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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5 化学療法

・抗がん剤治療には，術後再発抑制を目的とした補助化学療法と切除不能転移・再発大腸癌を対象とした全身化学療法がある。

1）補助化学療法

・術後補助化学療法は，治癒切除の行われた症例に対して再発を抑制し予後を改善する目的で，術後に実施される全身化学療法である。
・Stage Ⅲ結腸癌に関して，術後補助化学療法は再発抑制効果と生存期間の延長が示されている[61]。
・5-FU＋Leucovorin（LV）療法が標準的治療として確立している。

【適応基準】

① 治癒切除が行われた Stage Ⅲ結腸癌。
② 主要臓器機能が保たれている。

・再発高リスク Stage Ⅱ結腸癌に術後補助療法を行う場合もある。

コメント

（1）適応基準
- 臨床診断，または病理組織診断（根治度 A，Stage Ⅲ）が確認されている。
- PS 0～1 症例を対象とする。
- 術後合併症から回復している。
- 主要臓器機能が保たれている。
- 骨髄：白血球＞4,000/mm^3，血小板＞100,000/mm^{3}を原則とする。
- 肝機能：総ビリルビン＜2.0 mg/dl，AST/ALT＜100 IU/l を原則とする。
- 腎機能：血清クレアチニン：施設正常値上限以下を原則とする。
- 適切なインフォームド・コンセントに基づき，患者から文書による同意が得られている。
- 重篤な合併症を有さない。特に，腸閉塞，下痢，発熱など。

（2）Stage Ⅱ結腸癌に対する術後補助療法の有用性は検証されていない。しかし，再発高リスク Stage Ⅱ結腸癌には術後補助療法を行う場合もある。

（3）術後補助療法は，術後 4 週から 12 週頃までに開始することが望ましい。

（4）化学療法期間中は，切除不能転移・再発大腸癌に対する全身化学療法と同様の有害事象発生が予想される。少なくとも 2 週ないし 4 週毎に，自他覚症状の観察，臨床検査値の確認が必要である。

（5）Stage Ⅲ結腸癌を対象とした第Ⅲ相試験 Intergroup study[62]，NSABP (National Surgical Adjuvant Breast and Bowel Project) C-04[63]，IMPACT (Inter-

national Multicentre Pooled Analysis of Colon Cancer)-01[64]などでは，5-FU＋LV 療法の投与期間は 6 ヶ月である。

・投与法は，RPM I（Rosewell Park Memorial Institute）の週 1 回投与法が多い。

（6）経口抗がん剤による術後補助化学療法は，静注 5-FU＋LV 療法との同等性が欧米において報告されている[65,66]。

（7）国内では TAC-CR[67]および NSAS-CC[68]の成績から，Stage Ⅲ直腸癌では UFT 投与群が手術単独群に比べて有意に優れている結果が報告されている。

2）切除不能転移・再発大腸癌に対する化学療法

・切除不能と判断された転移・再発大腸癌の予後は約 8 ヶ月と報告され，現状では治癒させることができない。

・化学療法の目標は腫瘍増大を遅延させて症状コントロールを行うことである。

・PS 0～2 の症例を対象とした第Ⅲ相試験において，抗がん剤を用いない対症療法と比較し化学療法群に生存期間の有意な延長が検証された[69,70]。

【適応基準】

① PS0～2 症例

② 各種臓器機能が保たれている

③ 転移・再発巣が画像にて確認可能

・国内外の第Ⅲ相試験により，生存期間の延長が検証され，国内で使用可能な治療レジメンは以下の通りである。

(1) FOLFOX（infusional 5-FU/l-LV＋oxaliplatin）

(2) FOLFIRI（infusional 5-FU/l-LV＋irinotecan）

(3) IFL（5-FU/l-LV*＋irinotecan）

(4) 5-FU/l-LV*または de Gramont，sLV5FU2，AIO

(5) UFT/LV 錠

*：RPMI レジメ

コメント

（1）全身化学療法の適応となる転移部位は肝，肺，リンパ節，腹膜，局所が多い。骨，脳などの転移は症状緩和のための放射線照射の適応を考慮する。

（2）具体的な適応基準：化学療法実施の際には，以下の条件を参考に適応を判断することが望ましい。

1）臨床診断または病理組織診断が確認されている。

2）PS：0～2 を対象とする。PS 3 以上は全身状態を考慮して投与を判断する。

3）主要臓器機能が保たれている。

1. 骨髄：白血球＞4,000/mm^3，血小板＞100,000/mm^{3}を原則とする。
2. 肝機能：総ビリルビン＜2.0 mg/dl，AST/ALT＜100 IU/l を原則とする。
3. 腎機能：血清クレアチニン：施設正常値上限以下を原則とする。

4）インフォームド・コンセントに基づき，患者から文書による同意が得られている。

5）重篤な合併症を有さない。特に，腸閉塞，下痢，発熱など。

（3）治療実施に関連した注意点

・治療前には PS，体重，発熱の有無，自覚症状，血液検査結果を確認する。異常（値）を認める際には延期を検討する。

・治療継続時には，原則的に当日の検査結果に基づいて抗がん剤投与・継続の可否を判断する。

・前回投与時およびその後の経過において，治療関連の有害事象の有無や腫瘍関連症状の有無等を検討し，継続の可否を判断する。

・治療コースを繰り返す場合には，蓄積性の有害事象（食欲不振，倦怠感，下痢，皮膚障害，味覚障害など）に注意する。必要であれば治療を中断し，回復を待つ。

・治療効果判定は，CT，MRI など適切な画像診断を用いて，奏効度（RECIST：Response Evaluation Criteria In Solid Tumors や日本癌治療学会規準などを用いる）を判定する。

