図1 左閉鎖腔の郭清状況

よる50%の骨盤内再発リスクが減少すること，5年生存率が9%向上することを示した。

〔適 応〕

Rb，pMPではガイドラインで9%，当院[5]でも7%の転移を認めている。術前の深達度診断が確実でないことも含め，RbではMPから側方リンパ節郭清の適応としている。Rabではリンパ節転移頻度からSS，Aが適応。Raにとどまるものは側方転移は認められるが，他の遠隔転移再発が多くなるなど郭清効果が認められず，適応としていない。

3) 腸管軸方向

(1) 口側

口側の腸管傍リンパ節は腫瘍口側縁から10cm切除が腸管傍リンパ節の完全郭清とされ，従来と変わらない。血流の関係からもS状結腸最終枝領域まで切除することになる。対象症例では口側腸管傍リンパ節転移は腫瘍直下；179/1090例(16%)，口側0～5cm；130/1090例(12%)，口側5～10cm；67/1090例(6.2%)の頻度であった。口側の10cm切除は行うべきである。

(2) 肛門側

①壁内進展

肛門側壁内進展はほとんどが2cm以内であり，それ以上のものは他の進展因子を伴い，肛門側腸管を十分切除するだけでは根治性が得られない。

②間膜内リンパ節

さらに郭清として重要なことは肛門側腸間膜内リンパ節転移を遺残させないことでTME(total mesorectal excision)の本来の目的である。『大腸癌取扱い規約』では郭清対象となる肛門側腸管傍リンパ節の範囲は腫瘍肛門側3cm，Rbでは2cmとされた。われわれのデータでも肛門側間膜内リンパ節転移は，2cm以内19/1090例(1.7%)，2.1～4cm3/1090例(0.3%)と非常に少ない。むしろ，腹膜反転部以下では直腸間膜の構造が変化することを認識して切除距離を確保する。間膜は背側では薄くなり，上直腸動脈が2分岐から3分岐し腹側方に回り込んでくる。骨盤神経叢との剝離，Denonvilliers筋膜の認識(腫瘍の位置により本筋膜を切除側に入れるかどうかで剝離の容易さが異なってくる)，腹側でのいわゆる副中直腸動脈(下膀胱あるいは前立腺動脈との連絡枝)を認識して切離することが重要となる。

側方リンパ節郭清手技

『大腸癌取扱い規約』では片側の側方郭清はD2とされる。両側側方リンパ節転移は約10%に認められ，腫瘍の偏在で側方リンパ節転移が片側にとどまっているとは限らないので，われわれも常に両側側方郭清を行う。転移部位は263d，263p，283，273，280，293の順に頻度が多く，系統的な郭清が基本である。側方リンパ節転移例の5年生存率は約40%前後である。郭清効果を向上させるため，術中転移が判明すれば同側の内腸骨動静脈の合併切除，自律神経切除を行い，さらに術後は化学療法以外，体外照射も加える。

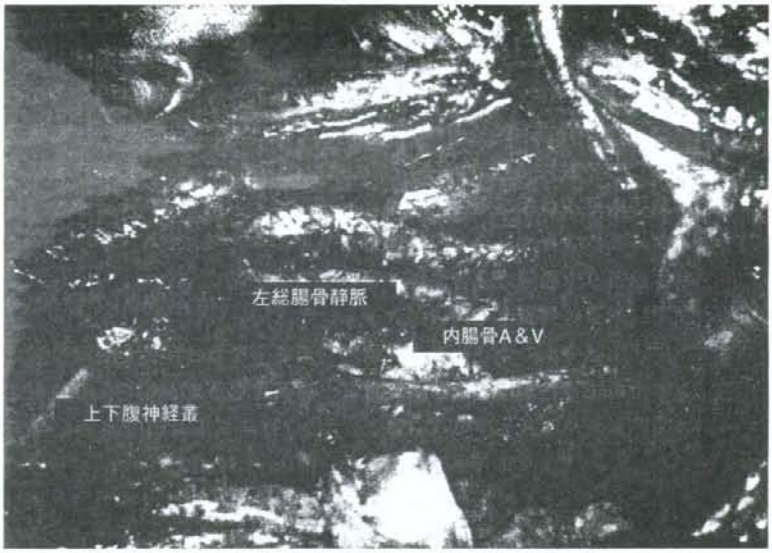
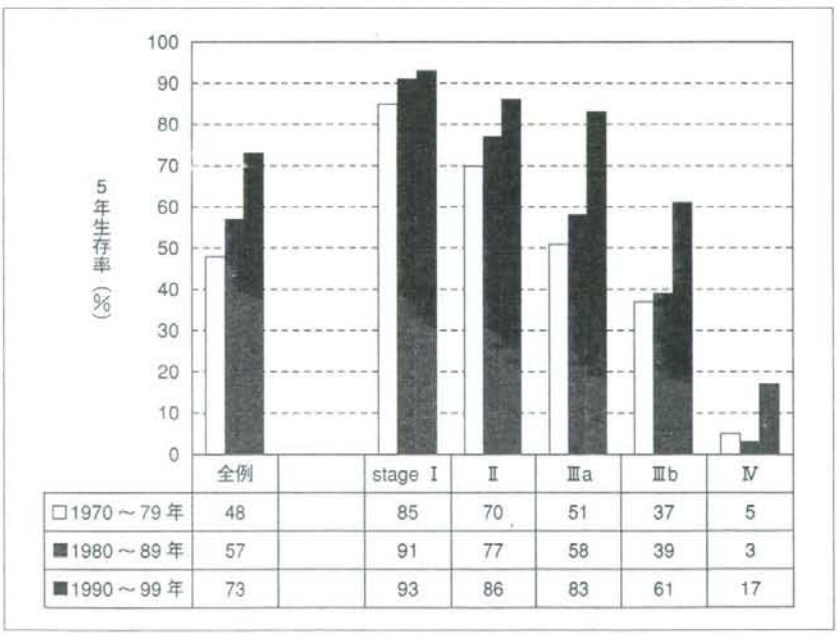


図2　左腸骨血管周囲リンパ節郭清状況



	全例		stage Ⅰ	Ⅱ	Ⅲa	Ⅲb	Ⅳ
□1970～79年	48		85	70	51	37	5
■1980～89年	57		91	77	58	39	3
■1990～99年	73		93	86	83	61	17

図3　直腸癌5年生存率の推移

A.　側方リンパ節郭清の手技の手順

(1)　截石位，Trendelenburg体位

(2)　術者は患者の左に立つ(左側郭清時は右に立つ)

