変更をしていた。放射線治療担当医に連絡し、放射線治療計画上、小腸線量が高くなっているため、耐容線量内に抑えるために一回早く標的体積の変更をしたことが分かり、放射線治療研究事務局として臨床的に妥当な逸脱と判断した。

現在、第Ⅰ相試験と合わせた18例の総合判定として、15例（83.3%）が遵守、3例（16.7%）で逸脱であり、違反例は認めていない。逸脱例に関しては、逸脱内容について登録施設へフィードバックをした。また、重要な周知事項についてはメーリングリストを通じて全参加施設の放射線治療責任者に連絡し、情報共有をした。JCOG大腸がんグループの班会議にても、本試験の放射線治療品質保証活動の進捗状況を報告した。

D．考察

多施設共同で実施する放射線治療を用いるがん臨床試験において、放射線治療内容の較差は臨床試験の結果に影響を及ぼすため、試験内容の質を保証することを目的とした放射線治療の品質保証活動は重要である。本試験でもプロトコール作成段階から品質保証活動を施行している。本年度治療内容について評価した8例の遵守率は昨年度の80%よりも増加しており、品質保証活動が機能しているものと考えられた。逸脱の1例については、治療担当医との連絡によって、有害事象のリスクに配慮したことによる臨床的に妥当な逸脱であることが分かり、全体として放射線治療内容の質は担保できていた。逸脱判明時での登録施設への治療内容についての連絡や逸脱内容のフィードバックは有用であると考える。今後も経時的にプロトコール遵守率が上がるように、放射線治療の品質保証活動を継続していく予定である。

E．結論

本試験は稀少疾患である肛門管扁平上皮癌に対して多施設共同で実施している臨床試験であるため、放射線治療の品質保証活動が重要である。現在までに登録例の放射線治療内容の質は保たれている。

F．健康危険情報

なし

G．研究発表

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2．学会発表

なし

H．知的財産権の出願・登録状況

1．特許取得

なし

2．実用新案登録

なし

3．その他

特記すべき事項なし

Ⅲ.　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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Ⅳ.　研究成果の刊行物・別刷り

大腸癌

佐藤武郎　渡邊昌彦

近年、わが国の大腸癌罹患率、死亡率は増加の一途をたどっている。2008年の人口動態統計では、全悪性新生物による死亡のなかで、女性の大腸癌による死亡率は最も高く、男性では肺癌、胃癌に次いで第3位であった。

大腸癌研究会では、2003年1月よりプロジェクト研究として大腸癌治療ガイドラインの作成作業が開始され、2005年に「大腸癌治療ガイドライン 医師用2005年版」が初版刊行された。以降、2009年と2010年に改訂されてきた。一方、海外の代表的なガイドラインとしては、米国立癌研究所（NCI）のPDQ®や、全米癌ネットワーク（NCCN）、英国立医療技術評価機構（NICE）のガイドラインとともに、悪性疾患を取り扱う各主要学会、米国臨床腫瘍学会（ASCO）や欧州臨床腫瘍学会（ESMO）のものがある。大腸癌治療のみならず、癌治療の標準化や均霑化には課題が山積みされているが、癌治療ガイドラインはこれらの一助になると考える。

本章では、ガイドラインを用いた大腸癌の外来診療について述べる。

診　断

大腸癌と診断されるまでの経緯は、検診や人間ドックなどで偶然の契機に発見された患者群と、下血や腹痛、便秘・下痢を繰り返す、貧血といった何らかの症状を有した患者群とに大別される。前述の群は、便潜血検査の陽性症例だけでなく、超音波検査や胸部X線検査で異常が認められ、大腸癌がその原発であることも経験する。便潜血陽性の場合は、積極的に大腸内視鏡検査や注腸造影検査での精査を行う必要がある。無症状の肝臓や肺の腫瘍では大腸癌からの転移症例も含まれるため、大腸の精査も行うことが大切である。下血や血便などの症状を有する患者には、必ず直腸診を行う。痔核や裂肛があっても大腸の精査を行うことが大腸癌を見逃さないためには重要である。また、他の疾患で通院中に貧血を認めた際にも大腸腫瘍を念頭に置く必要があり、まず便潜血検査を行うべきである。

大腸癌の診断が確定したら、治療方法を選択するうえで臨床病期の決定が重要である。病期分類には国際的に用いられるDukes分類、TNM分類と、わが国の「大腸癌取扱い規約」による病期分類（表1）がある。病期分類はいずれも、壁深達度、リンパ節転移、他臓器転移によって規定される。わが国の「大腸癌治療ガイドライン」は、「大腸癌取扱い規約」の進行度分類に基づいて治療方針を決定している。転移の検索には、腹部超音波検査や胸・腹部CT検査やPET/CT検査を行うが、転移性肝癌と他の疾患との鑑別には造影MRI（SPIOやEOB）検査が有用である。

