

ORIGINAL ARTICLE

A Randomized Trial of Chemoradiotherapy and Chemotherapy after Resection of Pancreatic Cancer

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ABSTRACT

BACKGROUND

The effect of adjuvant treatment on survival in pancreatic cancer is unclear. We report the final results of the European Study Group for Pancreatic Cancer 1 Trial and update the interim results.

METHODS

In a multicenter trial using a two-by-two factorial design, we randomly assigned 73 patients with resected pancreatic ductal adenocarcinoma to treatment with chemoradiotherapy alone (20 Gy over a two-week period plus fluorouracil), 75 patients to chemotherapy alone (fluorouracil), 72 patients to both chemoradiotherapy and chemotherapy, and 69 patients to observation.

RESULTS

The analysis was based on 237 deaths among the 289 patients (82 percent) and a median follow-up of 47 months (interquartile range, 33 to 62). The estimated five-year survival rate was 10 percent among patients assigned to receive chemoradiotherapy and 20 percent among patients who did not receive chemoradiotherapy ($P=0.05$). The five-year survival rate was 21 percent among patients who received chemotherapy and 8 percent among patients who did not receive chemotherapy ($P=0.009$). The benefit of chemotherapy persisted after adjustment for major prognostic factors.

CONCLUSIONS

Adjuvant chemotherapy has a significant survival benefit in patients with resected pancreatic cancer, whereas adjuvant chemoradiotherapy has a deleterious effect on survival.

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PANCREATIC CANCER, WITH AN OVERALL five-year survival rate ranging from 0.4 percent¹ to 4 percent,² has a poor prognosis and is one of the top 10 causes of death from cancer in the Western world.^{3,4} Surgical resection improves the outlook, although only about 10 percent of patients with pancreatic cancer are eligible for the procedure.⁵⁻⁹ Most treatment failures are due to local recurrence, hepatic metastases, or both and occur within one to two years after surgery.¹⁰⁻¹²

Adjuvant (postoperative) therapy may improve long-term survival,^{7-9,13-16} but its routine use is not universal⁸ because the results of randomized trials have been inconclusive.¹³ The Gastrointestinal Tumor Study Group (GITSG) randomly assigned 43 patients to receive surgery alone or chemoradiotherapy followed by maintenance chemotherapy.^{14,15} The median survival was significantly longer in the adjuvant-treatment group than in the surgery group (20 months vs. 11 months), with 5-year survival estimates of 18 percent and 8 percent, respectively.^{14,15} Three subsequent randomized studies, however, failed to confirm the benefit of adjuvant treatment.¹⁷⁻¹⁹ Moreover, it is unclear whether the survival advantage in the GITSG trial was due to the combination of chemoradiotherapy and maintenance chemotherapy or to only one of these treatments.¹³

The European Study Group for Pancreatic Cancer (ESPAC) undertook a large, multicenter trial to investigate the possible benefits of adjuvant chemoradiotherapy and maintenance chemotherapy in patients with pancreatic cancer. Although preliminary data indicated a survival benefit for adjuvant chemotherapy, the results were inconclusive owing to the short follow-up of only 10 months.^{20,21} In this report we summarize the results of this trial after it reached the primary end point and a median follow-up of 47 months among surviving patients.^{20,21}

METHODS

PATIENTS AND TRIAL DESIGN

The ESPAC-1 trial used a two-by-two factorial design in which, after resection of the pancreatic ductal adenocarcinoma, each patient was randomly assigned to receive chemoradiotherapy or chemotherapy, neither treatment, or both treatments (Fig. 1). The goal was to enroll 70 patients in each of the four groups, yielding combined data for 140 patients in each group for the two main treatment comparisons (chemoradiotherapy vs. no chemoradiotherapy and

chemotherapy vs. no chemotherapy) and giving the study the ability to detect absolute differences in the mortality rate at two years of more than 20 percent at a significance level of 5 percent with 90 percent power. The trial was approved by the ethics committees at the national and local level according to the requirements of each country, and all participants gave written informed consent.

Patients who had undergone a complete macroscopic resection²² of histologically proven pancreatic ductal adenocarcinoma underwent randomization with the use of a blocked method. They were stratified according to the randomization center (the United Kingdom, Switzerland, Germany, or France) and the status of the resection margin (positive or negative). Patients were followed up at three-month intervals until death. A subgroup of patients completed questionnaires about their quality of life.²³

