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

A Randomized Controlled Trial

John P. Neoptolemos, MD
Deborah D. Stocken, PhD
Claudio Bassi, MD
Paula Ghaneh, MD
David Cunningham, MD
David Goldstein, MD
Robert Padbury, MD
Malcolm J. Moore, MD
Steven Gallinger, MD
Christophe Mariette, MD
Moritz N. Wente, MD
Jakob R. Izbicki, MD
Helmut Friess, MD
Markus M. Lerch, MD
Christos Dervenis, MD
Attila Oláh, MD
Giovanni Butturini, MD
Ryuichiro Doi, MD
Pehr A. Lind, MD
David Smith, MD
Juan W. Valle, MD
Daniel H. Palmer, MD
John A. Buckels, MD
Joyce Thompson, MD
Colin J. McKay, MD
Charlotte L. Rawcliffe, MSc
Markus W. Büchler, MD
for the European Study Group for Pancreatic Cancer

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.

Author Affiliations are listed at the end of this article.
Corresponding Author: John P. Neoptolemos, MD, Liverpool Cancer Research UK Cancer Trials Unit, Cancer Research UK Centre, University of Liverpool, Fifth Floor, UCD Bldg, Daulby Street, Liverpool, L69 3GA, United Kingdom (j.p.neoptolemos@liverpool.ac.uk).

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

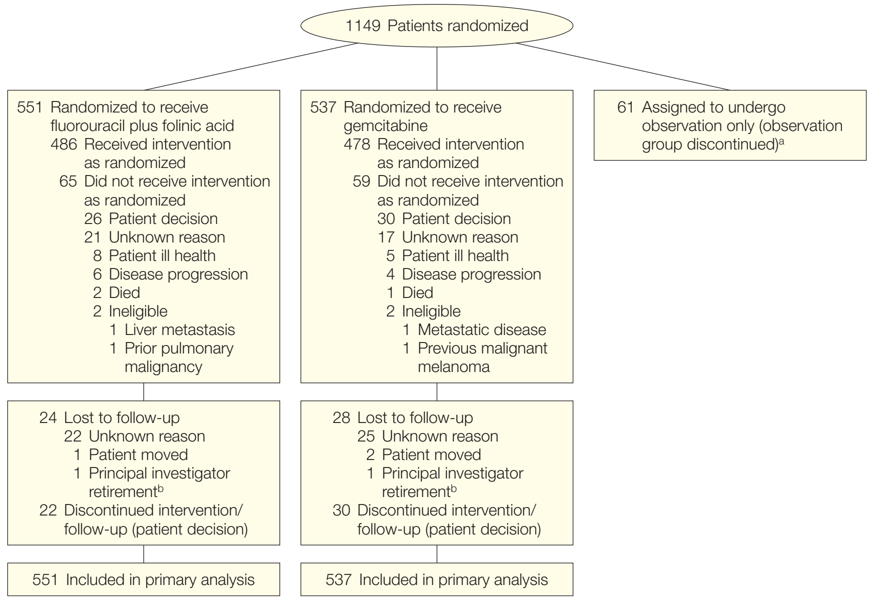
The trial was designed to test the primary hypothesis, ie, that overall length of survival does not differ between that achieved with adjuvant fluorouracil plus folinic acid and that achieved with gemcitabine. Secondary end points were progression-free survival, toxicity, and quality of life. Power calculations 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.

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.

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.

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).

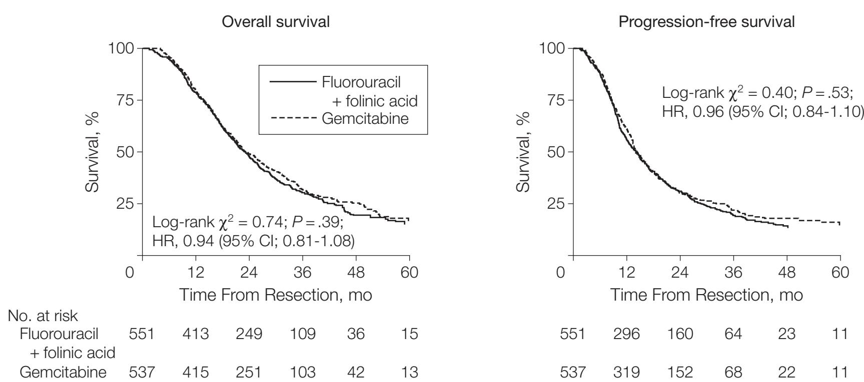
Survival estimates at 12 and 24 months were 78.5% (95% CI, 75.0%-82.0%) and 48.1% (95% CI, 43.8%-52.4%), respectively, for the fluorouracil plus folinic acid group and 80.1% (95% CI, 76.7%-83.6%) and 49.1% (95% CI, 44.8%-53.4%) for the gemcitabine group. Log-rank analysis revealed no statistically significant difference in survival estimates between the treatment groups (χ^2_1=0.7; *P*=.39; HR, 0.94 [95% CI, 0.81-1.08]).