・明らかな増悪がない場合は，原則として同一治療を繰り返し継続する。

・腫瘍マーカーの変動は参考に留める。

・前治療コースで重篤な有害事象が発現した場合は，上記の適応基準に回復した後に評価を行う。有効性が期待できれば，投与量の減量，投与間隔の延長などにて治療継続することは可能である。

・原則として明らかな病状の進行，重篤な有害事象の発生，患者の拒否のないかぎり，治療スケジュールを遵守する。

（4）大腸癌を適応症とする抗がん剤には 5-FU，mitomycin C，irinotecan（CPT-11），5-FU＋l-Leucovorin（LV），tegafur/uracil（UFT），5′-doxifluridine（5′-DFUR），carmofur（HCFU），UFT/LV（経口），S-1 などがある。

・2005 年に 5-FU の持続静注と l-LV の併用療法（de Gramont 療法[71]，sLV5FU2 療法，AIO 療法[72]（参照（5））と oxaliplatin（L-OHP）が国内において承認された。これらの持続静注法はポート留置を行い，2 日間にわたり持続点滴する方法で，手技が煩雑である。しかし，本療法を基礎にした FOLFOX[71,73]や FOLFIRI[74]では，高い奏効率，耐容可能な有害事象，生存期間の延長が報告されており，全身状態のよい症例では第一選択となると考える。また，ポート留置を好まない場合や全身状態のやや不良な症例で

は，従来の RPMI 法（週 1 回，急速静注）の 5-FU/l-LV 療法を選択してよい[75,76]。なお，第Ⅲ相試験にて延命効果が検証された急速静注の 5-FU＋l-LV に irinotecan を併用した IFL 療法[77,78]は，その後の第Ⅲ相試験 N9741 において FOLFOX 療法に劣る成績が報告され[73]，さらに術後補助療法の第Ⅲ相試験 C89803 でも治療関連死亡を含む有害事象が高いことが報告された[79]。

・5-FU/l-LV 後の二次治療として irinotecan 単独療法が用いられることが多い[80]。しかし，下痢，食欲低下，白血球減少などの重篤な有害事象を発生することがあり，投与に当たっては十分な注意が必要である。今後は，FOLFOX や FOLFIRI が一次治療として使用されることになると，FOLFOX→FOLFIRI あるいは FOLFIRI→FOLFOX のような順次療法が行われる可能性がある[74]。

・経口抗がん剤では，5-FU/l-LV 療法と臨床的同等性が検証された薬剤が優先的に選択されている。

・国内では UFT/LV（経口）併用療法[81-83]が，海外では capecitabine（国内未承認）[84,85]が一次治療として使用されている。

・S-1 の大腸癌治療での位置づけは今後の検討課題である[86,87]。

（5）5-FU/LV 療法の投与法（註：国内では L 型ロイコボリンが承認されており，投与量は欧米 dL 型ロイコボリンの半量で等量となる）には，RPMI 法（l-LV 250 mg/m^2，2 時間点滴；5-FU 600 mg/m^2，l-LV 開始 1 時間後に 3 分以内に緩徐に静注：毎週 1 回投与，6 週連続 2 週休薬，8 週毎繰り返す[75,76]，de Gramont 法（l-LV 100 mg/m^2，2 時間点滴；5-FU 400 mg/m^2，l-LV 終了直後に静注；5-FU 600 mg/m^{2}を 22 時間かけて点滴静注：これを 2 日間連続して行い，2 週毎に繰り返す）[71]，sLV5FU2 法（l-LV 200 mg/m^2，2 時間点滴；5-FU 400 mg/m^2，l-LV 終了直後に静注；5-FU 2,400～3,000 mg/m^{2}を 46 時間かけて点滴静注：2 週毎に繰り返す），AIO 法（l-LV 250 mg/m^2，2 時間点滴；5-FU 2,600 mg/m^{2}を 24 時間かけて点滴静注：6 週連続 2 週休薬，8 週毎繰り返す）[72]がある。

・持続点滴の際にはポート管理や，5-FU による皮膚症状などに留意が必要である。

（6）欧米では，FOLFOX（infusional 5-FU/LV/oxaliplatin）[71,73]や FOLFIRI（infusional 5-FU/LV/irinotecan）[74]，IFL（irinotecan/bolus 5-FU/LV）[78]などの三剤併用療法が推奨されている。

（7）肝動注療法は肝転移縮小率は高いが，生存期間に関しては全身投与に比較して有用性は検証されていなく，今後の課題である[88]。

（8）PS 3～4，あるいは高度の臓器障害のある患者は一般的に化学療法の適応となることは少ない。敢えて化学療法を行う場合はそのリスクについて十分なイ

ンフォームド・コンセントを行う必要がある。

（9）化学療法歴を有する治療抵抗性症例に対して化学療法を行う場合は，治療効果は低く，有害反応が強くなり，十分な観察と対応が必要である。

注1）PSについて

ECOGのPerformance Status（PS）の日本語訳

Grade	Performance Status
0	全く問題なく活動できる。 発病前と同じ日常生活が制限なく行える。
1	肉体的に激しい活動は制限されるが，歩行可能で，軽作業や座っての作業は行うことができる。例：軽い家事，事務作業
2	歩行可能で自分の身の回りのことはすべて可能だが作業はできない。 日中の50%以上はベッド外で過ごす。
3	限られた自分の身の回りのことしかできない。 日中の50%以上をベッドか椅子で過ごす。
4	全く動けない。自分の身の回りのことは全くできない。 完全にベッドか椅子で過ごす。

この基準は全身状態の指標であり，局所症状で活動性が制限されている場合は，臨床的に判断する。

注2）効果判定基準　RECISTガイドライン：

http://www.jcog.jp/SHIRYOU/fra_ma_guidetop.htm よりダウンロードできる。

注3）有害事象判定基準　CTCAE（Common Terminology Criteria for Adverse Events）Ver3.0：

http://www.jcog.jp/SHIRYOU/fra_ma_guidetop.htm より有害事象共通用語規準v3.0日本語訳JCOG/JSCO版(2004年10月27日)がダウンロードできる。

Original Paper

Postsurgical Surveillance for Recurrence of UICC Stage I Colorectal Carcinoma: Is Follow-up by CEA Justified?