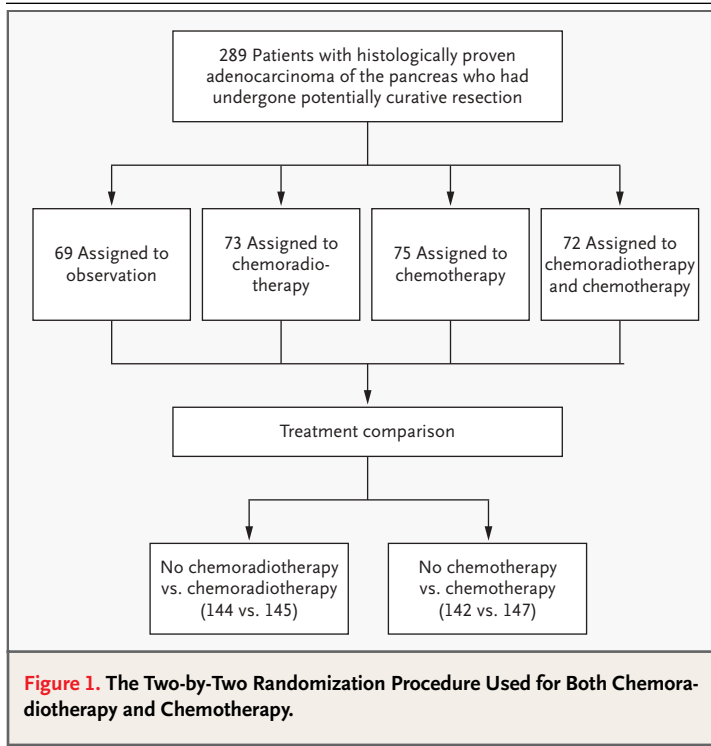
ADJUVANT THERAPY

Chemoradiotherapy consisted of a 20-Gy dose to the tumor given in 10 daily fractions over a two-week period plus an intravenous bolus of fluorouracil (500 mg per square meter of body-surface area on each of the first three days of radiotherapy and again after a planned break of two weeks). Chemotherapy consisted of an intravenous bolus of leucovorin (20 mg per square meter), followed by an intravenous bolus of fluorouracil (425 mg per square meter) on each of 5 consecutive days every 28 days for six cycles. Combination therapy consisted of chemoradiotherapy followed by chemotherapy, both administered as described above.

Adverse effects were assessed with the use of the Common Toxicity Criteria²⁴ and a clearly defined protocol for modifications and delays of treatment. The study required each center to treat patients according to its own quality-assurance standards for radiotherapy.

STATISTICAL ANALYSIS

The primary outcome measure was the two-year survival rate; secondary outcomes were the incidence of adverse effects and recurrence and measures of the quality of life. Survival was calculated from the date of resection until the date of death from any cause; for patients lost to follow-up, data were censored on the date the patient was last seen alive. Survival estimates were derived by the method of Kaplan and Meier,²⁵ and the log-rank test²⁶ was used to assess differences in survival estimates among the groups. Stratified log-rank analyses and Cox pro-



portional-hazards modeling²⁷ were used to investigate and adjust for major prognostic and stratification factors. Hazard ratios indicating the effects of treatment on the risk of death were calculated and displayed in Forrest plots.²⁸ Standardized area-under-the-curve methods²⁹ were used to assess the mean observed quality of life within 12 months after resection; the global quality of life was compared among the groups with the use of the nonparametric Wilcoxon two-sample test. All analyses were carried out according to the intention-to-treat principle, and all reported P values are two-sided.

RESULTS

A total of 289 patients from 53 hospitals in 11 European countries underwent randomization between February 1994 and June 2000. Three ineligible patients (one who had not undergone resection and two who had previously had breast cancer) were included in the analysis on an intention-to-treat basis. Clinical features and characteristics of the tumors were similar among the groups (Table 1). The median time from resection to randomization was 21 days (interquartile range, 14 to 35), and the median time from resection to the start of assigned treat-

ment was 46 days (interquartile range, 34 to 67) for the patients assigned to chemotherapy and 61 days (interquartile range, 47 to 80) for the patients assigned to chemoradiotherapy.

COMPLIANCE AND ADVERSE EFFECTS

A total of 145 patients were assigned to receive chemoradiotherapy (alone or with adjuvant chemotherapy), and 144 were assigned not to receive chemoradiotherapy — they received chemotherapy alone or were observed — according to the two-by-two design (Fig. 1). Treatment details were available for 128 of the 145 patients who received chemoradiotherapy (88 percent), of whom 90 (70 percent) received a total of 40 Gy according to the protocol, 27 (21 percent) received either more or less than 40 Gy, and 11 (9 percent) did not receive any chemoradiotherapy; most protocol violations were due to the patient's decision not to receive the randomly assigned treatment (50 percent) or to progressive disease (19 percent).

A total of 147 patients were assigned to chemotherapy (75 to chemotherapy alone and 72 to chemotherapy in combination with chemoradiotherapy), and 142 did not receive chemotherapy alone (69 were assigned to the observation group and 73 to the chemoradiotherapy group), according to the two-by-two design (Fig. 1). Treatment details were available for 122 of the 147 patients randomly assigned to receive chemotherapy (83 percent), of whom 61 (50 percent) received six cycles according to the protocol, 40 (33 percent) received fewer than six cycles, and 21 (17 percent) did not receive any chemotherapy; most protocol violations in this block were due to the patient's decision not to receive chemotherapy (33 percent) or to progressive disease (38 percent). Patients with a protocol violation were included in the analysis in their randomly assigned treatment group on an intention-to-treat basis.

Clinicians were asked to record the most severe episode of myelotoxic effects, stomatitis, diarrhea, and other adverse events. Adverse events of grade 3 or 4 were reported in 29 patients: 7 had hematologic events (2 patients assigned to chemotherapy alone and 5 to combination therapy), 9 had stomatitis (4 patients assigned to chemotherapy alone and 5 to combination treatment), 6 had diarrhea (2 patients assigned to chemotherapy alone and 4 to combination treatment), and 7 had other types of adverse events (2 patients assigned to chemoradiotherapy alone, 3 to chemotherapy alone, and 2 to combination treatment).

