表5　最近報告された進行膵癌に対する第III相試験

治療法	患者数	奏効率(%)	MST(月)	P値	報告者
Gem＋Oxaliplatin	157	26.8	9.1	0.13	Louvet, et al[26]
Gem	156	17.3	7.1		
Gem＋Capecitabine	160	10.1	8.4	0.31	Herrmann, et al[27]
Gem	159	7.9	7.3		
Gem＋Capecitabine	267	14	7.4	0.026	Cunningham, et al[28]
Gem	266	7	6.0		
Gem＋Erlotinib	285	8.6	6.4	0.025	Moore, et al[29]
Gem	284	8.0	5.9		

MST：生存期間中央値，Gem：gemcitabine

単剤療法よりも有意に生存期間を伸ばしたことが報告されたが，その差は小さく(中央値：6.4か月対5.9か月，P=0.025)，実用化するためには本療法に対する効果予知因子の解明が必要である[29]．その他，cetuximabやbevacizumabなどの分子標的薬剤とgemcitabineの併用療法の臨床試験が現在進行中で，報告が待たれている．

以上，遠隔転移を有する膵癌に対しては，gemcitabineが現在第一選択の抗癌剤として使用されており，さらに優れた治療を求めてさまざまな臨床試験が行われている．最近は，gemcitabine単剤よりも成績が上回った治療もいくつか報告されており，今後の展開が大いに注目されている．

おわりに

近年，進行膵癌にする治療は大きな変貌を遂げており，効果的な治療が少なかった10年前とは隔世の感がある．とはいえ長期生存に関してはまだまだ現状は厳しく，近い将来，診断・治療の両面で飛躍的な進歩が達成されることを期待したい．

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Lecture

解　説

切除不能膵がんの化学療法の現状と今後の課題*

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Key Words : pancreatic cancer, chemotherapy, gemcitabine, clinical trial

はじめに

膵がんは早期診断が難しいため，画像診断が進歩した現在でも8割近い患者が切除不能な進行がんの状態で発見されている．また，たとえ切除を受けてもその多くが再発するため，膵がん患者の予後はきわめて不良である．膵がん患者の予後を改善するためには，早期診断技術の向上とともに化学療法を含めた非切除治療の進歩が必要不可欠であり，予後改善を目指してさまざまな試みが行われている．本稿では，進行膵がんに対するそれらの試みについて最新の知見を交えて解説する．

標準治療

進行膵がんに対しては現在，代謝拮抗剤のgemcitabine(以下GEMと略す)が標準的な抗がん剤として認識されており，世界中で使用されている．その根拠となったのは1997年に北米のグループから報告された第Ⅲ相試験であり，その中でGEMの投与を受けた進行膵がん患者群はfluorouracil(以下5-FU)の投与を受けた患者群よりも症状緩和効果，生存期間ともに有意に優れていたことが報告された(生存期間中央値：GEM群5.7か月，5-FU群4.4か月，$p=0.0025$)[1](図1)．進行膵がんに対するGEMの効果はその後も多くの研究で認められており，わが国でも膵がんに対するGEMの保険適用が認められた2001年4月以降，

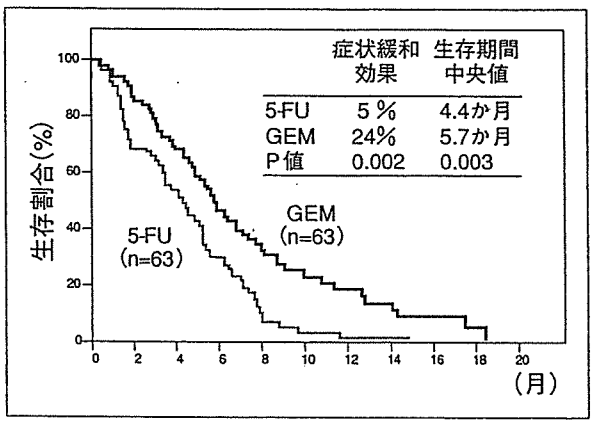

図1　GEM vs. 5-FU(文献[1]より引用)

膵がんに対するGEMの使用は急速に広まっている．図2にGEMの標準的な使用方法を示す．

新しい治療

GEMの登場により，進行膵がん患者でも積極的に治療を受けることによって症状の改善や延命が期待できるようになった．GEMの主な副作用は骨髄抑制や消化器症状などであるが一般に軽度であり，予後の短い膵がん患者にとってQOLを損わずに外来で治療ができるGEMのメリットは大きい．しかし，GEM単剤の効果には限界があるのも事実であり(奏効割合は一般に10％前後，生存期間中央値は6か月前後)，より優れた治療の開発が求められている．近年，新しい治療の開発が世界中で活発に行われており，GEM単剤をコントロールアームにした第Ⅲ相試験が次々

* Systemic chemotherapy for advanced pancreatic cancer : present and future.

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と報告されている(表1)．今回は，それらの中から注目を集めた，あるいは現在注目されている試験について述べる．

1．ゲムシタビン定速静注法

血中に投与されたGEMはデオキシシチジンキナーゼなどの酵素によりリン酸化されGEM三リン酸となり，生体内のデオキシシチジン三リン酸と競合してDNAに取り込まれて細胞死をひき起こす(図3)．GEMを効率よくリン酸化するためには，通常の投与方法(GEM 1,000mg/m²を30分かけて点滴静注)よりも，GEMを10mg/m²/minのゆっくりとした速度で投与する方が優れていることが基礎実験で示されており，これを定速静注法(fixed-dose rate infusion)と呼ぶ．Temperoらは，進行膵がん患者を対象にGEMの30分の投与法と定速静注法とを比較したランダム化第Ⅱ相試験を行い，定速静注法の方が生存期間が優れていたことを報告した[2]．これを受けて，われわれは日本人の膵がん患者を対象としたGEM定速静注法の第Ⅰ相試験を行い，1,200mg/m²/120minであれば日本人でも安全に投与できる可能性が高いことを報告している[3]．2006年度にはEastern Cooperative Oncology Group(ECOG)がGEM通常投与法 vs. GEM定速静注法 vs. GEM定速静注法＋oxaliplatinの3群を比較した大規模な第Ⅲ相試験の結果を米国臨床腫瘍学会(ASCO)で報告し，大いに注目を集めたが，GEM定速静注法は通常投与法よりも生存期間がやや長い傾向にあったものの(生存期間中央値：6.0か月 vs. 4.9か月)，残念ながら有意差は認められなかった[4](図4)．

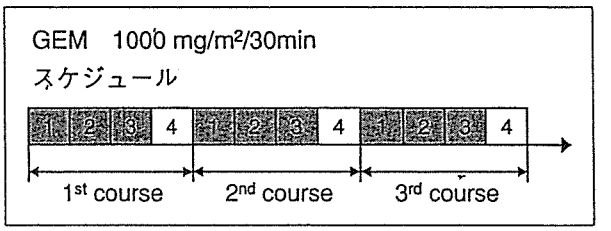


図2 GEMの投与方法
体表面積1 m²あたり1,000mgのGEMを30分かけて点滴静注する．週1回，3週間連続投与後1週休薬(3投1休)を1コースとして，明らかな病態の悪化や重篤な副作用を認めないかぎり継続する．投与当日の白血球数が2,000/mm³未満または血小板数が70,000/mm³未満の場合は，骨髄機能が回復するまで投与を延期する．

2．ゲムシタビン＋フッ化ピリミジン系抗がん剤

5-FUは古くから膵がんに対して使用されてきた抗がん剤であり，副作用も軽度であることからGEMとの併用が積極的に試みられてきた．し

表1 進行膵がんに対する化学療法の第III相試験

	Year	MST	*p* value
GEM vs. 5-FU	1997	5.7 vs. 4.4	0.025
GEM vs. Marimastat(25mg)	2001	5.6 vs. 4.2	0.78
GEM vs. BAY12-9566	2003	6.6 vs. 3.7	＜0.01
GEM vs. Exatecan	2004	6.6 vs. 5.0	0.09
GEM vs. FDR GEM	2006	4.9 vs. 6.0	0.05
GEM vs. GEM＋5-FU	2002	5.4 vs. 6.7	0.09
GEM vs. GEM＋5-FU＋LV	2005	6.2 vs. 5.9	0.68
GEM vs. GEM＋Capecitabine[a]	2005	7.3 vs. 8.4	0.31
GEM vs. GEM＋Capecitabine[b]	2005	6.0 vs. 7.4	0.026
GEM vs. GEM＋Pemetrexed	2004	6.3 vs. 6.2	0.85
GEM vs. GEM＋Irinotecan	2004	6.6 vs. 6.3	0.79
GEM vs. GEM＋Exatecan	2004	6.2 vs. 6.7	0.52
GEM vs. GEM＋Cisplatin	2002	6.0 vs. 7.6	0.12
GEM vs. FDR GEM＋Oxaliplatin[c]	2004	7.1 vs. 9.0	0.13
GEM vs. FDR GEM＋Oxaliplatin[d]	2006	4.9 vs. 5.9	0.16
GEM vs. GEM＋Marimastat	2002	5.5 vs. 5.5	0.95
GEM vs. GEM＋Tipifarnib	2004	6.1 vs. 6.4	0.75
GEM vs. GEM＋Erlotinib	2005	5.9 vs. 6.4	0.025

