を辿る乳癌の外科治療であるが，将来手術は無用となるのであろうか？　答えはノーである．マウスを用いた乳癌細胞株（MDAMB231）のモデル実験から，癌が転移巣を形成する際にまず原発巣からオステオポンチンが分泌され，宿主の骨髄から誘導された前駆細胞が転移巣の間質を形成し増殖に寄与することが報告された[18]．また，転移巣から遊離したCTCがmatrix metalloproteinaseやケモカインを介して原発巣のさらなる増殖に寄与していることが報告された[19]．一方，乳癌患者50例に同定されたDTCのうち，70％の細胞が$CD44^{+}CD24^{-/low}$の染色特性をもついわゆる癌幹細胞であることが示唆された[20]．以上から，原発巣の外科治療は微小な転移巣の増殖を抑制する可能性がある．しかし，転移巣を形成した癌細胞は原発巣より高い増殖能と転移浸潤能を獲得しているため，転移形成に重要なサイトカインを標的とした新たな治療戦略が必要と考えられる[18,19]．

## おわりに

早期乳癌ではセンチネルリンパ節生検による微小転移の診断は補助療法選択の一つの目安となる．早期乳癌におけるDTCと転移性乳癌におけるCTCは予後不良因子であるが，臨床試験に連動したトランスレーショナル研究が必要である．現時点でDTCとCTCの診断と結果に基づいた治療選択は推奨されない．いずれにせよ，手術可能な乳癌では外科治療が乳癌患者の予後を改善するうえできわめて重要であることに変わりはない．

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精密検査・診断・モニタリング

# 治療検査（治療モニタリングと腫瘍マーカー）

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**プライマリ・ケアにおけるポイント**

腫瘍マーカーとは，非侵襲的に採取された生体材料から検出され，がんを完治し得る段階で患者を選別できる特異性と感受性を備えた物質の総称である．乳がん診療，とりわけ進行再発乳がん患者の診療では，腫瘍マーカーは重要な検査項目である．ただし，その値だけで臨床症状や画像診断に基づく病態は説明できず，治療方針を決定することはできない．進行再発乳がんでは，画像診断に加えて，腫瘍マーカー値の時系列変化や複数の腫瘍マーカーのモニタリングが治療方針を決定するうえで参考となる場合がある．

## はじめに

初発乳がんにおける術前薬物療法の効果判定や，進行再発乳がんにおける治療の効果判定のモニタリングは，MRI・CT・PET-CT・超音波などの画像診断が基本である．しかし，腫瘍マーカーのモニタリングも有用な場合がある．腫瘍マーカーの定義や有用性は，1996年にtumor marker utility grading systemとしてまとめられ，乳がんの腫瘍マーカーについて「転移性乳がんにおける病勢のモニタリング」と「無再発乳がん患者における再発の発見に関する有用性」が報告された[1]．乳がん治療のモニタリングについて腫瘍マーカーを中心に解説する．

## Ⅰ 乳がんの腫瘍マーカー（総論）

### (1) 陽性率

初発乳がんにおける腫瘍マーカーの陽性率は数％から20％と低値であるが，進行再発乳がんにおける陽性率は30～70％と高値である（表1）[2]．薬物療法による乳がん治療の効果判定は画像検査が基本である．しかし，CT・MRI・PET-CTが生物学的な病勢を必ずしも正確に反映している訳ではない．また，頻回な画像検査は医療経済的にも負担が大きい．一方，腫瘍マーカーの測定は簡便で，迅速性に優れ，かつ非侵襲性である．初発乳がんでの測定の意義は乏しいが，進行再発乳がんでは治療効果を判定するうえで補助的な検査として有用である．

表1　乳がんにおける腫瘍マーカーと病期別陽性率（％）

| 血液マーカー | 病期 | | | | 再発例非切除例 | 良性 | 健常者 |
|---|---|---|---|---|---|---|---|
| | Ⅰ | Ⅱ | Ⅲ | Ⅳ | | | |
| CEA | 6 | 10 | 22 | 59 | 62 | 1 | 1 |
| CA 15-3 | 4 | 8 | 13 | 38 | 54 | 1 | 0 |
| NCC-ST 439 | 25 | 30 | 42 | 56 | 54 | 5 | 0 |
| HER2 | 13 | 13 | 10 | 38 | 51 | 5 | 0 |

（文献2）より改変）

### (2) サーベイランスとしての腫瘍マーカー

ASCO（American Society of Clinical Oncology）のガイドラインでは，乳がんのスクリーニング，診断，ステージングおよびサーベイランスに

**おいて，進行再発乳がんでは腫瘍マーカーが高値を示す傾向にあるとしながらもデーターは不十分であり，かつ生存率の改善と再発後の緩和医療に寄与しないということから腫瘍マーカーのモニタリングは推奨しないとされた**(表2)[2, 3]．同様に，日本乳癌学会による乳癌診療ガイドライン(2008年版)において術後の定期的な腫瘍マーカーの測定の有用性は明らかではないとされた(推奨グレードC)[5]．実地臨床では，腫瘍マーカーが異常値を示した初発乳がんで，術後正常値になったが再び異常値を認めたため精査によって遠隔転移再発が診断された症例もある．

表2　腫瘍マーカーに関するASCOガイドライン

| 腫瘍マーカー | ASCOのガイドライン |
|---|---|
| CA15-3 | 術後のモニタリングには推奨されない．<br>高値症例はup stagingの可能性がある． |
| CEA | 術後のモニタリングには推奨されない．<br>転移症例の治療のモニタリングには推奨されない． |
| HER2タンパク | 記載なし．<br>＊腫瘍での発現は初発時と再発時に評価すべきである． |

(文献4)より改変)

### (3)治療効果判定としての腫瘍マーカー

臨床的治療効果の判定基準としてRECIST (response evaluation criteria in solid tumors)のガイドラインが使用されている．このなかで，腫瘍マーカーについて，「治療開始前に血清腫瘍マーカーが基準値上限を超えて上昇している症例では，他病変がすべて消失した場合に完全奏功(CR)と判定するためには，基準値範囲内までの低下が認められなければならない」と記載されているが，「血清腫瘍マーカー単独では治療効果判定に使用できない」と定められている．

## II 乳がんの腫瘍マーカー(各論)

### (1)CA 15-3 (carbohydrate antigen 15-3)

ヒト乳脂肪膜上の糖タンパク質に対するモノクローナル抗体115D8と，乳がん肝転移組織抽出液を免疫源として得られたモノクローナル抗体DF3により認識される腫瘍関連抗原である．乳がんに特異性が高く，良性疾患やほかのがん腫で陽性を示すことはまれである．**ASCO腫瘍マーカーのガイドラインでは，乳がんの腫瘍マーカーとしてCA 15-3とCA 27.29(本邦未承認検査)を第一選択としている**[4]．病期の進行に伴うCA 15-3の上昇が指摘されているが，早期乳がんではCA 27.29のほうがCA 15-3より感度が高いという報告もある[3]．紅林らは，進行再発乳がんにおいてCA 15-3の陽性率は44.0%とCEAより有意に高く，ほかの転移部位と比べて肝転移を有する患者

#### HER2タンパクと分子標的治療

HER2タンパクに対するヒト化モノクローナル抗体であるトラスツズマブや，EGFR (ErbB1)とHER2 (ErbB2)のシグナル伝達においてチロシンキナーゼを阻害するラパチニブの登場によって，HER2タンパクが過剰発現した乳がんの予後は著しく改善した．抗がん剤にこの2つの薬剤を併用することで，HER2タンパクが過剰発現した乳がん症例の半数でがん細胞の完全消失が報告されている．以前はHER2タンパクが乳がんの予後不良因子の一つであったが，現在は分子標的治療の効果予測因子の一つである．腫瘍でのHER2タンパク発現に加えて，血清HER2タンパクの測定が治療効果のモニタリングになると期待されたが，現時点で十分なエビデンスはない．

