Effect of Adjuvant Chemotherapy With Fluorouracil Plus Folinic Acid or Gemcitabine vs Observation on Survival in Patients With Resected Periampullary Adenocarcinoma

The ESPAC-3 Periampullary Cancer Randomized Trial

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Context Patients with periampullary adenocarcinomas undergo the same resectional surgery as that of patients with pancreatic ductal adenocarcinoma. Although adjuvant chemotherapy has been shown to have a survival benefit for pancreatic cancer, there have been no randomized trials for periampullary adenocarcinomas.

Objective To determine whether adjuvant chemotherapy (fluorouracil or gemcitabine) provides improved overall survival following resection.

Design, Setting, and Patients The European Study Group for Pancreatic Cancer (ESPAC)-3 periampullary trial, an open-label, phase 3, randomized controlled trial (July 2000-May 2008) in 100 centers in Europe, Australia, Japan, and Canada. Of the 428 patients included in the primary analysis, 297 had ampullary, 96 had bile duct, and 35 had other cancers.

Interventions One hundred forty-four patients were assigned to the observation group, 143 patients to receive 20 mg/m^2 of folinic acid via intravenous bolus injection followed by 425 mg/m^2 of fluorouracil via intravenous bolus injection administered 1 to 5 days every 28 days, and 141 patients to receive 1000 mg/m^2 of intravenous infusion of gemcitabine once a week for 3 of every 4 weeks for 6 months.

Main Outcome Measures The primary outcome measure was overall survival with chemotherapy vs no chemotherapy; secondary measures were chemotherapy type, toxic effects, progression-free survival, and quality of life.

Results Eighty-eight patients (61%) in the observation group, 83 (58%) in the fluorouracil plus folinic acid group, and 73 (52%) in the gemcitabine group died. In the observation group, the median survival was 35.2 months (95% % CI, 27.2-43.0 months) and was 43.1 (95%, CI, 34.0-56.0) in the 2 chemotherapy groups (hazard ratio, 0.86; (95% CI, 0.66-1.11; χ^2=1.33; P=.25). After adjusting for independent prognostic variables of age, bile duct cancer, poor tumor differentiation, and positive lymph nodes and after conducting multiple regression analysis, the hazard ratio for chemotherapy compared with observation was 0.75 (95% CI, 0.57-0.98; Wald χ^2=4.53, P=.03).

Conclusions Among patients with resected periampullary adenocarcinoma, adjuvant chemotherapy, compared with observation, was not associated with a significant survival benefit in the primary analysis; however, multivariable analysis adjusting for prognostic variables demonstrated a statistically significant survival benefit associated with adjuvant chemotherapy

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PERIAMPULLARY CARCINOMAS arise from the head of the pancreas in the region of the ampulla of Vater and apart from pancreatic ductal adenocarcinoma comprise carcinomas of the bile duct, the ampulla itself, and the periampullary duodenum.[1,2] The incidence rates per 10^5 are 11.7 for pancreatic, 0.88 for bile duct, 0.49 for ampullary, and 0.01 for

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duodenal carcinomas.[3,4] The clinical presentation is similar to that of pancreatic ductal adenocarcinoma,[5,6] and together they represent a major cause of death.[1-4] Around 80% of periampullary adenocarcinomas are resectable and thus comprise around 30% to 40% of all resections for cancers in the head of the pancreas.[2]

Reported 5-year survival rates after resection are 37% to 51% for ampullary, 23% to 30% for bile duct, and 25% to 59% for duodenal cancers.[2,7-9] Unlike pancreatic cancer,[10] there are no controlled trials investigating adjuvant systemic therapy for periampullary tumors. The European Study Group for Pancreatic Cancer (ESPAC)-3 trial was designed to compare the survival benefit of adjuvant chemotherapy with observation following resection for patients with periampullary carcinoma and to compare fluorouracil plus folinic acid chemotherapy with that of gemcitabine. Separately the ESPAC-3 version 2 trial also compared these 2 chemotherapy regimens among 1088 patients with pancreatic ductal adenocarcinoma.[11]

METHODS

Patients and Trial Design

The ESPAC-3 trial was a 3 group randomized, international, open-label, phase 3 study designed to test the primary hypothesis that the median overall survival time for patients with periampullary cancer is longer for patients receiving adjuvant chemotherapy than those who do not. Secondary end points were the effect of the type of chemotherapy, toxicity, disease-free survival, and quality of life. The trial was approved by ethics committees at national and local levels according to the requirements of each of the participating countries. All patients entered into the study gave written informed consent following a full explanation of the study and after reading the patient information sheet. There were 100 hospital-based centers in 18 countries that were coordinated centrally by the Cancer Research United Kingdom Liverpool Cancer Trials Unit. The first patient entered the study on July 20, 2000.