(3)　開腹は正中切開

(4)　まず，後腹膜下筋膜上で自律神経を温存し，直腸切除，切断を行う

(5)　次に後腹膜下筋膜を切開し，自律神経を剝離

(6)　腸骨血管と尿管下腹筋膜間の剝離

(7)　総腸骨血管周囲，大動脈分岐部リンパ節の郭清

(8)　腹膜外アプローチにて閉鎖腔から膀胱外側の郭清(図1；閉鎖腔および下膀胱動静脈を外側から郭清)

(9)　内側から内腸骨リンパ節の郭清(図2；下腹神経を温存，

左総腸骨から内外腸骨血管周囲の郭清後)

(10) 骨盤神経叢外側と下膀胱動静脈の間で内腸骨末梢リンパ節の郭清

(11) ドレナージ・閉腹

D2郭清かD3郭清か

大腸癌研究会で行われている全国大腸癌登録の結果(第66回大腸癌研究会，固武医師による発表)では，進行癌においてはD2とD3の間には有意差があり，D3郭清の生存成績が優れていた。当院でも図3のごとく，とくにstage Ⅲでは経時的に生存率の改善が認められた。照射，化学療法の内容，適応は変わっておらず，大きな要因はリンパ節郭清の徹底と遠隔転移の切除であると判断しており，進行癌はD3郭清を基本とする。

まとめ

直腸癌治療における手術手技の役割はいまだに大きい。一人でも多くの患者を大腸癌から治癒させるために，手術侵襲の軽減，機能温存を考慮しつつ，少しでも根治性を高める努力を外科医は惜しんではならない。適切なリンパ節郭清はその根幹である。

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大腸癌の補助化学療法と今後外挿されるべき海外のエビデンス

濱口哲弥

stage IIIの結腸癌の術後補助化学療法の標準治療は，フルオロウラシル＋ホリナートカルシウム療法であったが，近年，オキサリプラチンの有用性が示され，海外ではFOLFOX療法が標準治療とされている．海外エビデンスの外挿には手術成績や病理の質の差を考慮する必要がある．

最新のエビデンス

まず経口薬のエビデンスについて述べる．転移性大腸癌において静注フルオロウラシル＋ホリナートカルシウム療法と経口薬テガフール・ウラシル＋ホリナートカルシウム，カペシタビンを比較した臨床試験において経口薬が静注療法と同等であると示されたことから，術後補助化学療法における経口薬の臨床的有用性が期待された．stage II/III結腸癌(47％/53％)を対象としてテガフール・ウラシル＋ホリナートカルシウム療法とフルオロウラシル＋ホリナートカルシウム療法とのランダム化比較試験を行い(NSABP C-06)[1]，生存期間(HR 1.014，95％CI 0.847～1.190)，無病生存期間(HR 1.004，95％CI 0.847～1.190)およびgrade 3，4の有害事象発生割合やQOLもほぼ同等であり，利便性でテガフール・ウラシル＋ホリナートカルシウム療法のほうが良好であるとの報告がなされた．また，stage III結腸癌を対象としたカペシタビンとフルオロウラシル＋ホリナートカルシウム療法とのランダム化比較試験(X-ACT)[2]において，無再発生存期間(HR 0.87，95％CI 0.75～1.00)，生存期間(HR 0.84，95％CI 0.69～1.01)は同等であり，有害事象では手足症候群の発生割合がカペシタビン群で多かったのに対して，ほかのgrade 3，4の有害事象発生割合はカペシタビンのほうが少なかった．現時点では術後補助化学療法における経口薬とイリノテカン，あるいはオキサリプラチン併用療法のエビデンスはない．

イリノテカンのエビデンスは，stage III結腸癌に対するIFL療法とフルオロウラシル＋ホリナートカルシウム療法との比較試験(CALGB C 89803)[3]の結果が報告され，IFL群の無再発生存期間，全生存期間における改善はみられず，好中球減少などの有害事象発生割合および治療関連死亡率がフルオロウラシル＋ホリナートカルシウム群に比べ有意に高かった．また，FOLFIRI療法とLV 5 FU 2療法と比較した2つのランダム化試験(ACCORD 2およびPETACC-3)の結果も報告されたが，いずれもFOLFIRI療法の有用性を示すことはできなかった．以上より，現時点では術後補助化学療法においてイリノテカンを使用することは推奨されない．

オキサリプラチンに関するエビデンスは，stage II/III結腸癌(40％/60％)を対象として**FOLFOX 4療法**とLV 5 FU 2療法とのランダム化比較試験(MOSAIC)[4]を行い，primary endpointである無病生存期間(HR 0.77，95％CI 0.65～0.91，p＝0.002)で優れており，stage別のsubset解析でもstage IIIではオキサリプラチンを加える意義が高いことが示された．しかし，FOLFOX 4群ではgrade 3の蓄積神経毒性が12.4％に出現し治療終了18カ月後においてもgrade 3の神経毒性が0.5％みられたと報告されている．また，stage II/III結腸癌(28％/62％)を対象とした**FLOX療法**とフルオロウラシル＋ホリナートカルシウム療法とのランダム化比較試験(NSABP C-07)[5]を行い，

用語解説——FOLFOX 4療法

ホリナートカルシウム200 mg/m²(l-LV 100 mg/m²)とオキサリプラチン85 mg/m²を2時間かけて点滴静注する．ホリナートカルシウム点滴終了後にフルオロウラシル400 mg/m²を3分以内に静注するとともにフルオロウラシル600 mg/m²を22時間かけて持続投与する．これを2日間連続して行い2週間毎に繰り返す．オキサリプラチン85 mg/m²はday 1にホリナートカルシウムとともに2時間かけて点滴静注する．これを12回投与する．

用語解説——FLOX療法

ホリナートカルシウム500 mg/m²(l-LV 250 mg/m²)を2時間かけて点滴静注する．フルオロウラシル500 mg/m²はホリナートカルシウム投与開始1時間後に3分以内に静注する．ホリナートカルシウムは2時間かけて投与する．これを1週毎に6回繰り返した後，2週間休薬する．これにオキサリプラチン85 mg/m²を1，3，5週目に投与する．これを1クールとして3クール投与する．

それぞれの3年無病生存割合は77％，72％とFLOX群で有意に良好であると報告した．これらオキサリプラチン併用療法の2つの試験結果から，現時点ではオキサリプラチン併用療法がstage Ⅲ結腸癌に対する国際標準療法といえる．しかし最近MOSAIC試験の6年生存率が公表され，FOLFOX 4群とLV 5 FU 2群ではその差はわずか2.6％であった．stage別ではstage Ⅱでは差はなく，stage ⅢではHRで0.80(95％CI 0.66～0.98，p＝0.029)と有意ではあったが6年生存率の差は4.4％(73.0％vs. 68.6％)であった．この生存率4.4％の差とFOLFOX 4による末梢神経障害や高額な治療費とのバランスは熟慮すべき問題である．

