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● 原 著 ●

ステージⅢ大腸癌に対する術後補助化学療法としてのカペシタビン（Xeloda®）内服療法の検討

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Oral Capecitabine as Postoperative Adjuvant Chemotherapy in Stage Ⅲ Colon Cancer Patients: Takashi Yamaguchi[*1], Meiki Fukuda[*1], Hisateru Yasui[*2], Shunsuke Okazaki[*2], Kimiyo Kubo[*3], Masako Tanaka[*3], Yoshiko Une[*4], Yuki Setoguchi[*4], Keita Hanada[*1], Sayaka Moriyama[*1], Masaki Tani[*1], Takahide Murakami[*1], Yoshihisa Okuchi[*1], Satoshi Ogiso[*1], Hiroaki Hata[*1], Shingo Sakata[*1], Tetsushi Otani[*1], Toshio Yamato[*1] and Iwao Ikai[*1] (*[1]*Dept. of Surgery*, *[2]*Dept. of Medical Oncology*, *[3]*Dept. of Nursing, and* *[4]*Dept. of Pharmacy, National Hospital Organization Kyoto Medical Center*)

Summary

Capecitabine (Xeloda®) has been a global standard drug for the treatment of colon cancer since large randomized controlled trials demonstrated its efficacy and safety in treating patients suffering from the disease. Few studies have been conducted to assess the effects of oral capecitabine treatment on Japanese patients. Therefor, we conducted this study to evaluate oral capecitabine as postoperative adjuvant chemotherapy in 50 patients who underwent surgery for stage Ⅲ colon cancer at our department. Patients received an 8 courses treatment with capecitabine during the study, and the incidence of adverse events, treatment completion rate, and treatment compliance were assessed. Adverse events were reported in a total of 46 patients (92%). The most common adverse event was hand foot syndrome (HFS), reported in 39 patients (78%), whereas bone-marrow toxicity and diarrhea were reported in as few as 2 (4%) and 3 (6%) patients, respectively. Both these events were mild in severity, and no patients required hospitalization, nor were they associated with treatment-related deaths. The median treatment duration was 8 courses ranging from 3 to 8 courses, and the 8 courses treatment completion rate was 96%. The relative dose intensity, which was used as a treatment compliance index, is expressed as the actual dose taken by the patient divided by the dose planned at baseline. The median and mean of the relative dose intensity were 100% (ranging from 37% to 100%) and 93%, respectively. The results of this study showed that the safety profile of oral capecitabine therapy was generally favorable, with a lower incidence and lesser severity of life-threatening bone-marrow toxicity and diarrhea, although the treatment is still associated with frequent HFS. This is the great advantage of capecitabine when it is used as postoperative adjuvant chemotherapy for gastrointestinal cancer. Indeed, a satisfactory treatment completion rate was achieved in this study while maintaining a sufficient dose and treating HFS, by reducing the dose, interrupting treatment, or providing appropriate corrective measures. **Key words**: Capecitabine, Colon cancer, Adjuvant chemotherapy (*Received Aug. 16, 2011/Accepted Dec. 5, 2011*)

要旨 カペシタビン（Xeloda®）は大規模無作為比較試験により有効性と安全性が証明され，大腸癌治療における世界的標準治療薬となっている。本邦におけるカペシタビンの使用成績の報告は少ないため，当院にてステージⅢ大腸癌術後補助化学療法としてカペシタビン内服療法を行った50例の有害事象の発現状況，8コース治療完遂割合，内服コンプライアンスを評価した。有害事象の発現は46例（92%）に認められた。hand foot syndrome（HFS）が39例（78%）と高頻度であった一方，骨髄毒性は2例（4.0%），下痢は3例（6.0%）と頻度が低く症状も軽度であり，入院加療を要した症例や治療関連死亡は認めなかった。投与コースの中央値は8コース（3～8コース），8コース治療完遂割合は96%であった。内服コンプライアンスの指標として用いた相対用量強度（実内服量/治療開始時予定投与量）の中央値は100%（37～100%），平均は93%であった。

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カペシタビン内服療法は高頻度のHFSというデメリットがあるものの，骨髄毒性や下痢の頻度が低く，また軽度であり，安全性が高かった。消化管術後の補助化学療法という観点からは特筆すべき長所であり，HFSを適切な処置・休薬・減量で対処することで十分な投与量を保ちながら高い治療完遂率を得ることができた。

はじめに

大腸癌治療ガイドラインではステージⅢ大腸癌に対する術後補助化学療法として5-FU/LV静注療法やUFT/LV内服療法，カペシタビン（Xeloda®）内服療法が推奨されている[1]。本邦における大腸癌の術後補助化学療法は，歴史的に5-FU系内服抗癌剤が簡便性を理由に科学的検証なく頻用されてきたが，近年の欧米での大規模無作為比較試験により内服抗癌剤の有用性が証明され，エビデンスに基づいた治療法となった。カペシタビン内服療法はステージⅢ結腸癌術後補助化学療法の第Ⅲ相比較試験であるXeloda in adjuvant colon cancer therapy（X-ACT）試験において，5-FU/LV静注療法と比較して主要評価項目である5年無病生存期間の非劣性が証明され，優越性に関しても境界領域の結果が得られた[2]。5年無再発生存期間においては有意な改善がみられ，さらには主要な有害事象の発現率が低く，より安全性が高いことも示された。この結果を受けて長らく内服抗癌剤治療を好まなかった欧米において，5-FU/LV静注療法とともにカペシタビン内服療法が5-FU系の新たな標準治療と位置付けられた[3]。治療効果と安全性の点で最も評価されたカペシタビンが，本邦においてもステージⅢ大腸癌術後補助化学療法の標準治療薬と考えられ，当院では2007年12月の保険承認以降使用してきた。本邦における補助化学療法におけるカペシタビンの安全性や継続可能性についての報告は少ないため，ステージⅢ大腸癌術後補助化学療法としてカペシタビン内服療法を行った症例の有害事象の発現状況，8コース治療完遂割合，内服コンプライアンスを評価した。