Surgery, Eligibility, and Pathology

Patients were eligible if they had undergone complete macroscopic (R0 or R1) resection for nonpancreatic ductal periampullary adenocarcinoma of the head of the pancreas (ampullary, intrapancreatic bile duct, nondescript, or other including periampullary duodenal cancer) with histological confirmation and with no evidence of malignant ascites, peritoneal metastasis, or spread to the liver or other distant abdominal or extraabdominal organs. The type and extent of resection were determined using an international classification.[12] Patients had to have a World Health Organization performance score 2 or less (range, 0-4, with 0 being normal and increasing with decreasing performance) and a life-expectancy of more than 3 months. Patients with previous use of neoadjuvant chemotherapy or other concomitant chemotherapy; with pancreatic lymphoma, macroscopically remaining tumor (R2 resection), or TNM (International Union Against Cancer, 1997)[13]; or with stage IVb disease were excluded. The pathology reports were reviewed by 2 pancreas pathologists (C.S.V. and F.C.) to subtype the ampullary tumors.

Randomization

Patients were randomly assigned to each treatment group on a 1:1:1 basis according to a computer-generated variable-size blocked randomization method by the Liverpool Cancer Trials Unit. Patients were stratified at randomization by country and resection margin status (R0 vs R1). The stratified randomization lists with preallocated groups were held in a locked cabinet within the Cancer Research United Kingdom Liverpool Cancer Trials Unit and were strictly controlled. The lists were accessible to designated ESPAC trial unit staff when required for randomization. Staff at participating sites faxed the details of each patient to the ESPAC trial coordinating and management team at the Liverpool Cancer Trials Unit. The eligibility criteria were checked for each patient and only then was the correct list in the randomization folder identified and faxed back to the referring center.

Chemotherapy

For 5 consecutive days every 28 days for 6 cycles, patients received 20 mg/m^2 of d,l folinic acid as an intravenous bolus followed by 425 mg/m^2 of fluorouracil as an intravenous bolus (24 weeks). Those in the gemcitabine (lyophilized powder diluted in normal saline) group received a 1000-mg/m^2 intravenous infusion over 30 minutes, which was administered once a week for 3 weeks out of every 4 weeks for 6 cycles (24 weeks). Adverse toxic effects were 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

Quality of life (QOL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) version 3 at baseline, at 3 and 6 months, and yearly until 5 years.[14] The questionnaire includes 5 functional scales, 3 symptom scales, 6 single items, and a global health status QOL scale. All are reported on a range 0-100; for the functional scales and the QOL scale, a high score represents a high level of functioning and QOL, but a high score for the symptom scales and items represents a high level of symptomatology. Mean score changes indicate the level of clinical significance: 5 to 10, little change for better or worse; 10 to 20, moderate change; and more than 20, a large change.[14]

Statistical Analysis

Accurate survival data and potential survival benefit for adjuvant chemo-

therapy were lacking at the time of study design, but it was estimated that adjuvant chemotherapy would result in a 10% to 15% absolute improvement in survival.[15] A 12% absolute improvement in 5-year survival would produce a hazard ratio (HR) of 0.68; an α of .05 and power of 80% would require 243 deaths and an estimate of 430 patients recruited. Patients were followed up until this number of events was attained.

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 without progression were censored at the date last seen alive. Survival estimates were calculated using the Kaplan-Meier method[16] and compared using the log-rank test.[17] Median (95% confidence intervals) 24-month and 60-month survival estimates are presented.

In secondary analyses the treatment effect was adjusted by stratification factors at randomization and other identified prognostic factors (prestated) in the multivariate setting using regression modeling.[18] Factors with a log-rank significance of $P<.25$ were considered for inclusion in Cox proportional hazards frailty modeling: sex, smoking status, diabetes, performance status, grade of disease, lymph node status, stage, and local invasion. Tumor size and age were included as continuous covariates. The stratification factors country (random effect), and resection margin status as well as treatment groups were included in all models. A stepwise regression approach was used. Postoperative carbohydrate antigen 19-9 levels were investigated within models, but since there were many missing values, this covariate was not selected in the final analyses. A model based on 415 patients with complete data (236 deaths) identified age, tumor type, tumor grade (poorly differentiated), lymph node involvement, and treatment (chemotherapy vs observation) as independent survival factors.

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 or 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 Fisher exact test. Quality of life was analyzed as previously described.[14]

All statistical analyses were carried out using SAS version 9.2 (SAS Institute Inc) and Stata version 12.0 (StataCorp) 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 434 patients recruited was randomized on the July 5, 2008. Data sets were collected from hospital departments, inpatient units, and clinics. The database was locked on September 9, 2011, following acquisition of predetermined events and database clean-up.

