Table 6 Differences in inter-reader (reader 1 and reader 2) quality scores

	Cecum/ascending colon	Transverse colon	Descending colon	Sigmoid colon	Rectum
PEG preparation	$P = 0.065$	$P = 0.540$	$P = 0.140$	$P = 0.359$	$P = 0.236$
PEG-C preparation	$P = 0.863$	$P > 0.999$	$P = 0.730$	$P = 0.615$	$P = 0.842$

colonoscopy, the integration of CT data with a CT colonography imaging system would most likely enhance the accuracy of preoperative diagnosis.

The common accepted technique of CT scans for preoperative clinical staging is single positioning. By contrast, dual positioning is the commonly acknowledged technique of CT colonography. Many studies have reported that dual positioning helps to distend the colon, thereby facilitating the detection of polyps [21–25]. There were several limitations of this study because dual positioning was not performed. We cannot compare which techniques were better for CT colonography but warrant examination. However, there were some reasons for not using dual positioning at CT scans in our study. The DCCTE with single positioning could visualize nearly the entire large intestine because the colon was distended enough not only by air but also much amount of tagged fluid of PEG-C preparation. Another advantage is decreased exposure to diagnostic radiation. Radiation dose is an important consideration [26]. The intrinsic high contrast between the colonic wall and the air insufflated to distend the colon allows low-radiation dose protocols [27, 28]. Such low-radiation dose protocols provide adequate colonic detail for colorectal polyp screening but result in very limited views of extracolonic organs. Low-radiation dose protocols are intuitively attractive for screening but may not be appropriate for preoperative staging of patients with colorectal cancer in whom extra colonic findings assume a high degree of importance [29].

Conclusion

In conclusion, DCCTE after PEG-C preparation produces much superior images to that of air-contrast CT enema after PEG preparation. Our results show that DCCTE and conventional colonoscopy after PEG-C preparation are feasible and safe procedures that can be used for preoperative evaluation in patients with colorectal cancer. Because DCCTE is useful for tumor localization and can visualize the course and length of the colon without additional preoperative examinations, we feel that it will ultimately help in contributing to the optimal use of MDCT data for preoperative evaluation. The question whether it might have effects on tumor staging and post-surgical outcome remains opens and warrants further examinations.

Further studies for single or dual positioning, radiation dose, and related costs have to be needed if DCCTE after PEG-C preparation will have a more impact on preoperative staging for colorectal tumor.

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Table 7 Distribution of Hounsfield unit values of residual fluid

	HU values		*P* value
	PEG preparation	PEG-C preparation	
Cecum/ascending colon			
Mean±SD	19.7±9.1[a]	433.2±176.9[b]	<0.0001
Range	8–65	170–890	
Rectum			
Mean±SD	20.6±9.1[a]	328.6±137.5[b]	<0.0001
Range	10–62	130–717	

SD Standard deviation
[a] *P* value=0.555 on comparison of the cecum/ascending colon with the rectum in PEG preparation, Mann–Whitney *U* test
[b] *P* value=0.0005 on comparison of the cecum/ascending colon with the rectum in PEG-C preparation, Mann–Whitney *U* test

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［連載］

最新 癌の化学療法マニュアル

第①回 総 論

島田安博*

はじめに—抗癌薬治療の意義

消化器癌をはじめとする固形癌に対する抗癌薬治療は，癌患者の多くをその治療対象とするが，有効な抗癌薬がなく，しばしば臨床的意義が疑問視されていた．すなわち，消化器毒性，血液毒性，神経毒性などの有害事象(副作用)と臨床効果とのバランスが妥当であるかという点である．手術不能癌に対する治療法として，抗癌薬治療の選択肢しか考慮されなかった時代には，患者の全身状態が不良であってもわずかの可能性に期待して抗癌薬治療を実施することもあった．最近では，ランダム化比較試験(RCT)により，抗癌薬治療を用いない群と積極的に抗癌薬治療を用いる群の治療成績を生存期間で比較・検討した結果が報告されている．胃癌や大腸癌では生存期間が2～3倍に延長することが示され，全身状態の良好な患者に対して積極的に抗癌薬治療が実施されている．これらのデータは抗癌薬治療が可能であった群と不可能であった群の比較でないことが重要である．不可能である群は，予後不良な患者が多く含まれ治療効果を見かけ上わるくみせるからである．

① 抗癌薬治療の適応とインフォームド・コンセント

抗癌薬治療の適応については，一般に以下の適応規準が用いられている．一般診療においては，これらを遵守することができない状況も起りうるが，そのさいには患者自身に十分に治療の必要性を説明する必要がある．

1) 組織学的に癌の診断がされている．

2) 転移を有し，治癒切除が不能である．術後補助療法の場合には，治癒切除が実施されたが，術後再発のリスクが高いと判断される症例．術前投与の場合には，抗癌薬投与後に治癒切除が期待される症例

3) 全身状態の指標であるPS(performance status)が0～1である．PS 2以上については有害事象が高度になる可能性も高く，適応を慎重に判断する．PS 4は一般に適応はない．

4) 年齢：20～75歳を目安とする．全身状態が良好であれば高齢者への抗癌薬治療は必ずしも禁忌ではないが，臓器機能が潜在的に低下している可能性があり，慎重な適応判断が必要である．

5) 主要臓器機能が保たれている．WBC，PLTなどの血液検査，T-Bil，AST/ALT，血清CREなどで規準を規定する．

6) 術前・術後の抗癌薬治療については，対象とする病期，根治度，治療開始と手術との間隔の規定などが必要である．術後補助療法では，手術の影響から回復を待って4～8週を目処に抗癌薬治療を開始することが多い．

7) 患者本人からインフォームド・コンセントが得られている．治療に関する説明と同意に関しては多くの議論が行われてきたが，現在では十分

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な説明の後，本人より文書にて同意を得ることが標準的である．癌の診断名，病期，治療内容，有害事象，合併症，治療関連死亡，医療費，他の治療法の選択肢などについて事前に説明し，患者自身から治療に関する同意を得ることが必須である．とくに試験的治療では，施設倫理審査委員会(IRB)の承認済みの書類にて実施することが義務づけられている．多忙な臨床現場で，このような時間を要する説明を行うことはたいへんであるが，治療を患者と医療者の共同作業と理解すれば，重要であることは明らかである．

8) 治療の妨げとなる合併症は除外するか，適切に治療を行いコントロールすることが必要である．高血圧，糖尿病，心臓病など，患者の高齢化に伴い生活習慣病を合併する患者は多くなっている．

Ⅱ 標準治療の確立とRCT—治療ガイドラインの意義

最近では多くの癌腫に対して治療ガイドラインが作成され発表されている．医師向けあるいは患者・家族向けが公表され，情報公開，情報共有にきわめて重要な役割を担っている．ガイドラインは本来RCTによる臨床試験成績に基づき，作成委員会でエビデンスが選別され，素案が作成される．その後，作成とは関連のない評価委員会にて科学的臨床的な妥当性が外部評価され，公表される．新規エビデンスが発表されると再度吟味されて改訂される．抗癌薬治療に関しては海外での多くのRCTによるエビデンスに基づき，エビデンスレベルと推奨度が決定されて公表されている．しかしながら，診断法や手術方法などに関しては，歴史的にRCTになじまず，手技の工夫，発明により進歩し，安全性，有効性が確認され臨床に受け入れられている．したがって，欧米式のガイドラインには厳密には当てはまらないが，国内を中心に多くの臨床実績が積まれており，これらを基礎に一般臨床を実施することは妥当であると考える．臨床実績が学会などの全国規模の組織で管理，維持されて一定の質が保証されており，膨大な症例数を経験しているがんセンターなどの専門病院の臨床成績に基づくのであれば，受け入れは可能と考える．当然，将来的にRCTを計画実施して新規エビデンスの創生が必要であることはいうまでもない．