Ⅰ．対象・方法

2008年2月～2010年10月までに，根治度Aの切除が行われたステージⅢ大腸癌の補助化学療法としてカペシタビン内服療法を行った患者のうち，ECOGのperformance status（PS）が0または1で主要臓器機能が保たれており，かつ治療の理解が十分得られた50例を対象とした。対象年齢の上限は設けなかった。カペシタビンの経口投与は2,500 mg/m^2/日に基づき設定された1日錠数を朝・夕食後の2回に分け，2週間連続投与の後，1週間休薬の3週間を1コースとした。大腸癌術後補助化学療法の標準的施行期間は6か月間であり，今回の検討でもX-ACT試験と同様に合計8コース投与（＝治療期間24週）を治療完遂と定義した。有害事象の判定は有害事象共通用語規準v 3.0日本語訳JCOG/JSCO版（CTCAE v 3.0）に従った。hand foot syndrome（HFS）のグレーディングに迷うことがあるが，その場合には低いグレードに判定した。グレード2以上の有害事象発現時には，基本的にカペシタビン適正使用ガイドの休薬・減量規定に従ったが，患者の希望や医師の判断も加味して適宜休薬・減量を行った。また，75歳以上の高齢かつPS1であった6例のうち，4例は開始時より1段階以内の減量を行った。内服コンプライアンスとして，相対用量強度（実内服量/治療開始時予定投与量）を用いた。

Ⅱ．結　果

患者背景を表1に示した。年齢の中央値は68歳（34～84歳），75歳以上の高齢者は13例（26%）であり，PS0が40例（80%），PS1が10例（20%）であった。病期はステージⅢaが37例（74%），ステージⅢbが13例（26%）であった。

有害事象の発現状況を表2に示した。HFSが39例（78%）と高頻度であった一方，骨髄毒性は2例（4%），下痢は3例（6%）と頻度が低かった。グレード3の有害事象はHFS 2例と血小板減少1例の合計3例（6%）であった。グレード3のHFS 2例中1例は2段階減量により8コース治療を完遂でき，1例は治療継続の理解が得られず中止となった。グレード3の血小板減少の1例は1週間の休薬にて改善し，1段階の減量により8コース治療完遂が可能であった。グレード4の有害事象はなく，入院加療を要した症例や治療関連死亡は認められな

表1 患者背景（n=50）

性別	男性	26例（52%）
	女性	24例（48%）
年齢	中央値	68歳
	範囲	34～84歳
	高齢者（75歳以上）	13例（26%）
ECOG	PS 0	40例（80%）
	PS 1	10例（20%）
病期	ステージⅢa	37例（74%）
	ステージⅢb	13例（26%）

ECOG: eastern cooperative oncology group
PS: performance status
病期: 大腸癌取扱い規約第7版による

表 2 有害事象（n=50）

	グレード1	グレード2	グレード3	全グレード
HFS	29例（58%）	8例（16%）	2例（4%）	39例（78%）
食欲不振	10例（20%）	1例（2%）	—	11例（22%）
高ビリルビン血症	1例（2%）	4例（8%）	—	5例（10%）
味覚障害	5例（10%）	—	—	5例（10%）
結膜炎	2例（4%）	2例（4%）	—	4例（8%）
下痢	1例（2%）	2例（4%）	—	3例（6%）
口内炎	2例（4%）	1例（2%）	—	3例（6%）
悪心	2例（4%）	—	—	2例（4%）
好中球減少	—	1例（2%）	—	1例（2%）
血小板減少	—	—	1例（2%）	1例（2%）
肝機能異常	—	1例（2%）	—	1例（2%）

HFS: hand foot syndrome

表 3 カペシタビン投与状況（n=50）

8コース治療完遂症例		48例（96%）
減量を要した症例		12例（24%）
治療開始時予定投与量	中央値	2,384
（mg/m^2/日）	範囲	1,879～2,683
	平均	2,395
実内服量	中央値	2,295
（mg/m^2/日）	範囲	1,006～2,661
	平均	2,231
相対用量強度	中央値	100%
	範囲	37～100%
	平均	93%

相対用量強度: 実内服量/治療開始時予定投与量

表 4 治療中止・減量の主原因となった有害事象

中止（2例）	グレード3 HFS	1例
	グレード2 HFS	1例
減量（12例）	グレード3 HFS	1例
	グレード3 血小板減少	1例
	グレード2 HFS	3例
	グレード2 肝機能異常	1例
	グレード2 ビリルビン高値	1例
	グレード2 下痢	1例
	グレード2 口内炎	1例
	グレード1 複合因子	3例

表 5 治療開始時予定投与量とHFSの関係（n=50）

	≧2,500 mg/m^2/日（n=17）	<2,500 mg/m^2/日（n=33）	p値
HFS（全グレード）	16例（94%）	23例（69%）	p=0.07
HFS（グレード2以上）	9例（52%）	2例（6%）	p=0.004

p値: χ^2検定（Fisher両側検定）

かった。また，8コース途中での再発は認められなかった。

投与状況を表3に示した。投与コースの中央値は8コース(3～8コース)，8コース治療完遂例は48例(96%)であった。規定以外の休薬を要した症例は20例（40%），減量を要した症例は12例（24%）であった。治療開始時予定投与量の平均は2,395 mg/m^2/日（1,879～2,683 mg/m^2/日）で，実内服量の平均は2,231 mg/m^2/日（1,006～2,661 mg/m^2/日）であった。内服コンプライアンスの指標として用いた相対用量強度（実内服量/治療開始時予定投与量）の中央値は100%（37～100%），平均は93%であった。

