

Influence of Resection Margins and Treatment on Survival in Patients With Pancreatic Cancer

Meta-analysis of Randomized Controlled Trials

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Objective: To assess the influence of resection margins and adjuvant chemoradiotherapy or chemotherapy on survival for patients with pancreatic cancer by meta-analysis of individual data from randomized controlled trials.

Data Sources: Structured MEDLINE search for published studies.

Study Selection: A meta-analysis of published randomized controlled trials and individual data.

Data Extraction: Individual data were obtained from 4 recently published trials (875 patients: 278 [32%] with R1 and 591 [68%] with R0 resections).

Data Synthesis: Kaplan-Meier estimates of survival were compared using log-rank analyses. Pooled hazard ratios of the effects of chemoradiotherapy and chemotherapy treatments on the risk of death were calculated separately and across groups according to resection margins

status. Six hundred ninety-eight patients (80%) had died, with a median follow-up of 44 months in the surviving patients. Resection margin involvement was not a significant factor for survival (hazard ratio [HR], 1.10; 95% confidence interval [CI], 0.94-1.29; log-rank $\chi^2=1.4$; $P=.24$). The 2- and 5-year survival rates, respectively, were 33% and 16% for R0 patients and 29% and 15% for R1 patients. Chemoradiotherapy in R1 patients resulted in a 28% reduction in the risk of death (HR, 0.72; 95% CI, 0.47-1.10) compared with a 19% increased risk in R0 patients (HR, 1.19; 95% CI, 0.95-1.49). Chemotherapy in R1 patients had a 4% increased risk of death (HR, 1.04; 95% CI, 0.78-1.40) compared with a 35% reduction in risk in the R0 subgroup (HR, 0.65; 95% CI, 0.53-0.80).

Conclusion: Adjuvant chemotherapy but not chemoradiotherapy should be the standard of care for patients with either R0 or R1 resections for pancreatic cancer.

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PANCREATIC CANCER REMAINS a leading cause of cancer death in the Western world with about 31 000 and 65 000 deaths per year in the United States and Europe, respectively.¹⁻³ Curative resection of pancreatic cancer can be performed only in 10% to 15% of patients owing to advanced stage and an overall 5-year survival rate of about 10%.^{1,2,4} Improvements in surgical technique have led to a significant reduction of perioperative morbidity and mortality in experienced centers in the subgroup of patients with resectable disease.⁵⁻⁷ The role of adjuvant treatment, either as radiotherapy or chemotherapy, might further improve survival. The European Study Group for Pancreatic Cancer 1 (ESPAC-1) trial was the first study powered to evaluate the effects of both adjuvant radiotherapy and chemotherapy, concluding no survival ben-

efit for chemoradiotherapy but a significant survival benefit for chemotherapy.^{8,9}

Several reports have shown resection margins to be an important factor for the

See Invited Critique at end of article

long-term prognosis of patients after pancreatic cancer resection.⁵⁻¹² Resection margin classification is the widely accepted method to define the extent of resection in patients with pancreatic cancer. An R0 resection is one that has no microscopic or macroscopic residual tumor in the specimen; an R1 has microscopic residual tumor on the surgical edges of the specimen; and an R2 defines the macroscopic residual cancer after a surgical procedure initially intended to be radical. Patients were divided into 3 different subgroups according to these definitions; each of them

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Table 1. Clinical and Tumor Characteristics Across Resection Margin Groups

Characteristic	No. of Patients (%)	
	Margin Positive	Margin Negative
No. for analysis	278 (32)	591 (68)
Trial		
Norway ¹³	0	47 (100)
EORTC ¹⁶	40 (34)	79 (66)
Japan ¹⁷	127 (83)	26 (17)
ESPAC, 2 × 2 ⁹	51 (18)	238 (82)
ESPAC, plus ^{8,15}	60 (23)	201 (77)
Age, y		
≤ 60	118 (43)	274 (46)
> 60	158 (57)	316 (54)
Missing data	2	1
Nodal involvement		
No	99 (37)	290 (51)
Yes	167 (63)	282 (49)
Missing data	12	19
Tumor grade		
Well	57 (22)	134 (26)
Moderate	133 (52)	273 (53)
Poor	40 (15)	107 (21)
Papillary	12 (5)	2 (0.5)
Other	15 (6)	2 (0.5)
Missing data	21	73
Tumor size, cm		
≤ 2	30 (22)	141 (27)
> 2	104 (78)	386 (73)
Missing data	144	64
Postoperative complications		
No	176 (77)	350 (72)
Yes	53 (23)	139 (28)
Missing data	49	102
Status		
Alive	52 (19)	124 (21)
Dead	226 (81)	467 (79)

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer.

