●特 集● 術前化学療法の新展開

大腸癌に対する術前化学療法

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Summary

Surgery continues to play an important role in the curative treatment of gastrointestinal cancer. Recently, considerable progress has been made in chemotherapy and radiotherapy. In particular, chemotherapy with FOLFIRI and FOLFOX has prolonged survival in patients with colorectal cancer. Molecular-targeted agents have also enhanced the effectiveness of chemotherapy. However, radical resection offers the potential for a cure and is unsurpassed by any other treatments. Nonetheless, further improvement in survival is unlikely to be achieved by surgery alone. Studying how treatment regimens highly effective against unresectable or recurrent colorectal cancer can be adapted to patients with resectable disease is thus an important issue. **Key words**: Advanced colorectal cancer, Neoadjuvant chemoradiation therapy, Neoadjuvant chemotherapy, **Corresponding author**: Takeo Sato, Department of Surgery, Kitasato University School of Medicine, 2-1-1 Asamizodai, Minami-ku, Sagamihara, Kanagawa 252-0304, Japan

要旨 消化器癌の根治的治療は未だに外科治療である。近年，化学療法や放射線療法は格段の進歩を遂げた。特に，大腸癌の化学療法はFOLFIRI，FOLFOX療法らの多剤併用化学療法によって生存期間の延長をもたらした。さらに，分子標的薬の出現により治療効果の上乗せがもたらされた。しかし，治癒をもたらす治療は根治的切除であり，これを凌駕することはない。一方，手術治療のみでのこれ以上の生存率の向上も困難である。このため，切除不能・再発大腸癌で高い治療効果のある治療法を切除可能な症例へいかに応用できるかが課題となる。

はじめに

消化器癌の根治的治療は未だに外科治療であるが，化学療法，放射線療法も格段の進歩を遂げた。特に，切除不能・転移再発大腸癌に対する化学療法は，1990年代後半から持続5-FU療法にcamptothecin（CPT-11）や，oxaliplatin（L-OHP）を加えたFOLFIRI療法，FOLFOX療法らの多剤併用化学療法によって生存期間の延長をもたらした。さらに，分子標的薬である抗VEGF抗体治療薬bevacizumab，抗EGFR抗体治療薬cetuximabやpanitumumabも実臨床で投与できるようになり，治療効果の上乗せがもたらされた。しかし，治癒をもたらす治療は根治的切除のみである。大腸癌に対する外科的治療の根治性は，腫瘍の占居部位や進行度で異なる。拡大手術か縮小手術を行うか，患者のquality of life（QOL）か根治性をとるか，正しい術式選択をすることが重要である。

大腸癌の外科治療は，他の消化器癌と比べても大きな役割を果たしている。原発巣だけでなく，転移巣も切除することで治癒が望めるからである。しかし，肝切除を行った後の約50～60%で再発を認める。手術のみでのこれ以上の生存率の向上は困難であり，このため，切除不能・再発大腸癌で高い治療効果のある治療法を切除可能な症例へいかに応用できるかが課題となる。

本稿では，大腸癌の術前治療を中心とした補助化学療法の現状と今後について述べる。

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表 1 Neo-adjuvant Tx or Conversion Tx？

Neo-adjuvant Tx: 手術が“大”前提
Conversion Tx: 治療手段の変更
化学療法の効果により，
手術が可能となった場合！

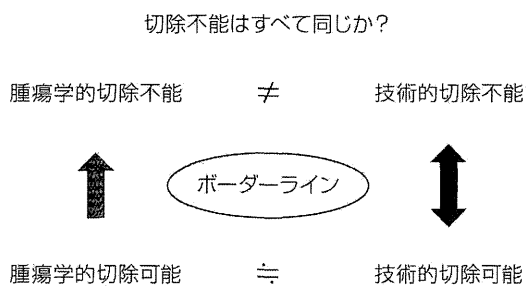

図 1 どのような治療戦略をとるか

Ⅰ．補 助 療 法

術後補助療法は，大腸癌治療ガイドライン[1]では以下のように記されている。R0 切除が行われた症例に対して，再発を抑制し予後を改善する目的で，術後に実施される全身化学療法である。治癒切除手術が行われた癌に対する補助化学療法の評価は，再発が確認されるまでの無再発生存期間（disease free survival: DFS）と生存期間（overall survival: OS）を指標として行われる。すなわち，術後補助化学療法は手術単独治療に毒性を加える治療のため，安全かつ統計学的にも十分な全生存期間の上乗せ効果が得られるものでなければならない。

結腸癌の「術後」補助化学療法の全生存期間への上乗せ効果は証明されている。特に，MOSAIC Trial[2]や NSABP C-07[3]，NO16968 試験[4,5]などの L-OHP を用いた化学療法が，5-FU/LV 療法に上乗せ効果があることが報告されている。一方，進行直腸癌の治療では，生存率の向上のみならず，独特の再発形式である局所再発のコントロールが重要な課題であるが，「術後」補助化学療法のエビデンスは本邦で行われた N・SAS-CC[6]の UFT 単独 1 年投与のみである。これは，欧米では手術＋化学放射線療法が標準治療と位置付けされているためと考える。しかし，術前・術後化学放射線療法では局所コントロールには優れているものの，生存率の向上に寄与する報告は乏しい。また，転移巣切除に関しての後の補助療法に関する大規模臨床試験の報告は皆無である。

1．術前化学療法と conversion therapy（表 1）

「術前」補助化学療法を定義する上で，「術後」補助化学療法の理論を規範として考えると，R0 切除を行うことが可能な症例に対して再発を抑制し，予後を改善する目的で術前に実施される全身化学療法となる。術前補助化学療法は手術前に毒性を加える治療のため，安全かつ統計学的にも十分な DFS，OS の上乗せ効果が得られ，また手術が安全に行われるものでなければならない。

一方，conversion therapy とは化学療法や（化学）放射線療法により切除不能癌を縮小して，手術に治療方法を変更することを指す。手術を予定していた症例の治療方法を化学療法に変更する場合も conversion therapy となるが，一般的には前者のみを指す。化学療法のみでは根治することは困難であるが，手術に治療方法を変更することによって根治の可能性が得られる。腫瘍学的切除不能の定義は侃侃諤諤されており，議論が分かれるが図 1 のように技術的切除不能癌やボーダーライン症例が conversion therapy の対象となる。

Ⅱ．原発巣に対する化学（放射線）療法

1．結 腸 癌

結腸癌では，根治切除後の補助化学療法の上乗せ効果は多くの臨床試験で証明されてきた。近年では，Stage Ⅲ結腸癌症例で新規抗癌剤である L-OHP を用いた FOLFOX 療法[2]，FLOX 療法[3]，XELOX 療法[4,5]がいずれも術後補助療法において L-OHP が全生存率への上乗せ効果があることが明らかになった。しかし一方で，切除不能・再発癌で用いられる分子標的薬である抗 VEGF 抗体薬[7-9]，抗 EGFR 抗体薬[10]は上乗せ効果をもたらさなかった。

結腸癌切除可能症例における術前化学療法の意義は明らかではない。しかし，他臓器浸潤や高度リンパ節転移を伴う結腸癌の予後は不良である。また，十二指腸や膵頭部浸潤を伴う上行結腸癌の場合も，拡大手術により切除は可能となることもあるが，膵頭十二指腸切除術などの侵襲は大きい。これらの予後不良症例や拡大手術を要する症例で，術前補助療法を行うことにより，患者の予後や QOL の向上に貢献する可能性もある。原発巣に対する化学療法の効果に関するデータは乏しいが，Schrag らが直腸癌において術前の FOLFOX＋bevacizumab 療法で完全奏効（pathological complete response: pCR）が 27%という報告をした[11]。高い抗腫瘍効果は予後向上に貢献する可能性は示唆される。しかし，現状では明らかなエビデンスはなく，R0 切除がもっとも重要であることに異論はないであろう。

2．直 腸 癌

補助療法としての放射線療法には，術前または術後に行う外照射と術中直接照射がある。術中照射は，局所再発の原因である外科的剝離断端陽性例や不足例での局所制御を目的としている。電子線照射を施行することが多

いが，高線量率小線源を用いることもある[12,13]。使用される電子線のエネルギーは腫瘍の深さにより選択する。術中照射は外科的剝離面や遺残腫瘍部位を直視下に照射することができる。さらに，小腸や膀胱などの正常臓器の防護が可能であるが，管理および照射施設の問題から行える施設が限られる。

一方，術前・術後照射に関しては，各々利点と欠点がある。術前照射に関しては，原発巣の縮小により括約筋温存手術の適応の拡大し得る可能性がある。また，腫瘍への供給血管が切離されていないため，化学療法の腫瘍・リンパ節への接触が多く，化学療法の効果が多く得られる可能性がある。さらに，手術による生体の侵襲がないため，治療コンプライアンスが高いことや化学療法後に検体を摘出するため，化学療法の奏効が病理学的に診断でき，感受性試験となる可能性があるなどの利点があげられる。欠点としては，治療期間が長期化（手術までの期間が長期化）する。他臓器に微小転移が存在すると，照射・化学療法による免疫力の低下が惹起され，転移巣が増大する可能性がある。また，術後の合併症の危険性が高まる可能性がある。さらには，over diagnosisによるover therapyをしている可能性があることがあげられる。一方，術後照射群は術中所見・切除検体による正確な病期診断が可能で，治療症例を限定できる利点がある。欠点としては，術中操作による骨盤腔内へ落ち込んだ小腸に放射線を照射する可能性や手術侵襲後の治療のため，治療コンプライアンスが低下する可能性がある。