治療中止・減量の主原因となった有害事象を表4に示した。複数の有害事象が原因となっている場合は中止・延期の判断に最も影響を及ぼしたものを記載した。中止の2例はHFSを主とする有害事象の発現により，治療継続の理解が得られず減量する前に中止となった。グレード1の有害事象で減量した3例は高齢など有害事象以外の因子も含めて考慮し，継続性を重視した症例であった。

治療開始時投与量とHFSとの関連性について表5に示した。基準投与量である2,500 mg/m^2/日を境界として，2,500 mg/m^2/日以上の高用量群17症例と2,500 mg/m^2/日未満の低用量群33症例におけるHFS発現率はそれぞれ94%，69%と高用量群で高い傾向にあったが，有意差は認めなかった（p=0.07）。一方，グレード2以上のHFS発現率はそれぞれ52%，6%と高用量群で有意に高かった（p=0.0004）。

Ⅲ. 考　察

大腸癌治療ガイドラインではステージⅢ大腸癌に対する術後補助化学療法として，2010年版より5-FU系薬剤単独に加え，オキサリプラチン併用療法も推奨療法に加わった。しかし，その対象選択に当たっては本邦における良好な手術成績を勘案し，生存期間の上乗せ効果のみならず，有害事象および医療コストを十分に考慮すべきとされている[1,4]。われわれはステージⅢbをはじめとする再発高リスク症例に対して，年齢やPSなどを考慮しオキサリプラチンの適応を個別に判断している。また，欧米ではオキサリプラチン併用療法が第一に推奨され高頻度に行われているものの，高齢者，特に75歳以上においては補助化学療法そのものが20～30%以下にしか行われておらず，内容も5-FU系単剤療法が中心となっている[5,6]。したがって，補助化学療法における5-FU系単剤療法は世界的にみても未だ中心的治療法であり，高齢者やPSの悪い症例に使用されることも多く，また，手術後早期に治療開始となる点からも安全性が非常に重要となる。とりわけ問題となるのは生命を脅かす可能性のある骨髄毒性や腸管毒性である。カペシタビンは骨髄毒性や腸管毒性の軽減を意図して開発された薬剤であり[7]，実際X-ACT試験においてもカペシタビン療法の骨髄毒性，下痢はそれぞれ全グレード（グレード3/4）で32%（2%），46%（11%）と5-FU/LV静注療法の63%（26%），64%（13%）に比べて有意に発現頻度が低いことが示された[2]。本邦では，大腸癌に対するカペシタビンの使用経験が浅く安全性の報告は少ないが，須藤らにより47例のステージⅢ大腸癌術後補助化学療法としてのカペシタビンの使用経験が報告されている[8]。骨髄毒性，下痢は全グレードにおいてそれぞれ12%，4%と低く，グレード3以上の毒性は認めなかった。自験例でも骨髄毒性，下痢は全グレードで4%，6%と発現は低頻度であり，グレード3以上の毒性としては血小板減少1例（2%）のみであった。経口フッ化ピリミジン薬剤の毒性に人種差があることは報告されているが[9]，須藤らの報告や自験例における骨髄毒性と下痢はX-ACT試験より大幅に低い頻度であり，欧米諸国に比して本邦ではカペシタビンがさらに安全に投与できることが示唆された。また，大腸癌ガイドラインにおけるもう一つの推奨補助化学療法であるUFT/LV内服療法はNSABP C-06試験で下痢を74%（グレード3は29%）[10]，本邦における角田らの99例の検討では下痢を33%（グレード3は6%）に認めた[11]。UFT/LV内服療法においても日本人では下痢の発現頻度が低かったが，それでも33%の下痢を認め，そのうちグレード3が6%でほとんどが入院加療を要したことを考えると，同一試験での比較ではないことを勘案してもカペシタビン療法の腸管毒性の少なさは際立っているといえる。その結果として，カペシタビン療法の8コース治療完遂率はX-ACT試験で83%，須藤らの報告で90%，自験例では96%といずれも同様に高かった。治療開始時投与予定量の平均は2,395 mg/m^2/日であることからも十分な投与量設定であり，実内服量の平均は2,231 mg/m^2/日で相対用量強度（実内服量/治療開始時予定投与量）の平均は93%と高く，高い完遂率のみならず減量の必要性が少なく，実際に十分量の投与が可能であったことが示された。

カペシタビン療法を継続する上で問題となるのはHFSである。X-ACT試験でのHFSは全グレードで60%，うちグレード3が17%，須藤らの報告ではそれぞれ87%，6.4%，自験例では78%，4%であり，いずれの検討でも高頻度に認めている。HFSは骨髄毒性や腸管毒性と異なり，生命を脅かすことはないため過小評価しがちであるが，苦痛が強くなれば内服コンプライアンスの低下につながるため，適切な管理にてquality of life（QOL）を維持する必要がある。自験例ではグレーディングに迷った場合は低いグレードに判定し，安易な休薬や減量を行わなかったが，治療中止に至った2例はいずれもHFSのために治療継続の理解が得られなかった症例であった。HFSが発現するコースの中央値は2コースで，全例5コース以内と比較的早期から発現することが多いため，化学療法開始時からのビタミンB_6や保湿剤の投与および日常生活における手足のケアが大切であり，外来看護師や薬剤師の協力も得て患者指導を行うことが望ましい。HFSの悪化を認める際には早めに皮膚科での受診を促し，比較的軽症のうちに対処して重症化を防ぐことが肝要である。QOLや完遂率の向上のみを求めるような安易な休薬・減量は避けるべきであるが，X-ACT試験においてもカペシタビン減量時の治療効果への影響は認められず[12]，継続可能な適正用量に休薬・減量することも重要である。