日本の現状

これまで十分なエビデンスがないなかで経口薬中心の治療が行われてきた．日本では，1970年代より手術単独を対照群とする比較試験が行われてきたが，結腸癌では術後補助化学療法の有用性を示した試験は皆無であった．その理由として，転移再発例では有効性が認められていないような少量投与法が採用されていたこと，試験デザインや管理運営法が不十分であったことなどが挙げられている．1996～2001年まで症例集積が行われたNSAS-CC試験(stage Ⅲ結腸癌・直腸癌を対象とした手術単独と術後テガフール・ウラシルの比較)では，結腸癌での予定症例数が500例であったものの335例と十分な症例集積がなされず，また主要評価項目である5年無再発生存率では手術単独で69.6％，テガフール・ウラシル群で71.3％とここでも術後補助化学療法の有用性を検証するには至らなかった．この試験での手術単独群の5年生存率が76.7％と，MOSAIC試験におけるstage ⅢのFOLFOX 4群とほぼ同等であったことは注目に値する．このような国内外の差は，おそらく手術の質のみならずリンパ節転移陽性を判断する病理の質の差が存在するためであろう．一方，日本臨床腫瘍研究グループ(JCOG)において，stage Ⅲの結腸癌を対象にフルオロウラシル＋ホリナートカルシウム療法とテガフール・ウラシル＋ホリナートカルシウム療法との比較試験が行われ，2006年11月に1,100例の登録が終了したところであり，国内最大規模の本試験の結果が待たれるところである．この試験により静注療法と経口薬との同等性の検証だけではなく，国内専門施設における3年無再発生存率や5年生存率などの成績も知ることができる．また，カペシタビンは国内でも2007年12月にX-ACTの試験結果をもとに大腸癌術後補助化学療法への適応拡大が承認された．また，オキサリプラチンは術後補助化学療法に対して保険承認されていない．

今後の方向性

海外では抗VEGF抗体であるベバシズマブや抗EGFR抗体であるセツキシマブの有用性を検討するための臨床試験が進行中である．国内ではこれら海外の臨床試験に参加することにより新規薬剤の承認を海外に後れを取らないようにしようとする一方で，国内でも大腸癌では十分なエビデンスのないS-1の有用性やオキサリプラチン併用療法の是非を検討する大規模臨床試験が計画されている．

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関連事項

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

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

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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.

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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.

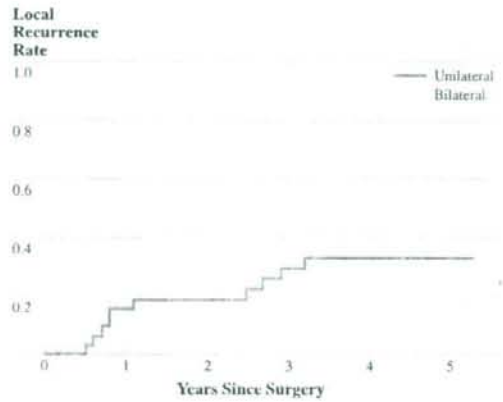

FIG. 1 Local recurrence in N+ patients

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	

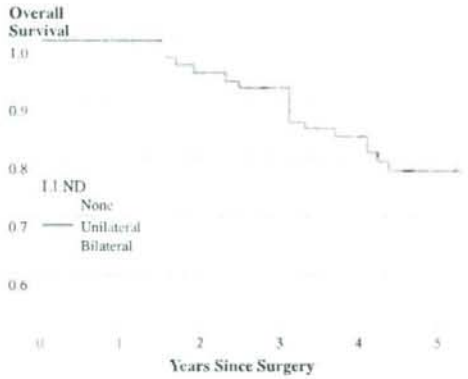

FIG. 2 Overall survival in all patients

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

DISCUSSION

Lateral lymph node dissection (LLND) was introduced in Japan in the 1970s and results in good survival and low local recurrence rates.[7–9] Since approximately 1984 several forms of nerve-sparing techniques, combined with LLND, have been developed. Bilateral and even unilateral complete autonomic nerve preservation (ANP) combined with LLND often maintains urinary function, but reports vary about the results in sexual function.[16–20] In the many decades of LLND surgery in Japan constant evaluation has taken place with the purpose of preventing overtreatment and minimizing morbidity.[21] Nowadays the policy in many Japanese hospitals is highly case-oriented, adapting the degree of surgical resection and ANP to the extent of cancer spread.[22] Whereas in the 1970s and 1980s in the National Cancer Center Hospital (NCCH) in Tokyo the standard procedure was to perform bilateral LLND in case of advanced rectal cancer, lately also unilateral LLND has been performed. The purpose of this study was to evaluate the treatment between 1993 and 2002 at the National Cancer Center Hospital for rectal carcinoma, at or below the peritoneal reflection, looking at the patterns of local recurrence and the risk factors for local recurrence. To our knowledge, there are no published results of unilateral lymph node dissection in rectal carcinoma.

The results of this study show 5-year local recurrence rate of 6.6% in rectal cancer at or below the peritoneal reflection by Japanese surgery. This primarily surgical approach compares favorably with results in Western countries, where neoadjuvant treatment is adopted as the standard in order to reduce local recurrence rates. Therefore, the Japanese concept of removing the lateral basins of lymph nodes spread can be considered successful. However, some questions still remain to be answered. The etiology of locally recurrent disease is not completely understood yet.

This study, although retrospective, provides further evidence of disease outside the TME envelope in higher-stage tumors. Bilateral LLND (5-year local recurrence rate 14%) resulted in better local control than unilateral LLND (5-year LR rate 33%) in N+ patients. Persistent disease in lateral lymph nodes that is left behind may account for some of the local recurrences, as would occur in standard TME surgery. However in that case, it would be expected that most of the recurrences would occur originating in this lateral basin. In this study we noted that only a part of the local recurrences was present in the lateral side walls. Most of the recurrences could not be explained by the anatomical position of the lateral lymph nodes. One can only speculate about other mechanisms of how tumor cells seed into the surgical resection volume. Maybe removal of the lateral lymph nodes also removes (microscopic) tumor cells which are in transit in the lateral lymph flow route, which could otherwise leak back into the surgical wound. This would explain why unilateral dissection is inferior to bilateral dissection, having more local recurrence in also the presacral, perineal, and anastomotic subsite, not only the lateral.

