1. 5-FU 投与法の検討—5-FU＋(leucovorin, LV) の至適投与法

5-FU＋LV については 5-FU の急速静注による RPMI (Rosewell Park Memorial Institute) の weekly 法[2], Mayo Clinic の 5 日間法[3], 5-FU の持続静注による de Gramont 法[4] や AIO 法[5] がある. 当初は Mayo Clinic の 5 日間法が利便性などから汎用されていたが, 白血球減少などの有害事象の頻度が高く, また LV の費用も安価となったことから, RPMI の weekly 法が汎用されてきている. 一方, 欧州ではフランスを中心に 5-FU 持続静注法が検討され, LV の 2 時間点滴直後に 5-FU の急速静注と 22 時間の持続点滴を 2 日間にわたり実施する de Gramont 法が有害事象の点で優れるとして汎用されている.

Mayo Clinic 法と de Gramont 法との第 III 相試験[4] の結果, 後者が消化器症状や白血球減少などの有害事象で頻度や程度が低く, 奏効率や無増悪期間・生存期間で優れると報告されている. また, ドイツを中心に, LV の 2 時間点滴に引き続き, 2.4～3.0 g/m² の高用量の 5-FU を 46 時間持続点滴で行う方法が使用されている[5]. これらの持続点滴法ではカテーテルの挿入, ポートの埋め込み, 注射部位の清潔管理に関する患者教育などが必要であるが, いったん導入すれば外来にて簡単に実施することが可能である.

最近では, irinotecan や oxaliplatin などとの併用療法の第 III 相試験成績により, 5-FU/LV の投与方法も急速静注から点滴静注へと移行してきている.

2. irinotecan (CPT-11) の臨床評価と新しい併用療法

irinotecan は, 日本国内で開発された I 型 DNA トポイソメラーゼ阻害剤であり, 5-FU 耐性大腸癌に対しても有効であることが報告されている[6]. その後, 英国を中心に 5-FU 治療抵抗性症例を対象とした BSC (Best Supportive Care) 群との第 III 相試験により, 二次治療としての臨床的意義が検証された[7]. また, 北米および欧州において一次治療としての意義が検討され, 投与スケジュールは異なるものの従来の 5-FU＋LV との比較において irinotecan 併用群の生存期間の延長が検証された[8),9]. これにより, 転移性大腸癌の標準治療は 5-FU＋LV から 5-FU＋LV＋irinotecan 併用療法へと書き換えられることとなった. 北米では, 急速静注法である 5-FU＋LV と irinotecan の併用療法である IFL 療法が標準とされ, 転移性大腸癌や術後補助療法の第 III 相試験での対照群として設定された. しかしながら, N 9741 と C 89803 試験の中間解析において, IFL 療法での有害事象の頻度が問題となり, 投与スケジュールの修正がなされている[10].

一方, 欧州では, 持続点滴の 5-FU＋LV である de Gramont 法に irinotecan を併用する FOLFIRI 療法が検討され, 高い奏効率と認容性が報告されている[11]. 主たる副作用は下痢, 悪心・嘔吐, 白血球減少であるが, 2 週ごとの投与は可能である. また, 後述する oxaliplatin と異なり, 蓄積性の末梢神経障害がないこと, 北米での oxaliplatin の高薬価の問題などから, まだ irinotecan の臨床的価値は十分認められると考えられる.

3. oxaliplatin の臨床評価と新しい標準療法

oxaliplatin は, cisplatin とは抗腫瘍スペクトラが異なる国産の新規白金系抗癌剤である[12]. 国内での臨床開発では十分な臨床効果を示すことができず, フランスを中心とした海外臨床試験の結果, その有効性が見出され, 単独よりも 5-FU＋LV との併用療法にて高い奏効率が報告された.

もっとも有名な併用療法は, FOLFOX 療法である[13]. de Gramont 法に oxaliplatin 85 mg/m² を併用し, 2 週ごとに繰り返す方法で

ある．悪心・嘔吐，食欲低下，下痢，白血球減少，血小板減少，肝機能低下などの有害事象が認められるが，腎機能低下は少ない．しかし，特異的な有害事象として咽頭・喉頭の違和感，末梢神経炎がある．とくに後者は蓄積性があり，800 mg/m² 以上でその頻度が高くなり，回復性が遷延するとされる[14]．FOLFOX 療法はいくつかの投与方法が検討されているが，すべて第II相試験であり，かつ前治療を有する症例での検討であり，個々の治療法の比較検討ができないという問題がある．現時点では比較試験で検討されている FOLFOX 4 療法や 5-FU＋LV の 2 日間の繰り返し投与を 1 日に簡便化した FOLFOX 6 療法[15]や FOLFOX 7 療法[16]が使用されている．しかしながら，どの治療スケジュールが優れるか否かについては十分なデータがない．

FOLOFX 4 療法は初回化学療法症例の転移性大腸癌を対象とした de Gramont 法との比較試験[13]において，奏効率と無増悪生存期間で優れる結果であったが，生存期間では有意差は認めていない．また，末梢神経障害や消化器症状がより強いという結果が示されている．

北米での 5-FU＋LV の急速静注療法である IFL 療法抵抗性症例を対象とした二次治療での FOLFOX 療法の評価は，de Gramont 法や oxaliplatin 単独と比較して，奏効率，無増悪生存期間などで優れる結果が報告されている[17]．これらの臨床試験成績から，oxaliplatin の大腸癌治療における意義は徐々に認知されるようになったが，最終的には北米での Inergroup 試験である N 9741 試験[18]の結果がもっとも大きなインパクトを与えた．N 9741 試験は，初回化学療法症例を対象として IFL 療法を対照群とし，FOLFOX 4 療法と IROX（irinotecan＋oxaliplatin）療法を試験群とした 3 アームの比較試験である．2003 年の ASCO において中間解析結果が報告され，奏効率，無増悪生存期間，生存期間，1 年生存率において北米の標準治療である IFL 療法を FOLOFX 4 療法が有意に上回るという衝撃的な結果であった．2004 年 ASCO ではその最終報告が行われ，FOLFOX 4 療法の優位性が確認された．米国では，この結果 oxaliplatin が大腸癌の一次療法として承認されている．今後は，FOLFOX 療法が転移性大腸癌の標準治療として認知され，infusional 5-FU＋LV の部分を経口抗癌剤である capecitabine へ置換した XELOX（capecitabine＋oxaliplatin）療法[19]などが利便性，医療経済性などの面から臨床評価をされることになる．

4. 経口抗癌剤の臨床評価とその位置づけ

経口抗癌剤はおもに国内において開発され，汎用されてきた歴史がある．とくに術後補助療法ではその利便性から長期にわたり使用されてきたが，十分な臨床的意義は確認されていなかった．米国において，経口抗癌剤の評価が進んだ 1990 年代に重要な大規模比較試験が実施されている．すなわち，転移性大腸癌を対象として，標準治療と考えられる 5-FU＋LV 療法を対照群として，経口抗癌剤を試験群として各薬剤複数の第 III 相比較試験が実施された．これらの試験は，経口抗癌剤による治療が，生存期間，無増悪生存期間，奏効率，有害事象などの重要な臨床評価項目において，標準治療である静注群に劣らないことを検証する非劣性デザインで行われている．いくら利便性が優れていても，あるいは医療経済的に優れていても，臨床的有用性で劣るのであれば，経口剤を臨床導入する意義はないという仮説である．DPD（dihydropyrimidine dehydrogenase）阻害薬である UFT/LV，5-FU＋eniluracil，および非 DPD 阻害薬である capecitabine の 3 種類の経口抗癌剤が検討された[20)~24)]．その結果，capecitabine のみで非劣性が検証され，米国において史上初めて大腸癌の一次治療薬として経口抗癌剤が承認されることになった．UFT/

