特集 最新の診療ガイドラインの実地診療応用への手引き

内視鏡外科診療ガイドライン

Practice guidelines for endoscopic surgeries

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内視鏡外科手術は，消化器外科をはじめ多岐にわたる外科領域の疾患に対して，低侵襲手術としてのカテゴリーを確立して，この20年余りの間で急速な発展を遂げた．従来型の手術と異なる新しい手術方法という特性を有しており，医療者が適切に手術適応を判断し，安全な治療を実践することを目的に，日本内視鏡外科学会は，2008年9月に「内視鏡外科診療ガイドライン」を作成・発行した．2009年9月，このガイドラインに関する学会員へのアンケート調査が施行され，一般臨床への浸透や治療方針変更への影響などその検証結果が報告されている．今後，このガイドラインは，新たに蓄積されるエビデンスを積極的に組み入れながら，改訂作業を繰り返し，その意義をさらに高めていくものと期待される．

はじめに

1987年に腹腔鏡下胆嚢摘出術が初めて行われて以来，内視鏡外科手術は，患者のQOLを重視する近年の医療，社会のニーズに合致し，「低侵襲手術(Minimally invasive surgery)」というカテゴリーを確立して，この20年余りの間に急速な発展を遂げた．その対象疾患は，消化器外科をはじめ，泌尿器科，産婦人科，呼吸器外科，小児外科，整形外科，麻酔科など外科系全般領域へと多岐にわたって拡がった[1]．本邦では，1990年より，各地で腹腔鏡下胆嚢摘出術が施行され始め，その対象は当初，良性疾患に限られていたが，その後早期癌，さらには進行癌にも施行されるようになってきた[2]．

新しい治療学が臨床に導入された当初は，それぞれの治療法に特有な合併症が頻発して，その順調な発展が損なわれるという歴史が古くから繰り返されてきている[3]．この分野においても，不幸にも2004年に刑事事件として取り扱われた腹腔鏡下前立腺摘除術の手術死亡例が発生した．この状況を受けて，日本内視鏡外科学会は，当時の北島政樹理事長のもと，医療者が適切に手術適応を判断し，安全な治療を実践することを目的に，2大プロジェクトとして，技術認定制度の立ち上げ

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とともに，ガイドラインの作成作業を開始した．当時のガイドライン委員長である谷川允彦教授をはじめ委員会のメンバーが中心となって，2008年9月，「内視鏡外科診療ガイドライン」[4]の発行が実現した．

本稿では，このガイドラインの作成手順，内容とガイドラインの実臨床への影響を検証するアンケート調査報告[5]について述べたい．

I. 内視鏡外科診療ガイドラインの理念と目的

内視鏡外科診療ガイドライン[4]によると，その理念と目的，また内容の特徴は以下の如くである．すなわち，従来型の外科治療とは異なる新しい治療様式であるため，その代表的な情報を，臨床医を含めた医療専門職ならびに患者・家族に提供する目的で作成されている．国内外の臨床研究や臨床試験の結果に基づき，各疾患の内視鏡外科診療のエビデンスレベルと推奨程度・推奨グレードが記載されている．

ここで留意すべき点は，内視鏡外科領域は歴史が浅いために質の高いエビデンスが一般に少なく，したがって，推奨グレードで表現すると多くが“C”(行うよう勧めるだけの根拠が明確でない)となり，その結果，ガイドラインとしての性格が曖昧となることである．

幹事委員会での討議によって，エビデンスが十分にある分野は推奨グレードで，その他の分野は“望ましい”などのより穏やかな表現法で記載し，「胆嚢領域」や「不妊症」などの分野ではあえてQ&A形式の記載方法を用いるなど，領域分科会ごとの創意工夫がなされている点が特徴的である．本診療ガイドラインを発刊する目的は以下の3点に集約されている．

①本学会技術認定取得者など内視鏡外科学診療に十分な経験と治療成績を修めている外科医を対象にした診療ガイドラインであり，最新の論文や専門家の意見などの科学的に重要なエビデンスに基づいて，各種疾患の治療の適応基準や治療方法の推奨を可能な限り明確にすること．

②不必要な治療を排除すること．

③情報を患者や家族に開示して，国民が安心して治療を受けられるようにすること．

それゆえ，経験の少ない医師や施設においては指導者が立ち会い，あるいは指導施設における十分な研修の後にガイドラインに基づいた診療が行われることが望まれる．

II. 内視鏡外科診療ガイドラインの作成過程と内容

各領域を代表する幹事委員が責任者となる領域分科会と関連学会・研究会から推薦された委員による評価委員会，ならびに外部評価委員会などによる組織体制として，図1のような過程で診療ガイドラインの作成が行われている．パブリックコメントの収集と外部評価委員会による最終評価を受け，2008年9月，「日本内視鏡学会診療ガイドライン第1版」[4]が発行されている．

III. 各領域における内視鏡外科診療ガイドライン

各領域のガイドラインうち，代表的な疾患について，その内容の骨子を以下に述べる．

1．食道癌(表1)

胸腔鏡下食道切除術は肺合併症の減少および手

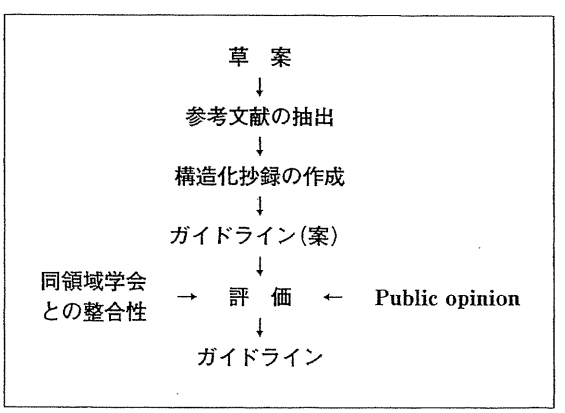

図1　内視鏡外科診療ガイドライン作成手順（文献4より引用改変）

術侵襲の軽減を目的に1992年から導入が始まった．わが国では，1995年から報告がみられ，2002年4月より胸腔鏡下食道切除術が社会保険診療報酬に収載されたこともあり，さらに普及が進んだ[6]．今回，最も多く研究・報告されている胸腔鏡下食道切除術に重点が置かれている．

2．胃食道逆流症(表2)

胃食道逆流症に対する内視鏡手術は，腹腔鏡手術と胸腔鏡手術の2種類があるが，臨床的には腹腔鏡手術が圧倒的に多く行われている[7]．エビデンスレベルの高い文献は腹腔鏡手術に限られるため，今回のガイドラインでは腹腔鏡手術について記載する．また，治療対象となる胃食道逆流症は人種差や食生活の違いにより欧米人に多いため，欧米での研究が中心となっている．

3．胃癌(表3)

胃癌に対する腹腔鏡下胃切除術は，1991年にわが国で最初に腹腔鏡補助下幽門側胃切除術として開発され[8]，現在，年々増加の一途をたどっている．日本内視鏡外科学会の第10回アンケート調査結果[2]では幽門側胃切除術が最も多く施行され(57.1%)，胃局所切除(31.4%)，胃内手術(5.7%)，噴門側胃切除術(2.0%)，胃全摘(1.2%)と続いている．本ガイドラインでは，最も多く施行され，研究されている腹腔鏡補助下幽門側胃切除術に重点が置かれている．

4．穿孔性消化性潰瘍(表4)

1990年にMouretら，Nathansonらにより，穿孔性消化性潰瘍に対する腹腔鏡下大網充填術が報告された．わが国においては，1992年に大上ら[9]により穿孔性十二指腸潰瘍に対する腹腔鏡下大網充填縫合閉鎖術が報告され，その簡便性，有用性から多数の施設で腹腔鏡手術が行われており，年々増加している．

表1 食道癌に対する胸腔鏡下食道切除術のガイドライン(文献4より引用)

■適応基準
食道癌治療ガイドラインによるとリンパ節転移の少ない表在癌が良い適応とされている．整容性に優れている点や術後疼痛の少ない点から胸腔鏡手術を導入する施設が増加しているが，縦隔リンパ節郭清は高度な内視鏡手術手技が要求されることから，各施設の手術チームの熟練度や施設の治療成績を正確に把握し説明したうえで行うべきである．
■推　奨
食道癌に対する胸腔鏡下食道切除術は開胸手術と同等の安全性と根治性を兼ね備えた低侵襲手術であるとする報告があるが，十分な症例数を有するランダム化比較試験はこれまで報告されていない．今後，開胸手術との比較によるエビデンスの高い臨床試験が望まれる．

表2 胃食道逆流症に対する腹腔鏡手術のガイドライン(文献4より引用)

■適応基準
胃食道逆流症に対する手術適応はさまざまな学会で提唱されているが，内視鏡手術の観点からSAGES(Society of American Gastrointestinal Endoscopic Surgeons)のガイドラインに記載されている適応がわが国でも参考になる．すなわち，①内科的治療に失敗した症例，②年齢，治療期間，医療費など諸事情により，内科的治療に成功しても外科治療が望ましい症例，③Barrett食道や狭窄，高度の食道炎を合併する症例，④巨大な食道裂孔ヘルニアによる出血や嚥下障害などの合併症を有する症例，⑤喘息，嗄声，咳嗽，胸痛，誤嚥などの非定型的な症状を有したり，24時間pHモニタリングで高度の逆流を証明し得る症例である．
■推　奨
より高度な逆流防止効果を期待するためには全周性のNissen手術が適しているが，術後早期の嚥下障害を回避するには非全周性の噴門形成術であるToupet手術または前壁噴門形成術が適している．噴門形成術の本来の目的である逆流防止効果を考えると前壁噴門形成術よりもToupet手術が優れている．したがって，Nissen手術またはToupet手術が推奨され，その選択には高度な逆流防止効果を期待するか，術後早期の嚥下障害を回避するかを考慮することが望ましい．

表3 胃癌に対する腹腔鏡下胃切除術のガイドライン(文献4より引用)

■適応基準

胃癌治療ガイドラインによる腹腔鏡手術の適応を推奨する.