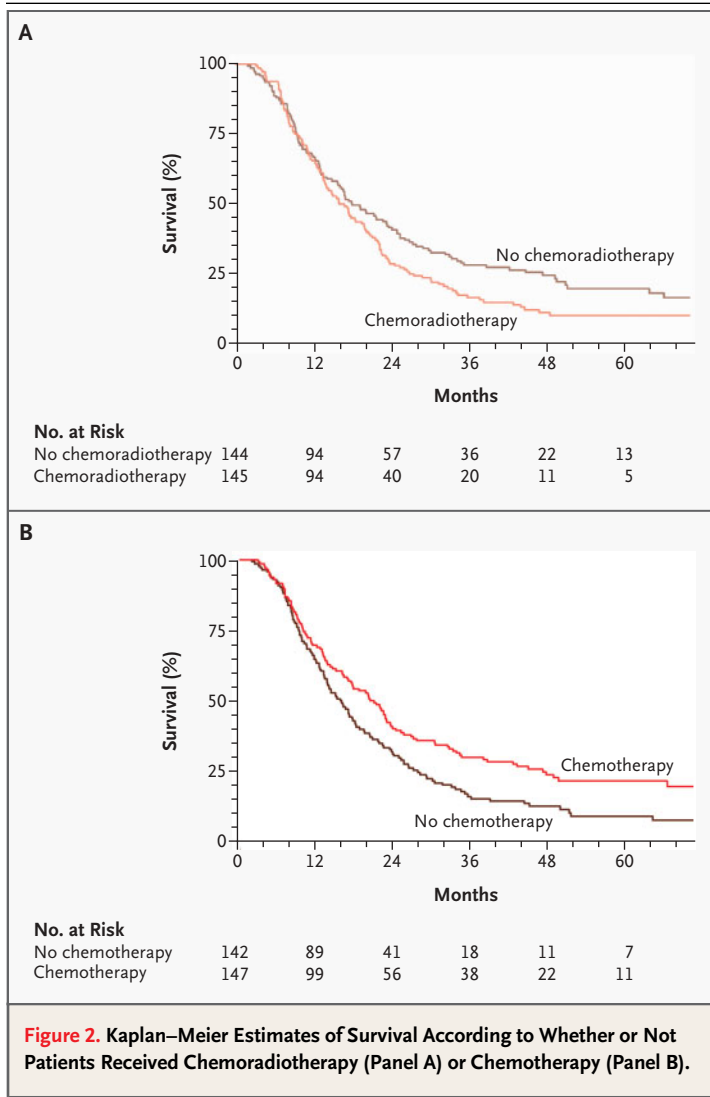
SURVIVAL

The analysis of survival was based on 237 deaths among the 289 patients (82 percent). The duration of follow-up was similar among the groups; the median was 47 months (interquartile range, 33 to 62)

for the 52 patients who were still alive at the time of the analysis. All but 12 deaths were disease-related: there were 2 treatment-related deaths (1 associated with chemoradiotherapy alone and 1 with combination treatment), 1 death from colon cancer, 1 from

Table 1. Characteristics of the Patients.

Characteristic	Random Assignment to Chemoradiotherapy		Random Assignment to Chemotherapy		Total (N=289)
	Received Chemoradiotherapy (N=145)	No Chemoradiotherapy (N=144)	Received Chemotherapy (N=147)	No Chemotherapy (N=142)	
Days to randomization					
Median	22	21	20	23	21
Interquartile range	14–35	13–35	14–36	13–35	14–35
Sex — no. (%)					
Male	79 (54)	91 (63)	82 (56)	88 (62)	170 (59)
Female	66 (46)	53 (37)	65 (44)	54 (38)	119 (41)
Age — yr					
Median	62	61	61	61	61
Interquartile range	52–68	55–66	54–67	54–67	54–67
Resection margins — no. (%)					
Negative	117 (81)	121 (84)	119 (81)	119 (84)	238 (82)
Positive	28 (19)	23 (16)	28 (19)	23 (16)	51 (18)
Nodal status — no. (%)					
Negative	59 (41)	60 (42)	68 (46)	51 (36)	119 (41)
Positive	77 (53)	78 (54)	73 (50)	82 (58)	155 (54)
Unknown	9 (6)	6 (4)	6 (4)	9 (6)	15 (5)
Tumor grade — no. (%)					
Well differentiated	29 (20)	33 (23)	35 (24)	27 (19)	62 (21)
Moderately well differentiated	80 (55)	68 (47)	73 (50)	75 (53)	148 (51)
Poorly differentiated	21 (14)	31 (22)	23 (16)	29 (20)	52 (18)
Unknown	15 (10)	12 (8)	16 (11)	11 (8)	27 (9)
Maximal tumor size — cm					
Median	3.0	3.0	3.0	3.0	3.0
Interquartile range	2.5–4.0	2.5–4.0	2.5–4.0	2.5–3.9	2.5–4.0
Smoking history — no. (%)					
Never	66 (46)	64 (44)	72 (49)	58 (41)	130 (45)
Past	33 (23)	39 (27)	33 (22)	39 (27)	72 (25)
Current	35 (24)	33 (23)	32 (22)	36 (25)	68 (24)
Unknown	11 (8)	8 (6)	10 (7)	9 (6)	19 (7)
Preoperative diabetes — no. (%)					
No	113 (78)	113 (78)	115 (78)	111 (78)	226 (78)
Yes	25 (17)	23 (16)	23 (16)	25 (18)	48 (17)
Unknown	7 (5)	8 (6)	9 (6)	6 (4)	15 (5)
Local invasion at operation — no. (%)					
No	101 (70)	102 (71)	106 (72)	97 (68)	203 (70)
Yes	29 (20)	30 (21)	24 (16)	35 (25)	59 (20)
Unknown	15 (10)	12 (8)	17 (12)	10 (7)	27 (9)
Involved adjacent structures on histologic analysis — no. (%)					
No	87 (60)	88 (61)	90 (61)	85 (60)	175 (61)
Yes	44 (30)	46 (32)	44 (30)	46 (32)	90 (31)
Unknown	14 (10)	10 (7)	13 (9)	11 (8)	24 (8)
Postoperative complications — no. (%)					
No	103 (71)	98 (68)	104 (71)	97 (68)	201 (70)
Yes	33 (23)	37 (26)	34 (23)	36 (25)	70 (24)
Unknown	9 (6)	9 (6)	9 (6)	9 (6)	18 (6)



ovarian cancer, 3 from pulmonary embolism, 1 from myocardial infarction, 2 from a ruptured aortic aneurysm, 1 from gastrointestinal bleeding, and 1 from unknown causes. Survival was calculated from the date of resection. A sensitivity analysis in which survival was calculated from the date of randomization did not change the interpretation of the results or the conclusions.

