Kishi K, Miyashiro I, Ohigashi H, Yano M, Ishikawa O, Miyamoto Y.	Feasibility of a Lateral Region Sentinel Node Biopsy of Lower Rectal Cancer Guided by Indocyanine Green Using a Near-Infrared Camera System.	Ann Surg Oncol	17	144-51	2009
Shirouzu K, Ogata Y.	Histopathologic tumor spread in very low rectal cancer treated with abdominoperineal resection.	Dis Colon Rectum.	52	1887-1894	2009

IV. 研究成果の刊行物・印刷

Int J Colorectal Dis (2009) 24:1085–1090
DOI 10.1007/s00384-009-0704-4

ORIGINAL ARTICLE

Risk factors of lateral pelvic lymph node metastasis in advanced rectal cancer

Shin Fujita · Seiichiro Yamamoto · Takayuki Akasu · Yoshihiro Moriya

Accepted: 1 April 2009 / Published online: 23 April 2009

Abstract
Background To clarify the risk factors of lateral pelvic lymph node (LPLN) metastasis of rectal cancer, we examined associations between LPLN status and clinicopathological factors including LPLN status diagnosed by computed tomography (CT).
Methods We reviewed a total of 210 patients with advanced rectal cancer, of which the lower margin was located at or below the peritoneal reflection, who underwent preoperative CT with 5-mm-thick sections and lateral pelvic lymph node dissection at the National Cancer Center Hospital between February 1998 and March 2006.
Results Forty-seven patients (22.4%) had LPLN metastasis. Multivariate analysis showed that LPLN status diagnosed by CT, pathological regional lymph node status, tumor location, and tumor differentiation were significant risk factors for LPLN metastasis. Among 45 patients with well-differentiated adenocarcinoma who were LPLN-negative and in whom CT had found no regional lymph node metastasis, none had LPLN metastasis. On the other hand, among 13 patients with moderate or less differentiated lower rectal adenocarcinoma who were LPLN-positive and in whom CT had revealed regional lymph node metastasis, 12 (92.3%) had LPLN metastasis.
Conclusions LPLN status diagnosed by CT, pathological regional LN status, tumor location, and tumor differentiation are significant risk factors for LPLN metastasis. Using these factors, patients can be classified as having a low or high risk of LPLN metastasis.

S. Fujita (✉) · S. Yamamoto · T. Akasu · Y. Moriya
Department of Surgery, National Cancer Center Hospital,
1-1 Tukiji 5-chome, Chuo-ku,
Tokyo 104-0045, Japan
e-mail: sfujita@ncc.go.jp

Keywords Rectal cancer · Lymph node dissection · Lateral pelvic lymph node · Risk factor

Introduction

Lateral pelvic lymph node dissection (LPLD) is widely performed for advanced lower rectal cancer in Japan, and the incidence of lateral pelvic lymph node (LPLN) metastasis has been demonstrated to be 15–30% [1–3]. In spite of the relatively high incidence of LPLN metastasis, most surgeons, except for those in Japan, do not perform LPLD, and instead adjuvant chemoradiotherapy and total mesorectal excision (TME) have become the standard therapy for rectal cancer. In order to clarify the indications for, and the possible benefits of, LPLD, a retrospective multicenter study was conducted in Japan, and this demonstrated that LPLD was effective for local control, and might be indicated for patients with T3–T4 lower rectal cancer [3]. The 5-year survival rate of patients with LPLN metastasis is about 40% [1–3], which is comparable with that of patients with resectable liver or lung metastasis. From this viewpoint, LPLN metastasis should be classified as distant metastasis, and resected if at all possible. Kim et al. demonstrated that LPLN metastasis is a major cause of local recurrence in patients who receive preoperative chemoradiotherapy without LPLD [4]. This indicates that LPLD should not be neglected even in the era of neo-adjuvant therapy for rectal cancer. Therefore, accurate preoperative diagnosis of pelvic lateral node metastasis is important. Although Yano et al. showed that conventional CT accurately predicted LPLN status [5], validation studies are necessary. In this study, therefore, we examined the association between clinicopathological factors, including CT diagnosis of lymph nodes and LPLN status, and

selected high-risk factors for LPLN metastasis, enabling classification of patients according to LPLN metastasis risk.

Patients and methods

Patients

We reviewed a total of 210 patients with advanced rectal cancer, of which the lower margin was located at or below the peritoneal reflection, who underwent preoperative computed tomography (CT) with 5-mm-thick sections and lateral pelvic lymph node dissection (LPLD) at the National Cancer Center Hospital between February 1998 and March 2006. All the patients underwent TME or tumor-specific mesorectal excision. Pelvic autonomic nerves were preserved completely or partially in 187 patients (89%). The patients were followed up at 3-monthly intervals for 2 years, and at 6-monthly intervals thereafter. Tumor markers were examined at every patient visit. CT of the liver and lung or abdominal ultrasonography with chest X-ray was performed at least every 6 months. Colonoscopy was performed twice within 5 years after surgery. Median follow-up time was 3.8 years. Six patients received preoperative or postoperative radiotherapy. Pathological stage III patients were given adjuvant chemotherapy.

