図4 下痢の種類とその発生メカニズム

プロスタグランジンE$_2$は腸管粘膜上皮のアデニレート サイクレースを活性化し，細胞内Caイオン濃度を上昇させることによって腸液の分泌を亢進させ，分泌性下痢を起こす（図4）．半夏瀉心湯の黄芩の成分であるオウゴニンや乾姜の成分であるショウガオールはプロスタグランジンE$_2$を抑制する効果がきわめて強いことから下痢抑制効果の有効成分と考えられている．イリノテカンによる下痢発生でもっとも特徴的なことは遅発性下痢を起こすことで，イリノテカンの活性代謝物SN-38が肝臓でグルクロン酸抱合体となり胆汁排泄され，腸内細菌叢のβ-グルクロニダーゼによって脱抱合され再活性化し，腸管粘膜上皮細胞から濃度依存的にClイオンの分泌を増加させ，これが腸管粘膜の細胞傷害をきたし下痢を起こす．半夏瀉心湯の黄芩の成分フラボノイド配糖体のバイリンには，β-グルクロニダーゼを阻害する活性があるため，活性型の腸管での再活性化を抑え，イリノテカンによる下痢を抑制すると考えられている[17]．したがって，イリノテカンの投与数日前から使用しておく必要があるが，早期下痢では発生してから投与しても効果が期待できる．半夏瀉心湯はイリノテカンの抗腫瘍効果に影響しないことは確認されている[18]．

　また，単盲検前向き試験が行われ，その有効性が確認されている[19]．今後はプラセボ対照の多施設二重盲検試験の実施が期待される．

▌口内炎

　化学療法中の口内炎の発症率は使用する抗がん薬の種類によって差がある．オキサリプラチンは10～20％程度だがイリノテカンでは40％，抗EGFR抗体など分子標的薬を併用することで60％程度まで増加する．発症原因としては，抗がん薬によって
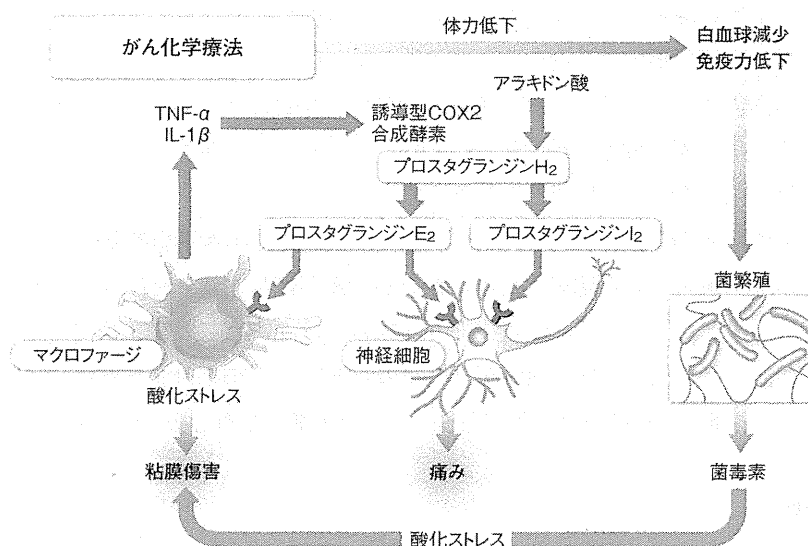
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図5 化学療法による口内炎発生メカニズム

発生する活性酸素による口腔粘膜細胞のDNA障害，各種サイトカインなどによるアポトーシス誘導，各種炎症性プロスタグランジンとくにプロスタグランジンE_2による疼痛出現，宿主の免疫能低下による細菌増殖などがあげられている（図5）．化学療法時の口内炎はQOLを著しく低下させるにもかかわらず，有効な治療手段はほとんどなく，予防的な手法として口腔内清潔や，抗がん薬の口腔内に到達する薬剤濃度を低下させる目的で氷などを口の中に含ませるクライオテラピーが報告されている．治療に関して最近，遺伝子操作で合成したケラチノサイト増殖因子が化学療法に起因する口内炎に対し治療的効果が確認され米国FDAでは承認されたが，わが国では未承認である．そのケラチノサイト増殖因子に関して安全性の面，つまりがん細胞に対する増殖因子となる可能性について十分な検討はなされていないことが危惧されている．

　口内炎による痛みは摂食障害の大きな原因となる．したがって，痛みをコントロールすることが治療における最初の大きな目標となる．口内炎の痛みは感覚神経へのプロスタグランジンE_2の作用で誘発されると考えられているが，半夏瀉心湯は炎症部位のプロスタグランジンE_2を濃度依存的に産生を抑制する効果が報告されており[20, 21]，痛みを早期に減弱させる効果が期待できる．抗がん薬による免疫力低下に伴い，口腔内環境，とくに口腔内細菌叢による二次感染も口内炎増悪への関与が示唆されているが，半夏瀉心湯の構成生薬である黄連の主要成分であるベルベリンは強い抗菌作用を有しており，細菌性細胞障害に対する抑制効果が報告されていることから，口腔内の細菌増殖抑制効果が期待される．そこで，われわれはこれらの局所作用を最大にするために半夏瀉心湯をコップ半分程度の水道水に1包（2.5g）を撹拌し，数回に分けて

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1回5秒以上含嗽使用した．痛みが強い部位には直接半夏瀉心湯を塗布することを考案し，大腸がん化学療法中に発生した口内炎に対し嗽て半夏瀉心湯を使用した後ろ向きの臨床試験を行ったところ，期待通りの有効性が確認できた[22]．現在，多施設プラセボ対照前向き二重盲検第Ⅱ相試験（HANGESHA試験）で，胃がん，大腸がん化学療法中に発生する口内炎を予防できるか検証中である．

　本来，服用するのが漢方薬の原則だが，口内炎に関して局所濃度を高める目的で含嗽を行い，化学療法による嘔気がある場合でも治療可能な方法であることから患者に推奨しやすい．また，イリノテカン使用時には服用してもらうことで下痢に対しても効果が期待でき一石二鳥である．潰瘍部分に直接塗布すると最初刺激を感じるが5分ほどで消失し，潰瘍部分の痛みが同時に消失することを筆者も含め多くが経験している．

■安全性

　偽アルドステロン症，間質性肺炎，肝機能障害などが報告されているが重篤なものはない．

　単一の化学物質の機序から対象疾患が明らかとなる西洋薬と比べて最初に経験則から対象疾患が明らかとなり，しかも多数の化学物質から構成される漢方薬は非常に厳しい立場にある．漢方薬にとって最優先事項は機序解明であり，それなくして世界的な展開は望めない．化学療法の発展は延命効果だけでなく副作用との戦いでもある．漢方薬は有力な武器となることが期待されており，本項ではエビデンス中心に効果を実感できる可能性が高い漢方薬を紹介した．

（河野　透）

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4. 局所進行大腸癌の down staging を目的とした neo-adjuvant therapy*

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〔要旨〕局所進行大腸癌の外科治療においては，たとえ遠隔転移を伴わなくとも，外科的切除縁の確保の課題や拡大切除の侵襲程度によっては，切除不能と判断せざるをえないことも多い．近年，化学療法や放射線療法の進歩により，切除不能大腸癌に対し down staging をめざした neo-adjunvant therapy を行い切除が可能となる，いわゆる conversion 例が多く報告されている．局所進行癌に対する conversion therapy についての詳細な検討はないものの，FOLFOX や FOLFIRI に分子標的治療薬を併用したレジメンおよび放射線療法との組み合わせの効果が，治癒切除率の向上と生命予後の延長という点で有望視されている．