・腹腔鏡補助下胃切除術(縮小手術A)
　EMRの適応とならない肉眼的M癌(cM, sM)でsN0
　分化型1.5 cm以下の肉眼的SM癌(cSM, sSM)でsN0

・腹腔鏡補助下胃切除術(縮小手術B)
　肉眼的SM癌(cSM, sSM)でsN0
　腫瘍径が2.0 cm以下の肉眼的SM癌(cSM, sSM)でD1+βリンパ節郭清で治療が期待できるsN1

■推　奨

胃癌に対する腹腔鏡下胃切除術は開腹手術と同等の安全性と根治性を兼ね備えた低侵襲性手術であるとする報告が多いものの, 十分な症例数を有したランダム化比較試験はこれまで報告されていない(グレードC). 今後, 開腹手術との比較によるエビデンスレベルの高い臨床試験が望まれる.

表4 穿孔性消化性潰瘍に対する腹腔鏡手術のガイドライン(文献4より引用)

■適応基準と推奨

身体的所見, 検査所見などから消化性潰瘍による穿孔性腹膜炎が疑われ, 患者に術前リスク(発症から24時間以上経過, 収縮期血圧90 mmHg以下, 併存疾患ありなど)がない場合, 診断および治療目的に腹腔鏡手術が推奨される. (推奨度A)

5. 大腸癌(表5)

1991年に米国のJacobsらが世界で初めて腹腔鏡下大腸切除術を報告し, 本邦では1993年に渡邉ら[10]が早期大腸癌に対する低侵襲手術として腹腔鏡下大腸癌手術を報告した. 導入初期には早期癌のみに適応されていたが, 2002年4月より腹腔鏡下手術の保険適応が大腸癌全体に拡大されたこともあり, 現在では欧米と同様に本邦においても進行大腸癌に適応される場合が多くなってきている. しかし, 進行大腸癌に対する長期成績はいまだ十分に明らかでない[11][12].

6. 虫垂炎(表6)

1983年, Semmの報告に始まる腹腔鏡下虫垂切除術(Laparoscopic appendectomy：LA)は, 他の腹腔鏡下手術と同様に, 低侵襲性で美容的にも優れていると考えられ, これまでに多くの施行例が蓄積されている. 虫垂炎手術全体からみると, 腹腔鏡下手術が占める割合は必ずしも高くなく, 本手術は準緊急手術であり, 器材の準備や全身麻酔の必要性, 研修医教育など, 施設の状況によって本法が必ずしも第一選択になっていないことがその要因と考えられる. しかし, 診断困難症例や肥満症例は, その有用性が評価されている[13].

7. 胆石症(表7)

わが国での腹腔鏡下胆嚢摘出術は1990年に報告されて以来, その低侵襲性により良性胆嚢疾患に対する標準的治療として, 広く一般認識されている. 1990年代初頭には, 急性炎症のない有症状胆嚢結石症のみが一般的な適応とされていたが, その後炎症のある有症状胆石症(急性胆嚢炎の項参照), 良性疾患である胆嚢ポリープや胆嚢腺筋症なども一般的な手術適応とされるようになってきた.

8. 乳腺疾患(表8)

乳腺内視鏡手術は内視鏡手術手技により手術創の縮小化と移動を実現し, 整容性と手術効果の両面を満足させることができる手術法である. しかし, 本法の施行にあたっては従来の乳腺手術と比較して特有の合併症が生じることが報告されており, 十分な知識とテクニックの習得が必要である.

イドライン委員長である谷川允彦教授が中心となってアンケート調査を行い，その結果が報告されている[5]．この調査では一般消化器外科，小児外科，整形外科に限定して行われている．

1．アンケート調査の方法

質問項目は，各領域に共通した14項目(表9)と，それぞれの領域固有の質問項目に分けて記載を求めている．前途の3科について，それぞれ日本内視鏡外科学会会員と日本小児内視鏡外科・手術手技研究会の施設会員94名ならびに日本内視鏡低侵襲脊椎外科学会の世話人の合計2,111名の先生方に発送し，合計709名(34%)から回答を得ている．

表9　アンケート質問項目(領域共通)(文献5より引用)

①診療GLを持っているか
②診療GLを参照するか
③参照したい理由
④診療GLの有用性
⑤診療GLの欠点
⑥患者用診療GLが必要か
⑦診療GLが患者ICに有用か
⑧患者用診療GLが不必要の理由
⑨自施設の治療方針の決定方式は
⑩各領域固有の一般的質問
⑪Q&A形式の記載の方がよいか
⑫欧米の診療GLをみたことがあるか
⑬診療GL出版後に治療方針に変化があった
⑭診療GLの記載内容をもとにした患者クレームがあったか

2．調査結果

一般消化器外科領域の調査結果では，回答施設の20%が大学病院ないしがん専門病院であり，DPC施行病院が67%であった．“診療ガイドラインを持っている”が65%，“常にあるいは時々参照”は67%であった．“有用性をあげるとすれば”の理由で“統一した治療の適応が示された”ないし，“参考文献，参考データが示された”が87%であり，“有用と思わない”は2%ときわめて少なかった．また，“EBMに基づいていない”や“施設の治療方針とかけ離れている”などの欠点の指摘は34%である一方，“とくに欠点はない”が34%と相半ばした．“診療ガイドライン出版後の治療方針変更の有無”については“大幅に変わった”は0%とまったくなかったが，“一部変わった”が38%であり，“まったく変わらない”は50%であった(図2，3)．

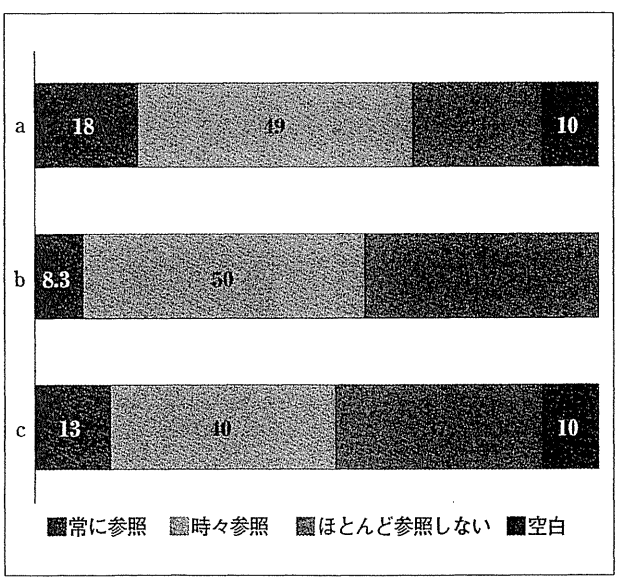

図2　診療ガイドライン参照程度(文献5より引用改変)
a：一般外科消化器外科　b：整形外科　c：小児外科

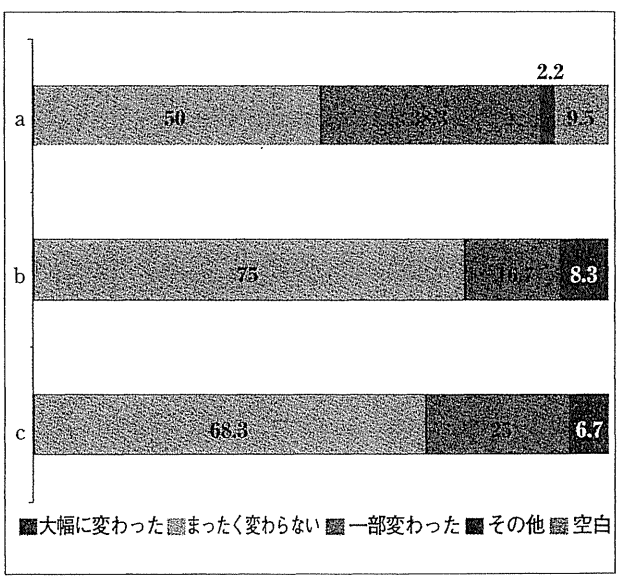

図3　診療ガイドライン出版後，治療方針変更の有無
(文献5より引用改変)
a：一般外科消化器外科　b：整形外科　c：小児外科

表5 大腸癌に対する腹腔鏡下手術のガイドライン(文献4より引用)

■適応基準と推奨

・盲腸・上行結腸，S状結腸・直腸S状部の癌でStage 0，Iに対する腹腔鏡下手術は低侵襲手術として有用と考えられ，推奨される．Stage 0，Iでも横行結腸，左結腸曲近傍の下行結腸あるいは直腸の癌の場合には難易度が高くなるため，慎重に適用すべきである．

・Stage II，IIIに関しては，多施設での長期成績が十分明らかになっていないため，積極的には推奨されない．とくに，腫瘍の占居部位が，横行結腸，左結腸曲近傍の下行結腸あるいは直腸にある場合には，各施設(手術チーム)の熟練度や正確なデータ(成績)を説明した上で十分なインフォームド・コンセントのもとで行うことが望まれる．

・Stage IVに関しても積極的には推奨されない．すなわち，肝転移，腹膜転移や他臓器浸潤があっても場所・個数や程度によって開腹手術で取りきれる場合，逆に姑息切除でもリンパ節転移が高度で腹腔鏡下手術が困難な場合などがあるため，個々の症例で十分な検討と適切なインフォームド・コンセントに基づいて手術を行うことが望まれる．

表6 虫垂炎に対する腹腔鏡下手術のガイドライン(文献4より引用)

■適応基準と推奨

術前に虫垂炎の診断確定が困難な場合や肥満患者などに対して腹腔鏡下手術は有用と考えられ，推奨される．穿孔あるいは膿瘍形成が疑われる場合には腹腔鏡下手術は積極的には推奨されない．その他多くの一般的な合併症のない虫垂炎の場合には，施設の技術と設備状況を考慮した上で，腹腔鏡下手術を選択することも有用である．

表7 腹腔鏡下胆嚢摘出術のガイドライン(文献4より引用)

■適応基準と推奨

・腹腔鏡下胆嚢摘出術
　有症状胆嚢結石に対する手術治療は腹腔鏡下胆嚢摘出術が望ましい．(推奨度A)
・腹部手術既往症例に対する適応
　腹部手術既往のある症例に対しても腹腔鏡下胆嚢摘出術は適応となるが，個々の症例に対して手術創の位置や手術歴(回数，手術部位，腹膜炎の有無)を十分考慮して手術適応を決定することが望ましい．(推奨度C)
・高齢者症例に対する適応
　高齢者に対しての腹腔鏡下胆嚢摘出術は望ましく，全身状態を勘案して手術適応を決定する．(推奨度C)
・妊産婦症例に対する適応
　妊産婦症例に対しての腹腔鏡手術は適応であるが，妊娠中期の手術が望ましい．(推奨度C)
・肥満症例に対する適応
　肥満症例に対しては腹腔鏡下胆嚢摘出術が望ましい．(推奨度C)
・肝硬変症例に対する適応
　肝硬変症例ではChild A，Bに対しての腹腔鏡下胆嚢摘出術が望ましい．(推奨度B)
・慢性肺障害症例に対する適応
　慢性肺障害症例に対して腹腔鏡下胆嚢摘出術は推奨できる．(推奨度C)