Diagnosis

All the patients underwent preoperative CT with 5-mm-thick sections using intravenous contrast media, and lymph nodes more than 5 mm in diameter were considered positive (Fig. 1). A radiologist interpreted the CT images preoperatively, and one author (SF) interpreted the images postoperatively. The author finally determined the lymph node status. Lymph nodes were classified according to their location. Lymph nodes in the lateral pelvic area outside the pelvic plexus and hypogastric nerves along the internal ileac, external ileac, common ileac vessels, and in the obturator space were considered LPLN. Patients with LPLN metastasis were classified as stage III in this study. Lymph nodes in the area lying along the inferior mesenteric vessels were considered regional lymph nodes. Tumor size and annularity were determined preoperatively by colonoscopy, barium enema, or virtual colonoscopy. Depth of invasion (T) and tumor location were determined preoperatively by CT or magnetic resonance imaging (MRI), and tumor location was finally confirmed during surgery. All the cancers were biopsied and a pathological diagnosis obtained before surgery.

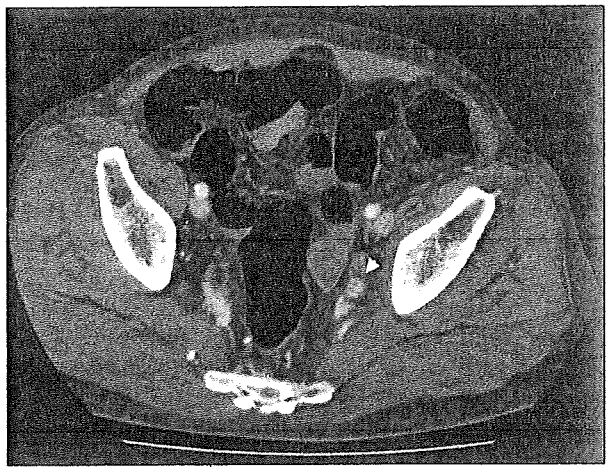

Fig. 1 Representative lateral pelvic lymph node swelling detected by CT. Left lateral pelvic lymph node swelling is seen (*arrowhead*). The lymph node diameter is 10 mm. This patient underwent lateral pelvic lymph node dissection and metastasis was found by pathological examination 201 × 285 mm

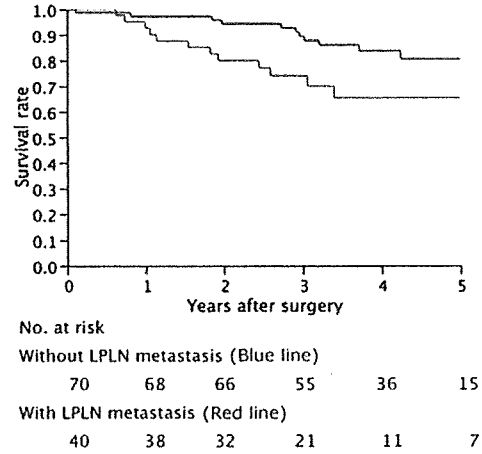

Fig. 2 Survival curves for patients with stage III rectal cancer with and without LPLN metastasis. 201×285 mm

Statistical analysis

Statistical analysis was carried out by the chi-squared test. Survival rates were calculated by the Kaplan–Meier method, and survival curves were compared by the log-rank test. A logistic regression model was used for multivariate analysis. Data differences between groups were considered statistically significant at $P<0.05$.

Results

Incidence of LPLN metastasis and prognosis

Among the 210 patients, 47 (22.4%) had LPLN metastasis. The survival curves for stage III patients are shown in

Fig. 2. The survival rate of stage III patients with LPLN metastasis was significantly poorer than that of stage III patients without LPLN metastasis (P=0.014). Although the follow-up period was insufficient, the estimated 5-year survival rate for the patients with LPLN metastasis was 54%. The incidence of local recurrence in stage III patients with LPLN metastasis was 22.5% (9/40) and that in stage III patients without LPLN metastasis was 10.0% (7/70). Although the incidence of local recurrence in stage III patients with LPLN metastasis was higher than that in stage III patients without LPLN metastasis, the difference was not statistically significant (P=0.074).

Table 1 Incidence of LPLN metastasis and preoperative clinicopathological factors

	LPLN metastasis positive (n=47)	LPLN metastasis negative (n=163)	P
Age (years)			0.749
<60	25	91	
≥60	22	72	
Sex			0.336
Male	30	116	
Female	17	47	
CEA (ng/ml)			0.072
≤5	25	110	
>5	22	53	
Tumor location			0.018
Ra	3	35	
Rb	44	128	
Clinical T			0.616
T1, 2	4	14	
T3	31	118	
T4	12	31	
Regional LN status			0.014
Negative	13	78	
Positive	34	85	
LPLN status			<0.001
Negative	18	147	
Positive	29	16	
Tumor size (cm)			0.673
≤5	22	82	
>5	25	81	
Annularity			0.197
≤2/3	23	97	
>2/3	24	66	
Tumor differentiation			<0.001
Well	14	92	
Moderate	26	66	
Poor, mucinous	7	5	

Ra tumor center located above the peritoneal reflection; *Rb* tumor center located below the peritoneal reflection

Table 2 Incidence of LPLN metastasis and postoperative clinicopathological factors

	LPLN metastasis positive (n=47)	LPLN metastasis negative (n=163)	P
Pathological T			0.058
T1, 2	4	38	
T3	40	111	
T4	3	14	
Pathological regional LN status			<0.001
Negative	7	84	
Positive	40	79	
Lymphatic invasion			<0.001
Negative	17	116	
Positive	30	47	
Venous invasion			0.002
Negative	11	80	
Positive	36	83	
Perineural invasion			0.001
Negative	27	131	
Positive	20	31	
Tumor budding			0.073
Negative	15	76	
Positive	32	87	

Associations of LPLN metastasis with clinicopathological factors

Associations of LPLN metastasis with preoperative clinicopathological factors are shown in Table 1. LPLN status and regional lymph node status diagnosed by CT, tumor location, and tumor differentiation were significantly associated with LPLN metastasis. Associations of LPLN metastasis with postoperative clinicopathological factors are shown in Table 2. Pathological regional lymph node status, lymphatic invasion, venous invasion, and perineural invasion were significantly associated with LPLN metastasis. Multivariate analysis showed that LPLN status diagnosed by CT, pathological regional lymph node status, tumor location, and tumor differentiation were significant risk factors for LPLN metastasis (Table 3).