はじめに

進行大腸癌の治療において，外科的切除は治癒を期待できるもっとも強力な治療法であることはいうまでもなく，『大腸癌治療ガイドライン』においても治癒切除可能であれば外科的切除が第一選択枝として推奨されている[1]．しかし，肝・肺・腹膜などへの同時性転移や，原発巣の周囲組織・臓器への進展により治癒切除不能な場合には化学療法が行われてきたが，必ずしも満足できる成績は得られていなかった．

近年，化学療法や放射線療法の進歩により，切除不能大腸癌の中にも，これらの治療により腫瘍が縮小し，治癒切除可能となる症例を経験する機会が増した．このような治療戦略を近年 conver-sion therapy と称し，切除不能大腸癌の治癒をめざす治療法として注目されている．特に，遠隔転移を伴わない局所進行大腸癌は Stage II もしくは Stage III であることから，徹底的な局所管理により長期生命予後が期待できるため，積極的な集学的治療の介入に期待が寄せられている．本稿では，このような切除不能局所進行癌に対する down staging をめざした neo-adjuvant therapy について解説する．

I. Conversion therapy

Conversion therapy とは，薬物療法や放射線療法で奏効性が得られ，治癒切除不能と判断されていた大腸癌が切除可能となり，治療方針を手術治療へと移行することをさす[2]．本邦ではそれに相

表1. 進行大腸癌に対する分子標的治療薬を併用した一次治療の成績

試験名（年）	化学療法レジメン	患者数	奏効率（%）	conversion達成率（%）
NO16966 (2008)[4]	FOLFOX/CapeOX	701	38	6.1
	FOLFOX/CapeOX + Bmab	699	38	8.4
CRYSTAL (2009)[5]	FOLFIRI	599	38.7	1.7
	FOLFIRI + Cmab	599	46.9*	4.8#
OPUS (2009)[6]	FOLFOX	73	37	4.1
〔K-ras wild〕	FOLFOX + Cmab	61	61*	9.8#
COIN (2011)[7]	FOLFOX/CapeOX	367	57	13.0
〔K-ras wild〕	FOLFOX/CapeOX + Cmab	362	64	15.0
NORDIC VII (2012)[8]	FLOX	97	46	8.0
〔K-ras wild〕	FLOX + Cmab	97	47	11.0#
PRIME (2010)[9]	FOLFOX	331	48	7.0
〔K-ras wild〕	FOLFOX + Pmab	325	55*	8.3#

Bmab：bevacizumab，Cmab：cetuximab，Pmab：panitumumab，$*p < 0.05$，#R0切除

当する用語はないものの，『大腸癌治療ガイドライン』（2010年度版）においては，「切除不能進行再発大腸癌に対する化学療法が奏効して切除可能となることがある」として言及されている[1]．切除不能となる要因としては，肝・肺などの同時性遠隔転移や，周囲臓器浸潤などの局所因子があげられる．切除不能大腸癌が術前治療により切除可能となった場合，初期評価で治癒切除可能と判断され手術が施行された症例と比較し，遜色ない治療成績が報告されている[3]．なかでも局所進行大腸癌は，遠隔転移を伴わない Stage II もしくは Stage III であることから，治癒切除を行うことにより根治の可能性が高まると考えられるため，conversion therapy への移行をふまえたより積極的な治療介入により down staging をめざすべきと考えられる．

II. 化 学 療 法

臨床試験において有用性が示されており，かつ保険診療として国内で使用可能な一次療法としての化学療法レジメンは，FOLFOX ± bevacizumab，CapeOX ± bevacizumab，FOLFIRI ± bevacizumab，5-FU + l-leucovorin (LV) ± bevacizumab および K-ras 野生型であれば FOLFOX ± cetuximab/panitumumab，FOLFIRI ± cetuximab/panitumumab，さらに認容性に問題のある場合には tegafur/uracil（UFT）+ LV を選択することができる．しかし，conversion therapy をめ

ざした neo-adjuvant therapy にもっとも適したレジメンについては，確立されているとはいえないのが現状である．特に局所進行癌に対する conversion therapy については，肝転移に対するそれに比べ詳細な検討に乏しく，いまだ症例報告が散見されるのみである．Conversion therapy をめざすうえでは，腫瘍を縮小し切除を可能とする目標にかなった，より奏効率の高い，また全身に与える有害事象の影響が少ないレジメンを選択するのが望ましい．分子標的治療薬である bevacizumab と，cetuximab，panitumumab は，それぞれ既存の治療法への上乗せ効果が示されており（表1），併用を考慮すべきである．これら分子標的治療薬と，oxaliplatin，irinotecan を用いたレジメンの組み合わせについては数々の臨床試験が行われている．

BEAT 試験[10]では，oxaliplatin，irinotecan に bevacizumab を併用し，conversion 達成率がそれぞれ10.4 %，8.0 %と報告している．CRYSTAL 試験[5]では，FOLFIRI に cetuximab を併用し，奏効率・無増悪生存期間・全生存期間のみならず，conversion 達成率も cetuximab 併用群で良好であった．特に K-ras 野生型例において，治療開始8週後に20 %以上の腫瘍縮小が得られた割合は，FOLFIRI 単独で45 %，FOLFIRI + cetuximab で64 %と差を認め，cetuximab の早期腫瘍縮小効果が示唆される結果となった．K-ras 野生型の同時性肝転移例に対して FOLFOX あるいは FOLFIRI
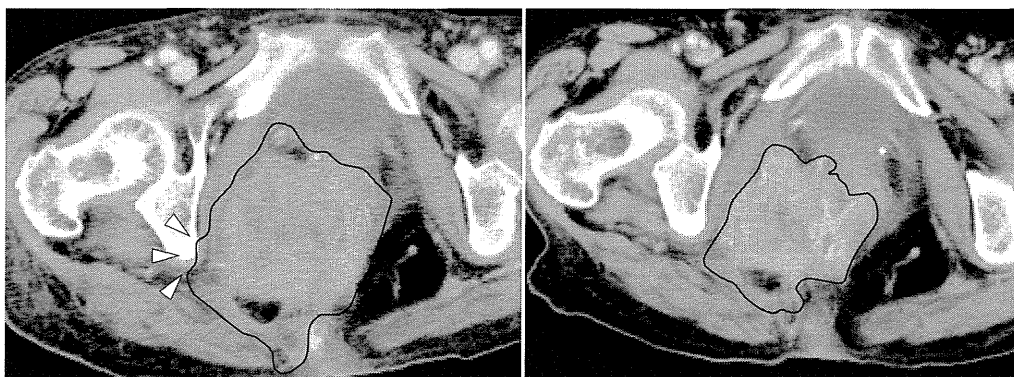
a. 化学療法前. 膀胱浸潤・子宮浸潤および右坐骨浸潤（矢頭）が疑われ切除不能と判断されている. なお, 遠隔転移は認めない（腫瘍径 71 × 54 mm, CEA 値 60.4）.

b. 化学療法後. mFOLFOX6 + cetuximab を 4 コース（8 週間）施行したところ腫瘍の著明な縮小を認め, 骨盤内臓全摘術を施行し, R0 切除が達成できている（腫瘍径 48 × 41 mm, CEA 値 9.1）.

図1. 症例. mFOLFOX6 + cetuximab で早期縮小が得られた局所進行直腸癌の骨盤部 CT

表2. 直腸癌に対する術前化学放射線療法の成績

試験名または報告者（年）	化学療法レジメン	放射線療法	患者数	pCR（％）
RTOG0012（2006）[15]	5-FU + CPT-11	1.8 Gy, 28 ～ 30 Fr	53	26
EXPERT（2006）[16]	CapeOX	1.8 Gy, 30 Fr	70	24
CALGB89901（2006）[17]	5-FU + OX	1.8 Gy, 28 Fr	32	25
Crane CH（2010）[18]	CapeOX + Bmab	1.8 Gy, 28 Fr	25	32
EXPERT-C（2012）[19]	CapeOX + Cmab	1.45 Gy, 25 Fr / 5.4 Gy, 3 Fr	46	16

Bmab：bevacizumab, Cmab：cetuximab, pCR：組織学的完全奏効率

に cetuximab を併用した CELIM 試験[11]では, FOLFOX 併用群で奏効率と conversion 達成率において, 有意差はないものの良好な結果であった. 一方, panitumumab に関しては conversion therapy に対する報告は少なく, 今後の報告をまちたい.