Patient Characteristics

One hundred forty-three patients were randomized to fluorouracil plus folinic acid, 146 to gemcitabine, and 145 to observation. FIGURE 1 shows the study flow chart. The clinical characteristics of patients and surgical and pathological details are shown in TABLE 1. Eighty ampullary tumors were classified as intestinal, 46 as pancreatobiliary, 9 as mixed, and 162 as indeterminate.

Treatment

Fluorouracil Plus Folinic Acid. The total protocol fluorouracil dose was 2125 mg/m^2 per cycle, providing an overall dose of 12 750 mg/m^2. Twenty-eight patients (20%) did not start their allocated treatment and 70 (49%) received the full 6 cycles. The median total fluorouracil dose administered was 9960 mg/m^2 (range, 2125-12 750 mg/m^2) and the median percentage of the protocol dose was 78% (range, 17%-100%).

Gemcitabine. The total protocol dose was 3000 mg/m^2 of gemcitabine per cycle providing an overall dose of 18 000 mg/m^2. Sixteen of 141 patients (11%) did not start their allocated treatment and 70 (50%) received the full 6 cycles. The median total dose administered was 15 750 mg/m^2 (range, 2,000-18,543 mg/m^2) and the median percentage of the protocol dose was 88% (range, 11%-103%).

Median time from randomization to the start of chemotherapy was 10 days (interquartile [IQR], 5-17 days) for the fluorouracil plus folinic acid group and 8 days (IQR, 6-14 days) days for the gemcitabine group. The median time taking chemotherapy was 4.8 months (IQR, 4.1-5.0 months) for the fluorouracil plus folinic acid group and 5.1 months (IQR, 4.4-5.3 months) for the gemcitabine groups.

Overall Survival

Two hundred forty-four patients (57%) had died at the time of analysis, 88 (61%) in the observation group, 83 (58%) in the fluorouracil plus folinic acid group, and 73 (52%) in the gemcitabine group. The median length of follow-up for the 184 living patients was 58.2 months (IQR, 41.8-68.3 months); 55.9 months (IQR, 38.4-65.1 months) for the 60 patients in the fluorouracil plus folinic acid group; 59.9 months (IQR, 40.8-71.9 months) for the 68 patients in the gemcitabine group; and 58.3 months (IQR, 48.4-67.0 month) for the 56 patients in the observational group. Overall 168 alive patients (91%) had been followed up for more than 2 years. Bivariable analyses of survival factors by clinical, surgical and pathological variables are shown in TABLE 2.

Treatment Effect

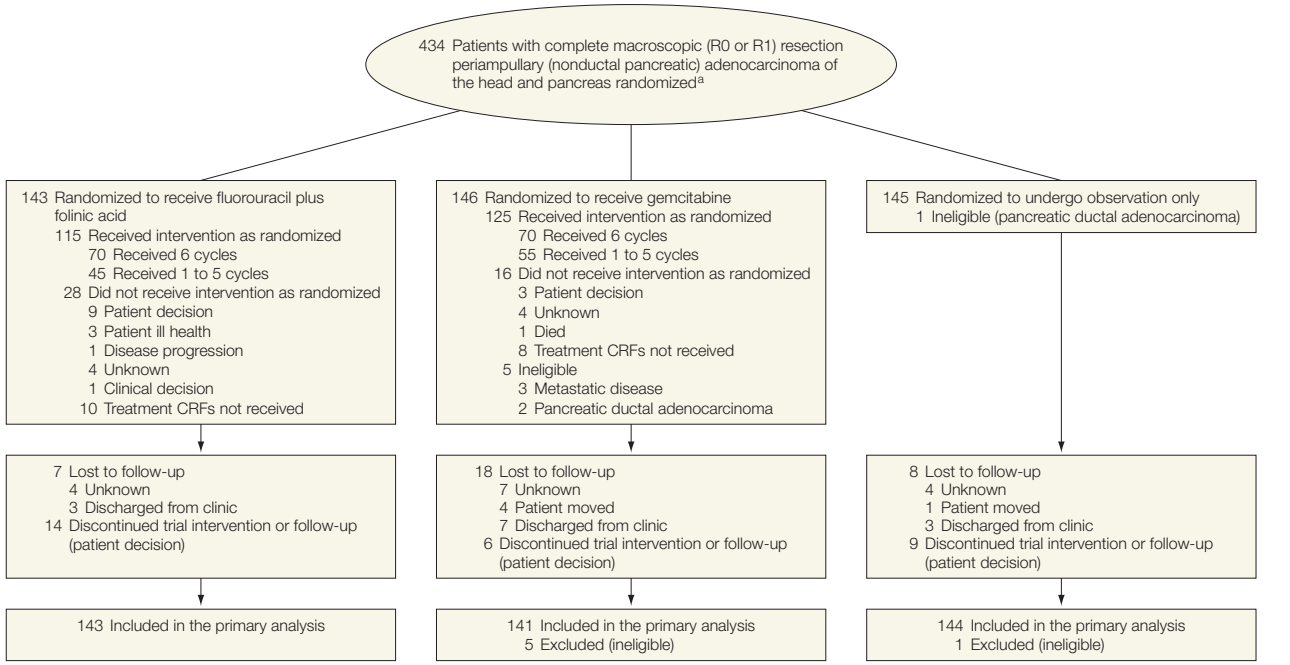
For the primary analysis, in the observation group, the median survival was 35.2 months (95% CI, 27.2-43.0 months) and in the chemotherapy group 43.1 months (95% CI, 34.0-56.0 months). This resulted in a HR of 0.86 (95% CI, 0.66-1.11; $P=.25$). There were 88 deaths (61%) in the observation group, 83 (58%) in the fluorouracil plus folinic acid group, and 73 (52%) in the gemcitabine group. Adjusting for independent prognostic variables (age, bile duct cancer, poor tumor differentiation, and positive lymph nodes) using multiple regression analysis; the HR for chemotherapy compared with observation was 0.75 (95% CI, 0.57-0.98; Wald $\chi^2=4.53$; $P=.03$).