[a]：Herrmannら，[b]：Cunninghamら，[c]：Louvetら，[d]：Poplinら，MST：median survival time(生存期間中央値)，FDR：fixed-dose rate(定速静注)，LV：leucovorin

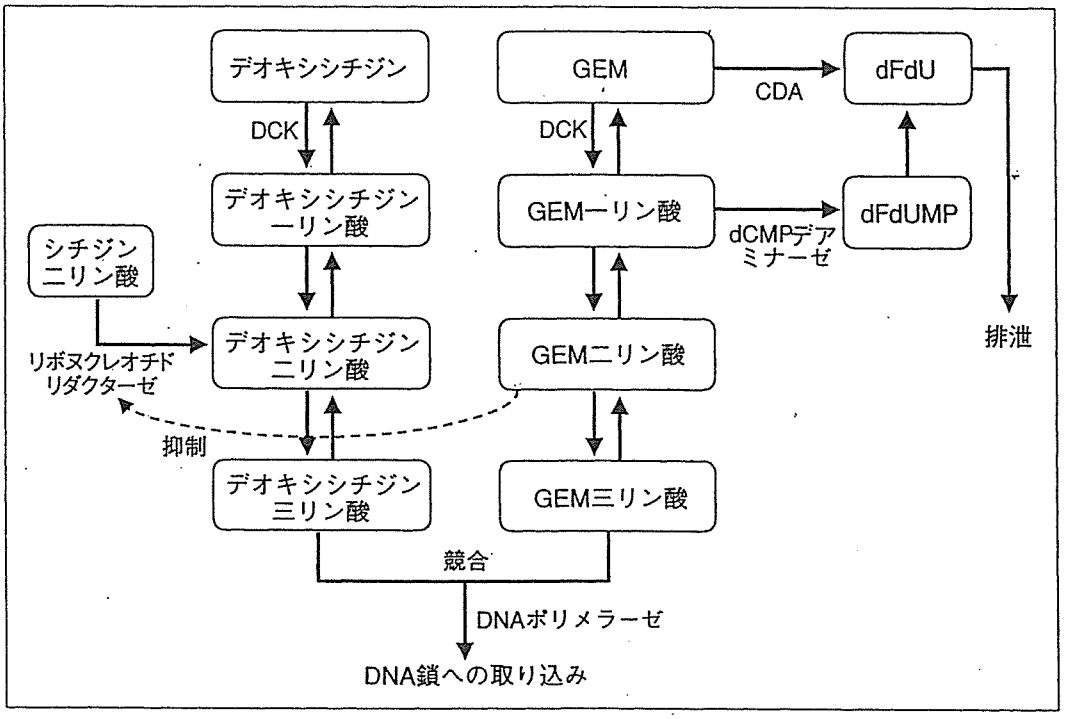


図3　GEMの代謝経路
DCK：デオキシシチジンキナーゼ，CDA：シチジンデアミナーゼ，dCMP：デオキシシチジン一リン酸，dFdU：ゲムシタビンウラシル体，dFdUMP：ゲムシタビンウラシル体一リン酸

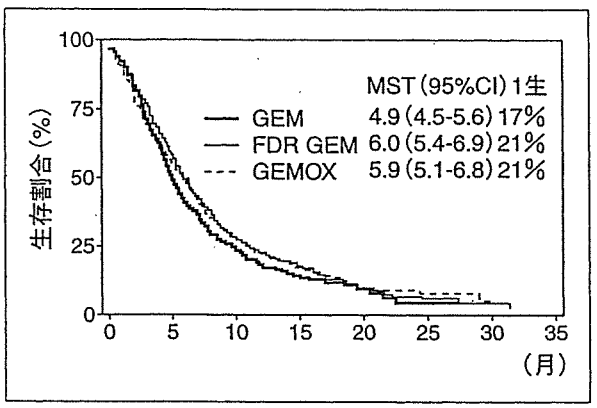


図4　GEM vs. FDR GEM vs. GEMOX
FDR：fixed-dose rate（定速静注），GEMOX：FDR GEM＋oxaliplatin，MST：生存期間中央値，1生：1年生存割合　（文献[4]より引用）

かし第Ⅱ相試験では比較的良好な成績が示されたものの，GEMとbolus infusionの5-FUを併用したBerlinらの第Ⅲ相試験ではGEM単剤を上回る成績は得られなかった[5]．また，GEMにcontinuous infusionの5-FUとleucovorinを併用したレジメンに関しても，第Ⅲ相試験でGEM単剤群に対するsurvival benefitを示すことはできなかった[6]．

一方，5-FUは時間依存性の抗がん剤であることから，血中に長時間持続的に5-FUを放出することができるcapecitabineやS-1などの経口フッ化ピリミジン製剤の効果が最近注目されている．CapecitabineとGEMとの併用療法に関しては，現在までに2つの第Ⅲ相試験が報告されており，Herrmannらスイスを中心としたグループが行った試験では，全身状態の良好な例（KPS90以上）のみを対象としたサブグループ解析では併用群の方がGEM単剤群よりも優れた生存期間を示したものの（生存期間中央値：10.5か月 vs. 7.5か月，$p=0.024$），全体を対象とした解析では有意差は認められなかった[7]．一方，Cunninghamら英国のグループが行った試験では，有意差をもってGEM＋capecitabine群の方が優れていたことが示された（生存期間中央値：7.4か月 vs. 6.0か月，$p=0.026$）[8]（図5）．GEM＋capecitabine併用療法が，今後進行膵がんに対する標準治療として世界的に受け入れられるためには，さらなる研究の蓄積が必要と考えられるが，今後の進展が期待されている．

S-1は5-FUのプロドラッグであるtegafurに効果と安全性を高めることを目的としてCDHPとOxoを組み合わせた配合剤であり，わが国では胃がんや頭頸部がんなどに広く使用されている．膵