経口剤の欠点として，体表面積に従った添付文書の錠数設定では基準投与量2,500 mg/m^2/日を中心に開始時投与量が2,300～2,700 mg/m^2/日の範囲でばらつきが生じる。自験例において，開始時投与量が2,500 mg/m^2/日以上となる高用量群は2,500 mg/m^2/日未満の低用量群に比べ，HFS発現率が有意差はないものの高い傾向にあり，グレード2以上のHFS発現率は高用量群で有意に高かった。治療を完遂できず中止となった2例についても，開始時投与量は2,500 mg/m^2/日を超えていた。UFT/LV内服療法におけるコンプライアンスでも同様の報告がみられ，Meguroらは大腸癌術後補助化学療法

で，UFT/LV内服開始時の体表面積当たりの投与量が多い症例では内服コンプライアンスが有意に悪いことを示した[13]。カペシタビンは服用する錠数が多く内服しづらいといわれることがあるが，逆に1錠ずつの減量により，投与量を大幅に落とすことなく，きめ細かな用量設定が可能になるという利点を有するととらえることもできる。添付文書の設定錠数が体表面積当たりどれぐらいの量に相当するのかを計算し，基準の2,500 mg/m^2/日より高用量になる場合は年齢，PS，腎機能など他の投与量調整因子とともに検討し，初期からの減量やHFS発現時に早めの減量を考慮するなど工夫を行うことも必要である。

カペシタビン療法は高頻度のHFSというデメリットがあるものの，腸管毒性が低いことは特筆すべき長所であり，消化管術後という観点からも非常に使いやすい利点を有しているといえる。また，カペシタビン療法は欧米や本邦で効果や安全性のみならず，医療経済学的にも優れていることが示され[14,15]，大腸癌術後補助化学療法における5-FU系標準治療薬と考えられる。本邦において行われているステージⅢ大腸癌補助化学療法に関する大規模試験として，JCOG0205（5-FU/LV静注療法とUFT/LV内服療法の比較），JCOG0910（カペシタビン内服療法とS-1内服療法の比較），ACTS-CC（UFT/LV内服療法とS-1内服療法の比較）[16]がある。これら5-FU系薬剤どうしの効果や有害事象の比較の最終結果が得られるまでは，標準治療であるカペシタビン内服療法を実地臨床において安全に使いこなすことが重要である。骨髄毒性や腸管毒性など重篤な有害事象が少なく安全であることを基盤として，高頻度に起こるHFSを適切な処置・休薬・減量で対処することで，十分な投与量とQOLのバランスを保ちながら治療完遂することが可能である。

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Original Paper

The Features of Late Local Recurrences Following Curative Surgery for Rectal Cancer

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Key Words: Locally recurrent rectal cancer; Late onset recurrence; Clinicopathological character; Early onset recurrence.

ABSTRACT

Background/Aims: Rectal cancers are characterized by high incidence of local recurrence after curative surgery, in some cases it occurs after 5 years. To determine the features of late locally recurrent rectal cancer (LRRC) is important for its management. **Methodology:** The medical records of 110 patients with LRRC after curative surgery were reviewed. We examined the relationship between the interval between surgery and appearance of LRRC and various clinicopathological factors by dividing patients into the early (recurrence before 5 years after surgery) and late (recurrence after more than 5 years) recurrence groups. **Results:** In the late-recurrence group (n=7), well-differentiated adenocarcinoma was significantly higher (p=0.0031) and venous invasion was significantly lower (p=0.0105) than the early-recurrence group (n=113). Multivariate Cox regression analysis identified histological grade and venous invasion of primary lesion as independent predictors for early-onset LRRC (p=0.0396 and p=0.0009, respectively). The presence of symptoms at the time of diagnosis was the only factor that significantly related to resectability of LRRC (p=0.015). **Conclusions:** For detection of asymptomatic LRRC, which can lead to curative resection, follow-up program after curative resection of rectal cancer should be designed based on the histological grade and venous invasion of primary tumor.

INTRODUCTION

Local recurrence of rectal cancer (LRRC) is a difficult problem after curative surgery for primary advanced rectal cancer. A multi-center study indicated that the rate of local recurrence was 8.8% (145/1647) after curative resection of rectal cancer and this rate was higher than that of pulmonary (7.5%, 124/1647) and hepatic recurrence (7.3%, 121/1647) (1).

Surgical intervention is currently one of the best treatment choices for LRRC and curative treatment can be provided only by radical surgery (2-6). According to several reports that discussed the postoperative prognostic factors for LRRC, R0 resection is the only reliable prognostic factor (7). Early detection of LRRC is important in terms of achieving R0 resection. The interval between the cure of primary tumor and local recurrence (LR) is usually short; 50% of LRs appear during the first year from the diagnosis of the primary tumor (8). However, long-term follow-up of patients who had undergone curative surgery for rectal cancer demonstrated that the rate of late-onset LR (defined as >5 years after curative surgery) was 11% (9). Longer follow-up may be more appropriate for assessment of patients with locally advanced rectal cancer based on data from two studies (10,11) that showed continuing risk of recurrence after 5 years. Despite these facts, after 5 years, the need for further examination and visits are left to the discretion of the patient and physician (12) and follow-up programs is still controversial (1).