Median survival was 53.1 months (95% CI, 42.3-72.5 months) for patients with ampullary cancer, 20.9 months (95% CI, 17.0-27.5 months) for patients with bile duct cancer, and 32.6 months (95% CI, 17.4-∞ months; the infinity symbol indicates that the upper CI value is inestimable) for patients with other cancers ($\chi^2_2=27.75$; $P<.001$; FIGURE 2A). Median survival for the ampullary pancreatobiliary group was 56.0 months (95% CI, 36.0-∞ months) and 43.1 months (95% CI, 25.5-58.4 months) for the ampullary intestinal group ($\chi^2_1=1.16$; $P=.28$).

Median survival for the observation group was 35.2 months (95% CI, 27.2-43.0 months); for patients treated with fluorouracil plus folinic acid, 38.9 months (95% CI, 24.6-56.0 months); and for patients treated with gemcitabine, 45.7 months (95% CI, 36.5-∞ months; Figure 2B). The HR for fluorouracil plus folinic acid vs observation was 0.95 (95% CI, 0.71-1.28; Wald $\chi^2=0.11$; $P=.74$) and for gemcitabine vs observation, 0.77 (95% CI, 0.57-1.05; Wald $\chi^2=2.69$; $P=.10$), not significant by log-rank analysis across the 3 groups ($\chi^2_2=2.96$; $P=.23$). In secondary analyses adjusting for prognostic variables using multiple regression analysis, the HR for chemotherapy compared with observation was 0.75 (95% CI, 0.57-0.98; Wald $\chi^2=4.53$; $P=.03$) and for gemcitabine, 0.70 (95% CI, 0.51-0.97; Wald $\chi^2=4.65$; $P=.03$; TABLE 3). Tests of heterogeneity within pathological or demographic subgroups did not reveal any significant findings.

The 105 patients with ampullary cancer in the observation group survived a median of 40.6 months (95% CI, 30.6-61.4 months; 59 deaths); 100 patients in the fluorouracil plus folinic acid group, 57.8 months (95% CI, 32.8-84.0 months; 50 deaths); and 92 patients in the gemcitabine group, 70.8 months (95% CI, 45.3-∞ months; 42 deaths). The 31 patients with bile duct cancer in the observation group survived a median of 27.2 months (95% CI, 15.4-31.9 months; 24 deaths); 31 in the fluorouracil plus folinic acid group, 18.3 months (95% CI, 12.9-28.7 months; 24 deaths); and 34 in the gemcitabine group, 19.5 months (95% CI, 16.2-36.1 months; 25 deaths). The 8 patients with other tumors in the observation group survived a median of 28.7 months (95% CI, 4.7-∞ months; 5 deaths); 12 in the fluorouracil plus folinic acid group, 22.4 months (95% CI, 9.6-54.6 months; 9 deaths); and 15 in gemcitabine group had high but not

Figure 1. Study Flow Diagram



[a] Screening data on the number excluded and reasons were not collected routinely as part of the trial.