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KEY WORDS:
UICC stage I colorectal carcinoma; Follow-up; Surveillance; CEA

ABBREVIATIONS:
Carcinoembryonic Antigen (CEA)

ABSTRACT

Background/Aims: This study was undertaken to investigate whether it will be possible to reduce the times and types of postoperative examinations for surveillance in patients with UICC stage I colorectal carcinoma. In addition, the value of CEA in postoperative surveillance is discussed.

Methodology: A review was performed of 541 patients who underwent curative resection for UICC stage I colorectal carcinoma between January, 1985 and December, 1998. Periodic check-up was routinely conducted to identify recurrence.

Results: The median follow-up was 82 months. The recurrence rate was 2.9% in the UICC stage Ia (pT1N0M0) group, and 5.6% in the Ib (pT2N0M0) group. Cancer-specific survival rates at 5 years were 99.3% and 97.6%, respectively ($p=0.0354$). Recurrences occurred more frequently in patients with lower rectal carcinoma ($p=0.0415$). Curative-intent salvage surgery was performed in 61.9% (13/21) for recurrent lesions. Between the patients who were CEA positive (13/21; 61.9%) and those who were CEA negative at the time of recurrence, there was no significant difference in the prognosis.

Conclusions: The incidence of recurrence was low after curative surgery in patients with UICC stage I colorectal carcinoma, and it is therefore possible to reduce times and types of postoperative examinations. CEA measurement alone appears to be sufficient.

INTRODUCTION

Currently, a main topic for discussion with regard to the surveillance after colorectal carcinoma surgery is whether intensive follow-up for detecting recurrence earlier and initiating the treatment of it practically contributes to the improvement in prognosis for colorectal carcinoma patients. In nonrandomized cohort studies and randomized studies, significant differences in the time of confirming recurrence, the surgical resectability of recurrent lesion, and the 5-year survival rate between intensive follow-up group and control group (traditional follow-up or no follow-up group) were reported (1-5). At the same time, there are other studies that have reported no significant difference in these points (6-12). However, in those previous studies, the numbers of cases that were reviewed ranged from 98 to 1247, and there were a variety of disease stages from UICC stages I through IV. One study reported that although the resectability after recurrence was higher by more than 10% in an intensive follow-up group than in the control group, no significant difference was obtained, probably due to the small number of cases (13). In two studies using meta-analysis that were reported lately, the 5-year survival rates were 9% to 14% greater in the intensive follow-up group than in the control group (14,15).

Recently, advances in diagnostic techniques have enabled the detection of colorectal carcinoma at earlier stages in Japan (16). At our institution, the proportion of UICC stage I cases in all colorectal carcinoma patients receiving the first-line treatment was 14% (12/86) in 1980, but it increased to 25% (71/284) in 2000. It is important to conduct a cost-effective follow-up in view of the risk for recurrence (17,18). In fact, for UICC stage I colorectal carcinoma patients, the rate of recurrence is lower, and hence fewer times and screening examinations may be reasonable and warranted for the postoperative surveillance, compared with UICC stages II-IV colorectal carcinoma patients (19).

In the present study, we utilized the prospective follow-up database at a single institution to analyze the long-term outcomes of UICC stage I colorectal carcinoma patients, and to investigate whether it will be possible to reduce the times and types of screening examinations for postoperative surveillance. In addition, the present study discusses the value of CEA (carcinoembryonic antigen) in performing surveillance after curative surgery for UICC stage I colorectal carcinoma.

METHODOLOGY

Between January, 1985 and December, 1998,

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2,550 primary colorectal carcinoma patients were treated at our institution. Patient information and follow-up data were prospectively collected and added to the department database. Of those patients, the present study selected 541 (21.2%) cases of UICC stage I colorectal carcinoma undergoing curative resection combined with surgical lymph node clearance, in order to review the time and form of recurrence, the changes in CEA levels at recurrence, and the rate of re-resectability. For analysis, the 541 cases of UICC stage I colorectal carcinoma were divided into two groups: 313 patients with stage Ia colorectal carcinoma (pT1N0M0) and 228 patients with stage Ib colorectal carcinoma (pT2N0M0).

In terms of the follow-up of a patient with stage I colorectal carcinoma, we routinely conducted a periodic check-up every six months until two years after the operation, and subsequently once per year from the 3rd to 5th postoperative year. Clinical examination, abdominal ultrasound, and CEA measurement were performed at each visit, and chest X-ray was performed once per year. CEA was defined as positive when the level was increased above the cut-off value. Colonoscopy or barium enema was conducted once within one year of the first surgery, and was repeated at intervals of one to two years depending on the findings of the prior examination. When a patient complained of a symptom that suggested recurrence or had an increased level of CEA without symptoms, we employed other types of examinations in addition to the periodic check-up.

The clinicopathologic parameters were compared using Student's t test and the Fisher's exact test as appropriate. Cancer-specific survival curves and disease-free survival curves were estimated using the Kaplan-Meier technique and were compared by means of the log-rank test. For cancer-specific survival, only cancer-related deaths were considered; data on the patients who died from other causes or who were still alive at the end of the study were censored. A P value of less than 0.05 was considered significant.