表8 乳腺疾患に対する内視鏡手術のガイドライン
(文献4より引用)

■適応基準と推奨

良性腫瘍：単発症例で摘出に際し整容性の面から創の延長を必要としない症例．

悪性腫瘍：乳房温存療法のガイドラインおよび従来法の適応に準拠し，かつ腫瘍が皮膚または筋膜に浸潤していないか近接していない症例．

IV. 内視鏡外科診療ガイドラインの検証

発行されたガイドラインが一般臨床にどのように利用され，影響しているかを検証することは重要である．内視鏡外科診療ガイドラインに関して，発刊後1年を経過した2009年9月に，当時のガ

おわりに

「内視鏡外科診療ガイドライン」の発刊までの経緯およびその内容と，このガイドラインが臨床現場にどのように影響しているかを検証するためのアンケート調査について概説した．今後，この新しい分野である内視鏡外科手術のガイドラインは，新たに蓄積されるエビデンスを積極的に組み入れながら改訂作業を繰り返し，その意義をさらに高めていくものと期待される．

文　献

1) 猪股雅史，北野正剛，白石憲男：内視鏡外科治療の現況と展望．日本臨牀 68(7)：1232-1238, 2010.
2) 内視鏡外科手術に関するアンケート調査－第10回集計結果報告－．日鏡外会誌 13：499-611, 2010.
3) 猪股雅史，北野正剛：がん手術の進歩．治療 91(10)：2496-2500, 2009.
4) 日本内視鏡外科学会編：内視鏡外科診療ガイドライン2008年版．金原出版，東京，2008.
5) 谷川允彦，奥田準二，宇山一朗ほか：内視鏡「外科診療ガイドライン」出版はどのように実臨床に影響しているか？－アンケート調査結果から－．日鏡外会誌 15：727-737, 2010.
6) Akaishi T, Kanada I, Higuchi N, et al：Thoracoscopic en-block esopagectomy with radical mediastinal lymphadenectomy. J Thorac Cardiovasc Surg 112：1533-1540, 1996.
7) 森 俊幸，跡見 裕：食道裂孔ヘルニア．日鏡外会誌 104：587-592, 2003.
8) Kitano S, Iso Y, Moriyama M, et al：Laparoscopy-assisted Billroth I gastrectomy. Surg. Laparosc. Endosc 4：146-148, 1994.
9) 大上正裕，北島政樹，若林 剛：十二指腸潰瘍穿孔例に対する腹腔鏡下手術．消化器内視鏡 4(8)：1227-1234, 1992.
10) 渡邊昌彦，大上正裕，寺本龍生ほか：早期大腸癌に対する低侵襲手術の適応．日消外会誌 26：2548-2551, 1993.
11) Kitano S, Kitajima M, Konishi F, et al：A multicenter study on laparoscopic surgery for colorectal cancer in Japan. Surg Endosc 20(9)：1348-1352, 2006.
12) 猪股雅史，衛藤 剛，白石憲男ほか：進行結腸癌に対する腹腔鏡下手術－厚生労働省班研究に基づく本邦の現況－．日本内視鏡外科学会雑誌 13(1)：47-53, 2008.
13) 猪股雅史，二宮繁生，田島正晃ほか：虫垂炎に対する腹腔鏡下手術の適応と限界．臨床外科 62(1)：35-40, 2007.

Cancer stem cell-related factors are associated with the efficacy of pre-operative chemoradiotherapy for locally advanced rectal cancer

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Abstract. Pre-operative chemoradiotherapy (CRT) is an important neoadjuvant therapy for locally advanced rectal cancer. In the present study, we investigated the factors that influence the efficacy of pre-operative CRT in locally advanced rectal cancer. We divided 50 patients with locally advanced rectal carcinoma treated with pre-operative CRT into two groups according to the grade of tumor response to pre-operative CRT: low-sensitivity group and high-sensitivity group. As candidates for the prediction of sensitivity to pre-operative CRT, clinicopathological factors and 12 biomarkers, including factors related to tumor growth, cell cycle, apoptosis, tumor stroma and cancer stem cells, were examined immunohistochemically in 48 resected specimens. Thirty-one tumors showed high sensitivity and 19 showed low sensitivity to pre-operative CRT. The status of stem cell-related factors, CD133 and CD24, was significantly associated respectively with sensitivity to pre-operative CRT (P=0.003, P=0.029). In 10 tumors positive for both CD133 and CD24, low sensitivity to CRT was found in 9 (90%), whereas in 16 tumors negative for both CD133 and CD24, low sensitivity was found in 3 (19%). Other pathological parameters were not associated with tumor response to pre-operative CRT. In conclusion, overexpression of cancer stem cell-related factors, CD133 and CD24, is associated with the sensitivity of locally advanced rectal cancer to pre-operative CRT.

Introduction

Colorectal cancer is a leading cause of morbidity and mortality in developed countries (1). In Japan, an increasingly Westernized diet has led to a high incidence of colorectal cancer. Patients with rectal cancers are known to have an increased rate of local recurrence and decreased survival time compared to patients with tumors of the colon, a result due primarily to the surgical constraints imposed by the location of the rectum within the pelvis (2).

Pre-operative chemoradiotherapy (CRT) is a neoadjuvant therapy for locally advanced rectal cancer that reduces the incidence of local recurrence and improves survival (3). Therefore, CRT is widely used in many countries of the world. However, several tumors show a marked response to CRT, whereas others do not. Furthermore, several adverse events related to CRT, such as enteritis, anorexia, cardiac/thromboembolic events, radiation dermatitis and hematologic toxicity, were reported to occur at frequencies of 6-43% (4). Thus, pre-operative indicators of chemoradiosensitivity are required to avoid unnecessary application of pre-operative CRT, yet little is known about potential biological markers that may be associated with response to pre-operative CRT.

Recently, the discovery of rare subpopulations of cancer stem cells has created a new focus in cancer research. The heterogeneity of tumors can be explained by the concept of cancer stem cells supported by anti-apoptotic signaling. There are a few reports on cancer stem cells related to chemoradiation resistance (5,6). Therefore, in this study we investigated the factors, including cancer stem cell-related factors, that influence the sensitivity of locally advanced rectal cancer to pre-operative CRT using surgical resected specimens to consider tumor heterogeneity.

Materials and methods

Patients. A total of 50 patients with locally advanced rectal carcinoma were treated with pre-operative CRT and surgical resection at the Department of Surgery I, Oita University Faculty of Medicine, or associated institutions (Beppu Medical Center, Nakatsu Municipal Hospital, Oita Prefectural Hospital and Nankai Hospital) between January 2000 and May 2010. Tumors were located at the middle or lower third of the rectum and were diagnosed as clinical stage T2, T3 or T4, Nx and M0 (UICC TNM Classification of Malignant Tumours, 2009). T stage was determined by computed tomography (CT) scan or endoscopic ultrasonography. No

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distant metastases were detected on plain chest X-rays or CT scans. Thirty-nine patients were treated with pre-operative CRT and another 11 patients were treated with pre-operative radiotherapy (RT) alone. The total dose of radiation in most cases was 45 Gy within 6 weeks, usually 1.5 Gy per treatment, five times per week. The total dose range was 40-50 Gy. Several chemotherapy regimens were used in the patients treated with CRT: TS-1 (80 mg/m^2) in 21 patients, 5-fluorouracil (5-FU)-based in 5 patients, tegafur/uracil (UFT) and leucovorin or UFT alone in 8 patients, and tegafur in 5 patients. Curative surgery that included total mesorectal excision was performed in all patients after an interval of approximately 4 weeks following completion of pre-operative treatment. Patient informed consent and approval of the local ethics committee was obtained prior to the study.

Immunohistochemistry. A total of 12 biomarkers were chosen as candidate predictive factors for the efficacy of pre-operative CRT (7-13). These factors included tumor growth-related factors, epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER2); cell cycle-related factors, p53, p21, Ki-67 and Bcl-1; apoptosis-related factors, Bcl-2 and apoptosis protease-activating factor-1 (APAF-1); tumor stroma-related factors, vascular endothelial growth factor (VEGF) and macrophage migration inhibitory factor (MIF); and cancer stem cell (tumor initiating cell)-related factors, CD133 and CD24. Postoperative resected specimens were used for immunohistochemistry.

Paraffin-embedded sections of tumor tissue from the resected rectum were cut at a thickness of 4 μm, deparaffinized in xylene and rehydrated. Endogenous peroxidase activity was blocked with 3% hydrogen peroxidase for 10 min. For antigen retrieval, sections were autoclaved at 121˚C in 10 mM citrate buffer, pH 6.0, for 10 min. Sections were then treated with primary antibodies. Immunostaining was performed by the avidin-biotin-peroxidase complex technique using a Histofine SAB-PO (Multi) kit (Nichirei Co., Tokyo, Japan) and diaminobenzidine for the visualization of the binding antibodies (14). The following primary antibodies were used: EGFR (clone EGFR113, 1:100; Lab Vision Inc., Fremont, CA, USA) (15); p53 (clone DO-7, 1:50; DakoCytomation, Glostrup, Denmark); p21 (clone SX118, 1:40; DakoCytomation); Ki-67 (clone MIB-1, 1:50; DakoCytomation); Bcl-1 (clone SP4; Nichirei Co.) (16); Bcl-2 (clone 124, 1:40; DakoCytomation); APAF-1 (NCL-APAF-1, 1:20; Novocastra, Newcastle, UK) (17); VEGF (VEGF A-20, 1:100; Santa Cruz Biotechnology, Santa Cruz, CA, USA) (18); MIF (FL-115, 1:200; Santa Cruz Biotechnology) (13); CD133 (ab19898, 1:200; Abcam, Tokyo, Japan) (19); and CD24 (clone SN3b, 1:100; Lab Vision Inc.) (20). Immunohistochemistry for HER2 was performed with HercepTest (DakoCytomation) (21). Negative controls were treated identically, omitting the primary antibodies. Tumor positivity for a given marker was evaluated using a pre-determined cut-off of 10% (the average of the percentage of tumor cells stained in five fields at x100 magnification: ≤10% tumor cell staining, negative; >10%, positive) according to previous studies (7,8,22). For Ki-67 immunoreactivity, staining was considered positive at >60% (23). Staining was assessed in the nucleus for p53, p21, Ki-67 and Bcl-1, and in the cytoplasm for EGFR, APAF-1, VEGF, MIF, CD133 and CD24. Immunoreactivity for Bcl-2 and HER2 expression was assessed in both the cytoplasm and/or the cell membrane. Staining intensity was not evaluated.