表1　進行度（Stage）

<table>
<tr><td rowspan="2"></td><td colspan="3">H0, M0, P0</td><td>H1, H2, H3, M1, P1, P2, P3</td></tr>
<tr><td>N0</td><td>N1</td><td>N2, N3</td><td>M1（リンパ節）</td></tr>
<tr><td>M</td><td>0</td><td colspan="3" rowspan="2"></td></tr>
<tr><td>SM
MP</td><td>Ⅰ</td></tr>
<tr><td>SS, A
SE
SI, AI</td><td>Ⅱ</td><td>Ⅲa</td><td>Ⅲb</td><td>Ⅳ</td></tr>
</table>

（大腸癌研究会，2009）

また、直腸癌の深達度や周囲臓器へ浸潤程度、リンパ節転移の診断には骨盤MRIが有用である。

管理・治療

(1) 内視鏡治療

内視鏡治療は侵襲度が低く、治療後の機能障害を残さない。転移のない粘膜内癌（Stage 0）や、粘膜下層に軽度浸潤した癌（＜1,000μm、Stage Ⅰ）は、リンパ節転移の可能性がきわめて低いため、内視鏡治療（局所切除）の適応である。

内視鏡での切除方法には、ポリペクトミーや内視鏡的粘膜切除術（EMR）、内視鏡的粘膜下層剝離術（ESD）がある。また、切除後の治療方針の決定のために、切除検体の緻密な組織学的検索が必須であるため、切除検体の取り扱いには種々の注意を要する。局所切除後に粘膜下層に高度な浸潤を伴う（＞1,000μm）癌であった場合は、リンパ節郭清を伴う腸管切除術を考慮する（図１）。

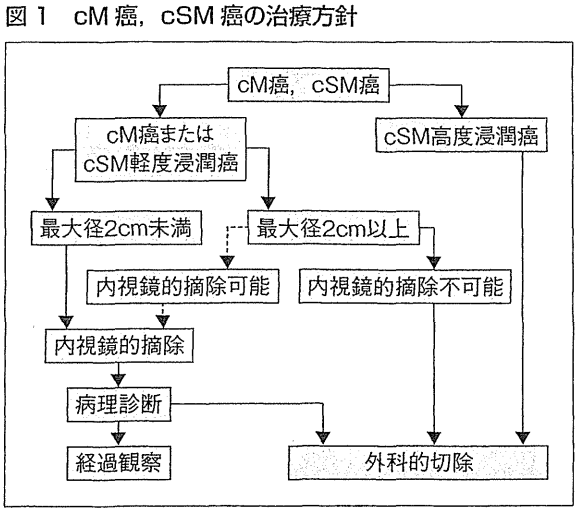
(2) 手術治療

Stage Ⅱ～Ⅲの進行大腸癌は、耐術能に問題がある症例を除き、所属リンパ節郭清を伴った手術の適応となる。早期癌でも、粘膜下層に高度に浸潤した癌（＞1,000μm）では、リンパ節転移の可能性が10％程度あるため、リンパ節郭清を伴う手術の適応となる。リンパ節郭清の目的は、癌が転移している可能性のあるリンパ節を予防的に切除し腫瘍の残存を減らし、根治性を得ることである。さらに最も信頼のおける予後因子であるリンパ節転移の有無により、病理学的な病期が決定される。

リンパ節郭清度は、術前、術中における腫瘍の壁深達度と、リンパ節転移によって決定する。術前にリンパ節転移を疑う場合は、主リンパ節郭清を行う（D3郭清）。リンパ節転移を認めない症例では、壁深達度に応じてリンパ節郭清を行うが、漿膜下層以上の浸潤が疑われる場合は一般的にD3リンパ節郭清を行う。固有筋層より浅層の浸潤癌でも、中間リンパ節郭清を行う必要がある（D2郭清）（図２）。

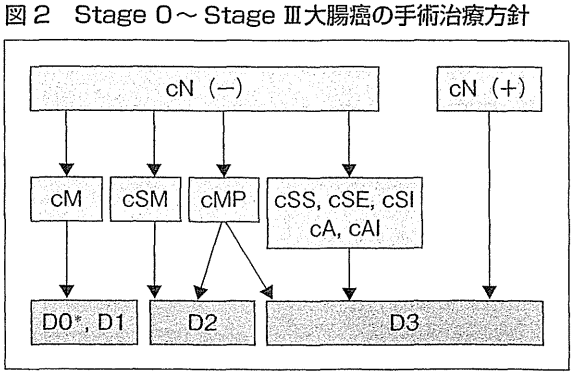
直腸癌に対する手術の原則は全直腸間膜切除術（TME）、またはTSMR（tumor specific mesorectal resection）である。側方リンパ節郭清の適応は、固有筋層を越える浸潤を来し、腫瘍下縁が腹膜反転部以下にかかる症例である。このような症例では側方リンパ節転移率が20％前後あり、側方リンパ節郭清を

