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 (*1Department 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，PhaseⅠで得られたCPT-11 80 mg/m^2（PhaseⅠ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．

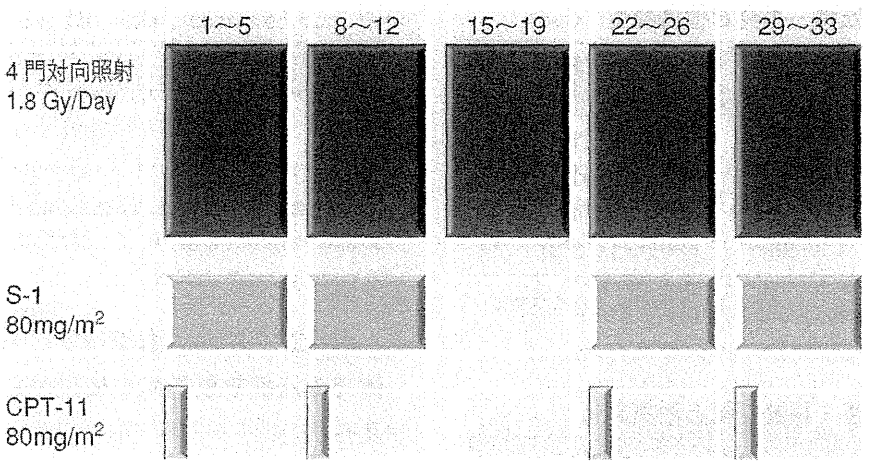

図1　プロトコール

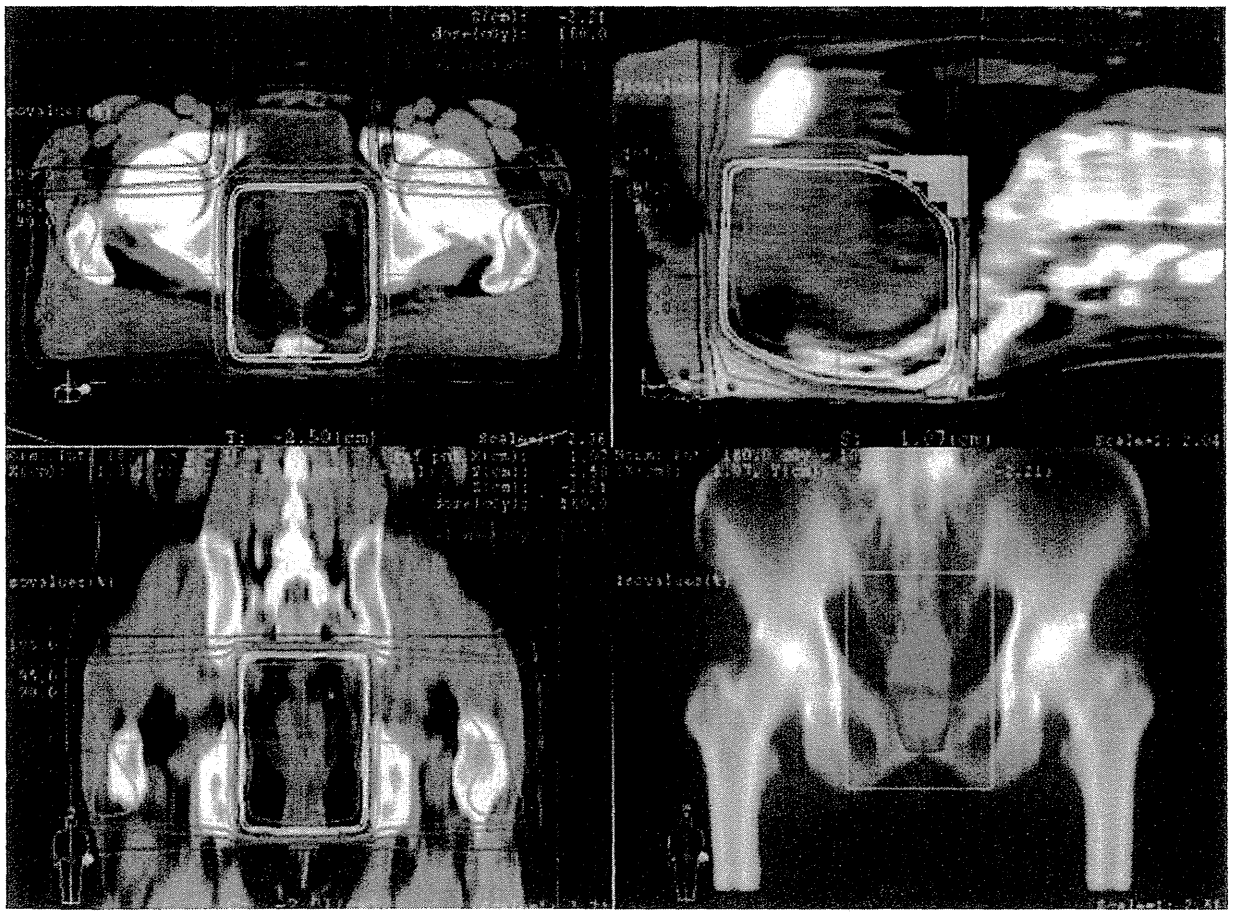

図2　放射線照射野

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，GradeⅠ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**）．

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．

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

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

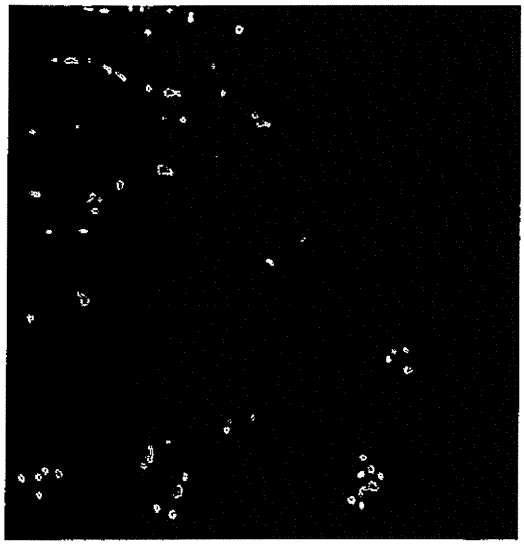

Fig. 1 Endoscopic findings of gastric tumor. Type 3 gastric cancer was identified in the greater curvature of the middle part of the remnant stomach