LV は無増悪生存期間で非劣性が検証されていないと判断されたが，欧州，日本では非劣性の検証がされたと判断され大腸癌に対して承認されている．一方，非可逆的 DPD 阻害薬である eniluracil 併用群は，非劣性が検証できず，臨床開発が中止された．このような大規模臨床試験により，初めて経口抗癌剤の臨床的意義が明確になったことは，利便性のみで経口抗癌剤を汎用している国内臨床現場にとって重要な警鐘と考えられる．この経口抗癌剤の競争を勝ち取った capecitabine は，現在 5-FU＋LV を含む各種併用療法において，置換可能かどうかを検討する比較試験でその併用療法での意義が検討されている．この結果，経口抗癌剤が静注療法に置き換えることが可能となれば，患者負担や臨床現場での負担が大幅に軽減することが可能となりその意義は大きい．

国内においては，現在 UFT/LV[25]，TS-1[26),27)] が使用可能となり，さらに capecitabine の海外用量での検討が終了している．UFT/LV は海外第 III 相試験成績と，日米の架橋試験成績により承認されたが，1日3回内服と LV 錠の高薬価が問題である．胃癌での高い奏効率を示した TS-1 は大腸癌でも 37%の奏効率が報告され，期待されているが，5-FU＋LV との比較試験成績がなく，併用療法あるいは単独療法での比較が必須である．capecitabine は hand-foot 症候群という特異な有害事象があり，これに伴う末梢神経障害が臨床上問題となっている．臨床症状の詳細な観察と，適切な減量が本剤を使用する際のポイントとなる．

また，最近の経口抗癌剤は従来と比較して高い奏効率が報告されているが，それとともに静注療法に匹敵する有害事象も発生するので十分な注意が必要である．有害事象を恐れ，投与量を大幅に減量するのであれば，高い奏効率を期待することは難しい．

5. 分子標的治療薬のインパクト

2003 年の ASCO でのもっとも衝撃的な報告は，分子標的治療薬である bevacizumab (Avastin®) の第 III 相試験成績[28)] の報告である．本剤は，VEGF (vascular endotherial growth factor) に対する単クローン抗体である．北米のかつての標準治療である IFL 療法を対照群として IFL＋bevacizumab 併用群を試験群として初回化学療法例を対象に比較検討がなされた．結果は，生存期間，無増悪生存期間，奏効率，奏効期間のいずれにおいても併用群が有意に優れるというものであった．さらに注目すべきは併用群の生存期間が 20.3 カ月と 20 カ月を超えたことである．また，有害事象では出血，血小板減少，蛋白尿，高血圧などが認められ，併用群において消化管穿孔が数例において認められている．本剤は，血管新生阻害剤として初めて生存期間を延長するという事実を示し，2004 年 2 月には米国において承認されている．

また，EGFR (epidarmal growth factor receptor) に対する単クローン抗体である cetuximab (Erbitux®) も 2003 年 ASCO において，その CPT-11 抵抗性大腸癌に対する比較試験成績[29)] が報告された．EGFR 陽性で CPT-11 治療抵抗性の症例に対して抗体単独と抗体＋CPT-11 併用群を比較する試験であり，奏効率や無再発生存期間での優位性は検証されたが，生存期間では有意でなかった．おもな有害事象はキメラ抗体であるため infusion reaction が認められること，掻痒を伴うにきび様の皮疹，爪の変形，肺臓炎などが報告されている．本剤も欧州に続き，2004 年 1 月に米国にて承認された．

これら新規薬剤は 5-FU＋LV，irinotecan，oxaliplatin に続く，第 4 の薬剤として大きな期待がもたれているが，現在その薬剤費の高価なことが米国においては大きな問題となっている．治療開始2カ月間の薬剤費が bevac-

izumab 併用で2万ドル，cetuximab 併用で3万ドルという事実[30]は，個々の症例のみならず，社会全体としてこのような不治の癌患者に対する高額医療をどのように受け入れるかのコンセンサスが必要である．

最先端医学の進歩が果たして対象患者の治療成績全体の底上げに貢献できるかどうか，今医療界が判断を問われている．

III stage III 大腸癌に対する術後補助療法

大腸癌に対する標準治療は外科切除であることは言うまでもないが，リンパ節転移を有するstage III 症例では，再発予防を目的とした術後補助化学療法を追加することが国際的標準治療である．5年生存率が70%前後とされ，5-FU+LV（国内ではIsovorin®）の週1回，6週投与，2週休薬を1サイクルとして，3サイクル18回投与，6カ月間という抗癌剤投与である．

1. 国内での臨床試験成績

国内においては，おもに経口抗癌剤とmitomycin C（MMC）の併用療法や，門脈注，術野散布などのいろいろな方法が検討されてきた．しかしながら，対象病期にstage I～III まで含んだり，治療群の割付方法，治療コンプライアンスが担保されない，必要症例数が不十分などのいくつかの問題があり，大規模試験結果が一般臨床へ十分にfeed back されていない．最近では直腸癌において，経口抗癌剤が手術単独群に比較して生存期間を延長する結果も報告されるようになり，国内の優れた手術成績に補助化学療法を併用する意義が徐々に明らかになってきている．また，1999年に国内承認された5-FU+Isovorin 療法の術後補助療法としての臨床導入が積極的に行われ，海外から10年以上遅れているが国際的標準治療が急速に広がってきている．

2. 海外での臨床試験成績—5-FU+LV 療法

海外において術後補助療法についてはNSABP（National Surgical Adjuvant for Breast and Bowel Project），Intergroup，IMPACT（International Multicentre Pooled Analysis of Colon Cancer Trials）などから継続的な臨床試験成績が報告されている．当初は手術単独が対照群であるが，その後5-FU+levamisole（LEV），5-FU+LV，5-FU+interferon などが臨床評価をされ，現時点では5-FU+LV の6カ月間投与が標準治療となっている．術後補助化学療法により5年生存率が7～8%改善すると報告されている．

現在，この治療法を対照群として新規薬剤や新規併用療法が試験治療群として検討されている．投与スケジュールは当初Mayo Clinic 法が採用されていたが，最近では血液毒性の点で，週1回のRPMI 法を使用することが多い．さらに転移性大腸癌での試験成績を受けて，de Gramont 法などの持続静注も補助療法として評価されている．

3. 最近の臨床試験成績（表 I-6-2）

転移性大腸癌での第III 相試験の結果を受け，生存期間の延長が検証された併用療法が次々と術後補助療法としての意義を検証する第III 相試験の試験治療群として採用された．術後補助療法の臨床試験は，数百例から1,000例を超える症例数が必要であり，長期の試験期間を要する．しかし，海外では第III 相試験が早期に開始され，術後補助療法としての意義が確認されている．

1) IFL 療法（C 89803 試験）

転移性大腸癌で，5-FU+LV より優れた生存期間を示したIFL（irinotecan+5-FU+LV）療法をstage III 結腸癌の術後補助療法として評価した臨床試験であり，2004年ASCO にて

表 I-6-2　最近の術後補助化学療法の第 III 相試験

レジメン	症例数	生存期間 OS	無病生存期間 DFS	無再発生存期間 RF
C 89803				
5-FU/LV (RPMI)	629			
IFL	635			
Stage III		p=0.88		p=0.84
NSABP C-06		5年	5年	5年
5-FU/LV (RPMI)	803	78.7%	68.3%	76.4%
UFT/LV	805	78.7%	66.9%	74.5%
Stage II/III		p=0.88	p=0.79	p=0.62
N-SAS-CC-01 (直腸)		3年		3年
Surgery alone	136	81%		60%
UFT	140	91%		78%
Stage III		p=0.0048		p=0.0014
X-ACT		3年	3年	3年
5-FU/LV (Mayo)	983	77.6%	60.6%	61.9%
Capecitabine	1004	81.3%	64.2%	65.5%
Stage III		p=0.0706	p=0.0528	p=0.0407
MOSAIC		3年	3年	
FL (De Gramont)	1123	86.6%	72.9%	
FL+Oxaliplatin (FOLFOX 4)	1123	87.7%	78.2%	
Stage II/III			p=0.002	