「標準治療」という言葉がガイドラインではしばしば使用されている．これの対語としては「試験治療」がある．胃癌治療ガイドラインでは，混乱した臨床現場を整理する目的もあり，治療法を「日常診療におけるStage分類別の治療法の適応」と「臨床研究としてのStage分類別の治療法の適応」に二分し，これになじみ深いT分類，N分類に基づくStage分類を重ねて整理している．「日常診療」ではここまでは実施しても過去の臨床実績からは治療成績は保証できる(確立された治療法)と明示している．一方，「臨床研究」に含まれる治療法は，現在検討中であり，確立された治療法ではないことを示している．もちろん，経験のある施設では「臨床研究」の治療法が「日常診療」になっていることもありうる．しかしながら，個々の治療法が現時点で確立された「日常診療」であるか，未確定要素を含んだ「臨床研究」であるかを治療担当医に認識をしてほしいということがガイドライン作成委員会の強い意向である．

臨床実績から臨床試験へ，データからエビデンスへ，今外科医が大きく変貌しつつあると内科医からもしっかり認識される．胃癌における大動脈周囲リンパ節郭清意義を検証するRCT，噴門部胃癌に対する開胸アプローチを検証するRCT，胃癌脾摘の意義を検証するRCT，胃癌腹腔鏡手術の意義を検証するRCT，直腸癌側方リンパ節郭清の意義を検証するRCT，結腸癌腹腔鏡手術の意義を検証するRCTなど手術手技を検証する多くのRCTが国内で実施されている．数年後には国内発のRCTエビデンスによるガイドラインの改訂が現実のものになることは確実である．このような臨床試験指向の中で，再度抗癌薬治療に関するRCTも見直されている．多くの術後補助療法や化学放射線療法のRCTがきわめて質の高い試験として実施されている．臨床医が臨床試験の意義に目覚めたともいえる大きな意識変化である．国内での臨床実績をRCTという国際共通語

で翻訳し，海外に向けて積極的に情報発信を目指しているのである．

治療ガイドラインを通じて日本全国の治療担当医が共通の認識で治療を行うことにより，治療格差が最小となることが理想である．さらに，ガイドラインに採用されている治療レジメンの根拠やその実際に関しても多くの雑誌で取り上げられているので参考にしていただきたい．また，各学会のホームページや日本病院機能評価機構のMINDSのウェブサイトでも概要や主要文献の抄録が確認できる．

Ⅲ 補助療法と転移性癌に対する抗癌薬治療

抗癌薬治療は，大きく分けて主たる治療法である手術療法と関連して実施される術前・術後補助療法と，切除不能進行・再発の転移性癌に対する抗癌薬治療の二つがある．

治療の目的は，前者は治癒切除の効果をより増強し治癒を目指す目的であり，後者は腫瘍増大による症状コントロールが目的である．したがって，治療方針に関しても若干異なる．補助療法では，転移性癌で有用性の確認された治療レジメンを最大限の支持療法を行って治療強度を維持して実施する．一方，転移性癌に対する治療も同様ではあるが，減量や休薬を適宜行い，腫瘍増大を抑制する期間を延長することがポイントとなる．このコンセプトは，従来行われてきた補助療法は少量長期間経口抗癌薬投与というものとまったく異なる．最近では，術後補助療法が転移性癌を対象としたRCTで評価された治療レジメンを減量なしにそのまま適応して再発抑制を確認していることが多く，結果的にもこの戦略により，術後補助療法の標準治療が確立されてきている．Stage III結腸癌に対する5-FU/leucovorin(LV)，FOLFOX，胃癌に対するS-1などはこの開発戦略による成果である．術後の回復状態が不十分であるので，減量して実施する，あるいは再発までの長期間継続することについての十分なエビデンスはないと考えられ，現状では臨床試験で規定された治療期間を基本として一般臨床では実施すべきと考えられる．

Ⅳ 経口抗癌薬の臨床的意義―日本における問題点

消化器癌や乳癌では，従来から治療担当医が外科医であることが通常であった．これは国内の癌治療が診断は内科，外科治療・抗癌薬は外科というすみ分けが行われてきたこと，さらには海外のような腫瘍内科医が育成されなかったことなどによると考えられる．臨床現場の多忙や静注治療を実施するための外来治療センターなどの基盤整備が不十分であったことから，抗癌薬治療の主役は静注抗癌薬よりも経口抗癌薬にならざるをえなかったのはやむをえない．結果的に世界的にももっとも経口抗癌薬の臨床経験に富む国となった．しかしながら，経口抗癌薬の表面的な利便性や有害事象が少ないというイメージのみが先行し，臨床的意義である生存期間や無再発生存期間などの評価項目での臨床評価が遅れてしまった．UFTやdoxifluridine，S-1あるいはcapecitabineなどの国内発の優れた経口抗癌薬の5-FU/LVとの大腸癌での直接比較であるRCTは海外において実施され，UFT/LVとcapecitabineの非劣性が検証されたのは最近のことである．この間に，大腸癌治療は再度静注治療法が主役となり，IFL，FOLFOX，FOLFIRIなど多忙な国内医療環境になじまない複雑な治療レジメンが標準治療と位置づけられるというジレンマを経験することになる．国内においてこれら静注治療法を導入しているあいだに海外ではcapecitabineの併用療法であるXELOX(capecitabine＋oxaliplatin)療法が積極的に評価され，転移性大腸癌ではXELOX療法とFOLFOX4療法の非劣性が検証されている．すなわち，経口抗癌薬の併用療法が静注療法に置き換え可能であるという証明がされたのである．経口抗癌薬の先進国であった日本が，結果としてその長所を生かすことなく欧米の後追いをしている現実はきわめて残念である．今後は，経口抗癌薬の長所をさらに伸ばすために術後補助療法での評価が実施されることになることが予想される．この点で，ACTS-GC試験により胃癌術後補助療法におけるS-1の臨床評価が国内で実施完了したこと

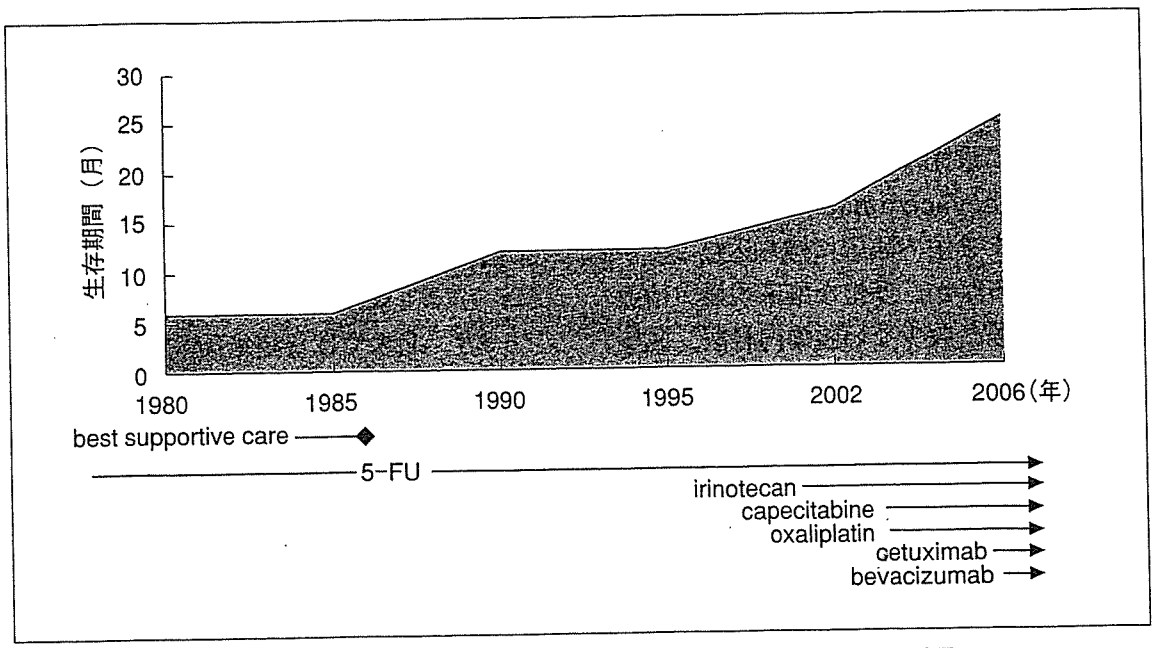

図1．転移性大腸癌治療成績の進歩．新薬登場と生存期間の延長

は特筆すべき快挙である．長期的戦略のもとに，全国規模で臨床試験を展開すれば十分国際的に評価される臨床試験を実施できるのである．このような実績をもとに，海外との国際共同試験における主要メンバーとしての参加が可能となると考えられる．