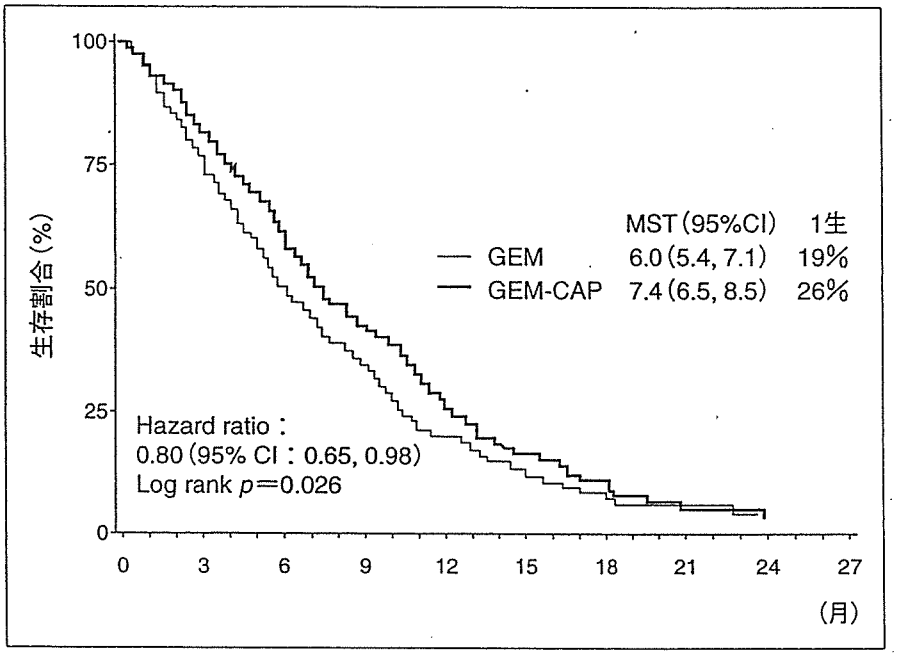
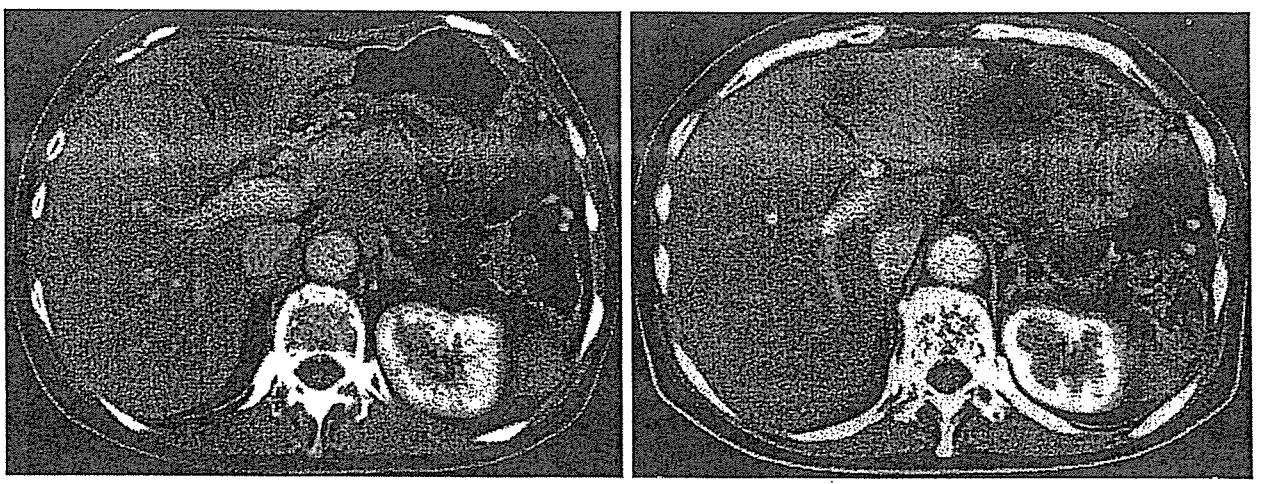


図5 GEM＋Capecitabine vs. GEM
MST：生存期間中央値，1生：1年生存割合(文献[8]より引用)



治療前　　3コース後

図6 S-1が奏効した症例
S-1による治療を3コース施行後，膵原発，肝転移ともに著明に縮小し，臨床症状の改善を認めた．

がんに対しては最近治験が行われ，国立がんセンター中央病院で行われた前期第Ⅱ相試験では19人の膵がん患者中4人にPRが認められた[9]．図6にS-1が奏効した一例を示す．さらに，多施設で行われた後期第Ⅱ相試験では奏効割合37.5%，生存期間中央値8.8か月という良好な結果が示されたため[10]，2006年8月に膵がんに対するS-1の保険適用が承認された．GEMとの併用療法にも期待が高まっており，われわれはGEMをday1，8，S-1をday1～14に投与し21日を1コースとして繰り返す方法を用いた第Ⅰ相試験を膵がん患者に対して行い33%の奏効割合を報告している[11]．現在，このスケジュールを用いた第Ⅱ相試験が多施設共同で行われており，その結果が期待されている．GEMとS-1の併用療法に関しては，中村らも異なったスケジュールを用いて第Ⅱ相試験を行っており，高い奏効割合(48%)と良好な生存期間中央値(12.5か月)を報告している[12]．

3．ゲムシタビン＋プラチナ系抗がん剤

CisplatinはGEMと併用すると相乗効果があることが知られており，非小細胞肺がんではGEMとcisplatinの併用療法は標準治療の一つになって

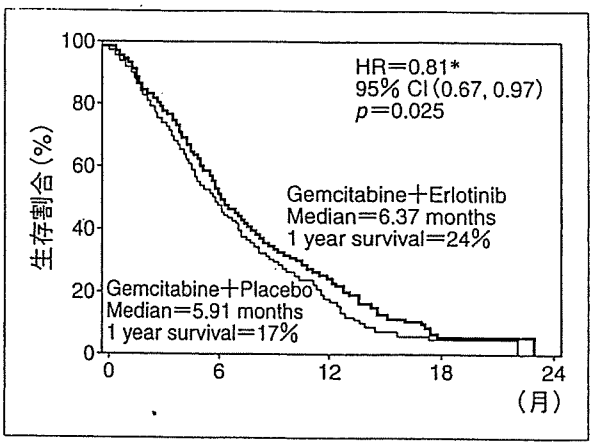


図7　GEM+Erlotinib vs. GEM
* Adjusted for PS, pain and disease extent at randomization　（文献[15]より引用）

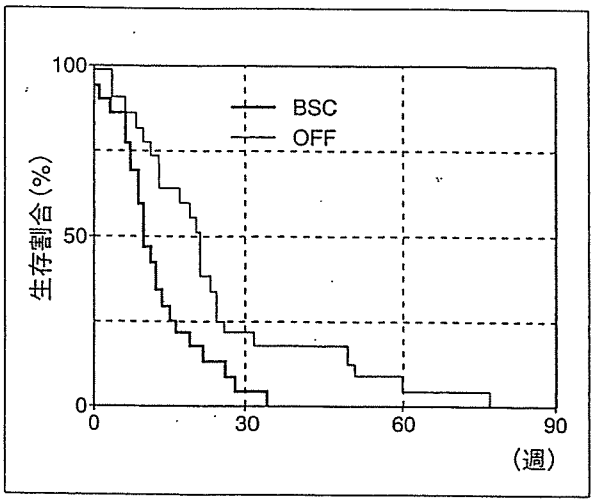


図8　セカンドライン化学療法：OFF vs. BSC
OFF：oxaliplatin+5-FU+leucovorin, BSC：best supportive care　（文献[19]より引用）

いる．膵がんにおいてもGEMとcisplatinの併用療法はいくつかの第Ⅱ相試験で良好な結果が報告されたが，第Ⅲ相試験ではGEM単剤よりも明らかに優れた生存期間を示すことはできなかった[13]．新しいプラチナ系抗がん剤のoxaliplatinも定速静注のGEMと併用した第Ⅱ相試験で良好な結果が示され注目されたが，Louvetらが行った第Ⅲ相試験では併用群の方が奏効割合および無増悪生存期間は有意に優れていたものの生存期間に関しては有意差を示すことができなかった（生存期間中央値：9.0か月 vs. 7.1か月，p=0.13)[14]．さらに，大規模な人数を集めて行われたECOGの第Ⅲ相試験でも，GEM定速静注法+oxaliplatinはGEM通常投与に対して明らかなsurvival benefitを示すことはできなかった[4]（図4）．

4．ゲムシタビン十分子標的薬剤

分子標的薬剤は現在膵がんに対してもっとも注目されている薬剤の一つである．2005年には上皮成長因子受容体（epidermal growth factor receptor；EGFR）tyrosine kinase阻害剤のerlotinibがGEMと併用することにより，GEM単剤よりも有意に生存期間を延長することが報告され，注目を集めた（中央値：6.4か月 vs. 5.9か月，p=0.025)[15]（図7）．GEM+erlotinibは進行膵がんに対する一つの選択肢として米国では承認されたものの，その差がわずかであったこと，併用群では下痢や皮疹などの副作用が認められたこと，併用療法が効くと思われる患者群を予測する方法がないことなどの理由よりGEM単剤に取って代わる治療という位置づけには至っていない．そのほか，抗EGFR抗体のcetuximabはGEMとの併用で12.2%の奏効割合と7.1か月の生存期間中央値を示しており[16]，現在第Ⅲ相試験が進行中である．血管内皮細胞成長因子（vascular endothelial growth factor；VEGF）阻害剤のbevacizumabもGEMと併用した第Ⅱ相試験で奏効割合21%，生存期間中央値8.8か月の結果を示し期待されていたが[17]，開発元であるGenentech社は最近同社のホームページで第Ⅲ相試験の中間解析結果を公表し，GEM+bevacizumabはGEM単剤の生存期間を有意に上回ることができなかったことを報告している[18]．