Chemoradiotherapy

The median survival was 15.9 months (95 percent confidence interval, 13.7 to 19.9) among the 145 patients who were assigned to chemoradiotherapy and 17.9 months (95 percent confidence interval, 14.8 to 23.6) among the 144 patients who were not as-

signed to receive chemoradiotherapy (hazard ratio for death, 1.28; 95 percent confidence interval, 0.99 to 1.66; P=0.05). Two-year and five-year survival estimates were 29 percent and 10 percent, respectively, among patients who received chemoradiotherapy and 41 percent and 20 percent, respectively, among those who did not receive chemoradiotherapy (Fig. 2A). The Forrest plot (Fig. 3) confirmed the lack of a statistically significant benefit of chemoradiotherapy whether or not patients were also randomly assigned to receive additional chemotherapy.

Chemotherapy

The median survival was 20.1 months (95 percent confidence interval, 16.5 to 22.7) among the 147 patients who received chemotherapy and 15.5 months (95 percent confidence interval, 13.0 to 17.7) among the 142 patients who did not receive chemotherapy (hazard ratio for death, 0.71; 95 percent confidence interval, 0.55 to 0.92; P=0.009). Two-year and five-year survival estimates were 40 percent and 21 percent, respectively, among patients who received chemotherapy and 30 percent and 8 percent, respectively, among patients who received no chemotherapy (Fig. 2B). The Forrest plot (Fig. 4) confirmed a significant survival benefit for chemotherapy whether or not patients were also randomly assigned to receive chemoradiotherapy.

Additional Survival Analyses

The median survival was 16.9 months (95 percent confidence interval, 12.3 to 24.8) among the 69 patients randomly assigned to observation, 13.9 months (95 percent confidence interval, 12.2 to 17.3) among the 73 patients randomly assigned to chemoradiotherapy, 21.6 months (95 percent confidence interval, 13.5 to 27.3) among the 75 patients randomly assigned to chemotherapy, and 19.9 months (95 percent confidence interval, 14.2 to 22.5) among the 72 patients randomly assigned to chemoradiotherapy plus chemotherapy. The respective five-year survival estimates were 11 percent, 7 percent, 29 percent, and 13 percent. This two-by-two trial did not have the statistical power to compare these four groups directly.

Influence of Prognostic Factors

Log-rank analysis of the characteristics of patients and tumors revealed no significant differences in survival with respect to sex; an age of 60 years or more, as compared with less than 60 years; and the presence of preoperative diabetes, local invasion at

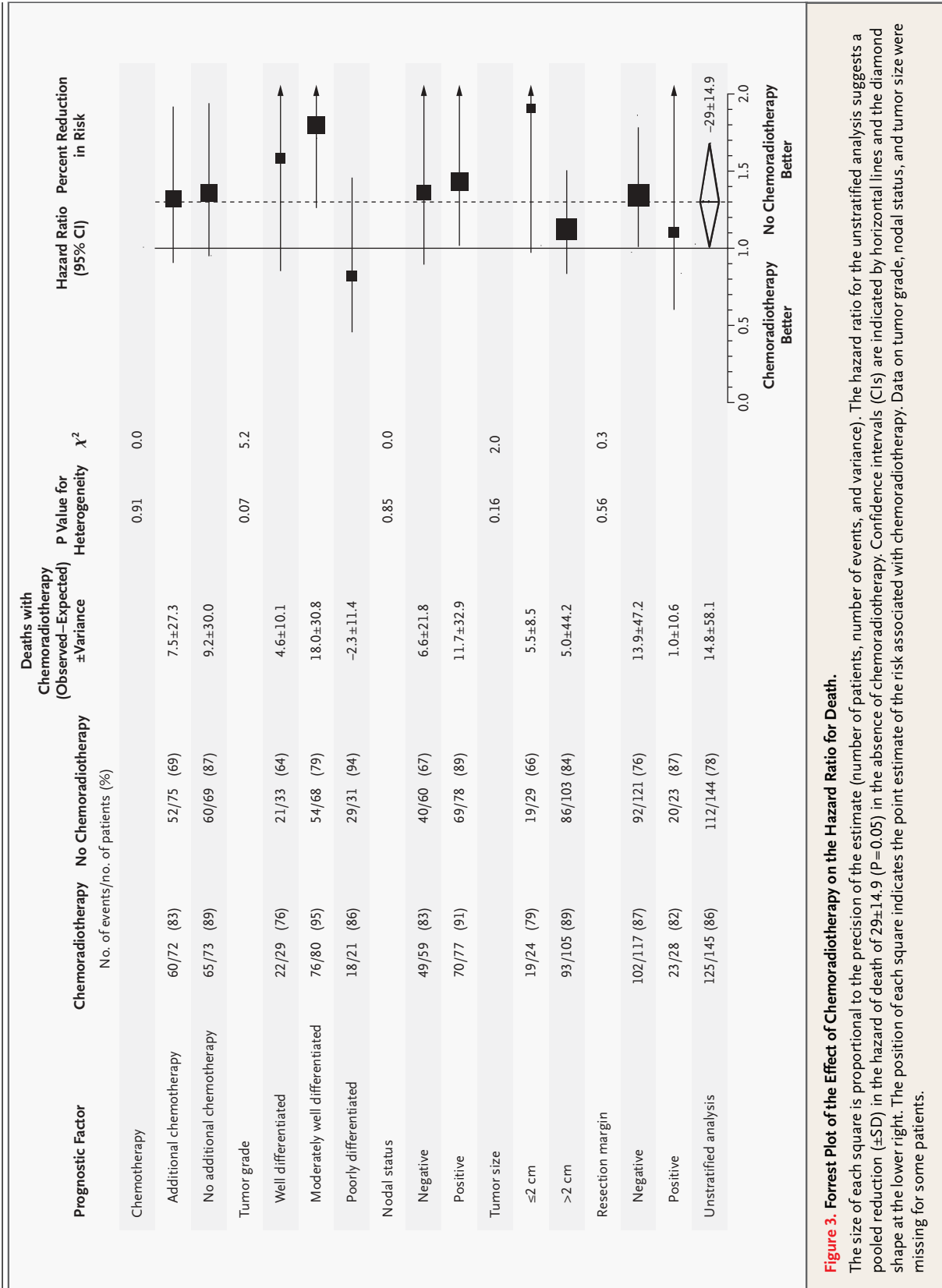


Figure 3. Forest Plot of the Effect of Chemoradiotherapy on the Hazard Ratio for Death.