Table 1. Patient Characteristics at Randomization (continued)

Characteristic	Fluorouracil + Folinic Acid (n = 551), No. (%)	Gemcitabine (n = 537), No. (%)	Total (N = 1088), No. (%)
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.

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).

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)		*P* Value[b]
	Grade 1/2, No.	Grade 3/4, No. (%)	Grade 1/2, No.	Grade 3/4, No. (%)	
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. Patients	No. Deaths	Survival Rate, % 12 mo	Survival Rate, % 24 mo	Survival, Median (95% CI), mo	HR (95% CI)	Log-Rank χ^2	*P* Value
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 χ^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 χ^2_3=25.2, $P<.001$), nodal status (Wald χ^2_1=41.7, $P<.001$), performance status (Wald χ^2_2=10.9, $P=.004$), tumor size (Wald χ^2_1=8.9, $P=.003$), and smoking status (Wald χ^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: CA199^(−0.5) + log(CA199).
[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.

Author Affiliations: Liverpool Cancer Research UK Cancer Trials Unit, Liverpool Cancer Research UK Centre, University of Liverpool, Liverpool, United Kingdom (Drs Neoptolemos and Ghaneh and Ms Rawcliffe); Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, United Kingdom (Dr Stocken); Department of Surgery, University of Verona, Verona, Italy (Drs Bassi and Butturini); the Royal Marsden National Health Service Foundation Trust, London and Surrey, United Kingdom (Dr Cunningham); Australasian Gastro-Intestinal Trials Group, Camperdown, New South Wales, Australia (Drs Goldstein and Padbury); Princess Margaret Hospital, Toronto, Ontario, Canada (Dr Moore); Department of Surgery, Faculty of Medicine, University of Toronto, University Health Network, Toronto (Dr Gallinger); Department of Digestive and Oncological Surgery, University Hospital Claude Huriez, Lille, France, and the French Federation of Surgical Research (Dr Mariette); Department of Surgery, University of Heidelberg, Heidelberg, Germany (Drs Wente and Büchler); Department of General, Visceral and Thoracic Surgery, University of Hamburg, Hamburg, Germany (Dr Izbicki); Department of Surgery, Technische Universität Munchen, Munich, Germany (Dr Friess); Department of Medicine A, Ernst-Moritz-Arndt-Universität Greifswald, Greifswald, Germany (Dr Lerch); Agia Olga Hospital, Athens, Greece (Dr Dervenis); Petz Aladar Hospital, Gyor, Hungary (Dr Oláh); Department of Surgery, Kyoto University, Sakyo, Kyoto, Japan (Dr Doi); Department of Oncology, Karolinska-Stockholm Söder Hospital, Stockholm, Sweden (Dr Lind); Medical Oncology, Clatterbridge Centre for Oncology, Clatterbridge Road, Bebington, Merseyside, United Kingdom (Dr Smith); Christie National Health Service Foundation Trust, Manchester, United Kingdom (Dr Valle); Queen Elizabeth Hospital, University Hospital Birmingham National Health Service Foundation Trust, Birmingham, United Kingdom (Drs Palmer and Buckels); Birmingham Heartlands Hospital, Birmingham (Dr Thompson); and Lister Department of Surgery, Glasgow Royal Infirmary, Glasgow, Scotland, United Kingdom (Dr McKay).

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.
Study concept and design: Neoptolemos, Stocken, Bassi, Ghaneh, Cunningham, Moore, Friess, Dervenis, Büchler.
Acquisition of data: Neoptolemos, Bassi, Cunningham, Goldstein, Padbury, Gallinger, Mariette, Wente, Izbicki, Lerch, Dervenis, Oláh, Butturini, Doi, Lind, Smith, Palmer, Buckels, Thompson, McKay, Rawcliffe, Büchler.
Analysis and interpretation of data: Neoptolemos, Stocken, Bassi, Ghaneh, Goldstein, Moore, Izbicki, Dervenis, Doi, Lind, Valle, Büchler.
Drafting of the manuscript: Neoptolemos, Stocken, Ghaneh, Goldstein, Wente, Dervenis, Oláh, Buckels, Rawcliffe, Büchler.
Critical revision of the manuscript for important intellectual content: Neoptolemos, Stocken, Bassi, Cunningham, Goldstein, Padbury, Moore, Gallinger, Mariette, Wente, Izbicki, Friess, Lerch, Dervenis, Butturini, Doi, Lind, Smith, Valle, Palmer, Thompson, McKay, Büchler.
Statistical analysis: Stocken, Cunningham.
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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.
Independent Data and Safety Monitoring Committee: R. P. Ahern, MSc (Institute for Cancer Research, London, United Kingdom), R. C. G. Russell, MD (Middlesex Hospital, London, United Kingdom), P. Clarke, MD (Clatterbridge Centre for Clinical Oncology, Wirral, United Kingdom).
Online-Only Material: eTables 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)