Table 1. Baseline characteristics and demographics (n = 106)

Characteristic	
Median age (range) (years)	62 (36–78)
Gender, n (%)	
Male	56 (52.8)
Female	50 (47.2)
Median bodyweight (range) (kg)	52.3 (33.1–95.0)
Smoking history,† n (%)	
Never smoker	39 (36.8)
Past smoker	37 (34.9)
Current smoker	30 (28.3)
ECOG PS, n (%)	
0	80 (75.5)
1	26 (24.5)
2	0 (0)
Disease status, n (%)	
Metastatic	88 (83.0)
Locally advanced	18 (17.0)
Primary tumor identified, n (%)	92 (86.8)
Primary sites, n (%)	
Head	46 (43.4)
Body and tail	23 (21.7)
Body	22 (20.8)
Tail	10 (9.4)
Other	5 (4.7)‡
Biliary drainage, n (%)	19 (17.9)
Sites of distant metastases, n (%)	
Liver	56 (52.8)
Distant lymph nodes	39 (36.8)
Lung	17 (16.0)
Other	26 (24.5)
Prior lines of therapy, n (%)	
None	101 (95.3)
One regimen	5 (4.7)§
Median CA19–9 (range) (U/mL)	
Median	776 (0–435 000)
Median CEA (range) (ng/mL)	
Median	4.8 (0.6–1100.1)

†Never smoker, never/hardly smoked; past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). ‡Whole of pancreas (n = 1); head and body (n = 3); other (n = 1). §Tegafur, gimeracil, oteracil potassium (S-1) (n = 3); 5-fluorouracil plus leucovorin (n = 2). CA 19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; ECOG, Eastern Co-Operative Group.

93.4% of the patients; most cases were mild to moderate in severity (87.7%, grade ≤2; 5.7%, grade ≥3). Other common non-hematological AE included anorexia, pruritus, fatigue, nausea and diarrhea. Most patients experienced some degree of hematological toxicity, with grade 3 or 4 neutropenia (neutrophil decreased), leucopenia (white blood cell count decreased) and anemia (hemoglobin decreased) occurring in 34.9%, 29.2% and 14.2% of patients, respectively. Only one treatment-related death occurred (due to gastrointestinal hemorrhage), which was probably due to arterial bleeding caused by the invasion of the primary tumor into the gastrointestinal tract. Although the likelihood of this event being treatment-related was deemed remote, a causal relationship could not be completely excluded because the event occurred during the study treatment administration period.

Treatment-related SAE were reported in 26 (24.5%) patients. These included nine ILD-like events (8.5%), the majority of which (n = 7) were grade 1–2 in severity. Importantly, all of these nine patients recovered or improved, and four of these patients did so without any treatment for ILD-like events. Other

Table 2. Treatment-related adverse events occurring in >30% of patients treated with erlotinib and gemcitabine (n = 106)

	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Non-hematological			
Rash	78 (73.6)	3 (2.8)	0 (0)
Anorexia	75 (70.8)	15 (14.2)	0 (0)
Pruritus	57 (53.8)	1 (0.9)	0 (0)
Fatigue	56 (52.8)	3 (2.8)	0 (0)
Nausea	56 (52.8)	6 (5.7)	0 (0)
Diarrhea	52 (49.1)	2 (1.9)	0 (0)
Dry skin	49 (46.2)	0 (0)	0 (0)
Stomatitis	38 (35.8)	0 (0)	0 (0)
Pyrexia	32 (30.2)	0 (0)	0 (0)
Hematological			
White blood cell count decreased	85 (80.2)	31 (29.2)	0 (0)
Platelet count decreased	77 (72.6)	9 (8.5)	0 (0)
Hemoglobin decreased	76 (71.7)	13 (12.3)	2 (1.9)
Hematocrit decreased	73 (68.9)	8 (7.5)	0 (0)
Neutrophil decreased	73 (68.9)	32 (30.2)	5 (4.7)
Red blood cell count decreased	72 (67.9)	8 (7.5)	0 (0)
ALT increased	59 (55.7)	10 (9.4)	0 (0)
AST increased	57 (53.8)	4 (3.8)	1 (0.9)
Weight decreased	53 (50.0)	3 (2.8)	0 (0)
Lymphocyte count decreased	46 (43.4)	14 (13.2)	0 (0)
Blood albumin decreased	35 (33.0)	0 (0)	0 (0)
Gamma-glutamyltransferase increased	35 (33.0)	12 (11.3)	1 (0.9)

ALT, alanine amino transferase; AST, aspartate amino transferase.

treatment-related SAE were anorexia (3.8%), vomiting, pyrexia and abnormal hepatic function (1.9% each). The baseline characteristics, treatment and outcomes of patients who developed treatment-related ILD-like events during the study are detailed in Table 3. The onset times of ILD-like events ranged from 7 to 187 days after the start of treatment. In these patients, a relatively long survival was observed (from 119 to 568+ days), and five patients received post-study therapy. All of these nine patients were past or current smokers, and six had emphysema at baseline (not detected prior to treatment, but diagnosed at the extramural review by a radiologist in the DSMC). Multivariate analyses were performed for the occurrence of ILD-like events using the logistic regression model and emphysema at baseline was indicated as a risk factor for onset of ILD-like events (odds ratio [95% CI], 12.13 [1.01–145.7]; P = 0.0491).

Adverse events led to erlotinib discontinuation in 30 patients (28.3%) and gemcitabine discontinuation in 27 patients (25.5%). The main reasons for treatment discontinuation were ILD (n = 6) and anorexia (n = 3); no patient discontinued treatment due to RASH or diarrhea. Due to the onset of AE, a total of 65 patients (61.3%) required one or more interruptions of erlotinib (36 patients [34.0%] for longer than seven consecutive days and 17 patients [16.0%] for longer than 14 consecutive days) and 56 patients (52.8%) had one or more skip of gemcitabine. Modifications in the erlotinib or gemcitabine dosage were required in 17 (16.0%) and 11 (10.4%) patients, respectively, due to AE.

Efficacy. The median OS was 9.23 months (95% CI, 8.31–10.78; Fig. 1A) and the 1-year survival rate was 33% (95% CI, 24–42). Median PFS was 3.48 months (95% CI, 2.63–3.78; Fig. 1B). Among the patients evaluable for tumor response (n = 64), the ORR was 20.3% (13/64; 95% CI, 11.3–32.2) and the DCR was 50.0% (95% CI, 37.2–62.8; CR, n = 0; PR, n = 13; stable disease, n = 19).

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Table 3. Characteristics, treatment and outcomes of patients with treatment-related ILD-like events (n = 9)

Event	Gender	Age (years)	Smoking status†	Days on treatment	ILD maximum grade	Suspicious findings of ILD	Steroids	Oxygen	ILD outcome	Presence of emphysema (assessed by radiologist)	Survival outcome (days)	Post-therapy (chemotherapy)
Lymphoid ILD	M	62	Past	82	1	Pyrexia	None	No	Improved	Yes	362	Yes
ILD	M	42	Current	50	3	Pyrexia	Pulse	Yes	Recovered	Yes	517	Yes
Organising pneumonia	M	60	Past	183	2	Respiratory symptoms	None	No	Improved	Yes	568+	Yes
ILD	F	62	Past	113	2	Cough	Oral	No	Recovered	Yes	376	No
ILD	F	74	Past	111	3	Cough, dyspnea	Pulse	Yes	Improved	None	183	No
ILD	M	60	Current	25	1	Pyrexia	Pulse	No	Recovered	None	119	Yes
ILD	M	77	Past	7	1	X-ray	None	No	Recovered	Yes	255	No
ILD	M	55	Past	187	1	CT	None	No	Recovered	Yes	415	No
ILD	F	60	Current	76	2	Cough	Oral	No	Recovered	None	346	Yes

†Past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). CT, computed tomography; F, female; ILD, interstitial lung disease; M, male.

The median OS was longer in patients who experienced RASH of grade ≥2 (n = 67) than in those with RASH of grade ≤1 (n = 39) (10.25 months [95% CI, 8.80–12.12] *vs* 8.31 months [95% CI, 6.18–9.99], respectively; Fig. 1C) and the 1-year survival rate was higher (39% [95% CI, 27–50] *vs* 23% [95% CI, 10–36], respectively). Similarly, the median PFS was longer in patients with RASH of grade ≥2 versus those with RASH grade ≤1 (3.61 months [95% CI, 3.48–5.32] *vs* 1.81 months [95% CI, 1.64–3.48]; Fig. 1D). While there was no notable difference in ORR between patients with RASH grade ≥2 and those with grade ≤1 (21.1% [95% CI, 9.6–37.3] *vs* 19.2% [95% CI, 6.6–39.4]), the DCR was higher in those with more severe RASH (60.5% [95% CI, 43.4–76.0] *vs* 34.6% [95% CI, 17.2–55.7]).

Pharmacokinetics. Plasma sampling for PK analyses was performed in all six patients enrolled in the first step. On day 8, the values of C_{max} were 1760 ± 456.9 ng/mL (mean ± SD) for erlotinib, 169.7 ± 64.5 ng/mL for OSI-420 and 22 700 ± 3272.9 ng/mL for gemcitabine. The AUC_{last} was 29 001 ± 6560 h ng/mL, 2748 ± 788 h ng/mL and 10 717 ± 1458 h ng/mL (mean ± SD), respectively. The mean t_{max} was 8.0 h (range, 2.0–23.9 h), 9.0 h (2.0–23.9 h) and 0.51 h (0.45–0.57 h), respectively. Also on day 8, the mean plasma $t_{1/2}$ was 54.92 h (range, 9.25–144.61 h), 32.79 h (10.36–60.46 h), and 0.63 h (0.31–1.14 h), respectively. The Cl/F of erlotinib and gemcitabine showed interindividual variability; the Cl/F on day 8 was 3972.6 ± 772.1 mL/h (mean ± SD; coefficient of variation 19.4%) and 146 580.4 ± 31 101.3 mL/h (21.2%), respectively.