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

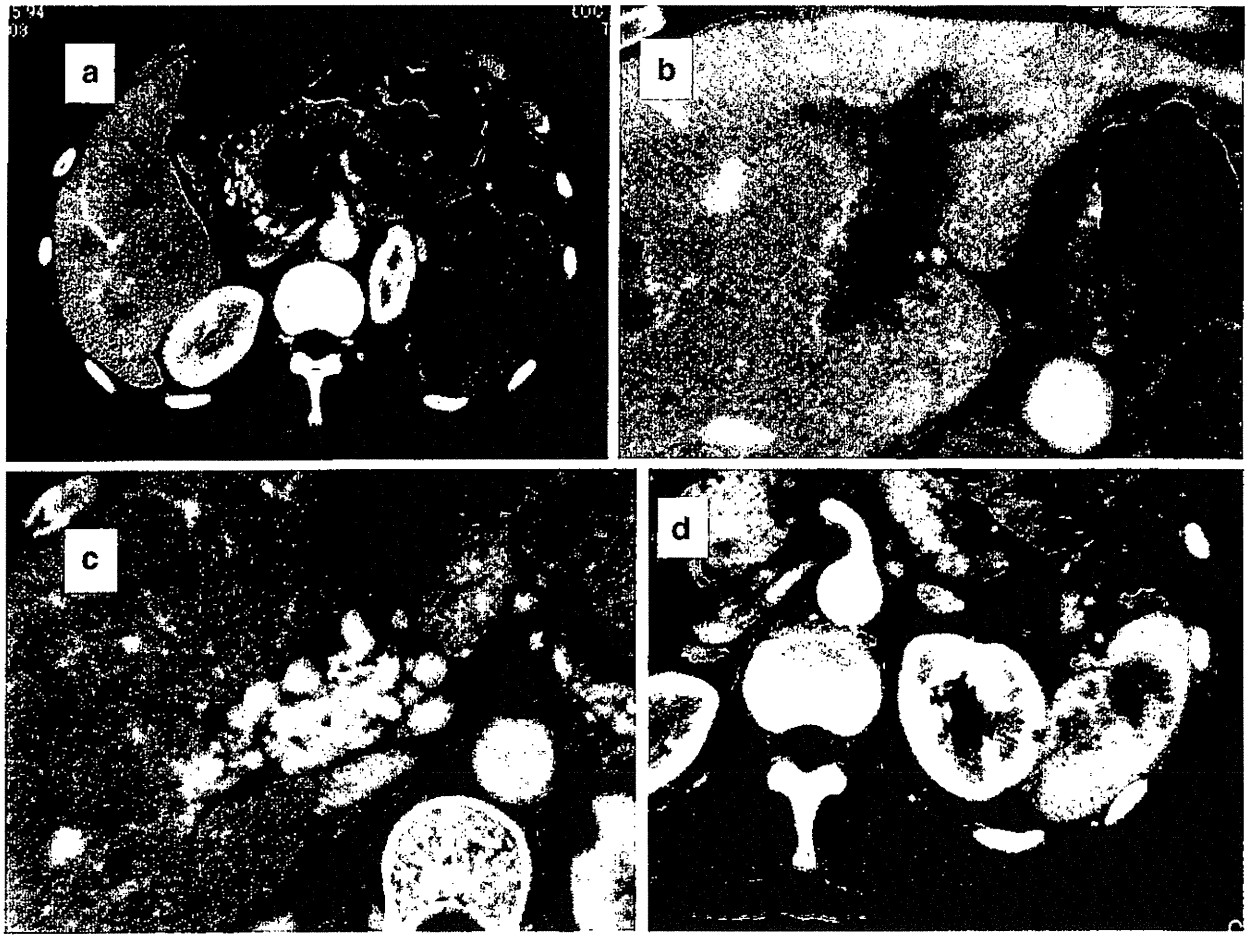

Fig. 2 Abdominal CT findings before chemotherapy. **a** Huge tumor thrombosis was identified in the portal vein. **b** Tumor thrombosis extended to the intrahepatic portal veins. **c** Collaterals were developed, suggesting portal hypertension. **d** Multiple splenic metastases were identified

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

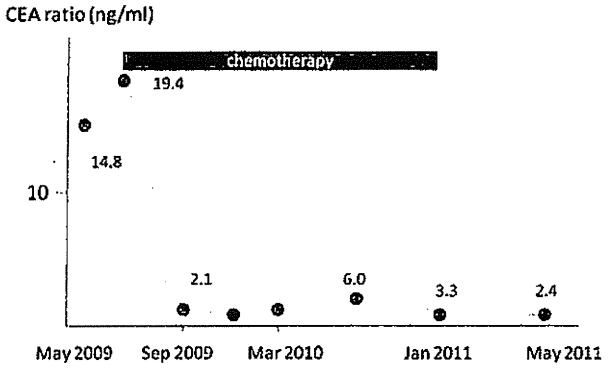

Fig. 3 Changes of serum CEA ratio during and after chemotherapy. Before chemotherapy, serum CEA ratio was 19.4 ng/ml but normalized after one course of chemotherapy