The aim of the present study was to examine the features of LRRC, especially to investigate the relationship between clinicopathological features and the interval between R0 resection and relapse.

METHODOLOGY

The medical records of 110 patients who were admitted to Osaka University and Osaka Medical Center for Cancer and Cardiovascular Diseases due to LRRC after curative resection of rectal cancer between 1982 and 2006 were reviewed retrospectively. In this study, none of the patients received preoperative chemotherapy or irradiation for primary rectal cancer. After surgery for the primary rectal cancer, patients with stage III/IV tumor received 5-fluorouracil-based chemotherapy. Postoperative surveillance was carried out according to clinical evaluation, laboratory tests (including serum carcinoembryonic antigen (CEA) concentration), abdominal CT/US, chest radiograph and colonoscopy.

In this study, local recurrence-free survival after curative resection of rectal cancer was defined as an interval between the time of primary rectal surgery and diagnosis of LRRC by clinical imaging. We examined the relationships between the interval of first appearance of LRRC and various clinicopathological factors by dividing patients into the early-recurrence group (n=103, median

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duration of LRRC onset 1.59 years; range 0.22-4.83) and the late-recurrence group (n=7, median duration of LRRC onset 6.02 years; range 5.02-8.32). Late-recurrence is often defined as recurrence occurring more than 5 years after the primary surgery. The selection of the 5-year period is based on the recommended practice of postoperative surveillance after surgery for CRC of 5 years (1,12). However, several studies indicated that the risk of LRRC after curative resection extends beyond the 5-year period (9,10). Therefore, to assess the features of late local recurrences and to provide important insights into the effective postoperative follow-up schedule, we selected the above follow-up period for late local recurrence.

Statistical analysis

Continuous data were expressed as median and range. Statistical analysis was

performed using the χ^2 test or Fisher exact test for categorical data and Mann-Whitney U test for non-parametric data. The Kaplan-Meier method was used to examine disease-free survival and the log-rank test was used to examine statistical significance. Prognostic factors were evaluated by univariate and multivariate analyses (Cox proportional hazard regression model). A p value less than 0.05 was considered significant. Statistical analysis was performed using JMP software (SAS Institute Inc, Cary, NC, USA).

RESULTS

Patient characteristics

Patient characteristics are listed in **Table 1**. As expected, the primary lesions in patients with LRRC were advanced, *i.e.* tumor invasion greater than sub-serosal was noted in 89% (98/110) of the patients, lymphatic invasion in 83% (91/110) and venous invasion in 63% (69/110). In total, 78 patients received postoperative adjuvant therapy (5-fluorouracil-based chemotherapy) after curative resection of the primary rectal cancer.

Period between curative resection of rectal cancer and appearance of first LRRC

The median period between curative surgery for rectal cancer and the appearance of first LRRC was 1.69 years (range; 0.22-8.23). Extremely late onset local recurrences occurred in 7 patients. The distribution of the time period between curative resection for primary rectal cancer and appearance of first LRRC was 31% (34/110) within the first year, 77% (85/119) within the first 3 years and 94% (103/110) within the first 5 years (**Figure 1**).

Clinicopathological findings and time period between primary resection of rectal cancer and LRRC

Table 1 lists the characteristics of patients of the early-recurrence and late-recurrence groups. Among the primary lesion-related factors, the proportion of patients with well-differentiated carcinoma was significantly higher in the late-recurrence group (p=0.0031) and the extent of venous invasion was significantly lower in the late-recurrence group (p=0.0105). Among the locally recurrent lesion-related factors, there were no significant differences in tumour diameter or serum level of CEA at the time of diagnosis.

Factors related to early-onset LRRC

Univariate analysis showed that venous invasion and histological grade of the primary lesion were significantly (p<0.05) associated with early recurrence (**Table 2**,

TABLE 1. Patient characteristics/clinicopathological findings and duration of LRRC onset.

		Onset of local recurrence		
	Total (n=110)	Early (n=103)	Late (n=7)	p value
Age (years)	62 (32-82)	62 (32-82)	63 (55-79)	0.2951
Gender (M:F)				
Male	74	68	6	0.4229
Female	36	35	1	
Primary lesion related factors				
Tumor location (Rb/others)				
Rb	58	55	3	0.7053
Others	52	48	4	
Depth of invasion *				
~mp	12	10	2	0.1683
ss (a)~	98	93	5	
Lymph node metastasis (±)				
Positive	60	57	3	0.7603
Negative	50	46	4	
Histological grade (well/others)				
Well	50	43	7	0.0031
Others (mod, por, muc)	60	60	0	
TMN stage (I, II, III, IV)				
I+II	46	42	4	>0.9999
III+IV	65	62	3	
Venous invasion				
Positive	69	68	1	0.0105
Negative	41	35	6	
Lymphatic invasion				
Positive	91	86	5	0.3477
Negative	19	17	2	
Post operative adjuvant therapy				
Done	78	75	3	0.1903
Not done	32	28	4	
Locally recurrent lesion related factors				
Tumor diameter of LRRC (cm)	3.5 (1.3-11.0)	3.8 (1.3-11.0)	3.0 (2.3-10.0)	0.8219
Serum CEA at the time LRRC was diagnosed (ng/mL)	7.7 (0.9-10222)	8.0 (0.9-1022)	7.7 (0.9-121)	0.7704

*mp: cancer invading into the muscularis propria, ss (a): cancer invading into the subserosa or the adventitia.