has been treated differentially in the past. Early prospective studies excluded R1 resections from adjuvant treatment and the R2 subgroup. That patients with R1 resections have a worse survival rate than R0 resection implies the need to stratify patients in controlled randomized trials of adjuvant treatment. The leading question is whether the R1 patients should be treated as part of the R0 subgroup in the adjuvant setting. The involvement of resection margins was shown to be an influential prognostic factor in the interim analysis of ESPAC-1,⁸ whereas earlier prospective studies were too small to include this factor.^{13,14} A detailed analysis of prognostic factors based on the interim analysis of the ESPAC-1 trial concluded that resection margin–positive pancreatic tumors represented a more biologically aggressive cancer.¹² These patients benefit from resection and adjuvant chemotherapy but not chemoradiotherapy. The magnitude of benefit for chemotherapy treatment, however, was reduced for patients with R1 margins vs those with R0 margins.¹²

In the final report of the ESPAC-1 trial, which included patients randomized in the original 2 × 2 design, the effect of resection margin status on survival was again

not significant ($P = .10$).⁹ The overall survival benefit for adjuvant chemotherapy, but not chemoradiotherapy, was confirmed in a recently published meta-analysis using individual patient data.¹⁵ Subgroup analyses, however, estimated that chemotherapy was less effective and chemoradiotherapy was more effective in patients with cancerous resection margins. Our aim was to further investigate the influence of resection margins through a meta-analysis of randomized controlled trials, providing more detail for the planning of subsequent trials to specifically investigate resection margin status.^{8,9,13-17}

METHODS

A protocol for the inclusion of trials into the meta-analysis was followed and has been previously reported.¹⁵ All included trials randomized patients with pancreatic ductal adenocarcinoma to adjuvant therapy following resection for pancreatic cancer. Patients with tumors other than pancreatic ductal adenocarcinoma were excluded. Patients were grouped according to the type of randomized adjuvant treatment (chemoradiotherapy or chemotherapy) and resection margin status at randomization (R0 or R1 resection).

The main outcome measure for analysis was overall survival measured from date of operation to the date of death (from all causes) or censor date. Kaplan-Meier¹⁸ estimates of survival were compared using standard and stratified log-rank tests.¹⁹ The log-rank expected numbers of deaths and variance were used to calculate individual and pooled hazard ratios (HRs) and confidence intervals (CIs). Pooled HRs indicating the effects of chemoradiotherapy and chemotherapy treatments on the risk of death and χ^2 tests for statistical heterogeneity (interaction) were calculated separately and across groups according to resection margin status.

RESULTS

PATIENTS

Four trials of adjuvant treatment for patients with resected pancreatic ductal adenocarcinoma were identified with individual data available on 875 patients.^{8,9,13-17} Important tumor and clinical characteristics, including resection margin status, were included for the studies as reported previously.¹⁵ The ESPAC-1 trial used a 2 × 2 factorial design and therefore randomized patients for both chemoradiotherapy and chemotherapy treatments. The meta-analysis included 477 patients who were randomized for chemoradiotherapy treatment (241 to receive chemoradiotherapy; 236 not to receive chemoradiotherapy) and 681 patients who were randomized for chemotherapy treatment (345 to receive chemotherapy; 336 patients not to receive chemotherapy).

Tumor characteristics across resection margin groups are presented in **Table 1**. Two hundred and seventy-eight (32%) patients had R1 resections and 591 (68%) had R0 resections at the time of randomization. Clinical and tumor characteristics generally appeared balanced between the R0 and R1 groups except for an increased proportion of node-positive patients in the R1 group (63% vs 49%).