図１　cM癌，cSM癌の治療方針



（大腸癌研究会，2010）

図２　Stage 0～Stage Ⅲ大腸癌の手術治療方針



*直腸癌では直腸局所切除を含む。

（大腸癌研究会，2010）

行うと骨盤内再発リスクは50％減少して５年生存率は８～９％改善すると予測されている。

近年、大腸疾患に対する腹腔鏡手術もわが国で広く行われるようになった。腹腔鏡手術による患者側の利点は、術創が小さいため、創痛の軽減や整容性の向上、早期離床、経口摂取の早期開始、その結果としての早期退院、社会復帰といった短期予後の改善にある。さらに、低侵襲性のみならず、拡大視効果による精緻なリンパ節郭清や神経温存、術後の癒着の低減などの利点がある。「大腸癌治療ガイドライン」では、腹腔鏡手術は開腹手術とは異なる手術手技の習得と局所解剖の理解が不可欠であり、手術チームの習熟度に応じた適応基準を個々に決定すべきであると記されている。

進行・再発癌は、手術で完全に切除ができれば根治を得ることがあるため、積極的に再発・転移巣の切除が考慮される。特に、肝転移の根治的治療は切除が最も有効な治療法として推奨されている。なぜなら、切除症例と非切除症例を比較することは許容し難いほどの差があるからである。ただし、術式には系統的切除と部分切除があるが、原則として切除断端に癌が露出しないことである。「大腸癌取扱い規約」では、肝転移を大きさと個数、原発巣のリンパ節転移でGrade分類（表２）している。

表２　肝転移症例の Grade

	H1	H2	H3
N0 N1	A	B	
N2	B	C	
N3 M1			

（大腸癌研究会，2009）

(3) 化学療法

a. 補助化学療法

術後補助化学療法は、再発を抑制し予後を改善する目的で、StageⅢ大腸癌でR0切除が行われた症例に対して術後に実施される全身化学療法である。治癒切除手術が行われた癌に対する補助化学療法の評価は、再発が確認されるまでの無再発生存期間（DFS）と生存期間を指標に用いる。「大腸癌治療ガイドライン」では、5-FU＋LV療法、UFT＋LV療法、カペシタビン療法、FOLFOX4またはmFOLFOX6療法が推奨されている。また、わが国でも2011年11月からXELOX療法も補助療法に用いることができるようになった。一般的に補助化学療法は術後約４～８週までに開始することが望ましく、投与継続期間は６カ月間といわれている。

b. 切除不能進行・再発大腸癌の化学療法

切除不能進行・再発癌の治療目的は、予後の向上とQOLの改善である。化学療法のみで治癒を望むことは難しく、化学療法の最近の進歩によっても、生存期間中央値（MST）は約２年である。化学療法が奏効して、切除可能となることもあるが、予後との相関は現状では明らかになっていない。