局所進行直腸癌に対する補助化学療法は，欧米を中心に多くの臨床試験が行われている。しかし，5-FU系抗癌剤を併用した化学放射線療法が主流になっているが，標準治療とされるレジメンはない。Swedish Rectal Cancer Trialでは，術前化学放射線療法が生存率の向上に寄与することが報告されたが[14]，その他の大規模臨床試験での追報告はみられない。一方，Guillemらは術前化学放射線療法でCRまたはCRに近い効果の得られた症例の予後がよいことを報告した[15]。

近年では，治療効果を高めるために術前化学放射線療法の内容が工夫され種々の報告がみられるようになった。

1990年のNIHの提言以降，直腸局所進行大腸癌の欧米での標準治療は化学放射線療法と手術療法の併用である。本邦では手術の治療成績がよいことから，化学放射線療法の検討が行われていないのが現状である。手術治療のRCTであるJCOG 0212，TME vs TME＋側方郭清の治療成績の結果が待たれるが，今後本邦でも補助化学放射線療法に関するRCTが行われることが望まれる。

Ⅲ．転移巣に対する術前化学療法

1．切除可能に対する術前化学療法（補助）

治癒的な肝切除が施行された症例でも，残肝再発が41～49%，次いで肺転移が20～30%であると報告されている[16]。このため，術前や術後に化学療法を施行して，残肝再発や肝外再発の抑制を試みてきた。しかし，現状では生存期間の延長を有意に延長させた報告はない。このようななかで，FOLFOX4を術前・術後に投与するEORTC 40983試験が行われた[17]。対象は転移個数が1～4個の治癒切除可能な症例で，手術単独群と術前・術後化学療法群とのRCTである。この結果は，intention-to-treat（ITT）解析では有意差は認めなかったが，適格例，切除例では，FOLFOX4投与群で3年無増悪生存期間（progression free survival: PFS）が36.2%で手術単独群（28.1%）よりも有意に高く，FOLFOX4群が生存期間の延長に寄与する可能性が示された。しかし，ITT解析では有意なPFSの差がなく，術後早期再発となる可能性がある化学療法中の他臓器転移出現例は肝切除適応から外れていること，FOLFOX4の完遂率の低さ（71.3%）などなどの批判的な意見も多く，解釈が難しい。しかし，欧米では術前・術後ともに補助化学療法のエビデンスが構築されていないものの，術前・術後の補助化学療法を推奨している。

切除可能症例での術前化学療法の利点は，腫瘍縮小によるR0手術の可能性や微小転移の抑制，生体内における化学療法の感受性の評価可能などが考えられる。一方，欠点としては転移巣以外の正常な組織への毒性，これに派生する合併症など，化学療法不応症例の腫瘍増大などが考えられる。治療中に腫瘍個数が増加する症例は，手術でも転移巣のコントロールが困難なことも多いが，切除の時期を逸した可能性も考えなくてはならない。

現状では，治癒し得る治療法は手術のみであり，術前補助化学療法に関して綿密に計画された臨床試験としては行うべきである。

2．切除不能・ボーダーラインに対する術前化学療法（conversion therapy）

大腸癌の肝転移の切除不能症例は，全身化学療法が第一治療選択となる。大腸癌の肝転移が切除可能か否かは，転移巣の大きさと分布，主要脈管浸潤の有無，残肝ボリューム，コントロール不能な肝外転移の有無，患者の全身状態，肝機能などによって決定されるが，施設間や外科医間でも見解は分かれる。さらに，系統的切除を行うことが多い欧米と部分切除を駆使する本邦では，術式に関して相違がある。したがって，切除の可否に関して

も，欧米と本邦では若干のずれが生じる。近年では全身化学療法の進歩により，化学療法後に手術可能となり，初診時切除不能症例でも，さらなる長期生存症例や根治症例も経験するようになった。CPT-11 や L-OHP，分子標的薬を用いることにより 11～37%で切除が可能になると報告されている[18-24]。

conversion therapy によって生存期間の延長が認められ，欧米でも注目を浴びるようになったのは CRYSTAL 試験の結果によると考えられる。同試験では FOLFIRI に cetuximab を併用することで，肝転移の R0 切除率が 4.5%から 9.8%に[25]，OPUS 試験でも *KRAS* 野生型患者に FOLFOX と cetuximab を併用することで R0 切除率が 4.1%から 9.8%へと[26]，いずれも 2 倍以上に増加している。切除不能な肝転移を有する大腸癌患者 111 例を対象にした CELIM 試験[24]では，術前化学療法として cetuximab を FOLFOX6 または FOLFIRI と併用した場合の奏効率および治療後の肝転移巣の切除率を第Ⅱ相無作為化試験により比較検討した。奏効率は FOLFOX6 群，FOLFIRI 群ともに同等に良好で 68% vs 57%，R0 切除率は FOLFOX6 群 38%，FOLFIRI 群 30%であった。FOLFOX や FOLFIRI といった標準的化学療法レジメンに cetuximab を併用することで良好な奏効率が得られ，肝転移巣切除の可能性が高まることが示された。この試験を行った Folprecht らにより，奏効率が上がるほど切除率が高くなる[27]ことも報告されている。一方，FOLFOX または XELOX に対する bevacizumab の上乗せ効果を検討した NO16966 試験[28]では，奏効率における bevacizumab の上乗せ効果は示されなかった。しかし，技術的に切除不能な肝限局転移症例を対象にした BOXER 試験[29]では，XELOX＋bevacizumab 療法を検討したところ，33% (10/30 例) が切除可能になったと報告されている。また，L-OHP ベースのレジメンではいわゆる blue liver (類洞拡張) が懸念されるが，bevacizumab の併用により blue liver が抑制される[30]という報告もある。

手術を何時行うかについての明らかな見解はない。しかし，6 コース以上の化学療法により肝切除後の合併症リスクが増加することが報告されていることから[31,32]，治療効果の発現までの期間が約 2～3 か月[33]ということも考慮して 4～6 コース終了時点で適切な評価を行い，可能であれば肝切除を行うことが望ましいと考える（図 2）。また，bevacizumab は血管新生抑制剤という性質上，術後合併症の増加などが懸念されたが，臨床試験では有意な上昇は認めていない[34,35]。肝切除までは半減期の 2 倍の約 5～8 週とした臨床試験が多い[34-36]。

現状では，どの化学療法剤，分子標的薬剤が conversion therapy に最も適しているかは明らかではない。したがって，患者状態，腫瘍状態を適切に評価して，治療方法を決定することが望ましい。

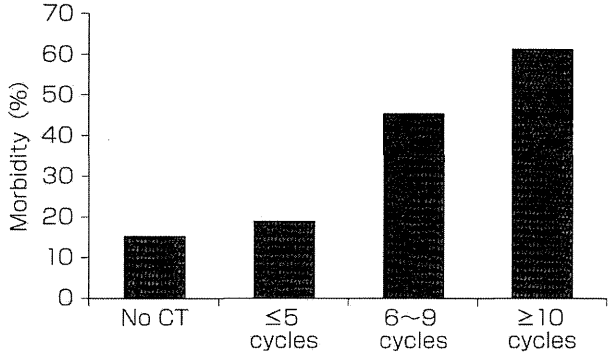

図 2 化学療法治療コース数と合併症[31]

おわりに

大腸癌化学療法の効果が認められるようになってから，まだ 10 年も経過していない。このため，まだ多くの可能性があるが，わかっていないことも多い。術後補助療法における L-OHP レジメンへの分子標的薬の上乗せ効果がないことは，われわれへの一つのサジェスチョンである。術前補助化学療法に関するエビデンスもまだ乏しく，今後のデータの蓄積が極めて重要である。現状でわかっていない clinical question の解消が，今後の新しい治療戦略につながると考えられる。

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特集

特集2　局所進行直腸癌に対する集学的治療

進行下部直腸癌に対する術前化学放射線療法の予後

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Relation between Outcomes and Response to Neoadjuvant Chemoradiotherapy in Locally Advanced Rectal Cancer: Sato T[*1], Ikeda A[*1], Naito M[*1], Ogura N[*1], Miura H[*1], Tsutsui A[*1], Nakamura T[*1] and Watanabe M[*1] ([*1]Department of Surgery, Kitasato University School of Medicine)

Objectives: To clarify the therapeutic effectiveness of neoadjuvant chemoradiotherapy (NCRT) with S-1 and irinotecan, we studied histopathological results and outcomes in a phase I / II study in patients with locally advanced rectal cancer treated at our hospital.