最終報告が行われた．1,264 例の stage III 結腸癌症例が IFL と FL (RPMI) の 2 群に割り付けられ，2.6 年の追跡期間で生存期間および治療成功期間ではともに有意差を認めることはできなかった．しかし，治療関連死亡例は 18 例と 6 例で有意 (p=0.008) に IFL に多く，grade 3～4 の好中球減少，発熱性好中球減少で有意に高頻度であった．この結果から，IFL を stage III の結腸癌術後補助療法に使用するべきでないと結論されている[31]．

2) NSABP C-06 試験

本試験は，米国において経口抗癌剤の臨床評価が進み，術後補助療法における意義を検証する目的で実施されたものである．RPMI の 5-FU+LV 療法を対照群として，試験群は UFT+LV 療法である．UFT+LV 療法は，本試験実施中に転移性大腸癌に対する第 III 相試験成績が報告されたが，米国 FDA では非劣性が検証されないと判定されている．

経口抗癌剤はその利便性から，臨床的有用性が確認されれば，静注療法と比較して利点があることは事実である．しかしながら，術後補助療法において無再発生存期間や生存期間が，標準治療である静注療法と同じか，優れているという臨床成績はない．このため，本試験が NSABP により実施された．2004 年 ASCO において，その最終成績が報告された．1,608 例の stage II/III を対象として UFT/LV 療法は 5-FU+LV 療法と比較して無再発生存期間 (p=0.62，5 年 UFT/LV：74.5 対 5-FU/LV：76.4)，無病生存期間 (p=0.79，5 年 UFT/LV：66.9 対 5 FU/LV：68.3) および生存期間 (p=0.88，5 年 UFT/LV：78.7 対 5-FU/LV：78.7) において非劣性が検証された．また有害事象では下痢，嘔吐では有意差はなかったが，治療中の QOL で経口群がよいとされ

ている．ただし，本試験成績の解釈において留意を要する点は，試験の対象がstage II/IIIであることである[32]．現在，JCOG 0205 MFとして国内においてstage IIIのみを対象として検討されている．

3）NSAS-CC-01試験

UFTは1981年に国内にて開発されたDPD阻害薬であるuracilを含む経口抗癌剤である．国内では，以前から術後補助療法に汎用されていたが，その臨床的意義は明確ではなかった．1997年にTAC-CR試験成績が報告され，直腸癌において手術単独群よりもUFT単独が無再発生存期間や生存期間を延長することが示された．しかしながら，症例数が少なく，追試の必要性があった．

1996年より厚生省の経口抗癌剤再評価を目的とした臨床試験NSAS-CC-01において，再度stage IIIの結腸・直腸癌を対象としてUFT単独12カ月内服対手術単独の比較試験が開始された．当時は国内では5-FU＋Isovorin療法は未承認であり，また手術単独群との優越性試験で経口抗癌剤の臨床的意義を明確にする目的で計画された．2004年ASCOにおいて直腸癌に関する中間解析成績が報告され，予想以上の経口抗癌剤の再発予防効果が検証された[33]．276例の直腸癌を対象とした2群比較試験であり，3年での無再発生存率はUFT：78%，手術単独：60%（HR：0.52，p＝0.0014），生存率はUFT：91%，手術単独：81%（HR：0.42，p＝0.0048）であった．有害事象でもT. Bil，AST/ALTの上昇以外は問題となるものはなかった．海外において毒性の高い放射線化学療法が主流であることを考慮すると，優れた手術と経口抗癌剤単剤のみという負担の少ない治療法で，きわめて優れた治療成績が得られることが示されたことはきわめて意義深いことである．

4）X-ACT試験

本試験も2004年，ASCOにおいて最終結果が報告された[34]．Dukes Cを対象として，capecitabine対Mayo法の5-FU/LVの比較試験である．1,987例を対象として無病生存期間を主評価項目，無再発生存期間，生存期間，耐用性，医療経済，QOLが副評価項目である．3年での無病生存期間はcapecitabine：64.2%，5 FU/LV：60.6%（HR＝0.87，p＝0.0528），無再発生存期間は65.5%対61.9%（HR＝0.86，p＝0.0407），生存期間は81.3%対77.6%（HR＝0.84，p＝0.0706）であった．有害事象では，hand-foot症候群がcapecitabine群で多く，下痢，口内炎，好中球減少，悪心・嘔吐，脱毛が5-FU/LV群で多い結果であった．

結論としては，capecitabineはMayo法の5-FU/LVと比較して，無病生存期間と生存期間では非劣性，無再発生存期間と安全性で優れ，静注治療に置き換えることができるとしている．しかしながら，特有の皮膚症状は患者にとって苦痛であり，今後，末梢神経障害を有するoxaliplatinとの併用での意義は慎重に検討する必要がある．

5）MOSAIC試験

2003年ASCOにおいて報告され，2004年にNEJMに発表されたoxaliplatinの術後補助療法としての意義を検証した臨床試験である[35]．stage II/IIIの結腸癌2,246例をFL（de Gramont法）とFL＋oxaliplatin（de Gramont＋oxaliplatin 85 mg/m² day 1）の比較試験である．無病生存期間を主評価項目とし，3年での無病生存期間はFL：72.9%対FL＋oxaliplatin：78.2%（p＝0.002）であった．有害事象では，発熱性好中球減少は，FL＋oxaliplatinで1.8%，grade 3の知覚性神経障害は治療中12.4%，1年後1.1%であり，消化器毒性は低いとされている．治療中の死亡は両群ともに6例（0.5%）に認められている．この試験成績により，欧州ではoxaliplatinの術後補助療法の適応が承認されるとのことである．

術後補助療法としてのirinotecan, UFT/LV, capecitabine, oxaliplatinはすべて転移性大腸癌での素晴らしい臨床試験成績を発展させたものであり，重要な治療成績向上といえる．しかしながら，これら新規治療は新たな有害事象や医療費の高騰をもたらしていることも事実である．とくに末梢神経障害はより長期的な視点での評価が必要であり，現在進行中の試験成績も含めた総合的判断が必要と考えられる．

IV stage IV 臓器転移治癒切除例に対する補助療法

肝転移は大腸癌の再発部位としてもっとも多く，かつ転移巣の切除により長期延命を得ることができるという臨床的特徴がある．最近では肝切除が安全に実施できるようになり，肝転移の治癒切除後の補助療法を検討する必要が出てきた．従来はリンパ節転移のあるstage IIIの術後補助療法である5-FU/LV療法や肝動注が行われているが，手術単独と比較して明らかな再発抑制は証明されていない．今後，臨床試験により，これら治療対象に対しても科学的評価が必要である．

まとめ

大腸癌に対する抗癌剤治療は，1990年代後半から10年足らずの間に大きな変貌を遂げた．科学的に計画された臨床試験の積み重ねにより，最短時間で新規治療法の評価と一般化を進め，転移性大腸癌の生存期間は今や無治療の8カ月から20カ月を超える時代となった．かつて抗癌剤がもっとも効かない癌腫として教科書に書かれていた大腸癌は，もっとも抗癌剤治療が有効な癌腫として評価されているのである．国内においても海外標準治療を早期に導入する努力が必要である．

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Diseases of the Colon & Rectum

Total Pelvic Exenteration With Distal Sacrectomy for Fixed Recurrent Rectal Cancer in the Pelvis