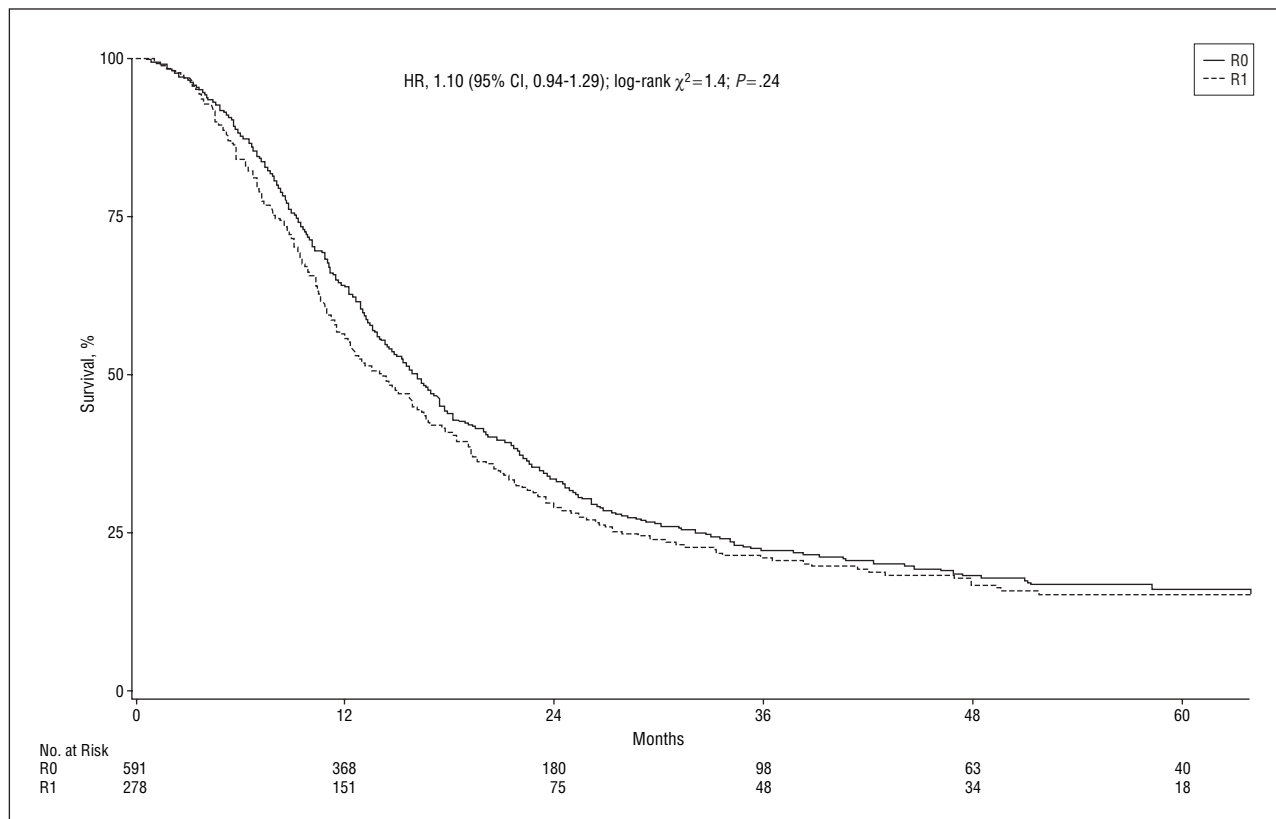


Figure 1. Overall survival according to resection margin status. CI indicates confidence interval; HR, hazard ratio.

SURVIVAL

Overall, 698 of the 875 patients (80%) had died, with a median follow-up of at least 24 months in surviving patients within individual trials and 44 months overall (interquartile range [IQR], 24.9-63.8 months). Two hundred twenty-six (81%) R1 patients and 467 (79%) R0 patients had died. Median follow-up of the 52 R1 patients who were still alive was 50 months (range, 0-105; IQR, 29-67 months) compared with 40 months (range, 0-106; IQR, 25-63 months) for the 124 living R0 patients.

Resection margin involvement was not a statistically significant prognostic factor (HR, 1.10; 95% CI, 0.94-1.29), log-rank $\chi^2=1.4$; $P=.24$) (**Figure 1**), though there was a trend for R1 patients to do worse, with a median survival of 14.1 months (95% CI, 11.9-16.4) compared with 15.9 months for patients with R0 resections (95% CI, 14.6-17.4) (**Table 2**). The 2-year and 5-year survival rates, respectively, were 33% and 16% for R0 patients and 29% and 15% for R1 patients.

Univariate log-rank analyses confirmed that tumor grade (log-rank $\chi^2=34.96$, $P<.001$), nodal involvement (log-rank $\chi^2=34.48$, $P<.001$), and tumor size (log-rank $\chi^2=6.07$, $P=.01$) were statistically significant prognostic factors of survival, though grade was missing from the Norwegian trial¹³ data and tumor size was missing from the Japanese¹⁷ trial data. Hazard ratio estimates (Table 2) were similar across resection margin groups for the effect of age and nodal involvement. Patients with moderately or poorly differentiated tumors had increased risk of death in both the R0 and R1 groups (less so in the R1 group). Increased

tumor size appeared to be less important in the R1 group compared with the R0 group.

CHEMORADIOTHERAPY TREATMENT

The overall pooled estimate of the HR indicated no significant difference in the risk of death with chemoradiotherapy (HR, 1.09; 95% CI, 0.89-1.32; stratified $P=.43$) with estimated median survivals of 15.8 months with chemoradiotherapy (95% CI, 13.9-18.1) and 15.2 months without (95% CI, 13.1-18.2).¹⁵ Two- and 5-year survival rates, respectively, were estimated at 30% and 12% with chemoradiotherapy and 34% and 17% without.¹⁵

The 188 R0 patients allocated to receive chemoradiotherapy had a median survival of 15.9 months (95% CI, 14.0-18.5) compared with 15.8 months in the 183 patients not allocated to chemoradiotherapy (95% CI, 13.4-20.1) (**Figure 2**). Two- and 5-year survival rates, respectively, were estimated at 30% and 10% with chemoradiotherapy and 38% and 20% without in R0 patients (**Table 3**). In the R1 group, the 53 patients allocated to chemoradiotherapy had a median survival of 14.7 months (95% CI, 11.5-20.5) compared with 11.2 months for the 53 patients not randomized to chemoradiotherapy (95% CI, 9.4-16.7). Two- and 5-year survival rates, respectively, were estimated at 30% and 18% with chemoradiotherapy and 19% and 8% without in R1 patients (Table 3).