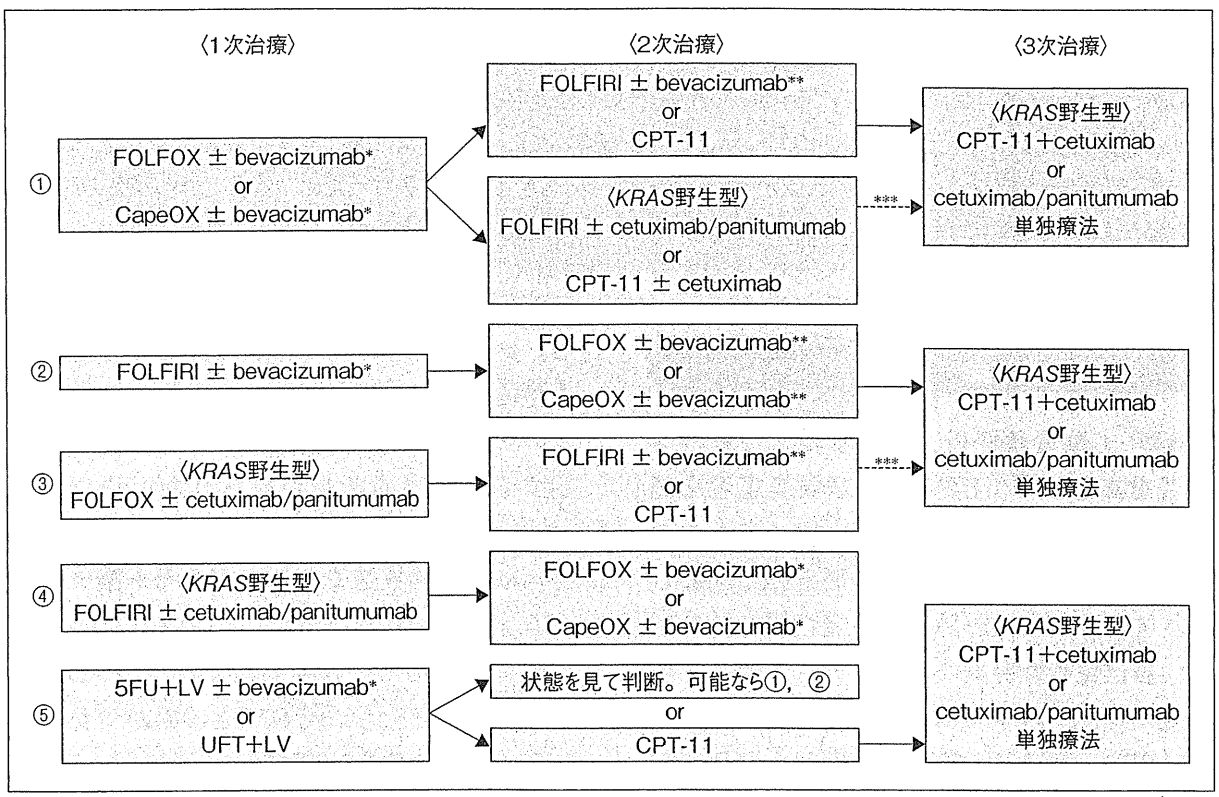
化学療法にはいわゆる抗癌薬と分子標的薬がある。分子標的薬のうち、上皮成長因子受容体を標的とした抗EGFR抗体薬は*KRAS*遺伝子の野生型で効果があるとされている。一方の血管内皮増殖因子阻害薬ではこのようなバイオマーカーは存在しない。「大腸癌治療ガイドライン」で推奨される化学療法を図３に示す。

経過・予後

大腸癌研究会の大腸癌全国登録（1991～1994年度症例）による、部位・病期別累積５

年生存率を表3に示す。補助療法にFOLFOX療法を導入する前のデータであるが、StageⅢaまでの予後は比較的良好である一方、StageⅢbの予後は不良であり、今後の報告が待たれる。

図3　切除不能・再発大腸癌に対する化学療法



*：bevacizumabの投与が推奨されるが，投与の適応でないと判断した場合はその限りではない。
**：1次治療においてbevacizumabを投与していない場合，および1次治療の効果が持続しているがCPT-11やL-OHPの毒性のために投与を中止した場合は，2次治療でbevacizumabの投与が推奨される。
***：2次治療までに抗EGFR抗体薬を未使用の場合。

（大腸癌研究会，2010）

表3　部位別累積5年生存率（下段：症例数）

Stage	0	Ⅰ	Ⅱ	Ⅲa	Ⅲb	Ⅳ	全Stage
結腸（C～S）	94.8% 1,183	90.6% 1,905	83.6% 3,037	76.1% 1,908	62.1% 995	14.3% 1,791	71.4% 10,819
直腸（Ra～Rb）	92.9% 581	89.3% 1,347	76.4% 1,232	64.7% 1,146	47.1% 669	11.1% 665	67.7% 5,640
全部位（C～P）	94.3% 1,960	90.6% 3,673	81.2% 4,839	71.4% 3,534	56.0% 1,846	13.2% 2,820	69.9% 18,672

（大腸癌研究会，2010より抜粋）

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Question 08

大腸

がんの転移

結腸がんが肺に転移。抗がん剤は効かないと言われたが…

65歳・男性。昨年7月にS字結腸がんの手術を受けました。そのときに肺転移が見つかり、9月に右肺のがんだけ切除しました。結腸からの転移による肺腫瘍に効く抗がん剤はないと言われたのですが本当でしょうか。また、抗がん剤のフォルフォックス療法というのがあると聞きました。その方法も適応できませんか。（東京都　K・K）