Subjects: We studied 76 patients enrolled in a phase I / II study of NCRT with S-1 (80 mg/m^2) and irinotecan (80 mg/m^2).

Results: The median follow-up was 4.6 years, and 20 patients (26.3%) had recurrence. The rate of recurrence according to tumor grade was 61.9% (13.21) in grade I, 24.0% (6/25) in grade II, and 3.3% (1/30) in grade III. Other types of cancer (outside of the radiation field) developed in 2 patients. Nine patients (11.8%) died, including 6 deaths (7.9%) from rectal cancer.

Conclusions: In grade III disease, only 1 patient with systemic metastases had recurrence. Among patients with grade I disease, a high proportion had distant metastases, irrespective of clinical characteristics. Our results suggest that treatment response to NCRT is related to outcomes in patients with locally advanced rectal cancer. Future clinical trials of NRCT in advanced lower rectal cancer should assess the relation between treatment response and outcomes. Ways to predict treatment response on the basis of biopsy specimens obtained before therapy should also be investigated.

Key words: Local advanced rectal cancer, Neoadjuvant chemoradiation therapy, S-1, CPT-11
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はじめに

わが国では大腸癌の罹患率は年々増加している．このまま罹患率の増加が続けば，2015年には，大腸癌（結腸癌＋直腸癌）患者は約17万人におよび，胃癌，肺癌を抜いて第1位となると予測されている[1]．欧米先進国においても大腸癌は肺癌についで癌による死因の第2位を占めており，世界的にみても大腸癌の予防・早期診断・治療法の開発は非常に重要な課題である．

進行直腸癌は進行結腸癌に比べて予後不良であり，治療では，全生存率の向上のみならず，独特の再発形式である局所再発のコントロールが重要な課題である．近年，全直腸間膜切除術（以下TME）は局所再発率の低下をもたらし，この方法は全世界で標準治療として受けられている．さらに，術後化学放射線療法が無再発生存率を向上させたGITSG 7175[2]の結果をから，米国のNIHはp-stage IIおよびIIIの直腸癌の標準治療として「切除＋術後化学放射線療法」を1990年

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から推奨している[3]．一方，その後に行われた術前放射線単独療法と手術単独との5つの比較試験では，術前放射線治療群の局所再発率が，手術単独群より明らかに低下した[4]．さらにSwedish Rectal Cancer Trial[5]では術前放射線療法の有意なsurvival benefitが証明された．一方，大規模第Ⅲ相試験であるEORTC22921試験は，化学療法併用の生存率向上を証明できなかった．しかし，その研究では，5年局所再発の制御は化学療法併用群が放射線療法単独群に比べ有意に優れており，5-FUベースの化学療法併用の意義が明らかになった[6]．これにより，術前の化学放射線療法が局所進行直腸癌の標準的治療として認められるにいたった．ただし放射線療法の線量，期間，照射範囲，および，併用薬剤の選択については一定の見解は得られていない．最近，Guillemらは術前化学放射線療法でCRまたはCRに近い効果の得られた症例の予後が良いことを報告し[7]，術前化学放射線療法によるDown Stagingと予後との相関も注目されている．

欧米が術前化学放射線療法＋TMEを標準化した一方で，わが国ではTMEに側方リンパ節郭清の局所再発率が欧米と同等であったため，補助放射線療法の大規模な臨床試験はほとんど行われなかった．このような状況でわれわれは，手術単独では局所再発のさらなる低下や生存率向上は望めず，化学，放射線療法の併用を検討する必要があると考えた．

そこで，テガフール・ギメラシル・オテラシルカリウム配合剤（S-1）のギメラシルが，癌の放射線感受性を著しく上昇させること[8]，塩酸イリノテカン（CPT-11）がTSmRNA量を低下[9]させてTS阻害時間を延長[10]することに注目した．また，5-FUはTopo-Ⅰを誘導し，TSとTopo-Ⅰは正の相関を示すことも知られていた[11,12]．TSを阻害する5-FU系抗癌剤とTopo-Ⅰ活性を阻害するCPT-11は作用機序が全く異なり，S-1とCPT-11の併用は理にかなっていると考えた．現在5Fuをベースとした化学放射線療法が標準治療とされており[3,13]，放射線療法とS-1，CPT-11の併用は理想的な組み合わせの化学放射線療法と考えた．臨床第Ⅰ相試験では，S-1とCPT-11の最大耐用量（MTD: maximum tolerated dose），および，推奨用量（RD: recommended dose）を決定し，病理学的奏効率を評価した．この結果，推奨容量内での奏効率が94.7％，pCR率が31.6％であり，治療効果がきわめて高いことが判明した[14]．さらに，Primary endpointを治療完遂率，Secondary endpointsを奏効率，安全性，局所再発率，全生存期間とした臨床第Ⅱ相試験を行った[15]．本稿では，中期予後を解析して，進行下部直腸癌に対する術前化学放射線療法の効果と予後の関係を検討した．

1 適格基準

組織学的検査が施行された，T3′, T4′, N0-3′の局所進行直腸癌患者のうち，Eastern Cooperative Oncology Group（以下ECOG）Performance Status 0-2の症例を対象とした．また，登録時年齢が20歳以上80歳以下で，前治療（放射線療法，化学療法，ホルモン療法など）が実施されておらず，主要臓器機能（骨髄，心，肺，肝，腎など）に高度の障害がないものに対象症例を限定した．

2 プロトコール

放射線照射は，直腸周囲1 cmに1.8 Gy/day，25日間分割照射とした（図1）．S-1は，80 mg/m^2/day，5日投与2日休薬で第1～5，8～12，22～26，29～33日目に経口投与する．CPT-11は第1, 8, 22, 29日目に静脈内投与した．CPT-11の投与量は，Phase Ⅰで得られたCPT-11 80 mg/m^2（Phase Ⅰ症例　では，40・60・70・80 mg/m^{2}を含む）投与とした（図2）．

3 対　象

術前化学放射線療法第Ⅰ・Ⅱ相試験にエントリーし，推奨容量（CPT-11 80 mg/m^2，S-1 80 mg/m^2）以下で治療が行われた76症例を対象とした．