安全性の観点からは, bevacizumab には oxaliplatin による類洞障害の抑制効果が示唆される一方で, 創傷治癒遷延や出血, 血栓などの副作用があり, 術後合併症に注意が必要である. Cetuximab には手術に対する明らかな影響がなく, また効果発現までの期間が短いとされ（図1）, K-ras 野生型例に対しては有望な薬剤と考える. 以上を局所進行大腸癌に適用すると, K-ras 野生型例であれば FOLFOX もしくは FOLFIRI に cetuximab

の併用, K-ras 変異型例であれば FOLFOX と bevacizumab の併用が conversion をめざすうえで有望と考えられる.

Ⅲ. 化学放射線療法

進行直腸癌に対して, 本邦では total mesorectal excision（TME）＋側方郭清により良好な局所制御が得られているが[12], 欧米では側方郭清のかわりに放射線化学療法が neo-adjuvant therapy として標準的に使用され[13], 同等の治療成績が得られている[14]. 最近では新規抗癌薬と放射線療法との併用により, さらに良好な治療成績が報告されており（表2）, これを局所進行直腸癌に対する conversion therapy に応用する考えもある. EXPERT-C 試験[19]では, XELOX ＋放射線療法

（RT）にcetuximabの併用による上乗せ効果が検討され，奏効率はXELOX，XELOX＋cetuximab，XELOX＋RT，XELOX＋cetuximab＋RTそれぞれで50％，70％，72％，89％とcetuximab＋RT併用群で高かった．一方で，放射線治療後の創傷治癒遅延により，縫合不全や骨盤内膿瘍を発症しやすいことが手術のうえでは懸念されるが，化学放射線療法の施行時期にかかわらず，術後合併症の発生率に差を認めなかったとする報告もある[20]．今後，放射線療法の有無によるconversion達成率，周術期合併症および晩期障害の有無について検討された試験がまたれる．

おわりに

大腸癌に対する化学療法や放射線療法の発展はめざましく，さらにこれらと切除を組み合わせたconversion therapyは，治癒切除不能な大腸癌に治癒の可能性をもたらした．特に局所進行大腸癌に対するconversion therapyは，治癒切除が達成できれば遠隔転移を伴わない分，より生存率の向上に寄与する可能性が示唆される．しかし，どのような対象にどのようなレジメンが望ましいのかといった点にはいまだ答えが出ておらず，さらに詳細な研究が求められる．

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お知らせ

◆真菌症フォーラム第14回学術集会

会　　期：2013年2月16日（土）

会　　場：第一ホテル東京（東京都港区新橋1-2-6/TEL 03-3501-4411）

会　　長：三鴨廣繁（愛知医科大学感染制御学教授）

テ　ー　マ：「深在性真菌症の診断・治療ガイドラインの改訂を目指して」

募集演題：深在性真菌症に関する演題を広く募集します．ホームページ（http：//www.mycoses.jp/）の専用フォームよりご応募ください

　　　　　1）ポスター発表：一般演題〔基礎・臨床・症例，PK/PD（要望演題）〕

　　　　　　※臨床症例の一例報告も歓迎いたします．皮膚表在性真菌症は対象外とさせていただきます

　　　　　2）優秀賞・奨励賞・トラベルグラントについて：応募演題は，抄録原稿ならびに当日発表をもとに採点し，優秀賞・奨励賞（賞状・副賞として賞金）を授賞します．また，トラベルグラントの設定があります

応募締切：2012年9月7日（金）12：00（厳守）

参 加 費：医療従事者3,000円，企業・メーカー 6,000円（抄録集・情報交換会会費を含みます．事前の登録はございません）

問 合 先：〒105-0004 東京都港区新橋2-20 新橋駅前ビル1号館3階
　　　　　（株）協和企画コンベンション事業本部内
　　　　　真菌症フォーラム第14回学術集会運営事務局（担当：飯塚　勉）
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　　　　　共催：真菌症フォーラム／ファイザー（株）

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Study of Gemcitabine Plus S-1, S-1 Alone, or Gemcitabine Alone in Patients With Locally Advanced and Metastatic Pancreatic Cancer in Japan and Taiwan: GEST Study

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See accompanying editorial doi: 10.1200/JCO.2013.48.7660

ABSTRACT

Purpose
The present phase III study was designed to investigate the noninferiority of S-1 alone and superiority of gemcitabine plus S-1 compared with gemcitabine alone with respect to overall survival.

Patients and Methods
The participants were chemotherapy-naive patients with locally advanced or metastatic pancreatic cancer. Patients were randomly assigned to receive only gemcitabine (1,000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle), only S-1 (80, 100, or 120 mg/d according to body-surface area on days 1 through 28 of a 42-day cycle), or gemcitabine plus S-1 (gemcitabine 1,000 mg/m^2 on days 1 and 8 plus S-1 60, 80, or 100 mg/d according to body-surface area on days 1 through 14 of a 21-day cycle).

Results
In the total of 834 enrolled patients, median overall survival was 8.8 months in the gemcitabine group, 9.7 months in the S-1 group, and 10.1 months in the gemcitabine plus S-1 group. The noninferiority of S-1 to gemcitabine was demonstrated (hazard ratio, 0.96; 97.5% CI, 0.78 to 1.18; $P < .001$ for noninferiority), whereas the superiority of gemcitabine plus S-1 was not (hazard ratio, 0.88; 97.5% CI, 0.71 to 1.08; $P = .15$). All treatments were generally well tolerated, although hematologic and GI toxicities were more severe in the gemcitabine plus S-1 group than in the gemcitabine group.

Conclusion
Monotherapy with S-1 demonstrated noninferiority to gemcitabine in overall survival with good tolerability and presents a convenient oral alternative for locally advanced and metastatic pancreatic cancer.

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INTRODUCTION

Pancreatic cancer (PC) is currently the eighth leading cause of cancer-related mortality worldwide, with an estimated 266,000 deaths in 2008.[1] Gemcitabine became the standard treatment for advanced PC, improving overall survival (OS) compared with fluorouracil.[2] Although various gemcitabine-based combination regimens have been evaluated, only erlotinib added to gemcitabine showed a survival benefit over gemcitabine, and that was marginal.[3]

Fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX), a gemcitabine-free combination regimen, has recently demonstrated a clear survival benefit compared with gemcitabine for patients with metastatic PC who have a performance status of 0 to 1.[4] However, because FOLFIRINOX is associated with significant toxicity, this regimen must be limited to patients with good performance status and requires close monitoring.[5]

In Japan, clinical trials of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) have been conducted since the early 2000s for patients with PC. S-1

is an oral fluoropyrimidine derivative shown to be effective for gastric and various other types of cancers.[6,7] Phase II studies of S-1 as first-line therapy for metastatic PC resulted in good response rates of 21.1% to 37.5%.[8,9] Consequently, S-1 was approved for the indication of PC in Japan in 2006. Development of gemcitabine plus S-1 (GS) studies have also been initiated, mainly in Japan, and two phase II studies reported high response rates of 44.4% to 48.5% and good median OS of 10.1 to 12.5 months.[10,11]

Because S-1 and GS have shown promising activity in PC, the present randomized phase III study (GEST [Gemcitabine and S-1 Trial] study) was designed to evaluate whether S-1 alone is noninferior to gemcitabine and whether GS is superior to gemcitabine alone for locally advanced and metastatic PC with respect to OS.