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PURPOSE: This study evaluates the effectiveness of total pelvic exenteration with distal sacrectomy for fixed recurrent tumor that developed from primary rectal cancer. METHODS: We investigated surgical indications, techniques to minimize blood loss and reduce complications, and oncological outcomes in 57 patients who underwent total pelvic exenteration with distal sacrectomy between 1983 and 2001. RESULTS: Forty-eight patients (84 percent) had negative margins. A comparison between two periods (1983–1992 and 1993–2001) showed that mean blood loss decreased from 4,229 to 2,500 ml ($P = 0.002$), indicating a favorable learning curve in minimizing blood loss. Two hospital deaths were observed in the earlier period and none in the later period. The most common sacral amputation level was the S3 superior margin, followed by the S4 inferior margin and the S2 inferior margin. The most frequent complication was sacral wound dehiscence in 51 percent, followed by pelvic sepsis in 39 percent. The incidence of pelvic sepsis in the later period was significantly decreased to 23 percent, compared with 72 percent in the earlier period ($P = 0.046$). Multivariate analysis showed that negative margins and negative carcinoembryonic antigen predicted improved survival. In 48 patients with negative margins, three-year and five-year disease-specific survival rates were 62 percent and 42 percent, respectively. CONCLUSION: Strict patient selection makes total pelvic exenteration with distal sacrectomy a feasible radical approach for fixed recurrent tumor. Careful performance of this surgical procedure along with the proper steps to decrease blood loss should achieve a favorable learning curve and low rate of surgical complications. [Key words: Rectal carcinoma; Local recurrence; Total pelvic exenteration; Sacrectomy; Surgical resection]

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Among recurrent rectal cancers after curative resection, locally recurrent tumor (LRT) is very common. Surgical series have shown that isolated LRT occurs in 4 percent to 33 percent of patients after curative resection, but effective treatment remains to be established.[1,2] For LRT cases, forms of radiotherapy, such as external beam radiotherapy and intraoperative radiotherapy (IORT), chemotherapy, and surgical treatment have been employed singly or as part of multimodality treatment over the last several decades. Such treatment has resulted in certain outcomes but none that are completely satisfactory.[3–13]

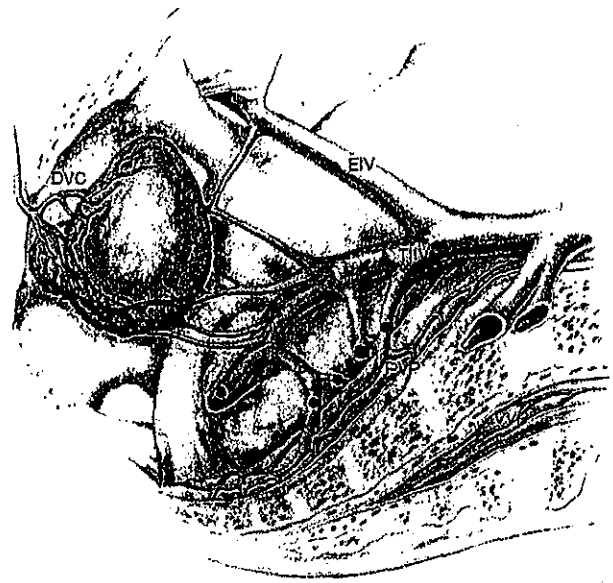
With the aid of high-quality tumor-site imaging studies, we have determined that radical resection with removal of affected neighboring structures was the only curative approach for LRT, as originally reported by Wanebo and Marcove.[3] In this study, we describe the surgical indications, technical aspects, and oncologic outcomes of total pelvic exenteration with distal sacrectomy (TPES) for fixed recurrent tumor (FRT).

PATIENTS AND METHODS

We investigated a total of 163 consecutive patients undergoing laparotomy to remove LRT between 1983

Table 1.
Patient Characteristics (N = 57)

Median age in years (range)	55 (29–73)
Gender	
Male	44
Female	13
Body mass index (range)	22.8 (15.0–28.7)
Median time (months) to local recurrence (range)	23 (7–102)
Liver metastasis	
No	52
Yes	5
Initial surgery	
Sphincter-preserving surgery	28
Abdominoperineal resection	29
Radiotherapy for primary rectal cancer	
Yes	2
No	55
Radiotherapy for local recurrence before re-resection	
Yes	23 (median,50 Gy; range, 30–80 Gy)
No	34
Dukes classification for primary growth	
A	3
B	16
C	38
Histologic type	
Well-differentiated adenocarcinoma	22
Moderately differentiated	27
Poorly differentiated	8



DVC : dorsal vein complex
EIV : external iliac vein
TIIV : trunk of internal iliac vein
BIIV : branch of internal iliac vein
PVP : presacral venous plexus
VVP : vertebral venous plexus

Figure 1. Intrapelvic venous plexus. DVC = dorsal vein complex; EIV = external iliac vein; PVP = presacral venous plexus; TIIV = trunk of internal iliac vein; VVP = vertebral venous plexus.

and 2001. The study excluded patients whose recurrent rectal cancer developed after local excision. In all patients, computed tomography of the lung, liver, and pelvis was performed, and serum carcinoembryonic antigen (CEA) was measured. After 1988, we employed magnetic resonance imaging. Positron emission tomography was not available during this period. We performed abdominoperineal resection or other limited surgeries in 51 patients, total pelvic exenteration (TPE) in 38 patients, and TPES for FRT in 55. The remaining 19 had unresectable LRT. Two patients receiving abdominoperineal resection with sacrectomy were included in the group of patients undergoing TPES for later analyses. Of the 57 TPES patients, 5 had their initial surgery at our institution, and the other 52 had it done at another institution. This study was designed to evaluate the significance of TPES for FRT. Patient characteristics are listed in Table 1. Median follow-up for survivors was 42 (range, 17–163) months. Disease-free survival (DFS) and disease-specific survival (DSS) curves were calculated with the Kaplan-Meier method. Multivariate Cox regression and log-rank test were used to compare survival curves. The difference between crude proportions was assessed by means of the chi-squared method.

Techniques to Reduce Surgical Invasiveness

Measures Against Blood Loss from Intrapelvic Venous Plexus (IVP). A schematic of the IVPs we encounter is shown in Figure 1. We had no methodical strategy for dealing with IVPs until 1992, but have devised the following procedure for dissecting IVPs on the basis of reviews of previous TPES surgeries to reduce blood loss. First, the dissection is made toward the distal sacrum while concurrently resecting the thickened Waldeyer's fascia with the presacral venous plexuses. Bleeding from this venous plexus can be stopped through a combination of electric cautery and gauze pack hemostasis. The important point in prevention of bleeding is the order in which ligations

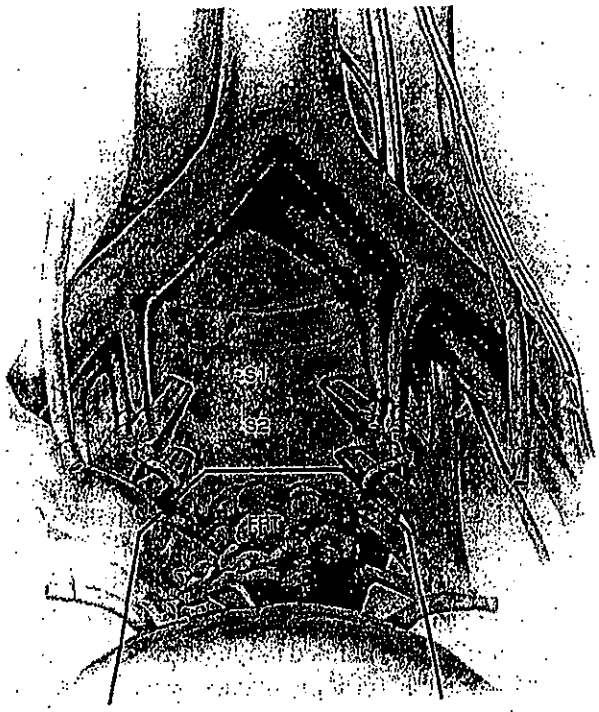


Figure 2. Schema of sacrectomy line and marked second sacral nerve. FRT = fixed recurrent tumor.

are done for two veins: 1) the dorsal penile complex and 2) the trunk of internal iliac vein (TIIV). The dorsal penile complex should be cut before the ligature of the TIIV. In treating the internal iliac vessels (both artery and vein), first the arterial trunk is doubly ligated and divided bilaterally, and then several branches of the internal iliac vessels perforating the pelvic wall are divided. Finally, the TIIV is tied and divided. Then, the patient is placed in a prone position for sacrectomy, using the padding operating frame to avoid increasing abdominal and vertebral venous pressure. To reduce bleeding during sacrectomy, detachment of the sacrospinous and sacrotuberous ligaments and muscles before sacral amputation is essential. Resection of the internal iliac vessels can greatly contribute to reducing blood loss during sacrectomy.