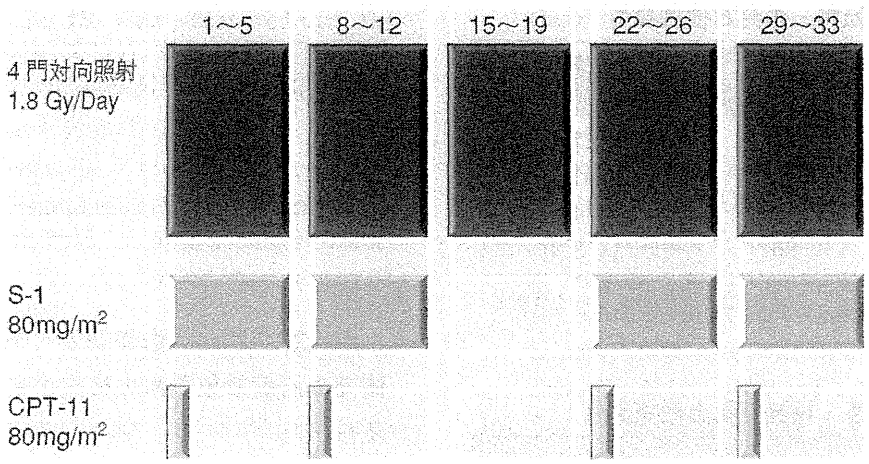

図1　プロトコール

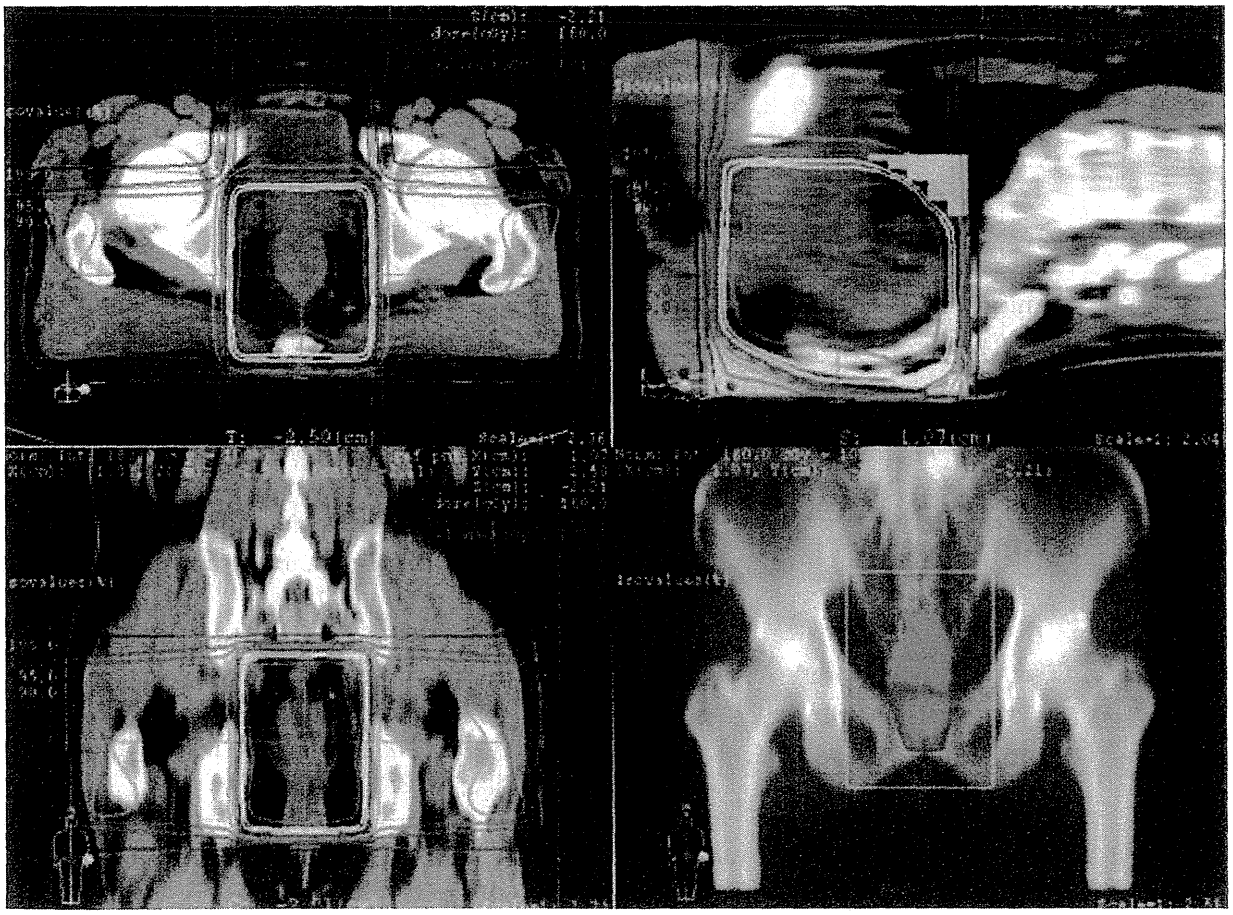

図2　放射線照射野

3 手　術

手術はTMEおよび両側自律神経温存しつつ両側側方リンパ節，すなわち，中直腸根リンパ節，内腸骨根リンパ節，閉鎖リンパ節のサンプリングを行った．括約筋温存手術の直腸肛門側の切離は，腫瘍下端から最低2 cm以上の切除距離を保ち施行し，肛門側縁が十分にとれない場合は　腹会陰式直腸切断術とした．

4 結　果

放射線照射線量およびS-1 80 mg/m^{2}は固定と

表1　転移・再発と他癌発生

病理学的奏効 n=76		再発 n=20
grade	n	n (%)
1	21	13(61.9)
2	25	6(24.0)
3	30	1(3.3)

Median Follow Up 4.6 yrs

表2　転移・再発臓器と他癌発生

	n (%)
肺	7(9.2)
肝臓	6(7.9)
大動脈周囲リンパ節	3(6.5)
全身	2(2.6)
骨盤内リンパ節	2(2.6)
原発性肺癌	2(2.6)
総　計	15(19.7)

Median Follow Up 4.6 yrs

して，CPT-11 40 mg/m^{2}を投与開始量とした．CPT-11 90 mg/m^{2}が最大の最大耐用量（MTD: maximum tolerated dose）で，CPT-11 80 mg/m^{2}が推奨用量（RD: recommended dose）であった．病理学的結果は，Grade 3（pCR）は30症例（39.5%），Grade 2は25症例（32.9%）で認められ，奏効率は72.4%であった．

観察期間中央値は4.6年で，遠隔転移再発症例数は20例（26.3%）であった．Grade別の再発率は，Grade Ⅰは13/21（61.9%），Ⅱは6/25（24.0%），Ⅲは1/30（3.3%）であった（**表1**）．再発臓器は，肝臓，肺が多く，続いて大動脈リンパ節転移であった（**表2**）．他癌発生は2例に原発性肺癌を認めた．また，死亡は9名で，原病死した症例は6例（7.6%）で，3例（6.5%）に他病死を認めた（**表3**）．

表3　死　亡

	n (%)
総　計	9(11.6)
原癌死	6(7.6)
他病死	3(6.5)

Median Follow Up 4.6 yrs

5 まとめ

Grade 3群の再発は全身転移をきたした1例のみで，Grade 1群では，臨床学的検討事項に関係なくきわめて高率に遠隔転移をきたした．NCRTの治療効果が局所進行直腸癌の予後に相関することが示唆された．治療効果と予後，治療前生検検体での治療効果予測の検討が最も重要であると考えられた．

おわりに

われわれの研究では，治療完遂率，短期予後および，pCR率，骨盤内再発率は今までの化学放射線療法を凌駕する有望な結果を得た．今後，さらなる検討を加える必要がある．

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CASE REPORT

Successful treatment of advanced gastric adenocarcinoma with portal tumor thrombosis by total gastrectomy following CDDP and S-1 therapy

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Abstract Gastric cancers with portal tumor thrombosis (GCPTs) are a rare entity, often concomitant with hematogenous metastases, and chemotherapy is mainly used to treat them. However, the outcome of GCPT is reported to be dismal. We experienced a case of GCPT with splenic metastases. A 53-year-old man was admitted for anorexia. Upper gastrointestinal scope revealed type 3 gastric cancer of the stomach. Abdominal computed tomography showed a huge tumor thrombus in the splenic vein extending to the hepatic hilus and multiple metastases to the spleen. S-1 was given orally from day 1 to day 21 and 60 mg of CDDP was administered intravenously. The cancerous thrombosis in the portal system and splenic metastases disappeared due to chemotherapy. Total gastrectomy with lymphadenectomy and splenectomy was carried out with curative intent after 10 courses of chemotherapy. Intraoperatively, no tumor thrombosis was identified and the gastric tumor was surgically removed. After surgery, the patient received adjuvant chemotherapy of S-1. After 6 months he is well and has not suffered from tumor relapse. A combination of CDDP + S-1 plus intervention surgery seems to be a promising option for GCPT.

Keywords Gastric cancer · Gastrectomy · Portal tumor thrombosis · Splenic metastasis · Chemotherapy

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Introduction

Gastric cancers with portal tumor embolism (GCPTs) are a rare entity with an incidence of 1.2 % in gastric cancers [1]. GCPTs are often concomitant with hematogenous metastases; curative surgery has not been indicated because they are regarded as being part of distant metastases, so intensive chemotherapy is applied [2–4]. However, the outcome of GCPTs is reported to be poor. Recently, the advent of new anticancer agents has provided us with a strong tool for treating gastric cancers with distant metastases including portal tumor embolism. In the current study, we successfully treated GCPT with multiple splenic metastases by R0 surgery following combination chemotherapy. We discuss recent treatment strategy for GCPTs with reference to English-language articles.

Case report

A 53-year-old man was admitted to Kagoshima University Hospital with anorexia and epigastric pain. He had a history of distal gastrectomy for peptic ulcer 40 years before. Upper gastrointestinal scope revealed type 3 gastric cancer in the remnant stomach (Fig. 1). Biopsy examination revealed well-differentiated adenocarcinoma. Abdominal computed tomography (CT) showed a huge tumor thrombus in the splenic vein extending to the intrahepatic portal vein (Fig. 2a, b). Several collaterals (Fig. 2c) and multiple metastases to the spleen were also identified (Fig. 2d). GCPT with multiple splenic metastases was diagnosed, and intensive chemotherapy was indicated. S-1 was given orally from day 1 to day 21 and 60 mg of CDDP was administered intravenously as previously reported [5]. High CEA anemia levels before chemotherapy normalized after chemotherapy (Fig. 3). After five

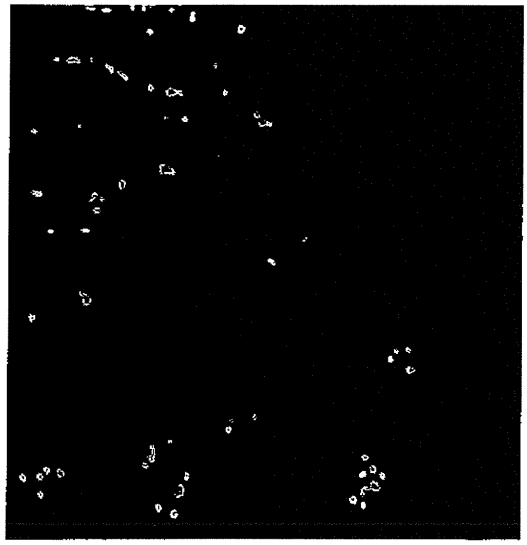

Fig. 1 Endoscopic findings of gastric tumor. Type 3 gastric cancer was identified in the greater curvature of the middle part of the remnant stomach

courses of chemotherapy, the cancerous thrombosis in the portal vein drastically shrunk (Fig. 4a) and splenic metastases also disappeared (Fig. 4d). Total gastrectomy with lymphadenectomy and splenectomy was carried out after 10 courses of chemotherapy with curative intent. No tumor thrombosis was identified during the operation. The primary gastric tumor also showed extensive shrinking and scarring (Fig. 5). Macroscopically and histologically, splenic metastases disappeared (Fig. 6) and residual cancer measuring 5 × 5 mm in diameter was found in the submucosal layer of the remnant stomach. Therefore, the histological grade of the tumor was estimated grade 2. After surgery, the patient received adjuvant chemotherapy of S-1. To date, he is well and has not suffered from recurrence of gastric cancer.