Table 1. Patient Characteristics at Randomization

Characteristic	No. (%) of Patients			
	Chemotherapy			
	Fluorouracil + Folinic Acid (n = 143)	Gemcitabine (n = 141)	Observation (n = 144)	Total (N = 428)
Age, median (IQR), y	63 (56-70)	61 (54-68)	61 (55-68)	62 (55-69)
Sex				
Men	91 (64)	84 (60)	86 (60)	264 (61)
Women	52 (36)	57 (40)	58 (40)	167 (39)
Tumor type				
Ampullary	100 (70)	92 (65)	105 (73)	297 (69)
Bile duct	31 (22)	34 (24)	31 (22)	96 (22)
Other[a]	12 (8)	15 (11)	8 (6)	35 (8)
Baseline performance status				
0	40 (29)	53 (38)	52 (36)	145 (34)
1	81 (58)	75 (54)	75 (52)	231 (55)
2	19 (14)	12 (9)	16 (11)	47 (11)
Diabetic				
No	113 (84)	115 (86)	104 (79)	332 (83)
Noninsulin dependent	14 (10)	8 (6)	18 (14)	40 (10)
Insulin dependent	8 (6)	10 (8)	10 (8)	28 (7)
Smoking status				
Never	55 (43)	50 (40)	63 (50)	168 (44)
Past	59 (46)	56 (45)	44 (35)	159 (42)
Present	14 (11)	19 (15)	19 (15)	52 (14)
Surgery				
Whipples resection	83 (62)	79 (62)	81 (62)	243 (62)
Pylorus preserving	50 (37)	44 (34)	45 (35)	139 (35)
Total pancreatectomy	1 (1)	5 (4)	4 (3)	10 (3)
Extent of resection				
Standard resection	102 (80)	96 (79)	95 (81)	293 (80)
Radical resection	22 (17)	21 (17)	18 (15)	61 (17)
Extended radical	4 (3)	5 (4)	4 (3)	13 (4)
Maximum tumor diameter, median (IQR), mm	23 (15-30)	20 (15-28)	20 (15-29)	20 (15-30)
Tumor grade differentiation				
Well	16 (12)	21 (15)	19 (14)	56 (13)
Moderately	76 (55)	87 (63)	93 (67)	256 (62)
Poorly	46 (33)	30 (22)	27 (19)	103 (25)
Lymph node involvement				
Negative	54 (38)	57 (40)	66 (46)	177 (41)
Positive	89 (62)	84 (60)	78 (54)	251 (59)
Resection margins				
Negative	123 (86)	120 (85)	117 (81)	360 (84)
Positive	20 (14)	21 (15)	27 (19)	68 (16)
Local invasion				
No	87 (66)	84 (65)	96 (73)	267 (68)
Yes	45 (34)	46 (35)	35 (27)	126 (32)
Tumor stage				
1	24 (18)	19 (14)	34 (24)	77 (19)
2	36 (26)	40 (30)	41 (29)	117 (28)
3	69 (51)	66 (49)	56 (39)	191 (46)
4a	7 (5)	10 (7)	11 (8)	28 (7)
Postoperative complications				
No	84 (67)	93 (72)	85 (65)	262 (68)
Yes	41 (33)	37 (28)	45 (35)	123 (32)
Hospital stay, No. of patients	130	127	122	379
Median (IQR), d	14 (11-20)	14 (11-19)	14 (10-20)	14 (11-20)
Postoperative CA 19-9 level, No. of patients	109	99	89	297
Median (IQR), KU/l	16 (7-36)	16 (8-35)	13 (6-29)	15 (7-34)
Surgery to randomization, median (IQR), d	50 (36-64)	50 (36-64)	51 (38-67)	50 (37-65)

Abbreviations: CA, carbohydrate antigen; IQR, interquartile range.
[a]Other includes 10 duodenal adenocarcinomas and 25 nondescript periampullary adenocarcinomas.

estimable survival with gemcitabine (6 deaths). Finally, there were no statistically significant differences in survival in response to treatment between the group of patients with pancreatobiliary subtype of ampullary tumors and the group of patients with the intestinal subtype of ampullary tumors.

Toxic Effects

One hundred thirteen patients (40%) reported 243 treatment-related serious adverse events, 160 attributable to in-patient hospitalization. Seventy patients (49%) receiving fluorouracil plus folinic acid reported 162 treatment-related serious adverse events (37 hospitalized) compared with 43 patients (30%) receiving gemcitabine who reported 81 events (22 hospitalized; $P = .002$). The numbers of patients who developed grade 3 or 4 toxicity in each group are shown in TABLE 4.