Overall, there was a nonsignificant increase in the risk of death estimated at 9% with chemoradiotherapy (95% CI, -11% to 32%).¹⁵ There was significant heteroge-

Table 2. Median Survival Times According to Resection Margin Status

Resected Margin Status	Margin-Positive Patients (n=278)				Margin-Negative Patients (n=591)			
	No. of Patients	No. of Deaths	Median Survival, mo (95% Confidence Interval)	Hazard Ratio (95% Confidence Interval)	No. of Patients	No. of Deaths	Median Survival, mo (95% Confidence Interval)	Hazard Ratio (95% Confidence Interval)
Resection margin	278	226	14.1 (11.9-16.4)		591	467	15.9 (14.6-17.4)	
Age, y								
≤60	118	97	15.8 (11.4-19.6)		274	220	16.3 (13.8-18.1)	
>60	158	127	13.1 (11.0-15.8)	1.08 (0.83-1.40)	316	246	15.7 (14.0-17.7)	0.95 (0.79-1.14)
Nodal involvement								
No	99	74	20.0 (15.1-27.8)	1.69 (1.30-2.21)	290	209	17.7 (15.5-22.0)	
Yes	167	144	11.5 (10.5-14.0)		282	245	14.2 (12.5-16.1)	1.51 (1.25-1.81)
Tumor grade								
Well	57	46	16.7 (12.1-22.8)		134	92	22.4 (18.1-32.0)	
Moderate	133	111	12.3 (10.6-15.8)	1.26 (0.91-1.75)	273	225	16.3 (14.4-17.8)	1.51 (1.22-1.87)
Poor	40	35	11.9 (8.5-17.5)	1.45 (0.93-2.27)	107	95	10.7 (8.7-12.9)	2.31 (1.70-3.13)
Maximum tumor size, cm								
≤2	30	25	14.4 (10.3-19.2)		141	100	22.0 (17.4-25.2)	
>2	104	85	13.1 (10.6-17.5)	0.89 (0.56-1.42)	386	319	14.8 (13.3-16.5)	1.38 (1.12-1.70)
Chemoradiotherapy								
No	53	45	11.2 (9.4-16.7)		183	144	15.8 (13.4-20.1)	
Yes	53	41	14.7 (11.5-20.5)	0.72 (0.47-1.10)	188	155	15.9 (14.0-18.5)	1.19 (0.95-1.49)
Chemotherapy								
No	114	92	13.2 (10.5-17.6)		222	187	13.4 (12.2-16.4)	
Yes	109	91	15.0 (11.7-18.1)	1.04 (0.78-1.40)	236	175	20.8 (17.7-23.2)	0.65 (0.53-0.80)