では有意に高いと報告した[6]．また，薬物療法後にCA15-3が20％以上低下する症例では，20％未満の低下あるいは上昇する群と比較して有意に長いtime to progressionが得られた．以上から，CA15-3が異常値を示す進行再発乳がんのモニタリングとして有用である．

### (2) CEA (carcinoembryonic antigen)

大腸がん抽出液中に胎児消化管粘膜上皮と共通の抗原性を有する糖タンパク質として同定された腫瘍関連抗原である．消化器がん，肺がん，卵巣がん，甲状腺髄様がんなどで陽性を示す．がん以外では，肝疾患，炎症性腸疾患，長期喫煙者などで軽度の上昇を認める．**ASCO腫瘍マーカーのガイドラインでは，初発乳がんならびに進行再発乳がんにおいてCEAの測定は推奨されていない**[4]．一方，測定可能病変が欠如したりCA 15-3やCA 27.29の上昇を伴う進行再発乳がんでは，CEAの上昇が治療無効を裏付ける所見として示唆された．

### (3) NCC-ST 439 (National Cancer Center ST 439)

低分化型胃腺がん由来細胞株を免疫原として作製されたモノクローナル抗体によって認識される抗原で，そのエピトープはムチン様高分子タンパク上に存在する糖鎖である．免疫組織化学的検討において本抗原は，消化器がんや肺がん，乳がんで高率に染色される．成田らは，再発乳がんについてCA15-3の感度，特異度がそれぞれ54.8％と98.3％であるのに対してNCC-ST 439はそれぞれ59.7％，88.3％であったと報告した(表3)[7]．しかし，CEAやCA 15-3と比較してNCC-ST439は偽陽性率が高い点に注意すべきである．

表3 乳がん術後サーベランスでの腫瘍マーカー

| | NCC-ST 439 | CA 15-3 | CEA |
|---|---|---|---|
| 敏感度(％) | 59.7 | 54.8 | 58.1 |
| 特異度(％) | 88.3 | 98.3 | 98.3 |
| 正診率(％) | 73.8 | 76.2 | 77.9 |

(文献7)より改変)

## 4 HER2 (ErbB2) タンパク

HER2 (ErbB2) タンパクは，がん遺伝子である*her2/neu* (*c-erbB-2*) の遺伝子産物であり，乳がん患者の20％程度に過剰発現が認められる．血清HER2タンパクが過剰発現した乳がん患者は，転移・再発しやすく予後が不良であると報告された[8]．**ASCO腫瘍マーカーガイドラインでは，腫瘍におけるHER2過剰発現について乳がんの初診断時と再発時に評価されるべきであるとしている**[4]．HER2陽性の進行再発乳がんにおける腫瘍マーカーとして血清HER2のモニタリングの意義が検討されてきたが，現時点で推奨に足る十分なエビデンスはない[4,8]．

### 5 骨転移の腫瘍マーカー (ICTP：pyridinoline cross-linked carboxyterminal telopeptide of type Ⅰ collagen)

Ⅰ型コラーゲンは骨基質の90％以上を占めるタンパク質であり，ピリジノリンまたはデオキシピリジノリンにより分子間において架橋を形成している．破骨細胞による骨吸収の際には骨組織のⅠ型コラーゲンが分解され，そのC末端部分からピリジノリンまたはデオキシピリジノリンによって架橋されたペプチドが血中に放出される．すなわち，血中ICTP値は骨吸収を反映する指標である．血中ICTP値は肺がん，乳がん，前立腺がんの骨転移症例では高値を示した．また，骨代謝に直接関与し骨吸収時に骨の分解産物として血中に放出されるTRACP5b (tartrate-resistant acid phosphatase-5b) について，WadaらはICTPとTRACP5bが骨転移を有する患者では骨転移を認めない患者との比較において有意に高値であり，両者の測定が骨転移患者のスクリーニングとモニタリングに有用であると報告した[9]．

## Ⅲ 展　望

乳がんにおける腫瘍マーカーについて，前向き臨床試験は少なくエビデンスレベルも低く推奨できるものは少ない．一般臨床で再発の早期発見を目的とした盲目的な腫瘍マーカーの測定は推奨されない．しかし，腫瘍マーカーのモニタリングが病勢を反映し有用であった進行再発乳がんを時に経験する．よって，腫瘍マーカーが異常値である進行再発乳がんでは，病状に応じて腫瘍マーカーのモニタリングは許容される．一方，乳がん治療はがんの個性を示す分子に狙いを定めた分子標的治療の時代を迎えている．HER2タンパクとトラスツズマブはその最たる例である．標的となる分子に関連する腫瘍マーカーが開発されれば，治療のモニタリングとして期待されるので臨床試験のなかで検証すべきである．

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# 手術にはどんな方法があるのですか？センチネルリンパ節生検について教えてください

乳がんの手術は，乳房とリンパ節に分けてそれぞれ治療を計画します．乳房の手術は，がんの広がりを画像で正確に診断してから部分切除（いわゆる温存手術）あるいは全切除を行います．皮膚や筋肉まで及ぶ乳がんではそこも一緒に切除します．最近は，手術後の見栄え（整容性）を考慮してあえて温存手術は行わず，全切除と再建手術を同時に行う場合もあります．リンパ節の手術は，リンパ節に転移を疑う場合には，わき（腋窩）のリンパ節を全部切除します．これを郭清といいます．もし転移がなさそうな早期がんであれば，センチネルリンパ節生検が標準治療です．センチネルリンパ節とは，がんの転移を見張るリンパ節を示します．乳がんからのリンパの流れを色素や放射性同位元素を用いて同定してリンパ節を生検します．センチネルリンパ節に転移がなければ郭清は省かれ転移があれば郭清します．これによって，郭清に伴う腕のむくみやだるさなどの後遺症が予防できるようになりました．

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## 解　説

乳がんの近代手術は19世紀後半に始まり130年近く経過した．現在，乳がんの治療体系における**手術の役割は局所コントロール**に位置づけられる．乳がんの予後は，マンモグラフィによる早期発見率の向上と薬物療法の進歩によって改善された[1, 2]．そのなかで，乳がんの手術は乳房の切除とその再建，リンパ節の生検あるいは郭清によって構成されている．

### 乳房の手術

#### 1．乳房全切除

**広範な乳管内進展を伴う乳がんや術前薬物療法によって縮小効果が乏しいⅡ期またはⅢ期乳がんが対象**である．皮膚浸潤あるいは胸筋浸潤を伴う場合は同部位を合併切除する．再建を伴わない場合は乳頭乳輪を合併切除する場合が多い．再建を伴う場合は乳頭直下に乳管内進展がなければ乳頭乳輪を温存し進展があれば合併切除する．

#### 2．乳房部分切除（乳房温存術）

**広範な乳管内進展を伴わない0期からⅡB期までの乳がんが対象**である．乳腺を円状あるいは楔状に切除する場合もあるが，術前のMRI画像あるいはCT画像によって乳管内進展の範囲を予測してその範囲を含めた部分切除を行っている．超音波画像をみながら腫瘍縁より2cm離した位置で乳房にマーキングを行い，術中にピオクタニンとキシロカインゼリーを混合したものをマーキングに沿って乳腺に注入し，切離面を確認しながら部分切除を行う．切除された乳腺の欠損部位は，整容性を考慮して温存乳腺を剥離受動して縫縮したり，漿液腫による整容性の保持を期待してそのまま閉創している．