The rationale behind the unilateral LLND is that the contralateral autonomic nervous system stays untouched, decreasing the chance of autonomic nerve injury. Studies report that, after LLND with nerve-sparing surgery, urinary function is maintained. Between 50% and 100% of males are sexually active, however with compromised ejaculation.[16,18,19,23] This is ascribed to traction and injury to nerves during the mobilization and electrocautery required for LLND.[18] Unfortunately we have no data on urinary and sexual function of this cohort, being unable to report on the results after unilateral LLND with nerve preservation. Therefore, the question of whether functional results are truly better remains unanswered.

The tumors of the patients who had TME without LLND were smaller and less advanced compared with those of LLND patients. This better staging is reflected in better survival. That only one patient who had standard TME surgery had local relapse (5-year local recurrence 0.8%) is striking. The selection for low-risk disease by pre- and intraoperative evaluation has obviously been accurate. Interesting however, is that pathology (Tables 1 and 2) showed that about 30% of the patients operated by TME had T3-stage or N-positive disease. Pathology seems to filter out more metastatic lymph nodes than preoperative imaging, but these (micro)metastases obviously have no oncologic consequences. Jump metastases (mesorectal negative, lateral positive) occurred in only 3% of the LLND patients, thus when mesorectal lymph nodes are unsuspected, risk for lateral lymph node recurrence is very low.

Preoperative evaluation in advanced disease is difficult. In this study local recurrence developed on the contralateral side after unilateral lymph node dissection, while these contralateral lymph node metastases were not suspicious on preoperative CT imaging. Meta-analysis report that assessment of lymph node status by CT is unreliable for clinical decision making, because the radiologist can only look at lymph node size.[24,25] Since 2002 in the NCCH magnetic resonance imaging (MRI) has been used, which is reported to be superior to CT because it can rely on additional morphological criteria, such as signal intensity and border contour.[26–28] Furthermore, lymph-node-specific contrast agents or molecular imaging might play a role in detecting micrometastases in the near future.[29]

In the West, (chemo)radiation is used instead of LLND. There are no (randomized) studies comparing preoperative

(chemo)radiotherapy and TME with LLND in similar patients, making it difficult to make a statement about which regimen is preferred in advanced rectal carcinoma. Western surgeons are hesitant to do lateral lymph node dissections for three reasons. First, in Western patients with a higher body mass index, nerve-sparing techniques are more difficult and the fear of excess morbidity is realistic. Further, it is well known that lateral lymph node status is reflective of overall mesenteric lymph node status and lateral lymph node positivity results in poor prognosis.[13,31] Lastly, although LLND has improved oncologic results in Japanese patients in historical studies and also the current study suggests that LLND is able to prevent residual tumor cells from developing into local recurrence, the clinical effectiveness of LLND has not been proved in a randomized fashion. Currently, the National Cancer Center Hospital is coordinating a multicenter randomized clinical trial comparing conventional TME with bilateral LLND in patients with rectal carcinoma. The results are awaited with anticipation, but it is questionable whether they will be applicable to Western patients.

Concluding, in this study patterns of local recurrence were evaluated in the treatment of rectal cancer, at or below the peritoneal reflection, with selective LLND. Overall local recurrence was 6.6% at 5 years. Local recurrence rate after standard TME was 0.8% in low-stage disease. In lymph-node-positive patients, 33% of the unilateral LLND patients had local relapse, significantly more than in the bilateral LLND group with 14% local recurrence. Either surgical approach, with or without LLND, requires reliable imaging during work-up.

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A Comparison Between the Treatment of Low Rectal Cancer in Japan and the Netherlands, Focusing on the Patterns of Local Recurrence

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Purpose: Differences exist between Japan and The Netherlands in the treatment of low rectal cancer. The purpose of this study is to analyze these, with focus on the patterns of local recurrence.

Methods: In The Netherlands, 755 patients were operated by total mesorectal excision (TME) for low rectal cancer, 379 received preoperative radiotherapy (RT+TME). Applying the same selection criteria resulted in 324 patients in the Japanese (NCCH) group, who received extended surgery consisting of lateral lymph node dissection and a wider abdominoperineal excision. The majority received no (neo) adjuvant therapy. Local recurrence images were examined by a radiologist and a surgeon.

Results: Five-year local recurrence rates were 6.9% for the Japanese NCCH group, 5.8% in the Dutch RT+TME group, and 12.1% in the Dutch TME group. Recurrence rate in the lateral pelvis is 2.2%, 0.8%, and 2.7% in the Japanese, RT+TME group, and TME group, respectively. The incidence of presacral recurrences was low in the NCCH group (0.6%), compared with 3.7% and 3.2% in the RT+TME and TME groups, respectively.

Conclusions: Both extended surgery and RT+TME result in good local control, as compared with TME alone. Preoperative radiotherapy can sterilize lateral extramesorectal tumor particles. A wider abdominoperineal resection probably results in less presacral local recurrence. Comparison of the results is difficult because of differences in patient groups.

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The main purpose of curative surgical treatment for rectal cancer is en bloc excision of the primary tumor with its locoregional lymph nodes. It has been demonstrated that nonradical removal of the tumor leads to persistence of tumor cells that contributes to the development of recurrent rectal cancer growth.[1,2] Local recurrence is known to cause severe morbidity.

With the total mesorectal excision (TME) procedure the rectum with its primary lymphovascular field of drainage is removed as an intact package, by dissection under direct vision along preexisting embryologically determined planes. Since its introduction, the TME approach has led to striking results, reflected by lower local recurrence rates and improved survival, and has been advocated as being superior to conventional surgery.[3,4]

However, the results of the TME technique for low tumors are not as good as for midrectal or higher tumors, with still a considerable local recurrence rate.[5,6] This is ascribed to the difficulty to obtain a wide circumferential margin (CRM) and the higher rate of perforations of the mesorectum and bowel wall, especially in the case of abdominoperineal resection (APR).[5,7,8]

In Western countries, the addition of (neo)adjuvant therapy to improve the local recurrence rate has been well studied. Both short and long course of preoperative (chemo)radiation have been shown to be effective.[9–12] However, it has also been shown that short-term radiotherapy cannot prevent local recurrence development when advanced tumor growth or surgical failure results in a positive CRM.[13]

In Japan, extended surgery is the gold standard and the APR technique involves a wide perineal skin incision, together with resection of ischiorectal adipose tissue and the levator ani muscle,[14] aiming for a wider circumferential tumor-free margin than in a standard Western APR. However, in Japan, the main focus is on the immediate harvesting of lymph nodes from the fresh specimen, which precludes assessment of the CRM at a later stage. Lateral lymph node dissection (LLND), in which dissection of the iliac and obturator lymph nodes with the primary tumor is performed, is the standard treatment for advanced rectal cancer located at or below the peritoneal reflection.[15,16] It has been reported that local recurrence and survival rates have improved since the introduction of LLND and are known to be significantly better than Western series with surgery only.[15,17]

The question remains whether local recurrence can be prevented best by more frequent use of adjuvant (chemo)radiation or by more extended surgery. The aim of this study was to compare the patterns of local recurrence after TME surgery, TME surgery with short-term preoperative radiotherapy, and Japanese extended surgery. The prospective databases of the Dutch TME trial and the National Cancer Center Hospital in Tokyo, with accurate follow-up, were used. The hypothesis is that recurrences in the lateral pelvic subsite would occur less often in the Japanese group than in the Dutch TME group, because the lateral lymph nodes are excised, with the mesorectum and perirectal fat tissue. In addition, the Japanese APR technique is more wide than the one used during the Dutch TME trial, also possibly leading to different patterns of recurrence in other pelvic subsites.