The size of each square is proportional to the precision of the estimate (number of patients, number of events, and variance). The hazard ratio for the unstratified analysis suggests a pooled reduction (\pm SD) in the hazard of death of 29 \pm 14.9 (P=0.05) in the absence of chemoradiotherapy. Confidence intervals (CIs) are indicated by horizontal lines and the diamond shape at the lower right. The position of each square indicates the point estimate of the risk associated with chemoradiotherapy. Data on tumor grade, nodal status, and tumor size were missing for some patients.

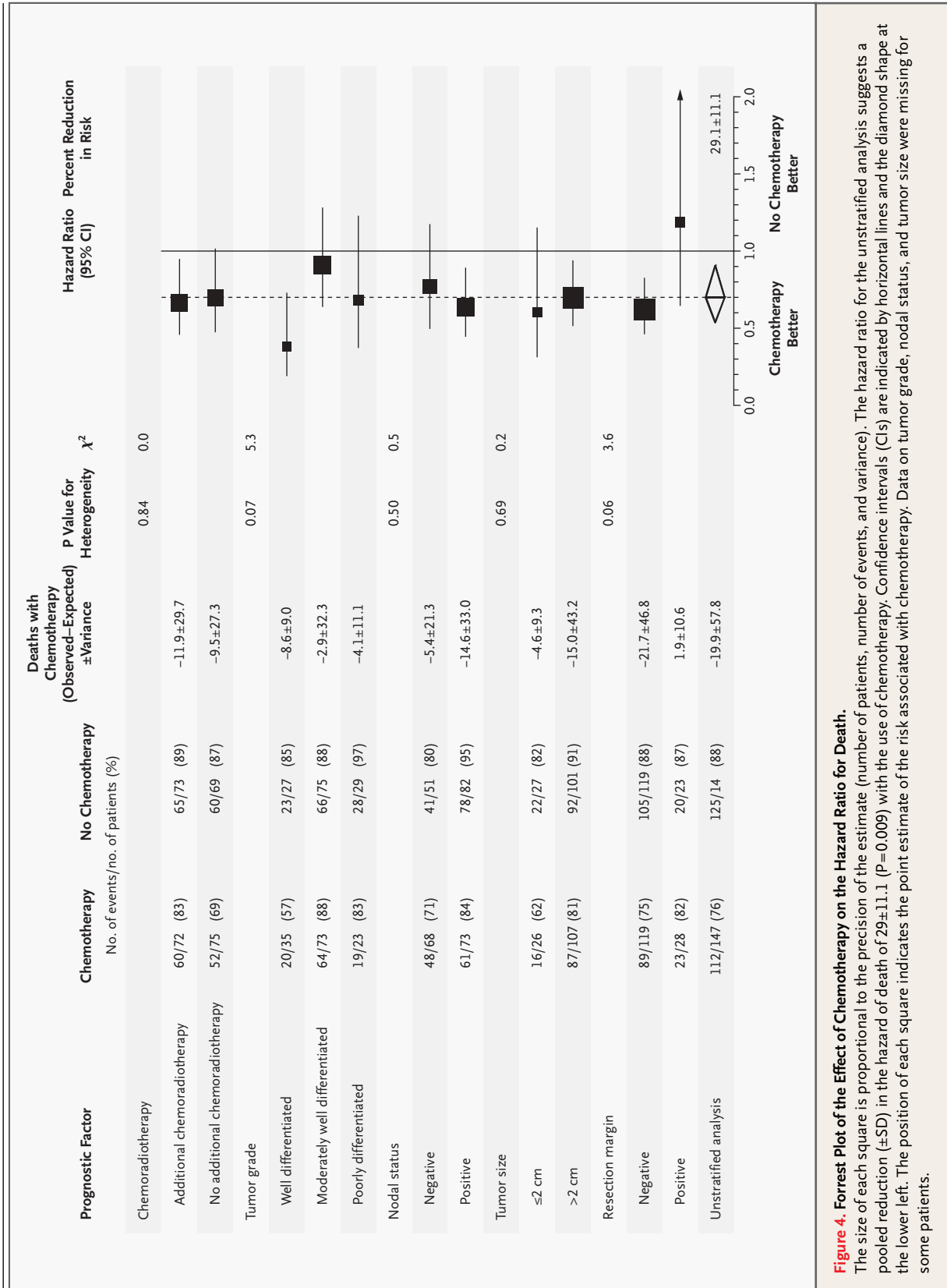


Figure 4. Forrest Plot of the Effect of Chemotherapy on the Hazard Ratio for Death.