Avoidance of Sacral Nerve Injury. We perform sacral amputation at or below the inferior margin of the second sacrum so that better postoperative quality of life (QOL) might be attained. Lumbosacral, and S1 and S2 sacral nerves can be identified during resection of the internal iliac vessels. The S2 sacral nerve can be marked with a rubber loop (Fig. 2) during the abdominal phase so that misrecognition of sacral nerves is prevented during sacrectomy.

RESULTS

Microscopically negative margins (R0) were seen in 48 patients (84 percent) and positive margins were seen in 9 patients; 3 of these patients received IORT in a palliative setting. A comparison between two periods (1983–1992 and 1993–2001) showed that mean blood loss decreased from 4,229 to 2,500 ml (P = 0.00207), indicating a favorable learning curve in minimizing blood loss (Table 2). There was no difference in operative time and hospital stay. The most common level of sacral amputation was the S3 superior margin in 23 cases, followed by the S4 inferior margin and the S2 inferior margin (Table 3). Three patients had more than 10 liters of blood loss, but all of them underwent TPES during the earlier period. Among them, there were two hospital deaths caused by renal failure and sepsis because of serious pelvic infection, respectively. No hospital death occurred in the latter period. The overall complication rate was 58 percent. The most frequent complication was sacral wound dehiscence in 51 percent, followed by pelvic sepsis in 39 percent. The incidence of pelvic sepsis in the later period was significantly decreased to 23 percent, compared with 72 percent in the earlier period (P = 0.046). Enteroperineal fistula (as caused by pelvic sepsis) was observed in three patients and as a late complication after radiotherapy in one; all the four patients underwent bypass surgery. One patient receiving 50 Gy radiotherapy had ileal conduit breakdown four months after TPES and needed bilateral nephrostomy for urine control. He has survived for more than nine years with impaired QOL. There was no correlation between level of sacrectomy and complications. All patients had denervation pain around the buttock lasting two to six months after TPES. Two patients needed analgesic drugs for more than one year and had no local re-recurrence.

Multivariate analysis of the eight factors shown in Table 4 indicates that R0 resection and negative CEA predicted improved survival. Survival curves show overall three-year DSS, DFS, and local control rates of 54 percent, 48 percent, and 57 percent, respectively, and overall five-year rates of 36 percent, 31 percent, and 41 percent, respectively. In 48 patients with R0, including five cases of hepatic metastasis, the three-year and five-year DSS rates were 62 percent and 42 percent, respectively, whereas there was no four-year survivor in those with R-positive, a result showing a significantly poor prognosis (P = 0.00778) (Fig. 3). There was no survival difference between those with

Table 2.
Surgical Invasiveness and Hospital Stay

	Earlier Period (1983–1992) (n = 18) Mean (Range)	Latter Period (1993–2001) (n = 39) Mean (Range)	*P* Value
Operative time (minutes)	769 (370–990)	682 (480–1,100)	0.38992
Blood loss (ml)	4,229 (1,800–16,300)	2,500 (673–8,468)	0.00207
Hospital stay (days)	37.5 (23–200)	35 (21–257)	0.2216

Table 3.
Level of Distal Sacrectomy and Complications

	Sepsis in Pelvis	Ileus	Fistula[a]
Middle amputation			
S2 inferior margin (n = 9)	5	2	1
S3 superior margin (n = 23)	8	1	1
Low amputation			
S3 inferior margin (n = 10)	5	1	2
S4 superior margin (n = 10)	2	1	
S4 inferior margin (n = 5)	2		

[a]Intestinal-perineal fistula caused by anastomotic leakage.

and those without radiotherapy before re-resection. Of five patients with synchronous hepatic metastasis, three were alive without signs of re-recurrence at 13, 26, and 96 months, respectively. Thirteen patients (23 percent) had lateral node metastases. Of these, six are alive, and three were long-term survivors for 64, 68, and 123 months, respectively. The most common site of re-recurrence was lung in 13 patients, followed by pelvis in 12.

DISCUSSION

If a patient with LRT has intractable pain, perineal ulcer, or other comorbid conditions, the QOL deteriorates remarkably, and probably has a miserable prognosis. Nevertheless, studies show that one-half of recurrences are confined to the pelvis without distant metastasis.[1]

Wong *et al.* evaluated the effect of radiotherapy on LRT, indicating that radiotherapy did not contribute to survival benefit as seen in other reports.[4,9] Attempts to improve outcomes by combining resection and IORT have been well described.[7,8,10,11] In fact, therapeutic policies for LRT vary remarkably. This is probably because 1) there are a variety of LRTs, ranging from mobile anastomotic recurrence to a huge mass occupying the pelvis; 2) an inappropriate surgical intervention may cause an iatrogenic cancer spread, leading to impaired QOL; and 3) although treatments other than complete resection may not produce a cure, the invasiveness of extended surgery is considered excessive.[10,11] If LRT involves only anterior organs, partial or total removal of the involved organs can achieve adequate surgical margins. A challenge is how to perform surgical treatment for FRT involving dorsal and/or dorsolateral structures, which accounts for a larger percentage of LRTs. In case of FRT, fixation is infrequently confined to one site and of a small range. In addition, anatomic planes in the pelvis are distorted by the initial surgery and it is difficult to determine and hold uninvolved margins during resection, especially after radiotherapy. For FRT, therefore, composite resection is inevitably required to encompass potentially involved pelvic walls. Wanebo tackled this problem with a new technique called abdominosacral resection, which was used by several other surgeons in the 1980s.[3,6,14,15] An FRT extends along the internal iliac vessels more frequently than primary rectal cancer, hence bilateral resection of internal iliac vessels is one of the pivotal steps in TPES.[16] The improved method of dealing with the intrapelvic venous system has allowed us to complete TPES with decreased blood loss, resulting in a favorable learning curve with low morbidity and no hospital deaths in the latter period. TPES has nonetheless been generally thought to be a demanding and formidable technique, consequently, the combination of limited resection and IORT is likely to become a standard procedure in the treatment for LRT.[5,7,8,10,11] Shoup *et al.* reported improved survival with resection and IORT, and a five-year DSS rate of 51 percent. However, their results cannot be easily compared with our results from treating FRTs, because they studied various LRTs.[13]

With regard to surgical indication, we performed TPES for FRT localized in the pelvis without distant metastasis. In cases of distant metastasis, however, we extended the indications to single-liver or two-liver metastases, but excluded lung metastasis and other

Table 4.
Clinicopathologic Variables and Survival Analysis

Variable (n)	Univariate Analysis 5-Year Survival (%)	Multivariate Analysis *P* Value	Relative Risk	*P* Value
Surgical margin				
Negative (48) *vs.* positive (9)	42 *vs.* 0	0.0012	3.39	0.0045
Serum CEA level				
<5 (18) *vs.* >5 (39)	54 *vs.* 26	0.0287	2.76	0.0257
Range of pain				
Limited (32) *vs.* radiating to buttock or thigh (25)	46 *vs.* 21	0.0431		
Tumor size, <5 cm (25) *vs.* >5 cm (32)	32 *vs.* 39	0.9115		
Level of sacrectomy, middle (32) *vs.* low (25)	36 *vs.* 36	0.9345		
Bone invasion, negative (45) *vs.* positive (12)	35 *vs.* 39	0.9731		
Type of initial operation				
Abdominoperineal (29) *vs.* low anterior (28)	30 *vs.* 42	0.3213		
Lateral node metastasis				
Negative (44) *vs.* positive (13)	42 *vs.* 34	0.9661		

CEA = carcinoembryonic antigen.