Biomarker analysis. Of the 106 patients enrolled, *EGFR* mutation status was evaluated in 47 patients (44.3%), all of whom had wild-type *EGFR*. The mutation status of the remaining patients was classified as unknown because samples were not available (30.2%), not examined (9.4%) or the results following sequencing were inconclusive (16.0%).

Discussion

This study was designed to initially assess the safety of erlotinib with gemcitabine for Japanese patients with pancreatic cancer, in whom there had been no prior exposure to either drug. As no significant safety concerns were raised in the first step of the study, enrollment of a further 101 patients was performed. Although the incidence of AE in this study was higher than in the PA.3 study, the incidence of grade 3–4 AE was similar.[28] Despite these results, no new AE specific to Japanese patients were observed. As expected, RASH and gastrointestinal events were among the most common AE in this study, and most of these cases were mild to moderate in severity.

Interstitial lung disease-like events were reported in nine patients (8.5%; grade 1/2/3, 3.8/2.8/1.9%) in the current study, while its incidence was reported to be 2.4% in patients treated in the erlotinib plus gemcitabine arm of the PA.3 study.[28] In addition, in Japanese patients with advanced pancreatic cancer, ILD-like events were reported in two (6.1%) of 33 patients treated with gemcitabine plus S-1, and were reported in three (1.1%) of 264 patients with gemcitabine monotherapy, respectively.[33,34] Likewise, the higher incidence of ILD-like events were documented using S-1 or erlotinib in combination with gemcitabine compared with gemcitabine as monotherapy in patients with pancreatic and biliary tract cancer.[35] On another front, outside of Japan, a high incidence of ILD-like events was reported in gemcitabine and paclitaxel combination therapy in patients with NSCLC.[36] From the above information, considering the higher incidence of ILD when gemcitabine is used in combination, an additive effect from such combinations cannot be ruled out.

In NSCLC, Japanese patients have an increased risk of developing ILD-like events when treated with EGFR TKI.[29,37–39] Fatal cases of ILD-like events have been reported following EGFR TKI administration for the treatment of NSCLC.[37–41] Importantly, however, no patients died due to an ILD-like event in this study. Seven patients experienced ILD-like events of grade 1–2 in severity. This may be due to active management of ILD-like cases during the study period. This management included regular and immediate chest X-rays, in addition to diagnosis with CT scans after any early signs and symptoms were observed (e.g. pyrexia, cough or dyspnea), timely discontinuation of the antitumor drugs (as a precautionary measure in case these drugs were associated with the symptoms) and appropriate treatment for the events (including oral/pulse steroids). By appropriately treating the early symptoms of ILD-like events, patients could restart antitumor therapy (chemotherapy: treatment change). In this study, the onset time for ILD-like events varied markedly between patients (7–187 days). It is therefore necessary to monitor the patients throughout the treatment period.

All of the patients who developed ILD in this study were current or past smokers, and smoking status has been shown to be a risk factor for ILD in the NSCLC population.[38] Results from the multivariate analyses in this study suggest that emphysema is also a risk factor for developing ILD; six of the nine

patients with ILD-like events were diagnosed with emphysema at baseline. Although the number of reports of an ILD-like event may have been artificially elevated due to underlying patient baseline characteristics and the active management of ILD-like events, these results demonstrate the need to consider the risk of ILD-like events in Japanese patients treated with TKI. In particular, it is important that chest CT scans are closely checked for the presence of emphysema or comorbid ILD and that pulmonary status is assessed prior to treatment administration.

This study corroborates the results of the combination of gemcitabine and erlotinib shown in the PA.3 study. The median OS in this study of 9.23 months was longer than those reported in trials with gemcitabine alone. In this study, patients who experienced skin toxicity of grade ≥2 had better outcomes than those with less severe toxicity or the overall study population. Retrospective analyses of data from the PA.3 and AViTA studies have found a significant association between the development of skin toxicity and efficacy in patients with pancreatic cancer treated with erlotinib-based therapy, although the precise mechanisms for the association between skin toxicity and effectiveness are unknown.[28,41,42]

Although the presence of mutations in the tyrosine-kinase region of the *EGFR* gene appears to predict a better response to erlotinib in NSCLC,[43,44] this has not yet been evaluated in pancreatic cancer. *EGFR* mutations are very rare in patients with pancreatic cancer;[45–47] indeed in the present study, no *EGFR* mutations were detected. Further work is required to determine whether *EGFR* mutations can be used as predictive markers for improved survival in Japanese patients receiving erlotinib and gemcitabine as treatment for advanced pancreatic cancer.

In conclusion, the present study shows that erlotinib in combination with gemcitabine is generally well tolerated in Japanese patients with advanced pancreatic cancer. This combination is associated with efficacy and survival outcomes, and the results of this study are consistent with the findings of the global PA.3 study.

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ORIGINAL CONTRIBUTION

Adjuvant Chemotherapy With Fluorouracil Plus Folinic Acid vs Gemcitabine Following Pancreatic Cancer Resection

A Randomized Controlled Trial

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Context Adjuvant fluorouracil has been shown to be of benefit for patients with resected pancreatic cancer. Gemcitabine is known to be the most effective agent in advanced disease as well as an effective agent in patients with resected pancreatic cancer.

Objective To determine whether fluorouracil or gemcitabine is superior in terms of overall survival as adjuvant treatment following resection of pancreatic cancer.

Design, Setting, and Patients The European Study Group for Pancreatic Cancer (ESPAC)-3 trial, an open-label, phase 3, randomized controlled trial conducted in 159 pancreatic cancer centers in Europe, Australasia, Japan, and Canada. Included in ESPAC-3 version 2 were 1088 patients with pancreatic ductal adenocarcinoma who had undergone cancer resection; patients were randomized between July 2000 and January 2007 and underwent at least 2 years of follow-up.

Interventions Patients received either fluorouracil plus folinic acid (folinic acid, 20 mg/m^2, intravenous bolus injection, followed by fluorouracil, 425 mg/m^2 intravenous bolus injection given 1-5 days every 28 days) (n=551) or gemcitabine (1000 mg/m^2 intravenous infusion once a week for 3 of every 4 weeks) (n=537) for 6 months.

Main Outcome Measures Primary outcome measure was overall survival; secondary measures were toxicity, progression-free survival, and quality of life.

Results Final analysis was carried out on an intention-to-treat basis after a median of 34.2 (interquartile range, 27.1-43.4) months' follow-up after 753 deaths (69%). Median survival was 23.0 (95% confidence interval [CI], 21.1-25.0) months for patients treated with fluorouracil plus folinic acid and 23.6 (95% CI, 21.4-26.4) months for those treated with gemcitabine (χ^2_1=0.7; P=.39; hazard ratio, 0.94 [95% CI, 0.81-1.08]). Seventy-seven patients (14%) receiving fluorouracil plus folinic acid had 97 treatment-related serious adverse events, compared with 40 patients (7.5%) receiving gemcitabine, who had 52 events (P<.001). There were no significant differences in either progression-free survival or global quality-of-life scores between the treatment groups.

Conclusion Compared with the use of fluorouracil plus folinic acid, gemcitabine did not result in improved overall survival in patients with completely resected pancreatic cancer.

Trial Registration clinicaltrials.gov Identifier: NCT00058201

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PANCREATIC CANCER IS ONE OF the major causes of cancer death globally, with a 5-year survival rate of less than 5%.[1,2] The outlook for those patients who can undergo surgical resection is better, and in specialized centers, resection rates greater than 15% can be achieved.[3] Although surgery cannot guarantee a cure, the 5-year survival does improve to around 10% following resection.[3] There is a clear need to improve long-term

See also p 1124 and Patient Page.

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survival in these patients. While the added survival benefit of adjuvant chemoradiotherapy with or without maintenance chemotherapy[4-7] remains unclear,[8] a more certain survival benefit has been demonstrated from adjuvant chemotherapy.[6,9-14]

The European Study Group for Pancreatic Cancer (ESPAC)-3 trial was designed to compare the survival benefit of adjuvant fluorouracil plus folinic acid vs gemcitabine, which during the conduct of the ESPAC-1 trial had become established as the standard care for advanced pancreatic cancer.[15] Initially this was a 3-group study that included an observation group based on the survival uncertainty of adjuvant chemotherapy[6]; however, the observation group was removed from the design following the definitive results of ESPAC-1.[12] In 2007, the Charité Onkologie Clinical Studies in GI Cancer (CONKO)-001 trial reported improved disease-free survival in patients randomized to receive adjuvant gemcitabine compared with those randomized to receive surgery alone.[13] With 1088 patients randomized, the ESPAC-3 trial represents the largest-ever adjuvant trial conducted in pancreatic cancer, to our knowledge, and results are presented herein.

METHODS

Patients and Trial Design

The ESPAC-3 trial was initially introduced as a 3-group study designed to compare the survival benefit of resection alone (observation) with either adjuvant fluorouracil plus folinic acid or gemcitabine. The first patient was entered on July 7, 2000. Following the definitive results from ESPAC-1,[12] the recommendation of the independent data and safety monitoring committee to cease randomization into the control group was adopted on June 20, 2003. The trial design of ESPAC-3 (version 2) therefore necessitated removal of the control group from the original ESPAC-3 (version 1) trial design. ESPAC-3 (version 2) is thus a 2-group, international, open-label, phase 3, randomized controlled study of adjuvant chemotherapies comparing fluorouracil plus folinic acid with gemcitabine.