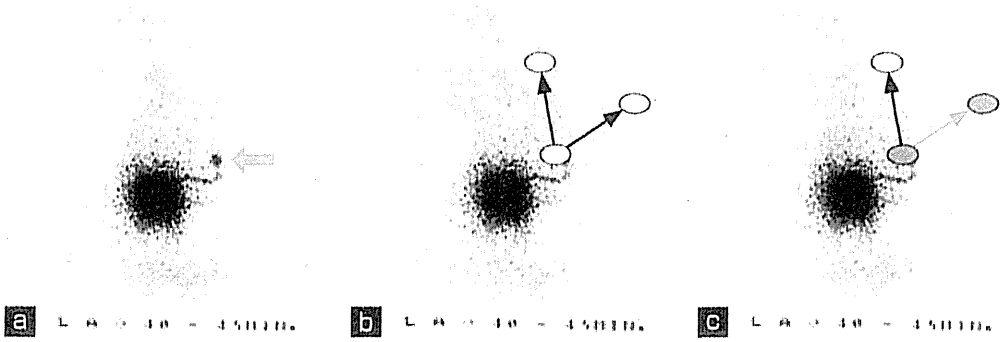

図1　センチネルリンパ節生検のコンセプト
リンパ管シンチグラムでRIを集積しhot spotとして描出されたリンパ節(a：⇨)をガンマプローブで同定する．もしここに転移がなければ(b：○)その下流のリンパ節にも転移はなく，もし転移があれば(c：◎)ほかのリンパ節にも転移があるかもしれない．センチネルリンパ節生検によってリンパ節転移の有無が正確に診断されてリンパ節郭清の個別化が実現した．

### 3．再建術

主に乳房全切除の場合が再建の対象である．同時再建と2期再建がある．同時再建は手術時間が短縮される一方，施設における再建外科チームの存在が欠かせない．再建法の詳細は専門書に委ねるが，腹直筋皮弁，広背筋皮弁，脂肪皮弁などさまざまである．最近は，まずテッシューエクスパンダーを挿入し拡張した後でシリコン挿入を行う人工物再建も積極的に行われている．しかし，2011年2月時点でシリコンは保険外請求のためシリコン挿入は自費診療となる．また，乳房部分切除を対象に乳房の欠損部に筋皮弁や脂肪弁を充填して整容性を保つ手術も行われている．

## リンパ節の手術

### 1．腋窩リンパ節郭清

触診や画像診断でリンパ節転移を疑う症例が対象である．このような症例では術前薬物療法が先行する場合が多いが，術前薬物療法によってリンパ節転移が病理学的に消失する可能性は20％前後であるため，薬物療法後もリンパ節郭清が標準治療である．郭清範囲は，腋窩静脈より尾側で小胸筋の外側の腋窩に当たるレベルⅠとその内側で小胸筋の裏面にあるレベルⅡである．広背筋へ分布する胸背動静脈とその神経，前鋸筋を支配する長胸神経は温存する．また，腫大したり癒合した高度なリンパ節転移が認められなければ肋間上腕神経の温存も試みる．腋窩リンパ節群の最上位に位置するレベルⅢと大小胸筋の間に位置するロッターリンパ節は転移を疑う場合のみ郭清あるいはサンプリングを行う．

### 2．センチネルリンパ節生検

**腫瘍からのリンパ流を直接受けるリンパ節がセンチネルリンパ節で，「見張りリンパ節」とも呼ばれている**[3]．センチネルリンパ節に転移がなければその下流のリンパ節にも転移はないはずでありリンパ節郭清は不必要である(図1)．センチネルリンパ節生検は，臨床的にリンパ節転移を伴わないⅠ期あるいはⅡA期乳がんが対象である．センチネルリンパ節を同定するトレーサーとして，医薬品として使用されるインジゴカルミンあるいはインドシアニングリーンなどの色素とスズあるいはフチン酸を99mテクネシウムで標識したラジオアイソトープ(RI)が用いられる．色素法の習得には少なくとも20例の手術経験を要する一方，RI法は5例程度の経験で習得できる．乳がんのセンチネルリンパ節生検は2010年4月に保険収載されたが，**初心者は経験者の指導の下に手技の習熟に努める必要**がある．手技の習熟と詳細なリンパ節の病理診断によってセンチネルリンパ節生検の同

定率と正診率はそれぞれ95％以上に到達することができる．この生検法によって，対象となる早期乳がんの60％はセンチネルリンパ節転移陰性であり，一律に行われていたリンパ節郭清に伴うリンパ浮腫などの後遺症が予防されるようになった．

## 手術に関する課題

### 1．乳房温存術

乳房温存療法は乳房部分切除と温存乳房内の再発を予防するための放射線治療からなる．しかし，個体差はあるが放射線治療による乳腺組織の繊維化のため，乳房温存療法後に変形した乳房を改めて形成することはきわめて困難である．一方，日本人女性において温存乳房に放射線治療を行った場合と行わなかった場合の乳房内再発率は9年間で9％と17％であり，温存乳房再発が予後を左右する遠隔転移再発の要因としても報告された[4]．時に，確実な局所コントロールと乳房の整容性を両立することは困難である．筆者らの施設では，1/4以上の乳房切除を要する症例では乳房部分切除に加えて乳房全切除と同時再建についても説明し，形成外科医からのアドバイスも受けて患者と家族が術式を選択できるように配慮している．

### 2．センチネルリンパ節生検

センチネルリンパ節生検によって，微小なリンパ節転移が容易に同定されるようになった．2002年にInternational Union Against Cancer（UICC）はリンパ節転移の新たな分類法を提唱した．0.2mm以下のisolated tumor cells（ITC），2mm以下のmicrometastasis（MIC），それより大きいmacrometastasisに分類された．ITCとMICをセンチネルリンパ節に認めた場合は補助薬物療法を行うことでセンチネルリンパ節転移陰性乳がんと同等の予後が期待されると報告された[5]．さらに，センチネルリンパ節転移陽性乳がんにおけるリンパ節郭清の意義に関する臨床試験も行われた．American College of Surgeons Oncology Group（ACOSOG）のZ0011試験では，Ⅰ期とⅡA期乳がんを対象にセンチネルリンパ節転移陽性患者をリンパ節郭清の有無によって2群に分けて予後を検討した[6]．その結果，1,900例の登録予定であったが，症例集積の遅延と再発率が低かったため2004年に試験は中止された．登録された郭清群445例中97例（27％）でセンチネルリンパ節以外にも転移を認めたが，6年の観察期間において非郭清群446例の所属リンパ節再発はわずか4例（1％）であった．非郭清群に所属リンパ節再発が少なかった原因として，90％以上の症例で補助薬物療法が行われたこと，温存乳房の照射野の一部に腋窩が含まれていた可能性が高いことがあげられる．現在，センチネルリンパ節に転移を認めた場合でも一律に郭清を行うかどうか重要な課題となっている．

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ORIGINAL ARTICLE

# Diverting stoma in rectal cancer surgery. A retrospective study of 329 patients from Japanese cancer centers

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**Abstract**
*Background* A diverting stoma (DS) has been constructed for many patients with low anterior resection (LAR), but it is still controversial whether DS can prevent anastomotic leakages. The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for anastomotic leakage.

*Patients and methods* This was a retrospective analysis of 329 middle or lower rectal cancer patients who underwent LAR with mechanical reconstruction using circular staplers. Clinical data were collected from five cancer centers in Japan.

*Results* The overall anastomotic leakage rate was 10.0% (33 of 329). We experienced one mortality in this series (0.3%; 1/329). Clinical factors associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection, simultaneous resection of other organs, and the level of anastomosis, respectively.