RESULTS

The patient demographics are summarized in **Table 1**. Compared with the UICC stage Ia group, the UICC stage Ib group included significantly more patients with lower rectal carcinoma ($p=0.0003$). Recurrence occurred in 9 of 313 (2.9%) UICC stage Ia group, and in 12 of 216 (5.6%) UICC stage Ib group. However, the difference between the two groups was not significant ($p=0.1793$). Disease-free survival rates at 5 years were 96.9% for the UICC stage Ia group and 94.9% for the UICC stage Ib group **(Figure 1a)**, with no significant difference between the two groups ($p=0.1575$). Cancer-specific survival rates at 5 years were 99.3% for the UICC stage Ia group and 97.6% for the UICC stage Ib group **(Figure 1b)**; there was a significant difference between the two groups ($p=0.0354$).

The performance rate of curative-intent salvage surgery for recurrent lesions in these recurrent carcinoma patients was 61.9% (13/21) **(Table 2)**. Recurrence was found at a median time of 19 months (range 6-66) after primary carcinoma resection. Only one patient with pelvic and hepatic recurrence was found after five-year routine follow-up.

Since the proportion of lower rectal carcinoma patients was significantly elevated in the UICC stage Ib group, we divided the sites of carcinoma into the lower rectum and other parts to evaluate recurrence rates and prognoses **(Table 3)**. Recurrences occurred in 10 of 145 (6.9%) patients with lower rectal carcinoma, and in 11 of 396 (2.8%) patients with colon or upper/middle rectal carcinoma. Between these two groups, the difference in the recurrence rate was significant ($p=0.0415$). Disease-free survival rates at 5

TABLE 1 Patient's Characteristics

		UICC stage Ia patients	UICC stage Ib patients	*P* value
Number of patients		313	228	
Sex ratio (Male:Female)		201:112	129:99	0.0750
Age (yr; mean and range)		60.7 (33-88)	62.0 (23-91)	0.1641
Location	Cecum	16	14	0.0003*
	Ascending colon	23	15	
	Transverse colon	18	7	
	Descending colon	7	5	
	Sigmoid colon	122	53	
	Upper rectum	28	23	
	Middle rectum	34	31	
	Lower rectum	65	80	
Operative procedures	Partial resection	45	4	
	Ileocecal resection	11	4	
	Right hemicolectomy	15	25	
	Transverse colectomy	3	5	
	Descending colectomy	7	2	
	Left hemicolectomy	0	4	
	Sigmoid colectomy	105	49	
	Anterior resection	91	93	
	Abdominoperineal resection	14	35	
	Abdominosacral resection with coloanal anastomosis	4	2	
	Transsacral partial resection	17	0	
	Hartmann's operation	1	4	
	Total pelvic exenteration	0	1	
Follow-up time (mo; range and median)		3-189 (80)	1-201 (85)	
Recurrence	Positive	9	12	0.1793
	Negative	304	216	
Sites of First Tumor Recurrence	Liver	7	5	
	Lung	1	6	
	Local			
	Pelvis	1	2	
	Anastomosis	1	1	
	Para-aortic lymph node	0	1	
Oncologic outcome	5-Year disease-free survival (%)	96.9	94.9	0.1575
	5-Year cancer-specific survival (%)	99.3	97.6	0.0354

*colon and upper/middle rectum *vs.* lower rectum.

years in patients with lower rectal carcinoma were 92.6%, and 97.3% in patients with colon or upper/middle rectal carcinoma **(Figure 2a)**, with the difference between the two groups significant ($p=0.0304$). However, the cancer-specific survival rates at 5 years were not significantly different between the groups ($P=0.2402$) **(Figure 2b)**.

Among the 21 recurrent cases, 13 (61.9%) individuals were CEA positive at the time of recurrence **(Table 4)**. With regard to the recurrent site and CEA positive rate, patients with hepatic recurrence showed a significantly higher rate of CEA positivity, compared with the patients with recurrence at other sites ($p=0.0272$). Between the patients who were CEA positive and those who were CEA negative at the time of recurrence, no significant difference in the prognosis after the detection of recurrence was found **(Figure 3a)**, in addition to in the prognosis after the first surgery **(Figure 3b)**.

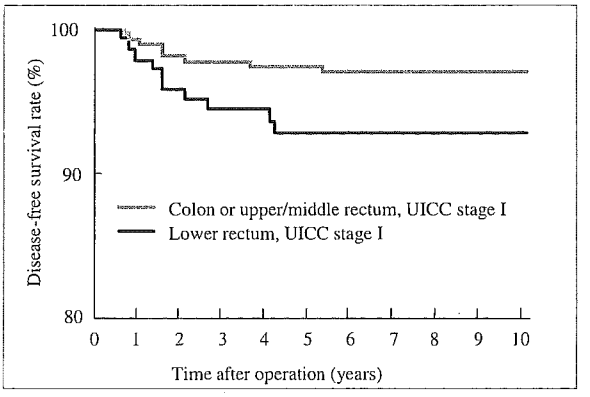

FIGURE 2a Cumulative disease-free survival curves for patients with lower rectal carcinoma and colon or upper/middle rectal carcinoma. The difference between the two groups was significant ($p=0.0304$).