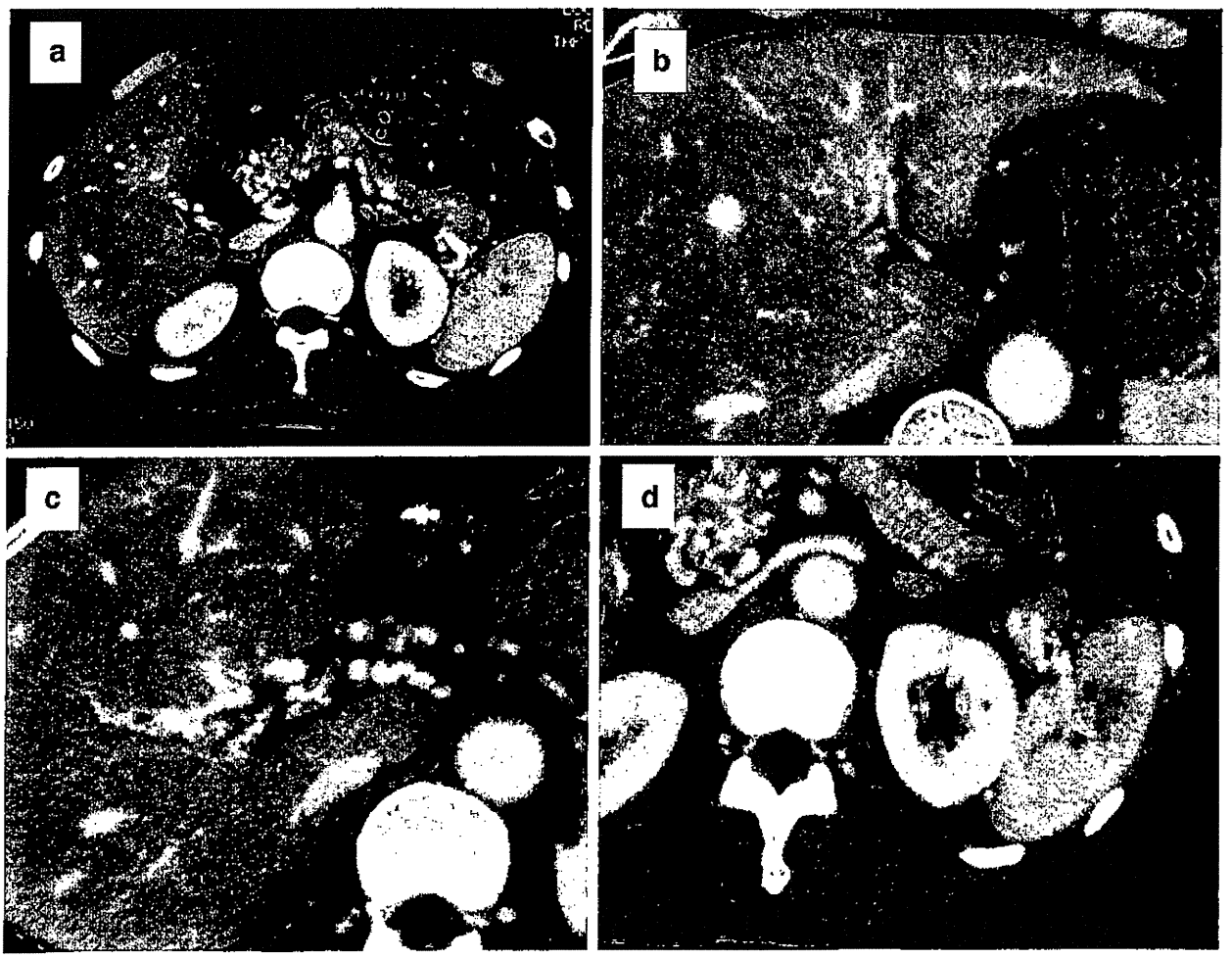

Fig. 4 Abdominal CT findings after chemotherapy. **a** Huge tumor thrombosis was not identified in the portal vein. **b** Tumor thrombosis of the intrahepatic also disappeared. **c** Collaterals were partially found in the hilus of the liver. **d** Multiple splenic metastases were not found after chemotherapy

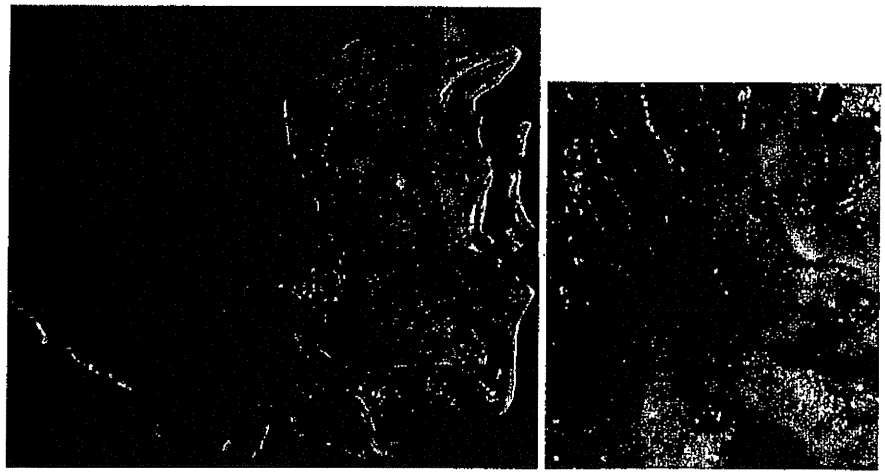

Fig. 5 Resected specimen of the stomach. Macroscopically gastric cancer was not identified in the remnant stomach