On univariate analysis, high ligation of the inferior mesenteric artery had a significantly high leakage rate, but not on multivariate analysis. DS construction had no connection with the overall leakage rate. Concerning the clinical course affected by DS, the frequency of urgent reoperation was significantly increased in patients without DS compared with those with DS, 11.1% and 54.2%, respectively ($p=0.04$).

*Conclusions* LAR was the safe and preferred option for rectal cancer patients with very low mortality and an acceptable leakage rate. DS did not have a relationship with overall anastomotic leakage, but did seem to mitigate its consequences and reduce the requirement for urgent abdominal reoperation.

**Keywords** Rectal cancer · Anastomotic leakage · Diverting stoma · Defunctioning stoma · Low anterior resection

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## Introduction

Anastomotic leakage is a major problem in rectal cancer surgery, because a sphincter-preserving operation has become standard for many rectal cancer patients. A

temporary diverting stoma (DS) has been constructed for many patients in low anterior resection (LAR). But the indication of DS construction for patients without intraoperative adverse events has not been clarified for a long time. Theoretically, DS was constructed to divert the fecal stream from anastomotic sites, and to protect fragile anastomotic sites. But it remains unproven whether diverting the fecal stream in itself directly prevents leakage. Several retrospective studies showed that the absence of DS was a risk factor for leakage in LAR, whereas others did not. Therefore, it is controversial whether DS can prevent anastomotic leakage. Although recent randomized studies [1, 2] and meta-analyses [3, 4] have shown that DS reduced the incidence of symptomatic leakage in LAR for rectal cancer, there is still limited evidence as to the impact of DS on leakage. Moreover, there have been few analyses about this issue in multicenter studies with a large number of patients from Japan.

The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for such leakage using data collected from five cancer centers in Japan.

## Patients and method

### Patients

We reviewed the clinical data from five cancer centers in Japan which participated in the "Studies on the standardization for diagnosis, treatment, and follow-up of colorectal cancer patients", sponsored by Grant-in-Aid 18-2 for Cancer Research from the Ministry of Health, Welfare and Labor of Japan. All data on patient demographics, comorbidities, and the histological results were investigated retrospectively from the clinical records of each hospital.

From 2002 to 2004, a total of 329 consecutive patients with primary rectal cancer underwent LAR, and were investigated in this series. LAR was performed on patients with middle or lower rectal cancer, and reconstructions were done using circular staplers. Coloanal anastomosis using the hand-sewn technique was excluded from this study. Patients with subtotal colectomy, total proctocolectomy, abdominoperineal resection, Hartmann's procedure, or with pull-through procedures were also excluded.

### Surgical procedure

The inferior mesenteric artery (IMA) was divided either at its origin or below the origin of the left colic artery (LCA). High ligation of IMA was defined as dividing IMA at its origin, while low ligation was defined as dividing IMA below the origin of LCA. For oncological lymph node dissection, we classify regional lymph nodes into three groups: perirectal, intermediate, and main lymph nodes. Perirectal nodes are lymph nodes in the mesorectum along the superior rectal artery. Intermediate nodes are lymph nodes along IMA between the origin of the left colic artery and the origin of the terminal sigmoid artery. Main nodes mean the lymph nodes along the IMA proximal to the origin of the LCA [5]. Lymph node dissection for UICC stage I is complete dissection of perirectal and intermediate lymph nodes, that is, low ligation without lymph node dissection around the root of IMA. Lymph node dissection for stage II, III, and IV is complete dissection of all regional lymph nodes, that is, high or low ligation with lymph node dissection around the root of IMA [6].

After total mesorectal excision or tumor-specific mesorectal excision [7], we performed rectal irrigation, while clamping the anal side of the tumor. The rectum was then divided transversely or vertically [8]. After that, we usually added lateral lymph node dissection for patients diagnosed with stage II, III, and IV [9]. Although the extent of lymphadenectomy for stage IV is still debatable, in the case that every distant metastasis (stage IV) was resectable, we perform full lymph node dissection.

Reconstruction was done using a circular stapler. Most anastomoses were straight, and colonic J pouch or transverse coloplasty pouch was sometimes used at the discretion of the operating surgeon. Intraoperative leakage test by transanal instillation of fluid or air was performed depending on the surgeon. Pelvic drain was used routinely.

### Indication of DS construction

No clear applicable criteria for DS construction were stipulated in the present study. The DS construction decision was made by the individual surgeon in each case.

### Definition of anastomotic leakage

Anastomotic leakage was defined clinically by the presence of the following: discharge of gas, pus, or feces from the drain or wound; discharge of pus per rectum; or rectovaginal fistula. All clinically suspicious anastomotic leakages were confirmed by one or more of the following image diagnoses: contrast study; CT scan; rectoscopy. If these cases were proven not to show anastomotic insufficiency by these imaging studies, they were defined as pelvic abscess

and not as anastomotic leakage. We did not perform routine diagnostic imaging after LAR to detect anastomotic dehiscence in clinically stable patients.

### Variables analyzed

Variables included in this analysis were age, gender, body mass index (BMI), bowel obstruction, tumor location, tumor invasion, adjuvant therapy, level of IMA ligation, lateral lymph node dissection, type of anastomosis (single stapling technique, SST; or double stapling technique, DST), pouch surgery, intraoperative blood loss, operating time, DS construction, synchronous resections of other organs (hepatectomies for simultaneous liver metastasis or extended surgery to adherent organs, or additional cancer resections for double cancers), tumor size, and distal resection margin of specimen.

Bowel obstruction was defined as stenosis preventing the passage of a colon fiberscope. Tumor location was classified into middle or lower rectum according to the main part of the tumor. Tumors in the lower rectum were defined as those in which the main part was located below the peritoneal reflection. Tumor location in relation to the anal verge was preoperatively measured using rigid scope or digital examination. Tumor invasion was classified according to the UICC-TNM classification (6th edition [10]) preoperatively. Tumor size and distal resection margin were measured on the specimen before fixation with formalin. The level of anastomosis from the anal verge was measured with a digital examination. But due to the retrospective nature of this study, when the data were not available, the distance was calculated from the tumor location and distal resection margin.

### Statistical analysis

In the univariate analysis, the chi-squared test and Mann–Whitney test were used. After univariate analysis, variables with a $p$ value$\leq$0.1 were selected for multivariate analysis. A multivariate analysis was performed using a binary logistic regression model. All $p$ values <0.05 were considered statistically significant.

**Table 1** Patient characteristics

| | |
|---|---|
| Gender | |
| Male | 215 |
| Female | 114 |
| Age(years) | 59.0±10.5 (23–87) |
| Tumor location (cm) | 6.1±1.7 (4.0–12.0) |
| Bowel obstruction | |
| No | 305 |
| Yes | 18 |
| Missing | 6 |
| Tumor invasion | |
| T1,T2 | 108 |
| T3,T4 | 215 |
| Missing | 6 |
| Neoadjuvant chemo Tx | |
| No | 324 |
| Yes | 5 |
| Anastomosis | |
| SST | 15 |
| DST | 314 |
| High ligation | |
| No | 142 |
| Yes | 183 |
| Missing | 4 |
| LLND | |
| No | 197 |
| Yes | 132 |
| Level of anastomosis (cm) | 4.1±1.4 (1.0–9.5) |
| Intraoperative bleeding (ml) | 598±590 (10–3723) |
| Operating time (min) | 240±104.1 (90–620) |
| BMI (k/m$^2$) | 22.6±3.1 (14.1–31.2) |
| Tumor size (cm) | 4.4±2.3 (0–12.0) |
| Simultaneous resection | |
| No | 292 |
| Yes | 37 |
| DS construction | |
| No | 209 |
| Yes | 120 |

Values are number or mean±standard deviation (ranges)

*DS* diverting stoma, *BMI* body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

## Results

### Patient characteristics

From 2002 to 2004, a total of 329 consecutive patients underwent LAR. Patient characteristics were shown in Table 1. One hundred and eighteen middle rectal cancer patients and 211 low rectal cancer patients were investigated in this series. Average distance from the lower edge of the tumor to the anal verge was 6.1 cm (4.0–12.0 cm). Average distance from anastomosis to the anal verge was 4.1 cm (1.0–9.5 cm).