Answer

フォルフォックス療法は試す価値があるかもしれない

大腸がん（結腸がん、直腸がん）からの肺転移性病変の治療の基本は、手術療法です。肺転移に限らず、肝転移や腹膜転移などでも外科切除が第一選択です。転移性病変が同時性（原発巣と一緒に発見された場合）でも、異時性（原発巣切除後に、時間がたってから発見された場合）でも、手術をすることによって転移性病変をなくすことができれば、手術をすべきであると考えます。

ただし転移の状況が多発性病変の場合や、手術することで残肺機能が大きく損なわれる場合には、手術は選択されません。

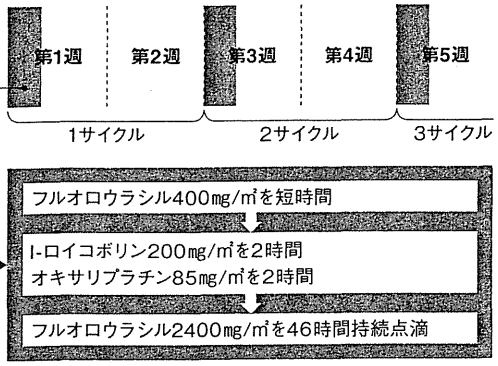
現時点では転移性病変切除後の補助化学療法（抗がん剤）のエビデンスはありません。ただし、ステージⅢ（リンパ節転移を伴う）に対する補助療法の有効性が確立している現在、ステージⅢよりも再発リスクが高い肺転移（ステージⅣに相当）切除例に対して補助化学療法を実地臨床として実施することは、一般的に容認されると考えられます。肝転移に関しては現在、「大腸がん肝転移切除後患者を対象としたmFOLFOX6（フォルフォックス）療法対手術単独によるランダム化Ⅱ／Ⅲ相臨床試験」が実施中で結果が待たれています。

では、どんな抗がん剤を使うのでしょうか。前述の臨床試験に準じてmFOLFOX6療法を12サイクル使用している場合が多いと思います。これは、「フルオロウラシル」（商品名＝以下同：5－FU）と「l－ロイコボリン」（レボホリナート）を組み合わせた治療に、オキサリプラチン（エルプラット）を同時併用する治療です。オキサリプラチンは、「白金製剤」という種類の抗がん剤で、1976年にわが国で最初に合成されました。

副作用として、冷たい物に触れると手足や口周辺のしびれや痛みを感じる末梢神経症状が現れます。そのため「手作業がしづらい」などの影響が出ます。その他、骨髄抑制（白血球減少、血小板減少）、吐き気、嘔吐、食欲不振、下痢、口内炎、味覚異常などがあります。副作用が出た場合は、投薬量の減少や治療の間隔の延長を試みます。

近年国内の大腸がん患者は急増し、死亡者数は男性では肺がん、胃がんについで第3位で、女性では第1位です（2009年がん研究振興財団ホームページより）。しかし、新規抗がん剤の出現により、転移のある大腸がんの治療成績は著しく改善しています。今後、さらなる成績の改善が期待できると思います。もう一度、主治医にご相談なさって、使用できそうな薬を検討してみてください。

表　mFOLFOX6療法のスケジュール



私が回答します

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下部直腸癌に対する直腸局所切除術の治療成績

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〔*Jpn J Cancer Chemother* 39(12): 2176-2178, *November*, 2012〕

Long-Term Outcome of Local Excision for Lower Rectal Cancer: Toshimasa Yatsuoka*1, Yoji Nishimura*1, Hirohiko Sakamoto*1, Yoichi Tanaka*1 and Masafumi Kurozumi*2 (*1*Division of Gastroenterological Surgery, and* *2*Division of Pathology, Saitama Cancer Center*)

Summary

In many practical cases, we cannot perform further surgical treatment for patients with T1 lower rectal cancer after local excision due to the patient's desire to avoid abdominoperineal resection. We reviewed the outcome of 15 patients in which local excision was performed for T1 lower rectal cancer from 2001 to 2009. The cases were classified into 3 groups [SM1 (n=3), SM2 (n=11), and SM3 (n=1)] by dividing the submucosal layer equally. In the initial operation, the round margins of all resected specimens were negative for cancer cells. We performed only 1 additional bowel resection after initial local excision for the SM3 case. The specimen removed by ultra-low anterior resection revealed lymph node metastasis in the mesorectum. Among the SM2 cases, recurrence occurred in only 1 patient, and ultra-low anterior resection was performed after the diagnosis of recurrence. Even though patients who had cancer with SM2 invasion did not undergo further bowel resection due to having other cancers or comorbidities or because of personal preference, there have been no other recurrences. Key words: Lower rectal cancer, Local excision, Submucosal invasion