5．セカンドライン化学療法

GEM登場後，膵がんに対して化学療法が積極的に行われるようになり，GEM不応例に対する二次治療の問題がクローズアップされるようになった．CPT-11, oxaliplatin, capecitabineなどさまざまな抗がん剤が試みられているが，今のところコンセンサスが得られた二次治療は存在していない．2005年にはoxaliplatinと5-FUとleucovorinの併用療法を二次治療に受けた患者群の方がbest supportive careを受けた患者群よりも有意に生存期間が長かったことが報告されたが（生存期間中央値：21週 vs. 10週，p=0.0077)[19]（図8），症例数が少なく確証は得られていない．われわれがGEM不応例20例に対してS-1による二

次治療を行った結果では，奏効割合は15%，生存期間中央値は4.5か月であった[20]．膵がんに対する二次治療の開発は今後さらに活発化すると思われる．

おわりに

症状緩和効果と延命効果を有するGEMの登場は，進行膵がん患者に対する治療を大きく前進させた．とはいえ長期生存に関してはまだまだ現状は厳しく，さらに有効な一次治療や二次治療の開発が期待されている．

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Hepatic Arterial Infusion of 5-Fluorouracil and Extrabeam Radiotherapy for Liver Metastases from Pancreatic Carcinoma

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ABSTRACT

Background/Aims: To examine the efficacy and safety of a combined modality therapy consisting of hepatic arterial infusion of 5-fluorouracil and external-beam radiotherapy in patients with advanced pancreatic carcinoma.

Methodology: Hepatic arterial infusion chemotherapy consisted of 5-FU 1000mg/m^2 administrated as a 5-hr continuous infusion once weekly. External-beam radiotherapy (total dose, 50Gy; 2Gy/day) was delivered to the pancreas tumor concurrently for 5-6 weeks. Seventeen patients with no distant metastases except to the liver were enrolled in this study.

Results: Patients received a median of 13 cycles of chemotherapy. Sixteen of 17 patients received a total radiotherapy dose of 50Gy. In one patient, treatment was discontinued after 24Gy of radiotherapy and 2 cycles of chemotherapy because of progressive disease. Nausea and vomiting were the most common types of toxicity. Grade 3 or worse toxicity was observed in 2 patients. Four patients developed gastroduodenal ulcers. Of the 16 patients, 7 (41%) showed a partial response, and 9 (53%) showed no change. The median overall survival was 4.5 months and 1-yr overall survival of 11.8% was observed.

Conclusions: The combined therapy is active and well tolerated, but results in a poorer prognosis, in spite of its high initial response rate.

KEY WORDS: Pancreatic carcinoma; Liver metastasis; Hepatic arterial infusion; 5-fluorouracil; Radiotherapy

ABBREVIATIONS: Hepatic Arterial Infusion (HAI); External-Beam Radiotherapy (EBRT); 5-fluorouracil (5-FU); Partial Response (PR); No Change (NC); Progressive Disease (PD); Carbohydrate Antigen 19-9 (CA19-9); Computed Tomography (CT); World Health Organization (WHO)

INTRODUCTION

Liver metastasis is a common progression of pancreatic carcinoma and the prognosis of patients in whom it occurs is extremely poor. Although gemcitabine has been shown to be an active agent in the treatment of advanced pancreatic carcinoma, it has not been observed to adequately prolong patient survival (1). Hepatic arterial infusion (HAI) of 5-fluorouracil (5-FU) has been performed in several clinical trials in patients with liver metastasis from colorectal cancer and the findings indicate that HAI results in a high response rate (2,3). In addition, with regard to pancreatic carcinoma, recent study of HAI chemotherapy after vascular supply distribution via superselective embolization has also demonstrated promising results (4). At the present time, combined external-beam radiation therapy (EBRT) and 5-FU therapy are considered standard treatment for locally advanced pancreatic carcinoma (5-7). Thus, EBRT combined with HAI therapy using 5-FU is thought to have high clinical applicability and may prove beneficial to patients with pancreatic carcinoma without distant metastases, except to the liver. We therefore conducted a phase 2 study of combined EBRT and HAI using 5-FU to clarify the efficacy and safety of this treatment in patients with pancreatic carcinoma with metastasis restricted to the liver.

METHODOLOGY

Seventeen patients with advanced pancreatic cancer complicated by liver metastasis underwent HAI chemotherapy and EBRT between February 1998 and November 2000 at the National Cancer Center Hospital East. The eligibility criteria for inclusion in this study were: 1) histological proof of adenocarcinoma of the pancreas, 2) no distant metastases on computed tomography (CT) staging, except to the liver, 3) no previous anti-cancer treatment, 4) a performance status of 0, 1, or 2 according to the World Health Organization (WHO) grading system (8), 5) adequate bone marrow functioning (blood cell count of 4,000 or greater, platelet count of 100,000 or greater, and hemoglobin of 10g/dL or greater), adequate renal function (serum creatinine level of less than 1.1mg/dL), and adequate hepatic function (serum bilirubin level of less than 3.0mg/dL, serum alanine and aspartate transaminase levels of less than 200 IU/L), 6) no serious complications, and 7) receipt of written informed consent from the patient. Percutaneous biliary drainage was performed in patients with obstructive jaundice, and patients were required to have a total serum bilirubin level of less than 3.0mg/dL before initiation of treatment. Patient characteristics are summarized in **Table 1**.

Hepatic arteriography was performed prior to

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TABLE 1 Patient Characteristics

Characteristic	No. of patients (%)
Gender	
Male	11 (65%)
Female	6 (35%)
Median age (range)	59 (50-77)
WHO performance status	
0	5 (29%)
1	10 (59%)
2	2 (12%)
Location of primary tumor	
Head	5 (29%)
Body/tail	12 (71%)
Median CEA, ng/mL (range)	8.6 (0.8-185)
Median CA 19-9, U/mL (range)	827 (21-14552)

WHO: World Health Organization;
CEA: carcinoembryonic antigen;
CA 19-9: carbohydrate antigen 19-9.

catheter placement to determine the degree of arterial blood supply to the liver. The gastroduodenal and right gastric arteries of all patients were ligated with steel coils to prevent drug perfusion into the stomach and the duodenum. A catheter was positioned in the gastroduodenal artery. Catheters were placed via the left subclavian artery. The port was connected to the catheter and implanted in the subcutaneous space of the left chest wall.

After implanting the catheter and the port, 5-FU (1,000mg/m^2) mixed with 100mg of hydrocortisone (Solu-Cortef; Pharmacia & Upjohn, New Jersey, USA) and 5,000 U of heparin, was administrated over 5 hours through a battery-operated ambulatory infusion pump. After drug infusion, 20mL of saline and 5,000 U of heparin were infused through the pump. Cycles of intra-arterial infusion were repeated once weekly, unless there was evidence of disease progression or unacceptable toxicity levels.

Radiation therapy was delivered using the conformal, arc rotation technique to deliver a 10-MV X-ray, in order to achieve a total dose of 50Gy, given in 25 fractions over 5 weeks. The radiation field included the primary tumor and a 1- to 3-cm margin which covered the pancreaticoduodenal and celiac axis lymph nodes. This field was defined during treatment-planning CT one or two days before radiation therapy.

The toxicity of treatment was scored weekly according to WHO criteria (8). Both radiotherapy and chemotherapy were suspended if grade 3 toxicity was encountered, and resumed upon recovery to a grade 2 level of toxicity.

Follow-up CT was performed every month for 6 months, and every 2 months thereafter, in order to assess objective tumor responses according to WHO criteria. Local progression was diagnosed when the primary tumor was enlarged on CT, or when obstructive jaundice occurred after treatment. Overall survival was measured from the first day of treatment, and the survival rate was calculated by the Kaplan-Meier method (9). Serum CA 19-9 levels were measured every month by immunoradiometric assay using the Centocor radioimmunoassay kit (Centocor, Inc., Malvern, PA).

Patients received a full explanation about this study and gave written informed consent after approval of the protocols by the Institutional Review Board of the National Cancer Center.

RESULTS

A total of 251+ cycles of HAI chemotherapy were administrated (median 13, range 2-34+). Of 17 patients, 16 received EBRT with a total dose of 50Gy. In the remaining patient, treatment was discontinued after receipt of 24Gy of EBRT and 2 cycles of HAI because of disease progression. Therapy was discontinued due to disease progression in 14 patients, hepatic arterial obstruction in 1, and duodenal ulcer in 1. One patient was still receiving HAI chemotherapy at the time of writing.