Neoadjuvant chemotherapy was performed for five patients, but others were treated by surgery alone. Neo-

adjuvant radiotherapy or chemoradiotherapy was not performed in this series, because preoperative therapy for resectable rectal cancer was not standard in Japan.

Synchronous resections included 20 extended resections for direct invasion of adjacent organs, 13 hepatectomies for liver metastasis, and five resections of double primary cancers.

## Morbidity and mortality

The overall rate of anastomotic leakage was 10.0% (33 of 329). We experienced only one mortality in this series (0.3%; 1/329). This patient died from a septic complication caused by anastomotic leakage in the case of LAR with DS 6 days after initial surgery.

## Diverting stoma

A DS was constructed in 120 patients (36.5%; 120 of 329) in initial LAR, respectively. Among the colorectal surgeons participating in this study, ileostomy was major and chosen for 92 (76.7%) patients, while transverse colostomy was done for 28 (23.3%) patients.

The DS construction rate had a significant association with tumor location. DS was constructed in only 12.7% of middle rectal cancer patients, but in 48.3% of low rectal cancer patients who experienced temporary stoma at initial LAR, respectively.

Other factors found to be significantly associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection,

**Table 2** Univariate analysis of factors related with DS construction

| | Diverting stoma | | Rate | *p*-value |
|---|---|---|---|---|
| | DS(−) | DS(+) | | |
| Gender | | | | |
| Male | 130 | 85 | 39.5 | 0.11 |
| Female | 79 | 35 | 30.7 | |
| Age (years) | 58.8±10.7 (23–87) | 59.4±10.2 (29–75) | | 0.42 |
| Tumor location (cm) | 6.4±1.6 (4.0–12.0) | 5.9±1.7 (4.0–12.0) | | 0.001 |
| Bowel obstruction | | | | |
| No | 195 | 110 | 36.1 | 0.76 |
| Yes | 11 | 7 | 38.9 | |
| Tumor invasion | | | | |
| T1,T2 | 71 | 37 | 34.6 | 0.50 |
| T3,T4 | 133 | 82 | 38.1 | |
| Neoadjuvant chemo Tx | | | | |
| No | 204 | 120 | 37.0 | 0.10 |
| Yes | 5 | 0 | 0.0 | |
| Anastomosis | | | | |
| SST | 8 | 7 | 46.7 | 0.40 |
| DST | 201 | 113 | 36.0 | |
| High ligation | | | | |
| No | 125 | 58 | 31.7 | 0.12 |
| Yes | 82 | 60 | 42.3 | |
| LLND | | | | |
| No | 146 | 51 | 25.9 | <0.0001 |
| Yes | 63 | 69 | 52.3 | |
| Level of anastomosis (cm) | 4.2±1.4 (1.0–9.0) | 3.8±1.4 (1.0–9.5) | | 0.002 |
| Intraoperative bleeding (ml) | 505±524 (10–2985) | 760±662 (17–3723) | | <0.0001 |
| Operating time (min) | 231±90.6 (90–559) | 318±102.7 (130–620) | | <0.0001 |
| BMI (k/m$^2$) | 22.9±3.0 (14.1–31.2) | 22.3±3.2 (15.8–30.8) | | 0.07 |
| Tumor size (cm) | 4.4±2. (0–12.0) | 4.4±2.3 (1.0–10.0) | | 0.97 |
| Simultaneous resection | | | | |
| No | 192 | 100 | 34.2 | 0.02 |
| Yes | 17 | 20 | 54.1 | |

Values are number or mean± standard deviation (ranges)

*BMI* body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

simultaneous resection of other organs, and level of anastomosis (Table 2).

Risk factors of anastomotic leakage

Clinical variables were analyzed to investigate the risk factors for anastomotic leakage (Table 3). On univariate analysis, LAR with high ligation of IMA had a significantly high leakage rate ($p<0.05$). There were increased but statistically insignificant impacts on leakage in males, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs.

Nine (7.5%) of 120 patients with DS had leakage, compared with 24 (11.5%) of 209 patients without DS ($p=0.25$). DS construction also had no relevance to the overall anastomotic leakage.

Risk factors of leakage limited to the LAR without DS were also investigated. As shown in Table 4, no obvious statistical significance was found with any clinical factor.

A multivariate analysis of risk factors for anastomotic leakage showed every factor including high ligation of IMA construction as not statistically significant (Table 5).

**Table 3** Univariate analysis of leakage risk factors

| | Leakage | | Rate | *p*-value |
|---|---|---|---|---|
| | No leakage | Leakage | | |
| Gender | | | | |
| Male | 190 | 25 | 11.6 | 0.19 |
| Female | 106 | 8 | 0.7 | |
| Age(years) | 58.8±10.6 (23–87) | 61.1±10.0 (40–76) | | 0.20 |
| Tumor location (cm) | 6.2±1.7 (4.0–12.0) | 6.5±1.7 (4.0–10.0) | | 0.31 |
| Bowel obstruction | | | | |
| No | 276 | 29 | 9.5 | 0.16 |
| Yes | 14 | 4 | 22.2 | |
| Tumor invasion | | | | |
| T1,T2 | 101 | 7 | 6.5 | 0.12 |
| T3,T4 | 189 | 26 | 12.1 | |
| Neoadjuvant chemo Tx | | | | |
| No | 291 | 33 | 10.2 | 0.59 |
| Yes | 5 | 0 | 0.0 | |
| Anastomosis | | | | |
| SST | 13 | 2 | 13.3 | 0.66 |
| DST | 283 | 31 | 9.9 | |
| High ligation | | | | |
| No | 135 | 7 | 4.9 | 0.02 |
| Yes | 157 | 26 | 14.2 | |
| LLND | | | | |
| No | 177 | 20 | 10.1 | 0.93 |
| Yes | 119 | 13 | 9.8 | |
| Level of anastomosis (cm) | 4.1±1.4 (1.0–9.5) | 4.4±1.3 (1.9–7.0) | | 0.13 |
| Intraoperative bleeding (ml) | 573±559 (10–3365) | 817±791 (40–3723) | | 0.06 |
| Operating time (min) | 261±102 (90–616) | 273±118 (113–620) | | 0.70 |
| BMI (k/m$^2$) | 22.7±3.1 (14.1–31.2) | 22.5±3.2 (16.1–27.0) | | 0.87 |
| Tumor size (cm) | 4.4±2.3 (0–12.0) | 5.0±2.3 (2.0–11.0) | | 0.18 |
| Simultaneous resection | | | | |
| No | 266 | 26 | 8.9 | 0.06 |
| Yes | 30 | 7 | 18.9 | |
| DS construction | | | | |
| No | 185 | 24 | 11.5 | 0.25 |
| Yes | 111 | 9 | 7.5 | |

Values are number or mean± standard deviation (ranges)