要旨 下部直腸癌に対して直腸局所切除術を施行した後，病理組織学的検査結果でリンパ節転移高リスク群のSM癌と判明されても，肛門温存の観点から患者の意向で追加の腸管切除を施行しない症例もある。2001～2009年までに，当科で経験した下部直腸SM癌に対する直腸局所切除術15例の治療成績について臨床病理学的に検討した。粘膜下層を単純に三等分してSM浸潤度を検討した結果，SM1癌3例，SM2癌11例，SM3癌1例であり，全例切除標本で切除断端癌細胞陰性であった。追加腸管切除を行ったのはSM3癌の1例のみで，超低位前方切除を施行した結果，251番リンパ節に転移を認めた。追加腸管切除を行わないSM2癌9例中で再発を来したものは1例であり，超低位前方切除術で救命し得た。残る症例は，他の癌や重篤な合併症などを理由に追加切除を受けなかったが，現時点で再発はみられていない。

はじめに

下部直腸癌に対する直腸局所切除術症例においては，病理組織学的検査結果でSM浸潤度1,000 μm以上や脈管侵襲陽性などのリンパ節転移高リスク群と判明しても，患者の意向により追加腸管切除を施行しない症例もある。

I. 目 的

SM浸潤陽性下部直腸癌に対する直腸局所切除術の治療成績について，臨床病理学的に検討する。

II. 対 象

当科で経験した2001～2009年までの下部直腸癌15例を対象にした。内視鏡的粘膜切除術後の症例ではSM浸潤度の実測が難しい場合もあり，SM浸潤度は粘膜下層を単純に三等分し，SM1，SM2，SM3の3層に分けて検討した。

III. 結 果

SM1癌3例，SM2癌11例，SM3癌1例で，すべて

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八岡 利昌

表 1　下部直腸癌に対する経肛門的および経仙骨的直腸局所切除症例

症例	年齢	性別	術式	形態	最大径	組織型	深達度	ly	v	N	追加治療
1	73	M	経肛門的	IIa	18	mod	SM1	0	0	x	
2	84	F	経肛門的	Is	73	wel	SM1	0	0	x	
3	57	F	経肛門的	Is	25	mod	SM1	0	1	x	
4	58	M	経仙骨的	Is	10	wel	SM2	1	0	0	
5	52	F	経肛門的	IIa	14	mod	SM2	1	1	x	超低位前方切除（再発時）
6	70	M	経肛門的	Is	20	wel	SM2	0	0	x	
7	44	M	経仙骨的	Isp	13	mod	SM2	2	2	0	
8	68	M	経肛門的	IIa	65	wel	SM2	0	1	1	経仙骨的
9	18	M	経肛門的	IIa	35	wel	SM2	1	1	x	
10	60	F	経仙骨的	Is	25	wel	SM2	0	2	0	
11	56	M	経肛門的	Is＋IIa	44	wel	SM2	0	1	x	経仙骨的
12	57	M	経仙骨的	Isp	20	wel	SM2	0	2	0	
13	58	M	経仙骨的	LST	23	wel	SM2	0	1	0	
14	61	M	経仙骨的	Isp	14	mod	SM2	0	0	0	
15	69	M	経肛門的	IIa	22	wel	SM3	1	0	1	超低位前方切除

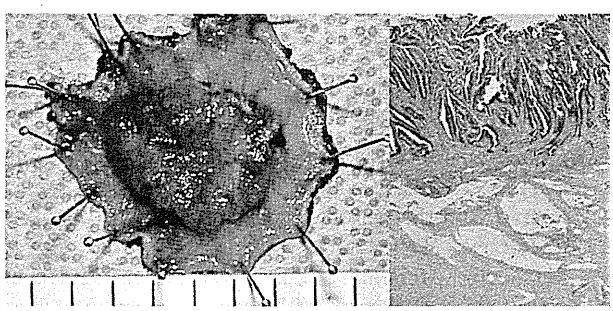

図 1　追加腸切除例の初回摘出標本および病理組織像

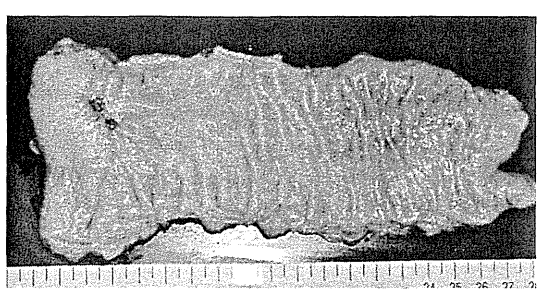

図 2　追加腸切除例の腸切除標本

中・高分化型腺癌であった（表 1）。全例において切除断端は癌細胞陰性であり，浸潤先進部の簇出は Grade 0/1 であった。11 例に脈管侵襲陽性を認めたため，所属リンパ節転移高リスク群として患者に対して十分な説明を行ったが，追加腸切除を行った症例は SM3 癌の 1 例のみであった（図 1）。本症例に対して 1 か月後に超低位前方切除術を施行した結果，251 番リンパ節に転移を認めた（図 2）。SM2 癌 11 例中 6 例に対してリンパ節のサンプリングを伴う経仙骨的直腸局所切除術を施行し，残る 5 例は経肛門的直腸局所切除術を施行した。追加腸管切除を行わなかった SM2 癌 9 例中再発を来したものは 1 例のみ