Manifestations of treatment-related toxicity are summarized in **Table 2**. No life-threatening toxicity was observed, but 2 patients (12%) encountered Grade 3 toxicity. Nausea and vomiting were the most common types of toxicity. Four patients developed gastroduodenal ulcers after EBRT. Of these patients, one required hospitalization due to bleeding, and another

TABLE 2 Treatment-Related Toxicity according to WHO Criteria

	No. of patients (%)	
	Grade	
Toxicity	2	3
Leucopenia	3 (18%)	0
Anemia	0	0
Thrombocytopenia	3 (18%)	0
Nausea/vomiting	6 (35%)	2 (12%)
Liver dysfunction	0	0
Diarrhea	0	0
Mucositis	0	0

WHO: World Health Organization.

TABLE 3 Changes in the CA 19-9 levels of Patients with Elevated CA 19-9 Levels after Treatment (>100 U/mL)

Case no.	CA 19-9 (U/mL) Before *	After #	Tumor response$	Survival (days)
1	14552		NC	80
2	13216		PD	35
3	9945		PR	84
4	3944	673	PR	402
5	3091	292	NC	86
6	1739	53	PR	349
7	1526		NC	136
8	1428		NC	133
9	827		NC	114
10	318		PR	264
11	212		NC	114
12	170	41	NC	234

CA 19-9: carbohydrate antigen 19-9, NC: no change, PR: partial response, PD: progressive disease. *Maximal levels before treatment are represented; #Minimal levels after treatment are represented where responses were observed; $Assessed by computed tomography.

TABLE 4 Patterns of Initial Disease Progression

	No. of patients
Peritoneum (ascites)	6
Peritoneum and lymph node	1
Liver	2
Liver and lymph node	1
Liver and bone	1
Lymph node	1
Bone	1

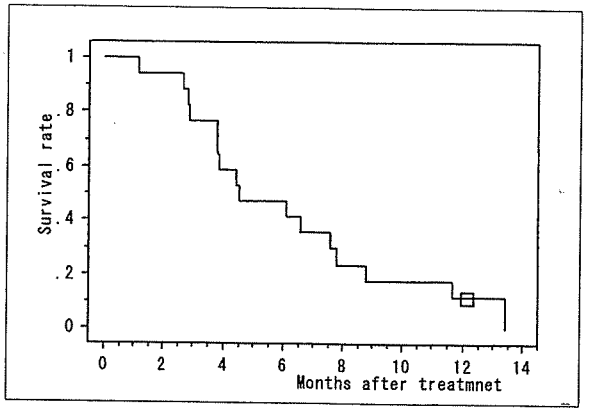

FIGURE 1 Overall survival curve for 17 patients treated with radiation and hepatic arterial 5-fluorouracil infusion. An open square indicates a censored case.

discontinued HAI therapy because of a refractory duodenal ulcer 5 months after initiation of treatment.

Seven (41%) patients had partial responses, 9 (53%) remained stable, and one showed progressive disease. Serum CA 19-9 levels were reduced by more than 50% in 4 of 12 patients (33%) who had pretreatment CA 19-9 levels of 100 U/mL or greater **(Table 3)**. Death from cancer was documented in 16 patients at the time of analysis. The initial sites of disease progression were documented in 13 patients **(Table 4)**. Peritoneal dissemination was the main cause of progression. Overall survival curves are shown in **Figure 1**. The median overall survival was 4.5 months and 1-yr overall survival was 11.8% observed.

DISCUSSION

Systemic chemotherapy using gemcitabine is considered standard therapy for advanced pancreatic carcinoma. However, a tumor response rate of only 5.4% and a survival time of 5.65 months have been observed with gemcitabine treatment, neither of which are satisfactory outcomes (1). High response rates of liver metastasis to HAI in patients with colorectal carcinoma have been reported (2,3,10). In a previous study (10), we employed continuous HAI of 5-FU for 5 days at a dose of 500mg/m^2/day every 4 weeks in order to treat liver metastasis from pancreatic carcinoma. The treatment was feasible but the overall response rate was only 8% at this dose and schedule. For treatment of liver metastasis from colorectal carcinoma, Arai *et al.* (3) reported a response rate of 78% after intermittent HAI of high-dose 5-FU once a week on an outpatient basis. In accordance with phase 1 and 2 studies, we therefore tried weekly HAI of 5-FU at a dose of 1000mg/m^2 for treatment of isolated liver metastasis from pancreatic carcinoma.

The toxicity associated with this regimen seemed to be mild. In the current study, grade 4 toxicity was not observed and the percentage of patients with grade 3 or worse toxicity was low (12%). Throughout the course of treatment, hematological toxicity was frequent but mild, and gastrointestinal toxicity was the only cause of treatment interruption. In a previous pilot study (11), hepatic artery occlusion was observed in 23% of patients and was the second cause of treatment discontinuation. However, occlusion of the hepatic artery occurred in only one patient (6%) in the current study. The frequency of hepatic artery thrombosis due to 5-FU infusion seemed to be lower with use of the intermittent schedule. On the other hand, gastroduodenal ulcers were frequently observed (24%), compared to a previous study in which HAI was administered continuously (8%) (11).

In the current study, an objective tumor response of 41% was noted following CT assessment. Serum CA 19-9 levels were reduced in 33% of patients with high initial CA 19-9 levels. Nine of the patients (53%) responded to therapy, as evaluated by CT or measurement of CA 19-9 levels. Greater response rates were observed with combination therapy than with any other form of systemic chemotherapy in the treatment of advanced pancreatic carcinoma. However, high response rates did not translate into prolonged survival for the patients in this study. For example, one of the patients who responded to treatment died due to peritoneal dissemination only 2.8 months after the initiation of the treatment. As shown in **Table 4**, peritoneal dissemination was the major cause of treatment failure. Hepatic extraction of 5-FU after HAI was estimated to be between 15-50% (12), thus, we expected a 150-500mg/m^2 weekly dose of 5-FU to produce a systemic anti-tumor effect. However, this dose seemed insufficient to reduce distant metastases, especially peritoneal dissemination. Surgical exploration revealed minute peritoneal metastasis in 12.5% of patients who had no distant metastases but locally unresectable pancreatic carcinoma, as assessed by CT staging (13).

Recently, excellent results have been reported using arterial infusion chemotherapy at the primary site of pancreatic carcinoma (4,14). In these reports, regional chemotherapy for pancreatic carcinoma was repeated for as long as catheters remained patent without occlusion or dislocation. Long-term tumor control might be obtained via this method, provided the tumor is responsive to the agent being infused. With respect to radiotherapy, however, it would be difficult to deliver a dose exceeding 72Gy to the pancreatic region, regardless of whether or not the tumor is responsive to radiotherapy (15). We will not select a higher dose of EBRT in combination with HAI in our next trial because we do not believe intensification of radiotherapy can reduce distant progression in pancreatic cancer patients. We do not know whether regional chemotherapy has the ability to reduce peri-

toneal dissemination from pancreatic carcinoma. However, this might explain the prolonged survival of patients in studies involving regional chemotherapy (4,14).

We conclude that liver metastasis from pancreatic cancer responds well to HAI, but that combination therapy fails to prolong the survival of such patients. Thus, we do not feel that a radiotherapeutic approach can be used to treat patients with pancreatic carcinoma who do not have distant metastases, except to the liver, as evaluated by clinical staging. Therefore, HAI should be used in combination with either systemic chemotherapy or regional chemotherapy at the primary site.

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Needle Tract Implantation of Hepatocellular Carcinoma and Pancreatic Carcinoma after Ultrasound-guided Percutaneous Puncture: Clinical and Pathologic Characteristics and the Treatment of Needle Tract Implantation

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Abstract. Tumor implantation along the needle tract following percutaneous procedures under ultrasonographic guidance for hepatocellular carcinoma (HCC) and pancreatic carcinoma (PC) has been well documented. The purpose of the present study was to investigate the correlation between the procedure, the pathologic differentiation of the primary tumor, and the treatment after implantation. Between July 1992 and March 2000, HCC patients (n = 372) who underwent biopsy, percutaneous ethanol injection (PEI) therapy and percutaneous microwave coagulation therapy (PMCT) and PC (n = 73) patients who underwent biopsy were retrospectively studied. Needle tract implantation was found in six of the HCC patients (1.6%) and one of the PC patients (1.4%). The interval to diagnosis ranged from 5 to 25 months (mean ± SD 11.2 ± 7.6 months) in the HCC patients. The needle tract implantation was evident for all procedure types in these patients (two after PEI alone, two after both biopsy and PEI, and one after PMCT) and for each degree of pathologic differentiation of the primary tumors (well differentiated in one, moderately differentiated in two, and poorly differentiated in one). Each implanted tumor was surgically resected, with no recurrence at the focal lesion. These results suggest that needle tract implantation develops regardless of the procedure or the pathologic differentiation of the primary tumor, and that surgical resection might be effective for controlling these implanted lesions.