Table I. Patient and treatment characteristics.

Characteristic	No. of patients (n=50)	%
Age (years)		
Median	64	
Range	40-83	
Gender		
Male	37	74
Female	13	26
Surgery		
Total pelvic exenteration	1	14
Abdominoperineal resection	24	48
Sphincter-preserving operation	19	38
Macropathology		
Circumscribed	41	82
Infiltrative	9	18
Histology[a]		
Well differentiated	9	19
Moderately differentiated	31	66
Poorly differentiated	3	6
Mucinous	4	9
T-category[a]		
pT1	2	4
pT2	8	17
pT3	27	57
pT4	10	21
N-category		
pN0	38	76
pN$^+$	12	24
Vessel invasion		
Negative	25	50
Positive	25	50
Tumor response (CRT sensitivity)		
High sensitivity	31	62
Low sensitivity	19	38

[a]Three tumors were excluded from the pathological study due to complete pathologic tumor regression. CRT, chemoradiotherapy.

Classification of response to pre-operative CRT. Tumor response to pre-operative CRT was evaluated pathologically on postoperative specimens according to the evaluation of the standard of therapeutic effect provided in the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus edited by the Japanese Society for Cancer of the Colon and Rectum (24). According to these standards, evaluation of the therapeutic effect was categorized according to five grades: grade 0, absence of regressive changes; grade 1a, regressive change of tumor <1/3; grade 1b, regressive change of

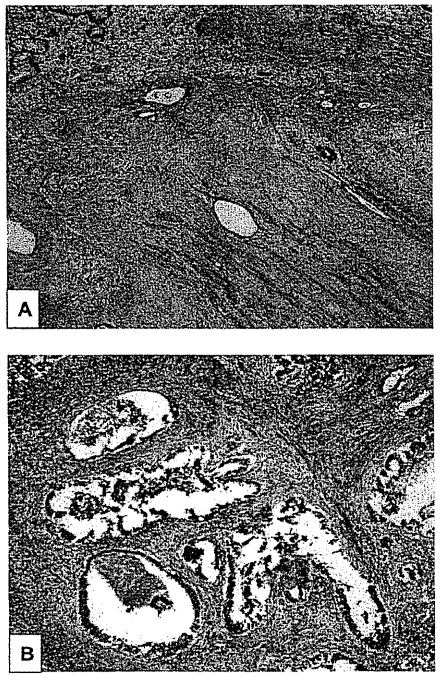

Figure 1. Photomicrographs indicating classification of the pathological response of pre-operative CRT in rectal cancer. (A) High-sensitivity case in which most tumor cells are replaced by fibrosis accompanying the infiltration of inflammatory cells (H&E stain; original magnification, x40). (B) Low-sensitivity case in which most tumor cells remain with mild tumor necrosis and regressive change (H&E stain; original magnification, x40).

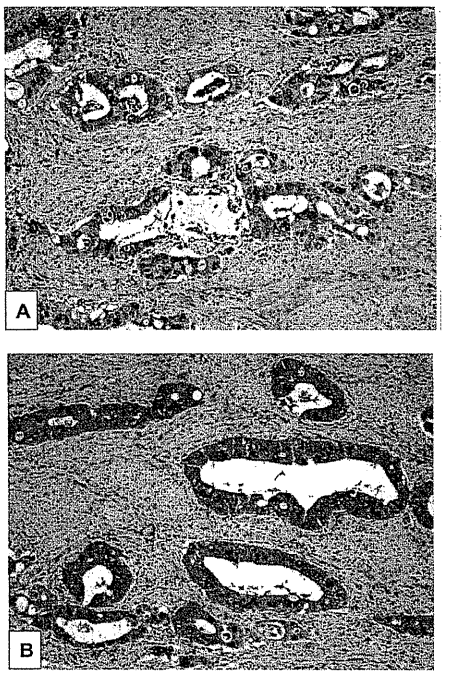

Figure 2. Photomicrographs showing immunohistochemical staining of CD133 and CD24 in rectal carcinoma. (A) Cytoplasmic expression of CD133 in tumor cells is observed (original magnification, x200). Glioblastoma tissue sections were used as a positive control. (B) Strong cytoplasmic expression of CD24 in tumor cells is observed (original magnification, x200). Ovarian serous adenocarcinoma tissue sections were used as a positive control.

tumor <2/3; grade 2, regressive change of tumor >2/3; grade 3, absence of residual tumor cells. We considered grades 0 or 1a to indicate low sensitivity and grades 1b, 2 or 3 to indicate high sensitivity to pre-operative CRT (Fig. 1).

Statistical analysis. For statistical comparisons of patient characteristics between the two groups (low sensitivity and high sensitivity), the Chi-square test, the Fisher's exact probability test or the unpaired t-test was used. A value of $P<0.05$ was considered statistically significant. All analyses were performed with SPSS Software (version 11.0) (SPSS Japan Inc., Tokyo, Japan).

Results

Patient and tumor characteristics. There were 37 (74%) men and 13 (26%) women included in the study. The median age was 64 years (range 40-83). Abdominoperineal resection was performed in 24 (48%) patients and a sphincter-preserving operation was performed in 19 (38%) patients. Macroscopic findings showed 82% of the tumors to be circumscribed tumors and, histologically, most (85%) of the tumors were of the well or moderately differentiated type. Lymph node metastasis was observed in 12 (24%) patients. Vessel invasion was observed in 25 (50%) patients. On the basis of the classification of responses to pre-operative CRT, 31 tumors showed high sensitivity and 19 tumors showed low sensitivity to pre-operative CRT (Table I).

Status of response to CRT according to various clinical parameters. Gender, age, macropathology, location, histology, N-category and surgery were not associated with tumor response (Table II). Of the 10 patients with pT1-2 tumors, 9 showed high sensitivity. The number of pT3-4 tumors showing high sensitivity was nearly equal to those showing low sensitivity ($P=0.034$). Of the tumors negative for vessel invasion, 21 of 25 showed high sensitivity, whereas 15 of 25 tumors positive for vessel invasion showed low sensitivity ($P=0.003$).

Response rates according to various pathological parameters. Factors related to tumor growth, the cell cycle, apoptosis and tumor stroma were not associated with tumor response (Table III). Only factors related to cancer stem cells (tumor-initiating cells) were associated with tumor response. A significant association was found between the resistance of the tumor to treatment and negative CD133 status ($P=0.003$), and there was a significant statistical correlation between the resistance of the tumor to treatment and positive CD24 status ($P=0.029$). In the high-sensitivity tumors, 3 tumors that had complete pathologic tumor regression were excluded from the pathological study (histology and T-category in Tables I and II) and immunohistochemical analysis since the resected specimens did not contain cancer cells (Fig. 2).

Response rates based on combinations of CD133 and CD24. When both CD133 and CD24 were positive, 9 of 10 (90%) tumors showed low sensitivity, whereas when both CD133 and CD24 were negative, 3 of 16 (19%) tumors showed low sensitivity (Table IV). Co-overexpression of CD133 and CD24 was associated with low sensitivity ($CD133^+$ and $CD24^+$ vs. others, $P=0.001$). Negative expression of both CD133 and

Table II. Response according to various clinical parameters.

Parameter	High sensitivity (n=31)	Low sensitivity (n=19)	P-value
Gender			0.481
Male	24	13	
Female	7	6	
Age (years)			0.635
Median	64	65	
Range	44-82	40-83	
Macropathology			0.715
Circumscribed	26	15	
Infiltrative	5	4	
Location			0.273
Upper	4	5	
Lower	27	14	
Histology[a]			0.102
Well/moderate differentiation	26	14	
Poor/mucinous differentiation	2	5	
T-category[a]			0.034
pT1/2	9	1	
pT3/4	19	18	
N-category			0.764
pN0	24	14	
pN1,2	7	5	
Vessel invasion			0.003
Negative	21	4	
Positive	10	15	
Surgery			0.464
LAR/Lap. LAR	13	6	
APR/Lap. APR	18	13	

[a]Three tumors were excluded from pathologic study due to complete pathologic tumor regression. APR, abdominoperineal resection (including total pelvic exenteration); Lap., laparoscopic; LAR, low anterior resection (including sphincter-preserving operation).

CD24 was associated with high sensitivity ($CD133^-$ and $CD24^-$ vs. others, P=0.030).

Discussion

The present study demonstrated that co-overexpression of cancer stem cell-related factors, CD133 and CD24, was significantly associated with locally advanced rectal cancer exhibiting low sensitivity to pre-operative CRT. This result suggests that these two biomarkers may influence sensitivity to pre-operative CRT.

In this study, we used resected specimens from patients who had been treated with pre-operative CRT. For identifying factors which predict the efficacy of CRT before treatment, the use of pre-treatment biopsy specimens is advisable. However, there is heterogeneity in the tumor (5). Therefore, biopsy specimens were not used, and resected specimens were used to investigate the entire tumor specimen.

For the evaluation of CD133 and CD24 expression, immunostaining was classified using the 10% cut-off scoring system. Although one report set the cut-off value to 50%, we adopted the standard system as it has been widely used in many studies. Expression of CD133 and CD24 was distributed evenly within the resected tumors. In the localization of staining, membranous expression of CD24 without cytoplasmic positivity was detected, but we did not include it as being indicative of positive expression.

The concept of cancer stem cells which has been proposed in the field of blood cancer (25) has been adjusted to address solid tumors, such as those of colorectal cancer (26). The fundamental cancer stem cell concept assumes that cancer cells exhibit a hierarchy, as do normal cells, and that a small fraction of cancer cells are maintained as 'cancer stem cells', which have the ability of self-renewal and differentiation (27). Cancer stem cells have recently been proposed to be the cancer-initiating cells that are responsible for tumorigenesis and for contributing to drug resistance in cancer (28). Although a comparatively large number of studies have been reported concerning cancer stem cells and resistance to either chemotherapy or radiotherapy in various cancers, there are few studies available concerning cancer stem cells and resistance to CRT (5).