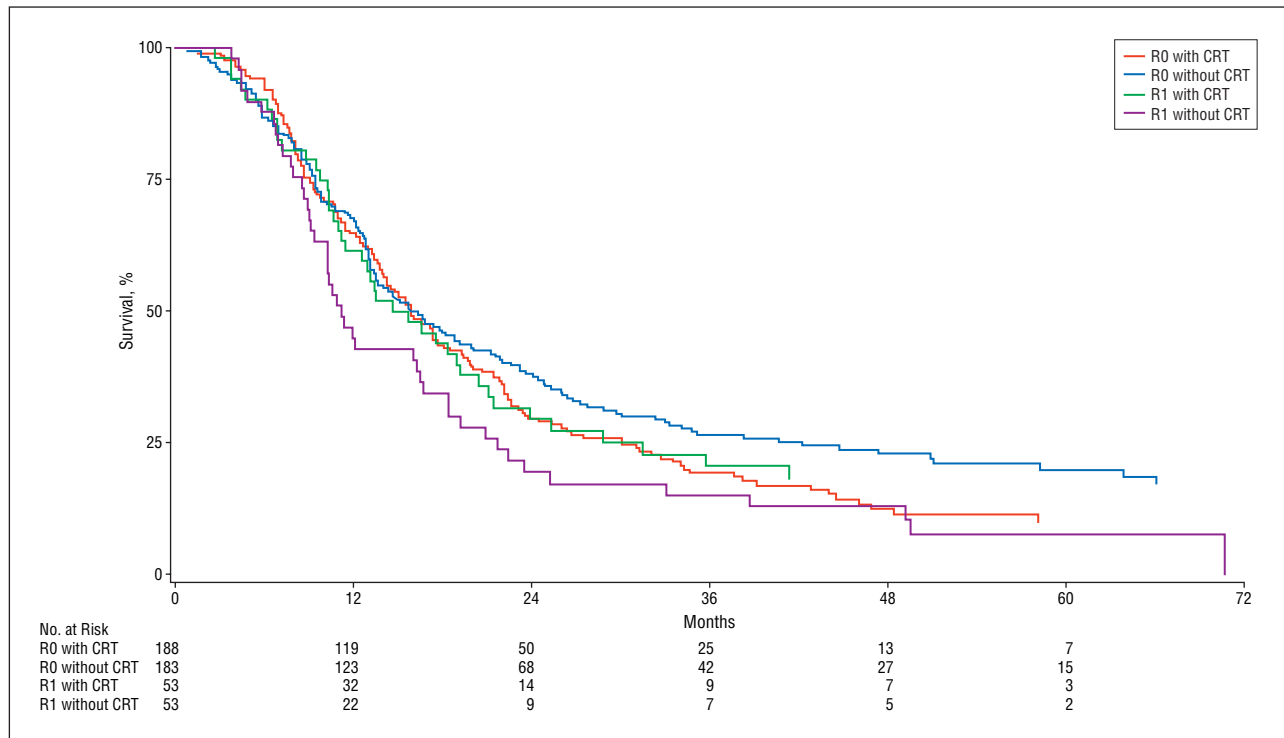


Figure 2. Overall survival rates according to resection margin status and whether or not chemoradiotherapy (CRT) was included in the treatment.

neity for the difference in the effect of chemoradiotherapy dependent on resection margin status ($\chi^2=4.2$, $P=.04$) in which chemoradiotherapy was estimated to be more effective in R1 patients: an estimated 28% reduction in the risk of death (HR, 0.72; 95% CI, 0.47-1.10) compared with an estimated 19% increased risk of death in R0 patients (HR, 1.19; 95% CI, 0.95-1.49).¹⁵

CHEMOTHERAPY TREATMENT

The overall pooled estimate of the HR indicated a 25% significant reduction in the risk of death with chemotherapy (HR, 0.75; 95% CI, 0.64-0.90; stratified $P=.001$), with median survival estimated at 19.0 months with chemotherapy (95% CI, 16.4-21.1) and 13.5 months with-

out (95% CI, 12.2-15.8).¹⁵ Two- and 5-year survival rates, respectively, were estimated at 38% and 19% with chemotherapy and 28% and 12% without.¹⁵

In the R0 group, the 236 patients allocated to chemotherapy had a 7-month survival advantage over the 222 patients randomized to no chemotherapy: 20.8 months (95% CI, 17.7-23.2) compared with 13.8 months (95% CI, 12.2-16.4) (**Figure 3**). Two- and 5-year survival rates, respectively, were estimated at 42% and 22% with chemotherapy and 27% and 10% without in R0 patients (Table 3). The effect was less apparent in the smaller subgroup of R1 patients: the median survival of the 109 patients allocated to chemotherapy was 15.0 months (95% CI, 11.7-18.1) compared with 13.2 months in the 114 patients randomized to no chemotherapy (95% CI, 10.5-

17.6). Two- and 5-year survival rates in R1 patients, respectively, were estimated at 29% and 14% with chemotherapy and 31% and 17% without (Table 3).

Overall, there was a reduction in the risk of death, estimated at 25%, in favor of chemotherapy (95% CI, 10%-36%).¹⁵ The beneficial effect of chemotherapy was apparent in the R0 subgroups but was not confirmed in the R1 subgroup. There was significant heterogeneity for the difference in the effect of chemotherapy dependent on resection margin status ($\chi^2=7.3$, $P=.007$) in which chemotherapy was estimated to be less effective in R1 patients: a 4% increased risk of death (HR, 1.04; 95% CI, 0.78-1.40) compared with 35% reduction in the risk of death in R0 patients (HR, 0.65; 95% CI, 0.53-0.80).¹⁵ The overall median survival according to randomized treatment and resection margins status is reported in **Table 4** and shown in **Figure 4** and **Figure 5**.

Table 3. Two- and Five-Year Survival Rates According to Resection Margin Status and Treatment

Resection Margin Subgroup	No. of Patients	Survival Rate (95% Confidence Interval)	
		2 y	5 y
CRT question			
R0 with CRT	188	0.30 (0.23-0.36)	0.10 (0.05-0.15)
R0 without CRT	183	0.38 (0.31-0.45)	0.20 (0.13-0.26)
R1 with CRT	53	0.30 (0.17-0.42)	0.18 (0.07-0.29)
R1 without CRT	53	0.19 (0.08-0.31)	0.08 (0-0.16)
CT question			
R0 with CT	236	0.42 (0.35-0.48)	0.22 (0.17-0.28)
R0 without CT	222	0.27 (0.21-0.33)	0.10 (0.05-0.14)
R1 with CT	109	0.29 (0.20-0.38)	0.14 (0.07-0.21)
R1 without CT	114	0.31 (0.22-0.40)	0.17 (0.10-0.24)

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy.