Disease-Free Survival

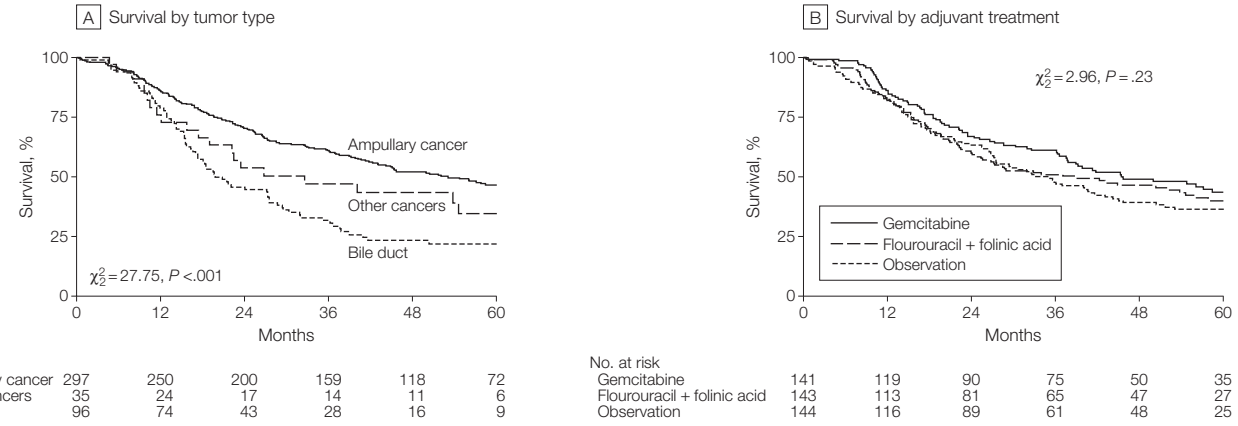
Two hundred sixty-seven patients (62%) developed local recurrence, me-

Table 2. Bivariable Analysis of Survival Factors

Factor	Bivariable Analysis (n = 428) No. of Patients	No. of Deaths	Survival Rates, mo 24	60	Survival, Median (95% CI), mo	HR (95% CI)	Log-Rank χ^2	*P* Value
Sex								
Men	261	144	62	42	45.1 (30.3-56.0)	1 [Reference]	0.61	.44
Women	167	100	65	37	36.2 (27.5-41.7)	1.11 (0.86-1.43)		
Tumor type								
Ampullary	297	151	70	47	53.1 (42.3-72.5)	1 [Reference]	27.75	<.001
Bile duct	96	73	46	22	20.9 (17.0-27.5)	2.13 (1.61-2.83)		
Other	35	20	54	35	32.6 (17.4- ∞)	1.39 (0.87-2.22)		
Smoking status								
Never	168	93	71	42	44.8 (36.1-58.4)	1 [Reference]	1.81	.41
Past	159	95	60	38	35.8 (25.5-45.4)	1.21 (0.91-1.61)		
Present	52	32	58	39	33.7 (21.6-01.8)	1.19 (0.79-1.77)		
Performance score								
0	145	75	67	42	50.3 (36.5-61.4)	1 [Reference]	2.98	.23
1	231	139	63	39	36.9 (27.6-43.1)	1.18 (0.89-1.56)		
2	47	28	51	33	25.3 (15.4-56.0)	1.44 (0.93-2.23)		
Resection margin status								
R0	360	191	66	44	45.6 (37.5-57.8)	1 [Reference]	19.97	<.001
R1	68	53	50	21	23.3 (15.0-32.6)	1.98 (1.46-2.70)		
Tumor grade								
Well	56	22	85	56		1 [Reference]	15.79	<.001
Moderate	256	142	64	41	39.8 (32.4-52.1)	1.69 (18-2.64)		
Poorly	103	72	49	31	23.4 (17.2-39.2)	2.46 (1.53-3.97)		
Lymph node involvement								
Negative	177	68	78	58	101.8 (58.4- ∞)	1 [Reference]	43.02	<.001
Positive	251	176	54	28	26.6 (22.2-32.6)	2.49 (1.88-3.30)		
Tumor stage								
1	77	29	80	60		1 [Reference]	35.53	<.001
2	117	54	71	51	61.4 (43.0- ∞)	1.33 (0.85-2.09)		
3	191	130	57	29	27.3 (23.5-36.1)	2.44 (1.63-3.66)		
4a	28	20	46	14	15.5 (10.7-40.2)	3.46 (1.95-6.14)		
Local invasion								
Yes	126	81	55	34	27.3 (22.0-41.6)	1.39 (16-1.82)	5.59	.02
No	267	147	68	42	44.1 (36.5-57.1)	1 [Reference]		
Postoperative CA 19-9 levels	297	173					1.71 (Wald)	.19
Chemotherapy								
No	144	88	63	36	35.2 (27.2-43.0)	1 [Reference]	1.33	.25
Yes	284	156	64	42	43.1 (34.0-56.0)	0.86 (0.66-1.11)		
Treatment group								
Observation	144	88	63	36	35.2 (27.2-43.0)	1 [Reference]	2.96	.23
Fluorouracil + folinic acid	143	83	60	40	38.9 (24.6-56.0)	0.95 (0.71-1.28)		
Gemcitabine	141	73	67	44	45.7 (36.5- ∞)	0.77 (0.57-1.05)		