Incidence of LPLN metastasis according to risk factors

In order to identify patients at low risk and high risk for LPLN metastasis preoperatively, patients were classified into four groups according to the significant risk factors of LPLN metastasis. Although pathological regional lymph node status was a significant risk factor for LPLN metastasis, regional lymph node status diagnosed by CT

Table 3 Multivariate analysis of clinicopathological factors associated with LPLN metastasis

	Odds ratio (95% C.I.)	*P*
LPLN status (positive/negative)	28.00 (9.19–102.46)	<0.001
Pathological regional lymph node status (positive/negative)	7.21 (2.19–28.08)	0.002
Tumor location (Rb/Ra)	12.56 (2.35–107.87)	0.009
Tumor differentiation (moderate, others/well)	4.05 (1.47–12.23)	0.009

C.I. confidence interval

was used for the classification, because pathological lymph node status was not clarified preoperatively. Tumors located at Ra (tumor center located above the peritoneal reflection) and tumors located at Rb (tumor center located below the peritoneal reflection) were analyzed separately, and other risk factors were used for the classification. Group I was the group with no risk factors. Group II was the group with negative LPLN status diagnosed by CT but with at least one of the other two risk factors. Group III was the group with positive LPLN status diagnosed by CT but without at least one of the other two risk factors. Group IV was the group with all of the risk factors. Incidences of LPLN metastasis according to this classification are shown in Table 4. Irrespective of tumor location, no patients (0/45) had LPLN metastasis in group I. On the other hand, in group IV, 50.0% (2/4) of the patients with Ra tumors and 92.3% (12/13) of the patients with Rb tumors had LPLN metastasis. When pathological regional lymph node status was used for this classification instead of regional lymph node status diagnosed by CT, 75 patients were classified into group I or group II without pathological lymph node metastasis, and these patients also had no LPLN metastasis.

Discussion

The incidence of LPLN metastasis in patients with advanced lower rectal cancer is 15–30% [1–3]. Although the prognosis of patients with LPLN metastasis is poor, the 5-year survival rate is 40%, being comparable to that of patients with resectable liver or lung metastasis. Sugihara et al. estimated that LPLD would improve the 5-year survival rate of patients with T3–T4 lower rectal cancer by 8% [3]. Therefore, LPLD for patients with LPLN metastasis should be considered. Because accurate diagnosis of LPLN metastasis is difficult, LPLD is routinely performed in Japan for stage II or III rectal cancer located at or below the peritoneal reflection. However, it is still unproved whether LPLD is necessary for patients without LPLN metastasis. In order to acquire level 1 evidence, we are currently performing a clinical trial to compare TME alone with TME plus LPLD for rectal cancer patients without LPLN metastasis (JCOG0212) (ClinicalTrials.gov Identifier NCT00190541). Because accurate preoperative diagnosis of LPLN metastasis is important for treatment of lower rectal cancer, we selected four high-risk factors for LPLN metastasis and were able to estimate the incidence of LPLN metastasis using a combination of these factors. Patients without LN metastasis diagnosed by CT and with well-differentiated adenocarcinoma have no LPLN metastasis, and would not require LPLD. On the other hand, more than 80% of patients with LPLN metastasis diagnosed by CT and with moderate or less differentiated adenocarcinoma have LPLN metastasis, and should undergo LPLD. Therefore, our classification is thought to be useful for determining the indications for LPLD.

Late adverse effects of LPLD are sexual and urinary dysfunction [6]. Recently, TME plus LPLD with autonomic nerve preservation has been performed in Japan, and the incidences of sexual and urinary dysfunction following this treatment have been comparable to those after TME [7–9]. Because the oncological outcome of TME plus LPLD with autonomic nerve preservation is also comparable to that without autonomic nerve preservation [10], the former has become the standard therapy for rectal cancer in Japan. However, when patients have LPLN metastasis or if the tumor has invaded the autonomic nerves, nerve preservation is not possible. Therefore, the autonomic nerves were not preserved in 11% of the patients in this series.

Sex, tumor location, depth of invasion, mesorectal LN status, tumor differentiation, and tumor size are reported to be factors associated with LPLN metastasis [3, 11]. Although our findings were comparable, these previous reports did not take into account LPLN status diagnosed by

Table 4 Incidence of LPLN metastasis according to risk factors

	Incidence of LPLN metastasis
Ra (*n*=38)	
Group I (*n*=7)	0.0% (0/7)
Group II (*n*=27)	3.7% (1/27)
Group III (*n*=0)	–
Group IV (*n*=4)	50.0% (2/4)
Rb (*n*=172)	
Group I (*n*=38)	0.0% (0/38)
Group II (*n*=93)	18.3% (17/93)
Group III (*n*=28)	53.6% (15/28)
Group IV (*n*=13)	92.3% (12/13)