PATIENTS AND METHODS

Study Design

This randomized phase III study, sponsored by Taiho Pharmaceutical in Japan and TTY Biopharm in Taiwan, was conducted as a postmarketing study in Japan and as a registration study in Taiwan and was in compliance with the Declaration of Helsinki. Data were collected by a contract research organization contracted by the sponsors and were analyzed by a bio-statistician (Y.O.). An independent data and safety monitoring committee reviewed efficacy and safety data. The study was approved by the ethics committee or institutional review board of each participating center.

Patients

All patients provided written informed consent. Enrollment criteria were locally advanced or metastatic PC, histologically or cytologically proven diagnosis of adenocarcinoma or adenosquamous carcinoma, no prior chemotherapy or radiotherapy for PC, age of more than 20 years (the protocol was amended to restrict the eligible age to < 80 years after four of the first eight patients who were ≥ 80 years experienced serious adverse events), an Eastern Cooperative Oncology Group performance status score of 0 to 1, and adequate organ functions (see Appendix, online only).

Treatment

Random assignment was performed centrally with stratification by extent of disease (locally advanced disease v metastatic disease) and institution using the minimization method. Patients allocated to gemcitabine alone received gemcitabine at a dose of 1,000 mg/m^2 intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle. Patients allocated to S-1 alone received S-1 orally twice daily at a dose according to the body-surface area (BSA) (< 1.25 m^2, 80 mg/d; ≥ 1.25 to < 1.5 m^2, 100 mg/d; ≥ 1.5 m^2, 120 mg/d) on days 1 through 28 of a 42-day cycle. Patients allocated to GS received gemcitabine at a dose of 1,000 mg/m^2 on days 1 and 8 plus S-1 orally twice daily at a dose according to the BSA (< 1.25 m^2, 60 mg/d; ≥ 1.25 to < 1.5 m^2, 80 mg/d; ≥ 1.5 m^2, 100 mg/d) on days 1 through 14 of a 21-day cycle. The dose levels of S-1 used in the GS group were based on the results of a previous phase II study of GS, in which 1,000 mg/m^2 of gemcitabine was combined with 120 mg/d, 100 mg/d, and 80 mg/d of S-1. In that study, the rate of treatment withdrawal due to adverse events was 41% (22 of 54 patients), the rate of grade 3 or worse neutropenia was 80%, and the dose was reduced in 56% of the patients (30 of 54 patients).[11] Consequently, 20 mg/d lower doses of S-1 than those used in the S-1 monotherapy group were used in the GS group in the present study.

In the event of predefined toxic events, protocol-specified treatment modifications were permitted (see Appendix).

Assessments

Physical examinations, CBCs, and biochemistry tests were usually checked at 2-week intervals in the S-1 group and at each time of administration of gemcitabine both in the gemcitabine group and in the GS group. All adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 3.0. Computed tomography or magnetic resonance imaging was performed every 6 weeks until disease progression, and response was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.[12] Quality of life was assessed using the EuroQol 5 Dimension questionnaire[13] at baseline and 6, 12, 24, 48, and 72 weeks after the study treatment had begun.

Statistical Analysis

The primary end point was OS, defined as time from date of random assignment to date of death from any cause. Secondary end points were progression-free survival (PFS), objective response rate, safety, and quality of life. PFS was counted from the date of random assignment to the date of death without progression or of progression as confirmed by the investigator's assessment. The median OS was assumed to be 7.5 months in the gemcitabine group, 8.0 months in the S-1 group, and 10.5 months in the GS group. To maintain a one-sided significance level of .025 for the entire study while testing two hypotheses (ie, noninferiority and superiority), the one-sided significance
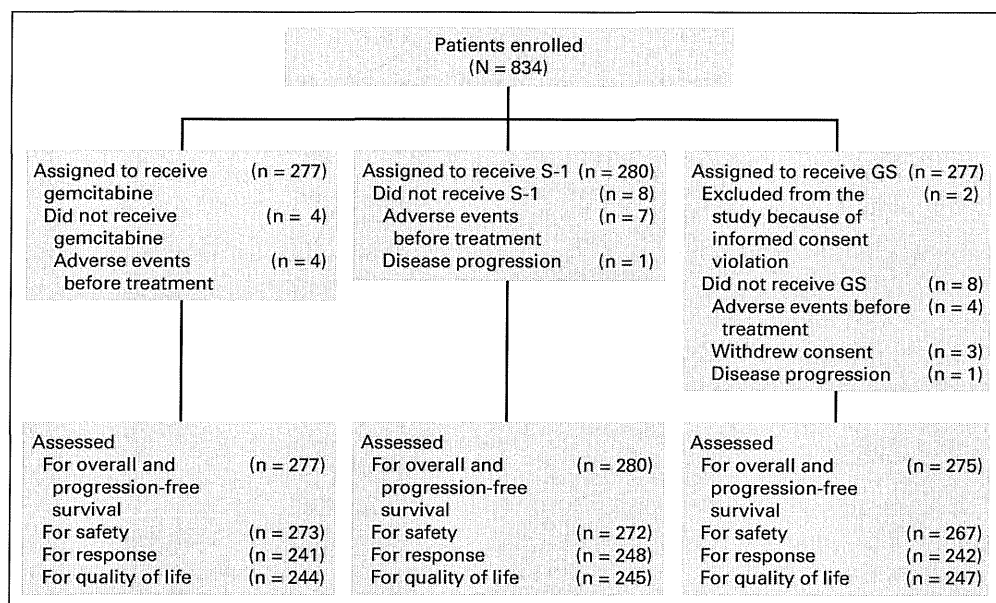

Fig 1. CONSORT diagram. GS, gemcitabine plus S-1.

level for each comparison was set at .0125. The statistical considerations are detailed in the Appendix.

The superiority of GS was evaluated by the stratified log-rank test. To assess the noninferiority of S-1, we used the Cox proportional hazards model to calculate two-sided, 97.5% CIs of the hazard ratio (HR). The noninferiority margin of S-1 was set at 1.33; that is, the null hypothesis was that the median OS with S-1 would be approximately 2 months shorter than with gemcitabine. We decided this setting was justified considering the convenience of S-1 and because there are few effective drugs for the disease. Furthermore, to interpret the obtained data, the Bayesian analysis of the log HR on the basis of the noninformative prior distribution was preplanned. Posterior probability with log HR within a stricter threshold (log 1.15) was also calculated.[14]

In each assigned group, the time-to-event distribution was estimated with the Kaplan-Meier method. The 95% CI of the median survival time was calculated by the method of Brookmeyer and Crowly.[15] In addition, the Greenwood formula[16] was used to calculate the 95% CI for survival rates. In subgroup analyses, interaction tests were performed to assess the homogeneity of the effect of treatment on OS.

The primary end point was analyzed for the full analysis set. All P value evaluations were two-tailed. Data analyses were done with SAS, version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Patients

Between July 2007 and October 2009, a total of 834 patients were enrolled from 75 institutions in Japan and Taiwan (768 in Japan and 66 in Taiwan). Two patients in the GS group were excluded from the study because enrollment was conducted before obtaining written informed consent. The remaining 832 patients were included in the full analysis set and used to calculate OS and PFS (Fig 1). The three treatment groups were well balanced with respect to demographic and baseline characteristics (Table 1).