For the pathologic diagnosis or treatment of hepatocellular carcinoma (HCC) and pancreatic carcinoma (PC), percutaneous needle biopsy, ethanol injection (PEI), microwave coagulation therapy (PMCT), and radiofrequency (RF) ablation under ultrasonographic (US) guidance have become increasingly common since the late 1980s [1–4]. Complications associated with these procedures have been reported [5, 6], however, with needle tract implantation of cancer cells being particularly well documented [7–16]. To increase the safety of these percutaneous procedures, such complications must be prevented or, at the very least, patients with implantations treated with a minimum load. To date, only a few studies have investigated the relations between such implantation and the procedure, the pathologic differentiation of the primary tumor, and treatment of the implanted tumor. Therefore we retrospectively investigated the clinical and pathologic characteristics and the treatment of needle tract implantation.

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Materials and Methods

The medical records of 372 patients with HCC (484 lesions; 296 men, 76 women; mean age of 62.7 ± 8.5 years) and 73 patients with PC (73 lesions; 48 men, 25 women; mean age of 59.5 ± 10.4 years) who underwent percutaneous biopsy, PEI, PMCT, or a combination of these procedures between July 1992 and March 2000 at the National Cancer Center Hospital East were retrospectively examined. Written informed consent was obtained from all patients prior to needle biopsy, PEI, or PMCT.

At our hospital, needle biopsy for HCC is performed when it is difficult to arrive at a definitive diagnosis of a liver tumor using radiologic examinations, dynamic computed tomography (CT), magnetic resonance imaging (MRI), or hepatic arteriography. In patients who underwent PEI or PMCT for the first time, needle biopsy was also performed immediately prior to treatment to confirm the diagnosis. PEI and PMCT were indicated for HCC lesions 3 cm or less in diameter and three or fewer in number. We performed PEI between July 1992 and March 1998 and PMCT between April 1998 and March 2000 as the treatment of choice for small HCCs. In PC patients, needle biopsy was performed only for those with (1) unresectable advanced disease, (2) locally advanced disease with definite invasion of the celiac artery, the superior mesenteric artery, or the portal vein (or all of them) from both sides of the tumor, or (3) distant metastases.

When needle biopsy, PEI, or PMCT was performed, we used a 3.5 MHz convex probe equipped with a lateral guide attachment. The most appropriate approach was chosen after local sterilization with povidone-iodine, which was also used as the contact medium.

In principle, the intercostal approach was used for lesions located in the right lobe and the medial approach for lesions in the left lobe. The medial approach was always used for pancreatic tumors.

Biopsy of the HCC or PC was performed using a 21-gauge needle (Sonopsy-C1; Hakko, Tokyo, Japan) using one or two punctures. When a needle was introduced for the second time, the needle was thoroughly washed in 10% alcohol prior to puncture. For PEI, one to three needles were introduced percutaneously into the tumor under ultrasonographic guidance. A 22 gauge, 15 cm Chiba needle (Top, Tokyo, Japan) was employed for puncture. A 2- to 5-ml aliquot of absolute ethanol (99.5%) was slowly injected through each needle. The injection was repeated twice a week for two to six sessions. While these needles were being removed, 1 ml of 1% lidocaine was slowly injected through each needle. For PMCT, a microwave tissue coagulator with a microwave frequency of 2450 MHz (Microtaze OT-110M; Azwell, Osaka, Japan) and an electrode needle 1.6 mm in diameter with a 1 cm long monopolar electrode at the tip (Azwell, Osaka, Japan) were used. First, a 14-gauge guide needle (Quickcut-C2; Hakko, Tokyo, Japan) was introduced percutaneously toward the tumor, and the electrode needle was placed into the tumor through this guide needle. Microwave coagulation was performed for 60 seconds at a setting of 60 W as one session, and depolarization was performed for 15 seconds at 20 mA after each session. The coagulation was repeated two to nine times according to tumor size. While the electrode needle and guide needle were being removed, the whole puncture route was exposed to microwave coagulation at 60 W.

Of the 484 HCC nodules in these 372 patients, 99 were diagnosed by clinical examination, including dynamic CT, angiography, and serum α-fetoprotein assay. The remaining 385 HCC nodules were histologically diagnosed by examining specimens obtained by ultrasonically guided needle biopsy using 21-gauge needles. The diagnosis of PC was based on histologic findings of specimens obtained by ultrasonically guided needle biopsy with 21-gauge needles. Based on the degree of pathologic differentiation according to World Health Organization (WHO) criteria, the HCCs and PCs were classified into three classes: well differentiated, moderately differentiated, and poorly differentiated.

For HCC, needle biopsy alone was performed for 31 lesions in 31 patients, and PEI alone was performed for 99 lesions in 69 patients; both biopsy and PEI were performed for 278 lesions in 204 patients, and both biopsy and PMCT were performed for 76 lesions in 68 patients. Among the 31 patients with HCC who underwent needle biopsy alone for diagnosing a hepatic tumor, radiotherapy was performed in 2 patients, hepatectomy in 11, and transcatheter arterial chemoembolization in 18.

Following needle biopsy, PEI, and PMCT, all patients were followed up with US, dynamic CT, or both at least every 3 months. Needle tract implantation was diagnosed when a newly developed tumor was seen by CT and US in the cutaneous or subcutaneous tissue just on the line of needle insertion. Follow-up time ranged from 1 year 6 months to 9 years 3 months.

Statistical analysis was performed using the χ^2 test for independence to compare the pathologic differentiation and some clinical characteristics. Statistical significance was established at the $p < 0.05$ level.

Results

The incidence of needle tract implantation in association with pathologic tumor cell differentiation of primary tumor and procedures is shown in Tables 1 and 2. Needle tract implantation was found in six of the HCC patients (1.6%) and one of the PC patients (1.4%). No other major complications accompanied the needle insertion procedures, except in the abdominal cavity of a patient with HCC treated by PMCT. The patient had severe thrombocytopenia (19,000/mm^3) due to liver cirrhosis, and the bleeding was controlled conservatively. Implantation occurred for each differentiation grade of the HCC tumors and in a PC patient with moderately differentiated adenocarcinoma. No statistical differences were seen between the pathologic differentiation of the primary tumor and implantation for either HCCs or PCs ($p = 0.54$, $p = 0.57$, respectively). Table 2 also shows that there was no statistical difference between the procedures and the needle tract implantation in HCC patients ($p = 0.63$).

Table 1. Incidence of needle tract implantation in association with pathologic tumor cell differentiation of primary tumors.

	HCC		PC	
Parameter	No.	Implantation	No.	Implantation
Pathologic differentiation				
Well	224	1 (0.5%)	6	0
Moderately	110	2 (1.8%)	27	1 (3.7%)
Poorly	51	1 (2.0%)	27	0
Unknown[a]	0	0	13	0
Not examined[b]	99	2 (2.0%)	—	—
Total	484	6 (1.2%)	73	1 (1.4%)

HCC: hepatocellular carcinoma; PC: pancreatic carcinoma.
[a]Unknown: adenocarcinoma was diagnosed by specimen obtained by needle biopsy, but pathologic differentiation was not determined.
[b]Diagnosis of HCC was made by clinical examination, including dynamic computed tomography, angiography, and measurement of serum α-fetoprotein concentration.

Table 2. Incidence of needle tract implantation in association with procedures.

	HCC		PC	
Parameter	No.	Implantation	No.	Implantation
Procedure				
Biopsy	31	1 (3.2%)	73	1 (1.4%)
PEI	99	2 (2.0%)	—	—
Biopsy and PEI	278	2 (0.7%)	—	—
Biopsy and PMCT	76	1 (1.3%)	—	—
Total	484	6 (1.2%)	73	1 (1.4%)

PEI: percutaneous ethanol injection; PMCT: percutaneous microwave coagulation therapy.