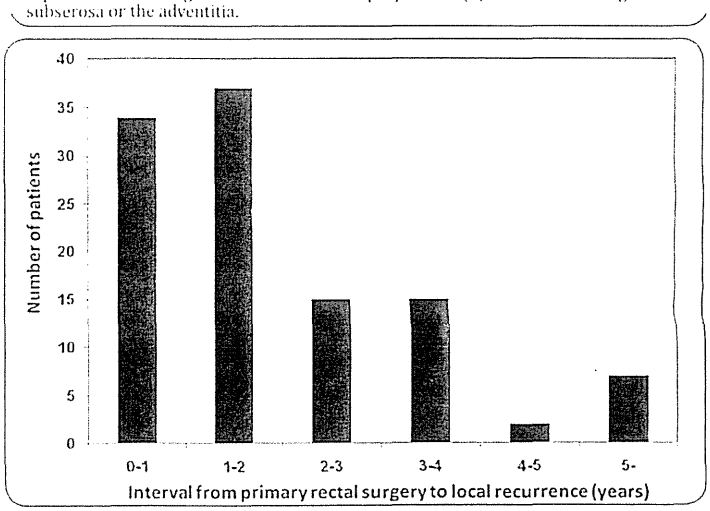

FIGURE 1. Distribution of the time period between curative resection for primary rectal cancer and first appearance of LRRC.

TABLE 2. Factors relating to early LRRC.

			Multivariate analysis	
	Total (n=110)	Univariate analysis, *p*-value	Relative risk (95% CI)	*p*-value
Gender (M:F)	130			
Male	74	0.1941		
Female	36			
Tumor location (Rb/others)				
Rb	58	0.4329		
Others	52			
Depth of invasion				
~mp	12	0.2453		
ss (a)~	98			
Lymph node metastasis (+/-)				
Positive	60	0.1901		
Negative	50			
Histological grade (well/others)				
Well	50	0.015	0.65 (0.436- 0.980)	0.0396
Others (mod, por, muc)	60			
TMN stage (I,II/III,IV)				
I+II	46	0.117		
III+IV	65			
Venous invasion				
Positive	69	0.0003	2.58 (1.347-3.146)	0.0009
Negative	41			
Lymphatic invasion				
Positive	91	0.2034		
Negative	19			
Post operative adjuvant therapy				
Done	78	0.5117		
Not done	32			

*mp: cancer invading into the muscularis propria; ss (a): cancer invading into the subserosa or the adventitia.

TABLE 3. Resectability of LRRC in early and late onset recurrent group.

	Interval from primary rectal surgery to local recurrence		
	Early onset group (n=103)	Late onset group (n=7)	*p* value
Resection of LRRC			
Done	71 (69%)	4 (57%)	0.6773
Not done	32	3	

TABLE 4. Factors relating to resectability of LRRC.

	Resection of LRRC		
	Done (n=75)	Not done (n=35)	*p* value
Tumor diameter of LRRC (cm)	3.5 (1.0-11.0)	4.5 (2.0-7.0)	0.3378
Serum level of CEA (ng/mL) at the time of diagnosis	7.1 (0.9-1022)	8.5 (1.0-318)	0.5864
Symptoms at the time of diagnosis*			
+	23	15	0.0115
-	37	6	

*There were no records as for symptoms at the time when LRRC was diagnosed in 19 patients.

Figure 2a,b). Multivariate Cox regression analysis identified histological grade and venous invasion of the primary lesion as independent predictors for early LRRC (p=0.0396 and p=0.0009, respectively, **Table 2**).

Resection of LRRC

Seventy five patients underwent resection of LRRC with curative intent, the other 35 patients had unresectable synchronous distant metastasis or highly advanced unresectable local recurrent lesion. The proportion of patients who underwent resection of LRRC was not different between the early- and late-recurrence groups (p=0.677, **Table 3**). Analysis of factors related to resectability of LRRC indicated that the presence of symptoms at the time of diagnosis was significantly related to resectability of LRRC (p=0.015, **Table 4**), but not tumor diameter of LRRC or serum level of CEA at the time of diagnosis.

DISCUSSION

Several reports have discussed the risk factors of LRRC after curative resection of rectal cancer and concluded that circumferential resection margin, depth of tumor invasion and lymph node metastases are risk factors for local recurrence (13-16). In addition to these factors, it is also important to know those variables that relate to the early/ late onset of local recurrence because they may provide useful information to determine the most appropriate follow-up after curative resection of rectal cancer. A number of studies suggested the possible role of preoperative CRT in delaying local failure onset (17,18). However, little is known about the factors that relate to early local recurrence after curative resection of rectal cancer. Our results indicated that patients with venous invasion of the primary rectal cancer or poorly-differentiated primary rectal cancer should be followed-up carefully for LRRC within the first 3 postoperative years and that the need for long-term follow-up (>5years) seems to be low. On the other hand, patients with relatively low-grade malignancy (*i.e.* those with well-differentiated primary rectal cancer and no venous invasion of the primary rectal cancer) need to have prolonged follow-up more than 5 years.

Maetani *et al.* (19) reported that the late onset of first recurrence was a favorable indicator. Nevertheless it is important to detect LRRC at an early stage for a curative resection since our data indicated that the existence of any symptoms was significantly related to resectability of LRRC. Detection of LRRC before the appearance of symptoms requires suitable follow-up based on the characteristics of LRRC. Several reports have also indicated that extensive follow-up can lead to early detection and a greater number of re-resections of local recurrence (15,20-23).

In Japan, most institutions adhere to intensive follow-up programs that typically include measurement of serum tumor marker every 3 months for the first 3 years and every 6 months for the next 2 years, hepatic imaging and chest x-ray every 6 months, pelvic CT for rectal cancer every year and colonoscopy every 1 to 2 years (1). In the present study, among the locally recurrent lesion-related factors, there were no significant differences between the groups in tumour diameter of LRRC, serum level of CEA at the time of diagnosis of LRRC and the proportion of patients who could undergo resection of LRRC with curative intent. These findings indicated that in our study series, late LRRC was not caused by delay of detection of relapse, but by the late-onset or slow growth rate of LRRC.