PATIENTS AND METHODS

Study Population

Patients were selected from the databases of the Dutch TME-trial and of the National Cancer Center Hospital (NCCH) in Tokyo.

A selection was made from a large prospective randomized multicenter study, the radiotherapy plus TME trial, in which 1530 Dutch patients were included between January 1996 and December

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1999. This trial analyzed the effect of short-term preoperative radiotherapy (5 × 5 Gy) in patients operated with a total mesorectal excision (RT+TME), compared with patients with TME alone (TME).[10] Inclusion criteria were the presence of a primary adenocarcinoma of the rectum, without evidence of metastatic disease at time of surgery, and tumor location within 15 cm from the anal verge. Patients with other malignant diseases or with fixed tumors were excluded. Standardized techniques for surgery, radiotherapy, and pathology were used.[18] Follow-up of all patients was conducted according to the trial protocol.[7] For the current study, the following patients were excluded from the analysis: no resection (n = 37), distant metastasis at operation (n = 91), and no tumor at operation (n = 15).

In the prospective database of the NCCH, Tokyo, a selection was made from January 1993 to April 2002, resulting in 923 consecutive patients operated for confirmed primary adenocarcinoma of the rectum. The patients underwent a low anterior resection (LAR), Hartmann, APR, or when a stage T4 tumor was suspected, pelvic exenteration. Surgery at the NCCH is performed according to the guidelines of the Japanese Research Society for cancer of the colon and rectum.[19] Lateral lymph node dissection was performed in low rectal cancer, when based on preoperative evaluation or intraoperative findings, TNM stage II or III disease was suspected. A decision was made for each patient individually, based on the side and the extension of the tumor, whether a uni- or bilateral LLND was performed. Accurate documentation of lymph node status and localization was obtained because all lymph nodes were dissected from the fresh specimen and their location and numbers were mapped in relation to the major arteries. After that, the specimen and all lymph nodes were examined histopathologically. Follow-up of all patients consisted of thoracic CT, abdominal CT, and pelvic CT-imaging every 6 months. For this study, similar selection criteria were applied to the patients from the NCCH as for the TME-trial patients, excluding the following patients: metastasis at the time of surgery (n = 134), other malignant diseases or double colorectal carcinoma (n = 62), fixed tumor during rectal examination (n = 15), and in situ carcinoma (n = 22).

The median follow-up of the Dutch RT+TME and TME patients alive was 7.0 years and of the Japanese NCCH patients 7.9 years.

Patient Selection

For both the Dutch and the Japanese groups, patients with low rectal tumors were selected. To match the groups as closely as possible, 2 different definitions of low rectal tumors had to be interpreted. In the Dutch TME trial, low rectal cancer was defined as tumors of which the lower edge was within 5 cm of the anal verge as measured by endoscopy. In Japan, 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.[20] The distance from the anal verge is often unreported. The anterior peritoneal reflection has been measured to be at 9 cm from the anal verge by intraoperative endoscopy.[21] With a mean tumor diameter of 4 cm in the Dutch TME trial, the distance between the lower border and the anal margin of the Japanese low cancers can thus be estimated as maximal 9−(4/2) = 7 cm. To match the tumors of the Japanese group, we therefore selected tumors from 0 cm up to 7.0 cm from the anal verge in the Dutch groups. Using these criteria, 324 Japanese patients were selected with rectal tumors at or below the peritoneal reflection and 755 patients from the Dutch database with tumors with the lower border from 0 cm up to 7.0 cm.

Definitions

In the Japanese group, the total amount of harvested lymph nodes consisted of mesorectal lymph nodes, and when LLND was done, also the lateral lymph nodes. In the Dutch group, the lymph node harvest consisted only of the mesorectal lymph nodes. The UICC 5th edition, 1997, classification system was used for both groups to define TNM-staging. All patients who developed local recurrence, defined as any recurrence of rectal cancer in the small pelvis, were identified from the databases. Local recurrence was either diagnosed clinically, radiologically, or histologically.

Methods

Analysis were made comparing 3 groups; the RT+TME group, the TME group, and the NCCH group. 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.B.) and a surgeon (G.B.) reviewed the images together for both the groups.

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.[22] When no images were available, the location of recurrence was classified using the radiology reports and clinical data. In 1 patient in the RT+TME group and in 2 patients in the NCCH group, insufficient information was provided to determine the location of recurrence with certainty.

Statistical Analysis

Statistical analysis was performed using SPSS package (SPSS 12.0 for Windows; SPSS Inc, Chicago, IL). χ^2 tests and one-way ANOVA tests, Bonferroni corrected, were used to compare individual variables. The cancer-specific survival was defined as the time between rectal cancer surgery and death caused by cancer. Survival was estimated using the Kaplan-Meier method. Cox regression was used to assess differences in survival outcomes between groups; results are reported as hazard ratios with associated 95% confidence intervals. All P values were 2-sided and considered statistically significant at 0.05 or less. For local recurrence, cumulative incidences were calculated accounting for death as competing risk.[23] 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. To account for possible confounding factors, multivariate analyses of local recurrence and cancer-specific survival were performed by first testing the effect of covariates in a univariate Cox regression. Covariates with trend-significant effects ($P < 0.10$) and group (RT+TME, TME, NCCH) were then selected for multivariate Cox regression.

RESULTS

Patient Characteristics

Patient characteristics and treatment details are listed in Table 1. The age at operation of the Japanese patients was significantly lower than that of the Dutch patients. In the Japanese group significantly more sphincter saving procedures had been performed, compared with the Dutch group. Lateral lymph node dissection was not performed in the Dutch patients, whereas 59% of the Japanese patients underwent unilateral or bilateral LLND.