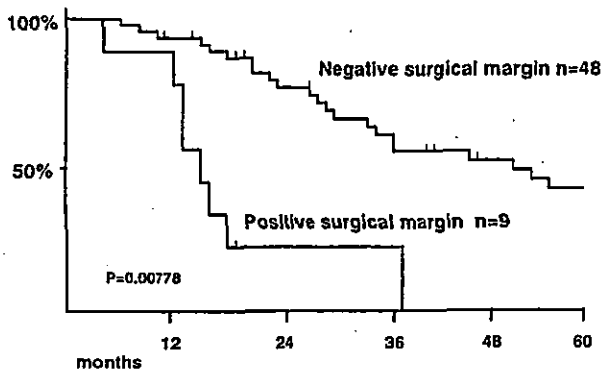


Figure 3. Disease-specific survival curve. The difference between the two groups was significant ($P < 0.00778$).

extrapelvic diseases. Contraindications included unresectable locally recurrent tumors growing into the sciatic notch, encasing the external iliac vessels, extending to the sacral promontory, or having leg edema from lymphatic and/or venous obstruction.

If prevention of pelvic infection is maintained, TPES can be a more acceptable and stable procedure for the treatment of LRT. Important factors in using TREP are prevention of bacterial contamination and complete hemostasis. Although omentoplasty into the pelvic cavity should be performed in all patients who have sufficient omentum, it was performed in only 60 percent of our patients in the latter period. Mannaerts *et al.* reported favorable results from using methods of filling dead space such as the musculocutaneous flap. They suggest that if omentoplasty cannot be performed, the musculocutaneous flap or the Vicryl mesh should be aggressively used.[11] We constructed ileal conduit in all patients. Ileoileostomy, after ileal conduit is constructed, should be lifted up above the pelvic brim and fixed to the mesentery so that it will not fall in the pelvis. This procedure is invariably required to prevent anastomotic leakage caused by pelvic sepsis, especially after radiotherapy.

Since we adopted the policy of preserving the bilateral S2 sacral nerves, serious complications such as walking disorder and spinal fluid leak have not occurred. In an outpatient clinical setting, we interviewed all 12 patients without re-recurrence who survived more than three years about their QOL. Although a decline in QOL caused by the double stomas is inevitable, they were able to return to work with satisfaction.[17]

Several factors, such as type of initial surgery, tumor size, and presence of severe symptoms, have been regarded as significant prognostic indicators, although a consensus on this has not been reached. It has previously been shown that in surgical treatment of primary rectal cancer, surgery-related factors and biologic factors are crucial.[18] The surgeon's technical skills and attitude may have more influence on important factors, including surgical margin status and complications, in LRT surgery than in primary rectal cancer surgery. Extended surgeries such as TPES should thus be undertaken in specialized centers that have an experienced complex-treatment team.

Suzuki *et al.* have established the degree of fixation to surrounding structures according to surgical and pathologic findings and have proposed their own staging method.[8] A staging system should be determined according to the degree of fixation and/or other prognostic factors so that treatment modalities

for LRT, especially surgical treatment, are given their appropriate place.

TPES has not been widely employed. However, with strict patient selection, TPES can be a feasible radical approach for FRT. Careful performance of TPES along with the proper steps to decrease blood loss from IVP should achieve favorable results. TPES can thus be included in the group of techniques that are stable and have fewer complications.

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Invited Commentary

To the Editor—Despite improvements in adjuvant therapy regimens and the virtually universal adoption of total mesorectal excision (TME) for surgical resection of middle and lower third rectal cancers, pelvic recurrence of rectal cancer remains a challenging clinical problem. Many of these patients have truly isolated locoregional recurrence and die with poorly controlled pelvic pain. External beam radiotherapy (EBRT) provides transient palliation but does not offer the hope of long-term survival.[1] Surgical resection of recurrent rectal cancer, particularly with involvement of the sacrum, is a formidable undertaking but offers three-year survival as high as 40 percent and five-year survival of 15 percent to 30 percent.[2–4]

Dr. Moriya and colleagues have presented a series of 57 patients who underwent total pelvic exenteration–distal sacrectomy (TPES), also known as abdominosacral resection (ASR), for resection of fixed pelvic recurrence of rectal cancer. In their total series of 163 patients with recurrent rectal cancer, 51 patients (31 percent) had disease amenable to resection by abdominoperineal resection, 38 (23 percent) by total pelvic exenteration, and 55 (34 percent) by TPES; 19 patients (12 percent) had unresectable recurrence. It is important to note that fully one-third of the patients with pelvic recurrence of rectal cancer required TPES to achieve complete resection.

Multiple studies have shown that the most important prognostic factor in patients with recurrent rectal

cancer is the ability to achieve complete resection. The authors report an admirable R0 resection rate of 84 percent, with an overall mortality of 5.3 percent (3 of 57 patients). Median follow-up for survivors was 42 months. Disease-specific survival for the patients who had R0 resection was 62 percent at three years and 42 percent at five years; this is an excellent result in this challenging group of patients. The most frequent complications were wound dehiscence (51 percent) and pelvic sepsis (39 percent). A multivariate analysis confirmed the presence of a negative surgical margin and CEA level <5 ng/ml as significant prognostic factors.

It is of interest in this series that only two patients (3.5 percent) had radiation for their primary rectal cancer, and less than one-half of the patients (23 patients, or 40.4 percent) had radiation before resection of their local recurrence. This represents a significant variance from American series. In most Western countries, radiation has become standard for adjuvant treatment of high-stage (Stage III or IV) primary rectal cancer. In our own experience, almost all patients with recurrent rectal cancer have received adjuvant radiation as part of their treatment for primary rectal cancer; of those patients who did not receive adjuvant radiation for the primary tumor, all without exception had radiation once recurrence was documented.

This highlights the issue regarding the most appropriate primary treatment for prevention of recurrence of rectal cancer. The adoption of total mesorectal excision (TME), championed by Heald *et al.*,[5] has revolutionized the surgical management of primary rectal cancer. This remarkable surgical achievement, which is a simple refinement of a very old technique, has greatly altered the oncologic landscape and permitted high local control rates with surgery alone. However, these results can be complemented by radiation, as underscored by the Dutch study.[6] The combination of excellent surgical control through R0 resection by the TME technique coupled with appropriate adjuvant radiation and chemotherapy in high-risk patients can greatly enhance the outcome in rectal cancer treatment, and diminish the need for retrieval surgery.

These comments notwithstanding, the technique reported here by Dr. Moriya and colleagues complements many other series and highlights the need to maintain techniques for control of local recurrence when it does occur. In our own series of patients with pelvic recurrence of rectal cancer, the majority had previously received adjuvant radiation. All had been resected by experienced surgeons, and many came to us to undergo "salvage" surgery after previous attempts had failed. In this challenging group of patients, we were able to achieve wide-field abdominosacral resection with no remaining disease in approximately 85 percent of patients, with five-year overall survival of 30 percent. These results are obtained at a cost, however; overall mortality in our series was 6 percent, and overall morbidity was substantial (in keeping with all other series, including the present report). Our ultimate goal should be the elimination of local recurrence of rectal cancer, so that aggressive resection techniques become unnecessary.