The trial was approved by ethics committees at the national and local level according to the requirements of each participating country. All patients entered into the study provided written informed consent following a full explanation of the study and reading of the patient information sheet. There were 159 centers in 17 countries: Australia and New Zealand (26), Canada (15), Czech Republic (1), Finland (1), France (15), Germany (13), Greece (3), Hungary (2), Ireland (2), Italy (3), Japan (7), Poland (1), Serbia (1), Sweden (8), Switzerland (1), and the United Kingdom (60).

Surgery and Eligibility

Patients were eligible if they had undergone complete macroscopic (R0 or R1) resection for ductal adenocarcinoma of the pancreas with histological confirmation and with no evidence of malignant ascites, peritoneal metastasis, or spread to the liver or other distant abdominal or extra-abdominal organs. The type and extent of resection was determined using an established international classification.[16] Patients had to be fully recovered from the operation, with a World Health Organization performance score of 2 or lower and a life expectancy of more than 3 months. Patients with previous use of neoadjuvant chemotherapy or other concomitant chemotherapy and with pancreatic lymphoma, macroscopically remaining tumor (R2 resection), or TNM stage IVb disease were excluded.

Randomization

Patients were randomly assigned to each treatment group on a 1:1 basis according to a computer-generated variable-size blocked randomization method. Patients were stratified at randomization by country and resection margin status (R0 vs R1).

Chemotherapy

Folinic acid (20 mg/m^2) was given as an intravenous bolus followed by intravenous bolus fluorouracil (425 mg/m^2) given on 5 consecutive days every 28 days for 6 cycles (24 weeks). Gemcitabine (lyophilized powder diluted in normal saline) was given as an intravenous infusion over 30 minutes (1000 mg/m^2), administered once a week for 3 out of every 4 weeks (1 cycle) for 6 cycles (24 weeks). Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 2), with a clearly defined protocol for modifications and delays.

Quality of life was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3) and ESPAC-32 patient questionnaires at baseline and at 3 and 6 months and yearly until 5 years.[17]

Statistical Analysis

The trial was designed to test the primary hypothesis, ie, that overall length of survival does not differ between that achieved with adjuvant fluorouracil plus folinic acid and that achieved with gemcitabine. Secondary end points were progression-free survival, toxicity, and quality of life. Power calculations were based on expected 2-year survival rates. The ESPAC-1 trial had shown that 2-year survival with fluorouracil plus folinic acid was in the order of 40% to 45%.[6,12] ESPAC-3 was powered to detect a clinically meaningful increase in survival of 10% with gemcitabine. Recruiting 515 patients (275 deaths) in each treatment group would allow 10% differences in 2-year survival to be detected using a 2-sided $\alpha = .05$ level of significance with at least 90% power.

Overall survival was measured from the date of resection to date of death from any cause. Patients remaining alive were censored at the date last seen alive. Progression-free survival was measured from date of resection to date of death from any cause or date of local tumor recurrence or metastases. Patients remaining alive and progression-

free were censored at the date last seen alive. Survival estimates were calculated using the Kaplan-Meier method[18] and compared using the unweighted Mantel-Haenszel version of the log-rank test.[19] Median, 12-month, and 24-month survival estimates are presented with 95% confidence intervals (CIs).

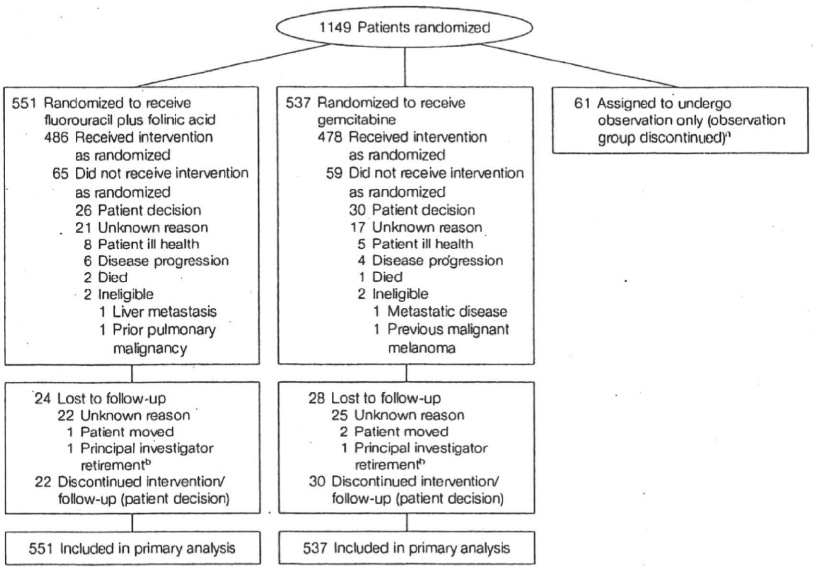
The hazard ratio (HR) of the treatment effect is presented for gemcitabine compared with that for fluorouracil plus folinic acid. Hazard ratios of the treatment effect within stratification subgroups at randomization are estimated (without significance testing) with tests of heterogeneity to determine if treatment effects differ across subgroups. The treatment effect was adjusted by stratification factors at randomization (country and resection margin status) and other identified prognostic factors in the multivariate setting using Cox proportional hazards modeling[20] incorporating a random effect into the hazard function for country effect. Factors with a log-rank significance of $P<.10$ were explored further in the multivariate setting using backward selection techniques. Classification variables were used for ordinal variables with more than 2 categories. The functional form of the relationship between continuous factors and log-hazard (specifically age, tumor size, and postoperative carbohydrate antigen 19-9 [CA19-9] level) was assessed, and factors were included in the multivariate models with a nonlinear transformation if appropriate.[21] The assumption of proportional hazards was assessed and confirmed by including a time-dependent covariate.

The number of patients receiving treatment and the percentage of protocol dose of chemotherapy and the range of total doses received was calculated. The number of patients experiencing at least 1 high-grade toxic episode (grade 3/4) of each toxicity type or serious adverse event is reported as a percentage of the total number of patients randomized within each treatment group. Proportions were compared using the Fisher exact test with the significance level set at $P<.005$ and with Bonferroni adjustment to account for multiple testing.

Quality-of-life domain scores were calculated according to the EORTC QLQ-C30 scoring manual and linearly transformed to produce a standardized score ranging from 0 to 100. Higher scores for the functional and global health scales indicated better quality of life, whereas higher scores for the symptom scales and items indicated poorer quality of life. Standardized area under the curve (AUC) scores[17] are average observed symptomatic and functional quality-of-life scores per month within a 12-month duration from surgery, calculated from the linearly transformed scores and compared across treatments using the Mann-Whitney nonparametric test.

All statistical analyses were carried out using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina) and R version 2.7.2 (R Project for Statistical Computing; http://www.r-project.org) on an intention-to-treat basis, retaining patients in their randomized treatment groups and including protocol violators and ineligible patients. A 2-sided significance level of $P<.05$ was used throughout.

Figure 1. ESPAC-3 Study Flow



ESPAC indicates European Study Group for Pancreatic Cancer.
[a] Discontinued in June 2003 owing to statistical evidence for survival benefit attributable to adjuvant chemotherapy.
[b] Principal investigator at research site retired from practice with no replacement.

RESULTS

The last of the 1088 patients recruited was randomized on January 8, 2007. The database was locked on March 18, 2009.

Patient Characteristics

Five hundred fifty-one patients were randomized to receive fluorouracil plus folinic acid, and 537 were randomized to receive gemcitabine (FIGURE 1). Four ineligible patients were reported (2 in each group) and have been included in the analysis on an intention-to-treat basis. The clinical characteristics of patients and surgical and pathological details are shown in TABLE 1.

Treatment

Four hundred eighty-six patients (88%) received 2326 cycles of fluorouracil plus folinic acid and 478 (89%) received 2464 cycles of gemcitabine. Sixty-five patients (12%) in the fluorouracil plus

Table 1. Patient Characteristics at Randomization

Characteristic	No. (%)		
	Fluorouracil + Folinic Acid (n=551)	Gemcitabine (n=537)	Total (N=1088)
Sex			
Men	301 (55)	297 (55)	598 (55)
Women	250 (45)	240 (45)	490 (45)
Age, y			
Median (IQR)	63 (56-70)	63 (56-69)	63 (56-69)
Range	34-85	31-81	31-85
Performance score			
0	201 (36)	170 (32)	371 (34)
1	286 (52)	303 (56)	589 (54)
2	64 (12)	64 (12)	128 (12)
Smoking status			
Never	207 (43)	189 (40)	396 (41)
Past	192 (39)	207 (44)	399 (42)
Present	87 (18)	78 (16)	165 (17)
Missing	65	63	128
Concurrent conditions			
None	240 (46)	263 (52)	503 (49)
Yes	277 (54)	240 (48)	517 (51)
Missing	34	34	68
Diabetes			
No	388 (75)	375 (75)	763 (76)
Non–insulin-dependent	54 (11)	51 (10)	105 (10)
Insulin-dependent	72 (14)	73 (15)	145 (14)
Missing	37	38	75
Postoperative CA19-9 level			
No.	394	373	767
Median (IQR), kU/L	26 (10-65)	22 (9-62)	24 (10-63)
Time from surgery to randomization, median (IQR), d	45 (29-57)	45 (30-57)	45 (29-57)
Hospital stay			
No.	494	478	972
Median (IQR), d	14 (10-20)	14 (10-20)	14 (10-20)
Resection margins			
Negative	356 (65)	348 (65)	704 (65)
Positive	195 (35)	189 (35)	384 (35)
Tumor grade			
Well differentiated	81 (15)	66 (13)	147 (14)
Moderately differentiated	327 (60)	336 (63)	663 (62)
Poorly differentiated	135 (25)	125 (24)	260 (24)
Undifferentiated	2 (0)	2 (0)	4 (0)
Lymph nodes			
Negative	162 (30)	145 (27)	307 (28)
Positive	387 (70)	391 (73)	778 (72)
Maximum tumor size			
No.	526	507	1033
Median (IQR), mm	30 (23-40)	30 (24-40)	30 (23-40)
Tumor stage[a]			
I	58 (11)	46 (9)	104 (10)
II	154 (28)	144 (27)	298 (28)
III	303 (56)	319 (61)	622 (58)
IVa	26 (5)	16 (3)	42 (4)
Surgery			
Whipple resection	290 (56)	299 (59)	589 (58)
Total pancreatectomy	28 (5)	15 (3)	43 (4)
Pylorus-preserving resection	162 (31)	150 (30)	312 (30)
Distal pancreatectomy	40 (8)	40 (8)	80 (8)