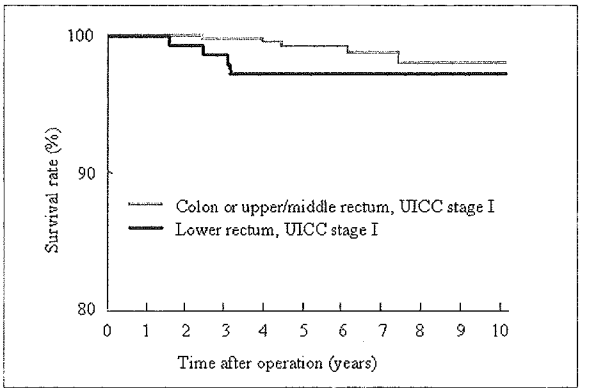

FIGURE 2b Cancer-specific survival curves for patients with lower rectal carcinoma and colon or upper/middle rectal carcinoma. The difference between the two groups was not significant ($p=0.2402$).

FIGURE 1a
Cumulative disease-free survival curves for UICC stage Ia group and UICC stage Ib group. The difference between the two groups was not significant ($p=0.1575$).

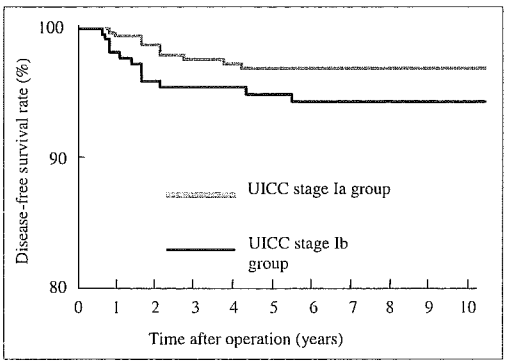

FIGURE 1b
Cancer-specific survival curves for UICC stage Ia group and UICC stage Ib group. The difference between the two groups was significant ($p=0.0354$).

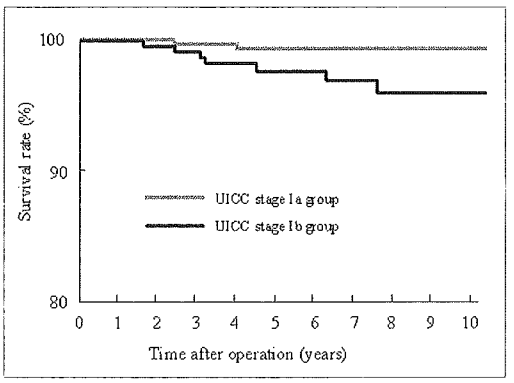

TABLE 2 Treatment of Recurrent Cancers

Treatment	No. of patients
Resection	
APR+radiation	3 (2*)
TPE+combined resection of sacrum	1 (1)
hepatic resection	9 (7*)
lung resection	5 (5)
Systemic chemotherapy	2
Hepatic artery infusion	2
Pelvic radiotherapy	1

( ), number of patients having curative-intent salvage surgery. *two patients underwent curative-intent salvage surgery for pelvic and hepatic recurrences.

DISCUSSION

For surveillance after curative surgery for colorectal carcinoma, a cost-effective method of follow-up should be established for consideration of the risk for recurrence. The probable subjects that the numbers of times and follow-up examinations can be reduced are UICC stage I patients. In the present study, we carried out follow-up examinations of a large number of UICC stage I patients over a long period at a single institution, and analyzed the data to clarify an appropriate method of surveillance. The present findings demonstrated that compared with the UICC stage Ia group, the UICC stage Ib group had a significantly lower rate of 5-year cancer-specific survival. In addition, lower rectal carcinoma involved a significantly higher incidence of recurrence. A recent study by Wichmann *et al.* (19) reported that between UICC stages Ia and Ib, there was an approximately 10% difference in the 5-year survival rate, although the difference did not achieve significance due to the small number of study patients. In the present study, however, the number of UICC stage I patients who were investigated was

much larger compared with the numbers reported in former studies, suggesting that the present study findings may help establish a method of follow-up for UICC stage I patients in the future.

In most carcinomas other than colorectal carcinoma, when recurrence is discovered after resection of the primary lesion, they are treated as a systemic disease and salvage surgery is infrequently indicated for the recurrent lesion. However, in colorectal carcinoma, resection of the recurrent lesion may improve patient prognosis. In this respect, research is required to determine whether intensive follow-up for detecting recurrence earlier and initiating the treatment of it will lead to improvement in prognosis for colorectal carcinoma patients. In earlier studies, the numbers of examinations and times of the check-up conducted were different (1-13). As a matter of course, it should be recognized that with advances in technologies, the precisions diagnostic examinations are being enhanced, and new effective methods of examination are being developed. Moreover, the treatment regimens have been changing rapidly; in recent years the indications for aggressive surgical resection for recurrent lesions have been expanded, and new chemotherapies that are useful for improving patient prognosis have been identified (20-23). For the reasons mentioned above, a study that retrospectively confirms the usefulness of follow-up will not able to avoid a bias caused by the times when the study was performed.

TABLE 3 Site of the Primary Tumor and Recurrence

	Colon and upper/ middle rectum	Lower rectum	*P* value
Number of patients	396	145	
Recurrence			
Positive	11	10	0.0415
Negative	385	135	
Oncologic outcome			
5-Year disease-free survival (%)	97.3	92.6	0.0304
5-Year cancer-specific survival (%)	99.1	97.1	0.2402

TABLE 4 Recurrent Disease and Results of Tumor Marker Monitoring at the Time of Recurrence

Tumor marker monitoring	Elevation	No elevation	*P* value
Number of patients	13	8	
Sites of recurrence			
Liver	11	1	0.0272
Lung	2	5	
Local (Pelvis and anastomosis)	3	2	
Para-aortic lymph node	1	0	
Interval to recurrence (mo; range and median)	6-66 (19)	9-32 (18)	0.3348
Oncologic outcome 5-Year survival following first recurrence (%)	52.7	87.5	0.2734
5-Year survival after primary surgery (%)	61.5	87.5	0.3558