Ⅴ 新規薬剤の臨床的意義（図1）

大腸癌治療を例にとると2005年のoxaliplatin承認以降，新規抗癌薬であるbevacizumabやcetuximabなどに多くの期待が寄せられている．患者数を考慮すると乳癌に対するtrastuzumabやリンパ腫に対するrituximab以上のインパクトが予想される．すでに多くの海外臨床成績が報告され，一次治療，二次治療での有効性や，5-FU/LV，IFL，FOLFOX4などの基本抗癌薬治療との併用の組み合せでの有効性が確認されているbevacizumabではさらに大きな期待が寄せられている．このような分子標的治療薬や抗体医薬品は新しい治療の可能性を開拓した点では大きな進歩である．癌の生物学的特徴の解析が臨床で開花したともいえる．しかしながら，その特異的な作用機序のために従来経験したことのない有害事象が報告されている．高血圧，腸管穿孔，血管塞栓などである．頻度は必ずしも高くはないが，経験がない事象ではしばしば発見，対応が遅れることがあるので十分に観察する必要がある．また，臨床的な有用性が認められた患者集団を再度確認する必要がある．治療抵抗性となった全身状態不良の患者に対する魔法の薬でないことは明らかである．適応対象を慎重に選択し，標準投与量をスケジュールに従い投与し，有害事象の発現に応じて適切に減量，休薬を実施することにより最大限の治療効果を実現できるのである．もちろん，併用される抗癌薬治療レジメンも今までの臨床試験成績を参考に，標準的投与量で実施すべきである．安全性を優先して，低用量で実施することで期待される有効性を実現することは一般に不可能である．また，分子標的治療薬は有害事象がなく，長期間腫瘍増大をきたさないという当初のキャッチフレーズは現在では受け入れられていないので，使用に関しては十分な知識が必要となる．

Ⅵ 先行する海外臨床試験の国内導入

海外臨床試験成績が海外学会やインターネットなどで先行発表される時代となり，国内臨床現場での混乱がみられる．国内メディアの偏向報道にも一因がある．毒性や医療費に関するマイナス面

に関する報道が不十分である．臨床医は，臨床試験成績を包括的に概観し，新治療によるベネフィットとリスクについて十分に自ら理解しなければならない．常に最先端には未知のリスクが伴う．すでに述べたbevacizumabに関しても，海外臨床成績をそのまま国内臨床に持ち込むことが現実的に可能であろうか．多忙な臨床現場，治療の主体を担う外科医，数少ない腫瘍内科医，医療費への無関心など多くの国内医療環境の問題点がある．海外との医療レベルを比較することは，国内での医療格差を考慮すればむずかしいことは容易に理解できるが，国内の標準的医療をどのレベルに求めるかは医療関係者のみならず，患者や医療費支払機関，さらには国民の合意が必要な大きな問題である．欧米と同様の最先端医療を享受したいのは患者の希望である．しかし，海外では医療を受けることのできない患者も多数おり，国家単位の医療レベルでは日本は決して低い国ではない．いわゆる先進医療をどの程度，どの時期に，誰が負担して国内導入に踏み切るか，最近の新規有効抗癌薬が登場したこの時期にこそ十分な議論が必要と考える．

Ⅶ 異なる国内医療環境における新治療の適応

国内の癌治療はX線検査，内視鏡検査，病理検査などの診断学，外科治療学を中心に臓器ごとに進歩してきた．この結果，治療成績はきわめて順調に向上してきたのも事実である．しかしながら対照的に，転移，再発癌患者の治療成績の進歩がみられないことも明らかとなった．

このような中，海外を中心に臨床評価された新規抗癌薬の登場により転移・再発癌の治療成績は着実に向上している．新規薬剤を国内導入するさいには，海外と比較して診断学，外科治療学の進歩している国内環境が大きなアドバンテージを有していることは明らかである．

ACTS-GCによる胃癌の術後補助療法やNSAS-CCおよびTAC-CRによる直腸癌の術後補助療法の成績は国内の優れた外科手術と，多くの切除リンパ節を検索してくれる病理医の共同作業が基礎にある．残念ながら海外では数施設以外に国内医療を再現することはむずかしいであろう．

一方，北米では胃癌術後補助療法は化学放射線療法であり，大腸癌術後補助療法がoxaliplatin併用のFOLFOX療法に移行している状況をみると，癌治療は診断，外科，抗癌薬治療(放射線治療)の集学的治療のたまものと再認識する．

治療戦略が異なる領域や，臨床試験が実施可能な領域では，国内環境への導入の可否につきなんらかの臨床試験で確認していく必要があると考えている．保守的な考えとの批判はあるが，臨床医として「エビデンスと経験」に基づいた医療を患者に提供するためには，海外データの直輸入には抵抗を感じてしまう．

臨床試験により多くのエビデンスが創生され構築された．治療成績が進歩したことも事実である．しかし，大多数の臨床現場でその事実を再現し，治療の進歩を患者に提供するためには，臨床医には多くの仕事が残されている．

おわりに

最近の抗癌薬治療の進歩は目覚ましい．これらは多くの海外臨床試験成績に基づくものである．患者は最善の治療効果を期待するのは当然であり，臨床医はそれに応える努力が必要である．しかし，医療の現場は日本国内の医療現場である．海外での治療進歩を目の前の癌患者でいかにして再現するかはまだ多くの問題を抱えているが，多くの臨床医が着実な進歩を実感しているのも事実である．第一線の臨床医が抗癌薬治療に精通して治療成績を向上することにおおいに期待したい．

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Review Article

Treatment Strategy for Locally Recurrent Rectal Cancer

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Despite radical surgery, up to 33% of patients with rectal cancer will develop locoregional relapse. The management of these patients is particularly challenging. Surgery is the mainstay of treatment for those with a mobile recurrence. However, the majority of patients develop recurrence involving the pelvic wall. In these patients, multimodality therapy including radical surgery and intraoperative radiotherapy have been reported with 5-year survival of up to 31% and local control rates of 50–71%. The most important factor for obtaining long-term local control and survival is R0 resection. Extended surgery such as abdomino-sacral resection has not been popular because of 5-year survival rates of 16–31%, and significant postoperative morbidity. Re-recurrence following surgery occurs locally and in the lung, and remains a significant problem. In surgical treatment for local recurrence, surgeon-related factors are crucial. A staging system using degree of fixation and other prognostic factors should be developed so that appropriate treatment modalities are applied to each case.

Key words: locally recurrent rectal cancer – multimodality therapy – extended surgery

INTRODUCTION

In patients who undergo radical surgery for rectal cancer, 4–33% develop locoregional relapse. Without treatment, these patients with locally recurrent rectal cancer (LRRC) have a median survival of ~8 months. If no treatment is given, they suffer from severe symptoms, especially pain, and their quality of life (QOL) becomes extremely poor (1–4). Nearly half of LRRCs are located in the pelvis without distant metastasis. The best treatment for LRRC in this setting is a complete resection of the recurrent tumor.

There are a number of different options for treating LRRC. There options are influenced by the nature of the LRRCs, which may present as a mobile recurrence or a huge mass occupying the pelvis.

In non-fixed recurrent tumors, complete resection can be achieved with limited surgery such as abdomino-perineal resection and the outcomes are relatively favorable.

When an LRRC grows within the narrow pelvis, it can easily invade the pelvic wall, appearing in the form of fixed recurrent tumor (FRT). If FRT involves only anterior structures, total pelvic exenteration achieves adequate margins. However, the majority of patients with LRRC present with dorsal and/or dorsolateral involvement of the pelvis. These patients present a particular challenge. Extensive surgery such as abdomino-sacral resection may be required. However, inappropriate surgical intervention in these patients may cause an iatrogenic cancer spread, leading to impaired QOL.