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

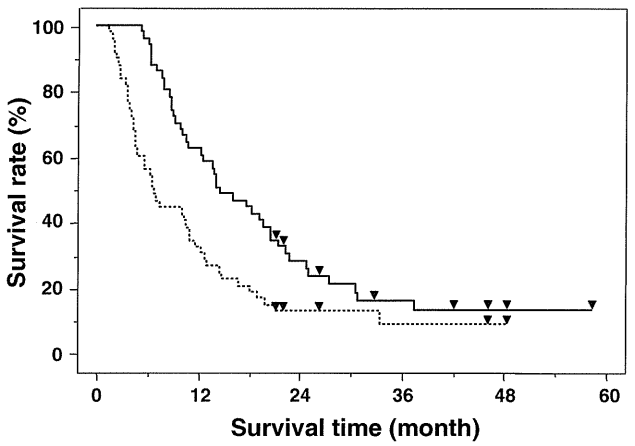

Fig. 1 Overall survival (*solid line*) and progression-free survival curves (*dotted line*) for all 50 patients

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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● 症 例 ●

膵癌同時性肝転移に対して抗癌剤感受性試験に基づく化学療法と定位体幹放射線治療を用いた集学的治療により良好な腫瘍制御効果が得られた1例

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A Case of Pancreatic Cancer with Liver Metastasis Controlled Effectively by Chemotherapy Based on Chemosensitivity Test and Stereotactic Body Radiotherapy: Hiroshi Kurahara[*1], Hiroyuki Shinchi[*1], Kosei Maemura[*1], Yuko Mataki[*1], Masahiko Sakoda[*1], Satoshi Iino[*1], Shinichi Ueno[*1], Yoshiyuki Hiraki[*2], Sonshin Takao[*3] and Shoji Natsugoe[*1] ([*1]*Dept. of Digestive Surgery, and* [*2]*Dept. of Radiology, Graduate School of Medical and Dental Sciences, Kagoshima University,* [*3]*Frontier Science Research Center, Kagoshima University*)

Summary

A 55-year-old woman was admitted to our hospital for pancreatic cancer with liver metastasis. We performed pancreatoduodenectomy, D2 dissection, and partial liver resection. Tissue from a resected liver metastasis was submitted to a chemosensitivity test. Based on the test results, we performed systemic chemotherapy with paclitaxel and hepatic artery infusion with gemcitabine for lung and liver metastasis after surgery. Furthermore, we added stereotactic body radiation therapy (SBRT) (48 Gy/4 Fr) for 3 liver metastases that showed enlargement after chemotherapy. Effective control of recurrent tumors was possible for 2 years and 5 month, and she maintained normal daily activities. She died of peritoneal dissemination 3 years and one month after surgery. Combined modality therapy with anticancer agents based on a chemosensitivity test and SBRT may be one useful therapy for pancreatic cancer with distant metastases. Key words: Pancreatic cancer, Chemosensitivity test, Stereotactic radiotherapy (*Received May 2, 2011/Accepted Jul. 6, 2011*)

要旨 症例は55歳，女性。肝転移を有する膵癌の加療目的にて当科紹介となった。膵頭十二指腸切除術，D2郭清，肝部分切除術を施行し，肝転移巣の一部を抗癌剤感受性試験（histoculture drug response assay: HDRA）に提出した。paclitaxel（PTX）と gemcitabine（GEM）の感受性が陽性と判定された。術後の肝転移および肺転移再発に対して PTX 全身化学療法，GEM 肝動注療法を施行し，さらに再増大する肝転移巣に対して定位体幹放射線治療（stereotactic body radiotherapy: SBRT）（48 Gy を3か所）を施行した。再発後2年5か月間の腫瘍増大制御が可能であり，その間社会復帰可能であった。術後3年1か月後に腹膜播種により死亡した。膵癌の非切除化学療法症例の生存期間が通常5～8か月であることを考慮すると，遠隔転移を有する膵癌に対して，HDRA に基づく化学療法と SBRT の組み合わせによる集学的治療が有効な治療手段の一つになる可能性が示唆された。