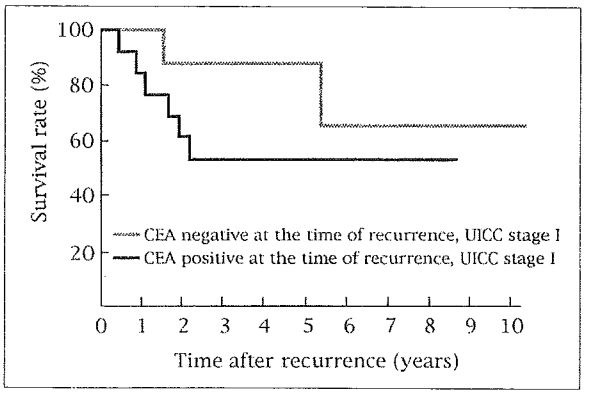

FIGURE 3a Cancer-specific survival curves after the detection of recurrence for patients who were CEA positive and CEA negative at the time of recurrence. The difference between the two groups was not significant (p=0.2734).

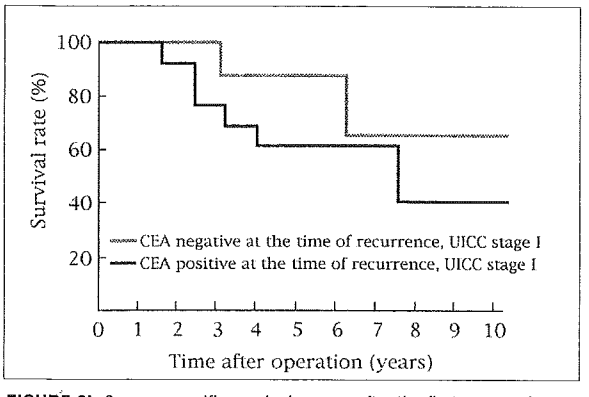

FIGURE 3b Cancer-specific survival curves after the first surgery for patients who were CEA positive and CEA negative at the time of recurrence. The difference between the two groups was not significant (p=0.3558).

With regard to the value of CEA in the postoperative surveillance, some benefits have been reported from the viewpoint of earlier detection of recurrence and cost-effectiveness in detecting potentially curable recurrent disease (24-26). However, no conclusion has been reached whether the earlier detection of recurrence using CEA may influence the prognosis. In the present study, 62% (13/21) of patients with recurrence showed an increased CEA level at the time of recurrence. In these patients, the follow-up that used CEA alone might have enabled the confirmation of recurrence if diagnostic imaging was performed at the point when an increased level of CEA was recorded. However, the question here is about those cases in which recurrence was confirmed first by diagnostic imaging without showing an increased level of CEA. Of these patients, 75% (6/8) remain disease-free to date, and there is a possibility that with the follow-up using CEA alone, asymptomatic recurrences without CEA elevation may not be detected. However, these 6 patients comprised only 1.1% (6/541) of all study patients, and it may therefore be inefficient to conduct the usual postoperative surveillance while burdening the remaining 99% patients with huge costs and effort. In all UICC stage I carcinoma patients, there was a low recurrence rate of 3.9% (21/541), and in addition,

because two-thirds of recurrences could be identified using CEA, the CEA test alone may be adequate at each visit, at least for UICC stage I patients.

Another problem in the CEA examination is that encountering a patient who shows false-positivity is inevitable. Moertel *et al.* (27) reported that when the preoperative CEA level was 5ng/mL or higher, false-positivity may appear approximately in 30% of such cases. If a UICC stage I patient shows an increased CEA level during the follow-up that uses CEA alone, it may be necessary to perform examinations for other carcinoma occurrences in addition to the metastasis and recurrence of the primary colorectal carcinoma.

A noteworthy aspect of the present study was that the patients with lower rectal carcinoma showed a significantly higher incidence of recurrence. Wichmann *et al.* (19) also reported that although there was no significant difference across UICC stage I patients, rectal carcinoma involved a higher rate of recurrence, with particularly more local recurrence, compared with colon carcinoma. The CEA positive rate in patients with local recurrence of rectal carcinoma was not as high as that in patients with hepatic metastasis (2,27,28). Hence, especially in conducting follow-up examinations of patients with lower rectal carcinoma, special attention should be paid to local recurrence, and when any symptom such as pain, hemorrhage, or change in bowel habit appears, necessary examinations should be performed early.

In the present study, the UICC stage Ia group included a significantly smaller number of patients with lower rectal carcinoma. This may be because some patients who had pT1 carcinoma at the lower rectum were followed up after undergoing trans-anal resection alone. The treatment of T1 and T2 carcinoma of the lower rectum is controversial, and several studies have suggested satisfactory tumor control after local excision for lower rectal T1 and T2 carcinoma (29,30). However, recent studies suggested that local excision of T1 and T2 rectal carcinoma is followed by a much higher recurrence rate than previously reported (31,32). In our institution, a radical surgery of low anterior resection or abdominoperineal resection is often indicated for T2 lesions and most T1 lesions with adverse risk factors, especially poorly differentiated carcinoma, lymphovascular invasions, incomplete excision, or massive invasion of carcinoma to the submucosal layer. Although most patients with T1 and T2 carcinoma lesions in the lower rectum in whom local recurrence develops after local excision can be salvaged by radical resection, the long-term outcome remains unknown (33).

In the field of the postoperative follow-up examination, the value of colonoscopy has been discussed. Periodic colonoscopy may be useful for detecting anastomotic and locoregional recurrences after colorectal carcinoma operation in addition to finding metachronous colorectal carcinoma (34,35). However, in UICC stage I patients, the anastomotic and locoregional recurrences have involved a very low proportion of 1% to 3%, according to previous and the present study (19). Particularly in patients with colonic carcinoma, there have been no anastomotic or locoregional recurrences observed at our institution. Performing colonoscopy is not warranted for the purpose of detecting anastomotic and locoregional recurrences in UICC stage I patients.