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CONVENTIONAL TREATMENT

In patients with LRRC who are unsuitable for surgical intervention, chemoradation is the main therapeutic option available. The effect of radiotherapy depends on the tumor size and the total radiation dose given. A dose of 45 Gy provides good palliation of pain in 50–80% of patients (5), with low risk of toxicity to the small intestine. However, an antitumor effect that may achieve complete response or survival benefit cannot be expected at this dose. Another approach is to administer a dose of 50 Gy to the same radiation field used for the treatment of the primary rectal cancer. The radiation field is then reduced to include only the site of tumor recurrence and a total dose of 60–70 Gy is delivered to this site. However, external beam radiotherapy (EBRT) alone has not been shown to achieve significant survival benefit.

For this reason, the combination of radiotherapy and chemotherapy is usually employed. The rationale for combined therapy includes (i) enhancement of cytotoxicity

using an antitumor agent and radiation, (ii) use of chemotherapy, which provides treatment of distant metastasis in addition to the local control of the tumor provided by radiotherapy and (iii) the potential to reduce the dosage of agents and therefore their toxicity by combining different treatment modalities without reducing the overall efficacy (6,7).

EBRT used alone or in combination with chemotherapy provides temporary symptomatic improvement in most patients. Median survival time is 14 months and time of local control is 5 months. Five-year survival rate in these patients is usually <5% (8).

Preoperative chemoradiation is used for primary rectal cancer to downstage the tumor and improve resectability. The same approach has also been used for LRRC. Rodel et al. (9) administered chemoradiotherapy preoperatively in 35 patients with LLRC using 5-FU (1000 mg/m^2/day). They reported that they achieved margin-free resections in 17 cases (61%). Other chemotherapy agents such as CPT-11 and Oxaliplatin are expected to play an important role in the management of these patients in the future (10).

MULTIMODALITY TREATMENT

Reports from some western centers suggest that improved local control and survival can be achieved in selected patients by the use of preoperative chemoradiotherapy, radical surgery and intraoperative radiotherapy (IORT) (11–22). This approach recognizes that satisfactory antitumor effect cannot be achieved by chemoradiation alone. The addition of IORT means that the maximum radiation dose possible can be delivered to the recurrent tumor. This has the potential to allow less extensive surgery to be undertaken.

One of the benefits of IORT is that it produces up to three times the biological effect produced by fractionated EBRT. In addition, IORT has the advantage of delivering radiation accurately to the tumor bed while displacing adjacent normal structures from the irradiation field. The use of IORT allows a reduction of the EBRT dose and so reduces toxicity of this modality. Mayo Clinic researchers reported a 3-year survival rate of 39% and a 5-year survival rate of 20% in 123 patients with LRRC who were treated with IORT and surgery (14). Mannaerts et al. (16,18) in the Netherlands used a preoperative radiotherapy dose of 50.4 Gy (30 Gy in patients who had received ratiotherapy) before surgery, during which they carried out IORT. The dose of IORT was determined by the R status of the resection. Patients who had undergone R0 resection (microscopically negative margins) were treated with a dose of 10 Gy, R1 resections (microscopically positive margins) with a dose of 15 Gy and R2 cases (macroscopically positive margins) with a dose of 17.5 Gy. Overall 3-year survival rate reached 58%. However, patients who had undergone R2 resection showed a worse prognosis in this series. Wiig et al. (19) reported a 5-year survival rate of 60% in patients given preoperative irradiation who had R0 resection. This does raise the question as to whether IORT is really necessary in cases with previous R0 resection, particularly as not all R0 cases in this series received IORT. It can be argued that a true R0 resection leaves no cancer cells to be eradicated by IORT. In clinical practice, however, because it is not always easy to differentiate fibrosis from recurrent cancer, some patients who undergo R0 resection may have residual disease and may benefit from IORT (20,21).

Abuchaibe et al. (12) and Bussieres et al. (15) have reported on patients with R2 resection given IORT but no postoperative EBRT. This strategy resulted in a poor outcome and suggests that additional EBRT is important in achieving local control. Irradiation of patients who have received radiotherapy previously has generally been avoided because of the fear of severe late radiation toxicity. Mohiuddin et al. (2,23) reported on 103 cases who received reirradiation and showed acceptable late toxicity (17% with chronic severe diarrhea, 15% with small bowel obstruction and 4% with fistula).

Despite the use of multimodality therapy, 5-year survival rates of patients with LRRC remain 22–31% and local control rates 50–71% (Table 1). IORT cannot be expected to compensate for R2 resection (13) and is itself associated with potential complications. The commonest side effects are ureteric stenosis and peripheral neuropathy. In a series of 123 cases at the Mayo Clinic (14), partial ureteric stenosis as a complication occurred in 6% of patients with 10% requiring insertion of ureteric stents. Peripheral neuropathy was observed in 16–34% of the patients.

Table 1. Outcome after multimodality therapy

Author	Year	No. of cases	Resection (%)	Surgery	5-YSR (%)	Re-local recurrence (%)
Willet et al. (11)	1991	30			27	38
Magrini et al. (32)	1996	16	100	Extended	48 (2Y)	36
Bussieres et al. (15)	1996	73	57	Mixed	31	29
Valentini et al. (17)	1999	47	45	Limited	22	31
Wiig et al. (19)	2000	107	41	Limited	30	50
Mannaerts et al. (18)	2001	33	64	Mixed	60 (3Y)	27
Hahnloser et al. (21)	2003	304	100	Limited	25	

5-YSR: 5-year survival.

Brachytherapy uses gamma rays or beta rays emitted by the encapsulated sealed radioactive source to carry out interstitial irradiation. More recently, concerns about the surgeon's exposure to radiation and patient isolation have seen the increased use of high-dose-rate remote afterloading system (24,25). Goes et al. (24) reported the use of afterloading tubes inserted intraoperatively after tumor reduction surgery to deliver brachytherapy in 30 previously irradiated patients. In these patients with LRRC, local control was achieved in 18 cases (64%) with a median follow-up period of 36 months. The advantage of brachytherapy is that it minimizes the amount of radiation to which surrounding tissues are exposed, and hence it is a useful method for previously irradiated patients. However, accurate placement of the afterloading tubes can be difficult because the recurrent lesion is surrounded by scar tissue and is deep within the pelvis. Alternative methods for placing the tubes accurately include CT-guided percutaneous insertion, but this is associated with the risk of small bowel injury and fistula formation if the tube damages a part of the small intestine lying within the pelvis. Consequently, brachytherapy has not yet become a standard therapy for LRRC.

COMBINED RESECTION

To achieve long-term local control and survival benefit in patients with LRRC, it is clear that it is necessary to achieve an R0 resection. This is a particular challenge when patients have FRTs with dorsal and/or dorsolateral involvement.

In 1981 Wanebo introduced the technique of abdomino-sacral resection, which was adopted by other surgeons (26–39). Extended surgery for FRT has not become popular because of reported 5-year survival rates of 16–31% (Table 2). Bozzetti et al.(34) indicated limitations of surgical treatment, and Wiggers et al. (33) showed a critical attitude toward extended surgery. In 1999, Wanebo et al. (36) reviewed the outcome of extended surgery in 53 patients. The operative mortality was 8%, the mean blood loss was more than 8000 ml and the mean operative time was ~20 h. All the patients had been irradiated previously. The overall 5-year survival rate was 31%, and the disease-free 5-year survival rate was 23%. High amputation of the sacrum was performed in 32 cases (60%) for pelvic recurrences extending to the sacral promontory or sciatic notch. In all cases, the internal iliac vessels were preserved and lymph node dissection in the pelvis was performed. Lateral node metastasis was observed only in one case (1.8%), which is a surprisingly low rate. It remains unclear as to whether this was due to the influence of radiation or due to the method used for searching the metastasis. One can hardly assert that extended surgery is acceptable in terms of both surgical invasiveness and oncological outcomes, and consequently this therapy has been positioned as a formidable and demanding treatment.