Table III. Response according to various pathological parameters.

Biomarker	High sensitivity (n=28)	Low sensitivity (n=19)	P-value
HER2			1.000
+	1	0	
-	27	19	
EGFR			0.453
+	4	5	
-	24	14	
VEGF			0.119
+	21	18	
-	7	1	
MIF			0.770
+	13	8	
-	15	11	
p53			0.137
+	24	19	
-	4	0	
p21			0.143
+	5	7	
-	23	12	
Ki-67			0.739
+	19	12	
-	9	7	
Bcl-1			1.000
+	7	4	
-	21	15	
Bcl-2			0.435
+	16	13	
-	12	6	
APAF-1			0.119
+	21	18	
-	7	1	
CD133			0.003
+	2	9	
-	26	10	
CD24			0.029
+	14	16	
-	14	3	

+, positive expression; -, negative expression.

Table IV. Response according to combinations of CD133 and CD24.

Case	High sensitivity (n=28)		Low sensitivity (n=19)	
	No.	%	No.	%
$CD133^+$ and $CD24^{+a}$	1	10	9	90
$CD133^+$ and $CD24^-$	1	100	0	0
$CD133^-$ and $CD24^+$	13	65	7	35
$CD133^-$ and $CD24^{-b}$	13	81	3	19

[a]($CD133^+$ and $CD24^+$) vs. others, P=0.001. [b]($CD133^-$ and $CD24^-$) vs. others, P=0.030.

CD133 and CD24 have been reported as cancer stem cell markers of colorectal cancer in previous studies (26,29,30). CD133 is a 5-transmembrane glycoprotein of 865 amino acids with a total molecular weight of 120 kDa. CD133 antigen expression has been found in such various undifferentiated cells as hematopoietic stem cells (31) and fetal brain stem cells (32). In cancer cells, CD133 has been found to be expressed on cancer stem or tumor-initiating cells in cancers, such as leukemia (33), brain tumors (34) and colorectal cancer. CD24 consists of a small protein core comprising 27 amino acids, which is extensively glycosylated and is bound to the cell membrane via a phosphatidylinositol anchor (35). Several reports have shown that CD24 is expressed in several solid tumors, such as those of small-cell lung cancer and neuroblastoma (36,37), but not in those of colorectal cancer.

Recently, positive clinical studies on the effectiveness of pre-operative CRT on locally advanced rectal cancer have been reported (38). However, pre-operative CRT is not effective in all cases and, actually, cases in which no antineoplastic effect was obtained also exist. Since the treatment period for pre-operative CRT is approximately 10 weeks, patients who obtain no response to CRT lose valuable time during which they could have been treated more effectively. Thus, it is necessary to investigate factors which influence the efficacy of pre-operative CRT.

The results of the present study suggest that the presence of CD133 and CD24 expression is associated with the efficacy of pre-operative CRT. Assuming that CD133 and CD24 are predictive factors of the sensitivity to pre-operative CRT, patients with both $CD133^+$ and $CD24^+$ are expected to have low sensitivity to CRT. So, it may be recommended that such patients undergo surgery without first undergoing CRT. However, since patients with both $CD133^-$ and $CD24^-$ are expected to have high sensitivity to CRT, it may be necessary to aggressively treat these patients first with pre-operative CRT.

In conclusion, the present study shows that the overexpression of cancer stem cell-related factors, CD133 and CD24, is associated with the sensitivity of locally advanced rectal cancer to pre-operative CRT. Further prospective studies are required to establish a new therapeutic system that appropriately uses pre-operative CRT for the benefit of patients with locally advanced rectal cancer. Our group is presently conducting a prospective study using biopsy specimens from pre-therapeutic tumors (UMIN003398). This retrospective study provides valuable information for realization of the ongoing prospective study.

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References

1. Jemal A, Siegel R, Ward E, *et al*: Cancer statistics, 2006. CA Cancer J Clin 56: 106-130, 2006.
2. Wolpin BM, Meyerhardt JA, Mamon HJ and Mayer RJ: Adjuvant treatment of colorectal cancer. CA Cancer J Clin 57: 168-185, 2007.
3. Sauer R, Becker H, Hohenberger W, *et al*: Pre-operative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351: 1731-1740, 2004.
4. Calvo FA, Serrano FJ, Diaz-González JA, *et al*: Improved incidence of pT0 downstaged surgical specimens in locally advanced rectal cancer (LARC) treated with induction oxaliplatin plus 5-fluorouracil and pre-operative chemoradiation. Ann Oncol 17: 1103-1110, 2006.
5. Ishii H, Iwatsuki M, Ieta K, *et al*: Cancer stem cells and chemoradiation resistance. Cancer Sci 99: 1871-1877, 2008.
6. Haraguchi N, Inoue H, Tanaka F, *et al*: Cancer stem cells in human gastrointestinal cancers. Hum Cell 19: 24-29, 2006.
7. Zlobec I, Vuong T and Compton CC: The predictive value of apoptosis protease-activating factor 1 in rectal tumors treated with pre-operative, high-dose-rate brachytherapy. Cancer 106: 284-286, 2005.
8. Negri FV, Campanini N, Camisa R, *et al*: Biological predictive factors in rectal cancer treated with pre-operative radiotherapy or radiochemotherapy. Br J Cancer 98: 143-147, 2008.
9. Zlobec I, Vuong T, Compton CC, *et al*: Combined analysis of VEGF and EGFR predicts complete tumour response in rectal cancer treated with pre-operative radiotherapy. Br J Cancer 98: 450-456, 2008.
10. Horst D, Kriegl L, Engel J, Kirchner T and Jung A: CD133 expression is an independent prognostic marker for low survival in colorectal cancer. Br J Cancer 99: 1285-1289, 2008.
11. Haraguchi N, Ohkuma M, Sakashita H, *et al*: $CD133^+CD24^+$ population efficiently enriches colon cancer initiating cells. Ann Surg Oncol 15: 2927-2933, 2008.
12. Choi D, Lee HW, Hur KY, *et al*: Cancer stem cell markers CD133 and CD24 correlate with invasiveness and differentiation in colorectal adenocarcinoma. World J Gastroenterol 15: 2258-2264, 2009.
13. He XX, Chen K, Yang J, *et al*: Macrophage migration inhibitory factor promotes colorectal cancer. Mol Med 15: 1-10, 2009.
14. Tanahashi J, Daa T, Gamachi A, *et al*: Human intestinal spirochetosis in Japan; its incidence, clinicopathologic features, and genotypic identification. Mod Pathol 21: 76-84, 2008.
15. Sato JD, Kawamoto T, Le AD, Mendelsohn J, Polikoff J and Sato GH: Biological effects in vitro of monoclonal antibodies to human epidermal growth factor receptors. Mol Biol Med 1: 511-529, 1983.
16. Cheuk W, Wong KO, Wong CS and Chan JK: Consistent immunostaining for cyclin D1 can be achieved on a routine basis using a newly available rabbit monoclonal antibody. Am J Surg Pathol 28: 801-807, 2004.
17. Paik SS, Jang KS, Song YS, *et al*: Reduced expression of Apaf-1 in colorectal carcinoma correlates with tumor progression and aggressive phenotype. Ann Surg Oncol 14: 3453-3459, 2007.
18. Rosmorduc O, Wendum D, Corpechot C, *et al*: Hepatocellular hypoxia-induced vascular endothelial growth factor expression and angiogenesis in experimental biliary cirrhosis. Am J Pathol 155: 1065-1073, 1999.
19. Dubrovska A, Kim S, Salamone RJ, *et al*: The role of PTEN/Akt/PI3K signaling in the maintenance and viability of prostate cancer stem-like cell populations. Proc Natl Acad Sci USA 106: 268-273, 2009.
20. Kim KH, Choi JS, Kim JM, *et al*: Enhanced CD24 expression in endometrial carcinoma and its expression pattern in normal and hyperplastic endometrium. Histol Histopathol 24: 309-316, 2009.
21. Press MF, Hung G, Godolphin W and Slamon DJ: Sensitivity of HER-2/neu antibodies in archival tissue samples: potential source of error in immunohistochemical studies of oncogene expression. Cancer Res 54: 2771-2777, 1994.
22. Yada K, Shibata K, Matsumoto T, Ohta M, Yokoyama S and Kitano S: Protease-activated receptor-2 regulates cell proliferation and enhances cyclooxygenase-2 mRNA expression in human pancreatic cancer cells. J Surg Oncol 89: 79-85, 2005.
23. Sadahiro S, Suzuki T, Maeda Y, *et al*: Predictors of tumor downsizing and regression with pre-operative radiotherapy alone and with concomitant tegafur/uracil (UFT) for resectable advanced rectal adenocarcinoma. Hepatogastroenterology 54: 1107-1112, 2007.
24. Japanese Society for Cancer of the Colon and Rectum: General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus: The 7th edition, revised version. Tokyo, Kanehara, 2009.
25. Lapidot T, Sirard C, Vormoor J, *et al*: A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature 367: 645-648, 1994.
26. Ricci-Vitiani L, Lombardi DG, Pilozzi E, *et al*: Identification and expansion of human colon-cancer-initiating cells. Nature 445: 111-115, 2007.
27. Reya T, Morrison SJ, Clarke MF and Weissman IL: Stem cells, cancer, and cancer stem cells. Nature 414: 105-111, 2001.
28. Jordan CT, Guzman ML and Noble M: Cancer stem cells. N Engl J Med 355: 1253-1261, 2006.
29. Ieta K, Tanaka F, Haraguchi N, *et al*: Biological and genetic characteristics of tumor-initiating cells in colon cancer. Ann Surg Oncol 15: 638-648, 2008.
30. Weichert W, Denkert C, Burkhardt M, *et al*: Cytoplasmic CD24 expression in colorectal cancer independently correlates with shortened patient survival. Clin Cancer Res 11: 6574-6581, 2005.
31. Yin AH, Miraglia S, Zanjani ED, *et al*: AC133, a novel marker for human hematopoietic stem and progenitor cells. Blood 90: 5002-5012, 1997.
32. Uchida N, Buck DW, He D, *et al*: Direct isolation of human central nervous system stem cells. Proc Natl Acad Sci USA 97: 14720-14725, 2000.
33. Bhatia M: AC133 expression in human stem cells. Leukemia 15: 1685-1688, 2001.
34. Singh SK, Clarke ID, Terasaki M, *et al*: Identification of a cancer stem cell in human brain tumors. Cancer Res 63: 5821-5828, 2003.
35. Fischer GF, Majdic O, Gadd S and Knapp W: Signal transduction in lymphocytic and myeloid cells via CD24, a new member of the phosphoinositol-anchored membrane molecules. J Immunol 144: 638-641, 1990.
36. Jackson D, Waibel R, Weber E, Bell J and Stahel RA: CD24, a signal-transducing molecule expressed on human B cells, is a major surface antigen in small-cell lung carcinomas. Cancer Res 52: 5264-5270, 1992.
37. Akashi T, Shirasawa T and Hirokawa K: Gene expression of CD24 core polypeptide molecule in normal rat tissues and human tumor cell lines. Virchows Arch 425: 399-406, 1994.
38. Roh MS, Colangelo LH, O'Connell MJ, *et al*: Pre-operative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 27: 5124-5130, 2009.