CT. As demonstrated in the present study, LPLN status diagnosed by CT was the most important risk factor associated with LPLN status. Therefore, accurate diagnostic imaging is important. In this study, the sensitivity, specificity, and accuracy of LPLN status diagnosis using CT were 62%, 90%, and 84%, respectively. Arii et al. demonstrated that the accuracy of LPLN status diagnosis using MRI was 83%, whereas that using CT was 77% [12]. Matsuoka et al. reported that MRI diagnosis of LPLN status had 67% sensitivity, 83% specificity, and 78% accuracy [13]. These results were comparable to ours. On the other hand, Yano et al. showed that CT diagnosis of LPLN status had 95% sensitivity, 94% specificity, and 95% accuracy [5]. However, because the number of patients they examined was small (n=39) and patients who did not undergo LPLD were excluded, the results were not directly comparable with other studies. Quadros et al. reported the preliminary results of LPLN detection using lymphoscintigraphy and blue dye [14]. However, the sensitivity and specificity were 17% and 79%, respectively. Tada et al. demonstrated the effectiveness of ultrasonographic examination for determining LPLN status, the sensitivity, specificity, and accuracy being 75%, 94%, and 93%, respectively [15]. Although this result was excellent, there were some problems and limitations; for example, obturator space lymph nodes were sometimes overlooked, and the use of ultrasonography in obese patients was difficult.

A meta-analysis of mesenteric lymph node diagnosis has indicated that the sensitivity and specificity of CT, MRI, and endoscopic ultrasonography are compatible [16]. Matsuoka et al. also demonstrated that multidetector-row CT was as equally effective as MRI for local staging of rectal cancer [17]. We preliminarily examined the capacity of MRI for diagnosis of lymph node status, and found that its sensitivity was higher and its specificity lower than that of CT, with roughly comparable accuracy. The use of new criteria for lymph node status instead of size [18], or a new MRI contrast agent [19], has been reported to yield better sensitivity and specificity for MRI diagnosis of mesenteric lymph nodes. However, further examinations will be necessary to establish an optimal approach for diagnosis of lymph node status using imaging modalities.

If patients with LPLN metastasis do not undergo LPLD, they would suffer LPLN or local recurrence. Kim et al. showed that adjuvant preoperative radiotherapy without LPLD was unable to control LPLN metastasis and local recurrence [4]: lateral pelvic recurrence was observed in 2.3%, 12.5%, and 68.8% of patients with LPLN measuring <5, 5–10, and≥10 mm, respectively, determined by MRI. On the other hand, Quadros et al. showed that patients who received preoperative adjuvant chemoradiotherapy did not develop LPLN metastasis [14]. A small randomized study that compared adjuvant radiotherapy with LPLD also suggested that LPLD was unnecessary for patients who underwent preoperative radiotherapy [20]. Syk et al. demonstrated that LPLN metastasis was not a major cause of local recurrence of rectal cancer [21]. A comparative study demonstrated that the local recurrence rate in Korean patients who received adjuvant chemoradiotherapy without LPLD was lower than that in Japanese patients who underwent LPLD alone [22]. Moreover, the local recurrence rate in patients with LPLN metastasis has been reported to be 25.6% [3]. In our study, the local recurrence rate in patients with LPLN metastasis was 22.5%, which was significantly higher than that in patients without LPLN metastasis. These facts suggest that LPLD alone is not sufficient for local control in patients with LPLN metastasis. Therefore, a combination of adjuvant radiotherapy with LPLD is thought to be important for treatment of advanced rectal cancer, and a randomized study is required to determine whether LPLD is necessary for patients with LPLN metastasis receiving preoperative chemoradiotherapy.

In conclusion, LPLN status diagnosed by CT, pathological regional LN status, tumor location, and tumor differentiation are significant risk factors for LPLN metastasis. Using these factors, patients can be classified as having a low or a high risk of LPLN metastasis. This classification suggests that LPLD should be considered in patients with advanced lower rectal cancer.

Funding Grant-in-Aid for Scientific Research from the Ministry of Health, Labor and Welfare of Japan.

References

1. Fujita S, Yamamoto S, Akasu T, Moriya Y (2003) Lateral pelvic lymph node dissection for advanced lower rectal cancer. Br J Surg 90:1580–1585
2. Ueno M, Oya M, Azekura K, Yamaguchi T, Muto T (2005) Incidence and prognostic significance of lateral lymph node metastasis in patients with advanced low rectal cancer. Br J Surg 92:756–763
3. Sugihara K, Kobayashi H, Kato T, Mori T, Mochizuki H, Kameoka S, Shirouzu K, Muto T (2006) Indication and benefit of pelvic sidewall dissection for rectal cancer. Dis Colon Rectum 49:1663–1672
4. Kim TH, Jeong SY, Choi DH, Kim DY, Jung KH, Moon SH, Chang HJ, Lim SB, Choi HS, Park JG (2008) Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. Ann Surg Oncol 15:729–737
5. Yano H, Saito Y, Takeshita E, Miyake O, Ishizuka N (2007) Prediction of lateral pelvic node involvement in low rectal cancer by conventional computed tomography. Br J Surg 94:1014–1019
6. Hojo K, Sawada T, Moriya Y (1989) 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 32:128–133