(continued)

folinic acid group and 59 (11%) in the gemcitabine group did not start treatment. Three hundred one patients (55%) in the fluorouracil plus folinic acid group and 323 (60%) in the gemcitabine group received all 6 cycles of treatment. Median time from randomization to the start of chemotherapy was 10 (interquartile range [IQR], 5-18) days for the fluorouracil plus folinic acid group and 8 (IQR, 5-14) days for the gemcitabine group. Median time receiving chemotherapy was 4.7 (IQR, 3.1-5.0) months for the fluorouracil plus folinic acid group and 5.1 (IQR, 4.0-5.3) months for the gemcitabine group. Median dose intensity was 79% (range, 3%-141%) of the planned protocol for the fluorouracil plus folinic acid group and 89% (range, 6%-122%) for the gemcitabine group.

Overall Survival

Seven hundred fifty-three patients (69%) had died at the time of analysis (388 [70%] in the fluorouracil plus folinic acid group and 365 [68%] in the gemcitabine group). Median length of follow-up of 335 living patients was 34.2 (IQR, 27.1-43.4; range, 0.4-86.3) months, equal across treatment groups. Overall, 282 of patients remaining alive (84%) had undergone follow-up for more than 2 years. Median survival was estimated as 23.2 months (95% CI, 21.7-24.9), with 12-month and 24-month rates estimated as 79.3% (95% CI, 76.9%-81.8%) and 48.6% (95% CI, 45.6%-51.6%), respectively. Median survival for patients treated with fluorouracil plus folinic acid was 23.0 (95% CI, 21.1-25.0) months and for patients treated with gemcitabine was 23.6 (95% CI, 21.4-26.4) months (FIGURE 2).

Survival estimates at 12 and 24 months were 78.5% (95% CI, 75.0%-82.0%) and 48.1% (95% CI, 43.8%-52.4%), respectively, for the fluorouracil plus folinic acid group and 80.1% (95% CI, 76.7%-83.6%) and 49.1% (95% CI, 44.8%-53.4%) for the gemcitabine group. Log-rank analysis revealed no statistically significant difference in survival estimates between

the treatment groups (χ^2_1=0.7; P=.39; HR, 0.94 [95% CI, 0.81-1.08]).

Progression-Free Survival

Six hundred eighty-eight patients (63%) developed local recurrence, metastases, or both; of these, 597 had died. Two hundred forty-four patients (22%) were alive and progression free. Progression-free survival analysis was based on all patients, of whom 844 (78%) had either progressive disease or died. The median progression-free survival was 14.3 (95% CI, 13.5-15.1) months, with 12-month and 24-month rates of 58.7% (95% CI, 55.7%-61.6%) and 30.1% (95% CI, 27.3%-32.9%), respectively. The median progression-free survival for patients treated with fluorouracil plus folinic acid was 14.1 (95% CI, 12.5-15.3) months and 14.3 (95% CI, 13.5-15.6) months for patients treated with gemcitabine (Figure 2).

Survival estimates at 12 and 24 months were 56.1% (95% CI, 51.8%-60.3%) and 30.7% (95% CI, 26.7%-34.6%), respectively, for the fluorouracil plus folinic acid group and 61.3% (95% CI, 57.1%-65.5%) and 29.6% (95% CI, 25.6%-33.5%) for the gemcitabine group. Log-rank analysis revealed no statistically significant difference in progression-free survival estimates between the treatment groups (χ^2_1=0.40; P=.53; HR, 0.96 [95% CI, 0.84-1.10]).

Toxicity

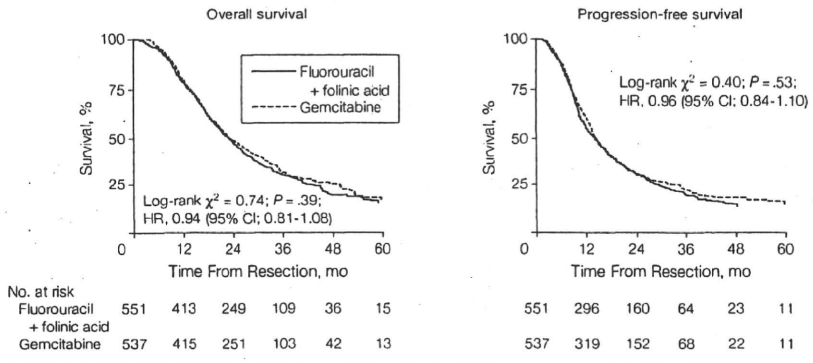
Patients receiving fluorouracil plus folinic acid had significantly increased grade 3/4 stomatitis (P<.001) and diarrhea (P<.001), whereas patients receiving gemcitabine reported significantly increased grade 3/4 hematologic toxicity (P=.003) (TABLE 2). One hundred seventeen patients (11%) reported 149 treatment-related serious adverse events, the majority attributable to inpatient hospitalization. Seventy-seven patients (14%) receiving fluorouracil plus folinic acid reported 97 treatment-related serious adverse events, compared with 40 (7.5%) receiving gemcitabine, who reported 52 events (P<.001).

Table 1. Patient Characteristics at Randomization (continued)

Characteristic	No. (%) Fluorouracil + Folinic Acid (n = 551)	Gemcitabine (n = 537)	Total (N = 1088)
Extent of resection			
Standard	364 (73)	364 (74)	728 (73)
Radical	102 (20)	82 (16)	184 (19)
Extended radical	36 (7)	47 (10)	83 (8)
Venous resection[b]			
No	430 (84)	435 (87)	865 (85)
Yes	83 (16)	67 (13)	150 (15)
Cholecystectomy			
No	122 (24)	117 (23)	239 (23)
Yes	396 (76)	391 (77)	787 (77)
Local invasion			
No	303 (58)	284 (57)	587 (57)
Yes	216 (42)	218 (43)	434 (43)
Other operative finding			
No	442 (85)	432 (87)	874 (86)
Yes	75 (15)	66 (13)	141 (14)
Postoperative complications			
No	405 (78)	372 (74)	777 (76)
Yes	112 (22)	131 (26)	243 (24)

Abbreviations: CA19-9, carbohydrate antigen 19-9; IQR, interquartile range.
[a] International Union Against Cancer (fifth edition, 1997) stages III and IVa are both equivalent to American Joint Committee on Cancer (seventh edition, 2010) stage IIB.
[b] Superior mesenteric vein or hepatic portal vein/superior mesenteric vein confluence.

Figure 2. Survival Results by Randomized Treatment



CI indicates confidence interval; HR, hazard ratio.

Prognostic Factors for Overall Survival

Univariate survival analysis of categorical variables revealed that not smoking, World Health Organization performance status 0, negative resection margins, negative lymph node status, well-differentiated tumors, stage I disease, and tumors with no local invasion were associated with improved survival (TABLE 3 and eFigure 1 and eFigure 2, available at http://www.jama.com). The increased risk of death in patients with positive margins compared with patients with negative margins was 35% (log-rank χ^2_1=16.3; P<.001; HR, 1.35 [95% CI, 1.17-1.56]). There was no significant difference in the effect of treatment across subgroups according to R status (test of heterogeneity, χ^2_1=0.3, P=.56). The continuous covariates of tumor diameter (Wald χ^2_1=10.1, P=.001) and postoperative CA19-9 level (Wald χ^2_2=126.6, P<.001) were also each significantly associated with survival at univariate

Table 2. Reported Toxicity

Toxicity Variable	Reported NCI CTC Version 2 Toxicity[a]				
	Fluorouracil + Folinic Acid (n = 551)		Gemcitabine (n = 537)		
	Grade 1/2, No.	Grade 3/4, No. (%)	Grade 1/2, No.	Grade 3/4, No. (%)	*P* Value[b]
WBC count	154	32 (6)	262	53 (10)	.01
Neutrophils	180	121 (22)	270	119 (22)	.94
Platelets	57	0	170	8 (1.5)	.003
Nausea	292	19 (3.5)	282	13 (2.5)	.37
Vomiting	159	17 (3)	131	11 (2)	.34
Stomatitis	304	54 (10)	96	1 (0)	<.001
Alopecia	189	1 (0)	135	1 (0)	>.99
Tiredness	340	45 (8)	351	32 (6)	.16
Diarrhea	333	72 (13)	194	12 (2)	<.001
Other	262	67 (12)	290	43 (8)	.03

Abbreviations: CTC, Common Terminology Criteria; NCI, National Cancer Institute; WBC, white blood cell.
[a] Toxicity grades defined per CTC Version 2.0.[22]
[b] From Fisher exact test with significance level set to $P<.005$ and with Bonferroni adjustment to account for multiple testing.

analysis but not age (Wald $\chi^2_1=0.7$, $P=.40$).