In conclusion, for UICC stage I patients, the incidence of recurrence was lower, and it is therefore possible to reduce the times and screening examinations for the postoperative surveillance. Regarding screening examinations, the CEA measurement every six months until two years after the operation, and subsequently once per year until the 5th postoperative year appears to be sufficient. Nevertheless, for patients with UICC stage Ib disease and those with lower rectal carcinoma, oncologists need to pay special attention because the rates of recurrence are significantly higher.

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Total Pelvic Exenteration with Distal Sacrectomy for Fixed Recurrent Rectal Cancer

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Four percent to 33% of patients with rectal cancer develop locoregional relapse after undergoing radical surgery with curative intent. Without treatment, the mean survival time for patients with local recurrence is only approximately 8 months, an associated severe symptomatic disease—especially pain—occurs, and their quality of life becomes remarkably deteriorated, probably with a miserable prognosis [1–4].

For cases with locally recurrent rectal cancer (LRRC), external beam radiotherapy, intraoperative radiotherapy, chemotherapies, and surgical treatments have been used singly or as part of a multimodality approach over the last several decades, resulting in certain outcomes that are not yet satisfactory [5–21]. For the purpose of attaining thorough margin-free resection, what we have been performing actively as our standard curative approach for fixed recurrent tumor (FRT) is radical resection with removal of affected neighboring organs and pelvic walls, including the sacrum, as originally reported by Wanebo and Marcove [6]. This article describes the surgical indications, contraindications, surgical techniques, oncologic outcomes, and complications of total pelvic exenteration with distal sacrectomy (TPES).

Patterns of growth in the pelvis

By cause and growth pattern of local recurrence, LRRC can be classified into three main categories.

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Anastomotic recurrence and perianastomotic recurrence

These suture line recurrences after low anterior resection are caused by implantation of cancer cells into the stump of anastomosis or insufficient resection of the rectal wall or mesorectum (Fig. 1). In the case of extramural invasion, however, it is difficult to distinguish between these two recurrences. When there is no extramural invasion or neighboring organ invasion, the basic surgical procedure is abdominoperineal resection (APR).

Perineal recurrence

Perineal recurrence is a recurrence that occurs after APR near the pelvic floor or perineal wound. From its early stage, perineal recurrence invades the coccyx, gluteal maximus muscle, or pelvic wall. Surgical margin-free resection seldom can be obtained by local excision alone. Many patients need resection of the pelvic wall or intrapelvic organs.

Pelvic recurrence

By occupied site, pelvic recurrence (Fig. 2) can be subdivided into anterior, lateral, and dorsal recurrences. Anterior pelvic recurrence is an LRRC that invades the anterior organs (ie, urogenital organs). For resecting this recurrent tumor, the basic surgical procedure is total pelvic exenteration (TPE). In women, if there is no obvious bladder invasion, it is possible to preserve urinary organs. This recurrence frequently is caused by insufficient resection for T4 rectal cancer. Lateral pelvic recurrence occurs because of lateral lymph node metastasis after total mesorectal excision or insufficient lateral node dissection. It begins to infiltrate the pelvic wall in its early stage. Dorsal pelvic recurrence is presacral extramural recurrence after APR or low

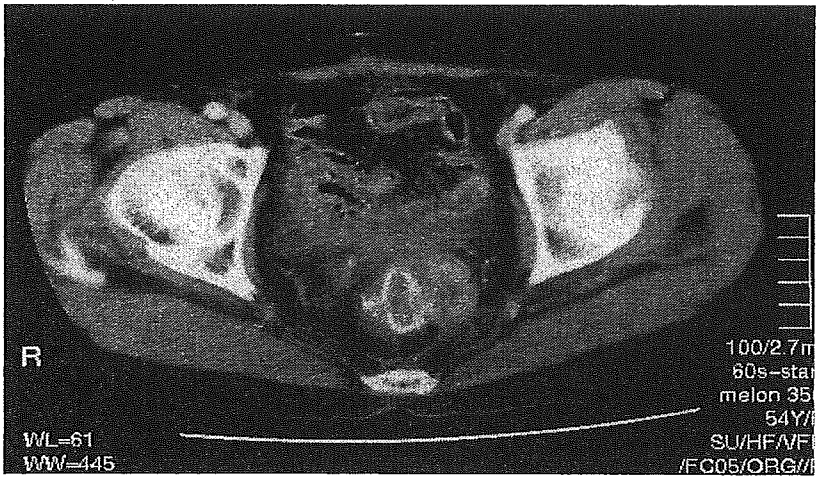

Fig. 1. Perianastomotic recurrence. A 54-year-old female patient underwent TPES for her FRT with 556 mL blood loss and no complication. At initial surgery 4 years ago, she received low anterior resection with D3 lymph node dissection and postoperative 60 Gy radiotherapy.