はじめに

膵癌では Stage Ⅳb が46%を占め，遠隔転移部位としては肝臓が20%で最多である[1]。今回，膵頭部癌同時性肝転移に対して切除術を施行し，その後の再発に対して抗癌剤感受性試験（histoculture drug response assay: HDRA）に基づく化学療法と定位体幹放射線治療（stereotactic body radiotherapy: SBRT）を用いた集学的治療により，良好な腫瘍制御効果が得られた症例を経験したので報告する。

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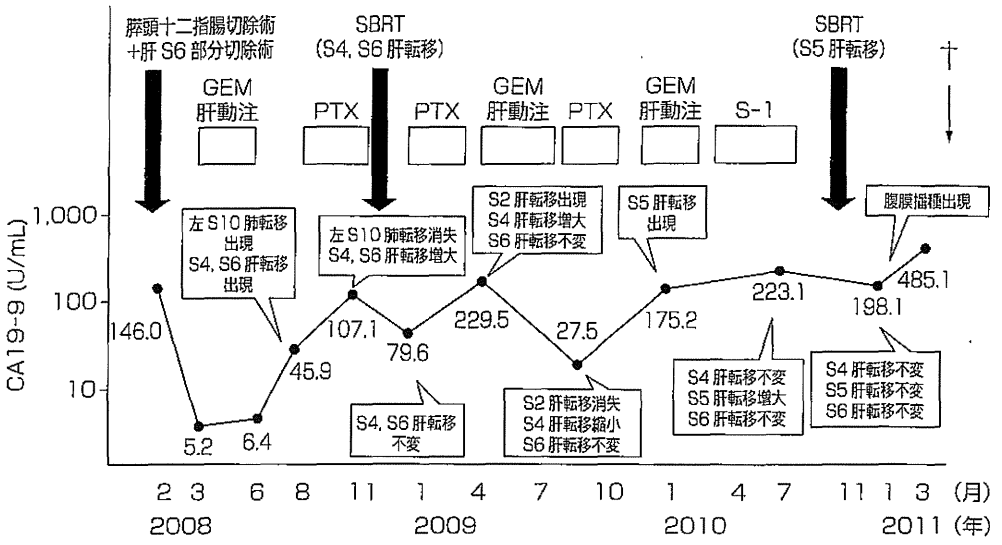

図 1 Clinical course

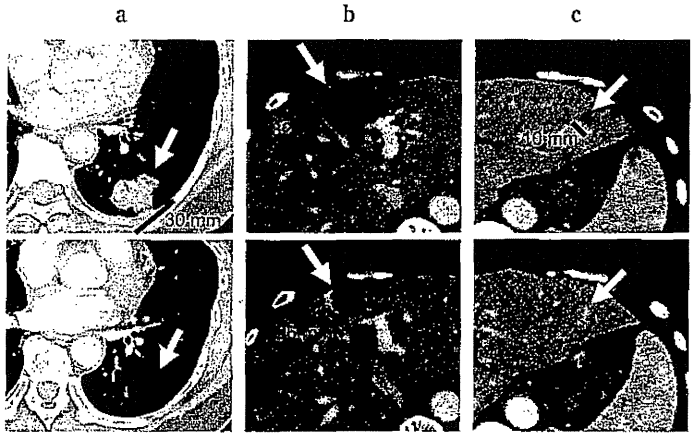

図 2 a: The lung metastasis was almost disappeared in CT by chemotherapy with PTX (arrow).
b, c: CT after hepatic artery infusion with GEM showed liver metastasis of the segment 4 reduced from 32 mm to 26 mm (arrow) and liver metastasis of the lateral segment was eliminated completely (arrow).

I. 症 例

患者: 55歳，女性。

主訴: 黄疸。

既往歴，家族歴: 特記すべきことなし。

現病歴: 2007年12月中下旬，皮膚黄染を自覚し近医を受診した。10 mm大のS6の肝転移を伴う膵頭部癌の診断であり，gemcitabine (GEM) 全身化学療法 (1,000 mg/m^2，3週投与1週休薬) を1コース施行した。肝転移が不変であったため，2008年1月下旬，当科紹介入院となった。