Table 2 shows an overview of the pathology results of the Japanese and the Dutch groups. Early T-stage cancer was found significantly more in the Japanese group, whereas stages T3 and T4 cancer were found more in the Dutch. The average amount of

TABLE 1. Patient Characteristics and Treatment Details

	RT+TME 379 patients	TME 376 patients	NCCH 324 patients	*P*
Sex				0.52
Male	244 (64)	234 (62)	215 (66)	
Female	135 (36)	142 (38)	109 (34)	
Age (yrs)				<0.001
Mean (SD)	64 (11)	64 (11)	58 (11)	
Type of resection				<0.001
Low anterior resection	160 (42)	159 (42)	195 (60)	
Abdominoperineal resection	193 (51)	199 (53)	113 (35)	
Hartmann	24 (6)	15 (4)	3 (1)	
Pelvic exenteration	2 (1)	3 (1)	13 (4)	
Lymph node dissection				<0.001
Standard TME	379 (100)	376 (100)	134 (41)	
Unilateral LLND	0	0	69 (21)	
Bilateral LLND	0	0	121 (38)	
Neoadjuvant therapy				<0.001
Preoperative radiotherapy	379 (100)	0	0	
None	0	376 (100)	324 (100)	
Adjuvant therapy				<0.001
Postoperative radiotherapy	3 (1)	52 (14)	5 (2)	
Postoperative chemotherapy	16 (4)	13 (3)	23 (7)	
None	360 (95)	315 (84)	297 (92)	

Values in parentheses are percentages.

TABLE 2. Pathologic Results

	RT+TME 379 patients	TME 376 patients	NCCH 324 patients	*P*
Amount of lymph nodes resected				<0.001
Mean (SD)	7.3 (6.0)	9.3 (6.4)	33.7 (18.5)	
T-stage				<0.001
T1	19 (5)	21 (6)	52 (16)	
T2	143 (38)	131 (35)	107 (33)	
T3	209 (55)	210 (56)	160 (49)	
T4	8 (2)	14 (4)	5 (2)	
N stage			*/†	0.82/0.62
N0	244 (64)	229 (61)	198/192 (61/59)	
N1	80 (21)	82 (22)	75/80 (23/25)	
N2	55 (15)	64 (17)	51/52 (16/16)	
TNM-stage*				0.27
Stage I	129 (34)	123 (33)	125 (39)	
Stage IIa	111 (29)	100 (27)	72 (22)	
Stage IIb	4 (1)	6 (2)	1 (0)	
Stage IIIa	27 (7)	19 (5)	26 (8)	
Stage IIIb	53 (14)	63 (17)	49 (15)	
Stage IIIc	55 (15)	64 (17)	51 (16)	
Tumor size (cm)				0.09
Mean (SD)	4.0 (1.6)	4.6 (1.7)	4.3 (2.1)	
Distal margin (cm)				0.46
LAR (SD)	2.1 (1.5)	1.9 (1.7)	1.9 (0.9)	
APR (SD)	4.3 (1.7)	4.1 (1.9)	4.2 (2.7)	

Values in parentheses are percentages.
*On basis of mesorectal lymph nodes.
†With extra positive lateral lymph nodes.

harvested lymph nodes was 34 in Japanese group and 8 in the Dutch groups. The N stages, whether lateral nodes were included or not, did not differ significantly. TNM stage did not differ significantly between the groups.

The cancer-specific survival was higher in the Japanese extended surgery group than both in the Dutch TME group as in the Dutch RT+TME group (Fig. 1A). The hazard ratios for death (95% CI) of the Dutch TME and RT+TME groups with respect to the Japanese group were 2.0 (1.2–3.3) and 1.7 (1.1–2.8), respectively.

Local Recurrence Patients

Twenty-three patients (6.9% 5-years percentage) in the Japanese extended surgery group, 24 patients (5.8%) in the Dutch RT+TME group, and 46 patients (12.1%) in the Dutch TME group were diagnosed with local recurrence (Table 3, Fig. 1B). The hazard ratio for local recurrence (95% CI) of the Dutch TME group compared with the Japanese group was 1.6 (1.0–2.8). The hazard ratio (95% CI) of the Dutch RT+TME compared with the Japanese group was 1.0 (0.6–1.8). The mean time to local recurrence in the Japanese group is 2.1 years, 1.5 years in the TME-group, and 2.6 years in RT+TME-group.

In the Japanese patients with local recurrence, 11 patients (48%) had distant metastases before or at the time of local recurrence diagnosis. In the Dutch TME patients with local recurrence this was the case in 9 patients (20%), in the RT+TME local recurrence this was the case in 13 patients (54%). When distant metastases diagnosed within 1 month of local recurrence diagnosis were considered as being simultaneous, these distant metastases rates were 62%, 30%, and 88% for the Japanese, Dutch TME, and Dutch RT+TME local recurrence patients, respectively. At the time of last follow-up or death 95%, 77%, and 88% had metastases in the respective groups.

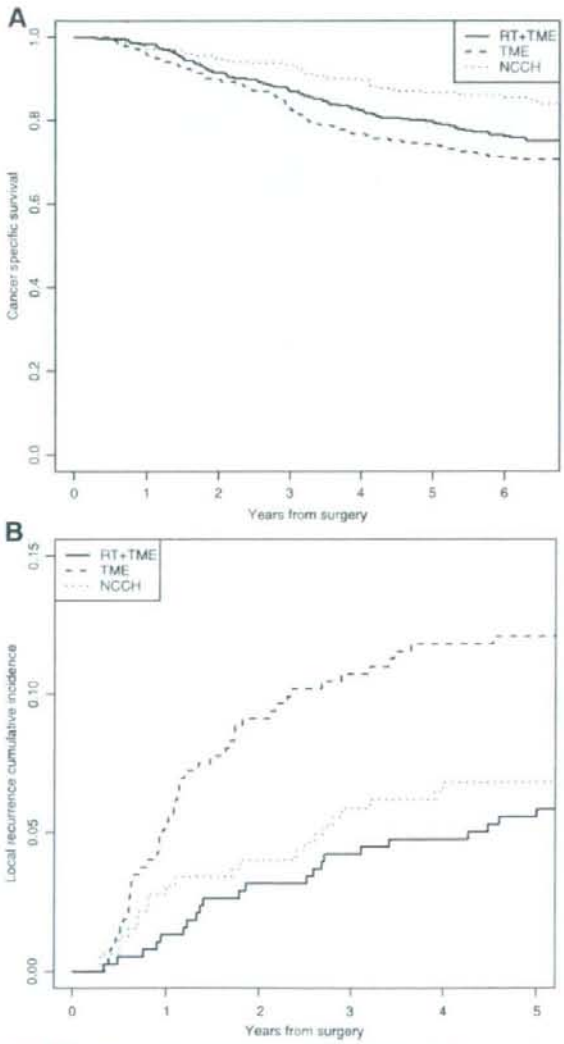

FIGURE 1. A, Cancer-specific survival, B,Local recurrence incidence.