7. Moriya Y, Sugihara K, Akasu T, Fujita S (1995) Nerve-sparing surgery with lateral node dissection for advanced lower rectal cancer. Eur J Cancer 31A:1229–1232
8. Sugihara K, Moriya Y, Akasu T, Fujita S (1996) Pelvic autonomic nerve preservation for patients with rectal carcinoma. Oncologic and functional outcome. Cancer 78:1871–1880
9. Havenga K, Enker WE, McDermott K, Cohen AM, Minsky BD, Guillem J (1996) Male and female sexual and urinary function after total mesorectal excision with autonomic nerve preservation for carcinoma of the rectum. J Am Coll Surg 182:495–502
10. Moriya Y, Sugihara K, Akasu T, Fujita S (1995) Patterns of recurrence after nerve-sparing surgery for rectal adenocarcinoma with special reference to loco-regional recurrence. Dis Colon Rectum 38:1162–1168
11. Ueno H, Mochizuki H, Hashiguchi Y, Ishiguro M, Miyoshi M, Kajiwara Y, Sato T, Shimazaki H, Hase K (2007) Potential prognostic benefit of lateral pelvic node dissection for rectal cancer located below the peritoneal reflection. Ann Surg 245:80–87
12. Arii K, Takifuji K, Yokoyama S, Matsuda K, Higashiguchi T, Tominaga T, Oku Y, Tani M, Yamaue H (2006) Preoperative evaluation of pelvic lateral lymph node of patients with lower rectal cancer: comparison study of MR imaging and CT in 53 patients. Langenbecks Arch Surg 391:449–454
13. Matsuoka H, Nakamura A, Masaki T, Sugiyama M, Nitatori T, Ohkura Y, Sakamoto A, Atomi Y (2007) Optimal diagnostic criteria for lateral pelvic lymph node metastasis in rectal carcinoma. Anticancer Res 27:3529–3533
14. Quadros CA, Lopes A, Araujo I, Fahel F, Bacellar MS, Dias CS (2006) Retroperitoneal and lateral pelvic lymphadenectomy mapped by lymphoscintigraphy and blue dye for rectal adenocarcinoma staging: preliminary results. Ann Surg Oncol 13:1617–1621
15. Tada M, Endo M (1995) Ultrasonographic examination for lateral lymphatic spread and local recurrence of rectal cancer. Preoperative detection and evaluation. Dis Colon Rectum 38:1047–1052
16. Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J (2004) Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging—a meta-analysis. Radiology 232:773–783
17. Matsuoka H, Nakamura A, Masaki T, Sugiyama M, Takahara T, Hachiya J, Atomi Y (2003) A prospective comparison between multidetector-row computed tomography and magnetic resonance imaging in the preoperative evaluation of rectal carcinoma. Am J Surg 185:556–559
18. Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, Dallimore NS, Williams GT (2003) Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology 227:371–377
19. Koh DM, Brown G, Temple L, Raja A, Toomey P, Bett N, Norman AR, Husband JE (2004) Rectal cancer: mesorectal lymph nodes at MR imaging with USPIO versus histopathologic findings—initial observations. Radiology 231:91–99
20. Nagawa H, Muto T, Sunouchi K, Higuchi Y, Tsurita G, Watanabe T, Sawada T (2001) Randomized, controlled trial of lateral node dissection vs. nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. Dis Colon Rectum 44:1274–1280
21. Syk E, Torkzad MR, Blomqvist L, Ljungqvist O, Glimelius B (2006) Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer. Br J Surg 93:113–119
22. Kim JC, Takahashi K, Yu CS, Kim HC, Kim TW, Ryu MH, Kim JH, Mori T (2007) Comparative outcome between chemoradiotherapy and lateral pelvic lymph node dissection following total mesorectal excision in rectal cancer. Ann Surg 246:754–762

Ann Surg Oncol (2009) 16:289–296
DOI 10.1245/s10434-008-0223-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Patterns of Local Recurrence in Rectal Cancer: A Single-Center Experience

M. Kusters[1,2], C. J. H. van de Velde[1], R. G. H. Beets-Tan[3], T. Akasu[4], S. Fujida[4], S. Yamamoto[4], and Y. Moriya[4]
[1]Department of Surgery, Leiden University Medical Center, K6-R, P.O. Box 9600, 2300 RC Leiden, The Netherlands; [2]Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands; [3]Department of Radiology, University Hospital Maastricht, Maastricht, The Netherlands; [4]Department of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan

ABSTRACT A cohort of patients operated at the National Cancer Center Hospital in Tokyo for rectal carcinoma, at or below the peritoneal reflection, was reviewed retrospectively. The purpose was to study the risk factors for local relapse and the patterns of local recurrence. Three hundred fifty-one patients operated between 1993 and 2002 for rectal carcinoma, at or below the peritoneal reflection, were analyzed. One hundred forty-five patients, with preoperatively staged T1 or T2 tumors without suspected lymph nodes, underwent total mesorectal excision (TME). Lateral lymph node dissection (LLND) was performed in suspected T3 or T4 disease, or when positive lymph nodes were seen; 73 patients received unilateral LLND and 133 patients received bilateral LLND. Of the 351 patients 6.6% developed local recurrence after 5 years. TME only resulted in 0.8% 5-year local recurrence. In lymph-node-positive patients, 33% of the unilateral LLND group had local relapse, significantly more ($p = 0.04$) than in the bilateral LLND group with 14% local recurrence. Local recurrence in the lateral, presacral, perineal, and anastomotic subsites was lower in the bilateral LLND group as compared with in the unilateral LLND group. We conclude that, in selected patients, surgery without LLND has a very low local recurrence rate. Bilateral LLND is more effective in reducing the chance of local recurrence than unilateral LLND. Either surgical approach, with or without LLND, requires reliable imaging during work-up.