Factors with a log-rank significance of $P<.10$ were considered for inclusion in the Cox proportional hazards frailty modeling: sex, smoking, performance status, grade of disease, lymph node status, stage (I/II vs III/IV), and local invasion. The continuous covariates tumor size and postoperative CA19-9 level were included under nonlinear transformations. Stratification factors (country [random effect] and resection margin status) and treatment group were included in all models.

A model based on 766 patients with complete data (545 deaths) identified grade of disease (Wald $\chi^2_3=28.8$, $P<.001$), nodal status (Wald $\chi^2_1=19.1$,

Table 3. Univariate Survival Analysis of Categorical Variables[a]

Factor	No.		Survival Rate, %		Survival, Median (95% CI), mo	HR (95% CI)	Log-Rank χ^2	*P* Value
	Patients	Deaths	12 mo	24 mo				
Sex								
Men	598	427	78.7	46.4	21.7 (20.3-24.2)	1 [Reference]	3.4	.06
Women	490	326	80.1	51.3	24.9 (22.7-27.5)	0.87 (0.76-1.01)		
Smoking status								
Never	396	271	82.8	52.6	25.5 (22.6-29.2)	1 [Reference]	8.1	.02
Past	399	281	78.3	48.0	22.9 (21.1-25.9)	1.12 (0.95-1.32)		
Present	165	128	75.8	42.0	20.4 (17.6-23.8)	1.36 (1.10-1.67)		
Performance score								
0	371	243	80.7	54.4	25.8 (23.6-28.6)	1 [Reference]	8.5	.02
1	589	418	79.9	47.1	22.6 (21.1-24.9)	1.20 (1.03-1.41)		
2	128	92	72.1	38.2	19.2 (16.9-22.6)	1.37 (1.08-1.74)		
Resection margins								
Negative	704	460	82.8	51.4	24.7 (22.8-26.9)	1 [Reference]	16.3	<.001
Positive	384	293	73.0	43.4	19.9 (17.7-23.0)	1.35 (1.17-1.56)		
Tumor grade								
Well differentiated	147	86	90.7	57.3	27.9 (23.9-36.1)	1 [Reference]	24.2	<.001
Moderately differentiated	663	457	81.7	51.4	24.7 (22.6-26.4)	1.31 (1.04-1.65)		
Poorly differentiated	260	199	66.6	36.5	17.1 (15.3-20.1)	1.79 (1.39-2.31)		
Lymph nodes								
Negative	307	161	86.1	63.1	35.0 (29.4-40.6)	1 [Reference]	52.3	<.001
Positive	778	589	76.7	43.2	21.0 (19.4-22.3)	1.89 (1.59-2.26)		
Tumor stage[b]								
I	104	53	87.0	57.0	32.8 (22.3-∞)	1 [Reference]	31.8	<.001
II	298	186	83.6	58.0	28.1 (24.8-31.7)	1.31 (0.96-1.77)		
III	622	468	76.2	42.9	20.7 (18.8-22.3)	1.88 (1.41-2.50)		
IVa	42	31	73.2	43.2	22.6 (15.1-27.0)	1.75 (1.13-2.73)		
Local invasion								
No	587	397	80.5	51.5	24.8 (22.3-27.1)	1 [Reference]	6.6	.01
Yes	434	326	77.5	44.7	21.8 (19.9-23.8)	1.21 (1.05-1.40)		
Treatment								
Fluorouracil + folinic acid	551	388	78.5	48.1	23.0 (21.1-25.0)	1 [Reference]	0.74	.39
Gemcitabine	537	365	80.1	49.1	23.6 (21.4-26.4)	0.94 (0.81-1.08)		

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Reporting where log-rank $P<.10$.
[b] International Union Against Cancer (fifth ed, 1997) stages III and IVa are both equivalent to American Joint Committee on Cancer (seventh ed, 2010) stage IIB.

$P<.001$), and CA19-9 level (Wald $\chi^2_2=110.4$, $P<.001$) as significant independent prognostic factors of overall survival (TABLE 4). To maximize the data for modeling, further analysis excluding CA19-9 level, which was associated with a substantial amount of missing data (321 patients), resulted in a model based on 1030 patients with complete data (715 deaths). This confirmed grade of disease (Wald $\chi^2_3=25.2$, $P<.001$), nodal status (Wald $\chi^2_1=41.7$, $P<.001$), performance status (Wald $\chi^2_2=10.9$, $P=.004$), tumor size (Wald $\chi^2_1=8.9$, $P=.003$), and smoking status (Wald $\chi^2_3=9.2$, $P=.03$) as significant independent prognostic factors of overall survival.

Tests of heterogeneity within pathological (eFigure 3) or demographic (eFigure 4) subgroups did not reveal any significant findings.

Quality of Life

Five hundred sixty-five patients (280 randomized to receive fluorouracil plus folinic acid and 285 to receive gemcitabine) completed quality-of-life questionnaires, including a baseline questionnaire. The subgroups were representative of patients in the main study based on patient characteristics. Of these, 438 completed 3-month questionnaires, 417 completed 6-month questionnaires, and 307 completed 12-month questionnaires. Standardized AUC scores are based on average standardized scores ranging between 0 and 100. There were no significant differences in mean standardized AUC for global quality-of-life scores across treatment groups conditional on patient survival; mean standardized AUC was 43.6 (SD, 20.1) for patients receiving fluorouracil plus folinic acid, compared with 46.6 (SD, 19.7) for those receiving gemcitabine ($P=.08$).

COMMENT

There have been few large randomized controlled trials of adjuvant treatment following resection in pancreatic cancer. The first of these, the ESPAC-1 trial,[6,12] concluded that chemotherapy with fluorouracil plus folinic acid improved overall survival but chemoradiotherapy did not.[6,12] The failure of adjuvant chemoradiotherapy to enhance survival was also reflected in the results of the EORTC multicenter prospective randomized trial.[5] The Radiation Therapy Oncology Group (RTOG) 9704 trial randomized 538 patients to receive either prechemoradiation and postchemoradiation gemcitabine or prechemoradiation and postchemoradiation fluorouracil.[7] The median survival in the 451 eligible patients was 16.7 and 18.8 months, respectively ($P=.34$), and in the 388 patients with cancer of the pancreatic head was 20.5 months vs 16.9 months, respectively ($P=.09$).[7] The primary end point in the CONKO-001 trial was disease-free survival.[13] This was 13.4 months for gemcitabine and 6.9 months for surgery alone ($P<.001$), while the median overall survival was 22.1 months and 20.5 months, respectively ($P<.06$).[13]

The ESPAC-3 trial found a median survival of 23.0 months for patients treated with fluorouracil plus folinic acid and 23.6 months for those treated with gemcitabine and a median progression-free survival of 14.1 months and 14.3 months, respectively. Tumor

Table 4. Cox Proportional Hazards Models[a]

Factor	HR (95% CI)	Wald χ^2	*P* Value
Including CA19-9			
Country (19 RE)	NA	0.7	.52
Resection margins (negative vs positive)	1.18 (0.99-1.40)	3.3	.07
Treatment (fluorouracil + folinic acid vs gemcitabine)	0.88 (0.75-1.05)	2.1	.15
Tumor grade			
Well differentiated	1 [Reference]	28.8	<.001
Moderately differentiated	1.72 (1.27-2.32)		
Poorly differentiated	2.32 (1.68-3.20)		
Missing	1.12 (0.53-2.36)		
Lymph nodes (negative vs positive)	1.60 (1.29-1.97)	19.1	<.001
CA19-9[b]	NA	110.4	<.001
Excluding CA19-9[c]			
Country (19 RE)	NA	0.8	.41
Resection margins (negative vs positive)	1.17 (1.01-1.37)	4.1	.04
Treatment (fluorouracil + folinic acid vs gemcitabine)	0.90 (0.78-1.04)	1.9	.16
Tumor grade			
Well differentiated	1 [Reference]	25.2	<.001
Moderately differentiated	1.27 (1.00-1.61)		
Poorly differentiated	1.81 (1.39-2.36)		
Missing	1.11 (0.56-2.22)		
Lymph nodes (negative vs positive)	1.82 (1.52-2.18)	41.7	<.001
Performance status			
0	1 [Reference]	10.9	.004
1	1.22 (1.03-1.43)		
2	1.49 (1.16-1.92)		
Maximum tumor size[d]	1.25 (1.08-1.45)	8.9	.003
Smoking			
Never	1 [Reference]	9.2	.03
Past	1.08 (0.91-1.29)		
Present	1.38 (1.11-1.71)		
Missing	1.22 (0.94-1.59)		

Abbreviations: CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; NA, not applicable; RE, random effects.
[a] See Table 3 for numbers of patients, numbers of deaths, and 12-month and 24-month survival rates.
[b] Second-degree fractional polynomial transformation applied: CA19@^(−0.5) + log(CA19@).
[c] Patients = 1030; deaths = 715.
[d] Log transformation applied; HR based on a 1-unit increase in log(tumor size).

grade, nodal status, tumor size, postoperative serum CA19-9 levels, performance status, and smoking were all independent prognostic factors of overall survival. Although resection margin status was significant on univariate analysis, this was not so on multivariate analysis, confirming the previous results of ESPAC-1 that primary tumor characteristics dominate outcome.[23]

The prognostic significance of CA19-9 level in ESPAC-1 mirrored that in the RTOG trial, with both studies using postresectional values.[24] This is important: preoperative levels are artificially elevated in the presence of obstructive jaundice, because CA19-9 is excreted in bile and there is no simple correction factor. In the CONKO-001 trial, patients with CA19-9 levels greater than 2.5 times the upper limit of normal were excluded, indicating that in that study there was a bias toward patients with a more favorable prognosis.[13] That tobacco smoking affected long-term outcome was a novel finding and should add further weight against the use of tobacco.