COMMENT

Ductal adenocarcinoma of the pancreas is considered a systemic disease at time of diagnosis with almost identical incidence and mortality rates. Surgical resection might be beneficial in prolonging survival; only in very few patients will the disease be cured radically. In a large population of well-selected, controlled patients with resections, the ESPAC-1 trial found that 18% of patients had R1 resections.⁹ R1 patients were reported to have only a marginally worse survival ($P=.10$), despite reports of a statistically strong effect on overall survival.^{5-7,11} Furthermore, overall almost half of the resected patients, irrespective of adjuvant treatment administered, experienced disease relapse only 12 months after operation,

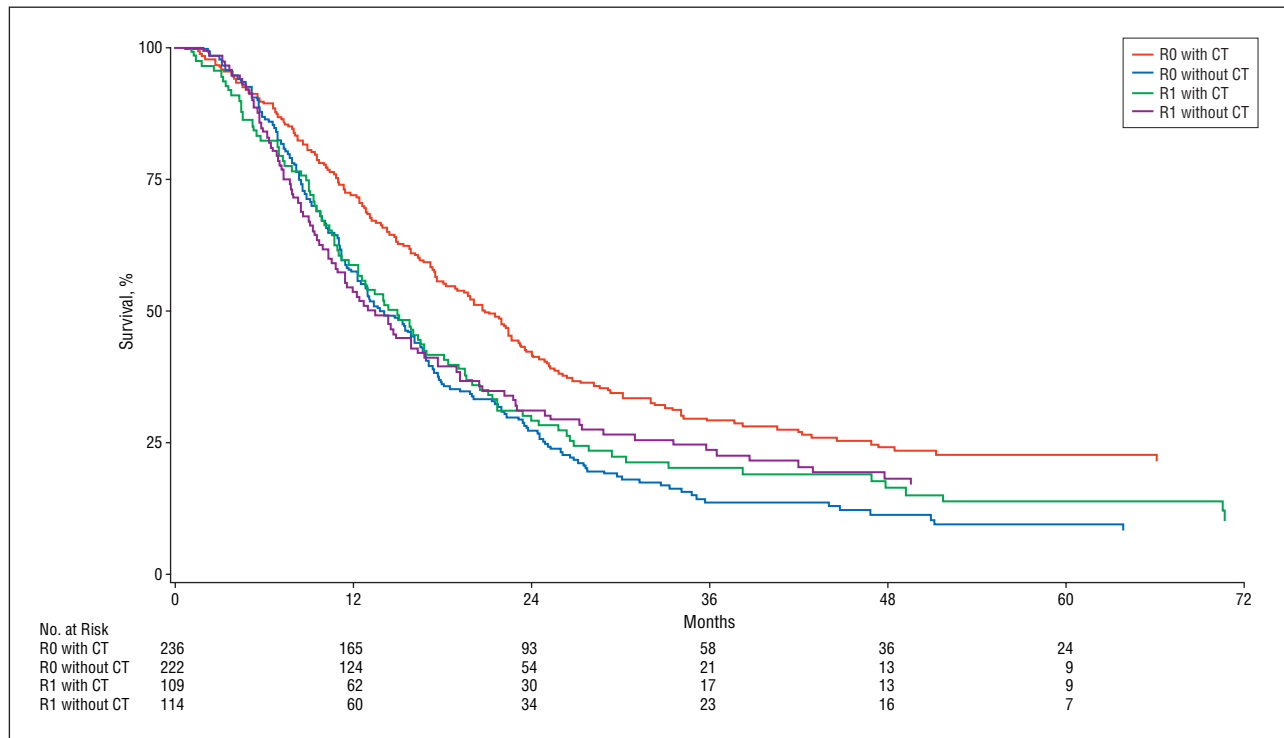


Figure 3. Overall survival rates according to resection margin status and whether or not chemotherapy (CT) was included in the treatment.

Table 4. Overall Median Survival According to Resection Margins Status and Different Combinations of Randomized Treatment

Actual Randomized Treatment	No. of Patients	No. of Deaths	Median Survival, mo (95% Confidence Interval)	Survival Rate (95% Confidence Interval)	
				12 mo	24 mo
R0 margins					
OBS	225	185	13.4 (12.3-16.1)	0.58 (0.52-0.65)	0.29 (0.23-0.36)
CRT	130	107	14.0 (12.5-15.9)	0.60 (0.51-0.68)	0.25 (0.17-0.32)
CT	178	127	20.1 (16.4-24.0)	0.71 (0.64-0.77)	0.42 (0.35-0.49)
CRT + CT	58	48	22.2 (17.5-26.7)	0.76 (0.65-0.87)	0.41 (0.28-0.53)
R1 margins					
OBS	130	106	11.9 (10.3-15.8)	0.49 (0.40-0.58)	0.27 (0.19-0.35)
CRT	39	29	17.5 (13.1-25.3)	0.71 (0.57-0.85)	0.35 (0.20-0.51)
CT	95	79	15.8 (12.3-19.6)	0.62 (0.52-0.72)	0.31 (0.22-0.41)
CRT + CT	14	12	10.7 (6.9-18.3)	0.36 (0.11-0.61)	0.14 (0-0.33)

Abbreviations: CRT, chemoradiotherapy; CRT + CT, chemoradiotherapy followed by chemotherapy; CT, chemotherapy; and OBS, observation.