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The Authors Reply

To the Editor—We are grateful for Professor Wanebo's and Dr. Varker's various thoughtful comments on our study. We read the Wanebo and Marcove article of 1981, and experienced our first case of total pelvic exenteration–distal sacrectomy (TPES) in 1983. As of March 2004, we have performed TPES in 74 cases. One of the factors that complicate this surgery is the dense scar made after radiotherapy or D3 dissection including lateral node dissection. As accurately com-

mented, in cases that undergo surgery after radiotherapy (previously irradiated cases), the appropriate dissection layer is distorted by the scar tissue, and thus the surgery tends to become excessively invasive. Radiotherapy has been used in less than one-half of our cases, but in Western countries, almost all of the cases are previously irradiated individuals. In this regard, our series is weighted in favor of surgery. In addition, Japanese patients have lower rates of obesity, atherosclerosis, and cardiovascular diseases that predispose toward complications, and we believe these factors have enabled us in obtaining a good learning curve. Also, when extended surgery is performed as the initial surgery, there is a chance of encountering greater difficulty in dissection than after radiotherapy, because of the postoperative scarring. Such cases cause Japanese surgeons considerably more stress than do irradiated cases. The difference in therapy for primary rectal cancer between Western countries and Japan (total mesorectal excision + radiotherapy *vs.* nerve-sparing surgery with D3) influences the relative difficulty of surgery for locally recurrent cancer. Probably this is the age of surgical conservatism, but we believe it is necessary to stress that some cases can be expected to be cured only by TPES. Although TPES has become a standard surgical technique, it is a mode of therapy that must be performed on the basis of strict patient selection. If possible, we wish to develop a less invasive surgical procedure that takes the place of TPES, by use of adjuvant therapies such as intraoperative radiotherapy and new antitumor drugs.

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Original Paper

Clinical and Pathological Prognostic Indicators with Colorectal Mucinous Carcinomas

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KEY WORDS:
Colorectal neoplasms; Adenocarcinoma; Mucinous; Signet-ring cell; Prognosis

ABBREVIATIONS:
Colorectal Mucinous Carcinomas (CMC); Carcinoembryonic Antigen (CEA); Signet-Ring Cell Carcinomas (SRCC)

ABSTRACT

Background/Aims: Colorectal mucinous carcinomas are considered to have a worse prognosis than typical adenocarcinomas. To evaluate the prognostic relevance of a series of clinical and pathological variables, patients with colorectal mucinous carcinomas were studied retrospectively.

Methodology: Ninety-eight patients who underwent surgery for colorectal mucinous carcinomas were included in this study. We firstly examined whether signet-ring cell carcinomas exhibited worse prognosis than the other mucinous carcinomas. Prognostic factors were then analyzed by both univariate and multivariate analysis for 70 patients who underwent complete resection.

Results: The overall five-year survival rate was 44%. Amount of signet-ring cells was a non-significant indicator of poor prognosis. For the cases whose cancers were completely resected, four parameters (liver metastasis, lymph node involvement, vessel involvement, spread beyond the bowel wall) were significantly related to prognosis on univariate analysis. With the multivariate analysis, liver metastasis and spread beyond the bowel wall were independent variables.

Conclusions: This study reaffirmed the importance of liver metastasis and spread beyond the bowel wall for prediction of prognosis with colorectal mucinous carcinomas for cases who undergo complete resection. In addition, the presence of signet-ring cells is a non-significant indicator of a poor prognosis.

INTRODUCTION

Primary colorectal mucinous carcinomas (CMC) including signet-ring cell carcinomas (SRCC) are generally thought to exhibit a more aggressive clinical course and to have a less favorable prognosis as compared with typical colorectal adenocarcinomas (1-6). However, there are CMC patients who survive for long periods without recurrence.

Therefore, prediction of prognosis is important for deciding whether adjuvant therapy should be given. The purpose of the present study was to review medical records and pathological specimens for 98 patients with CMC and evaluate the prognostic relevance of clinical and morphological parameters.

METHODOLOGY

Between 1975 and 1990, 1875 patients with primary colorectal carcinomas whose tumors invaded beyond the mucosal layer underwent surgery at the National Cancer Center Hospital, Tokyo, Japan. Among them, CMC was identified in 98 cases (5.2%). Medical records and pathological sections of these cases with primary CMC were reviewed. Informed consent was obtained from all patients prior to surgery. All of the patients were followed for at least 5 years or until death. In line with the 1989 WHO criteria (7), histological diagnosis of CMC was made when more than 50% of the tumor was composed of extracellular mucin. The tumor was defined as SRCC when more than 50% of the tumor cells were composed of signet-ring cells, based on examination of all available sections (2).

Clinical variables tested included gender, age, tumor site, gross appearance, tumor size, preoperative serum carcinoembryonic antigen level, status of liver metastases and peritoneal dissemination, and macroscopic completeness of resection, obtained from the medical records. The criteria for grading each clinical variable are summarized in **Table 1**. For gross appearance, the classification defined by Borrmann for advanced gastric cancers was used (8): polypoid or fungating (type 1), excavating (type 2), ulcerated and infiltrating (type 3) and infiltrating (type 4). The size of the tumor was determined by measuring the largest diameter. Cases of cancers considered to have been completely resected were defined as curative, and those with remnants as non-curative. Patients with liver metastasis, peritoneal dissemination or direct invasion to other organs were placed in the curative group when these were completely resected macroscopically.

Histological variables evaluated included Dukes' stage (9) modified by Turnbull *et al.* (10), depth of transmural invasion, lymph node involvement, distant

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TABLE 1 The Criteria for Grading Each Variable

Clinical Variables	
Gender	: male; female
Age (years)	: ≤59; 60≤
Site of tumor	: colon; rectum
Gross appearance	: type 1; 2; 3; 4
Size of tumor (mm)	: ≤49; 50≤ - ≤79; 80≤
CEA level (ng/dL)	: ≤4.9; 5.0≤
Liver metastasis	: absent; present
Peritoneal dissemination	: absent; present
Macroscopic completeness of resection	: curative; non-curative
Morphologic Variables	
Dukes stage	: A; B; C; D
Spread beyond the bowel wall	: t2; t3; t4
Lymph node involvement	: n0; n1; n2; n3
Distant metastasis	: m0; m1
Vessel involvement	: absent; present
Structure of tumor cells	: trabecular; scattered
Pattern of growth	: expanding; infiltrating
Cytological atypia	: mild; severe
Percentage volume of signet-ring cells	: ≤49%; 50%≤

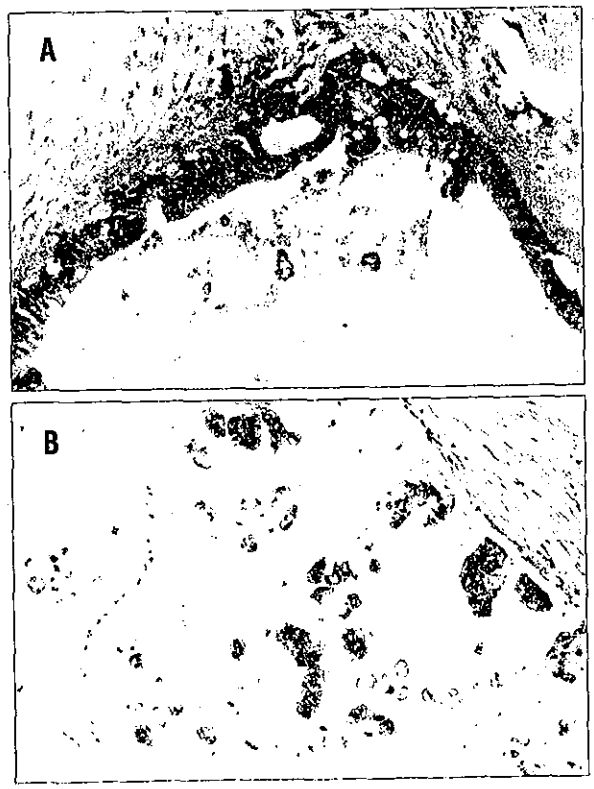

FIGURE 1 (A) Trabecular type showed marked intraluminal growth, as opposed to outpouching, producing a pseudocribriform pattern. **(B)** Scattered type was recorded either when cells were single or arranged in small clusters.