Discussion

Tumor embolism in the portal system occurs as a result of multiple aggregates of tumor cells, and has been described

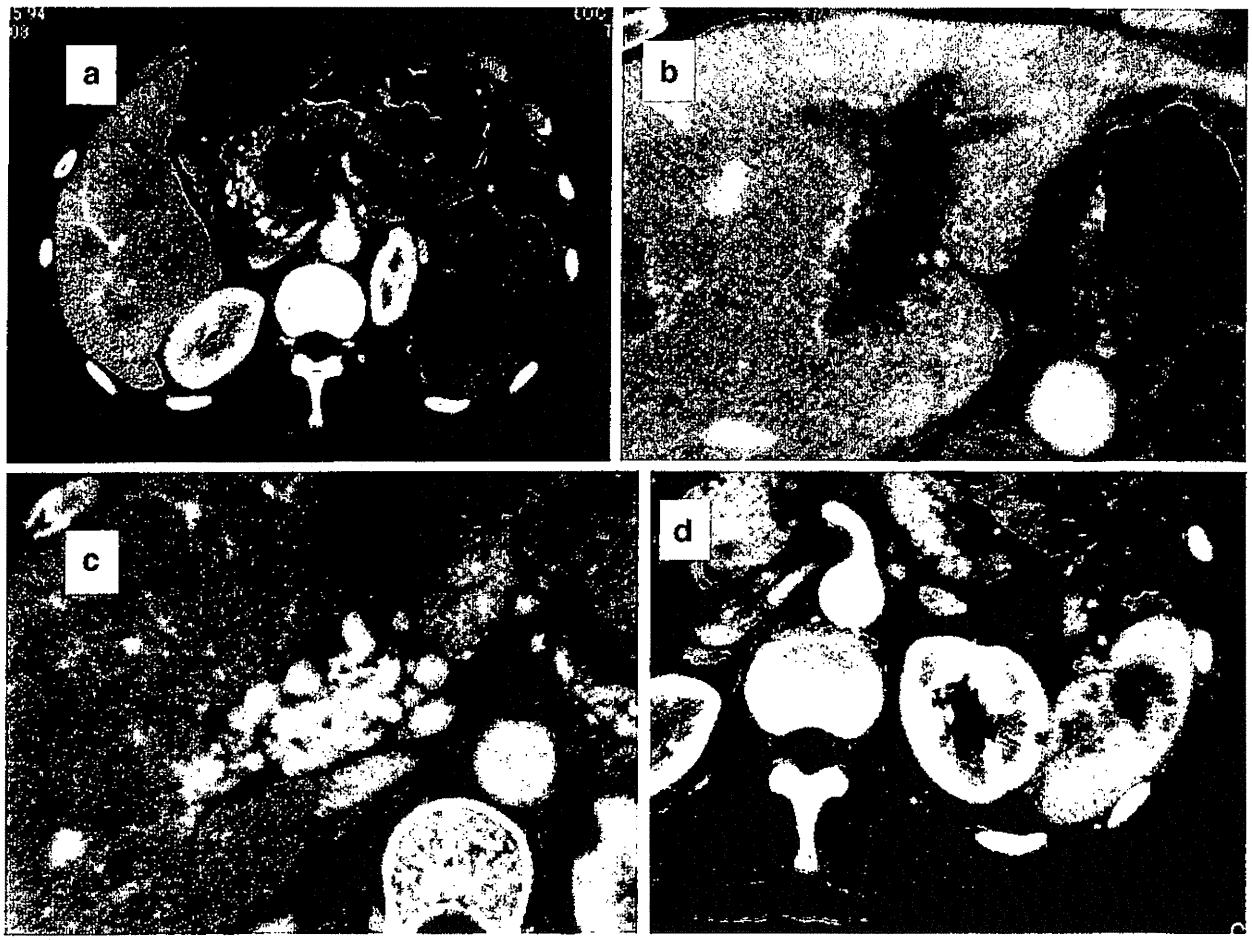

Fig. 2 Abdominal CT findings before chemotherapy. **a** Huge tumor thrombosis was identified in the portal vein. **b** Tumor thrombosis extended to the intrahepatic portal veins. **c** Collaterals were developed, suggesting portal hypertension. **d** Multiple splenic metastases were identified

in patients with various malignancies including carcinoma of the breast, stomach, pancreas, liver and prostate [6]. Although it has been reported that aggressive surgery for GCPT without distant metastases improved the outcome [7, 8], generally tumor embolism is often concomitant with hematogenous metastases like in the current case, so chemotherapy is applied first. Eom et al. retrospectively analyzed postoperative outcome in 51 cases of GCPT. They disclosed the clinical features of GCPT—median survival of GCPT was 5.4 months and gastric cancer with portal vein tumor thrombus had a poor prognosis. Recently, anticancer agents have become available for recurrent or advanced gastric cancer. Marked clinical efficacy of S1 plus CDDP has been reported [3], showing high efficacy of the current regimen for hematogenous distant lesions of gastric cancer. Hoshimoto et al. [8] demonstrated a case of GCPT successfully treated with a combination of TS-1 and CDDP; therefore, we followed their regimen when planning chemotherapy for our patient. To date, a definite chemotherapeutic regimen for GCPT has not been demonstrated. The combination of TS-1 and CDDP is regarded

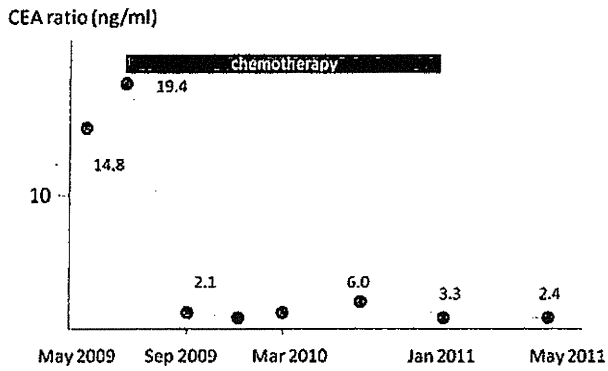

Fig. 3 Changes of serum CEA ratio during and after chemotherapy. Before chemotherapy, serum CEA ratio was 19.4 ng/ml but normalized after one course of chemotherapy