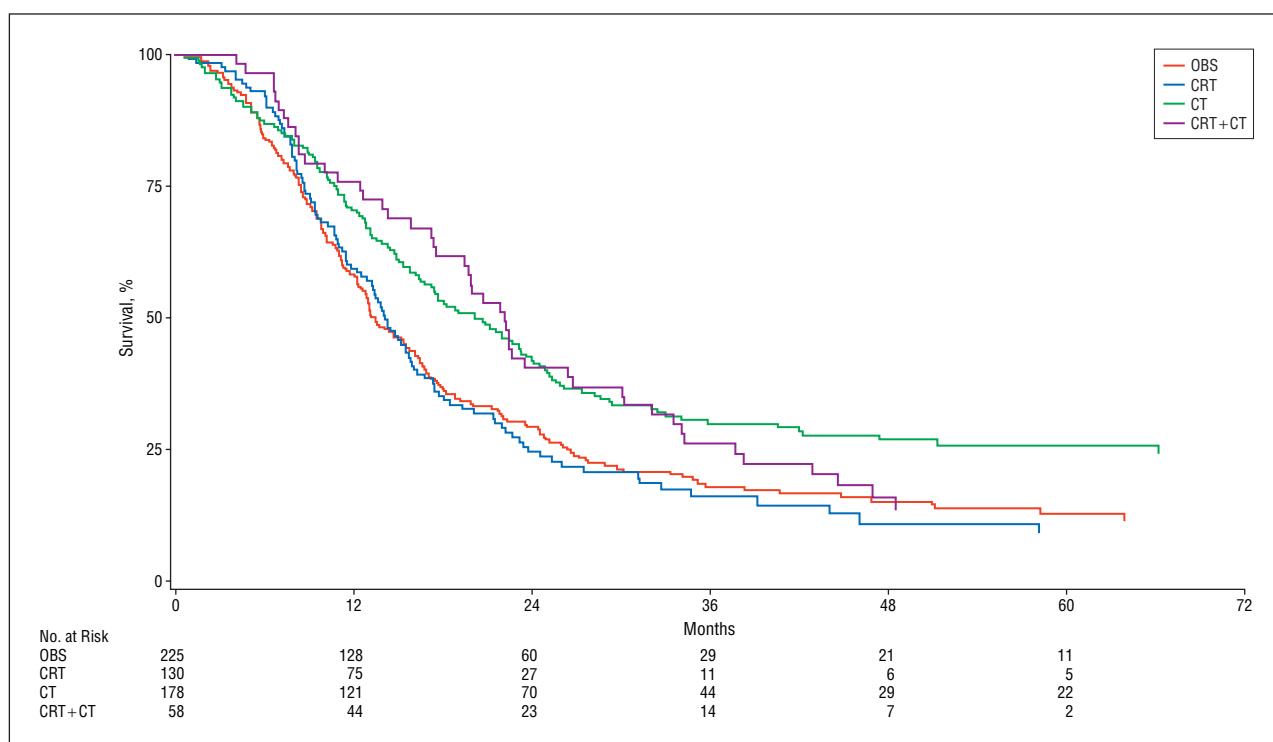


Figure 4. Overall survival according to different combinations of randomized treatment in patients who had clear resection margins (R0). CRT indicates chemoradiotherapy; CT, chemotherapy; and OBS, observation.

grossly more than the rate of R1 resections. In this regard, it is evident that the ductal pancreatic cancer must be considered a systemic disease even in those few cases of apparent R0 resections. This finding is confirmed by the results of the long-term follow-up trial by Takada et al¹⁷ in 2002. The 5-year disease-free survival of the 2 R0 subgroups of patients randomized (treated vs observed) was almost the same (13.3% vs 12.8%). The importance of this single tumor parameter and the influence on post-operative therapy is debatable, but for the same reason, it is mandatory to investigate the effect of adjuvant treatment, specifically in R1 patients. All the randomized controlled trials of adjuvant treatment for patients with resected pancreatic cancer were included in this study.^{8,9,13-17} A total of 278 R1 patients were identified, 106 of whom

were randomized for chemoradiotherapy (53 to receive and 53 not to receive chemoradiotherapy); 223 were randomized for chemotherapy (109 to receive and 114 not to receive chemotherapy). The ESPAC-1 trial used a 2 × 2 design, so that there was a group of R1 patients who were randomized for both chemoradiotherapy and chemotherapy treatments. Furthermore, 32% of all randomized patients within the meta-analysis had R1 resections influenced greatly by the Japanese trial¹⁷ in which 83% of the pancreatic ductal patients had resection margin positivity. With an overall median follow-up of 44 months in the surviving 177 patients in the meta-analysis, the mortality rates in R0 and R1 subgroups, respectively, were almost the same (79% vs 81%). The difference between the subgroups was small after 2 years