Patterns of Local Recurrence

In Table 3 the patterns of local recurrence for the 3 groups are shown. Presacral recurrences (Fig. 2) occurred in 3.7% of the RT+TME patients and in 3.2% of the TME patients. In the Japanese group only 0.6% of the patients developed presacral recurrence. When only looking at the patients operated by APR, 5-year local recurrence rates in the presacral subsite were 6.5% in the RT+TME group, 4.4% in the TME group, and 1.8% in the Japanese group.

In this study, the lateral recurrence (Fig. 3) rate in the nonirradiated TME-group is 2.7%, comprising 24% of all local recurrences. The hazard ratio of lateral recurrence in the RT+TME group (0.8%) versus the TME group (2.7%) is significantly different from zero (HR = 5.3, 95% CI: 0.6–43.9). In the Japanese group, 2.2% developed local recurrence in the lateral pelvic subsite, not differing significantly from the Dutch groups. When only T3 and T4 tumors are selected, similar trends are observed.

Circumferential Resection Margin and Lateral Lymph Nodes

In the Dutch TME-group, 23% (88/376) of the patients showed CRM involvement on pathologic examination. Of these CRM-positive patients, the 5-year local recurrence percentage was 33%. In the CRM-negative cases, this was 9%. In the RT+TME-group, 20% (77/379) of the patients showed CRM involvement. Of these CRM-positive patients, the 5-year local recurrence rate was 25%. In the CRM-negative cases, 3% developed local recurrence in 5 years, versus 9% in the TME-group (HR = 0.4, 95% CI: 0.2–0.8).

Of the Japanese group it is not possible to report on CRM involvement; the immediate harvesting of lymph nodes from the fresh specimen precludes assessment of the CRM at a later stage. For the 190 patients operated by uni- or bilateral LLND, the 5-year local recurrence rate was 36% in the lateral node positive patients and 7% in the lateral negative patients (HR = 6.4, 95% CI: 2.6–15.7).

DISCUSSION

We compared Western and Japanese treatment results, looking at the patterns of local recurrence. The Japanese group differs from the Dutch groups in that the patients received extended surgery consisting of lateral lymph node dissection and a wider APR.

The main limitation of the present study is the difficult comparison of the group of Japanese patients with the group of Dutch patients. There are many sources of potential bias, such as nonrandomization and upstaging, as described previously.[24] Japanese patients are younger and have tumors with lower T-stage,

TABLE 3. Patterns of Local Recurrence

	Absolute No. LR 5-yrs (%)			Relative Distribution of LR*		
	RT+TME 379 pts	TME 376 pts	NCCH 324 pts	RT+TME 24 pts	TME 46 pts	NCCH 23 pts
presacral	14 (3.7%)	12 (3.2%)	2 (0.6%)	58%	26%	9%
lateral	3 (0.8%)	11 (2.7%)	8 (2.2%)	13%	24%	35%
anterior	4 (0.8%)	11 (3.0%)	1 (0.3%)	17%	24%	4%
anastomosis	2 (0.5%)	8 (2.1%)	5 (1.6%)	8%	17%	22%
perineum	0 (0%)	4 (1.1%)	5 (1.6%)	0%	9%	22%
unknown	1 (0%)	0 (0%)	2 (0.6%)	4%	0%	4%
	24 (5.8%)	46 (12.1%)	23 (6.9%)			
Hazard Ratio	1.0	1.6	1.0			
95% CI†	0.6–1.8	1.0–2.8				

*Local recurrence per pelvic subsite, as a percentage of all local recurrences.
†Hazard Ratio for local recurrence after multivariate analysis, with 95% CI as compared to the NCCH group.

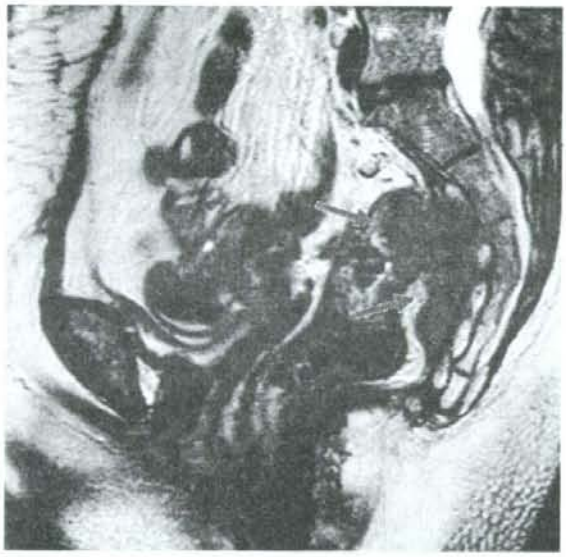

FIGURE 2. MR image of presacral local recurrence, sagittal MR image of locally recurrent mass in the presacral subsite.

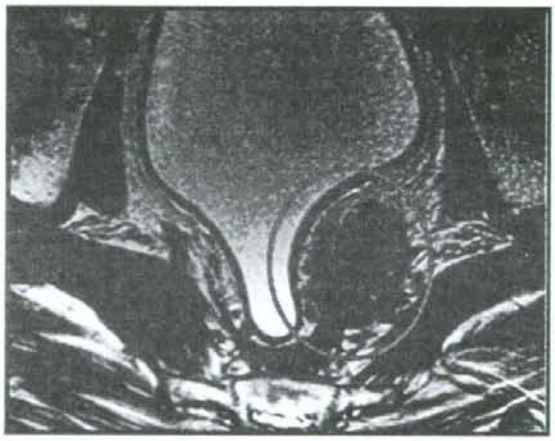

FIGURE 3. MR image of lateral recurrence, transverse MR image of local recurrence in the extramesorectal region (lateral subsite), highly suggestive of local relapse from nodal metastasis in the lateral lymph nodes.

although differences in local recurrence are still significant after multivariate analysis. Lymph node yield is much higher in the Japanese patients, which is probably because of differences in pathologic examination methods.[17] The differences in survival are undoubtedly more related to these differences than to any treatment effect. The definition and measurement of distal rectal cancer is different in the 2 countries, and although we tried to match the 2 groups as closely as possible, 1 or the other group may contain more distal tumors. The findings of the present study and the interpretation of the results therefore require some caution. Notwithstanding these limitations, the present study can give insight in the merits of the approaches and the mechanism of preventing local recurrences.