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ORIGINAL ARTICLE

Laparoscopic Versus Conventional Palliative Resection for Incurable, Symptomatic Stage IV Colorectal Cancer: Impact on Short-Term Results

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Background: Issues surroundings the safety and efficacy of palliative laparoscopic resections for patients with stage IV colorectal cancer have not been explicitly examined in the literature. We describe our experience with laparoscopic procedures for patients with stage IV incurable symptomatic colorectal cancer and compare perioperative outcomes with a contemporaneous group of patients who underwent conventional open procedures.

Methods: We retrospectively reviewed data from laparoscopic resections performed in patients for symptomatic stage IV colorectal cancer between 1999 and 2009. Data regarding patient demographics, perioperative morbidity and mortality, intraoperative blood loss, operative time, length of postoperative hospital stay, and time from surgery to chemotherapy were assessed.

Results: A total of 29 patients were identified and of these patients, 11 (38%) underwent palliative laparoscopic resections and 18 (62%) underwent conventional open resection for stage IV colorectal cancer. In comparing laparoscopic to conventional procedures, the length of postoperative hospital stay in the laparoscopic resection group was significantly shorter than that in the open resection group (median, 17 vs. 20 d, $P < 0.05$). Significant differences were present between the 2 groups when following features were compared: leukocyte on day 1 (median, 7.87 vs. 8.70×10^9/L) and day 3 (median, 6.40 vs. 7.80×10^9/L), albumin level on day 7 (median, 38.0 vs. 29.8 g/L), and C-reactive protein level on day 7 (median, 0.6 vs. 2.8 mg/dL). There were no significance differences between the 2 groups in intraoperative blood loss (median, 105 vs. 155 mL), operative time (median, 271.5 vs. 187.5 min), time to intake of solid food (median, 4 vs. 4 d), the rate of postoperative complications, perioperative mortality, or a duration from surgery to chemotherapy (median, 22 vs. 28 d).

Conclusions: Palliative laparoscopic resection is a safe and feasible option with acceptable morbidity and mortality in patients with stage IV colorectal cancer. Importantly, in this group of difficult-to-treat patients, our results compare favorably with those from previously published reports on open procedures.

Key Words: laparoscopic resection, stage IV, colorectal cancer

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Colorectal cancer, a very treatable and often curable disease, is managed by surgical resection. Unfortunately, approximately 19% of patients present with stage IV disease, and the reported 5-year survival rates for stage IV colon and rectal cancer are only 10.4% and 8.0%, respectively.[1] Although the role of resection of the primary tumor in patients with stage IV colorectal cancer remains controversial,[2–6] the majority of patients with incurable synchronous metastases and symptoms of colorectal cancer can only be treated with palliative procedures such as resection, stoma creation, and endoscopic stenting. Little is found in the literature to help guide a surgeon's decision making when managing patients with symptomatic colorectal cancer and synchronous metastasis.

Laparoscopic resections have become an accepted therapeutic option for patients with colorectal cancer after the publication of large randomized trials which confirmed the safety and oncologic equivalency of these procedures to open resection.[7–9] These trials showed that laparoscopic resections were associated with improved early postoperative recovery while maintaining similar cancer-related survival. Unfortunately, little information can be gleaned from these trials regarding the role of laparoscopy in patients with stage IV disease.

In this study, we reviewed our experience with laparoscopic resection of primary colorectal cancers in incurable symptomatic patients with synchronous metastatic disease. To assess the safety and efficacy of these procedures, we compared the perioperative outcomes of these patients with those of a contemporaneous group of patients who underwent open resection for the same disease.

PATIENTS AND METHODS

We conducted a retrospective chart review of all patients who underwent colorectal resection for symptomatic, incurable stage IV colorectal cancer between January 1999 and December 2009 at the Department of Gastroenterological Surgery, Oita University Faculty of Medicine. Patients were divided into 2 groups according to the approach: laparoscopic colorectal resection group and open colorectal resection group. Basically, laparoscopic colorectal resection was indicated to incurable stage IV colorectal cancer from 2003. When preoperative examinations demonstrated that a tumor invaded to the adjacent organ, open resection was performed. All operations were performed by 3 well-experienced, board-certified laparoscopic colorectal surgeons (K.Y., M.I., and S.K.) at our institution.

Demographics with regard to age, sex, location of primary lesion, and presence of complications such as bleeding, abdominal pain, and obstruction were assessed. Outcomes including estimated blood loss, transfusions required, operative time, time to solid food intake, length of postoperative hospital stay, rate of conversion to open

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surgery, postoperative complications, and postoperative blood analysis were compared between the 2 groups.

Laparoscopic resection is defined as follows. For right-sided colon, transverse colon, descending colon, and proximal sigmoid colon lesions, each colon was mobilized initially, and the vascular pedicles were divided at their origin or pericolic area together with the draining lymph nodes intracorporeally. The laparoscopic no-touch isolation technique, so-called "medial-to-lateral" approach, was performed. The bowel loop was delivered under a wound protector through a 4 to 6 cm incision. The division of the marginal vessels and the anastomosis were performed extracorporeally. Anastomosis was performed by functional end-to-end anastomosis. For distal sigmoid colon and rectal lesions, after mobilization of the left colon and splenic flexure, if necessary, intracorporeal ligation of the inferior mesenteric vessels followed by mobilization of the rectum and mesorectum was performed. The medial-to-lateral approach was also employed. After the completion of full mobilization by cutting the peritoneum from the lateral side, intracorporeal transection of the distal bowel was performed. Through a 4 to 6 cm incision under wound protector made over the mid-lower port site, the bowel was exteriorized and divided with appropriate proximal bowel, and the proximal anvil was then placed. The anastomosis was performed by means of the double-stapling technique.

Differences in clinicopathologic data between the groups were analyzed by χ^2 test or the Fisher exact test, and differences in continuous variables were analyzed by Student t test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Eighteen patients underwent open colorectal resection, and 11 patients underwent laparoscopic colorectal resection for symptomatic, incurable stage IV tumors as palliative surgery. Demographics regarding age, sex, symptom types, primary tumor location, and location of incurable metastasis are shown in Table 1. Patients with stage IV disease in whom a resection was impossible (ie, those undergoing a proximal diverting ostomy or palliative bypass) or who were without symptoms were not included in this review. About patients' demographics, there is no difference as to age and sex. Although the other items were not statistically analyzed because of an insufficient number of patients, it was considered that there were not apparent differences regarding the items between the groups. The majority of symptoms experienced were obstruction and abdominal pain, and the majority of primary tumors were located in the sigmoid colon and rectum in both the groups. In both the groups, liver metastasis was the most common cause for palliative surgery, and lung metastasis was the second most common cause. In the open resection group, another site of metastasis was the paraortic lymph nodes.

Short-term outcomes including pathologic findings in both the groups are shown in Table 2. All 10 cases that underwent anterior resection in both the groups did not create stoma. In comparing the laparoscopic resection group with the open resection group, there were no significant differences in estimated blood loss (median, 105 vs. 155 cc), operative time (median, 271.5 vs. 187.5 min), transfusions required (1 patient in the open resection group required transfusion), duration of time to solid food intake (median, 4 vs. 4 d), or mortality rates (no postoperative mortality in either group). However, duration of postoperative hospital stay was significantly shorter (median, 20 vs. 17 d, $P < 0.05$). There were no differences between the open and laparoscopic resection groups in postoperative complications occurred in 4 patients. Wound infection occurred in 3 patients, 2 undergoing open resection and 1 undergoing laparoscopic resection, and 1 patient developed bacterial enteritis. No patients experienced anastomotic leakage in either group. No patients in the laparoscopic resection group were converted to open surgery. Significant differences were present between the 2 groups when following features were compared: leukocyte on day 1 (median, 7.87 vs. 8.70×10^9/L) and day 3 (median, 6.40 vs. 7.80×10^9/L), and albumin level on day 7 (median, 38.0 vs. 29.8 g/L). Serum C-reactive protein (CRP) showed an increase after operation in both the groups, but the decrease was more rapid in the LAC group, showing significant differences in the CRP level on day 7 (median, 0.6 vs. 2.8 mg/dL). There were no differences in primary tumor size (median, 53.5 vs. 59.0 mm) or distribution of tumor differentiation, depth, or node status between the groups. One case in laparoscopic group did not demonstrate preoperatively that a tumor invaded to the adjacent organ, but operative finding turned out to be a slightly invaded peritoneum, which was dissected easily.

TABLE 1. Patient Demographics

	Open (n = 18)	Laparoscopic (n = 11)	P
Age (median, range)	62.5 (43-86)	59.5 (43-80)	NS
Sex			NS
Male/Female	10/8	6/5	
Symptoms			
Obstruction	16	9	
Bleeding	2	2	
Perforation	0	0	
Location			
Ascending colon	5	3	
Transverse colon	2	3	
Descending colon	1	0	
Sigmoid colon	3	0	
Rectum	7	5	
Incurable metastasis			
Liver	9	6	
Lung	3	3	
Peritoneum	5	2	
Others	1	0	

NS indicates not significant.