入院時現症: 身長151 cm，体重42 kg。黄疸を認めず，Karnofsky performance status (KPS) 100であった。

入院時血液検査所見: CA19-9が82.0 U/mLと上昇していた。他に異常所見を認めなかった。

入院時画像所見: 腹部CTにて25 mm大の膵頭部腫瘍と，S6に10 mm大の肝転移を認めた。腹部US，SPIO-MRIおよびFDG-PETでも他に遠隔転移を認めなかった。以上から，膵頭部癌，cTS2 (25 mm)，cT4 (CH+，S+，RP+)，cN0，cM1 (HEP)，cStage Ⅳbと診断した。年齢が若くKPSが良好であること，膵頭部癌は遺残なく切除可能であること，化学療法施行期間中に新たな遠隔転移が出現せず単発肝転移のみであることから，当院倫理委員会の承認の下，十分なインフォームド・コンセントを行い，切除術後HDRAに基づく化学療法を施行する方針とした。

II. 臨床経過

2008年2月中旬，膵頭十二指腸切除術，D2リンパ節郭清，肝S6部分切除術を施行した。腹膜播種を認めず，洗浄腹水細胞診は陰性であった。肝転移巣の一部をHDRAに提出した。最終診断はwell differentiated tubular adenocarcinoma，INF β，ly2，v2，ne1，mpd−，Ph，TS2 (35×25 mm)，nodular type，T3 (DU+，CH+，

S+, RP+, PV−, A−, PL−), N1 (13a: 1/12, 17a: 2/12), M1 (HEP), PCM−, BCM−, DPM−, Stage Ⅳb であった。HDRA にて GEM, 5-FU, CDDP, paclitaxel (PTX), CPT-11 の5剤のうち GEM と PTX が感受性ありと判定された。図1に治療経過を示す。3月中旬から術後補助化学療法として GEM 肝動注療法（週1回1,200 mg, 3週投与1週休薬）を開始した。Grade 3 の好中球減少のため，1コース2回目から800 mg，2コース目から500 mg に減量して計3コース施行した。経過観察中の8月に肝転移(S4: 20 mm, S6: 10 mm)と肺転移(左S10: 30 mm)，CA19-9 上昇を指摘され，PTX 全身化学療法（週1回150 mg，1週投与1週休薬）を開始した。11月には肺転移は消失した(図2a)が，肝転移が増大(S4: 30 mm, S6: 15 mm）したため，二つの肝転移に対してそれぞれ SBRT（48 Gy/4 Fr）を施行した。2009年4月に S4 の肝転移が軽度再増大（32 mm）し，肝外側区に新たな肝転移（10 mm）が出現したため，GEM 肝動注療法(週1回1,000 mg, 3週投与1週休薬)を開始した。5コース施行後の10月には肝外側区の肝転移は消失し，S4 の肝転移も縮小傾向（26 mm）となった（図2b, c)。その後は PTX 全身投与を再開した。PTX の総投与量は2,850 mg であり，Grade 3 以上の有害事象は好中球減少のみであった。2010年1月に新たな肝転移（S5: 10 mm）が出現したため，GEM 肝動注療法（週1回1,000 mg, 3週投与1週休薬）を3コース施行するも肝転移増大傾向であったため，4月から S-1 内服（100 mg/body，2週投与2週休薬）を開始した。その後も CA19-9 が上昇傾向であったため，11月に S5 の肝転移に対して SBRT (48 Gy/4 Fr) を施行し，その後肝転移の大きさは不変であったが，CA19-9 は減少傾向となった。2011年2月には腹膜播種による腹水貯留が出現し，3月下旬に死亡された。

Ⅲ. 考　察

遠隔転移を有する膵癌に対しては，GEM を用いた化学療法が第一選択として推奨されている[2]。しかし，切除不能膵癌に対する GEM の効果は決して満足できるものではなく，生存期間中央値（median survival time: MST）は4.9〜8.4か月[2]である。現在では S-1 も保険適応であり治療の主体を担っているが，十分な成績とはいえず（MST 8.8か月[3]），より有効な集学的治療の開発が必要である。

HDRA は，癌に対する個別化治療の一手段としての有用性が報告されている[4,5]。当科では2005年6月から Stage Ⅳb 膵癌に対する HDRA を施行しており，その良好な成績（MST 13.6か月）を報告してきた[6,7]。一方，SBRT は三次元的多方向からの照射により，周囲正常組織への影響を制限し，標的病変に高線量を集中させることで高い局所制御を目的としている。30〜60 Gy を3〜4回で照射するため，短期間で治療可能である。肝転移に対する新しい治療法として，その腫瘍制御効果が注目されており，結腸癌肝転移に対する SBRT の2年局所制御率は71〜86%と報告されている[8,9]が，膵癌肝転移に対する治療効果の報告はほとんどない。