The absence of an overall survival difference between postoperative adjuvant fluorouracil plus folinic acid compared with gemcitabine contrasts with the findings of a much smaller study in patients with nonresected advanced pancreatic cancer that showed a survival benefit with gemcitabine as compared with fluorouracil.[15] The fluorouracil regimen used in that trial (600 mg/m^2 bolus once weekly without folinic acid) was less intensive than that used in ESPAC-3.[15] This fluorouracil regimen may be less efficacious than the Mayo Clinic regimen, but there are no large randomized trials that have directly compared these 2 treatments in pancreatic cancer.

In conclusion, gemcitabine did not result in improved overall survival compared with fluorouracil plus folinic acid in patients with resected pancreatic cancer. As a logical progression from these data we have designed the ESPAC-4 trial, currently in progress, to compare combination chemotherapy with gemcitabine plus capecitabine, an orally active fluoropyrimidine,[25] with gemcitabine alone.

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Author Contributions: Dr Neoptolemos had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

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Study supervision: Neoptolemos, Bassi, Ghaneh, Padbury, Izbicki, Friess, Dervenis, Oláh, Butturini, Smith, Palmer, Thompson, Büchler.

Ms Rawcliffe was the trial coordinator responsible for central administration ensuring ethical standards for collection and verification of data. The results were interpreted by the ESPAC working party (all of the above). Drs Neoptolemos, Ghaneh, and Stocken prepared the initial draft and were responsible for collating changes proposed by the aforementioned into the final paper before final approval by all participants in the European Study Group for Pancreatic Cancer.

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The Full List of ESPAC Specialists Who Contributed to the Treatment of Patients in the ESPAC-3 Trial is presented in the eAppendix.

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Online-Only Material: eFigures 1 through 4 and the eAppendix are available at http://www.jama.com.

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If we have made obvious mistakes, we should not try, as we generally do, to gloss them over, or to find something to excuse . . . them; we should admit to ourselves that we have committed faults, and open our eyes wide to all their enormity, in order that we may firmly resolve to avoid them in the time to come.

—Arthur Schopenhauer (1788-1860)

Slow Parenchymal Flattening Technique for Distal Pancreatectomy Using an Endopath Stapler: Simple and Safe Technical Management

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ABSTRACT

Backgropund/Aims: The appropriate closure of the pancreatic remnant after a distal pancreatectomy remains controversial. To describe a safer and simple distal pancreatectomy using an endopath stapler, with special emphasis on the slow parenchymal flattening technique.
Methodology: The slow parenchymal flattening technique (SFT) for a distal pancreatectomy using an endopath stapler (Echelon 60) was applied to avoid a destruction of pancreas capsule and parenchyma for a soft friable pancreas. In this technique, the pancreas was gently compressed with an atraumatic intestinal clamp for a few minutes prior to the stapling dissection. Then, the closure jaw of endopath stapler was closed carefully and slowly taking more than 5 minutes at the fixed speed before dissection.
Results: SFT using the Echelon 60 was performed for 22 consecutive patients who required a distal pancreatectomy. Only one patient (4.5%) developed a symptomatic pancreatic fistula (ISGPF classification grade B). There were no mortalities or severe pancreatic fistula (ISGPF classification grade C) in this series.
Conclusions: The SFT using the Echelon 60 can be performed easily, which enables surgeons to achieve confident pancreas stump without any tissue injury.

KEY WORDS: Distal pancreatectomy; Slow parenchymal flattening technique; Endopath stapler

ABBREVIATIONS: Slow Parenchymal Flattening Technique (SFT); Intraductal Papillary Mucinous Neoplasm (IPMN)

INTRODUCTION

Recent advances in surgical technique have reduced the operative mortality rate of a pancreatic resection, yet the morbidity rates have remained essentially unchanged, ranging from 30 to 40% (1-3). A pancreatic fistula is the main cause of postoperative morbidity and is associated with numerous further complications, such as an intra-abdominal abscess, wound infection, sepsis and hemorrhage. The surgical technique and the surgeon are considered the most relevant risk factors for fistula formation. Several closure techniques have been introduced for the pancreatic remnant in an attempt to reduce complications and in particular pancreatic fistulas after distal pancreatectomy. These include hand-sewn suture techniques, stapled closure technique or a combination of ultrasonic dissection devices, pancreaticoenteric anastomosis, or sealing with fibrin glue (3-13).

Since modern surgical stapling instruments have found a wide range of uses in gastrointestinal surgery, the establishment of safe and alternative techniques for a distal pancreatectomy using stapler has been attempted. The most important and difficult technical factor for stapler dissection is to prevent a pancreatic tissue tear during compression. The slow parenchymal flattening technique (SFT) has been performed using an Echelon 60 and an atraumatic intestinal clamp for a distal pancreatectomy to avoid a destruction of pancreas capsule and parenchyma for a soft pancreas since 2006.

SURGICAL TECHNIQUE

The spleen and the distal pancreas were mobilized after division of the gastrocolic ligament with visualization of the pancreas. The splenic artery and vein were individually ligated using double stitches of 3-0 vicryl close to the planned dissection line of the pancreas. The pancreas was gently compressed with an atraumatic intestinal clamp at the transection line for a few minutes prior to the stapling dissection (**Figure 1A**; a case for distal transection line, **2A**; a case for proximal transection line). This procedure reduced the thickness of the pancreatic parenchyma at the site of planned resection and facilitated subsequent application of the linear stapler across the pancreas. The pancreas was transected with a stapling device, using the Echelon 60 (Ethicon Endo-surgery; Johnson & Johnson, Cincinnati, OH, USA) with a gold cartridge (compressible thickness to 1.8 mm). The device gives a staple line consisting of a triple row of closely placed staples. The articulation is provided

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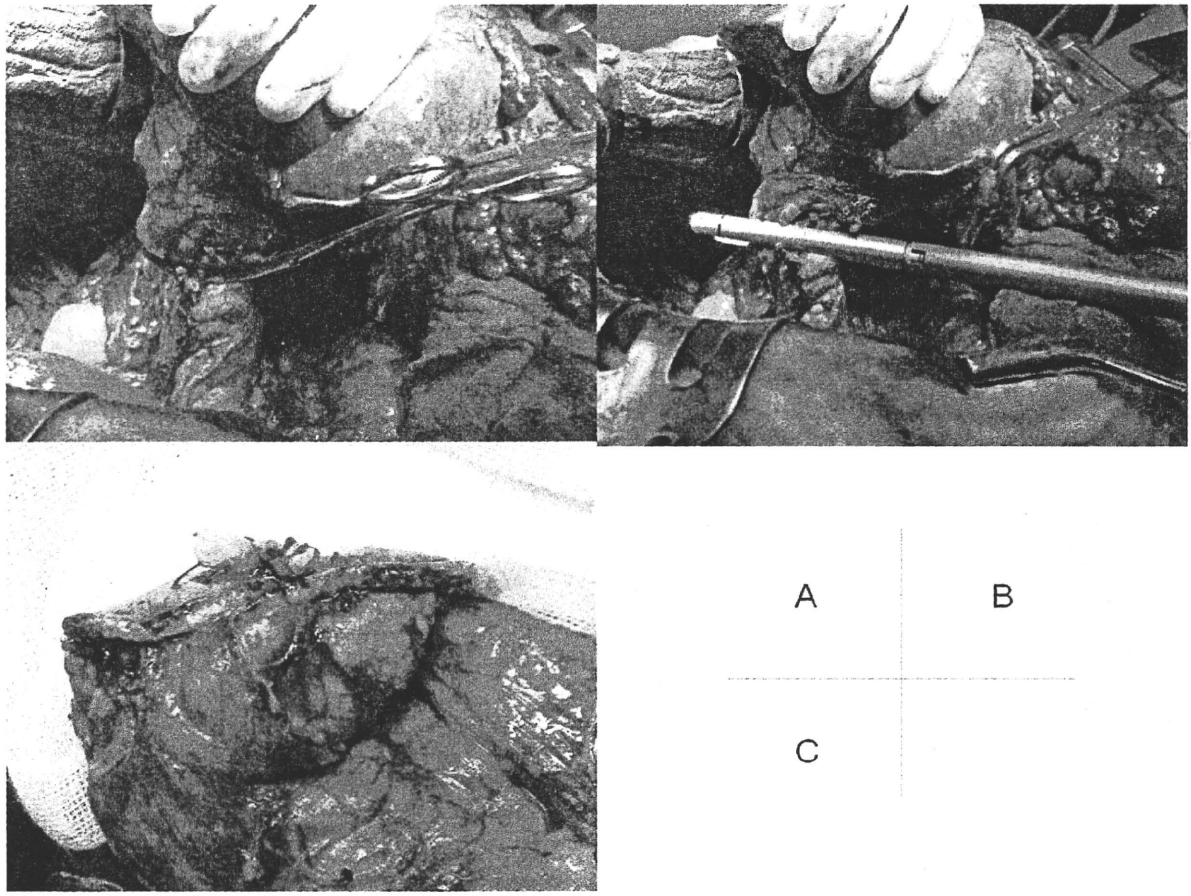

FIGURE 1
The pancreas was transected with slow flattening technique at distal cutting line. Prior to the application of the stapler, the pancreas was gently compressed with an atraumatic intestinal clamp at the transection line for a few minutes (**A**). The closure jaw of the Echelon 60 was closed carefully and slowly taking more than 5 minutes at the fixed speed (**B**). The staple dissection provides a secure staple line without any tissue or capsule tears (**C**).