Study Treatment

The median duration of treatment was 2.6 months in the gemcitabine group, 2.6 months in the S-1 group, and 4.3 months in the GS group. The main reasons for treatment discontinuation were either disease progression (202 patients [72.9%] in the gemcitabine group,

Table 1. Demographics and Baseline Characteristics of Patients (full-analysis set population)

Characteristic	Gemcitabine (n = 277) No.	Gemcitabine (n = 277) %	S-1 (n = 280) No.	S-1 (n = 280) %	GS (n = 275) No.	GS (n = 275) %	Total (N = 832) No.	Total (N = 832) %
Sex								
Male	170	61.4	170	60.7	158	57.5	498	59.9
Female	107	38.6	110	39.3	117	42.5	334	40.1
Age, years								
< 65	134	48.4	145	51.8	137	49.8	416	50.0
≥ 65	143	51.6	135	48.2	138	50.2	416	50.0
ECOG PS								
0	181	65.3	178	63.6	172	62.5	531	63.8
1	96	34.7	102	36.4	103	37.5	301	36.2
Extent of disease								
Locally advanced	66	23.8	68	24.3	68	24.7	202	24.3
Metastatic	211	76.2	212	75.7	207	75.3	630	75.7
Type of tumor								
Adenocarcinoma	272	98.2	276	98.6	272	98.9	820	98.6
Adenosquamous carcinoma	5	1.8	4	1.4	3	1.1	12	1.4
Pancreas excision								
No	254	91.7	264	94.3	248	90.2	766	92.1
Yes	23	8.3	16	5.7	27	9.8	66	7.9
Tumor location*								
Head	122	44.0	110	39.3	116	42.2	348	41.8
Body	88	31.8	124	44.3	102	37.1	314	37.7
Tail	68	24.5	55	19.6	66	24.0	189	22.7
Biliary drainage								
No	202	72.9	217	77.5	209	76.0	628	75.5
Yes	75	27.1	63	22.5	66	24.0	204	24.5
CEA, ng/mL								
Median	5.7		5.6		5.9		5.7	
IQR	3.0-20.1		2.5-18.4		2.5-20.7		2.6-19.5	
CA19-9, U/mL								
Median	1,044		726		441		712	
IQR	52-5,002		64-5,000		45-5,090		55-5,002	
CRP, mg/dL								
Median	0.40		0.50		0.40		0.43	
IQR	0.11-1.38		0.18-1.57		0.15-1.60		0.15-1.57	

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; GS, gemcitabine plus S-1; IQR, interquartile range.
*Including patients with tumors involving multiple sites.

215 [76.8%] in the S-1 group, and 162 [58.9%] in the GS group) or adverse events (40 patients [14.4%] in the gemcitabine group, 38 [13.6%] in the S-1 group, and 76 [27.6%] in the GS group). The median relative dose-intensity was 83.0% in the gemcitabine group, 96.1% in the S-1 group, and 83.3% for gemcitabine and 87.4% for S-1 in the GS group.

Survival

The median duration of follow-up for surviving patients was 18.4 months (range, 0.3 to 36.9 months) as of July 31, 2010. The analysis of OS was based on 710 deaths (85.3%) among the 832 patients. The median OS was 8.8 months (95% CI, 8.0 to 9.7) in the gemcitabine group, 9.7 months (95% CI, 7.6 to 10.8) in the S-1 group, and 10.1 months (95% CI, 9.0 to 11.2) in the GS group (Fig 2A). OS rates at 12 and 24 months were respectively 35.4% and 9.2% in the gemcitabine group, 38.7% and 12.7% in the S-1 group, and 40.7% and 14.5% in the GS group. The noninferiority of S-1 to gemcitabine with respect to OS was demonstrated (HR, 0.96; 97.5% CI, 0.78 to 1.18; $P < .001$ for

noninferiority). The Bayesian posterior probability that the HR of S-1 relative to gemcitabine would be less than 1.15 was calculated to be 98% on the basis of the noninformative prior distribution. However, GS failed to improve OS at a statistically significant level as compared with gemcitabine (HR, 0.88; 97.5% CI, 0.71 to 1.08; $P = .15$).

The analysis of PFS was based on 793 events (95.3%) among the 832 patients. The median PFS was 4.1 months (95% CI, 3.0 to 4.4) in the gemcitabine group, 3.8 months (95% CI, 2.9 to 4.2) in the S-1 group, and 5.7 months (95% CI, 5.4 to 6.7) in the GS group (Fig 2B). PFS rates at 6 and 12 months were respectively 29.8% and 9.1% in the gemcitabine group, 26.9% and 7.2% in the S-1 group, and 47.9% and 20.3% in the GS group. S-1 was shown to be noninferior to gemcitabine with respect to PFS (HR, 1.09; 97.5% CI, 0.90 to 1.33; $P = .02$ for noninferiority), and GS significantly improved PFS compared with gemcitabine (HR, 0.66; 97.5% CI, 0.54 to 0.81; $P < .001$).

Subgroup analyses of survival according to pretreatment characteristics showed no significant interaction between S-1 and gemcitabine in any subgroup (Fig 3A). However, GS showed a favorable HR compared with gemcitabine in the subsets of patients with locally advanced disease or patients with a performance status of 1 (Fig 3B).

Response to Therapy

The objective response rate was 13.3% (95% CI, 9.3 to 18.2) in the gemcitabine group, 21.0% (95% CI, 16.1 to 26.6) in the S-1 group, and 29.3% (95% CI, 23.7 to 35.5) in the GS group (Table 2). The objective response rate was significantly higher in the S-1 group ($P = .02$) and in the GS group ($P < .001$) than in the gemcitabine group.

Second-Line Chemotherapy

Second-line chemotherapy was performed in 184 patients (66.4%) in the gemcitabine group, 185 (66.1%) in the S-1 group, and 172 (62.5%) in the GS group. In the gemcitabine group, 140 patients (50.5%) received S-1 alone or S-1–based regimens, and in the S-1 group 162 (57.9%) received gemcitabine alone or gemcitabine-based regimens as second-line chemotherapy. The most common second-line regimens in the GS group were gemcitabine alone (61 patients), GS (53 patients), S-1 alone (24 patients), irinotecan (six patients), and fluorouracil/leucovorin plus oxaliplatin (four patients). In Japan and Taiwan, the use of treatments such as erlotinib, oxaliplatin, and irinotecan for PC was not approved at the time of this study; hence gemcitabine, S-1, or both were used in most patients as second-line chemotherapy.