Abbreviations: Blank cells, median survivals had not been reached because more than 50% of the patients were still alive at the lock down date; CA, carbohydrate antigen; HR, hazard ratio; The infinity symbol, the upper value of the confidence interval is inestimable.
[a]With treatment split as observation, fluorouracil plus folinic acid, gemcitabine there was only a small change in HRs for tumor type, tumor grade, and lymph node involvement.

Figure 2. Patient Survival by Treatment and Tumor Type



The median survival time for ampullary cancer was 53.1 months (95% CI, 42.3-72.5 months); for other cancers, 32.6 months (95% CI, 17.4-∞ months); and intrapancreatic bile duct carcinomas, 20.9 months (95% CI, 17.0-27.5 months; χ^2_2=28.93; P<.001. B, The median survival times for observation was 35.2 months (95% CI, 27.2-43.0 months); for fluorouracil plus folinic acid, 38.9 months (95% CI, 24.6-56.0 months); and for gemcitabine, 45.7 months (95% CI, 36.5-∞ months). The hazard ratio for fluorouracil plus folinic acid vs observation is 0.95 (95% CI, 0.70-1.28; Wald χ^2=0.11; P=.74) and for gemcitabine, 0.77 (95% CI, 0.57-1.05; Wald χ^2=2.69; P=.10); adjusted to fluorouracil plus folinic acid, 0.79 (95% CI, 0.58-1.08; Wald χ^2=2.26; P =.13); and for gemcitabine, 0.70 (95% CI, 0.51-0.97; Wald χ^2=4.65; P =.03).

tastases, or both, 244 of whom had died. One hundred sixty-one patients (38%) were alive and their disease had not progressed. The overall median disease-free survival was 24.0 months (95% CI, 19.5-30.0 months). Disease-free survival for patients with intestinal ampullary cancer was 45.7 months (95% CI, 25.3-∞ months) and 20.6 months (95% CI, 10.8-27.6 months) for patients with pancreatobiliary ampullary cancer (χ^2_1=6.26; P=.01).

The median disease-free survival was 19.5 months (95% CI, 14.2-30.3 months) in the observation group, 23.0 months (95% CI, 17.0-51.9 months) for patients treated with fluorouracil plus folinic acid, and 29.1 months (95% CI, 19.5-45.4 months) for patients treated with gemcitabine (χ^2_2=1.48, P=.48). Cox proportional hazards modeling gave similar results to those for overall survival and with the same regression variables. The HR for fluorouracil plus folinic acid vs observation was 0.69 (95% CI, 0.51-0.95; χ^2_1=5.24; P=.02); for gemcitabine, 0.68 (95% CI, 0.50-0.95; χ^2_1=5.30; P=.02).

Table 3. Multiple Regression Analysis of Survival Factors

Factor	Multiple Regression Analysis (n = 415) Hazard Ratio (95% CI)	Wald χ^2	*P* Value
Country (random factor)		0.98	.16
Age		5.18	.02
Resection margin			
Negative	1 [Reference]		
Positive	1.13 (0.79-1.60)	0.45	.50
Tumor type			
Ampullary	1 [Reference]		
Bile duct	2.05 (1.50-2.79)	20.38	<.001
Other	1.43 (0.87-2.34)	1.97	.16
Tumor grade			
Well	1 [Reference]		
Moderately	1.44 (0.91-2.27)	2.39	.12
Poorly	2.09 (1.28-3.43)	8.59	.003
Lymph node involvement			
Negative	1 [Reference]		
Positive	2.65 (1.96-3.58)	40.39	<.001
Chemotherapy			
No	1 [Reference]		
Yes	0.75 (0.57-0.98)	4.53	.03
Chemotherapy			
Observation	1 [Reference]		
Fluorouracil + folinic acid	0.79 (0.58-18)	2.26	.13
Gemcitabine	0.70 (0.51-0.97)	4.65	.03

Quality of Life

Two hundred forty-six patients (83 randomized to fluorouracil plus folinic acid, 84 to gemcitabine, and 79 to observation) completed baseline and subsequent QOL questionnaires. The subgroup was representative of patients in the entire study. Of these patients, 170 completed 3-month; 153, 6-month; and 129, 12-month questionnaires. Of the 15 QOL domain scales, only loss of appetite in the groups receiving either chemotherapy regimen was significant compared with the observation group