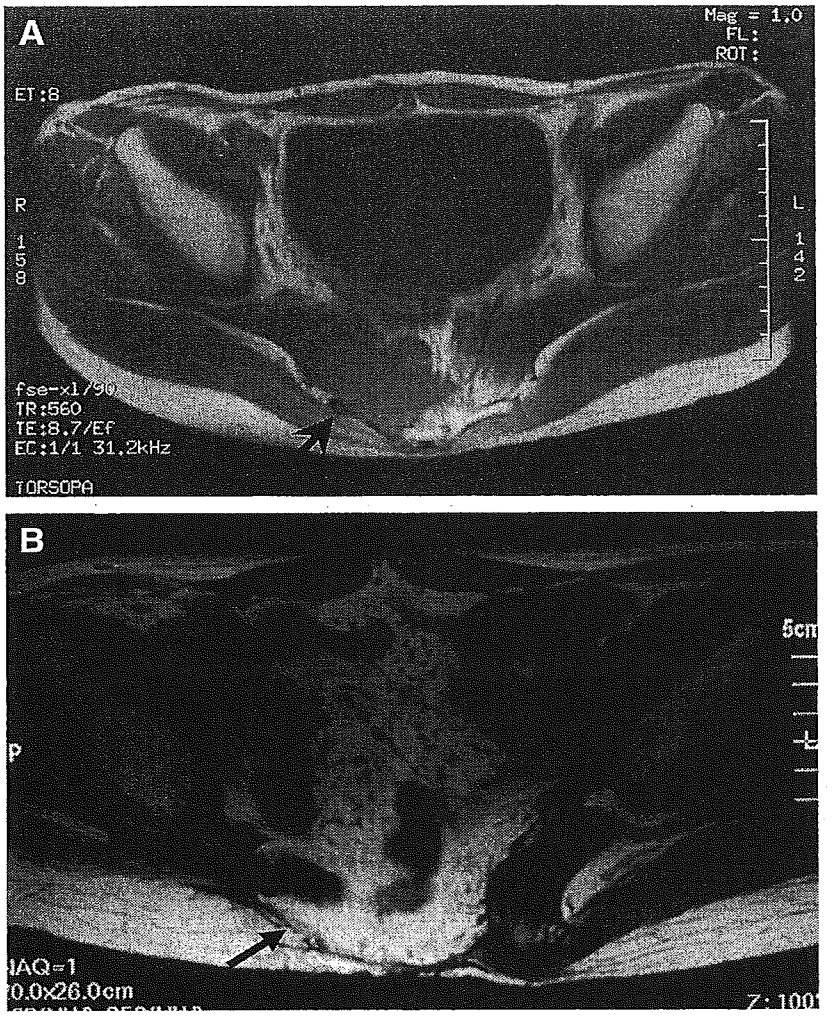

Fig. 2. (*A*) Dorsolateral pelvic recurrence with sacral bone invasion. A 47-year-old male patient underwent TPES for his FRT (*arrow*) with 673 mL blood loss and no complication. At initial surgery 1.5 years ago, he received low anterior resection. (*B*) Postoperative MRI. The patient is alive without re-recurrence 4 years after TPES.

anterior resection that invades the pelvic wall. It forms itself into FRT from its early stage. The cause of this recurrence may be extramesenteric lymphatic spread, insufficient resection of the mesorectum, or a cut into the mesorectum during operation. This pattern of recurrence is common patterns.

Why total pelvic exenteration with distal sacrectomy is the standard surgery for fixed recurrent tumor

Therapeutic policies for LRRC vary remarkably. The probable reasons for this are as follows: (1) there are various LRRCs, ranging from mobile recurrences to huge masses that occupy the pelvis, (2) an inappropriate surgical intervention may cause an iatrogenic cancer spread, leading to impaired quality of life, and (3) although treatments other than complete resection may not bring cure, the invasiveness of surgeries such as TPES is

considered excessive. In non-fixed recurrent tumors, complete resection can be achieved more often with limited surgery, such as APR or low anterior resection, and the outcomes are relatively favorable. LRRC grows within the narrow pelvis, and when the tumor size becomes larger to some extent, it can invade the pelvic wall easily and appear in the form of FRT. A challenge for the surgeon is the surgical treatment for FRTs with lateral or dorsal involvement, which comprises a larger percentage.

Such fixation is infrequently confined to one site and is of small range; many of those cases show fixations to the components surrounding the LRRC (eg, bony pelvis, including sacrum and coccyges; non-bony pelvis, including coccygeus muscle, piriform muscle, internal iliac vessels, inferior hypogastric plexus, sacral nerve plexus, obturator internus muscle, and sacrospinous and sacrotuberous ligaments; and residual anterior organs in the pelvis). Their anatomic planes are distorted, and it is difficult to determine and hold uninvolved margins during resection. For FRT cases, composite resection is inevitably required to encompass potentially involved pelvic walls, especially the distal sacrum. Only this strategy enables the R0 extirpation en bloc. Especially after APR, the LRRC grows while being sandwiched between the anterior organs and sacrum. Wanebo and Marcove [6] tackled this difficult problem using the new technique of abdominosacral resection, followed by several surgeons in 1980s [8,9,10,12].

Techniques to preserve the anterior organs and inferior hypogastric plexus for surgical treatment of FRT have been reported [16]. Those approaches, however, are likely to reduce local radicality, because the anatomic pathway around the autonomic nerve plexuses and ureter disappears and is replaced by scar tissue caused by initial surgery, especially after extended surgery. FRT in the deep pelvis also is often fixed more extensively than expected before surgery, which also justifies our experience-based strategy that TPES is positioned as the standard surgery for FRT. This technique is considered to be demanding and formidable because of high rates of mortality and morbidity [6,12,13,19]; consequently, combination of limited resection and intraoperative radiotherapy is likely to become standard in the treatment of FRT [17,22–29]. Whether an emphasis is placed on composite resection or multimodality treatment, surgeons have the same view that the key treatment to obtain local control and survival benefit is R0 surgery [22,28–31]. Is it really possible to carry out R0 resection for FRT by conventional surgery? Having been able to ensure R0 resection for FRT and develop secure surgical techniques, we consider that there are no therapies superior to TPES in treating FRT.

Evaluation by imaging and patient selection

Once the diagnosis of LRRC is made, detailed study should be conducted in terms of surgical indication from two aspects: (1) whether distance metastasis