Our data indicates that patients with venous invasion of rectal cancer or poorly-differentiated rectal cancer

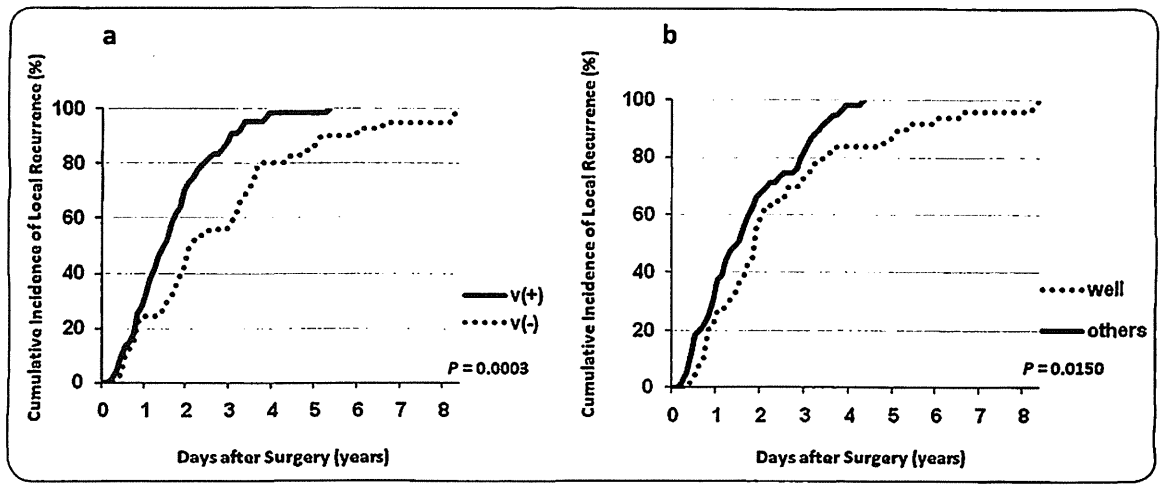

FIGURE 2. Cumulative incidence of local recurrence. Venous invasion (a) and histological grade (b) of primary lesion were significantly associated with early onset of LRRC ($p<0.05$).

might be better to undergo intensive follow-up for LRRC within the first 3 postoperative years, whereas those with tumors associated with relatively low malignant features need to be under long-term follow-up (>5 years). This study is too small to draw definitive conclusions, but it provides meaningful information for the management of patients after curative resection of rectal cancer.

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Clinical Trial Notes

Prospective Feasibility Study to Evaluate Neoadjuvant-synchronous S-1 + RT for Locally Advanced Rectal Cancer: A Multicenter Phase II Trial (UMIN ID: 03396)

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In Western countries, the standard treatment for locally advanced rectal cancer is preoperative chemoradiotherapy followed by total mesorectal excision. However, in Japan, the treatment results without preoperative chemoradiotherapy are by no means inferior; therefore, extrapolation of the results of preoperative treatment in Western countries to Japan is controversial. We consider that survival may be improved by preoperative chemoradiotherapy with new anticancer agents as they are expected not only to decrease the local recurrence rate but also to prevent distant metastases. We are conducting a multicentre Phase II study to evaluate the safety and efficacy of neoadjuvant chemoradiotherapy using S-1 in patients with locally advanced rectal cancer. The primary endpoint is the rate of complete treatment of neoadjuvant chemoradiotherapy. Secondary endpoints are the response rate of neoadjuvant chemoradiotherapy, short-term clinical outcomes, rate of curative resection and pathological evaluation. The short-term clinical outcomes are adverse events of neoadjuvant chemoradiotherapy and surgery-related complications. Thirty-five patients are required for this study.

Key words: rectal cancer – neoadjuvant chemoradiotherapy – S-1

INTRODUCTION

The standard treatment for locally advanced rectal cancer is well known to differ between Japan and Western countries. In Western countries, multimodal therapies such as preoperative short-term intensive radiotherapy or conventional long-term radiotherapy in combination with 5-fluorouracil (5-FU)-based chemotherapy have gained widespread acceptance for the treatment of locally advanced rectal adenocarcinoma (1). These treatments provide improved local control when compared with surgery alone, although only one study has shown a survival benefit (2). The local control benefit of preoperative radiotherapy remains relevant even in the era of total mesorectal excision (TME) (3). The addition of chemotherapy to preoperative conventional long-term radiotherapy (RT) has been demonstrated to be feasible, with enhanced tumoricidal effects (4). In Japan, TME or tumor-specific mesorectal excision followed by adjuvant chemotherapy without preoperative treatment is a standard strategy, and lateral lymph node (LN) dissection is added in patients with lower rectal cancer (5). The results of the surgical treatment without RT in Japan are by no means inferior to those in Western countries that do use RT with surgery. Therefore, extrapolation of the results of preoperative treatment in Western countries to Japan is controversial.