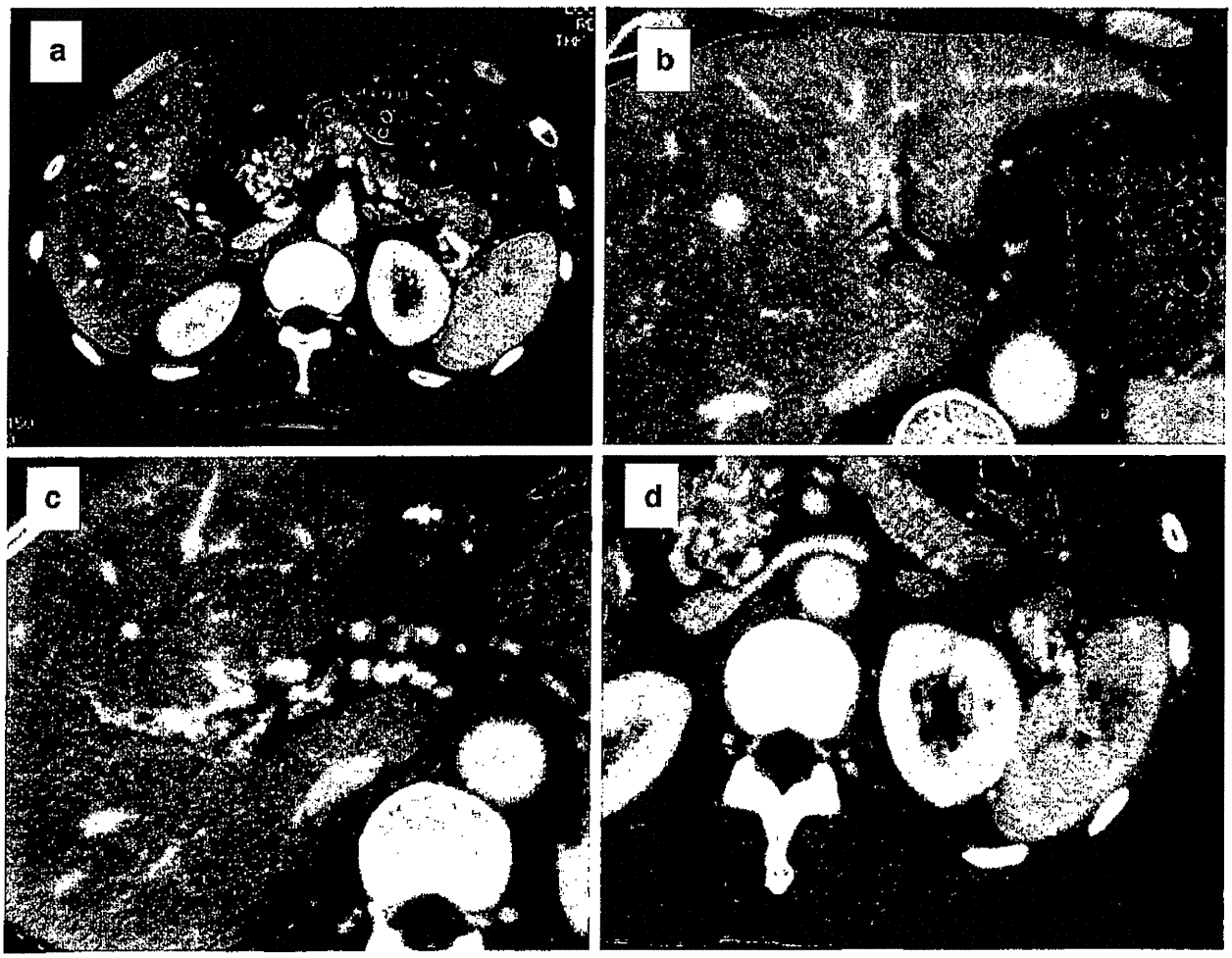

Fig. 4 Abdominal CT findings after chemotherapy. a Huge tumor thrombosis was not identified in the portal vein. b Tumor thrombosis of the intrahepatic also disappeared. c Collaterals were partially found in the hilus of the liver. d Multiple splenic metastases were not found after chemotherapy

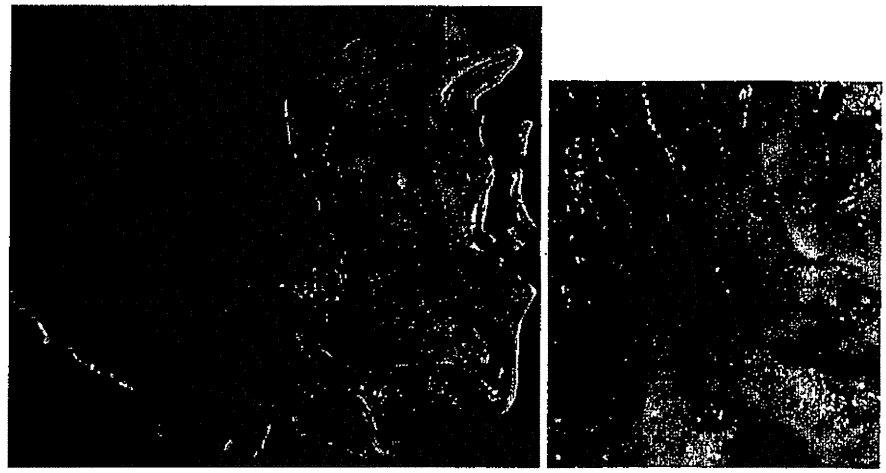

Fig. 5 Resected specimen of the stomach. Macroscopically gastric cancer was not identified in the remnant stomach

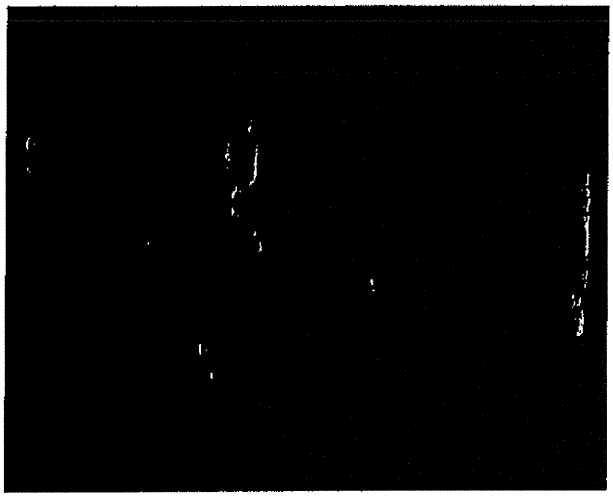

Fig. 6 Resected specimen of the spleen. Multiple splenic metastases also disappeared macroscopically and histologically

as standard chemotherapeutic regimen for advanced gastric cancer in Japan; this combination seems to be suitable for treating rare cases of GCPT. In the current case, we decided to add R0 surgery after chemotherapy; this was because the primary lesion was still present after 10 courses of chemotherapy although the portal thrombus and splenic metastases had disappeared. We previously reported that additional surgery following chemotherapy is useful for cases of stage IV gastric cancer after identifying the disappearance of distant metastases [9] and our patient seems to be included in this group. Additional surgery may enable removal of minute cancer cells leaving the patient free from chemotherapy; however, the timing of the operation and term of postoperative chemotherapy have been unclear.

In conclusion, GCPTs are a rare entity; the combination of CDDP + S1 seems to be a promising therapeutic regime. When the thrombosis and distant lesions are controlled, additional surgery with curative intent may be advisable to overcome this difficult situation.

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

A phase II study of oral S-1 with concurrent radiotherapy followed by chemotherapy with S-1 alone for locally advanced pancreatic cancer

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Abstract
Background/purpose S-1 is a new oral fluoropyrimidine anticancer agent shown to be effective for pancreatic cancer. In a previous phase I trial, we evaluated the safety of S-1 combined with radiotherapy to determine the maximum tolerated dose and dose-limiting toxicity in patients with unresectable pancreatic cancer. The recommended dose of S-1 for phase II trials of chemoradiotherapy was determined as 80 mg/m^2/day given on days 1–21 of a 28-day cycle. This phase II study was conducted to further evaluate the efficacy and toxicity of radiotherapy combined with S-1 (UMIN000004794).
Methods Eligible patients had locally advanced and unresectable pancreatic cancer without distant metastases, an Eastern Cooperative Oncology Group performance status of 0–1, adequate organ and marrow functions, and no prior anticancer therapy. Patients initially received 4 weeks of chemoradiotherapy. S-1 was given orally at a dose of 80 mg/m^2/day twice daily on days 1–21. Radiotherapy was delivered in fractions of 1.25 Gy twice daily, 5 days per week for 4 weeks (total dose: 50 Gy in 40 fractions). One month after the completion of chemoradiotherapy, S-1 was administered for 14 days followed by a 14-day rest period. This cycle was repeated as maintenance therapy until disease progression or unacceptable toxicity.
Results Fifty patients were enrolled in this phase II study. Median follow-up was 14.6 months (range 5.4–58.9 months). Forty-three patients (86%) completed the scheduled course of chemoradiotherapy. There was no treatment-related death or grade 4 toxicity. The major toxic effects were leukopenia and nausea. The objective tumor response according to the Response Evaluation Criteria in Solid Tumours criteria was partial response in 15 patients (30%) (95% confidence interval (CI), 18–45%), stable disease in 23 (46%), and progressive disease in 12 (24%). Median progression-free survival and median overall survival were 6.7 months (95% CI, 4.7–11.2 months) and 14.3 months (95% CI, 10.8–20.8 months), respectively. Survival rates at 1 and 2 years were 62 and 27%, respectively.
Conclusions Combination therapy with S-1 and radiation in patients with locally advanced and unresectable pancreatic cancer is considered a promising, well-tolerated regimen that can be recommended as an effective treatment for locally advanced pancreatic cancer.

Keywords S-1 · Phase II study · Pancreatic cancer · Chemoradiotherapy

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Introduction

Adenocarcinoma of the exocrine pancreas (pancreatic cancer) carries a very poor prognosis [1, 2]. In patients with locally unresectable disease, the results of randomized

trials by the Gastrointestinal Tumour Study Group indicate that concurrent treatment with external-beam radiation therapy (EBRT) and 5-fluorouracil (5-FU) results in significantly better survival than EBRT or chemotherapy alone [3, 4]. Concurrent EBRT and 5-FU is now generally accepted as a standard treatment for locally advanced pancreatic cancer. However, only modest benefits were obtained in early combined-modality trials, with a median survival of only 10 months. To improve the efficacy of treatment, various anticancer agents, such as gemcitabine, and different radiation schedules have been evaluated in clinical trials [5–10]. To date, however, the optimal regimen for chemoradiotherapy remains elusive [11]. The development of new agents and combination regimens is needed to improve survival in patients with unresectable advanced pancreatic cancer.

S-1 is a new oral fluoropyrimidine derivative combining tegafur with two modulators, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate, in a molar ratio of 1:0.4:1 [12]. CDHP is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase, an enzyme involved in the degradation of 5-FU. CDHP in combination with tegafur thus prolongs the duration of effective 5-FU concentrations in serum and tumour tissue. Potassium oxonate is a reversible competitive inhibitor of orotate phosphoribosyltransferase, an enzyme participating in 5-FU phosphoribosylation in the gastrointestinal mucosa. Potassium oxonate ameliorates the gastrointestinal toxicity of tegafur by decreasing 5-fluorodeoxyuridine monophosphate production in the gastrointestinal mucosa [13]. Recent clinical trials of S-1 have reported promising results in various solid tumors, including pancreatic cancer [14–16]. A recent phase II clinical trial of S-1 as a single agent obtained an objective response rate of 37.5% in patients with metastatic pancreatic cancer in Japan [17].