The size of each square is proportional to the precision of the estimate (number of patients, number of events, and variance). The hazard ratio for the unstratified analysis suggests a pooled reduction (\pm SD) in the hazard of death of 29 \pm 11.1 (P=0.009) with the use of chemotherapy. Confidence intervals (CIs) are indicated by horizontal lines and the diamond shape at the lower left. The position of each square indicates the point estimate of the risk associated with chemotherapy. Data on tumor grade, nodal status, and tumor size were missing for some patients.

operation, and postoperative complications, but borderline effects were found for current smoking ($P=0.07$), positive resection margins ($P=0.10$), and the presence of involved adjacent structures on histologic analysis ($P=0.10$). Increasingly differentiated tumors ($P<0.001$), the presence of lymph-node involvement ($P<0.001$), and a maximal tumor size of more than 2 cm, as compared with 2 cm or less ($P=0.003$), had significant adverse influences on survival. Stratifying treatment effects according to each of these factors did not influence the overall treatment result.

Cox regression modeling identified the grade of disease, tumor size (retained as a continuous variable), and lymph-node status as independent prognostic factors, adjusted for two stratification factors at randomization: randomization center (United Kingdom, Switzerland, Germany, or France) and resection-margin status (negative or positive) (Table 2). The analysis confirmed an adjusted hazard ratio for death of 1.47 (95 percent confidence interval, 1.10 to 1.95) with the use of chemoradiotherapy and an adjusted hazard ratio for death of 0.77 (95 percent confidence interval, 0.58 to 1.01) with the use of chemotherapy (Table 2). The interaction between chemotherapy and chemoradiotherapy in patients who underwent randomization according to the two-by-two design was tested with the use of a for-

mal log-rank test and a multiplication interaction term, and the results of both were nonsignificant.

RECURRENCE

Of 158 patients who were known to have had a tumor recurrence, local recurrence alone was reported in 56 (35 percent), distant metastases alone in 53 (34 percent), and both types in 43 (27 percent); the site of recurrence was unknown in 6 patients (4 percent). Known recurrences were identified in 84 of 102 patients who were assigned to chemoradiotherapy (82 percent) and in 74 of 106 patients who did not receive chemoradiotherapy (70 percent). The median time to recurrence was 10.7 months (95 percent confidence interval, 8.8 to 15.5) among patients who received chemoradiotherapy and 15.2 months (95 percent confidence interval, 9.8 to 22.2) among those who did not receive chemoradiotherapy ($P=0.04$), with estimated 12-month recurrence-free survival rates of 46 percent and 55 percent, respectively. The disease recurred in 79 of 110 patients who received chemotherapy (72 percent) and in 79 of 98 patients who did not receive chemotherapy (81 percent). The median time to recurrence was 15.3 months (95 percent confidence interval, 10.5 to 19.2) among patients given chemotherapy and 9.4 months (95 percent confidence interval, 8.4 to 15.2) among patients who were not given chemotherapy

Table 2. Cox Regression Model of the Effect of Chemoradiotherapy and Chemotherapy, Adjusted for Prognostic and Stratification Factors.*

Variable	β Coefficient <i>estimate</i> ± <i>SE</i>	χ^2	P Value	Hazard Ratio (95% CI)
Base model of independent prognostic factors				
Increasingly differentiated tumor	0.635±0.120	27.95	<0.001	1.89 (1.49–2.39)
Maximal tumor size†	0.191±0.059	10.37	0.001	1.21 (1.08–1.36)
Positive nodes	0.449±0.146	9.52	0.002	1.57 (1.18–2.09)
Base model plus effects of chemoradiotherapy				
Increasingly differentiated tumor	0.649±0.120	29.18	<0.001	1.91 (1.51–2.42)
Maximal tumor size†	0.171±0.060	8.20	0.004	1.19 (1.06–1.33)
Positive nodes	0.504±0.148	11.58	<0.001	1.66 (1.24–2.21)
Chemoradiotherapy	0.383±0.145	6.97	0.008	1.47 (1.10–1.95)
Base model plus effects of chemotherapy				
Increasingly differentiated tumor	0.622±0.120	26.85	<0.001	1.86 (1.47–2.36)
Maximal tumor size†	0.197±0.059	11.28	<0.001	1.22 (1.09–1.37)
Positive nodes	0.439±0.146	9.04	0.003	1.55 (1.17–2.07)
Chemotherapy	-0.267±0.141	3.60	0.058	0.77 (0.58–1.01)

* The base model includes 249 patients and 209 deaths and has been adjusted for the two stratification factors at randomization: randomization center (United Kingdom, Switzerland, Germany, or France) and resection-margin status (negative or positive). A hazard ratio of more than 1 indicates an increased risk of death. CI denotes confidence interval.

† Maximal tumor size was a continuous variable.

($P=0.02$), with estimated 12-month recurrence-free survival rates of 58 percent and 43 percent, respectively.

QUALITY OF LIFE

Questionnaires regarding the quality of life were completed by 152 of the 289 patients (53 percent), a representative sample of the main study group. There were no significant differences in the mean observed quality of life within 12 months after resection between patients who received chemotherapy and those who did not receive chemotherapy ($P=0.75$) or between patients who received chemoradiotherapy and those who did not receive chemoradiotherapy ($P=0.17$).

DISCUSSION

The results of the ESPAC-1 trial, which was a large, adequately powered, randomized trial of adjuvant treatment for resectable pancreatic cancer, show a significant survival benefit for adjuvant chemotherapy. The effect of adjuvant chemotherapy is particularly encouraging, since 18 percent of the patients had positive resection margins, a criterion for exclusion in the GITSG trial.^{14,15} Our results also show that adjuvant chemoradiotherapy not only fails to benefit patients but also reduces survival when it is given before chemotherapy.