*BMI* body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

**Table 4** Univariate analysis of leakage risk factors (without DS patients)

| | Leakage | | Rate | *p*-value |
|---|---|---|---|---|
| | No leakage | Leakage | | |
| Gender | | | | |
| Male | 114 | 16 | 12.3 | 0.63 |
| Female | 71 | 8 | 10.1 | |
| Age(years) | 58.7±10.8 (23–87) | 59.7±10.1 (40–76) | | 0.65 |
| Tumor location (cm) | 6.4±1.6(4.0–12.0) | 6.3±1.6 (4.0–10.0) | | 0.61 |
| Bowel obstruction | | | | |
| No | 173 | 22 | 11.3 | 0.64 |
| Yes | 9 | 2 | 18.2 | |
| Tumor invasion | | | | |
| T1,T2 | 65 | 6 | 8.5 | 0.28 |
| T3,T4 | 115 | 18 | 13.5 | |
| Neoadjuvant chemo Tx | | | | |
| No | 180 | 24 | 11.8 | 0.54 |
| Yes | 5 | 0 | 0.0 | |
| Anastomosis | | | | |
| SST | 7 | 1 | 12.5 | 0.63 |
| DST | 178 | 23 | 11.4 | |
| High ligation | | | | |
| No | 108 | 17 | 13.6 | 0.47 |
| Yes | 75 | 7 | 8.5 | |
| LLND | | | | |
| No | 130 | 16 | 11.0 | 0.72 |
| Yes | 55 | 8 | 12.7 | |
| Level of anastomosis (cm) | 4.2±1.4 (1.0–9.0) | 4.2±1.1(2.2–7.0) | | 0.89 |
| Intraoperative bleeding (cm) | 480±502 (10–2985) | 703±650 (40–2720) | | 0.07 |
| Operating time (cm) | 228±88 (90–552) | 248±108(113–559) | | 0.60 |
| BMI ($k/m^2$) | 22.9±3.0 (14.1–31.2) | 22.7±3.1 (16.1–27.0) | | 0.82 |
| Tumor size (cm) | 4.3±2.3 (0–12.0) | 5.0±2.4 (2.0–11.0) | | 0.26 |
| Simultaneous resection | | | | |
| No | 171 | 21 | 10.9 | 0.31 |
| Yes | 14 | 3 | 17.6 | |

Values are number or mean± standard deviation (ranges)

*BMI* body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Clinical course affected by DS construction

The clinical course affected by DS was also investigated, focusing on the necessity of urgent abdominal reoperation for anastomotic leakage. Nine of 120 (7.5%) patients who underwent LAR with DS experienced leakage. Of these nine, only one patient (11.1%) needed urgent reoperation for peritonitis, and eight patients were treated conservatively. Twenty-four of 209 (11.5%) patients who underwent LAR without DS experienced leakage, and 13 (54.2%) of them needed urgent reoperation, while 11 patients were treated conservatively (Table 6). The need for reoperation was significantly increased in patients without DS compared to those with DS, 54.2% and 11.1%, respectively ($p=0.04$).

**Table 5** Multivariate analysis of leakage risk factors

| | *p*-value | Odds ratio (95% CI) |
|---|---|---|
| High ligation | 0.17 | 1.9 (0.77–4.54) |
| Intraoperative bleeding | 0.78 | 1.0 (0.99–1.00) |
| Simultaneous resection | 0.12 | 2.2 (0.82–6.09) |

## Discussion

LAR was the safe and preferred option for middle or low rectal cancer patients with very low mortality and an acceptable leakage rate among the institutes participating in this study. DS did not have a statistically significant

**Table 6** Clinical course affected by diverting stoma

| DS in initial LAR | | Leakage | | Conservative therapy | Urgent operation | Rate of urgent operation | |
|---|---|---|---|---|---|---|---|
| | | | % | | | % | |
| DS(+) | 120 | 9 | 7.5 | 8 | 1 | 11.1 | $p$=0.04 |
| DS(−) | 209 | 24 | 11.5 | 11 | 13 | 54.2 | |

relationship with the overall leakage rate. Although we cannot conclude the value of DS in terms of leakage prevention from this retrospective study, DS did seem to mitigate the consequences of leakage and reduce the need for urgent abdominal reoperation for leakage. There have been few reports about this issue in multicenter studies with a large number of patients from Japan.

With the advances in surgical procedures and devices in recent decades, sphincter-preserving surgery has become the treatment of choice for rectal cancer patients. In addition, simple and easy reconstruction has become possible thanks to circular stapling devices, even in low-level anastomosis within a narrow pelvis.

However, anastomotic leakage is still a major problem in rectal cancer surgery, sometimes resulting in severe morbidity or mortality. Since stapled anastomosis developed in the 1970s, the mortality of sphincter-preserving operations has decreased. In 1975, Fain et al. [11] reported their experience of mechanical suturing in 165 rectal cancer patients with a mortality of 2.4%. Now, symptomatic anastomotic leakage has been reported to occur in 5% to 20% of cases [12–20], and when present, the associated risk of postoperative mortality is increased to between 6% and 22% [15]. The present study encountered very low mortality (1/329; 0.3%), which is not inferior to the 0.8% recently described [2]. Our result shows the obviously improved safety of LAR using mechanical anastomosis in the Japanese cancer centers participating in this study.

Several risk factors for anastomotic leakage have been reported [12–20], and the relationship between DS and leakage was discussed in many retrospective or non-randomized prospective studies. Wong et al. [21] reported no statistical difference between patients who were defunctioned (3.8%; 28/742) and those who were not (4%; 13/324). So, they concluded that DS did not reduce the postoperative leak rate. They also concluded that a stoma carried a certain morbidity and also added to the cost of the entire operation, so it should not be performed routinely. On the other hand, Peeters et al. [18] reported that the absence of DS was significantly associated with a higher leakage rate: 43 (8.2%) of 523 patients with DS had leakage, compared with 64 (16.0%) of 401 patients without DS ($p$<0.001). In the present study, DS construction had no association with the overall anastomotic leakage rate. This reflects our low leakage rate in cases without DS (11.5%; 24 of 209). This rate is comparable to the leakage rate in cases with DS in a randomized controlled trial by Matthiessen et al. (10.3%; 12 of 116) [1].

Although absence of DS was not a risk factor of leakage in this study, because of a general selection bias of nonrandomized study including ours, we cannot conclude whether or not DS can prevent the leakage. This bias results from the selective creation of DS for the patients anticipated to undergo "risky" anastomosis by each surgeon as shown in this investigation. We can also point out another bias, namely that clinically unapparent leakages might have been missed in either group because no systematic assessment of the anastomosis for clinically stable patients was performed in the present study.

Only four randomized control studies sought to investigate the association between DS and leakage [1, 2, 22, 23]. Matthiessen et al. [1] reported the result of intraoperative randomization of a patient undergoing LAR for rectal cancer within 15 cm from the anal verge, and anastomosed within 7 cm. 10.3% (12 of 116) of patients with defunctioning stoma ($n$=116) had symptomatic leakage, against 28.8% (33 of 118) of those without stoma ($n$=118). They concluded that defunctioning stoma significantly decreased the rate of symptomatic leakage and was therefore recommended in LAR for rectal cancer. Pakkastie et al. [22] and Graffner et al. [23], on the other hand, could not find any statistical difference between the two groups in their randomized studies comprising 50 and 38 patients, respectively. But due to the small sample, no firm conclusion could be made. So, it is still controversial whether DS can prevent anastomotic leakage. The problem is the limited evidence about this issue. The value of DS in preventing leakage should be evaluated by more prospective studies in the future. And prospective, randomized studies are also warranted to address this issue.