S-1 has also been shown to be a potent radiosensitizer in human solid tumor xenografts [18, 19], suggesting that a combination of radiotherapy and S-1 may improve survival in patients with locally advanced pancreatic cancer. However, the efficacy and safety of chemoradiation therapy with S-1 have not yet been fully investigated in patients with pancreatic cancer [20–23]. We previously performed a phase I study to evaluate the safety and determine the maximum tolerated dose (MTD) of S-1 plus radiotherapy in patients with unresectable pancreatic cancer [24]. The recommended dose of S-1 combined with radiation was estimated to be 80 mg/m^2/day given on days 1–21. Our findings suggested that a combination of S-1 and radiation was a promising and well-tolerated regimen that may be able to be used on an outpatient basis. The present phase II study was conducted to further evaluate the efficacy and toxicity of EBRT combined with S-1 for locally advanced and unresectable pancreatic cancer.

Patients and methods

Objectives

The primary endpoint of this study was objective tumor response. The secondary endpoints were toxicity, progression-free survival, and overall survival.

Eligibility

Patients with histologically or cytologically confirmed adenocarcinoma of the pancreas were enrolled from October 2005 through October 2008 at Kagoshima University Hospital. Eligible patients had incurable, locally advanced or unresectable disease on clinical or surgical staging examinations. Patients with distant metastatic disease were excluded. Our criteria for locally advanced and unresectable disease were as follows: tumor infiltration into the hepatic artery, superior mesenteric artery, or celiac axis and/or unreconstructable superior mesenteric vein/portal vein occlusion. Eligibility criteria also included the following: age 20 years or over; Eastern Cooperative Oncology Group performance status of 0–1; measurable or assessable disease; life expectancy of >3 months; no prior anticancer therapy; adequate organ functions as defined by leukocyte count of 4,000/mm^3, hemoglobin 9.0 g/dL, platelet count 100,000/mm^3, bilirubin 1.5 mg/dL, and creatinine 0.7 mg/dL.

The exclusion criteria were as follows: active infection; severe heart disease; interstitial pneumonitis or pulmonary fibrosis; pleural effusion or ascites; active gastroduodenal ulcer; pregnant or nursing women; severe mental disorder; active concomitant malignancy; or other serious medical conditions. Patients who lacked sufficient integrity of the gastrointestinal tract or who had mal-absorption syndrome were also excluded. The protocol was approved by the Human Studies Group at the Kagoshima University School of Medicine. All patients gave written informed consent before participation.

Treatment program

Patients initially received 4 weeks of chemoradiotherapy. S-1 (Taiho Pharmaceutical Co., Ltd. Tokyo, Japan) was administered orally twice daily at a dose of 80 mg/m^2/day from days 1 to 21. EBRT was delivered with 10 MV photons using a conformal technique in fractions of

1.25 Gy twice daily, 5 days per week for 4 weeks. Therefore a total dose of 50 Gy was delivered in 40 fractions over the course of 4 weeks [25]. The radiation field included the primary tumor and adjacent lymph nodes (pancreaticoduodenal and celiac axis), as defined by computed tomography-assisted treatment planning before the initiation of chemoradiotherapy. One month after the completion of chemoradiotherapy, S-1 was administered for 14 days followed by a 14-day rest period. This cycle was repeated as maintenance therapy until disease progression or unacceptable toxicity.

Toxicity and efficacy evaluation

Toxicity was graded according to the National Cancer Institute: Common Toxicity Criteria, version 3.0. Standard antiemetic therapy was prescribed as required. Antidiarrheal drugs were not given prophylactically, but could be used for the symptomatic treatment of diarrhea of grade 2 or higher. Chemotherapy was withheld on the development of grade 2 or higher nonhematologic toxicity or grade 3 or higher hematologic toxicity. Chemotherapy was resumed at the same dose level when toxicity was grade 1 or when the granulocyte and platelet counts were $\geq$1,500 and $\geq$100,000/mm^3, respectively. Radiation could be withheld because of toxicity at the discretion of the treating physician.

Physical examinations, complete blood cell counts, and serum chemical analyses were performed at least once weekly. Tumors were evaluated by computed tomography every 3 months. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) by three independent radiologists who were blinded to the patients. Serum CA19-9 concentrations were measured every 4 weeks. A value of 37 U/mL was defined as the upper limit of normal. Overall survival time was calculated from the date of treatment initiation to the date of death or the last follow-up. Progression-free survival time was calculated from the date of treatment initiation until documented disease progression or death from any cause (whichever occurred first).

Statistical analysis

All data are presented as percentages of patients or as means ± standard deviation of the mean. Percentages were compared by the χ^2 test, and means were analyzed by the Mann–Whitney test. The required number of patients was determined according to the optimal two-stage design. The threshold response rate and expected response rate were 20 and 40%, respectively. The sample size of this trial was 44 patients, with a type I error of 5% and a power of 90%. Tumor response and toxicity were evaluated on an intention-to-treat basis. The Kaplan–Meier method was used to estimate overall survival and progression-free survival.

Results

Patients and treatments

Between October 2005 and October 2008, 50 patients were enrolled. The median age of the subjects was 66 years (range 49–78 years), and the median follow-up time was 14.6 months (range 5.4–58.9 months). The clinical characteristics of the patients are summarized in Table 1. All 50 patients had locally advanced and unresectable pancreatic cancer without distant metastases. Two tumors were classified as stage IIB (T3N1M0), 21 tumors were as stage III (T4N0M0), and 27 were as stage III (T4N1M0), respectively, according to the International Union Against Cancer (UICC) 2002 TNM classification. The two stage IIB tumors had extensive involvement of the jejunal branch below the superior mesenteric vein.

Forty-three patients (86%) completed the full regimen of chemoradiotherapy. The remaining seven patients (14%)

Table 1 Patient and tumor characteristics

Characteristics	No. of patients (%)
Patients enrolled	50
Gender	
Men	24 (48)
Women	26 (52)
Age (years)	
Median (range)	66 (49–78)
ECOG performance status	
0	44 (88)
1	6 (12)
Tumor location	
Head	36 (72)
Body-tail	14 (28)
Tumor size (cm)	
Median (range)	4.0 (2.0–8.0)
Stage of tumor	
IIB: T3N1M0	2 (4)
III: T4N0M0	21 (42)
III: T4N1M0	27 (54)
Serum CEA (ng/mL)	
Median (range)	3.7 (1.3–20.1)
Serum CA 19-9 (U/mL)	
Median (range)	343 (1–7,068)

Tumor stage was evaluated according to UICC-TNM Classification, 6th edition

ECOG Eastern Cooperative Oncology Group

required a reduction in the dose of S-1 or radiation because of adverse events. Two patients with grade 3 fatigue discontinued radiotherapy after 40 and 30 Gy, respectively. Five patients refused S-1 treatment on days 15–21 because of grade 1 or 2 appetite loss.

Forty patients (80%) received maintenance chemotherapy with S-1 after chemoradiotherapy, for a total of 388 cycles (median 8, range 1–50). Of the remaining 10 patients, nine had deterioration of general condition due to disease progression before initiating chemotherapy, and one patient refused treatment because of general fatigue.

Toxicity

All 50 patients were evaluated for toxicity during chemoradiotherapy (Table 2). There was no treatment-related mortality or grade 4 toxicity. Hematologic toxicity, particularly leukopenia (40%), was a common adverse effect of combined treatment with S-1 and radiation. Gastrointestinal toxicity, such as anorexia (28%) and nausea (34%), was also frequent. Grade 3 toxicities included leukopenia (6%), fatigue (4%), and skin rash (2%). Nearly all toxic effects were mild and transient. No patient discontinued treatment because of leukopenia or skin rash. Two patients with grade 3 fatigue stopped treatment after receiving a radiation dose of 30 and 40 Gy, respectively.

Toxicity during maintenance chemotherapy is summarized in Table 3. Anorexia was a common adverse effect (30%). There was no grade 3 or 4 toxicity during the maintenance chemotherapy. There were no apparent late radiation toxicities during the study.

Efficacy and survival

Tumor response was determined in all treated patients ($n = 50$). Fifteen patients (30%) had a partial response (95% confidence interval (CI), 18–45%), 23 (46%) had stable disease, and 12 (24%) had progressive disease associated with the development of distant metastases. The serum CA19-9 concentration decreased to below 50% of the baseline value in 18 patients (42%) and entered the normal range in 6 patients (14%) among 43 patients who had a pretreatment value higher than the upper limit of normal (37 U/mL). Two patients were able to undergo curative resection after 4 and 11 months chemoradiotherapy, respectively.