In 2004, we reported the treatment outcome of total pelvic exenteration with distal sacrectomy (TPES) in 57 patients with FRT (39). The operative mortality was 3.5%, and the median blood loss and operative time were 2500 ml and 682 min, respectively. These results are different from those reported by Wanebo et al. (36). We have analyzed factors that may be responsible for this difference. Our patients with primary rectal cancer undergo total mesorectal excision or a more extended surgery, whereas in the US less extensive surgery was generally performed. All Wanebo's patients received preoperative radiotherapy resulting in pelvic fibrosis. However, in our patients postoperative scarring after extensive primary resection leads to more technical difficulties in the resection of the recurrent disease. In addition, half of our patients received preoperative radiotherapy. Our conclusion is that overall the difference in results is not related to the extent of the initial surgery the patient had undergone or to whether radiation was given preoperatively. The major difference between the two series is the extent of the sacral resection. In contrast to Wanebo, we limited the level of the sacral amputation to the inferior margin of the second sacral vertebra or below in order to preserve the second sacral nerves. High sacral amputation is associated with more severe morbidity including mobility difficulties and a significantly impaired QOL. After less extensive sacral amputation, patients achieved an acceptable QOL except for living with double stomas and temporary pain owing to the resection of sacral nerves (39,40). For our patients, we achieved survival rate of 61% at 3 years and 46% at 5 years. Despite these improved results compared with the Wanebo's series, local re-recurrence and lung metastasis occur in more than 90% of the patients.

Measures to prevent further local recurrence and metastatic disease remain a challenge in the management of these patients. We conclude that surgical treatment including pelvic

Table 2. Outcome after combined resection

Author	Year	No. of cases	TPE	PW	RT	5-YSR (%)	Re-local recurrence (%)
Hafner et al. (28)	1991	21	11		1	20	38
Maetani et al. (35)	1998	59	39	43	26	25	61
Wanebo et al. (36)	1999	53	27	53		31	49
Yamada et al. (38)	2001	60	30	23		16	
Moriya (39)	2004	57	57	57	23	36	25

TPE, total pelvic exenteration; RT, radiotherapy; PW, resection of pelvic wall; 5-YSR: 5-year survival.

wall resection and IORT is the optimum method for improving local control rates in patients with LRRC. New antitumor agents such as CPT-11, UFT, Capecitabine and Oxaliplatin have shown efficacy in the treatment of rectal cancer and will play an increasing role in patients with metastatic disease.

PROGNOSTIC FACTORS

The factors that predict the success of the surgery for LRRC remain controversial. Several parameters such as the type of initial surgery, tumor size, presence of severe symptoms and the serum CEA level before re-resection have been assessed as potential prognostic indicators (41). Willet and Wanebo found improved resectability in patients having initial low anterior resection compared with initial APR (11,31). In contrast, we found no difference in either resectability or survival in patients who developed FRT (39). Among other factors, negative CEA and R0 resection were associated with better prognosis. Shoup et al. (42) reported that vascular invasion and R1/R2 resection are factors for poor prognosis. Both reports emphasize that the most important prognostic factor is whether R0 resection was achieved or not.

It has already been shown that in surgical treatment for primary rectal cancer, surgeon-related factors as well as biological factors are crucial. Surgical margin status and complications are exclusively determined by the surgeon's technical skills (43). Complicated surgery such as TPES or abdomino-sacral resection should be undertaken only in specialized centers that have particular expertise with such complex surgery.

STAGING SYSTEM

There is no established method of staging for patients with LRRC. Suzuki et al. (44,45) have assessed the degree of tumor fixation to surrounding structures according to surgical and pathological findings, and proposed their own staging method. Valentini et al. (17) also reported a similar staging system based on CT scan. They mentioned that degree of fixation is an independent prognostic factor. Wanebo et al. (36) have proposed a new staging system for stages TR1-2–TR-5, which are determined by the extent of invasion.

It is very important that a staging system is developed for these complex patients so order that the appropriate therapy is undertaken.

CONCLUSION

The management of patients with LRRC presents a formidable challenge. Potentially, there are a large number of therapeutic options available. Surgery remains the optimum treatment of local recurrence, if this can be achieved with acceptable QOL. The role of chemotherapy and radiotherapy remains to be clarified. IORT has the potential to improve local disease control in patients in whom an R0 or R1 resection can be achieved.

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Adjuvant Chemotherapy with Uracil–Tegafur for Pathological Stage III Rectal Cancer after Mesorectal Excision with Selective Lateral Pelvic Lymphadenectomy: A Multicenter Randomized Controlled Trial

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Background: Although adjuvant radiotherapy was proved to be effective for local control of rectal cancer even after standardized mesorectal excision, the role of adjuvant chemotherapy after such standardized surgery remains to be clarified. We aimed to assess the efficacy of a combination of uracil and tegafur for pathological stage III rectal cancer treated by standardized mesorectal excision with selective lateral pelvic lymphadenectomy.

Methods: We randomly assigned patients with completely resected stage III rectal cancer, who underwent standardized mesorectal excision with selective lateral pelvic lymphadenectomy, to receive either oral uracil–tegafur (400 mg/m^2 tegafur per day) for one year or no treatment. Standardization and quality control of the surgery and pathological techniques were ensured by use of the guidelines of the Japanese Society for Cancer of the Colon and Rectum. The primary endpoint was relapse-free survival. The secondary endpoint was overall survival.

Results: We enrolled and randomized 276 patients. Excluding two ineligible patients, 274 were included in the analysis. Planned interim analysis 2 years after accrual termination revealed significant prolongation of relapse-free survival ($P = 0.001$) and overall survival ($P = 0.005$) in the uracil–tegafur group. The 3-year relapse-free survival and overall survival rates were 78 and 91% in the chemotherapy group and 60 and 81% in the surgery-alone group, respectively. Local recurrence rates were low in both groups. Grade 3 events occurred in 17% of the chemotherapy patients, but no grade 4 or more events occurred.

Conclusion: Adjuvant chemotherapy with uracil–tegafur improves survival of patients with stage III rectal cancer after standardized mesorectal excision with selective lateral pelvic lymphadenectomy.

Key words: adjuvant chemotherapy – uracil–tegafur – rectal cancer – surgery

INTRODUCTION

The quality of surgical procedures has prognostic significance for local control and survival in rectal cancer (1,2). However, the lack of standardization for surgery and limitations of surgical information in previous adjuvant trials is well documented (3). The Dutch Colorectal Cancer Group was the first to adopt standardized mesorectal excision (4,5) in a rectal cancer adjuvant study (6). Mesorectal excision involves complete resection of the mesorectum by precise, sharp dissection under direct visualization (4,5) and is recommended in the Guidelines 2000 for Colon and Rectal Cancer Surgery (5).

The Dutch group clearly showed that preoperative radiotherapy is effective for local control even when standardized mesorectal excision is performed (6). Previous studies evaluating adjuvant radiotherapy, but not using standardized surgery, also showed its advantages in local control and survival (7,8). Therefore adjuvant radiotherapy has been recommended as the standard treatment. However, this approach was challenged by the results of a randomized

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trial which revealed no additional survival benefit from radiotherapy when chemotherapy was administered (9). Furthermore, radiotherapy entails risks of morbidity and mortality (6,7,10–12).

We started the National Surgical Adjuvant Study of Colorectal Cancer 01 randomized trial at the same time as the Dutch trial started (6). The aim of our trial was to evaluate the efficacy of postoperative adjuvant chemotherapy with a combination of uracil and tegafur (a prodrug of fluorouracil) taken orally after standardized mesorectal excision with selective lateral pelvic lymphadenectomy in stage III rectal cancer. Selective lateral pelvic lymphadenectomy is defined as selective application of extended lateral pelvic lymph node dissection, to resect the iliac and obturator lymph nodes when lateral pelvic lymph node involvement is clinically suspected (5,13–15).

We adopted mesorectal excision with selective lateral pelvic lymphadenectomy alone as the control treatment because it was the standard for stage III rectal cancer in Japan (13–15). We did not choose adjuvant radiotherapy because, in addition to the reasons mentioned above, local recurrence rate after mesorectal excision with selective lateral pelvic lymphadenectomy in Japan had been 7–15% in high-volume centers (14,15). Instead, we used oral uracil–tegafur, which was reported to be effective as adjuvant therapy for lung cancer in recent studies (16), because previous studies suggested efficacy of uracil–tegafur for prolonging disease-free survival in rectal cancer (17,18). Bolus fluorouracil and folinic acid, the present world standard for stage III colon cancer, was not used, because folinic acid was not approved in Japan until 1999. We present the results of the planned interim analysis at a median follow-up of 3 years.