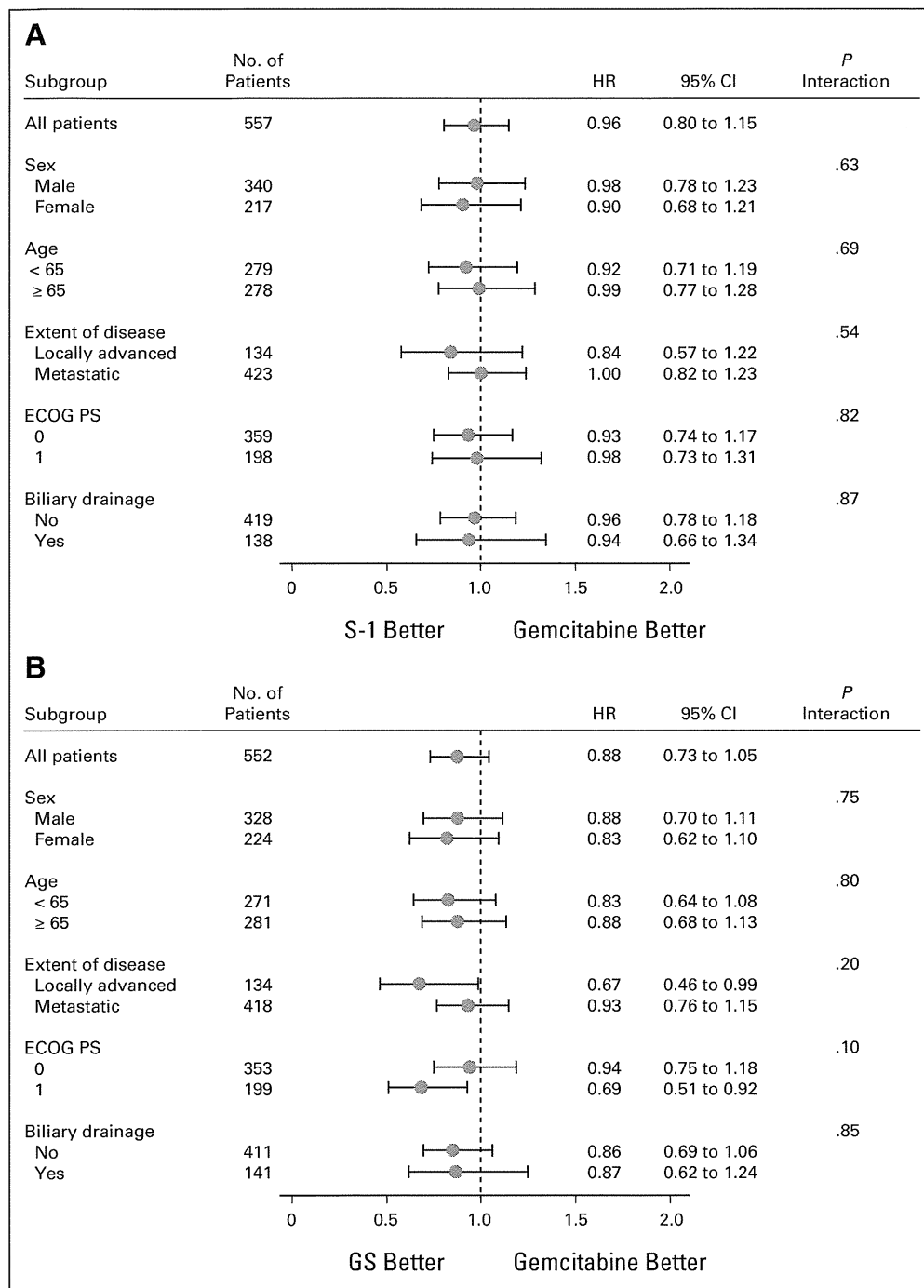## Adverse Events and Quality-Adjusted Life-Years

The major grade 3 or worse adverse events are listed in Table 3. Patients in the gemcitabine group had significantly higher incidences of grade 3 or worse leukopenia, neutropenia, thrombocytopenia, elevated AST levels, and elevated ALT levels as compared with patients in the S-1 group. However, the incidence of grade 3 or worse diarrhea was higher in the S-1 group than in the gemcitabine group. Patients in the GS group had significantly higher incidences of grade 3 or worse leukopenia, neutropenia, thrombocytopenia, rash, diarrhea, vomiting, and stomatitis than patients in the gemcitabine group.

There were three deaths considered possibly related to the protocol treatment (interstitial lung disease, sepsis, and acute hepatitis B) in the gemcitabine group, one in the S-1 group (unknown cause), and
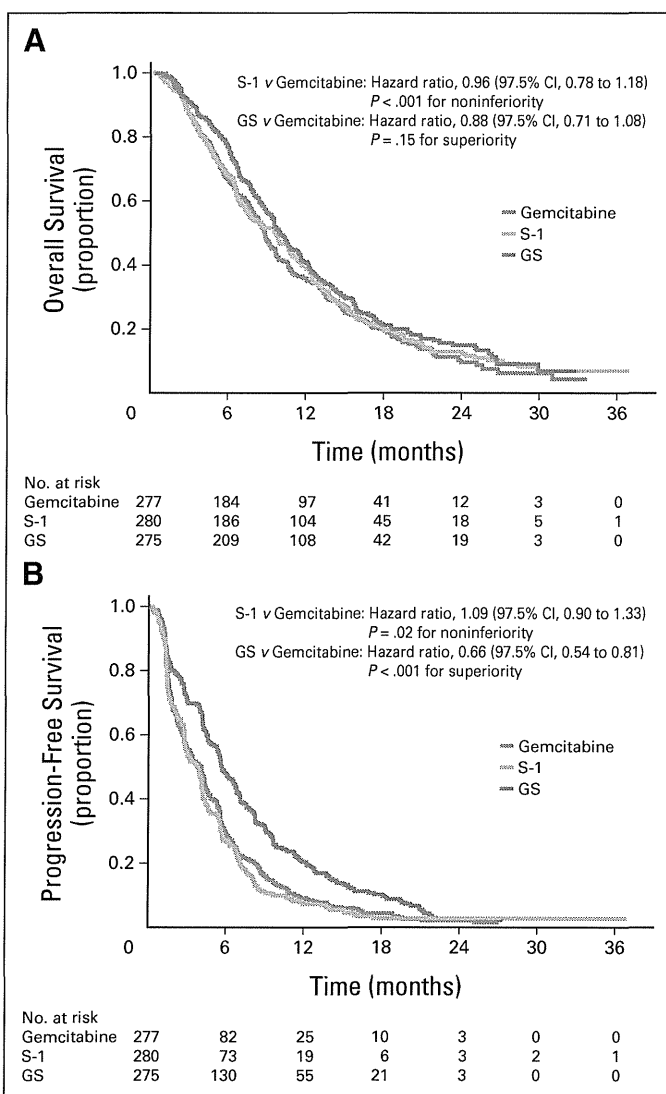
Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival according to treatment group. GS, gemcitabine plus S-1.

A

S-1 v Gemcitabine: Hazard ratio, 0.96 (97.5% CI, 0.78 to 1.18)
$P < .001$ for noninferiority
GS v Gemcitabine: Hazard ratio, 0.88 (97.5% CI, 0.71 to 1.08)
$P = .15$ for superiority

No. at risk

Gemcitabine	277	184	97	41	12	3	0
S-1	280	186	104	45	18	5	1
GS	275	209	108	42	19	3	0

B

S-1 v Gemcitabine: Hazard ratio, 1.09 (97.5% CI, 0.90 to 1.33)
$P = .02$ for noninferiority
GS v Gemcitabine: Hazard ratio, 0.66 (97.5% CI, 0.54 to 0.81)
$P < .001$ for superiority

No. at risk

Gemcitabine	277	82	25	10	3	0	0
S-1	280	73	19	6	3	2	1
GS	275	130	55	21	3	0	0

A

Subgroup	No. of Patients		HR	95% CI	P Interaction
All patients	557		0.96	0.80 to 1.15	
Sex					.63
Male	340		0.98	0.78 to 1.23	
Female	217		0.90	0.68 to 1.21	
Age					.69
< 65	279		0.92	0.71 to 1.19	
≥ 65	278		0.99	0.77 to 1.28	
Extent of disease					.54
Locally advanced	134		0.84	0.57 to 1.22	
Metastatic	423		1.00	0.82 to 1.23	
ECOG PS					.82
0	359		0.93	0.74 to 1.17	
1	198		0.98	0.73 to 1.31	
Biliary drainage					.87
No	419		0.96	0.78 to 1.18	
Yes	138		0.94	0.66 to 1.34	

0   0.5   1.0   1.5   2.0

S-1 Better   Gemcitabine Better

B

Subgroup	No. of Patients		HR	95% CI	P Interaction
All patients	552		0.88	0.73 to 1.05	
Sex					.75
Male	328		0.88	0.70 to 1.11	
Female	224		0.83	0.62 to 1.10	
Age					.80
< 65	271		0.83	0.64 to 1.08	
≥ 65	281		0.88	0.68 to 1.13	
Extent of disease					.20
Locally advanced	134		0.67	0.46 to 0.99	
Metastatic	418		0.93	0.76 to 1.15	
ECOG PS					.10
0	353		0.94	0.75 to 1.18	
1	199		0.69	0.51 to 0.92	
Biliary drainage					.85
No	411		0.86	0.69 to 1.06	
Yes	141		0.87	0.62 to 1.24	

0   0.5   1.0   1.5   2.0

GS Better   Gemcitabine Better

Fig 3. Forest plots of treatment effects on overall survival in subgroup analyses. Forest plots show effects on overall survival of patients in each subgroup. (A) S-1; (B) gemcitabine plus S-1 (GS). Each blue circle shows the treatment response. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

four in the GS group (unknown cause associated with myelosuppression, cerebral infarction, cerebrovascular disorder, and interstitial lung disease). The results of quality-adjusted life-years (QALYs) are in the Appendix and the details of quality-of-life assessments will be reported elsewhere.