Postoperative treatments in the 2 groups are shown in Table 3. Almost all patients underwent postoperative chemotherapy: 4 patients did not undergo chemotherapy because of their general condition or because consent could not be obtained. In the open resection group, patients received FU/CDDP (n = 5), FOLFOX (n = 3), FU/LV (n = 3), TAI (n = 3), or UFT (n = 1). In the laparoscopic resection group, patients received FOLFOX (n = 8) or FU/LV (n = 2). The regimen was different according to the treatment standard at each particular time of treatment. There were no significant differences in the time from surgery to the start of postoperative chemotherapy between the laparoscopic and open resection groups (median, 22 vs. 28 d).

DISCUSSION

In Japan, approximately 20% of patients with colorectal cancer have metastatic disease at the time of

TABLE 2. Comparison of Results Between Open and Laparoscopic Techniques

	Open (n = 18)	Laparoscopic (n = 11)	P
Perioperative results			
Procedure			
Left colectomy	5	2	
Right colectomy	6	4	
Anterior resection	5	5	
Anteroposterior resection	2	0	
Operative time (median, minute)	187.5 (110-475)	271.5 (120-460)	NS
Estimated blood loss (median, cc)	155.0 (20-730)	105.0 (10-300)	NS
Transfusions	1	0	
Conversion to open surgery	—	0	
Postoperative mortality	0	0	
Time to solid food intake (median, days)	4	4	NS
Postoperative length of stay (median, days)	20	17	0.039
Overall morbidity	3	1	NS
Anastomotic leakage	0	0	
Wound infection	2	1	
Bacterial enteritis	1	0	
Blood analysis			
Leukocyte			
Day 1 (median, $\times 10^9$/L)	8.70 (7.70-21.4)	7.87 (3.90-11.0)	0.039
Day 3 (median, $\times 10^9$/L)	7.80 (4.80-11.5)	6.40 (3.20-11.2)	0.05
Day 7 (median, $\times 10^9$/L)	7.08 (4.5-12.7)	5.30 (3.40-8.20)	NS
C-reactive protein			
Day 1 (median, mg/dL)	6.59 (2.4-10.4)	4.40 (1.9-8.0)	NS
Day 3 (median, mg/dL)	8.0 (0.3-10.5)	3.54 (1.1-12.1)	NS
Day 7 (median, mg/dL)	2.8 (0.2-7.7)	0.60 (0.2-3.1)	0.019
Albumin			
Day 7 (median, g/L)	29.8 (24.8-48.0)	38.0 (31.7-42.0)	0.039
Day 14 (median, g/L)	34.0 (25.0-45.0)	37.0 (33.0-46.0)	NS
Pathologic findings			
Tumor size (mm)	59.0 (30-98)	53.5 (24-98)	NS
Depth			NS
SE (A)	14	10	
SI (AI)	4	1	
pN stage			NS
Positive	12	10	
Negative	6	1	

A; AI; pN, node stage; SE, tumor with serosal invasion; SI, tumor with invasion into adjacent organs.

diagnosis.[10] Although major advances in systemic chemotherapy have expanded the therapeutic options for these patients and have improved median survival from < 1 year to 20 months or longer, < 10% of patients treated with chemotherapy alone are still alive at 5 years.[11] Therefore, it is important both to maintain the quality of life of patients with such poor prognosis and to perform their chemotherapy smoothly. In general, patients with clearly incurable metastatic disease and symptomatic primary tumors (bleeding, obstruction, and perforation) should be considered for resection of their primary tumor followed by systemic chemotherapy. In this study, we excluded asymptomatic patients because the best treatment strategy for asymptomatic incurable colorectal cancer still remains unclear.

TABLE 3. Postoperative Chemotherapy

	Open (n = 18)	Laparoscopic (n = 11)	P
Chemotherapy performed	15	10	NS
Treatment regimen			
FU/CDDP	5	0	
FOLFOX	3	8	
FU/LV	3	2	
TAI	3	0	
UFT	1	0	
Interval from operation to chemotherapy (median, days)	28	22	NS

It is generally accepted that laparoscopic procedures offer significant perioperative benefits to patients; several randomized trials have confirmed that laparoscopic resection for patients with curable colorectal cancer results in improved postoperative analgesia, shortened hospital stay, and more rapid return to normal diet.[6–8] Unfortunately, the applicability of laparoscopic procedures to patients with symptomatic metastatic disease is controversial. Although Moloo et al[12] reported palliative benefits of laparoscopic colorectal resection compared with curative stage I-III surgery, few reports exist comparing laparoscopic colorectal resection with open colorectal resection for incurable stage IV colorectal cancer. Law et al[13] compared laparoscopic versus open resection for stage IV metastatic colorectal cancer; however, their report included potentially curable cases such as those of resectable liver metastasis. The present patient series describes our experience with laparoscopic procedures for patients with stage IV incurable

symptomatic colorectal cancer and compares their perioperative outcomes to a contemporaneous group of patients undergoing conventional open procedures. Perioperative outcomes for patients undergoing palliative laparoscopic procedures seemed to be similar to those for patients undergoing conventional open procedures. There were no significant differences between the groups across the majority of variables examined with the exception of length of hospital stay, which was significantly shorter in the laparoscopic resection group than in the open resection group (median, 17 vs. 20 d, $P < 0.05$). In our institute, we did not adopt clinical path for incurable stage IV patients in laparoscopic and conventional procedures, which might cause the long postoperative hospital stay. This study clarified that postoperative increase of leukocyte count and CRP level was less pronounced, and decrease of these inflammatory parameters was more rapid after LAC than after OC. That may be associated with a shorter length of postoperative stay in LAC than in OC. Of course, we recognize that our data included colon and rectal cancer, which generally differed in terms of difficulty of operative procedures; however, subgroup analysis which compared the short outcome of colon cancer only between laparoscopic and open group, and short outcome of rectum only between both the groups demonstrated the results equal with this study that compared the outcome of colon including rectum between laparoscopic and open group.

New systemic chemotherapy with modern combination regimens (FOLFOX, FOLFIRI) induced major histologic tumor regression in the primary tumor in approximately 70% of cases.[14] Combining these regimens with a targeted agent such as bevacizumab or cetuximab may result in even higher rates of histologic tumor regression. These results support a policy of earlier chemotherapy in the management of symptomatic patients with incurable metastatic colorectal cancer. Among the patients in this study, there was no significant difference between the groups in the interval from palliative surgery to the start of postoperative chemotherapy. However, the regimen was different according to the treatment standard at each particular time of treatment and then OC group included the TAI, which was local treatment and oral UFT. In this study, the median survival times and the 1-year survival rate for laparoscopic group during a median follow-up period of 13 months were 12.0 months and 55%, respectively, whereas the median survival times and the 1-year survival rate for conventional group during a median follow-up period of 14 months were 11.4 months and 50%, respectively.

In conclusion, the laparoscopic approach is safe and effective in the treatment of symptomatic metastatic colorectal cancer. The minimally invasive approach of the laparoscopic procedure is beneficial because it results in less estimated blood loss, shorter time to first bowel movement, fewer postoperative complications, and shorter length of hospital stay. We recognize the limitations of a retrospective study and also the difficulty of performing a randomized study in such patients. Nevertheless, we believe this series provides important information for the operative treatment of symptomatic incurable colorectal cancer and may be the basis for future prospective studies. The current guidelines for the surgical treatment of colorectal cancer in Japan recommend that a laparoscopic procedure should be performed for stage 0 and stage I cancer located in the colon and rectosigmoid colon.[15] Further studies are needed to evaluate the impact of laparoscopic versus open surgery on surgical outcomes and to establish treatment options that will provide the best results for patients with symptomatic incurable colorectal cancer.

CONCLUSIONS

Laparoscopic colorectal resection for incurable metastatic and symptomatic colorectal cancer can be performed less invasively and safely without increased morbidity in comparison with open colorectal resection.

REFERENCES

1. National Cancer Institute 2007; SEER Cancer Statistics Review 1975–2003 US Department of Health and Human Services, Bethesda. http://seer.cancer.gov/statfacts/html/colorect.html.
2. Cook AD, Single R, McCahill LE. Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. *Ann Surg Oncol.* 2005; 12:637–645.
3. Stelzner S, Hellmich G, Koch R, et al. Factors predicting survival in stage IV colorectal carcinoma patients after palliative treatment: a multivariate analysis. *J Surg Oncol.* 2005;89:211–217.
4. Nash GM, Saltz LB, Kemeny NE, et al. Radical resection of rectal cancer primary tumor provides effective local therapy in patients with stage IV disease. *Ann Surg Oncol.* 2002;9: 954–960.
5. Sarela AI, Guthrie JA, Seymour MT, et al. Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer. *Br J Surg.* 2001;88:1352–1356.
6. Scoggins CR, Meszoely IM, Blanke CD, et al. Nonoperative management of primary colorectal cancer in patients with stage IV disease. *Ann Surg Oncol.* 1999;6:651–657.
7. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med.* 2004;350:2050–2059.
8. Jayne DG, Guillou PJ, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASSIC Trial Group. *J Clin Oncol.* 2007;25: 3061–3068.
9. Buunen M, Veldkamp R, Hop WC, et al; Colon Cancer Laparoscopic or Open Resection Study Group. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol.* 2009;10:44–52.
10. Japanese Society for Cancer of the Colon and Rectum. *Colorectal Cancer Therapy (in Japanese).* Tokyo: Kanehara; 1995.
11. Cedermark BJ, Blumenson LE, Pickren JW, et al. The significance of metastases to the adrenal glands in adenocarcinoma of the colon and rectum. *Surg Gynecol Obstet.* 1997;144: 537–546.
12. Moloo H, Bédard EL, Poulin EC, et al. Palliative laparoscopic resections for Stage IV colorectal cancer. *Dis Colon Rectum.* 2006;49:213–218.
13. Law WL, Fan JK, Poon JT, et al. Laparoscopic bowel resection in the setting of metastatic colorectal cancer. *Ann Surg Oncol.* 2008;15:1424–1428.
14. Karoui M, Koubaa W, Delbaldo C, et al. Chemotherapy has also an effect on primary tumor in colon carcinoma. *Ann Surg Oncol.* 2008;15:3440–3446.
15. Japanese Society for Cancer of the Colon and Rectum. *The Guideline for Colorectal Cancer Therapy (in Japanese).* Tokyo: Kanehara; 2005.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Laparoscopy-Assisted Distal Gastrectomy for Early Gastric Cancer: A Video Demonstration

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ABSTRACT

Background. Laparoscopic gastrectomy with lymph node dissection, such as laparoscopy-assisted distal gastrectomy (LADG), has been widely accepted as the treatment for early gastric cancer with the risk of lymph node metastasis, especially in Asia since 1991.[1–3]

Purpose. We demonstrate our standard techniques for LADG with lymph node dissection and show their pitfalls during operation.