The European Organization for Research and Treatment of Cancer (EORTC) randomly assigned 218 patients with pancreatic or ampullary tumors to adjuvant chemoradiotherapy (but no maintenance chemotherapy) or surgery alone.¹⁷ There was no significant difference in survival between the groups, including the 114 patients with pancreatic cancer, with median survivals of 17 and 13 months in the treatment and observation groups, respectively, and with 5-year survival estimates of 23 percent and 10 percent, respectively.¹⁷ Even apart from the high dropout rate, however, the study was statistically underpowered. A Norwegian study randomly assigned 61 patients (14 with ampullary tumors) to adjuvant chemotherapy (doxorubicin, mitomycin, and fluorouracil) or surgery alone.¹⁸ The median survival was significantly longer in the adjuvant-treatment group than in the observation group (23 months vs. 11 months), but the 5-year survival rate was not (4 percent vs. 8 percent).¹⁸ This trial was also statistically underpowered, and the results discouraged further use of the doxorubicin-containing regimen

because of its toxicity.¹⁸ A Japanese trial reported no benefit from adjuvant chemotherapy, but its design precluded definitive conclusions from being drawn.¹⁹

Evidence that adjuvant chemoradiotherapy for pancreatic cancer improves local control is inconclusive,³⁰⁻³² and better local control has not been shown to correlate with increased survival.^{14,15,17,33,34} In our trial, the rates of local recurrence were not significantly different between patients who received chemoradiotherapy and those who did not receive chemoradiotherapy. Similar findings were reported in the EORTC trial.¹⁷ An analysis of 100,313 U.S. patients with pancreatic cancer in the National Cancer Database revealed that 9044 patients (9 percent) had undergone a pancreatectomy.⁸ Of these 9044 patients, only 39.9 percent had received adjuvant treatment: 6.5 percent had received radiotherapy, 5.1 percent chemotherapy, and 28.3 percent a combination of the two.⁸ The five-year survival rates were 23.3 percent after resection alone, 13.0 percent in the adjuvant-radiotherapy group, 17.4 percent in the adjuvant-chemotherapy group, and 17.0 percent in the combination-therapy group.⁸ Given such results, it is not surprising that there has been uncertainty regarding the use of adjuvant treatment for pancreatic cancer.

The survival curves in our trial began to separate in favor of adjuvant chemotherapy at 8 months after resection, but the curves showing the disadvantage of chemoradiotherapy did not begin to separate until 14 months. The simplest explanation for these observations is that chemoradiotherapy delayed the administration of chemotherapy (which in our trial resulted in a delay in both local and distant recurrences) and consequently reduced the potential benefit of chemotherapy that is derived from delivering it as soon as possible after resection. We conclude that standard care for patients with resectable pancreatic cancer should consist of curative surgery followed by adjuvant systemic chemotherapy.

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APPENDIX

The following persons participated in the ESPAC-1 Trial: *Specialists* — Austria: P. Steindorfer (Graz); Belgium: J.F. Gigot (Brussels); France (French Associations for Surgical Research): P. Segol (Caen); J. Chipponi (Clermont-Ferrand); J.M. Hay (Colombes); D. Cherqui, P.-L. Fagniez, B. Malassagne (Creteil); M.S. Sbai-Idrissy (Eaubonne); L. Gambiez, P. Quandalle, J.P. Triboulet (Lille); A. Gainan (Limoges); B. Derousseaux (Lomme); B. Sastre (Marseille); S. Houry, H. Mosnier (Paris); M. Veyrieres (Pontoise); O. Bouche (Reims); G. Fourtanier (Toulouse); Germany: U. Kletha (Chemnitz); J. Schmidt (Heidelberg); J. Scheele (Jena); G. Weiland (Lahr); B. Gerdes (Marburg); W. Weber (Trier); Greece: J.K. Poulantzas (Athens); J. Androulakis (Patras); G. Blantzas, D. Botsios, E. Hatzitheoklitos, C.H. Sbarouris (Thessaloniki); Hungary: L. Flautner, T. Tihanyi (Budapest); P. Sapy (Debrecen); A. Olah (Gyor); P. Horvath-Ors, D. Kelemen (Pecs); M. Wenczl (Szombathely); Italy: G. Marzoli (Bolzano); O. Pieramico (Merano); F. Meduri, S. Pedrazzoli (Padua); F. Dominioni (Varese); G. Butturini (Verona); Spain: C. Pera (Cordoba); Sweden: I. Ihse, Å. Andrén-Sandberg (Lund); Switzerland: S. Hunziker (Aarau); K. Buser (Bern); R. Stupp (Lausanne); J. Largiader (Lucerne); G. Pichert, R. Trüb (Zurich); United Kingdom: J. Buckels, I. Fernando (Birmingham); D. Alderson, S. Falk (Bristol); P. De Takats (Cambridge); R. Carter, D. Hochhauser, C. Imrie (Glasgow); T. Leese (Lancaster); A. Crellin, D. Sebag-Montefiore, M. Seymour (Leeds); D. Lloyd, F. Madden (Leicester); M. Hartley, S. Myint, J. Slavin, D. Smith, R. Sutton (Liverpool, Wirral); P. Price, B. Davidson (London); T. Podd (Newcastle); F. Daniel, A. Kingsnorth (Plymouth); C. Baughan, C. Johnson (Southampton); F. Adab (Stoke on Trent); D. Cunningham (Surrey); *Independent Data and Safety Monitoring Committee* — R.C.G. Russell (Middlesex Hospital, London), P. Clarke (Clatterbridge Center for Clinical Oncology, Wirral, United Kingdom), R.P. A'Hern (Royal Marsden Hospital, London); *Trial Design* — J.P. Neoptolemos, M.W. Büchler, H.G. Beger, C. Bassi, P. Pederzoli, D.J. Kerr, D. Spooner, J.A. Dunn; *Recruitment* — J.P. Neoptolemos, M.W. Büchler, H.G. Beger, C. Bassi, P. Pederzoli, D.J. Kerr, D. Spooner, J.A. Dunn, M. Falconi, C. Dervenis, F. Fernandez-Cruz, F. Lacaine, A. Pap, H. Friess; *Statistical Analysis and Preparation of Reports* — D.D. Stocken; *Trial Coordinator* — H. Hickey; *Writing Committee* — J.P. Neoptolemos, D.D. Stocken.