In this study extended surgery, as performed in the NCCH in Japan, results in good local control (5-year local recurrence rate, 6.9%). This is significantly less than after TME-surgery alone, which showed 12.1% local recurrence. Preoperative radiotherapy and TME-surgery also results in good local control (5.8%). The better local control is also reflected in the fact that the recurrences develop later when radiotherapy is given (2.6 years postoperatively) or more extended surgery is performed (2.1 years), compared with the 1.5 years after TME surgery. The high percentage of distant metastases at time of local recurrence diagnosis after RT+TME or extended Japanese surgery can also be seen as a marker of good local control, because now mainly patients with the worst disease get local recurrence, as if local recurrence is a sign of systemic disease.

The Japanese wider perineal resection is likely to result in less positive margins than in standard perineal resections, where the "coning in" is probably responsible for the high percentage of 23% involved margins in standard TME. Almost in 1 of 4 of these margin positive patients developed a local recurrence in this study. Unfortunately, pathology techniques differ between Japan and The Netherlands, making it impossible to draw firm conclusions on CRM involvement in the Japanese group. It has been described that recurrence rates after APR are far worse than after LAR. Even the pioneer of TME surgery, professor Heald, reported local recurrence in only 5% of cases 10 years after LAR, but in his patients who

underwent an APR, the local recurrence rate was as high as 36%.[25] Heald et al recently published an anatomic and radiologic study, in which they observed that in the lowest part of the rectum the mesorectum tapers and terminates at the pelvic floor.[26] Also Nagtegaal et al[5] concluded that following the mesorectum downward along the sphincter muscles is associated with increased occurrence of positive CRM. In the TME-trial, perforations in the anal canal were described, stressing the need for a more extended approach.[8,27] Holm et al recently reported on extended abdominoperineal resection, showing a low risk of CRM involvement.[28] It could be suggested that a wider perineal approach has a major contribution to good local control.

In the Dutch TME trial presacral recurrences were the most common type of recurrences. This was also reported in a large overview reported by Roels et al.[22] It is intriguing that this type of recurrence was uncommon in the Japanese group. The exact pathogenesis of presacral recurrences has been puzzling, as it is the easiest plane of dissection of a rectal cancer operation with often a wide margin of mesorectal fat. One could hypothesize that presacral recurrences result from implants of tumor cells originating from positive margins or tears or perforations at the tumor site. Through the force of gravity these implants would occur most often in the midline in the low/mid presacral area. Seventy-five percent of the presacral recurrences develop after APR surgery in the Dutch group, and radiotherapy apparently cannot sterilize these tumor particles. If this hypothesis were to be correct, presacral recurrences would occur less often with surgical techniques that avoid tumor spill, such as the wider perineal resections in the Japanese group. Of course this theory remains speculative.

The effect of the application of uni- or bilateral LLND on prevention of lateral recurrence is questionable. In the Japanese group, 2.2% developed local recurrence in the lateral pelvic subsite, not differing significantly from the Dutch groups. In this study, the lateral recurrence rate in the nonirradiated TME-group is 2.7%, comprising 24% of all local recurrences. The difference in lateral recurrence in the RT+TME group (0.8%) versus the TME group (2.7%) shows that radiotherapy plays a significant role in the reduction of local recurrence in the lateral pelvic subsite. Further, the significant lower local recurrence rate of CRM-negative RT+TME patients compared with CRM-negative TME-patients suggests the sterilization of tumor deposits outside the mesorectum. Only few reports are published about local recurrence in the lateral pelvis. In the overview report of Roels et al,[22] 6% of all patients and 21% of the patients with local recurrence had a relapse in the lateral pelvic subsite. Also Kim et al[29] reported recently that even after preoperative chemoradiotherapy combined with TME 24 of 366 (6.6%) patients with stage T3 or T4 tumors up till 8 cm from the anal verge developed lateral recurrence. Syk et al[30] reported only 2 of the 33 recurrent tumors originating from lateral pelvic lymph nodes in a population-based cohort. However, the study did not focus on low rectal tumors only and might be biased because patients who had a R1-resection or short distal resection margin were excluded. In the current report only low rectal tumors were studied and incomplete resection was not an exclusion criterion.

In the choice between more extensive surgery or preoperative radiotherapy as a means to improve the local recurrence rate, the morbidity associated with the treatment plays a major role. Patients who undergo radiotherapy have been shown to have an increased risk of sexual dysfunction and incontinence. In the Dutch TME-trial, 76% of the TME and 67% of the RT+TME male patients who were previously active were still active.[31] For female patients, these figures were 90% and 72%, respectively. Preoperative radiotherapy resulted in more erection and ejaculation problems in men, and vaginal dryness and pain during intercourse in women. Fecal incontinence was observed in 51.3% of the RT+TME patients, as compared with 36.5% in the TME patients. Regarding the lateral lymph node dissection, before nerve-sparing surgery, sexual dysfunction was present in as many as 96% of the patients.[32] LLND with nerve-sparing techniques 50% to 75% of the men are reported to be sexually active, although ejaculation is often compromised.[33,34] Urinary function is maintained well, but there are no reports on fecal continence. Although in Japan nerve-sparing techniques in LLND surgery are used to minimize damage the autonomic nervous system in the pelvis,[15,35] most Western surgeons feel that in Western patients, with a higher body mass index, nerve preserving techniques are more difficult and will lead to an excess morbidity. There is 1 report on results in 9 Western patients with locally advanced rectal cancer operated by LLND and ANP, with 1 patient with erection dysfunction and 1 patient suffering from retrograde ejaculation.[36] Currently, the National Cancer Center Hospital in Tokyo coordinates a multicenter randomized clinical trial comparing conventional TME versus LLND in patients with low rectal carcinoma, addressing the questions of survival benefit and morbidity. The inclusion of about 600 patients will be completed by the end of 2009.

Magnetic resonance imaging (MRI) is currently considered as the most reliable in staging rectal cancer. Preoperative MRI modalities are further improving and techniques are developed to distinguish better between nonmetastatic and metastatic lymph nodes by, for example, lymph node specific contrast enhancement.[37] With present day MRI, sometimes patients are identified with clearly involved or suspected lateral lymph nodes. As often preoperative chemoradiation is the choice of treatment in these cases, it is doubtful whether the lateral lymph nodes can be fully sterilized. Also, the risk for disseminated disease is high and prognosis is unfavorable for lateral lymph node positive patients. For these patients, it may be wise to consider a combination of treatments: neoadjuvant chemoradiation, a lateral lymph node dissection, and possibly even systemic therapy.

In conclusion, both extended surgery and preoperative radiotherapy with standard TME surgery result in good local control in the treatment of distal rectal cancer, as compared with TME alone.

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