Procedures and Pitfalls. This is a case presentation of a 61-year-old man with early gastric cancer of the gastric body who underwent LADG with D1+ suprapancreatic lymph node dissection. The principles of this procedure are shown in this video. To prevent operative complications, appropriate use of forceps and instruments, such as a vessel-sealing system, ultrasound coagulation devices, and circular or linear staplers is important in laparoscopic procedures. In addition, an appropriate approach to layers and vessels is needed. In general, the major intraoperative complications during LADG are bleeding, and the major postoperative complications are anastomotic problems, including stenosis or leakage. Previous reports have demonstrated that the risk factors of complications in LADG were comorbidities, the surgical experience, and visceral fat.[4–6]

Conclusions. LADG for early gastric cancer is a relatively safe and effective procedure. To achieve laparoscopic gastrectomy more safely, the surgeons must try to prevent intra- or postoperative complications.

REFERENCES

1. Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc.* 1994;4:146–8.
2. Yang H-K. Laparoscopic gastric surgery in Asia. *Asian J Endosc Surg.* 2008;1:11–3.
3. Etoh T, Shiraishi N, Kitano S. Current trends of laparoscopic gastrectomy for gastric cancer in Japan. *Asian J Endosc Surg.* 2009;2:18–23.
4. Kitano S, Shiraishi N, Uyama I, Sugihara K, Tanigawa N, Japanese Laparoscopic Surgery Study Group. A multicenter study on oncologic outcome of laparoscopic gastrectomy for early cancer in Japan. *Ann Surg.* 2007;245:68–72.
5. Kim MC, Kim W, Kim HH, Ryu SW, Ryu SY, Song KY, Lee HJ, Cho GS, Han SU, Hyung WJ. Risk factors associated with complication following laparoscopy-assisted gastrectomy for gastric cancer: a large scale Korean multicenter study. *Ann Surg Oncol.* 2008;15:2692–700.
6. Kim HH, Hyung WJ, Cho GS, Kim MC, Han SU, Kim W, Ryu SW, Lee HJ, Song KY. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report–a phase III multicenter, prospective, randomized Trial (KLASS Trial). *Ann Surg.* 2010;251(3):417–20.

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Short-Term Outcomes of Laparoscopic Intersphincteric Resection for Lower Rectal Cancer and Comparison with Open Approach

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Key Words

Laparoscopic surgery, complications · Intersphincteric resection, laparoscopic, open · Rectal cancer, lower

Abstract

Background/Aims: To evaluate the short-term surgical outcomes of laparoscopic intersphincteric resection (ISR) for lower rectal cancer, and to compare them with a case-control series of open ISR. ***Methods:*** Between July 2002 and March 2011, 29 patients with lower rectal cancer underwent laparoscopic ISR, and 22 of 29 patients who underwent laparoscopic ISR were compared with the control open ISR group of patients matched for age, gender, operative procedure and pathological stage. ***Results:*** There was no perioperative mortality, 8 complications occurred in 7 patients, and the morbidity rate was 24.1% (7/29). Leakage occurred in 1 patient (3.4%) in the laparoscopic ISR group. Regarding the matched case-control study, the operative time was significantly longer ($p = 0.0007$), but blood loss was significantly lower ($p = 0.0003$) in the laparoscopic ISR group. The median postoperative hospital stay was 8 days in the laparoscopic ISR group, which was significantly shorter than in the open ISR group (14 days). Postoperative complication rates were similar. In the laparoscopic ISR group, the levels of C-reactive protein on postoperative days 1–3 were significantly lower than in the open ISR group. ***Conclusions:*** Laparoscopic ISR for lower rectal cancer provides benefits in the early postoperative period without increasing morbidity or mortality.

Introduction

Controversy still persists regarding the appropriateness of laparoscopic surgery (LS) for patients with rectal cancer because of concerns over the safety of the procedure and the uncertainty of the long-term outcome. The advantages of LS for rectal cancer have been reported; LS for rectal cancer is associated with a reduction in intraoperative blood loss and the number of transfused patients; however, laparoscopic rectal excision has procedural complexities and technical difficulties, and LS in patients with rectal cancer is technically demanding [1]. Due to the high complication rate, it is unclear whether LS for rectal cancer should be regarded as a minimally invasive surgery [2].

Abdominoperineal resection was originally the standard surgery for patients with rectal adenocarcinoma located within 5 cm from the anal verge [3]. Intersphincteric resection (ISR) was developed in the 1980s to avoid permanent colostomy for such patients, and this procedure by the open approach became well established in the 1990s [4–6]. ISR involves resection of part or all of the internal sphincter from a per anal approach and restoration of bowel continuity while obtaining sufficient margins for rectal cancers involving or close to the anal canal, and ISR is performed in combination with total mesorectal excision.

At our institution, open ISR was introduced in the 1990s, and laparoscopic ISR was started in 2002 following

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advances in laparoscopic techniques. In previous reports, we have demonstrated that open ISR for rectal cancer is technically feasible and oncologically safe; however, laparoscopic ISR is still not an established technique, and there are only a few reports on the use of this procedure [7–12]. Moreover, due to the lack of comparative study, it is currently still controversial as to whether laparoscopic ISR can be regarded as a minimally invasive surgery. The aims of the present study are to evaluate the surgical outcomes of laparoscopic ISR for lower rectal cancer, and to compare these outcomes with a control series of cases treated by open ISR.

Patients and Methods

Between July 2002 and January 2011, we performed 29 continuous laparoscopic ISR for selected patients with lower rectal cancer, and the study took the form of a single-center, prospective, observational, case-series analysis. Moreover, 22 of 29 patients who underwent laparoscopic ISR were compared with 22 of 159 control open ISR patients matched for age, gender, operative procedure and pathological stage. Seven patients who underwent laparoscopic ISR were excluded from the comparative study because we could not find a matched open ISR case.

Selection criteria for open ISR were as follows: (1) sufficient medical fitness; (2) normal sphincter function; (3) distance between the lower edge and the dentate line of <3 cm; (4) no involvement of the external sphincter, and (5) no signs of disseminated disease or clinical T4 disease. Because the safety of LS in cancer patients remains to be established, candidates for laparoscopic ISR were basically patients who were preoperatively diagnosed with T1 or T2 disease. Laparoscopic ISR was also performed in patients who were preoperatively diagnosed with T3/4 but wished to undergo LS. Six patients registered for the clinical trial, a phase II trial to evaluate laparoscopic surgery for stage 0/I rectal carcinoma [13], are included in the present study. We excluded the following groups of patients from laparoscopic resection: patients with tumors of >8 cm; patients with a prior history of extensive adhesions; patients with severe obesity (body mass index >30); patients with intestinal obstruction, and patients who did not consent to LS.

All patients were evaluated before surgery by clinical investigation, including barium enema or computed tomographic colonography, total colonoscopy, chest X-ray, abdominal ultrasonography, endorectal ultrasonography, thin-section helical CT, or high-resolution magnetic resonance.

LS was converted to open surgery when open techniques were used to cope with unexpected intraoperative difficulties, regardless of the size of the wound.

The techniques of open and laparoscopic ISR have been thoroughly described previously [7–9, 14, 15]. After mobilization of the left colon and splenic flexure, intracorporeal high ligation of the inferior mesenteric vessels was performed. Recently, the laparoscopic median-to-lateral approach has been indicated. In this approach, medial-to-lateral retroperitoneal dissection of the mesocolon and early division of the inferior mesenteric vessels were performed, which preserved the inferior mesenteric plexus and superior hypogastric plexus. After full mobilization of the rectum, the intersphincteric plane between the puborectalis and the internal sphincter was cautiously dissected as caudad as possible under laparoscopic vision. After retractors were applied to the anal canal, it was closed just below the tumor by purse-string sutures, and then irrigated with povidone iodine followed by saline. After irrigation, the anal canal mucosa and internal sphincter were circumferentially incised, and the intersphincteric plane was dissected cephalad. A resection margin of at least 1 cm was always attempted. After removal of the rectum through the anus, the pelvic cavity and anal canal were washed, and then a coloanal anastomosis was made using 4-0 absorbable vertical mattress sutures. A pelvic drain was placed, and a defunctioning ileostomy was made. In all cases, the retroperitoneum was not repaired.

Parameters analyzed included gender, age, body mass index, prior abdominal surgery, preceding local resection, ASA classification, pathological stage, size of the tumor, lymph nodes removed, operative time, operative blood loss, conversion, combined surgery, colonic pouch, days to resume diet, duration of postoperative hospital stay, and both intraoperative and postoperative complications within 30 days of surgery. Pathological staging was performed according to the TNM stage. White blood cell count and C-reactive protein (CRP) in serum were measured preoperatively and on postoperative day 1 routinely, and on postoperative days 2 and 3 if necessary. Data on combined surgical techniques were all included in the analyses of cancer surgeries.

Our institutional review board does not mandate obtaining its approval for the collection of patient clinical records prospectively and for publication as an institutional case-series study. All patients gave their informed consent for usage of their data for analysis in the future.

Statistical analysis was performed using SPSS ver. 11.0 software (SPSS, Chicago, Ill., USA), and Student's t test, the Mann-Whitney U test, and Fisher's exact test were used as appropriate. A p value of <0.05 was considered significant.

Results

Patient demographics of the case-series analysis are summarized in table 1. All the operations were completed laparoscopically in this series. Positive margin rate was 0 in the present series. With regard to simultaneous surgical techniques, 1 patient underwent laparoscopic cholecystectomy for a gallbladder stone. There was no perioperative mortality, 8 complications occurred in 7 patients, and the morbidity rate was 24.1% (7/29). Anastomotic leakage occurred in 1 patient (3.4%). The postoperative course of the patient with anastomotic leakage was uneventful except for urinary tract infection that was managed by per oral antibiotics, and the patient was discharged on the 8th postoperative day without symptoms. Two months after the initial operation, routine radiological examination before ileostomy closure demonstrated a minor anastomotic leakage. The patient was symptom