METHODS

Patients and Study Design

Enrollment began in October 1996. Eligible patients had undergone a microscopically verified complete resection of pathological stage III adenocarcinoma of the rectum according to the 1992 Tumour Node Metastasis (TNM) Classification of Malignant Tumours (International Union Against Cancer) (19), by standardized mesorectal excision with selective lateral pelvic lymphadenectomy. Other inclusion criteria were the center of the tumor being located between the levels of the first sacral bone and the anal canal; an age of 20–75 years; the absence of preoperative anticancer treatment, previous cancer and synchronous multiple cancers; an Eastern Cooperative Oncology Group performance status of 0, 1 or 2; a leukocyte count of at least 4000/mm^3; a platelet count of at least 100 000/mm^3; serum aspartate aminotransferase and alanine aminotransferase levels that were no more than twice the upper limit of the normal range; a serum total bilirubin level of at most 1.2 mg/dl; a blood urea nitrogen level of at most 25 mg/dl; a serum creatinine level of at most 1.5 mg/dl; normal electrocardiogram; and an absence of severe postoperative complications uncontrolled by the time of registration.

An open-label study design was used. After written informed consent had been obtained, we randomly assigned the patients to postoperative adjuvant treatment with uracil–tegafur or to surgery alone. Randomization was performed by telephone or fax at the central trial office within 42 days after operation. Patients were allocated by the minimization method with Zelen's adjustment for inter-institutional imbalance. The factors used for balancing were the site of the primary tumor (above versus below the rectovesical fossa or rectouterine fossa), primary tumor stage (pT1 or pT2 versus pT3 or pT4) and N stage (pN1 or pN2 versus pN3). The primary endpoint was relapse-free survival and the secondary endpoint was overall survival. The trial was approved by the institutional review board of each participating center.

TREATMENT

Quality Control for Surgery and Pathology

All of the 28 participating centers are the high-volume centers which treated more than 100 colorectal cancer patients per year and institutional members of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) (13). The JSCCR has held a general assembly and sessions intended to improve treatment of colorectal cancer twice every year, and has standardized treatment. The JSCCR has provided guidelines for standardized surgical treatment and pathological evaluation (13). All procedures and pathological evaluations were in accordance with the fifth edition of the guidelines published in 1994 (13).

Mesorectal excision was the baseline procedure for all patients. The definitions of the mesorectum and mesorectal excision were the same as those from the Guidelines 2000 (5,13–15). In addition, extended lateral pelvic lymph node dissection (5,13–15) was performed in cases with clinically suspected lateral lymph node disease, as recommended by the JSCCR guidelines (13–15).

The quality of surgery was monitored by the surgeon's report on the location and clinical stage; extent of the resection of the bowel; mesorectum; and lymph nodes, and the pathologist's documentation of the pathological stage; number of resected and positive lymph nodes in each lymph node group; extent of bowel resection; and anal, oral and radial margin status (13).

Adjuvant Chemotherapy

In the treatment group, uracil–tegafur (UFT®, Taiho Pharmaceutical Co., Tokyo, Japan; 400 mg/m^2 tegafur per day) in the form of 100 mg units (100 mg of tegafur plus 224 mg of uracil) was given orally twice daily for 5 consecutive days every weekday for 1 year, starting 6 weeks postoperatively. The dose was rounded up or down to the nearest

100 mg. All patients but one received 3 units of uracil–tegafur (300 mg of tegafur and 672 mg of uracil) twice daily. The patients were asked at each follow-up visit whether they had taken the units as prescribed.

Adverse events were graded according to the toxicity grading criteria of the Japan Clinical Oncology Group, which consist of the Common Toxicity Criteria of the National Cancer Institute with minor modifications (20). Grades range from 0 (none) to 5 (fatal) (20). If a moderate (grade 2) adverse event occurred, the dose of uracil–tegafur was reduced to 250 mg/m^2 per day of tegafur. Treatment was stopped if, despite dose reduction, there was anything of the following: a grade 2 or higher adverse event, a leukocyte count of <3000/mm^3, an aspartate aminotransferase or alanine aminotransferase level of more than 2.6 times the upper limit of the normal range, a total bilirubin level of more than two times the upper limit of the normal range, moderate or severe anorexia, one or more vomitings per day or four or more bowel movements per day.

Follow-up

All the patients were evaluated every 4 months for the first 2 years after surgery and every 6 months for the next 3 years. The evaluation included a physical examination, a complete blood count, blood chemical tests, serum tumor markers, chest roentgenography, and abdominal ultrasonography or computed tomography. A pelvic computed tomography was performed every 6 months. In addition, patients receiving uracil–tegafur had a physical examination, a complete blood count and blood chemical tests every month during the first year.

Statistical Analysis

The sample size was calculated by the method of Schoenfeld and Richter. The study was designed to detect a hazard ratio for relapse or death of 0.67 in the uracil–tegafur group compared with the control group with 80% power at a two-sided α-level of 0.05. Assuming a 5-year relapse-free survival rate of 50% in the surgery-alone group, a 2-year accrual period and a 5-year follow-up, the targeted sample size was 400. In April 2000, the accrual period was extended to 5 years based on the actual accrual rate.

Interim analysis was planned 2 years after accrual termination. Early termination would be considered at the time of the interim analysis if the one-sided P value of the log-rank test for the primary endpoint was below 0.005, according to the Lan-DeMets spending function method.

Relapse-free survival was defined as the time from surgery until the appearance of the first recurrence of cancer, or death from any cause, and overall survival was defined as the time from surgery until death from any cause. All comparisons between the treatment groups were made on the intention-to-treat principle. Survival curves were estimated by the Kaplan-Meier method, and differences in survival were evaluated with the log rank test.

RESULTS

Accrual and Interim Analysis

From October 1996 to April 2001, 276 patients were enrolled and randomly assigned to one of the two treatment groups (Fig. 1). The study group decided to stop recruitment in April 2001, because a rapid, further enrollment could not be expected and evaluation of the treatment would be possible through a meta-analysis including the data obtained from this study and existing data (17,18,21). Planned interim analysis was conducted by the data and safety monitoring committee on 13 December 2003. Sufficient results favoring the treatment arm caused the committee to recommend a prompt disclosure of the results. This report is based on the results presented to the data and safety monitoring committee.

Patient Population

Of the 276 enrolled patients 2 (one in each group) proved to be ineligible so that data from 274 patients (139 in the uracil–tegafur group and 135 in the surgery-alone group) were included in the analysis (Fig. 1). The characteristics of the patients are shown in Table 1 and were well balanced in the two groups.

Quality of Surgery

The quality of the surgical procedures (Table 2) was similar in both groups. All patients underwent at least mesorectal excision. Extended lateral pelvic lymph node dissection was added in 38% of the patients, most of whom had a tumor locating below the rectovesical fossa or rectouterine fossa. Distal margins of the mesorectum and rectum were sufficient in both groups. Anal, oral and radial margins were microscopically negative in all the patients. More than

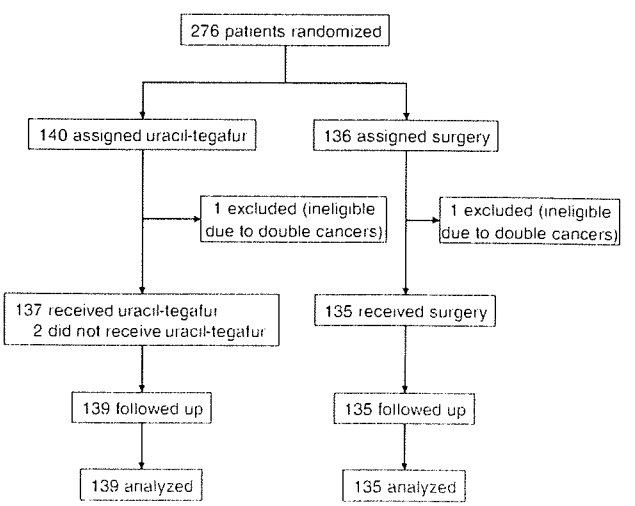

Figure 1. Study profile

Table 1. Characteristics of the patients

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Age (years, mean [range])	58 (32–75)	57 (30–75)
Sex		
Female	56	53
Male	83	82
Location of the center of the tumor		
Below the promontrium	43	39
Below the lower edge of the second sacral bone	39	43
Below the rectouterine fossa or rectovesical fossa	57	53
Pathological tumor stage*		
T1	8	11
T2	21	16
T3	94	90
T4	16	18
Pathological nodal stage*		
N1	88	89
N2	22	22
N3	29	24
Positive lateral pelvic lymph node	11	7
Type of resection		
Anterior resection	113	109
Hartmann operation	1	0
Abdominoperineal resection	24	25
Other	1	1

*The 1997 TNM Classification of malignant tumors (International Union Against Cancer).