First Received: 13 August 2008;
Published Online: 18 November 2008

C. J. H. van de Velde
e-mail: c.j.h.van_de_velde@lumc.nl

For rectal cancer, surgery is the principal treatment in order to cure. Total mesorectal excision (TME) removes the primary tumor with its surrounding mesorectum as an intact package, preventing residual tumor cells in the mesorectum from developing into local recurrence.[1,2] In advanced lesions neoadjuvant (chemo)radiotherapy can downstage tumors, but good surgical quality is still essential in order to achieve total clearance of tumor cells.[3]

The Japanese concept of surgical treatment of rectal cancer has evolved from anatomical studies in which three lymphatic flow routes were identified.[4,5] The upper route is along the superior rectal artery to the inferior mesenteric artery; the lateral route reaches from the middle rectal artery to the internal iliac and obturator basins; and the downward route extends to the inguinal lymph nodes. The upper and lateral routes were shown to be the main two routes of rectal cancer spread, with the peritoneal reflection as the limitation between the two lymphatic areas.[6] Consequently, lateral lymph node dissection (LLND) was developed in Japan in order to resect the tumor with the primary locoregional lymph node basins beyond the mesorectal plane.[7] LLND has resulted in better survival and lower recurrence rates than conventional surgery.[8,9]

A problem is that the lateral lymph node routes are anatomically close to the pelvic autonomic nerve plexus, requiring challenging surgery to preserve these during LLND.[10] In order to prevent damage to autonomic nerves, nowadays case-oriented policy is practised in Japan, adopting LLND only in advanced disease at or below the peritoneal reflection.

The aim of this study is to evaluate the treatment of rectal cancer between 1993 and 2002 at the National Cancer Center Hospital (NCCH), looking at patterns of local recurrence and the risk factors for local recurrence.

PATIENTS AND METHODS

Patients

From 1993 to 2002, 923 patients were operated for confirmed primary adenocarcinoma of the rectum at the National Cancer Center Hospital (NCCH) in Tokyo. Surgery was performed according to the guidelines of the Japanese Research Society for Cancer of the Colon and Rectum.[11,12] The rectum was defined as located below the lower border of the second sacral vertebra. The peritoneal reflection is the most important landmark in defining the location of the tumor, and *low* rectal carcinoma is defined as a tumor of which the major part is located at or below the reflection.[13]

For this analysis the following patients were excluded: metastasis at the time of surgery ($n = 134$) and in situ carcinoma ($n = 22$). Of the remaining 767 patients, only patients with rectal carcinoma at or below the peritoneal refection were selected, resulting in 360 patients.

Neoadjuvant chemotherapy was given to some patients with suspicion of stage T4 disease ($n = 3$) in other hospitals, before referral to the NCCH. Neoadjuvant radiotherapy was not routinely given, so no patients received preoperative radiotherapy. Sometimes in the case of positive lymph nodes, adjuvant radiotherapy ($n = 5$) or chemoradiotherapy ($n = 1$) was given. The nine patients who received neoadjuvant chemotherapy and adjuvant (chemo)radiation were excluded, leaving 351 patients for analysis.

Methods

Until 2002 preoperative evaluation at the NCCH consisted of computed tomography (CT) imaging and endoscopic ultrasonography for all patients. Based on preoperative imaging and intraoperative findings, standard total mesorectal excision (TME) was performed in T1 or T2 stage disease without suspected lymph nodes. Lateral lymph node dissection (LLND) was added to TME in stage T3 or T4 rectal cancer at or below the peritoneal reflection, or when positive mesorectal lymph nodes were suspected. Unilateral LLND was performed when the tumor was located lateral in the low rectum, bilateral LLND when the tumor was located centrally. When the lateral lymph nodes were 1 cm or larger on preoperative imaging or intraoperative findings, bilateral extended lymph node dissection was performed, consisting of dissection of the complete internal iliac artery and the autonomic nerve system. When there was no suspicion on positive lateral lymph nodes, autonomic nerve preservation (ANP) was carried out.

Accurate documentation of lymph node status and localization is obtained because all lymph nodes are harvested and recorded from the fresh specimen. The definition of mesorectal lymph nodes is pararectal location or in the direction of the mesentery. Lateral lymph nodes are located along the iliac or obturator arteries.

Follow-up of all patients consisted of thorax, abdominal, and pelvic CT imaging every 6 months. Median follow-up of patients alive was 7.9 years.

All patients who developed local recurrence, defined as any recurrence of rectal cancer in the lesser pelvis, were identified. Local recurrence was diagnosed clinically, radiologically or histologically.

For all locally recurrent patients the available preoperative images and the images at the time of discovery of the local recurrence were retrieved. A specialized oncologic radiologist (R.G.H.B.-T.) reviewed the images. Examining the images, the site of the local recurrence was determined. The sites were classified into the following regions: lateral, presacral, perineal, anterior or anastomotic. The same borders for the respective sites were used as defined by Roels et al.[14] When no images were available, the location of recurrence was classified using the radiology reports and clinical data. In one patient insufficient information was provided to determine the location of recurrence with certainty.

Statistical Analysis

Statistical analysis was performed using the SPSS package (SPSS 12.0 for Windows; SPSS Inc., Chicago, IL) and R version 2.5.1. *T*-tests and chi-square tests were used to compare individual variables. Survival and cumulative recurrence incidences were estimated using the Kaplan–Meier method. Differences between the groups were assessed using the log-rank test. All *p*-values were two-sided and considered statistically significant at 0.05 or less. For local recurrence, cumulative incidences were calculated accounting for death as competing risk.[15] Similarly, cumulative incidences were calculated for subsite of local recurrence, with death and other types of local recurrence as competing risks, and for cancer-specific survival, with death due to other causes as competing risk. Multivariate analyses of local recurrence and overall survival were performed by first testing the effect of covariates in a univariate Cox regression. Covariates with trend-significant effects (p-value < 0.10) were then selected for multivariate Cox regression. The following variables were studied for local recurrence and overall survival: age, sex, operative procedure, degree of lateral lymphadenectomy, T-stage, mesorectal lymph node N-stage, lateral lymph node positivity, maximum tumor diameter, differentiation, and autonomic nerve preservation.