REFERENCES

- Bramhall SR, Allum WH, Jones AG, Allwood A, Cummins C, Neoptolemos JP. Treatment and survival in 13,560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study. *Br J Surg* 1995;82:111-5.
- Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin* 2003;53:5-26.
- Fernandez E, La Vecchia C, Porta M, Negri E, Lucchini F, Levi F. Trends in pancreatic cancer mortality in Europe, 1955-1989. *Int J Cancer* 1994;57:786-92.
- Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000: the global picture. *Eur J Cancer* 2001;37:Suppl 8:S4-S66.
- Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. *Am J Surg* 1993;165:68-72.
- Nitecki SS, Sarr MG, Colby TV, van Heerden JA. Long-term survival after resection for ductal adenocarcinoma of the pancreas: is it really improving? *Ann Surg* 1995;221:59-66.
- Birkmeyer JD, Warshaw AL, Finlayson SR, Grove MR, Tosteson ANA. Relationship between hospital volume and late survival after pancreaticoduodenectomy. *Surgery* 1999;126:178-83.
- Sener SF, Fremgen A, Menck HR, Winchester DP. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. *J Am Coll Surg* 1999;189:1-7.
- Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas — 616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000;4:567-79.
- Griffin JE, Smalley SR, Jewell W, et al. Patterns of failure after curative resection of pancreatic carcinoma. *Cancer* 1990;66:56-61.
- Westerdhal J, Andrén-Sandberg Å, Ihse I. Recurrence of exocrine pancreatic cancer — local or hepatic? *Hepatogastroenterology* 1993;40:384-7.
- Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. *World J Surg* 1997;21:195-200.
- Neoptolemos JP, Cunningham D, Friess H, et al. Adjuvant therapy in pancreatic cancer: historical and current perspectives. *Ann Oncol* 2003;14:675-92.
- Kalser MH, Ellenberg SS. Pancreatic cancer: adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 1985;120:899-903. [Erratum, *Arch Surg* 1986;121:1045.]
- Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. *Cancer* 1987;59:2006-10.
- Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. *Ann Surg* 2003;237:74-85.
- Klinkenbijl JH, Jeekel J, Sahnoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg* 1999;230:776-84.
- Bakkevoeld KE, Arnesjo B, Dahl O, Kambeid B. Adjuvant combination chemotherapy (AMF) following radical resection of carcinoma of the pancreas and papilla of Vater — results of a controlled, prospective, randomised multicenter study. *Eur J Cancer* 1993;29A:698-703.
- Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer* 2002;95:1685-95.
- Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet* 2001;358:1576-85.
- Neoptolemos JP, Stocken DD, Dunn JA, et al. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. *Ann Surg* 2001;234:758-68.
- Jones L, Russell C, Mosca F, et al. Standard Kausch-Whipple pancreaticoduodenectomy. *Dig Surg* 1999;16:297-304.
- Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-76.
- Cancer Therapy Evaluation Program. Common toxicity criteria, version 2.0. Bethesda, Md.: Division of Cancer Treatment & Diagnosis, National Institutes of Health, March 1998.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Peto R, Pike MC, Armitage P, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;35:1-39.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Early Breast Cancer Trialists' Collaborative Group. Introduction and methods sections reproduced from: Treatment of early breast cancer. Vol. 1. Worldwide evidence 1985-1990. Oxford, England: Oxford University Press, 1990.
- Qian W, Parmar MKB, Sambrook RJ, Fayers PM, Girling DJ, Stephens RJ. Analysis of messy longitudinal data from a randomized clinical trial. *Stat Med* 2000;19:2657-74.
- Whittington R, Bryer MP, Haller DG, Solin LJ, Rosato EF. Adjuvant therapy of resected adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys* 1991;21:1137-43.

31. Foo ML, Gunderson LL, Nagorney DM, et al. Patterns of failure in grossly resected pancreatic ductal adenocarcinoma treated with adjuvant irradiation +/- 5 fluorouracil. *Int J Radiat Oncol Biol Phys* 1993;26:483-9.
32. Chakravarthy A, Abrams RA, Yeo CJ, et al. Intensified adjuvant combined modality therapy for resected perampullary adenocarcinoma: acceptable toxicity and suggestion of improved 1-year disease-free survival. *Int J Radiat Oncol Biol Phys* 2000;48:1089-96.
33. Johnstone PA, Sindelar WF. Patterns of disease recurrence following definitive therapy of adenocarcinoma of the pancreas using surgery and adjuvant radiotherapy: correlations of a clinical trial. *Int J Radiat Oncol Biol Phys* 1993;27:831-4.
34. Willett CG, Lewandrowski K, Warshaw AL, EfidJ, Compton CC. Resection margins in carcinoma of the head of the pancreas: implications for radiation therapy. *Ann Surg* 1993;217:144-8.

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CORRECTION

**A Randomized Trial of Chemoradiotherapy and
Chemotherapy after Resection of Pancreatic Cancer**

A Randomized Trial of Chemoradiotherapy and Chemotherapy after Resection of Pancreatic Cancer . On page 1201, under "Adjuvant Therapy," the first sentence should have read, "Chemoradiotherapy consisted of a 20-Gy dose to the previous tumor bed given in 10 daily fractions over a two-week period plus an intravenous bolus of fluorouracil (500 mg per square meter of body-surface area on each of the first three days of radiotherapy) and again after a planned break of two weeks," rather than "a 20-Gy dose to the tumor given in 10 daily fractions over a two-week period plus an intravenous bolus of fluorouracil (500 mg per square meter of body-surface area on each of the first three days of radiotherapy and again after a planned break of two weeks)," as printed.