Recently, new anticancer agents have markedly improved the response rate and prognosis of unresectable and recurrent colorectal cancer. Locally advanced rectal cancer may be controlled by the addition of new anticancer agents. In Western countries, new treatment strategies have been tested, including the addition of new cytotoxic drugs and/or

molecular-targeted drugs to fluoropyrimidine-based chemoradiotherapy concurrently or before chemoradiotherapy (6,7). On the other hand, there is a concept that oral chemotherapy has major advantages over intravenously administered treatment in terms of pharmacoeconomic considerations and patient preferences, because oral treatment can be administered on an outpatient basis, thereby reducing the length of patients' hospital stays (8). Over time, the role of oral chemotherapy in the treatment of malignant disease is expected to become increasingly significant. S-1 (TS-1, Taiho Pharmaceutical) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil) and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1:0.4:1 (9,10). The rate of response to treatment with S-1 alone exceeded around 40% in two Phase II trials involving patients with advanced or recurrent colorectal cancer (11,12). Furthermore, S-1 has been demonstrated to enhance the radiation response of human colon cancer xenografts resistant to 5-FU (13). In 2011, Sadahiro et al. (14) reported that the efficacy of chemoradiotherapy with S-1 seems to be equivalent to the efficacy reported for chemoradiotherapy with capecitabine. However, the dose of S-1 (100 mg/m^2) in our study is different from that of S-1 (80 mg/m^2) in the above-mentioned study. We planned the present study in order to obtain the more excellent efficacy.

We consider that survival may be improved by preoperative treatment with new anticancer agents, S-1 as they are expected to decrease local recurrence due to their effect of bulk reduction, to obtain a high rate of complete treatment of neoadjuvant chemoradiotherapy and to prevent distant metastases.

We conducted our own Phase II study to confirm the safety and efficacy of the chemoradiotherapy using S-1 before surgery. Our administration schedule of S-1 is 100 mg/m^2/day for 5 days, and followed by no administration for 2 days. The total dose of S-1 per week is 500 mg/m^2/week. On the other hand, S-1 at 80 mg/m^2/day is the standard dose used as a single agent for systemic therapy, which gives a total of 560 mg/m^2/week. Because the total dose of S-1 per week in our study (500 mg/m^2) is less than the standard amount per week (560 mg/m^2), Phase I trial has not been conducted.

The institutional review board of each participating center approved the study protocol. This study was registered at the UMIN Clinical Trial Registry as UMIN000003396 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF THE OITA TRIAL

Purpose

To evaluate the feasibility and efficacy of neoadjuvant CRT for locally advanced rectal cancer.

Study Setting

A multi-institutional (17 specialized centers), interventional Phase II trial. This study is registered with UMIN-CTR, number C003396.

Resources

This study was supported by a part of Grants-in-Aid for Clinical Cancer Research from the Japanese Ministry of Health, Labour and Welfare (22-Clinical Cancer-027).

Endpoints

The primary endpoint is the rate of complete treatment of neoadjuvant chemoradiotherapy. Secondary endpoints are the response rates of neoadjuvant chemoradiotherapy, short-term clinical outcomes, rate of curative resection and pathological evaluation. The short-term clinical outcomes are adverse events of neoadjuvant chemoradiotherapy, surgery-related complications. The response rate is evaluated using RECIST, and the adverse events including preoperative chemoradiotherapy and surgical complication are evaluated using CTCAE v4.0.

Eligibility Criteria

Tumors are staged according to the TNM classification system.

Inclusion Criteria

For inclusion in the study, patients must fulfill the following requirements before neoadjuvant chemoradiotherapy: (i) histologically proven rectal carcinoma; (ii) tumor located in the rectum (Ra,Rb,P); (iii) cancer classified as T3–4, N0–3 and M0, according to the TNM classification system; (15) no bowel obstruction; (v) age >20 and <80 years; (vi) sufficient organ function; (vii) no history of gastrointestinal surgery; (viii) no history of chemotherapy or radiotherapy and (ix) provide written informed consent.

Exclusion Criteria

The exclusion criteria are as follows: (i) synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*; (ii) critical drug sensitivity to S-1; (iii) severe pulmonary emphysema, interstitial pneumonitis or ischemic heart disease; (15) pregnant or lactating women; (v) severe mental disease; and (vi) continuous systemic steroid therapy.

Treatment Method

For the locally advanced rectal carcinoma, two cycles of neoadjuvant chemotherapy with S-1 (100 mg/m^2 on Days 1–5, 8–12, 22–26 and 29–33) is administered, and

irradiation (total 45 Gy/25 fr, 1.8 Gy/day, on Days 1–5, 8–12, 15–19, 22–26 and 29–33) is performed.

Additional Treatment

Resection of the rectum with D3 lymphadenectomy is performed according to the Japanese Classification of Colorectal Carcinoma (Japanese Society for Cancer of the Colon and Rectum. General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus, 6th edn, 1998 (in Japanese)). Operation is performed during the 4th and 8th week after the end of the neoadjuvant chemoradiation therapy. Proposed operations are anterior resection with or without covering ileostomy and anterior peritoneal resection. When the preoperative and intraoperative findings demonstrate that the lateral LNs metastasis is not suspected, lateral LNs dissection is not performed. The adjuvant chemotherapy is not specified.

Follow-up

Patients are observed by their surgeon every 3–4 months after operation. Blood tests, abdominal computed tomography and plain chest X-ray are carried out at each visit.

Study Design and Statistical Method

This trial is designed to achieve the feasibility and efficacy of neoadjuvant CRT with S-1 for locally advanced rectal cancer in terms of completion rate, efficacy and adverse events of neoadjuvant chemoradiation and curative resection rate. If the feasibility and efficacy of neoadjuvant CRT with S-1 is shown, neoadjuvant CRT with S-1 will be the preferred treatment. The planned sample size is 35 patients, which was calculated by Southwest Oncology Group's two-stage attained design (16) based on a target rate of treatment completion of 90% and a minimum completion rate of 70%, with an a error of 0.05 and b error of 0.15.

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Conflict of interest statement

None declared.

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