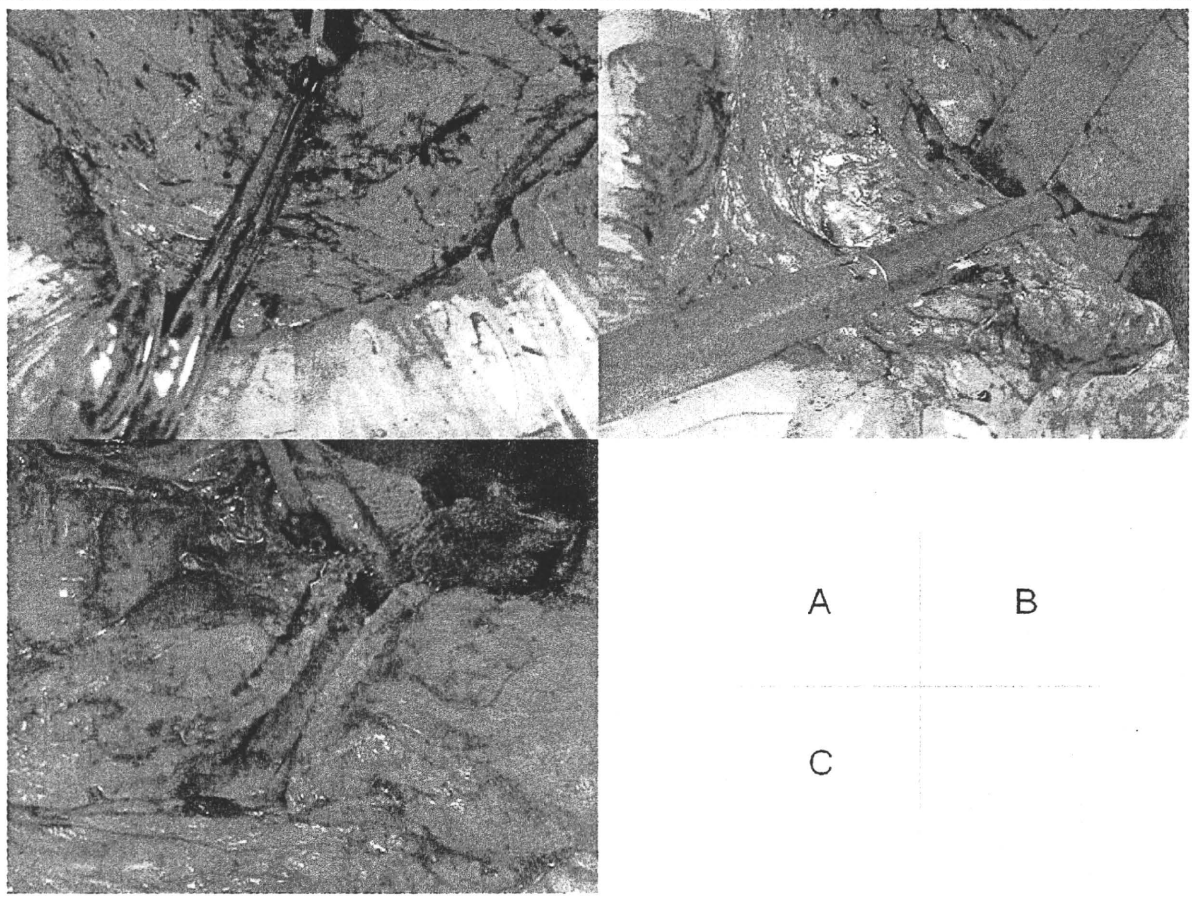

FIGURE 2
The pancreas was transected with slow flattening technique at proximal cutting line above the portal vein. Prior to the mobilization of distal pancreas, the pancreas head was gently dissected from portal vein at the transection line (tunnelling). The pancreas was gently compressed with an atraumatic intestinal clamp at the transection line for a few minutes (**A**). The closure jaw of the Echelon 60 was closed carefully and slowly taking more than 5 minutes at the fixed speed (**B**). The staple dissection provides a secure staple line without any tissue or capsule tears as well as distal dissection (**C**).

with the Echelon 60 stapler because the pressure is even throughout the entire length of the closure jaw; the pressure on the tissue is more uniform than with other devices. The closure jaw of the Echelon 60 was closed carefully and slowly taking more than 5 minutes at the fixed speed (**Figure 1B**; a case for distal transection line, **2B**; a case for proximal transection line). To ensure hemostasis of the pancreatic stump, the stapler was not released immediately after firing and the jaws of the stapler were held shut for about 2 minutes. Ligation of the main pancreatic duct was not necessary and minor bleeding from the stump could be easily controlled by compression or coagulation by electrocautery. This staple procedure with several inventions provides a secure staple line (**Figure 1C, 2C**). The histological findings of the pancreas treated by the SFT revealed that confident pancreas stump "sealed" or "packed" by a fibrous capsule without any tissue injury (**Figure 3**).

A 10-mm soft silicon drain was placed near the stump of the remnant pancreas. Amylase levels in the serum and drainage fluid were measured on postoperative day 1 and 3. The drain was removed on postoperative day 4 when the symptomatic pancreatic fistula (ISGPF classification grade B+C) and bacterial contamination were absent.

RESULTS

From February 2006 to May 2010, 22 consecutive patients with a soft friable pancreas underwent a distal pancreatectomy using the SFT with the Echelon 60 and an atraumatic intestinal clamp. Slow flattening of pancreatic parenchyma was performed using the Echelon 60 with gold cartridge (closed height 1.8mm) taking more than 5 minutes before transection. The International Study Group classification for pancreatic fistula (ISGPF) was utilized (15). Intraoperative and postoperative variables with the SFT are summarized in **Table 1.** Only one of the 22 patients developed a symptomatic pancreatic fistula (ISGPF grade B). Although 8 of 22 patients (36%) developed an asymptomatic pancreatic fistula (ISGPF grade A), there were no mortalities or severe pancreatic fistula (ISGPF grade C) in this series.

DISCUSSIONS

The appropriate closure of the pancreatic remnant after a distal pancreatectomy is still debated. A systematic review appraised all available surgical alternatives for handling the pancreatic remnant after a distal pancreatectomy (16). These different techniques, such as duct ligation, ultrasonic dissection, pancreatico-enteric anastomosis, hand-sewn and stapler closure, reflect the clinical difficulty in this field. The most commonly used techniques for pancreatic remnant management are stapler and suture closure. However, neither suture closure nor stapler closure could be shown to be a significantly influencing factor with respect to pancreatic fistula formation, although there was a trend towards pancreatic leaks occurring more often after hand

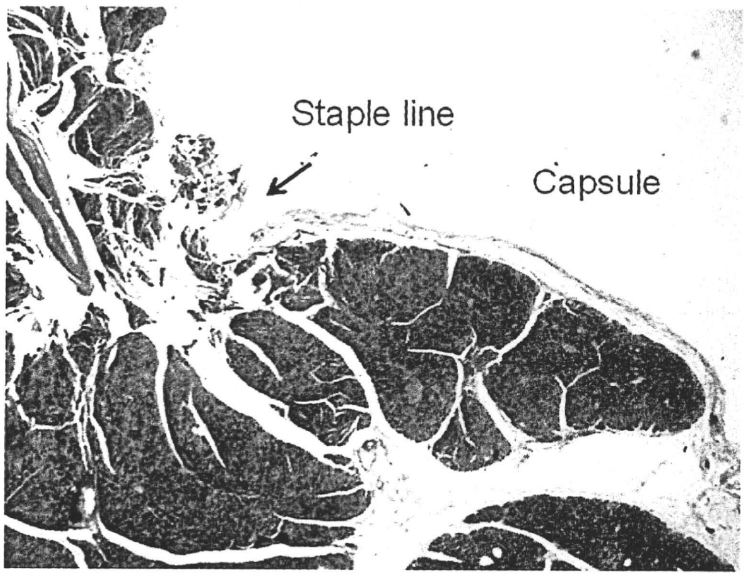

FIGURE 3 The histological findings (H & E staining) of the pancreas treated by slow flattering technique revealed that pancreas stump is "packed" and "sealed" by a fibrous capsule without any tissue tears.

TABLE 1 Patient Characteristics, Indications And Outcomes

Age (range; years)	63 (23-80)
Gender (male: female)	14:8
Indication	
Pancreatic tumor	19
Ductal adenocarcinoma	9
Lymphepitherial cyst	2
Neuroendocrine tumor	2
Epidermoid cyst	2
IPMN	1
Metastasis	1
Aberrant pancreas	1
Other tumor	4
Operative time (min)	
Distal pancreatectomy (DP)	228 (158-350)
Spleen preserving DP (n=3)	270 (210-380)
Blood loss (ml)	350 (71-1846)
Blood transfusion (pts)	0
Pancreatic fistula	
Asymptomatic	
Grade A	8 (36.0%)
Grade B	1 (4.5%)
Grade C	0
Other morbidity	2 (9.0%)
Bleeding	0
Wound infection	0
Abscess	1 (4.5%)
Delayed gastric emptying	1 (4.5%)
Re-laparotomy	0
Mortality	0
Hospital stay (days)	18 (10-40)
Drain amylase level (U/l)	
POD 1	6481 (165-21688)
POD 3	871 (22-3408)

suturing. The study by Bassi *et al.* is the only randomized controlled trial that compared the two techniques (17). They observed that using the stapler technique had better results in comparison to the suture closure (stapler 14% vs. hand suture 33%). Conversely, a recently published large consecutive series of distal pancreatectomies indicated that stapler closure is associated with a significantly higher fistula rate (14). There was a difference in the pancreas fistula rate between the three different methods, with 15.9% in stapler group, 9.3% in the suture group and 8.3% in the seromuscular patch group. In the series, the pancreas was transected using an ETS flex 45cutter with a white vascular cartridge. This device might cause pancreatic capsular and parenchymal injury and contribute to the higher incidence of pancreatic fistula. The incidence of pancreas fistula might reflect torn out or tissue tears of the pancreatic parenchyma during transection.