Table 2. Quality of surgery

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Lymph node dissection		
Mesorectal excision	89	81
Mesorectal excision plus extended lateral pelvic lymphadenectomy	50	54
Distal margin of the mesorectum		
2–4 cm	7	2
> 4 cm or total mesorectal excision	132	133
Distal margin of the bowel (cm)		
Median (range)	3 (0.3–10.5)	3.5 (0.5–8)
Number of resected lymph nodes		
Median (range)	21 (1–80)	20 (2–108)

12 lymph nodes were resected in 80% of the patients. The rate of positive lateral pelvic lymph node metastasis was 17% (18/104) in the patients who underwent extended lateral pelvic lymph node dissection.

Table 3. Adverse events

Adverse event	Uracil–tegafur Grade of Toxicity*			Surgery alone Grade of Toxicity*		
	2	3	4	2	3	4
	% of patients					
Leukopenia	5	0	0	1	0	0
Thrombocytopenia	1	0	0	0	0	0
Anemia	4	0	0	2	0	0
Increase in bilirubin	51	9	0	17	2	0
Increase in aspartate aminotransferase	4	2	0	2	0	0
Increase in alanine aminotransferase	10	3	0	6	1	0
Anorexia	7	1	0	1	1	0
Nausea or vomiting	3	1	0	1	1	0
Diarrhea	5	1	0	1	1	1
Skin eruption	6	1	0	0	0	0
Alopecia	0	0	0	0	0	0

*Adverse events were graded according to the toxicity criteria of the Japan Clinical Oncology Group, which consists of the Common Toxicity Criteria of the National Cancer Institute with minor modifications. Grades range from 0 (none) to 5 (fatal).

Adverse Events and Compliance

Of the 139 patients assigned to the uracil–tegafur group, 137 actually took uracil–tegafur and two withdrew from the trial before drug administration (Fig. 1). Moderate (grade 2) and severe (grade 3) events were observed in 65 and 17% of the patients in the uracil–tegafur group and in 39 and 4% of the patients in the surgery-alone group, respectively. Observed adverse events are listed in Table 3. A life-threatening (grade 4) event occurred only in one patient in the surgery-alone group. There was no fatal event.

Compliance with instructions to take uracil–tegafur was calculated on the basis of the number of patients who actually took uracil–tegafur and the number of patients who were assigned to it, excluding those with a recurrence and those who died. The rate of compliance, with or without dose reduction, was 93% at 3 months, 88% at 6 months, 83% at 9 months and 80% at 12 months. The reasons for discontinuation of uracil–tegafur were a cancer recurrence (18 patients), an adverse event (8 patients), patient withdrawal due to adverse events (10 patients) and patient withdrawal due to other causes (4 patients).

Relapse Free Survival

The median follow-up among surviving patients was 3.0 years. At the last follow-up, 32 patients in the uracil–tegafur group and 53 in the surgery alone group had recurrence or had died (Table 4). The 3-year estimate of relapse free survival for the uracil–tegafur group was 78% (95% CI 71–86%). That for the surgery alone group was 60% (95% CI 51–69%) (Fig. 2). Patients receiving uracil–tegafur had significantly better

relapse-free survival than those undergoing surgery alone ($P = 0.0014$). The hazard ratio for any recurrence in the uracil–tegafur group as compared with the surgery-alone group was 0. 52 (95% CI 0. 33–0. 81).

Overall Survival

At the last follow-up, 12 patients in the uracil–tegafur group and 27 in the surgery-alone group had died. The 3-year estimate of overall survival for the uracil–tegafur group was 91% (95% CI 86–97%). That for the surgery-alone group was 81% (95% CI 73–88%) (Fig. 2). Thus patients with uracil–tegafur had significantly better overall survival than those with surgery alone ($P = 0.0048$). The hazard ratio for death in the uracil–tegafur group compared with the control group was 0.42 (95% CI 0. 21–0.83).

Table 4. Pattern of the first recurrence

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Local alone	6 (4%)	9 (7%)
Anastomotic recurrence	3	4
Pelvic recurrence	3	5
Distant alone	23 (17%)	39 (29%)
Liver metastasis	11	21
Lung metastasis	7	15
Liver and lung metastases	1	0
Others	4	3
Local plus distant recurrences	2	4
Death from other diseases	1	1
Overall events	32 (23%)	53 (39%)

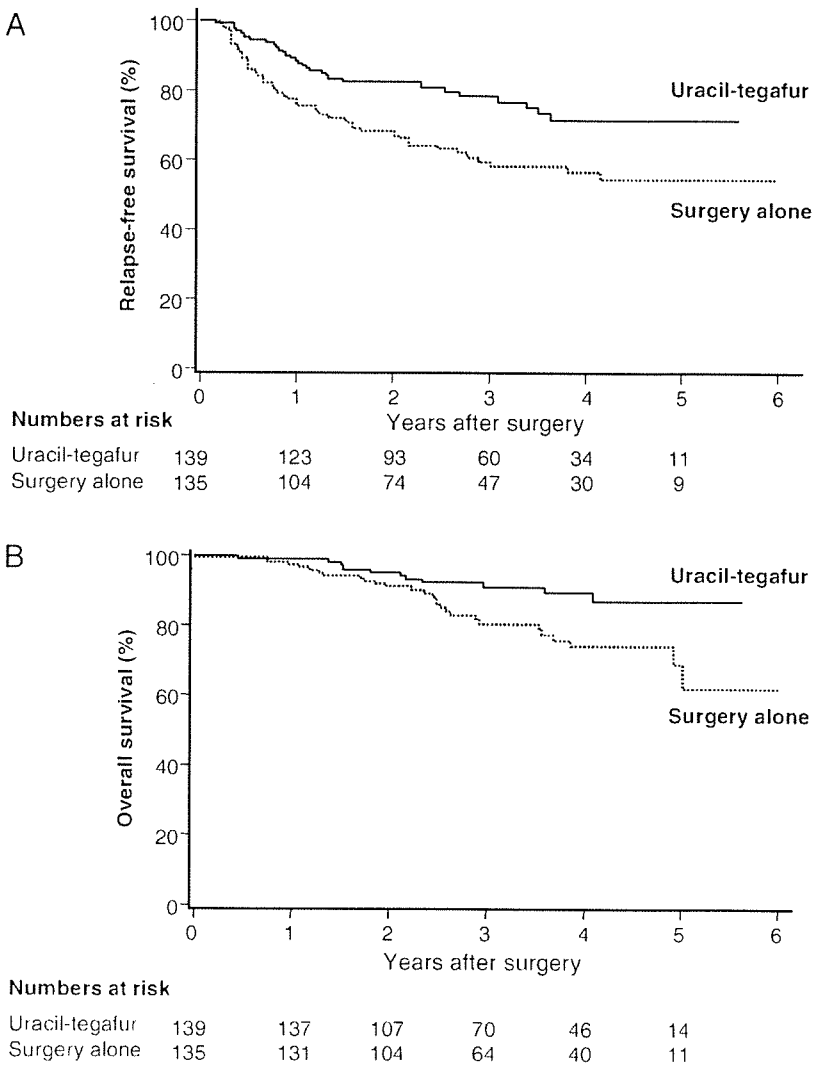

Figure 2. (A) Kaplan–Meier estimates of relapse-free survival. (B) Kaplan–Meier Estimates of overall Survival. At 3 years the rate of relapse-free survival was 78% in the uracil–tegafur group and 60% in the surgery-alone group ($P = 0.0014$). The rate of overall survival was 91% in the uracil–tegafur group and 81% in the surgery-alone group ($P = 0.0048$).