DISCUSSION

The overall and PFS curves in the S-1 group were nearly identical to those in the gemcitabine group, confirming the noninferiority of S-1

to gemcitabine in terms of OS and PFS (Fig 2A, 2B). Toxicity profiles of these two drugs differed slightly: gemcitabine tended to show hematologic toxicity, whereas S-1 tended to show GI toxicity. However, both S-1 and gemcitabine were generally well tolerated. Furthermore, the results of QALY evaluation demonstrated that S-1 and gemcitabine were equivalent. Hence our results suggest that S-1 can be used as first-line therapy as a convenient oral alternative for locally advanced and metastatic PC. To the best of our knowledge, this is the first phase III study to demonstrate the noninferiority of a single anticancer agent to gemcitabine alone for locally advanced and metastatic PC.

Table 2. Objective Response Rates (patients with measurable lesions)

Variable	Gemcitabine (n = 241)		S-1 (n = 248)		GS (n = 242)		P (χ^2 test)	
	No.	%	No.	%	No.	%	Gemcitabine v S-1	Gemcitabine v GS
Response								
Complete response	1	0.4	0	0	2	0.8		
Partial response	31	12.9	52	21.0	69	28.5		
Stable disease	119	49.4	105	42.3	102	42.1		
Progressive disease	75	31.1	69	27.8	37	15.3		
Objective response rate*	32	13.3	52	21.0	71	29.3	.02	< .001
95% CI	9.3 to 18.2		16.1 to 26.6		23.7 to 35.5			
Disease control rate†	151	62.7	157	63.3	173	71.5	.88	.04
95% CI	56.2 to 68.8		57.0 to 69.3		65.4 to 77.1			

Abbreviation: GS, gemcitabine plus S-1.
*The objective response rate was defined as the proportion of patients who had a complete response or partial response.
†The disease control rate was defined as the proportion of patients who had a complete response, partial response, or stable disease.

At the time of planning this study, the participants of nearly all phase III trials included both patients with locally advanced as well as those with metastatic PC. However, because locally advanced and metastatic diseases are two clinical entities, it is recently recommended that patients with locally advanced disease should be studied separately from those with metastatic disease.[17] Although this study included locally advanced disease, subgroup analysis of extent of disease showed no significant interaction between S-1 and gemcitabine (Fig 3A). Moreover, the OS curve in the S-1 group was still similar to those in the gemcitabine group in both locally advanced and metastatic disease (Fig 4A, 4B). Regarding pathologic diagnosis, our study included adenosquamous carcinoma, although its percentage was very low (1.4% of whole population). When the data were reanalyzed after

excluding patients with adenosquamous carcinoma, the results for OS for gemcitabine versus S-1 was unchanged (HR, 0.96; 95% CI, 0.81 to 1.15). The selection of one treatment over the other will depend primarily on patient preference, clinical factors, or drug costs, as biomarkers indicating effective use of S-1 or gemcitabine do not exist at this time.
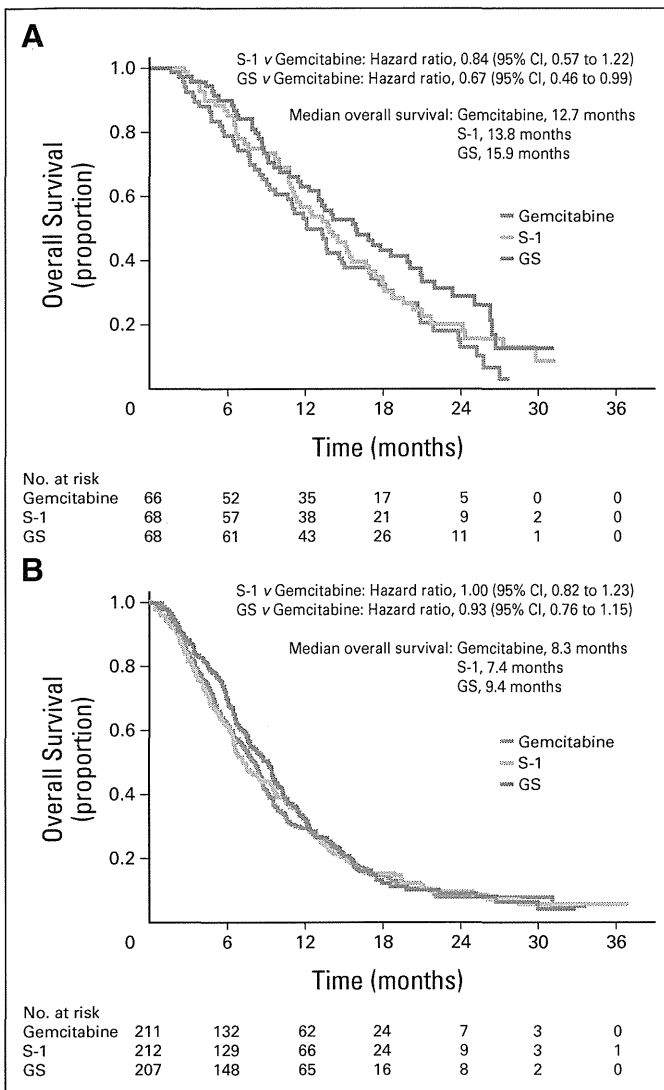
Regarding GS, the OS did not differ significantly from gemcitabine, although the PFS was significantly longer in the GS group. Second-line chemotherapy mainly with S-1 in the gemcitabine group may be one reason for this discrepancy. The median OS in the gemcitabine group was 8.8 months, which is longer than those previously reported for gemcitabine in other phase III studies for locally advanced and metastatic PC.[2,3,18-24] Although the efficacy of second-line

Table 3. Grade 3 or Worse Adverse Events (safety population)

Event	Gemcitabine (n = 273)		S-1 (n = 272)		GS (n = 267)		P (Fisher's exact test)	
	No.	%	No.	%	No.	%	Gemcitabine v S-1	Gemcitabine v GS
Hematologic								
Leukocytes	51	18.7	10	3.7	101	37.8	< .001	< .001
Neutrophils	112	41.0	24	8.8	166	62.2	< .001	< .001
Platelets	30	11.0	4	1.5	46	17.2	< .001	.05
Hemoglobin	39	14.3	26	9.6	46	17.2	.11	.41
Nonhematologic								
ALT	41	15.0	16	5.9	29	10.9	< .001	.16
AST	41	15.0	21	7.7	32	12.0	.01	.32
Bilirubin	26	9.5	39	14.3	23	8.6	.09	.77
Fatigue	10	3.7	18	6.6	13	4.9	.13	.53
Rash	2	0.7	2	0.7	11	4.1	1.00	.01
Anorexia	20	7.3	31	11.4	25	9.4	.11	.44
Diarrhea	3	1.1	15	5.5	12	4.5	.004	.02
Mucositis/stomatitis	0	0.0	2	0.7	6	2.2	.25	.01
Nausea	5	1.8	5	1.8	12	4.5	1.00	.09
Vomiting	2	0.7	4	1.5	12	4.5	.45	.006
Febrile neutropenia	1	0.4	1	0.4	5	1.9	1.00	.12
Infection with normal ANC	6	2.2	7	2.6	6	2.2	.79	1.00
Pneumonitis	5	1.8	0	0.0	2	0.7	.06	.45

NOTE. Grades of adverse events were defined according to the Common Terminology Criteria for Adverse Events (version 3.0).
Abbreviations: ANC, absolute neutrophil count; GS, gemcitabine plus S-1.