Primary tumor and implanted tumor characteristics in patients and the outcomes of these patients are shown in Tables 3 and 4. All implanted tumors were palpable and detected by both US and CT. The interval until the development of the implantation was 2 to 8 months for moderately and poorly differentiated tumors, whereas that for well differentiated tumors was more than 12 months. The interval until the development of the implantation in patients with HCC was 5 to 25 months (11.2 ± 7.6 months, mean ± SD); it was 2 months in the PC patient.

All seven patients with implantation tumors underwent surgical resection. All of these tumors were resected with at least a 1 cm diameter margin. No recurrences in the cutaneous or subcutaneous tissue were detected in five patients with HCC or in the one patient with PC. In the remaining HCC patients (case 5, Table 3), a repeat

Table 3. Clinicopathologic features in patients with needle tract implantation.

Case no.	Primary tumor characteristic				Interval (months)[a]
	Location	Size (mm)	Procedure	Differentiation	
1	S5–8	80	Biopsy	Poorly	5
2	S8	20	Biopsy + PEI	Moderately	5
3	S8	20	Biopsy + PEI	Moderately	8
4	S7	20	PEI	Not examined	10
5	S2	10	PEI	Not examined	14
6	S6	27	Biopsy + PMCT	Well	25
7	Pb[a]	47	Biopsy	Moderately	2

Cases 1 to 6 were hepatocellular carcinoma; case 7 was pancreatic carcinoma.

Pb: pancreas body.

[a]Period between the procedure and the development of needle tract implantation.

Table 4. Outcomes in patients with needle tract implantation.

Case no.	Implanted tumor		Treatment	Survival time (months)[a]	Outcome
	Size (mm)	Differentiation			
1	30	Poorly	Resection	10	Deceased
2	30	Moderately	Resection	13	Living
3	20	Moderately	Resection	6	Living
4	15	Moderately	Resection	64	Deceased
5	25	Well	Resection	44	Living
6	27	Well	Resection	4	Living
7	10	Moderately	Resection	12	Deceased

Cases 1 to 6 were hepatocellular carcinoma; case 7 was pancreatic carcinoma.

[a]Time from the date of resection of the implanted tumor.

operation was required owing to the redevelopment of an implanted tumor in the subcutaneous tissue after the first surgical resection. However, this patient was eventually cleared, with no recurrence of the implanted tumor. Of the six patients with HCC, two died of primary tumor progression and four remain living. The PC patient with the implanted tumor did not experience recurrence of the tumor in the needle tract but later died of primary tumor progression (Tables 3, 4).

Discussion

Percutaneous liver puncture under ultrasonographic guidance, percutaneous liver biopsy, PEI, PMCT, and RF ablation, have been widely performed for the purpose of gaining an exact diagnosis and determining the appropriate treatment. Furthermore, although detection of small pancreatic tumors using US, enhanced CT, and MRI is now possible, an exact diagnosis of some pancreatic tumors is difficult using only diagnostic imaging methods, making a pancreatic biopsy necessary to obtain a definitive diagnosis of a tumor without typical findings on any examination. Several reports of needle tract implantation after biopsy and PEI in patients with HCC [7–12, 16], as well as a few with PC, have been reported [13–15].

Smith [6] reported that the incidence of needle tract implantation was only 0.005% (3/63,108 cases) in 1984. However, that report used results from a review of the literature and the results of a hospital survey, and it included various abdominal tumors, salivary gland adenoma, prostatic carcinoma, and breast carcinoma. Furthermore, the incidence of this complication may have been increasing as the use of US-guided percutaneous puncture has become more widespread. For instance, Ishii et al. [16] reported an incidence of needle tract implantation in HCC patients of 1.1% (4/384 tumors) in 1998, similar to the 1.6% (6/484 tumors) in HCC patients and 1.4% (1/73 tumors) in PC patients in the present study.

In previous reports, the implanted tumor in HCC patients was demonstrated in the early phase as a hyperattenuated lesion, same as the primary tumor in the early phase of enhanced dynamic CT [9, 10]. In the present study, needle tract implantation occurred even in well differentiated HCCs and PCs, which are mostly considered hypovascular tumors on dynamic CT. In some cases, the tumors appear hypovascular on dynamic CT and are subjected to percutaneous needle biopsy or ablation therapy, which also carries the risk of needle tract seeding. In the present study, all implanted tumors were palpable; and at the beginning they were diagnosed by complaints of a mass in the abdominal or chest wall in most patients. Furthermore, all primary lesions also were visible at the same site of the implanted tumors by US and CT, enabling confirmation of needle tract seeding.

The interval between the procedure and the development of needle tract implantation has been reported to be 6 to 46 months after needle biopsy or PEI (or both) [8, 11, 12, 16]. In the present study, this interval was 5 to 25 months for the HCC patients. Furthermore, pathologic differentiation correlated with the interval from puncture to development of the implantation, and there was a tendency for these implanted tumors to develop earlier with moderately or poorly differentiated HCCs than with well differentiated HCCs. With PCs, needle tract implantation tends to develop earlier than with HCCs. Ferrucci et al. [13] reported that needle tract seeding occurred 3 months after biopsy of a pancreatic carcinoma under CT guidance. In the present study, seeding was also observed 2 months after needle biopsy under ultrasonographic guidance in one patient with PC. These findings suggest that follow-up for at least 2 years is required for detection of needle tract implantation in patients who undergo these percutaneous procedures according to the primary tumor, especially well differentiated tumors.

Ishii et al. [16] reported that the risk of needle tract implantation in HCC patients treated by PEI increases when the tumor size is > 2 cm in diameter. However, in the present study, four of the six implanted tumors occurred in primary HCC tumors ≤ 2 cm in diameter, possibly because smaller lesions are increasingly detected by US or CT. Furthermore, the present study has demonstrated that needle tract implantation occurs without regard to pathologic differentiation or procedure. In patients who underwent PMCT, the whole puncture route was coagulated to prevent bleeding by microcoagulation while the needle was being removed. We had thought that needle tract implantation would seldom occur in these patients, but 1 of the 76 patients (1.3%) who underwent PMCT had an implantation. Thus needle tract implantation should be considered during follow-up examinations in all patients who undergo percutaneous needle puncture.

Radiation therapy or surgical resection is generally performed for implanted tumors from an HCC [7–10, 16]. However, there is not yet a consensus on the most suitable treatment for such implanted tumors. Surgical resection is used to treat implanted tumors at our hospital with good results. In the present series, only one HCC patient required another operation owing to significant

invasion of surrounding vessels by the implanted tumor. Surgical resection was, and can be, safely performed for needle tract implantation tumors in all patients. In addition, if the implanted tumor is small and located only in the cutaneous region, surgical resection can be performed under local anesthesia. Thus we believe surgical resection to be the most valuable method for treating implantation tumors.

To avoid needle tract implantation, there are some general points of which physicians should be aware when inserting needles into tumors. (1) Piston-like motion of the needle in the tumor should be avoided, as this procedure can break malignant tissue into smaller pieces. (2) To avoid pieces of malignant tissue falling when a needle is released from a tumor, physicians must constantly absorb debris using negative pressure. (3) After a puncture is performed, there is the danger of cancer cells drifting away from the needle tract into the abdominal cavity and subcutaneous tissue owing to the high pressure of ethanol or normal saline solution injected into the tumor. (4) If an operation on a liver or pancreatic tumor is performed, the route of the needle tract must be resected with the primary tumor.

It is noteworthy that, despite following these guidelines, needle tract implantation still occurred with an incidence of about 1% in the present study. This underlines the importance of performing percutaneous needle biopsy only when absolutely necessary. Furthermore, it is also important that implanted tumors are diagnosed early by follow-up examinations that check for implantation regardless of the pathologic differentiation or the procedures performed. This practice enables surgical resection for the implantation tumor to be safely performed using general or local anesthesia.