Other reported risk factors include male gender [13–16], level of anastomosis [12–15], previous radiation therapy [13, 14], absence of pelvic drainage [18], poor bowel preparation [12], blood transfusion [12], immunosuppression, and underlying vascular insufficiency. Among these risk factors, male gender and level of anastomosis were widely accepted as significant for leakage. In the present study, there were increased impacts on leakage in male gender, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs. Although statistical significance was not reached, these factors were

comparable to those in previous reports. In the present investigation, due to the retrospective nature of the study design, the level of anastomosis was calculated from the tumor location and distal resection margin when data were not available. And in some patients, tumor location was measured only by digital examination and not by rectoscopy, these might introduce bias. Although the anastomotic level was not associated with leakage, this data should be evaluated with caution.

High ligation of IMA was the only leakage risk factor on univariate analysis in the present study. Lange et al. [24] systematically reviewed the literature concerning the level of ligation and concluded that preserving IMA and left colic artery was anatomically less invasive with respect to circulation and autonomous innervations of the proximal limb of anastomosis. Seike et al. [25] measured the colonic blood flow at the proximal site of the anastomosis by laser Doppler flowmetry to evaluate the influence of high ligation. They proved a significant reduction of colonic blood flow at the proximal site after clamping IMA. Our result also suggested the possibility that blood flow reduction on anastomotic sites leads to more leakage.

In the present study, we reported our low leakage rate in cases without DS (11.5%; 24 of 209). This rate is comparable to the leakage rate in cases with DS in a randomized controlled trial by Matthiessen et al. (10.3%; 12 of 116) [1]. This may have some association with our patient population that neoadjuvant radiotherapy or chemo-radiotherapy was not performed in this series. Neoadjuvant radiation therapy is considered to be a risk factor by some authors [13, 14]. Although randomized multicenter trials have shown that neoadjuvant radiation does not increase postoperative morbidity [26–28], Peeters et al. [18] retrospectively analyzed risk factors from the database of the Dutch Colorectal Cancer Group, and reported that a defunctioning stoma was constructed more often in patients who had received radiation, and that the absence of a DS was significantly associated with a higher leakage rate.

We also reported our low mortality. This reflects our low leakage rate in cases without DS and our appropriate decision of reoperation for peritonitis in cases without DS. We considered that our appropriate decision lead to low mortality rate and high reoperation rate (54.2%). In the present study, a DS constructed at the time of initial surgery obviously reduced the necessity of an urgent reoperation after overt leakage, proving the clinical benefits of DS in this regard. The important objective of DS was not to eliminate leakage but to decrease the risk of reoperation. However, DS construction did not guarantee the complete safety of LAR. In fact, we experienced one mortality in a patient with DS in this series, so complete elimination of leakage and severe septic complications was not feasible.

In conclusion, we clearly demonstrated the outstanding safety of LAR with very low mortality and acceptable leakage rate in our group. Although this retrospective study could not prove whether DS can prevent leakage itself, we found that it could mitigate the need for urgent abdominal reoperation for leakage. To define clear criteria for DS construction, a well-designed randomized control study is genuinely needed in the future.

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# Postoperative Lymphocyte Percentage Influences the Long-term Disease-free Survival Following a Resection for Colorectal Carcinoma

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**Objective:** The aim of this study is to examine the relationship between postoperative laboratory parameters of inflammation and the disease-free survival in patients undergoing resection for colorectal cancer.
**Methods:** Six hundred seventy-five consecutive patients who underwent an elective resection for primary colorectal cancer from October 1999 to March 2004 were included in this study. We examined the associations between cancer recurrence and white blood cell count, lymphocyte percentage, neutrophil percentage and C-reactive protein.
**Results:** Lymphocyte percentage on postoperative days 3 and 7 was significantly higher in patients without recurrence than in those with recurrence. Lymphocyte percentage on postoperative day 7 differed the most between the two groups. On postoperative day 7, Stage II patients with lymphocyte percentage >15% had significantly longer survival compared with the patients with lymphocyte percentage ≤15%. A multivariate analysis showed lymphocyte percentage ≤15% on postoperative day 7 to be an independent prognostic factor, along with lymph node metastases and serosal invasion. Logistic regression analysis showed that blood loss (>250 ml) and postoperative complications were significant independent predictors of lymphocyte percentage ≤15% on postoperative day 7.
**Conclusions:** Lymphocyte percentage ≤15% on postoperative day 7 is an independent prognostic factor for the patients undergoing a resection for colorectal cancer.

*Key words: colorectal carcinoma – lymphocyte percentage – less invasive surgery*



## INTRODUCTION

Surgery remains the definitive treatment for advanced colorectal cancer. However, major surgery causes significant alterations in metabolic, immune and endocrine functions. It has been well documented that major surgery alters multiple immune parameters and accelerates tumor growth (1–4). Links between cancer and inflammation have not been elucidated. In some types of cancer, inflammatory conditions are present before a malignant change occurs. The mediators and cellular effectors of inflammation are important constituents of the local environment of tumors (5). Some studies show that the presence of inflammation is correlated with poor prognosis in the patients with malignancies (6,7). However, the impact of the postoperative inflammatory response on the recurrence of cancer has not been elucidated.

Laparoscopic surgery has led to great progress in the treatment of colorectal cancer. Recently, published randomized trials comparing laparoscopic and open surgery do not show inferior oncologic results in patients who undergo laparoscopic surgery (8,9). Lacy et al. (10) report significant improvement in 3-year survival in patients with advanced stage cancer who undergo laparoscopic surgery. The better survival might be attributed to the favorable immunologic response and lower stress response in patients who have undergone laparoscopic surgery.

The prognostic value of biological markers in patients with advanced cancer has been investigated in palliative care. There is some evidence that abnormalities in certain laboratory parameters [e.g. leukocytosis, lymphocytopenia and an elevated C-reactive protein (CRP) level] have prognostic values (11). However, the prognostic values of these

parameters in the perioperative period have not yet been examined in patients undergoing potentially curative surgery.

We examined the preoperative and postoperative white blood cells (WBCs), neutrophil percentage (NEUTRO%), lymphocyte percentage (LYMPH%) and level of CRP. The aim of this study is to clarify the impact of these parameters on the recurrence of cancer.

## PATIENTS AND METHODS

### Patients

Patients with histologically proven colorectal cancer who had undergone a potentially curative resection and had routine laboratory findings were included in this study. We retrospectively reviewed a database of 675 patients between August 1999 and March 2004 at the National Cancer Center East. Demographic and clinical data (age, sex, tumor location, tumor stage, differentiation, carcinoembryonic antigen (CEA) level, surgical approach, operating time, blood loss and postoperative complication) were collected. Patients with an emergency operation, non-curative resection, no laboratory data or preoperative chemoradiotherapy were excluded. The surgical approach was decided with the consent of the patients after thorough discussion on the advantages and disadvantages of the approaches. Patients with large, fixed tumors with invasion to other organs were advised against laparoscopic resection.

### Data Collection

Routine laboratory measurements were taken before the operation and on postoperative days (PODs) 1, 3 and 7. In all blood samples, WBC, LYMPH%, NEUTRO% and CRP were measured.

### Statistical Analysis

The statistical analysis was performed using the SPSS 11.0.1 Statistical Software Package (SPSS Inc., Chicago, IL, USA). Comparisons of categorical ordinal variables were performed using the Pearson $\chi^2$ test. The Mann–Whitney *U*-test was used to compare laboratory data at each time point between two groups. Survival rates were calculated with the Kaplan–Meier method, and differences between the curves were tested using the log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model. Logistic regression analysis was used to estimate the odds ratio with 95% confidence intervals for LYMPH% $\leq$ 15%. A *P* value of $<0.05$ was considered to be statistically significant.