A

S-1 *v* Gemcitabine: Hazard ratio, 0.84 (95% CI, 0.57 to 1.22)
GS *v* Gemcitabine: Hazard ratio, 0.67 (95% CI, 0.46 to 0.99)

Median overall survival: Gemcitabine, 12.7 months
S-1, 13.8 months
GS, 15.9 months

Gemcitabine
S-1
GS

No. at risk

Gemcitabine	66	52	35	17	5	0	0
S-1	68	57	38	21	9	2	0
GS	68	61	43	26	11	1	0

B

S-1 *v* Gemcitabine: Hazard ratio, 1.00 (95% CI, 0.82 to 1.23)
GS *v* Gemcitabine: Hazard ratio, 0.93 (95% CI, 0.76 to 1.15)

Median overall survival: Gemcitabine, 8.3 months
S-1, 7.4 months
GS, 9.4 months

Gemcitabine
S-1
GS

No. at risk

Gemcitabine	211	132	62	24	7	3	0
S-1	212	129	66	24	9	3	1
GS	207	148	65	16	8	2	0

Fig 4. Kaplan-Meier estimates of overall survival in (A) locally advanced disease and (B) metastatic disease. GS, gemcitabine plus S-1.

III studies, a combination of gemcitabine plus capecitabine did not significantly prolong survival as compared with gemcitabine alone.[19,20] The results of a meta-analysis of these phase III studies, however, demonstrated that survival was significantly prolonged by combined treatment, with an HR of 0.86,[20] which is similar to the HR for GS in the present study (0.88).

One limitation of our study is that it is uncertain whether our results can be simply extrapolated to Western patients because pharmacokinetics and pharmacodynamics of S-1 between Westerners and East Asians may be different.[26,27] Although S-1 is available for PC only in Japan at the moment, if S-1 is used in Western patients, its effectiveness should be monitored and the dose should be carefully adjusted accordingly. Another potential limitation is that the protocol-specified noninferiority margin of 1.33 may be large. However, the result of point estimate of the HR of S-1 was 0.96 and actual upper limit of the 97.5% CI was 1.18, which was sufficiently lower than the prespecified margin of 1.33. Furthermore, Bayesian posterior probability with log HR within a stricter threshold (log 1.15) was 98%.

Given that most gemcitabine-based combination regimens have not been shown to be significantly superior to gemcitabine alone and that FOLFIRINOX has demonstrated overwhelming superiority to gemcitabine in a phase III study, reporting an HR of 0.57,[4] the development of gemcitabine-free combination regimens for first-line treatment seems to be warranted. However, because FOLFIRINOX requires the placement of a central venous access port for continuous intravenous infusion of fluorouracil, it can be expected that S-1, an oral fluoropyrimidine, will replace the continuous infusion of fluorouracil in the future.

In conclusion, this study has verified the noninferiority of S-1 to gemcitabine, thereby suggesting that S-1 can be used as first-line therapy for locally advanced and metastatic PC. Because S-1 was confirmed to be a key treatment for PC, S-1–based regimens are expected to be developed in the future to improve the management of this formidable disease.

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therapy was not analyzed in this study, a phase II study of second-line S-1 in patients with gemcitabine-refractory PC showed a 15% response rate and 58% disease control rate.[25] Compared with the GS group, which had no promising second-line therapy, the use of S-1 as second-line therapy in the gemcitabine group might have contributed to prolonged survival.

The lack of a significant difference in OS between gemcitabine and GS suggests that gemcitabine and S-1 could be used sequentially rather than concurrently. However, the GS group showed a high response rate and favorable PFS, with a better HR of 0.66 compared with other gemcitabine-based combination regimens in other phase III studies (HR = 0.75 to 1.07).[3,18,20,22,24] Furthermore, the GS group showed a favorable HR for OS in patients with locally advanced disease or patients with a performance status of 1 in the subgroup analyses. Therefore, it is speculated that there may be room to select GS therapy, depending on the profile of the patients and further investigations.

Regarding oral fluoropyrimidines other than S-1, capecitabine has been studied in patients with PC, mainly in the West. In two phase

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Acknowledgment

Appendix

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Details of Adequate Organ Functions in Enrollment Criteria and Main Exclusion Criteria

Adequate organ functions were defined as follows: leukocyte count $\geq$ 3,500/μL, neutrophil count $\geq$ 2,000/μL, platelet count $\geq$ 100,000/μL, hemoglobin level $\geq$ 9.0 g/dL, serum creatinine level $\leq$ 1.2 mg/dL, creatinine clearance $\geq$ 50 mL/min, serum AST and ALT levels $\leq$ 150 U/L, and serum total bilirubin level $\leq$ 2.0 mg/dL or $\leq$ 3.0 mg/dL if biliary drainage was performed.

Main exclusion criteria were as follows: pulmonary fibrosis or interstitial pneumonia; watery diarrhea; active infection; marked pleural effusion or ascites; and serious complications such as heart failure, peptic ulcer bleeding, or poorly controlled diabetes. Pancreatic cancers other than adenocarcinoma or adenosquamous carcinoma (eg, anaplastic carcinoma) were excluded from the study.

Dosage Adjustment Guideline for Toxicities

All treatment cycles were repeated until disease progression, unacceptable toxicity, or patient refusal. If patients had a leukocyte count of less than 2,000/μL, a neutrophil count of less than 1,000/μL, a platelet count of less than 70×10^3/μL, or grade 3 or worse rash, the administration of anticancer agents was postponed. S-1 was temporarily halted both in S-1 and in GS groups if patients had a creatinine level of 1.5 mg/dL or higher or grade 2 or worse diarrhea or stomatitis. Treatment was discontinued if these events did not resolve within 4 weeks after treatment suspension. In patients who experienced febrile neutropenia, grade 4 leukopenia, neutropenia, or thrombocytopenia or grade 3 or worse rash, the dose of gemcitabine was reduced by 200 mg/m^2. In patients with febrile neutropenia; grade 4

leukopenia, neutropenia, or thrombocytopenia; a creatinine level of 1.5 mg/dL or higher; or grade 3 or worse diarrhea, stomatitis, or rash, the dose of S-1 was reduced by 20 mg/d.

Sample Size Determination: Statistical Methods

In the initial plan, the total target number of patients was set at 600, given a statistical power of 80%, an enrollment period of 3 years, and a follow-up period of 2 years. However, because patient enrollment was faster than expected, the target number of patients was revised to 750 to provide the study with a statistical power of 90%. Consequently, the final analysis was performed after the occurrence of 680 events had been confirmed. An interim analysis was not performed. Although the actual median OS in the gemcitabine group was better than initially expected, because an adequate number of patients had been enrolled, a power of $\geq$ 90% was maintained on recalculation of the power on the basis of the actual results.

Quality of Life

To assess the quality of life, the health status of patients on the EQ-5D questionnaire was converted into a single simple utility index ranging from 0 for death to 1 for complete health. Quality-adjusted life-years (QALYs) for individual patients were estimated as the product of the utility index during follow-up and survival time and were compared between the groups, using the generalized Wilcoxon test.

As a result, median QALYs were 0.401 in the gemcitabine group, 0.420 in the S-1 group, and 0.525 in the GS group. The QALY value in the S-1 group was similar to that in the gemcitabine group, and there was no statistically significant difference between the two groups (P = .56). The QALY value in the GS group was significantly better than that in the gemcitabine group (P < .001). The details of quality-of-life assessments will be reported elsewhere.