organ metastasis, vascular invasion, tumor structure (tubular configuration), pattern of growth, cytological atypia and % volume of signet-ring cells. The pathologic sections examined were stained with hematoxylin and eosin. Each slide was examined and the tumors were graded by one pathologist, who was unaware of the clinical outcome. The criteria for grading each morphologic variable are summarized in **Table 1.** Spread beyond the bowel wall, lymph node involvement and distant metastasis were all defined according to TNM clinical classification (11). There were no carcinomas *in situ* or tumors within the submucosa. Trabecular type showed marked intraluminal growth, as opposed to outpouching, producing a pseudocribriform pattern **(Figure 1A).** Scattered type was recorded either when cells were single or arranged in small clusters **(Figure 1B)** (12). As suggested by Jass *et al.* (13), tumors were defined as expanding or infiltrating following the morphologic guidelines previously defined by Ming for gastric carcinomas (14). Tumors were classified as having mild or severe atypia according to the grade of cytological atypia of the tumor cells in infiltrating portions. With mild atypia, the nucleocytoplasmic ratio was low, but the nuclei were elongated, crowded and appeared stratified. Mucus secretion was usually preserved **(Figure 2A).** With severe atypia, the nuclei were greatly enlarged, ovoid or round, hyperchromatic and often contained a prominent nucleolus. Mitoses were numerous, with occasional abnormal mitotic figures. Mucus production appeared absent **(Figure 2B).**

During the first step, we examined whether SRCC exhibited a worse prognosis than the other mucinous carcinomas. The Kaplan-Meier method was used to obtain overall survival curves (15). Deaths from other causes were treated as events at the time of death. Dif-

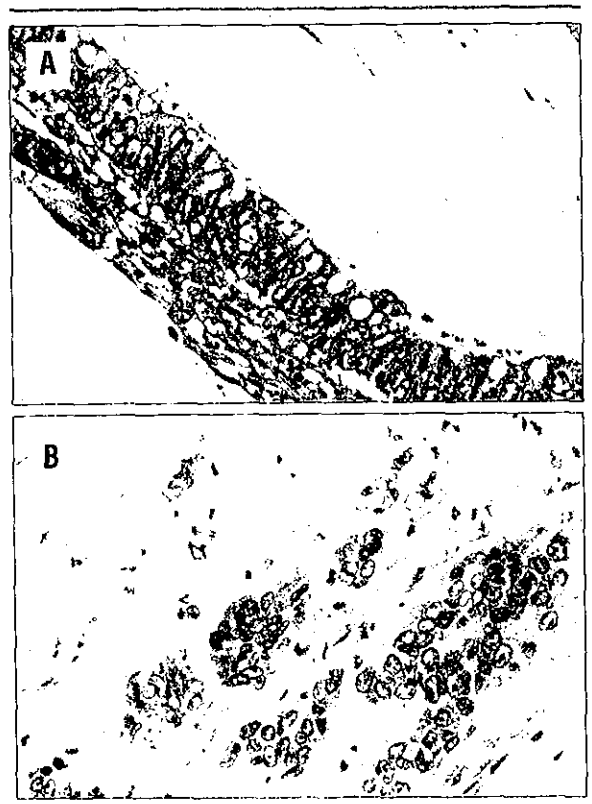

FIGURE 2 (A) In mild atypia, the nucleocytoplasmic ratio was low, but the nuclei were elongated, crowded and appeared stratified. **(B)** In severe atypia, the nuclei were greatly enlarged, ovoid or round, hyperchromatic and often contained a prominent nucleolus. Mitoses were numerous, and there might be abnormal mitotic figures.

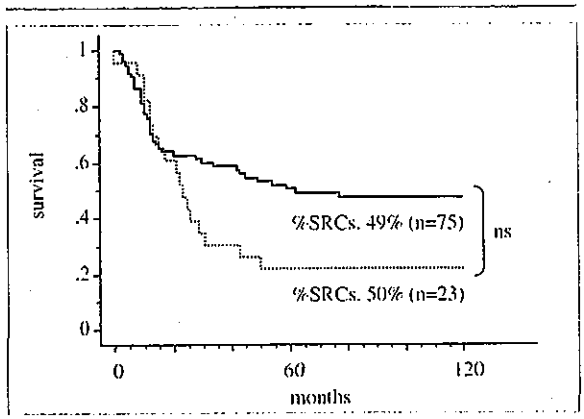

FIGURE 3 Comparison of survivals of SRCC and other typical CMC. There was no statistically significant difference between the two. %SRCs: percentage of signet-ring cells.

ferences were compared using the log-rank test. This method was used for all univariate analyses.

During the second step, univariate and multivariate analyses were conducted to find prognostic factors for the patients who underwent macroscopically complete resection. Multivariate analyses were performed by the Cox regression model (16).

RESULTS

The patients comprised 56 men and 42 women. The median age was 60 years (range 29 to 90 years). Thirty-three tumors were located in the right colon (cecum, ascending colon), 10 in the left colon (transverse, descending, sigmoid colon) and 55 in the rectum or rectosigmoid junction, according to the International Classification of Diseases (17). Six were Dukes' A cancers; 21 Dukes' B, 41 Dukes' C and 30 Dukes' D. Curative surgery was performed on 70 (71%) patients. Overall 5-year survival was 44%. None of the patients were suffering from risk factor disease such as ulcerative colitis, Crohn's disease, familial adenomatous polyposis or hereditary non-polypotic colon cancer.

SRCC was found in 23 cases. Amount of signet-ring cells was a non-significant indicator of poor prognosis. Survival curves with respect to this variable are shown in **Figure 3.** None of the SRCC were Dukes' A; 2 were Dukes' B, 13 were Dukes' C and 8 were Dukes' D.

The results of univariate analyses for the cases where cancers were completely resected are summarized in **Table 2.** Prognosis was strongly related to liver metastasis, lymph node involvement and vessel involvement. Spread beyond the bowel wall exhibited significant association with prognosis. On multivariate analysis, liver metastasis and spread beyond the bowel wall were significant variables after adjusting other prognostic factors **(Table 3).**

DISCUSSION

In any series of colorectal cancers, mucus production will range from trace to a considerable abun-

TABLE 2 Univariate Analysis for the 70 Curative Cases

Factor	n	5-yr survival	*P* value
Gender			
male	39	64.1	ns
female	31	58.1	
Age			
≤59	38	60.5	ns
60≤	32	62.5	
Site of tumor			
colon	29	69.0	ns
rectum	41	56.1	
Gross appearance			
1	11	81.8	ns
2	47	61.7	
3	11	45.5	
4	1	0.0	
Size of tumor			
≤49	18	50.0	ns
50≤ - ≤79	37	62.2	
80≤	15	73.3	
CEA level			
≤4.9	32	68.8	ns
5.0≤	37	56.8	
Liver metastasis			
absent	64	63.2	<0.01
present	6	0.0	
Peritoneal dissemination			
absent	68	62.1	ns
present	2	50.0	
Dukes stage			
A	6	100.0	ns
B	21	71.4	
C	35	54.1	
D	8	33.3	
Spread beyond bowel wall			
t2	9	88.9	0.02
t3	19	63.3	
t4	42	33.3	
Lymph node involvement			
n0	29	75.9	<0.01
n1	15	60.0	
n2	9	11.1	
n3	17	64.7	
Distant metastasis			
m0	62	62.7	ns
m1	8	33.3	
Vessel involvement			
absent	35	77.1	<0.01
present	35	45.7	
Structure of tumor cells			
trabecular	60	66.7	ns
scattered	10	30.0	
Pattern of growth			
expanding	23	73.9	ns
infiltrating	47	55.3	
Cytological atypia			
mild	15	86.7	ns
severe	55	54.6	

ns: not significant ($p>0.05$).