Median progression-free survival and median overall survival were 6.7 months (95% CI, 4.7–11.2 months) and 14.3 months (95% CI, 10.8–20.8 months), respectively. Overall survival rates at 1, 2, 3, and 4 years were 62% (95% CI, 48–76%), 27%, 15%, and 12%, respectively (Fig. 1). At the time of analysis, 42 patients had died of disease progression. Disease progression was documented in 45 patients (90%). As summarized in Table 4, the pattern of initial disease progression was distant metastasis in 27 patients (54%), local progression of the pancreatic tumor in 12 (24%), and both in 6 (12%).

Discussion

Concomitant radiotherapy and chemotherapy is commonly used to treat locally unresectable pancreatic cancers [8]. S-1 is expected to improve the outcomes of chemoradiotherapy

Table 2 Toxicity during chemoradiation ($n = 50$)

Toxicity	Grade					Toxicity of grade* 1–4 (%)	Toxicity of grade 3–4 (%)	Toxicity of grade 4 (%)
	0	1	2	3	4			
Hematological toxicity								
Leukopenia	30	12	5	3	0	40.0	6.0	0
Neutropenia	46	4	0	0	0	8.0	0	0
Anemia	50	0	0	0	0	0	0	0
Thrombocytopenia	48	1	1	0	0	4.0	0	0
Non-hematological toxicity								
Nausea	33	9	8	0	0	34.0	0	0
Vomiting	49	0	1	0	0	2.0	0	0
Anorexia	36	7	7	0	0	28.0	0	0
Diarrhea	47	1	2	0	0	6.0	0	0
Stomatitis	49	1	0	0	0	2.0	0	0
Rash	49	0	0	1	0	2.0	2.0	0
Fever	49	1	0	0	0	2.0	0	0
Fatigue	47	0	1	2	0	6.0	4.0	0

* National Cancer Institute Common Toxicity Criteria, version 3.0

Table 3 Toxicity during maintenance chemotherapy ($n = 40$)

Toxicity	Grade					Toxicity of grade* 1–4 (%)	Toxicity of grade 3–4 (%)	Toxicity of grade 4 (%)
	0	1	2	3	4			
Hematological toxicity								
Neutropenia	38	1	1	0	0	5.0	0	0
Non-hematological toxicity								
Nausea	39	0	1	0	0	2.5	0	0
Vomiting	39	0	1	0	0	2.5	0	0
Anorexia	28	7	5	0	0	30.0	0	0
Diarrhea	39	0	1	0	0	2.5	0	0
Stomatitis	39	0	1	0	0	2.5	0	0
Rash	38	0	2	0	0	5.0	0	0
Fatigue	39	0	1	0	0	2.5	0	0

* National Cancer Institute Common Toxicity Criteria, version 3.0

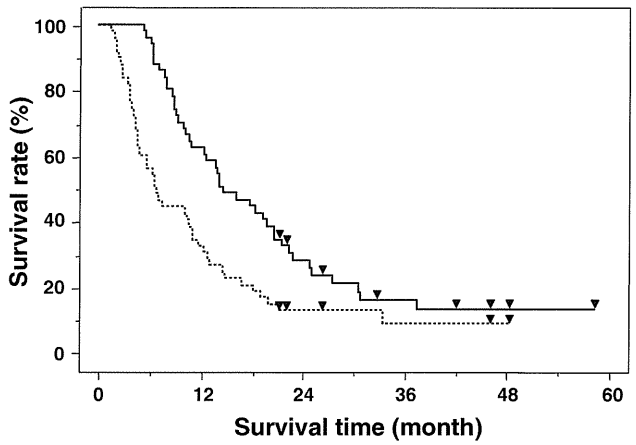

Fig. 1 Overall survival (*solid line*) and progression-free survival curves (*dotted line*) for all 50 patients

Table 4 Patterns of initial disease progression ($n = 50$)

	No. of patients (%)
None	5 (10%)
Distant metastases	27 (54%)
Liver	10
Peritoneum	9
Liver and peritoneum	3
Peritoneum and pleura	1
Lung	1
Lung and lymph node	1
Pleura	1
Lymph node	1
Local progression	12 (24%)
Local progression and distant metastases	6 (12%)
Liver	2
Peritoneum	3
Lung	1

for locally advanced pancreatic cancer because of its high palliative effectiveness, as well as its potent radiosensitizer activity [26–28]. The preliminary results of a Japanese phase II study of S-1 in patients with advanced pancreatic cancer demonstrated high safety and effectiveness [16, 17]. However, regimens combining S-1 and radiation have not yet been fully investigated in patients with advanced pancreatic cancer [20–23]. We conducted this phase II study to further evaluate the efficacy and toxicity of radiotherapy combined with S-1 for locally advanced and unresectable pancreatic cancer. Our regimen, combining the standard daily dose of S-1 for systemic chemotherapy (80 mg/m^2/day) with concurrent radiotherapy, was based on the results of our previous phase I study [24]. In addition, maintenance treatment with S-1 was given after chemoradiotherapy in this phase II study.

To date, three phase I studies of S-1 and concurrent radiotherapy, including our regimen, and two phase II studies have been reported in locally advanced pancreatic cancer [20–24] (Table 5). In other phase I/II studies of S-1 and radiotherapy for locally advanced pancreatic cancer, radiotherapy was delivered in 1.8 Gy daily fractions to a total dose of 50.4 Gy (SFRT: standard fractionated radiotherapy) [20–23]. Unlike other studies, hyperfractionated radiotherapy (HART: 50 Gy at 1.25 Gy/fraction twice daily) was adopted in the current study. HART was introduced as a way to increase the total tolerated dose and maximize local control without significantly increasing late complications, as compared with conventional SFRT [29]. We have previously performed a comparison study between HART and SFRT with concomitant low-dose gemcitabine for unresectable pancreatic cancer [25]. This study showed that the HART/gemcitabine regimen has equivalent efficacy and safety and a shorter treatment time as compared with the SFRT/gemcitabine regimen. Based on this background, the present study employed HART.

Table 5 Clinical trials of S-1 with radiation in pancreatic cancer

Authors	Year	Phase	*n*	RT dose (Gy)	Response rate (%)	MST (months)	1-year sur. (%)
Sudo et al. [20]	2007	I	16	50.4	43.8	13.7	71.3
Ikeda et al. [21]	2007	I	21	50.4	19	11	42.9
Shinchi et al. [24]	2007	I	17	50	36	12.3	NA
Kim et al. [22]	2009	II	25	50.4	24	12.9	43
Sudo et al. [23]	2010	II	34	50.4	41	16.8	70.6
Present study		II	50	50	30	14.3	62

n number of patients, *RT* radiation therapy, *MST* median survival time, *sur.* survival, *NA* not available

In this study, radiotherapy plus S-1 was associated with relatively mild toxicity. The main grade 3 toxic effects were leukopenia (6%), fatigue (4%), and skin rash (2%). There were no serious adverse events or treatment-related deaths. This combination was well tolerated and feasible in patients with locally advanced pancreatic cancer. The toxicity profile was similar to those in other studies of S-1-based chemoradiation [20–23]. There were no late radiation toxicities during the study.

In the present study, the tumor response rate and the disease control rate were 30 and 76%, respectively. The median survival was 14.3 months, and the overall survival rates at 1, 2, 3, and 4 years were 62%, 27%, 15%, and 12%, respectively. As shown in Table 5, the median survival time has varied between 11 and 16.8 months in other phase I/II studies. Our results compare favorably with those of other phase I/II studies [20–23].

Maintenance chemotherapy with S-1 was administered to delay or reduce the development of distant metastases in responding or stable patients after S-1 and radiotherapy. In this study, to reduce toxicity and improve therapeutic compliance, S-1 was administered for 14 days followed by a 14-day rest period. Consequently, there was no grade 3 or 4 toxicity during the maintenance chemotherapy. Fourteen out of 40 patients (35%) received maintenance chemotherapy with S-1 for more than 12 cycles with less toxicity.

As stated above, our regimen for S-1 combined with radiotherapy showed promising antitumor effectiveness and a good survival benefit in patients with locally advanced pancreatic cancer. It is particularly noteworthy that five patients survived for longer than 3 years. Administration of S-1 chemotherapy after chemoradiotherapy might have been partly responsible for the favorable survival in the present study. In patients with locally advanced pancreatic cancer treated with chemoradiation, it is important to enhance local tumor control and simultaneously reduce the risk of distant metastases. In addition to controlling local disease by acting as a potent radiosensitizer, S-1 acts systemically as a chemotherapeutic agent [19]. S-1 plus radiation may thus improve long-term survival in patients with advanced cancer who receive chemoradiation.

In summary, our combined regimen of S-1 and radiation was effective and well tolerated with low toxicity in patients with locally advanced and unresectable pancreatic cancer. Moreover, because S-1 is administered orally, S-1 plus radiation can be given on an outpatient basis, with no need for hospitalization. The ability of S-1 to deliver prolonged, effective plasma concentrations of 5-FU without the need for intravenous access or an infusion pump makes it an attractive alternative to conventional regimens combining chemotherapy and radiation. Our results are very promising and suggest that S-1 combined with radiation can be recommended as a standard treatment for locally advanced pancreatic cancer.

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