Stapler transection of the pancreas has been found to be a simple and quick method of closure of the proximal pancreas. However, the incidence of pancreatic fistulas after a distal pancreatectomy using a stapler device is reported to range from 0 to 16% (4, 9, 13, 14, 17-21). This variation might reflect the difference of the technical management for stapling or stapler device. The most important and technically difficult step of stapler dissection is to prevent a pancreatic tissue tear during compression. The importance of the compression speed of the closure jaw during pancreas transection using the stapler has not yet been previously described. In the method described in this study, the pancreas was gently and slowly compressed with an Echelon 60, which provides precise and uniform wide compression throughout the entire length of the closure jaw and provide 6-row capability, for 5 minutes to prevent pancreatic tissue tearing during compression.

Appropriate cartridge selection might be another important factor to reduce the damage to the pancreatic parenchyma. The Gold or Blue cartridge (1.8 or 1.5mm compressible thickness) is thought to be appropriate for the pancreas with soft friable texture. Single stapling with 60mm length cartridge is recommended for a distal pancreatectomy, since a staple on the staple line is thought to be a risk factor for leakage in the gastrointestinal anastomosis (22). An inappropriate cartridge is thought to induce tissue tears of the pancreatic parenchyma during transaction especially in fibrotic hard pancreatic tissue. The larger staples (Green; 2.0mm compressible thickness) are particularly reliable for a hard pancreas affected by chronic pancreatitis. In addition, the surgeons must pay attention to avoid the distortion of the pancreas and staple line during compression and transection.

The clinical results suggested the advantage of the SFT with a stapler and an intestinal clamp in a distal pancreatectomy. It provides a simple and safe alternative to the standard closure technique with a staple device. A prospective randomized control trial must also be conducted to substantiate the results of this study. This should verify whether a SFT of the pancreatic transection is truly superior to the conventional technique.

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BRIEF ARTICLE

^{18}F-fluorodeoxyglucose positron emission tomography in the diagnosis of small pancreatic cancer

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Abstract

AIM: To investigate the role of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in the diagnosis of small pancreatic cancer.

METHODS: This study involved 31 patients with proven invasive ductal cancer of the pancreas. The patients were divided into 3 groups according to the maximum diameter of the tumor: TS1 (maximum tumor size ≤ 2.0 cm), TS2 (> 2.0 cm and ≤ 4.0 cm) or TS3-4 (> 4.0 cm). The relationships between the TS and various diagnostic tools, including FDG-PET with dual time point evaluation, were analyzed.

RESULTS: The tumors ranged from 1.3 to 11.0 cm in diameter. Thirty of the 31 patients (97%) had a positive FDG-PET study. There were 5 patients classified as TS1, 15 as TS2 and 11 as TS3-4. The sensitivity of FDG-PET, computed tomography (CT) and magnetic resonance imaging (MRI) were 100%, 40%, 0% in TS1, 93%, 93%, 89% in TS2 and 100%, 100%, 100% in TS3-4. The sensitivity of FDG-PET was significantly higher in comparison to CT and MRI in patients with TS1 ($P < 0.032$). The mean standardized uptake values (SUVs) did not show a significant difference in relation to the TS (TS1: 5.8 ± 4.5, TS2: 5.7 ± 2.2, TS3-4: 8.2 ± 3.9), respectively. All the TS1 tumors (from 13 to 20 mm) showed higher SUVs in FDG-PET with dual time point evaluation in the delayed phase compared with the early phase, which suggested the lesions were malignant.

CONCLUSION: These results indicate that FDG-PET with dual time point evaluation is a useful modality for the detection of small pancreatic cancers with a diameter of less than 20 mm.

Key words: Ductal carcinoma; Pancreas; ^{18}F-fluorodeoxyglucose; Positron emission tomography; Pancreatic cancer; Dual time point evaluation

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INTRODUCTION

Pancreatic cancer is the 5th leading cause of cancer-related mortality in Japan, with an estimated 20 000 deaths attributable to the disease[1,2]. The annual mortality rate closely

approximates the annual incidence, thereby reflecting a generally short survival time associated with pancreatic cancer, which is generally less than 1 year. Cancer of the pancreas has the shortest median survival time out of all cancer types in a stage for stage basis. Early diagnosis is the most important factor for improving the overall survival and quality of life in patients with pancreatic cancer.

Recently, positron emission tomography (PET) has demonstrated superiority to computed tomography (CT), ultrasonography (US), and endoscopic US (EUS) in its sensitivity and specificity in diagnosing pancreatic cancer[3-6]. Furthermore, the metabolic activity of the tumor may be of prognostic significance. We have been reported the efficacy of delayed additional ^{18}F-fluorodeoxyglucose PET (FDG-PET) imaging in the differential diagnosis of malignant from benign lesions in patients who are suspected of having pancreatic cancer[7]. Furthermore, the detection rate of liver metastases smaller than 1 cm in diameter from pancreatic cancer was only 33% on early image and 58% on delayed image[7]. However, the role of dual time point FDG-PET in the diagnosis of small pancreatic cancers has yet to be established.

Therefore, the present study investigated whether small cancers of the pancreas could be accurately diagnosed by FDG-PET with dual time point evaluation.

MATERIALS AND METHODS

Patients

Thirty-one patients with pancreatic carcinoma suspected on the basis of conventional radiological studies (22 males and 9 females; mean age, 65 years; age range, 44-82 years) and who underwent FDG-PET between 2003 and 2007 were retrospectively selected. Patients were excluded from this study if they had poorly controlled diabetes mellitus (presenting with blood glucose level > 200 mg/dL prior to PET imaging). Conventional radiological staging was performed by means of CT or magnetic resonance imaging (MRI). The location of the cancer was in the head of the pancreas in 17 patients and in the body and tail in 14 patients. Twelve of the 31 cancers were diagnosed to be unresectable, and 19 patients eventually underwent surgery with a curative intention, although the cancer turned out to be unresectable in 7 because of intraoperative findings.

Methods

The patients were divided into 3 groups according to the maximum diameter of the tumor: TS1 (maximum size ≤ 2.0 cm), TS2 (> 2.0 cm and ≤ 4.0 cm) or TS3-4 (> 4.0 cm) as indicated by the classification system of the Japan Pancreas Society. FDG-PET was analyzed semi-quantitatively using the standardized uptake values (SUVs). The sensitivity of diagnosing pancreatic cancer was examined for FDG-PET, CT, MRI and the serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) with regard to the size of the tumor. The details of SUVs, the histological findings and correlation of CT findings were evaluated in patients with TS1 pancreatic cancer. This study was performed retrospectively by collecting and analyzing data from the patient records.

FDG-PET

The FDG-PET images were acquired with a PET machine (Siemens EXACT HR+, CTI, Knoxville, TN, USA). The patients were required to fast for at least 4 h before PET imaging. The emission images were acquired (early image) 1 h after the intravenous administration of 5 mCi of FDG. Delayed PET emission images of the upper abdomen were acquired at 2 h after administration of ^{18}F-FDG, using 2 or 3 bed positions with a 3-min acquisition at each[7]. This acquisition was immediately followed by a transmission scan of the same transverse planes, using a 2-min acquisition at each bed position. The early and delayed PET images were reviewed independently and consecutively by 2 radiologists with extensive experience in FDG-PET imaging. PET images were compared with the corresponding CT and/or MRI images for accurate anatomical identification of the tumor. The findings were considered to be positive when both radiologists strongly suspected malignant disease. In addition, the images were analyzed semi-quantitatively using the SUV, as reported elsewhere. Briefly, for semi-quantitative analysis, a region of interest was placed over the entire FDG-avid lesion including the largest amount of radioactivity using the transverse PET image. The SUV was calculated as: SUV = (activity in region of interest in mCi)/(injected dose in mCi/weight in kg).

CT

CT studies were performed with a multidetector row CT scanner (Aquilion, Toshiba, Tokyo, Japan). Helical images of the abdomen were routinely obtained and reconstructed with 5 mm thickness. After pre-contrast CT scans, arterial dominant phase images of dynamic CT were obtained starting 40 s after the beginning of the intravenous bolus injection (3 mL/s) of 100 mL of iodized contrast medium at 350 mg/mL. The pancreatic phase and the late phase (near equilibrium phase) were also obtained, starting at 60 and 180 s after injection, respectively. The CT images were interpreted independently and consecutively by 2 radiologists with extensive experience of more than 10 years in CT scanning. The findings of the CT scans were considered positive when both radiologists strongly suspected malignant disease due to a discrete low-attenuation mass within the pancreas.

MRI

Two 1.5 T superconducting units, Signa Advantage (General Electric, Milwaukee, WI, USA, USA) and Visart (Toshiba, Tokyo, Japan), were used for MRI. T1-weighted gradient-echo imaging; FS-T2-weighted turbo SE imaging and heavily T2-weighted turbo SE images were acquired in the order of scan after initial T1-weighted localizing images were obtained in the coronal and trans-axial directions.

Statistical analysis

The χ^2 test was employed for a statistical comparison of