Table 4. Reported Toxicity[a]

Measure	No. (%) of Patients With CTC Grade 3 or 4[b]		*P* Value
	Fluorouracil + Folinic Acid (n = 143)	Gemcitabine (n = 141)	
Neutrophils	37 (24)	34 (24)	.79
Diarrhea	20 (14)	5 (4)	.003
Stomatitis	16 (11)	0	<.001
Tiredness	14 (10)	12 (9)	.84
White blood cell count	12 (8)	14 (10)	.69
Vomiting	5 (3)	1 (1)	.21
Nausea	5 (3)	0	.06
Platelets	2 (1)	2 (1)	≥.99
Alopecia	0	1 (1)	.50
Other	0	0	

[a] None of the 144 patients in the observation group had experience adverse events.
[b] Patients with at least 1 National Cancer Institute common toxicity criteria (CTC) version 2 grade 3 or 4 event.

at 3 and 6 months (χ^2_2=7.01; *P*=.03) but equalized by 12 months (eSupplement, A-O available at http://www.jamanetwork.com). There was a decrease in overall QOL at 3 months for the fluorouracil plus folinic acid group compared with observation (*P*=.03), with an increase in nausea and vomiting (*P*=.05) and diarrhea (*P*=.05) and with similar effects for gemcitabine (QOL, *P*=.001; nausea and vomiting, *P*=.006; and diarrhea, *P*=.006).

COMMENT

To our knowledge, this is the largest randomized trial conducted in this group of patients. Based on the null hypothesis the unadjusted primary analysis of the primary outcome of survival did not demonstrate a significant benefit for adjuvant chemotherapy. Multivariate analysis, correcting for prognostic variables, found a statistically significant survival benefit to chemotherapy and specifically for gemcitabine compared with observation, notwithstanding the better safety profile compared with fluorouracil plus folinic acid, but these results should be considered hypothesis generating. There were different survival outcomes by tumor type, although age, poorly differentiated tumor grade, and lymph node involvement were also independent survival factors.

A clear survival advantage for each specific tumor type could not be embraced in the trial design because the relative low incidence for each of the tumor types would have demanded a very large number of patients with unreasonably long and unattainable timelines.[3,4] From a pragmatic point of view, there were strong arguments to combine the different tumor types because the clinical presentation is very similar and they are treated in exactly the same way by surgery.[5,6] Moreover, tissue and molecular profiling cuts across these tumor types[19-21] and have been productively combined in previous studies.[22-26] In the ABC-02 trial,[25] doublet therapy using gemcitabine plus cisplatin favored improved survival compared with gemcitabine monotherapy in a mixed group of patients with advanced intrahepatic, hilar and extrahepatic bile duct cancers and gallbladder and ampullary cancers mirroring another smaller study.[26] From this periampullary ESAC-3 trial, however, it is clear that improving survival results in the adjuvant setting for intrapancreatic bile duct cancer is much more challenging and may need to be considered as a completely separate entity. Thus grouping may need to be avoided not only with ampullary cancer but also more proximal bile duct cancers.

Although there was no single review of histological sections, all the pathology reports were reviewed centrally by several experienced pathologists, so this is unlikely to be a source of systemic error. In the absence of controlled trials, there has been a recent tendency to vary the treatment of patients with ampullary cancer based on whether the tumor displayed an intestinal or pancreatobiliary histological phenotype.[19-21] At the start of this trial, this dichotomized classification was not being widely applied. In the present study, there were no statistically significant differences in survival between these ampullary subtypes.

In patients with resectable disease attempts at improving survival have included more extensive surgery[26] and adjuvant chemoradiation[6,24,26-28] but have not been successful. At the time of designing this study, the best evidence for adjuvant therapy for pancreatic cancer was from the ESPAC-1 trial, demonstrating a significant improvement in survival with the addition of fluorouracil plus folinic acid using the Mayo regimen.[10,15] In other cancer types, infusional fluorouracil regimens are commonly used. Although there are differences in toxicity profile, evidence of superior efficacy over the Mayo regimen in the adjuvant setting is lacking. Indeed in the parallel ESPAC-3 version 2 trial for pancreatic ductal adenocarcinoma of the pancreas,[11] gemcitabine was not superior to the Mayo regimen with respect to the primary end point of overall survival.

Although this study found support for the use adjuvant chemotherapy to improve survival in patients with periampullary cancers, this effect was modest, indicating a need for further improvements and warranting the testing of combination chemotherapies.

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Online-Only Material: The eAppendix is available at http://www.jama.com.

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