Résumé. L'implantation tumorale le long du trajet de la ponction percutanée à l'aiguille sous guidance échographique pour carcinome hépatocellulaire (CHC) et cancer pancréatique (CP) est bien documentée. Il existe quelques études explorant le mode d'implantation tumorale le long de la ponction après ces actes. Le but de cette étude a été d'établir une corrélation entre la ponction, la dédifférentiation anatomopathologique de la tumeur primitive et le traitement de l'ensemencement tumoral. Entre juillet 1992 et mars 2000, tous les patients porteurs de CHC (n = 372) ayant eu, par voie percutanée, soit une biopsie (B), soit une injection d'éthanol (IE) ou un traitement par micro-ondes (MO) et tous les patients porteurs de CP (n = 73) ayant eu une biopsie, ont été étudiés rétrospectivement. On a découvert une dissémination tumorale chez six des patients porteurs de CHC (1.6%) et chez un des patients porteurs de CP (1.4%). L'intervalle entre la ponction et le diagnostic d'ensemencement allait de 5 à 25 mois (moyenne ± ET: 11.2 ± 7.6 mois) chez les patients CHC, l'implantation tumorale ayant été retrouvée après tous les types d'intervention percutanée (deux après IE seule, deux après B et IE et un après MO) et dans tous les types de dédifférentiation histopathologique des tumeurs primitives (bien différenciée dans un, peu différenciée dans deux, et indifférenciée dans un). Dans tous les cas, on a pu exciser chirurgicalement le tissu pathologique, sans aucune récidive locale. Ces résultats suggèrent que la dissémination tumorale se produit quelque soit le procédé employé, le degré de dédifférenciation de la tumeur primitive et que la résection chirurgicale peut être efficace pour contrôler ces lésions de dissémination.

Resumen. Está demostrada la implantación tumoral a lo largo del trayecto de la aguja tras procedimientos de punción percutánea, bajo control ecográfico, en carcinomas hepatocelulares (HCC) y carcinomas de páncreas (PC). Se han efectuado pocas investigaciones de cómo se produce la implantación a lo largo del trayecto de la aguja tras estos procedimientos diagnóstico-terapéuticos. El objetivo del trabajo fue averiguar si existe una correlación entre la técnica, la diferenciación del tumor primario y el tratamiento de los implantes. Se estudiaron retrospectivamente desde julio de 1992 a marzo de 2000 los HCC (n = 372) que fueron biopsiados, sometidos a tratamiento con inyección percutánea de etanol o con coagulación percutánea por microondas. Además, se estudiaron los PC (n = 73) que fueron simplemente biopsiados. Implantación tumoral en el trayecto de la aguja se constató en 6 pacientes con HCC (1.6%) y en 1 con PC (1.4%). En los pacientes portadores de un HCC el tiempo que transcurrió hasta efectuar el diagnóstico osciló entre los 5 y 25 meses (media ± desviación estándar: 11.2 ± 7.6 meses). En estos pacientes la implantación, a lo largo del trayecto de la aguja, se evidenció con todas la diferentes técnicas empleadas [2 tras instilación exclusiva de etanol (PEI), 2 tras biopsia y PEI y uno tras coagulación (PMCT)] y con cualquier grado de diferenciación del tumor primario (bien diferenciado en 1 caso, moderadamente diferenciado en 2 y pobremente diferenciado en uno). Cada implante tumoral fue extirpado quirúrgicamente sin recidiva alguna. Estos resultados demuestran que la implantación a lo largo del trayecto de la aguja no depende, ni de la técnica realizada ni del grado de diferenciación del tumor primario y que la resección quirúrgica del implante constituye el tratamiento de elección.

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Chapter II

CHEMORADIATION THERAPY FOR LOCALLY ADVANCED PANCREATIC CARCINOMA: INTRAOPERATIVE AND CONFORMAL EXTERNAL BEAM RADIATION THERAPY WITH OR WITHOUT PROTRACTED 5-FLUOROURACIL INFUSION

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ABSTRACT

Purpose: We reviewed retrospectively two studies which we conducted before to clarify the efficacy and feasibility of chemoradiation therapy with a combination of intraoperative radiation therapy (IORT) and conformal external beam radiation therapy (EBRT) alone in one study and with protracted therapy 5-fluorouracil (5-FU) in another study in patients with locally advanced pancreatic carcinoma.
Methods: Fifty-four patients with unresectable locally advanced pancreatic carcinoma diagnosed on the basis of the dynamic computed tomography findings and who satisfied the criteria for our clinical studies were reviewed. There were 24 patients in the radiation therapy alone study (Group A) and 30 in the chemoradiation therapy study (Group B).

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The radiation therapy in both studies consisted of IORT (25 Gy) followed by EBRT (40 Gy in 20 fractions, 5 times/week) beginning 2 to 4 weeks after IORT. In group B, protracted 5-FU infusion (200 mg/m^2) was concurrently combined with EBRT. We compared efficacy and adverse effects on these regimens.

Results: At laparotomy cancer spread in the abdomen was detected in 20 of the 54 patients: 9 of the 24 patients in group A and 11 of the 30 patients in group B. It had spread to the liver in 10 patients, to the peritoneum in 5 patients, to both the liver and peritoneum in 4. patients, and to a distant lymph node in one patient. The overall response rate for the primary pancreatic tumor was 25% in group A and 23% in group B. Grade 3 or 4 toxicity was observed in 50% of the patients in group A and 54% of the patients in group B. The most common toxicities were anorexia and nausea. The overall median survival time (MST) of the 54 patients was 7.7 months, and the 1- and 2-year survival rates were 29.6% and 9.3%, respectively. The MST of the 34 patients without cancer spread in the abdomen was 11.9 months, as opposed to 5.4 months in the 20 patients with cancer spread in the abdomen ($P<0.0001$). However, there was no significant difference in survival between group A and group B.

Conclusions: Approximately one-third of patients clinically diagnosed with locally advanced pancreatic carcinoma already had metastatic disease at the time of diagnosis. The chemoradiation regimen consisting of IORT plus EBRT and continuous infusion 5-FU was no better than radiation therapy alone. Systemic chemotherapy should be developed as part of chemoradiation therapy for locally advanced pancreatic carcinoma.

Key words: pancreatic carcinoma, intraoperative radiation therapy, conformal external-beam radiation therapy, chemoradiation therapy, 5-fluorouracil.

INTRODUCTION

Unresectable pancreatic carcinoma without distant metastasis is classified as "locally advanced," and patients with locally advanced cancer have a particularly poor prognosis. Based on the results of three randomized trials chemoradiation therapy or chemotherapy alone has been thought to be a reasonable approach to the treatment of locally advanced disease.[1-3] In previous reports on the treatment of locally advanced pancreatic carcinoma the external-beam radiation therapy (EBRT) doses ranged from 40 Gy to 55 Gy, and various chemotherapy regimens using 5-fluorouracil (5-FU) were combined with radiation therapy in an effort to improve the efficacy of radiation therapy.[4-6] In other studies, high radiation doses have been administered by using combinations of intraoperative radiation therapy (IORT) and EBRT or high-dose conformal radiation therapy.[7-11] IORT or conformal irradiation using a three-dimensional irradiation system enables the radiation dose to tissues surrounding the pancreas to be reduced.

Between January 1993 and May 2001, we conducted two consecutive prospective studies of intensive chemoradiation therapy consisting of a fixed radiation dose delivered by IORT followed by conformal EBRT with or without protracted infusion of 5-FU for locally advanced pancreatic carcinoma.[12,13] In the first study, we used combined radiotherapy consisting of IORT plus EBRT to evaluate the efficacy and feasibility of intensive radiotherapy alone. In the second study we combined the same radiotherapy with concurrent

infusion of 5-FU. We then retrospectively compared the results in the patients treated by radiotherapy alone and chomeradiotherapy in these two clinical studies and assessed the efficacy and feasibility of intensive radiotherapy and chemoradiation therapy in patients with locally advanced pancreatic carcinoma.

Table 1. Patient Characteristics

	No. of patients in each study	
Variable	IORT±EBRT (n=24)	IORT+EBRT with 5-FU (n=30)
Gender		
Male	11	19
Female	13	11
Median age (range)	61 (45-83) years	58 (32-75) years
ECOG performance status		
0	13	19
1	10	9
2	1	2
Primary site		
Head	13	10
Body and tail	11	20
Tumor size (cm)		
$> 2.0, \leq 4.0$	11	15
$> 4.0, \leq 6.0$	13	15
Metastasis not detected by CT		
Absent	15	19
Present	9	11
CA19-9 before treatment (U/mL)		
≤ 37	7	10
$> 37, < 500$	10	11
> 500	7	9

ECOG, Eastern Cooperative Oncology Group; IORT, intraoperative radiation therapy; EBRT, external beam radiation therapy; 5-FU, 5-fluorouracil.