RESULTS

Clinicopathology

Patient characteristics and treatment details are listed in Table 1. Of the 351 studied patients, 145 had standard TME surgery without LLND, 73 underwent unilateral LLND, and 133 patients received bilateral LLND. LLND was performed in significantly younger patients and more often in combination with a non-sphincter-saving procedure, compared with patients who had not undergone an LLND. The tumors in the LLND patients had higher T- and N-stages and were significantly larger. Comparing the clinicopathological characteristics between the unilateral and the bilateral LLND, no significant differences were found, except that unilateral LLND was more often combined with autonomic nerve preservation (ANP).

Mean lymph node harvest was 21 LNs in standard TME (Table 1). After unilateral LLND the mean number of recovered LNs was 38, and after bilateral LLND this was 45 ($p = 0.004$).

Table 2 shows the outcomes of lymph node involvement for all 351 patients, stratified by T-stage. Overall lymph node involvement was 42%, and lateral lymph node

TABLE 1 Clinicopathological characteristics

	No LLND ($n = 145$)	Unilateral LLND ($n = 73$)	Bilateral LLND ($n = 133$)	p*	p**
Sex ratio (M:F)	96:49 (66:34)	47:26 (64:36)	86:47 (65:35)	0.95	0.97
Mean age (years)	61	57	57	0.03	0.98
Operation					
Sphincter-saving	112 (77)	36 (49)	63 (47)		
Not sphincter-saving	33 (23)	37 (51)	70 (53)	<0.001	0.79
Adjuvant chemotherapy					
No	139 (96)	67 (92)	121 (91)		
Yes	6 (4)	6 (8)	12 (9)	0.24	0.85
T-stage					
T1	52 (36)	3 (4)	3 (2)		
T2	47 (32)	27 (37)	37 (28)		
T3	46 (32)	40 (55)	83 (62)		
T4	0 (0)	3 (4)	10 (8)	<0.001	0.37
Meso LN positive					
0	102 (70)	44 (60)	64 (48)		
1–3	30 (21)	19 (26)	39 (29)		
>4	13 (9)	10 (14)	30 (23)	0.003	0.28
Lat LN positive					
No	–	62 (85)	109 (82)		
Yes	–	11 (15)	24 (18)	–	0.59
ANP					
No	3 (2)	2 (3)	17 (13)		
Yes	142 (98)	71 (97)	116 (87)	<0.001	0.02
Differentiation					
Well	75 (52)	27 (37)	50 (38)		
Moderate	67 (46)	44 (60)	75 (56)		
Poor	2 (2)	2 (3)	8 (6)	0.18	0.29
Tumor size					
0–4 cm	106 (73)	31 (42)	42 (32)		
>4 cm	39 (27)	42 (58)	91 (68)	<0.001	0.12
Diss. LN (mean)	21	38	45	<0.001	0.004

Values in parentheses are percentages

* p value between no LLND, unilateral LLND, and bilateral LLND

** p value between unilateral LLND and bilateral LLND

Meso mesorectal; *Lat* lateral; *LN* lymph node; *ANP* autonomic nerve preservation

TABLE 2 Lateral lymph node dissection and lymph node status, stratified by T-stage

Stage	LLND		LNI		LNI	LLNI
T1: 58	No LLND	52 (90%)	N0	47	8/58 = 14%	1/58 = 2%
			Upper pos	5		
	LLND	6 (10%)	N0	3		
			Upper pos, lat neg	2		
			Upper neg, lat pos	0		
			Upper pos, lat pos	1		
T2: 111	No LLND	47 (42%)	N0	33	32/111 = 29%	7/111 = 6%
			Upper pos	14		
	LLND	64 (58%)	N0	46		
			Upper pos, lat neg	11		
			Upper neg, lat pos	2		
			Upper pos, lat pos	5		
T3: 169	No LLND	46 (27%)	N0	22	97/169 = 57%	19/169 = 11%
			Upper pos	24		
	LLND	123 (73%)	N0	50		
			Upper pos, lat neg	54		
			Upper neg, lat pos	5		
			Upper pos, lat pos	14		
T4: 14	No LLND	0 (0%)	N0	–	12/14 = 86%	8/14 = 57%
			Upper pos	–		
	LLND	14 (100%)	N0	1		
			Upper pos, lat neg	4		
			Upper neg, lat pos	0		
			Upper pos, lat pos	8		
Total: 351		207/351 = 59%*			149/351 = 42%	35/351 = 10%

LLND lateral lymph node dissection; *LNI* lymph node involvement (upper and lateral lymph nodes); *LLNI* lateral lymph node involvement; Upper, upper lymph nodes; *Lat* lateral lymph nodes; *pos* positive; *neg* negative

* Percentage of patients submitted to LLND

involvement was 10%. Jump metastases (mesorectal lymph nodes negative and lateral lymph nodes positive) occurred in 3% (7/207) of the patients with LLND.

Local Recurrence

At time of last follow-up 23 of the total of 351 patients had developed local recurrence (6.6% 5-year local recurrence rate). In the patients who had not undergone LLND, only one patient (0.8%) had local recurrence at the site of the anastomosis. In the unilateral LLND group, 12 of the 73 patients (5-year 15.4%) had local relapse. This was more than in the bilateral LLND group, with 10 of 133 local recurrences (5-year 8.3%). In N+ patients (Fig. 1), the difference between the uni- and bilateral LLND (32.8% versus 14.2%, respectively) was significant ($p = 0.04$).