Pattern of Recurrence

Details of the pattern of first recurrence are shown in Table 4. At the last follow-up, the rates of overall local recurrence were 5.8% (8/139) for the uracil–tegafur group and 9.6% (13/135) for the surgery-alone group. Adjuvant uracil–tegafur reduced the rates of distant metastases. The rates of overall distant metastases were 18% (25/139) for the uracil–tegafur group and 32% (43/135) for the surgery-alone group. Liver and/or lung metastases composed the majority of distant metastases in both treatment groups.

DISCUSSION

This trial demonstrated the efficacy of postoperative adjuvant chemotherapy with uracil–tegafur after standardized mesorectal excision with selective lateral pelvic lymphadenectomy in pathological stage III rectal cancer. At the planned interim analysis, we found that the 3-year estimate of both relapse-free survival (78%) and overall survival (91%) of the uracil–tegafur group were significantly better than the surgery-alone group (60 and 81%, respectively). The data and safety monitoring committee concluded that the results confirmed the findings of previous studies (17,18) and a recent meta-analysis (21) which showed the effectiveness of uracil–tegafur for rectal cancer.

Rates of local recurrence have been reported to be 20–36% in series of non-standardized, conventional surgery for stage III rectal cancer, with a follow-up of 5 years (3,7,8). For experienced surgeons in mesorectal excision, however, they are 7.5–12% (22,23). At a median follow-up of 3 years, the local recurrence rate was 9.6% in the surgery-alone group of our trial. Although comparisons of such figures should be interpreted cautiously, this shows that a standardized mesorectal excision with selective lateral pelvic lymphadenectomy may achieve good results even in a multicenter setting. Moreover, it may possibly be better than the 2-year local recurrence rate of 8.2% in the mesorectal-excision-alone group of the Dutch trial (6), considering that 56% of patients of the Dutch trial had stage 0–II tumors (6).

Lateral pelvic lymph node metastases from rectal cancer occur outside the mesorectum and appear to account for a major cause of local recurrence. The incidence of lateral pelvic lymph node metastases was reported to be 9–14% (14,15). If the patients have such metastases and undergo only mesorectal excision, the patients have apparent residual tumor in case of recognizable metastases or develop local recurrence after seemingly curative surgery in unrecognizable metastasis cases. Extended lateral pelvic lymph node dissection is a surgical procedure to resect such macroscopic or microscopic metastases (5,14,15). Therefore, this procedure potentially has a similar local control effect to adjuvant radiotherapy. Whether lateral dissection can be an alternative to radiotherapy should be tested in a randomized controlled trial assessing local control, survival, mortality and morbidity. To conduct such trials, accuracy for detection of lateral pelvic metastases may be a problem. Indeed, in our trial, only 17% of the patients who underwent lateral dissection actually had lateral metastases. To avoid such over-treatment, an accurate diagnostic modality detecting metastasis is necessary.

Between 1990 and 1994, the JSCCR registered 25 224 patients with colorectal cancer. (24) Among them, 2789 patients had curative resection of stage III rectal cancer and their 3-year overall survival rate was 75% (24). In the surgery-alone group of our trial, the 3-year overall survival was 81%. Introduction of revised guidelines, standardized surgical procedures assured by precise documentation and participation of colorectal specialists from high-volume centers may have contributed to this improvement. Quality of surgery is already known as an independent prognostic factor for survival in rectal cancer (1,2), and case volume per surgeon also influences the outcome (3,25).

However, the quality of surgery has no influence on the initial occurrence of distant metastases (1). Even when better-quality surgery reduces local recurrence, occult distant metastases necessitate further treatment to improve survival. We found that, in addition to the efficacy of mesorectal excision with selective lateral pelvic lymphadenectomy, uracil–tegafur further decreased the rate of local recurrence from 9.6 to 5.8%. The rate of distant metastasis was almost halved from 32 to 18%, including a substantial reduction in the rates of liver and lung metastases. Uracil–tegafur appears to improve survival mainly through reduction of distant metastases when applied along with such operations.

The recent meta-analysis assessing randomized controlled trials using oral fluorouracil-based adjuvant chemotherapy for stage I–III colorectal cancer revealed that 1 year chemotherapy reduced the risk of death by 11% ($P = 0.04$) and the risk of recurrence or death by 15% ($P < 0.001$) as compared with surgery alone (21). However, of the three previous randomized trials that compared uracil–tegafur adjuvant therapy with surgery alone in rectal cancer, two revealed significantly improved relapse-free survivals, but none demonstrated an advantage in overall survival (17,18). In these trials, eligible stages were I–III, the dosage of tegafur was 400 mg per day, the compliance was 48–70% and local recurrence rates in surgery-alone group were 19–34% (17,18,21). The significantly better relapse-free and overall survivals in our uracil–tegafur group may be attributable to a selection of stage III patients, a higher dosage of 600 mg per day, better compliance and better quality of surgery. In the meta-analysis, hazard reduction was more marked in early-stage disease (21). In contrast, our results show that a higher dosage may also be effective for advanced stage disease.

We found that 1-year treatment with uracil–tegafur was safe and well tolerated. Grade 3 events occurred in 16.5% of the patients and consisted mainly of increases in bilirubin and aminotransferases. No grade 4 or grade 5 events were observed. Previous colon cancer adjuvant trials showed that the overall incidences of grade 3 or more events in patients treated with different regimens were 38% or more for fluorouracil plus folinic acid (26,27), 38% for uracil–tegafur plus

folinic acid (27), 30% for capecitabine (26) and more than 41% for oxaliplatin with fluorouracil plus folinic acid (28). The most frequent events included neutropenia, diarrhea, vomiting and hand-foot syndrome. Therefore, the safety profile of uracil–tegafur compares favorably with those of the previous regimens. Consequently, 80% of our patients completed 1 year of treatment, including dose modification. A study using a therapy preference questionnaire demonstrated that, after having experienced both oral and intravenous fluorouracil regimens, most patients preferred an oral regimen (29). The most important reasons for their preference included the convenience of taking the medication at home, less stomatitis and diarrhea, and preference of pills over injections (29). In addition, we should mention that uracil–tegafur is less expensive than the other regimens in this country, where medical costs are becoming an increasingly important issue.

Thus the most significant findings of our trial can be summarized as follows. Peroral monotherapy using uracil–tegafur achieved survival prolongation of stage III rectal cancer patients, without an addition of any other active agents, including folinic acid. This makes it possible to provide less toxic, yet effective, and convenient adjuvant chemotherapy for such patients.

However, several issues may limit the wider applicability of our findings. The numbers of patients recruited were smaller than those of recent rectal cancer adjuvant trials (6,7), although our trial was aimed solely at stage III tumor. The median follow-up time of our study was only 3 years, though disease-free survival with 3-year follow-up is suggested to be an appropriate primary endpoint to replace overall survival with 5-year follow-up (30). We used mesorectal excision with selective lateral pelvic lymphadenectomy that is a standard treatment only in Japan, and did not use mesorectal excision with radiotherapy, a world-standard combination. We could not use fluorouracil plus folinic acid, a standard adjuvant chemotherapy for stage III colon cancer, and neither the recently reported effective regimens including capecitabine and oxaliplatin (26–28). While the standard adjuvant chemotherapy course for colorectal cancer is 6 months (26–28), we opted for chemotherapy of 1 year. Therefore, the appropriateness of our approach should be tested further through comparison with recent standard adjuvant radiotherapy and chemotherapy.

In conclusion, radiotherapy has been considered to be standard adjuvant therapy worldwide for stage III rectal cancer. The present study indicates that uracil–tegafur treatment improves relapse-free survival and overall survival after mesorectal excision with selective lateral pelvic lymphadenectomy. This approach may become one of the treatment options for stage III rectal cancer and may deserve comparison with other treatment approaches.

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