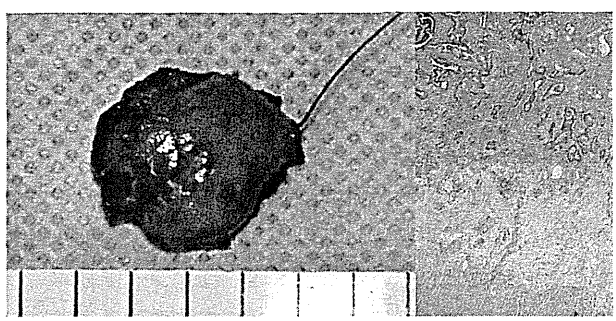

図 3　リンパ節再発症例の初回摘出標本および病理組織像

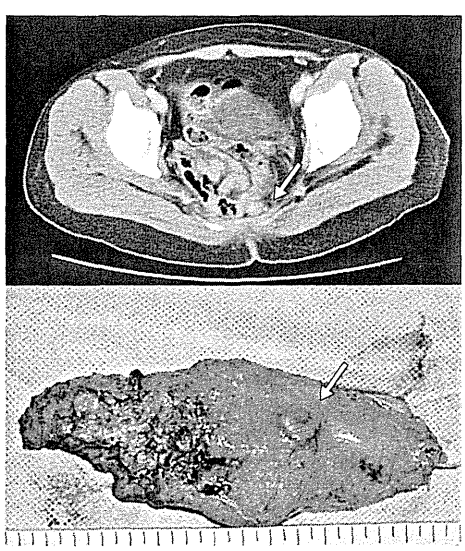

図 4　リンパ節再発症例の再発時 CT 検査および摘出標本

であり（図 3），初回手術 6 か月に直腸間膜内リンパ節を認めたため，超低位前方切除術を施行し，現在も無再発生存中である（図 4）。残る 8 例は，他の癌や重篤な術前合併症などを理由に追加切除を受けなかったが，現時点で再発はみられていない（観察期間中央値 48 か月）。

IV. 考　察

進行直腸癌に対しては total mesorectal excision (TME) を行うことで予後が改善することが欧米で報告されたが，下部直腸癌に対する超低位前方切除においては，double stapling technique (DST) 吻合あるいは経肛門吻合のいずれにおいても，ある程度の肛門機能低下は不可避である[1]。一方，内視鏡的粘膜切除が開発され，早期直腸癌患者の一部は腸切除を回避できるようになったものの，下部直腸癌では手技的に切除困難を伴う症例があり，腸切除を余儀なくされることもある。その点，直腸局所切除は肛門温存が可能である上に機能低下が軽微であり，早期の下部直腸癌に対しては有用な術式である[2,3]。また，内視鏡切除では腸穿孔や術後出血の可能性があるが，直腸局所切除では腫瘍切除と欠損部の縫合閉鎖を直視下に確実に施行できる[4]。さらに直腸局所切除は，全層切除を行うことにより詳細な病理検索が可能である。内視鏡的粘膜切除では，分割切除はもちろん，たとえ一括切除できたとしても直腸局所切除に比べると病理学的検索に限界がある。

欧米では直腸局所切除に放射線化学療法と組み合わせた治療がすでに開始されており，筋層に及ぶ腫瘍に対しても適応が拡大しているが，本邦ではリンパ節転移の危険がある SM 癌に対してはリンパ節郭清を伴う腸切除が推奨されている[5]。ゆえに直腸局所切除の術式選択に当たっては，術前壁深達度診断とリンパ節転移診断が極めて重要である。画像診断技術が向上したとはいえ，注腸造影，下部消化管内鏡検査，骨盤造影 CT および MRI 検査を組み合わせても，現時点での術前壁深達度診断とリンパ節転移診断は 90% 前後である。今後，さらに画像診断技術が発展して，術前壁深達度診断とリンパ節転移診断率が向上することによって，直腸局所切除がより正しく選択されると思われる。