今回われわれは，HDRA の結果に基づいた化学療法と SBRT を用いた集学的治療を施行した。肺転移に関しては PTX が奏効し，肝転移に関しては GEM が有効であったと考えられる。PTX は GEM 抵抗性の膵癌に対する二次治療薬としての有効性が報告されている[10]。転移部位による抗癌剤の有効性の違いに関しては，今後さらに症例を重ね検討していく必要がある。一方，SBRT は著明な腫瘍縮小効果は認めなかったが，stable disease (SD) 期間を延長させる可能性があると思われた。術後3年1か月にて腹膜播種により死亡したが，再発後2年5か月間の腫瘍増大制御が可能であり，その間は社会復帰可能であり良好な QOL を維持できた。遠隔転移を有する膵癌に対して HDRA に基づく化学療法と，SBRT の組み合わせによる集学的治療が有効な治療手段の一つになる可能性が示唆された。

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胃癌に対する化学療法後の手術

Salvage surgery for stage Ⅳ gastric cancer followed by chemotherapy

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【ポイント】

◆ 化学療法後の手術後に再燃のリスクが高い症例は，組織学的な非奏効例，肉眼型が4型，遠隔病変として腹膜播種であった．

◆ CR症例であっても切除標本内には遺残腫瘍がみられるため，腫瘍の除去に外科治療は有効である．

◆ 術後化学療法から解放された無再発症例を7例経験し，手術介入の意義が確認できた．しかし，介入の時期や切除範囲，術後の治療内容について明らかにするためには，さらなる症例の集積が必要である．

臨外　67(1)：26～30，2012

はじめに

近年，化学療法の進歩に伴って切除不能進行胃癌の治療成績は劇的に向上しており，高度進行胃癌に対する治療戦略は手術療法から化学療法へと大きく流れが変わってきている．抗癌剤の胃癌への期待が薄かった1990年代までは，進行胃癌に対する大動脈周囲リンパ節郭清，食道浸潤胃癌に対する縦隔リンパ節郭清，他臓器浸潤胃癌に対する合併切除，腹膜播種に対する腹膜切除，あるいは肝転移に対する肝切除など，拡大手術が積極的に行われてきた．これらの臨床的意義が様々な角度から検討されたが，強いエビデンスレベルをもって拡大手術の意義を見出すことはできなかった[1]．2000年代に入り，胃癌に高い奏効率を示す新規抗癌剤が登場し，進行胃癌に対する拡大手術は再考されるようになってきた．一方，遠隔転移を伴い切除不能と考えられてきた高度進行胃癌が化学療法によって遠隔病変や原発巣が消失，あるいは著明に縮小する症例を経験するようになってきた．

本特集のテーマである「切除困難例への化学療法後の手術」のうち，本稿では従来手術の適応とならない遠隔転移を伴うような高度進行胃癌へ化学療法を行い，化療著効後の根治を意図した切除を扱う．最近，学会などの特別演題で「化学療法後の手術療法の意義」がテーマとして頻回に取り上げられており，胃癌治療のホットな話題の1つとなっている．われわれは2002年から高度進行胃癌に対し，多施設共同試験も兼ねて隔週のパクリタキセル＋S-1療法を行ってきた．本稿では化学療法後に遠隔転移の消失あるいはコントロールされた症例に対する手術の治療成績について述べるとともに，最近の胃癌化学療法後の手術療法に関する文献をレビューし，化療奏効後の介入手術の意義について考察する．

化学療法後の手術療法の治療成績（文献から得られた考察）

最新の「胃癌治療ガイドライン」（第3版）[2]では，SPIRITS試験によってS-1＋シスプラチンの組み合わせが切除不能・再発胃癌に対する標準治療と位置づけられている．以前の平均生存期間の中央値（median survival time：MST）は約6～9か月であったが，このSPIRITS試験では奏効率は54%，平均生存期間は11か月と大幅に治療成績の向上がみられた．