## RESULTS

The median follow-up duration was 46.3 months. Within the observation period, 124 patients developed recurrence. We compared laboratory data (WBC, LYMPH%, NEUTRO% and CRP) from patients with recurrence and those without recurrence. WBC and NEUTRO% on PODs 3 and 7 in patients without recurrence were significantly lower than in those with recurrence (Fig. 1a and c). LYMPH% on PODs 3 and 7 in the patients without recurrence was significantly higher than in patients with recurrence (Fig. 1b). The difference in LYMPH% on POD 7 (LYMPH%7POD) was most evident between the two groups. We compared clinicopathological factors and disease-free survival according to LYMPH%7POD. The patients with $\leq$15% LYMPH%7POD were classified in the low group and those with more than 15% LYMPH%7POD were classified in the high group. The median of LYMPH%7POD was 15.8%.

The correlation between clinicopathological factors and LYMPH%7POD are shown in Table 1. LYMPH%7POD was significantly correlated with gender ($P = 0.01$), tumor location ($P < 0.01$) and tumor stage ($P < 0.01$). Disease-free survival was significantly higher ($P < 0.01$) in the LYMPH%7POD $>$ 15% group than in the LYMPH% 7POD $\leq$ 15% group (Fig. 2). Three-year survival rates in patients with LYMPH%7POD $\leq$ 15% and in those with LYMPH%7POD $>$ 15% were 70.7 and 85.1%, respectively. More patients with advanced stage cancer had LYMPH%7POD $\leq$ 15%; therefore, disease-free survival was compared according to TMN tumor stage. As shown in Fig. 3, patients with LYMPH%7POD $>$ 15% had longer survival compared with those with LYMPH%7POD $\leq$ 15% in Stage II. Only three patients with Stage I tumors had recurrence, and there was no significant difference between the two groups in Stage I. Disease-free survival in the patients with Stage III and VI tumors was longer in the LYMPH%7POD $>$ 15% group, but the difference was not statistically significant. To determine the importance of the LYHPH%7POD as a predictor of disease recurrence, a multivariate analysis using the Cox proportional hazards model was performed. The analysis identified LYMPH%7POD $\leq$ 15% as an independent prognostic factor, along with lymph node metastases and serosal invasion (Table 2).

To identify the meaning of LYMPH%7POD, we performed logistic regression analysis with adjustments for operating time, blood loss, CEA, differentiation, lymph node metastases, serosal invasion, postoperative complications and laparoscopic surgery. Table 3 shows that blood loss ($>$250 ml) and postoperative complications were significant independent predictors of LYMPH%7POD $\leq$ 15%. The extent of tumor spread, such as lymph node metastases and serosal invasion, was not a significant predictive factor.

## DISCUSSION

To date, laboratory parameters, such as CRP (6,7), lymphocytopenia and leukocytosis (12,13), have been described as significant prognostic factors in patients with advanced

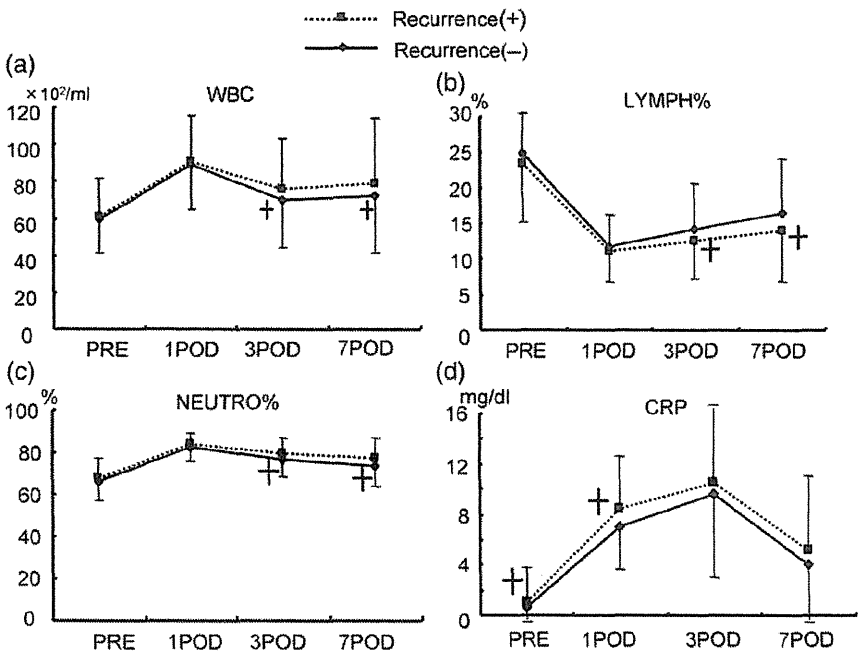


**Figure 1.** White blood cell (WBC), lymphocyte percentage (LYMPH%), neutrophil percentage (NEUTRO%) and C-reactive protein (CRP) in patients undergoing resection for colorectal carcinoma. Sample points were taken preoperative (PRE) and on postoperative days 1 (1POD), 3 (3POD) and 7 (7POD) ($^{+}P < 0.05$).

**Table 1.** The correlation between clinicopathological factors and LYMPH%7POD

| | Lymph%7POD | | *P* value |
|---|---|---|---|
| | >15% ($n = 248$) | ≤15% ($n = 258$) | |
| Median age | 63.6 | 62.6 | 0.31 |
| Sex (M/F) | 143/105 | 178/80 | 0.01 |
| Tumor location | | | |
| Right side | 52 | 39 | <0.01 |
| Transverse | 23 | 17 | |
| Left side | 11 | 9 | |
| Sigmoid | 81 | 41 | |
| Rectum | 81 | 152 | |
| Stage | | | |
| I | 68 | 39 | <0.01 |
| II | 88 | 81 | |
| III | 80 | 100 | |
| IV | 11 | 37 | |
| Differentiation well or moderately | 233 | 236 | 0.52 |
| Poorly and others | 9 | 13 | |

LYMPH%7POD, lymphocyte percentage on postoperative day 7.

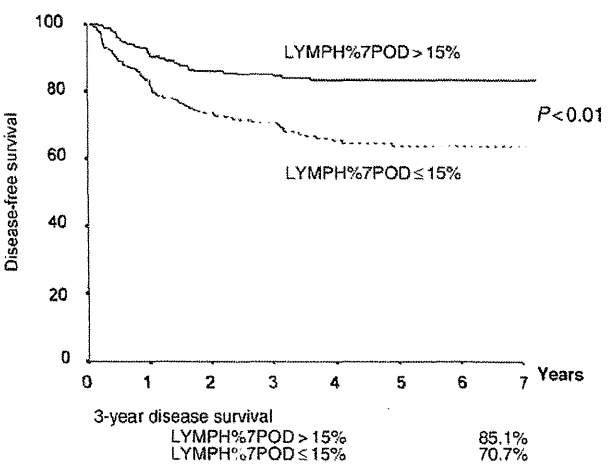


**Figure 2.** The disease-free survival rates of the patients with LYMPH%7POD > 15% and those with LYMPH%7POD ≤ 15%.

cancer. However, little information is available regarding the prognostic role of postoperative laboratory parameters in patients undergoing a resection of colorectal carcinoma. In this study, we evaluated whether postoperative laboratory data, such as WBC, LYMPH%, NEUTRO% and CRP, are associated with recurrence of colorectal carcinoma. This study demonstrated LYMPH%7POD ≤ 15% to significantly correlate with the recurrence of carcinoma as well as lymph node metastases and serosal invasion.

The LYMPH% is an important parameter in patients with advanced cancer (11,14,15). Some reports demonstrated that the neutrophil–lymphocyte ratio predicts survival in patients with colorectal cancer (16–18). Our results suggest that decreased LYMPH% may indicate an impaired host immune response to the tumor or inflammatory conditions that are