In multivariate analysis (Table 3) including uni- and bilateral LLND patients, lateral lymphadenectomy, mesorectal lymph node N-stage, and lateral lymph node positivity were independent risk factors for local recurrence. Compared with patients with bilateral LLND the relative risk for local recurrence was 4.0 for unilateral LLND patients.

Table 4 reports the sites of the local recurrences for the uni- and bilateral LLND groups. The rate of lateral recurrence in the unilateral LLND patients was 5.6%, and in the bilateral LLND patients was 3.3%. It was noticed that the three patients who developed lateral local recurrence on the ipsilateral side after unilateral LLND had lower lymph node harvest (mean 28 LNs) than the patients who developed no lateral recurrence after unilateral LLND (mean 38 LNs). However, the number of patients is too low to draw any firm conclusion from this finding.

Distant Recurrence and Survival

At local recurrence diagnosis 40% of the unilateral LLND patients and 60% of the bilateral LLND patients had distant metastases. One year after local recurrence diagnoses these figures were 70% and 80% in the uni- and bilateral LLND patients, respectively.

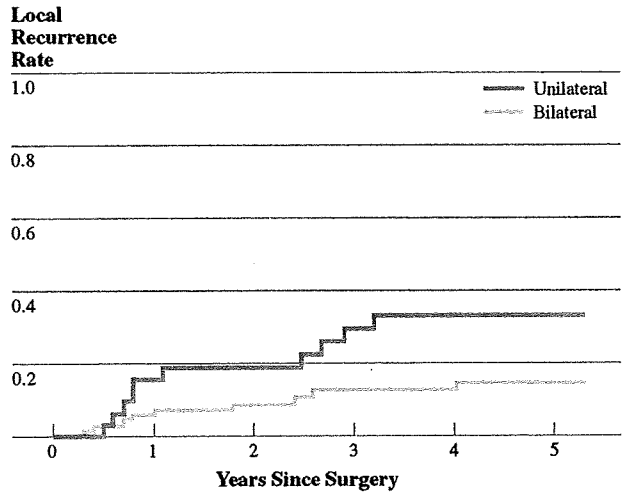

FIG. 1 Local recurrence in N+ patients

Figure 2 shows the survival curves of the TME-only, and uni- and bilateral LLND patients. Overall 5-year survival was 89% for patients who had standard TME. Five-year overall survival in the unilateral LLND group was 78%, which did not differ significantly from the bilateral LLND group (77%) ($p = 0.37$).

The multivariate Cox regression analysis, when including the uni- and bilateral LLND groups, identified T-stage, mesorectal lymph node N-stage and lateral lymph node positivity as independent factors for death risk.

Two years after local recurrence diagnosis 37% of the unilateral LLND patients was still alive, as compared with 60% of the bilateral LLND patients. The number of patients is however too low to conclude significant better survival for bilateral LLND patients.

TABLE 3 Multivariate analysis for local recurrence

Variable	HR	95% CI	*p*
Lateral dissection			0.003
Unilateral	1.00		
Bilateral	0.25	0.10–0.64	
T-stage			0.09
T1 + T2	1.00		
T3 + T4	2.99	0.84–10.73	
N-stage mesorectal LN			0.008
0 pos	1.00		
1–3 pos	2.71	0.75–9.85	
> 4 pos	7.22	2.01–25.94	
Lateral LN status			0.007
Negative	1.00		
Positive	3.53	1.41–8.85	

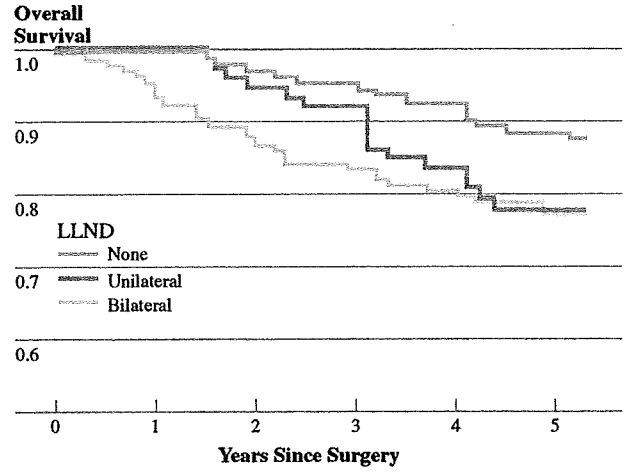

FIG. 2 Overall survival in all patients

TABLE 4 Sites of local recurrence

Site of local recurrence	All patients			Only N+ patients		
	Unilateral LLND ($n = 73$)	Bilateral LLND ($n = 133$)	*p*	Unilateral LLND ($n = 32$)	Bilateral LLND ($n = 74$)	*p*
Lateral	5 (5.6)	4 (3.3)		4 (13.2)	3 (4.6)	
Ipsilateral	*3 (3.4)*			*3 (9.9)*		
Contralateral	*2 (2.2)*			*1 (3.3)*		
Presacral	2 (2.8)	0 (0)		2 (6.7)	0 (0)	
Perineal	2 (2.8)	2 (1.7)		1 (3.1)	2 (3.4)	
Anterior	0 (0)	1 (0.9)		0 (0)	1 (1.8)	
Anastomotic	3 (4.2)	2 (1.6)		3 (9.8)	2 (3.0)	
Unknown	0 (0)	1 (0.8)		0 (0)	1 (1.4)	
Total	12	10		10	9	
5-Year LR rate	15.4%	8.3%	0.06	32.8%	14.2%	0.04

Values in parentheses are the 5-year local recurrence rates per subsite