結　語

直腸局所切除術は肛門温存が可能であり，侵襲が少なく，全層切除により詳細な病理検索が可能であるという利点があり，正しく選択されれば非常に有用な術式である。

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

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See Comment page 565

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Summary

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

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

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

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

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

Introduction

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

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

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

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

Methods

Study design and participants

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

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

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

See Online for appendix

Randomisation and masking

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

Procedures

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

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

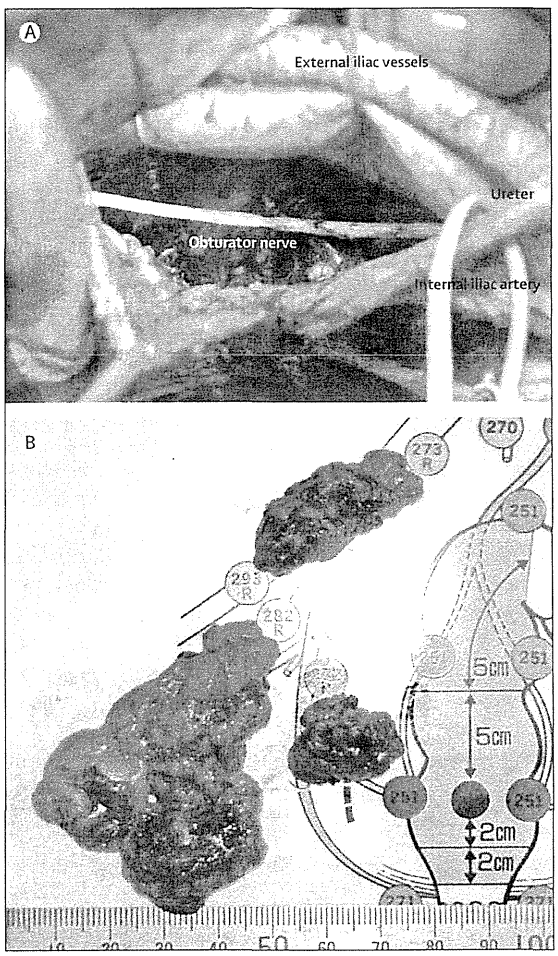

Figure 1: **Lateral lymph node dissection**
(A) The obturator fossa after lateral lymph node dissection, with the dissected fatty and connective tissues (right side). (B) Dissected fatty and connective tissues including lymph nodes.

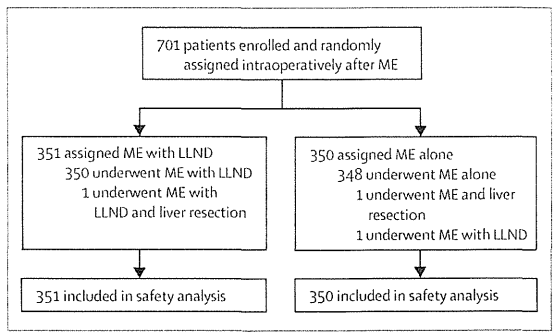

Figure 2: **Trial profile**
We did not collect data for the number of eligible patients before enrolment. ME=mesorectal excision. LLND=lateral lymph node dissection.

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

For surgical quality control and assurance, intraoperative photographs were taken. In the mesorectal excision alone group, five photos were taken: the site of inferior mesenteric artery ligation, the preserved right and left hypogastric nerves, and the anterior and posterior sides of the resected specimen. In the mesorectal excision with lateral lymph node dissection group, 11 photos were taken: the site of inferior mesenteric artery ligation, the preserved right and left hypogastric nerves, the right and left internal iliac artery, the right and left obturator fossa, the anterior and posterior sides of the resected specimen, and the right and left dissected fatty and connective tissues in the lateral pelvic lymph node area. These photographs were assessed and scored by the committee for quality control and assessment of surgery, and the surgical procedure was discussed and assured according to the score at meetings held twice a year.

Adjuvant chemotherapy with the Roswell Park regimen of intravenous fluorouracil (500 mg/m²) and L-leucovorin (250 mg/m²) was given to patients with pathological stage III tumours in both groups. Patients who were stage II did not receive adjuvant chemotherapy.[16] This regimen consisted of three courses of six doses of weekly chemotherapy followed by a 2-week rest. Adjuvant radiotherapy was not used.

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

Statistical analysis

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

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

Role of the funding source

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

Results

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

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

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

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

Table 1: **Characteristics of patients**

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

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

Table 2: **Operative details**

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

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

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

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

Discussion

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

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

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

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

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

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

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

Panel: Research in context

Systematic review

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

Interpretation

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

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

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

Contributors

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

Conflicts of interest

We declare that we have no conflicts of interest.

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