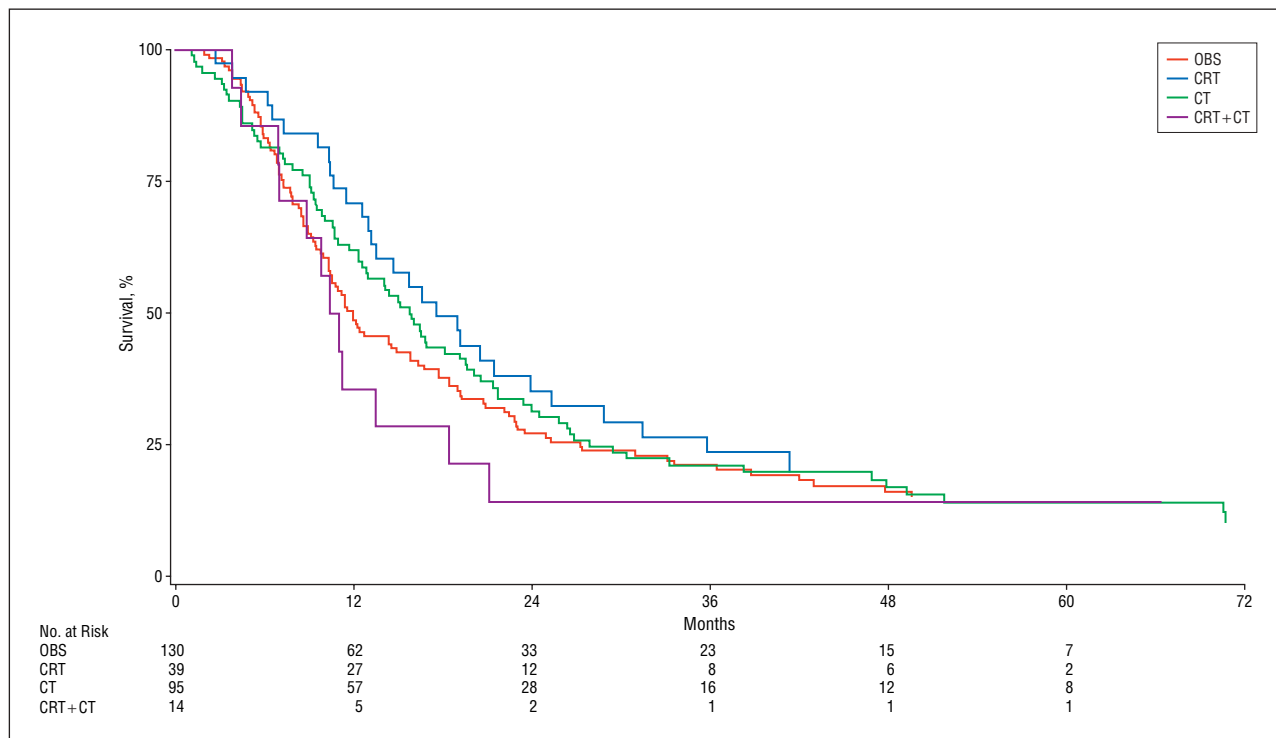


Figure 5. Overall survival according to different combinations of randomized treatment in patients who had microscopically involved resection margins (R1). CRT indicates chemoradiotherapy; CT, chemotherapy; and OBS, observation.

(33% vs 29%) and has almost vanished after 5 years (16% vs 15%). Tumor grade and size and nodal involvement were statistically significant prognostic factors of survival. The importance of resection margins positivity on survival was less evident in the meta-analysis (HR, 1.10; 95% CI, 0.94-1.29; log-rank $\chi^2=1.4$; $P=.24$) compared with previous studies.^{5-7,11} In particular, 2- and 5-year survival rates were almost equal in the 2 subgroups and the survival curves question whether the problem is related to having pancreatic cancer instead of receiving any adjuvant treatment. Moreover, this meta-analysis confirmed that chemoradiotherapy did not appear to improve overall survival for resected patients; R0 patients, in particular, did not appear to benefit from chemoradiotherapy. The meta-analysis revealed a possible beneficial effect for chemoradiotherapy within the R1 subgroup, with an estimated 28% reduction in the risk of death (HR, 0.72; 95% CI, 0.47-1.10) compared with an estimated 19% increased risk of death in R0 patients (HR, 1.19; 95% CI, 0.95-1.49).¹⁵ However, the R1 subgroup was underpowered, with only 106 patients included in this comparison. The meta-analysis demonstrated that chemotherapy did not appear to be as effective in the R1 subgroup, mimicking the effect of chemoradiotherapy in the R0 subgroup. Additional controlled trials are needed to find better treatments in patients with R1 resections for ductal adenocarcinoma of the pancreas.

Future prospective studies should work to precisely define positive resection margins and to better understand the relevance of different resection margins. Adjuvant trials in pancreatic cancer will be guided in part by the results of ongoing trials and, where available, how survival relates to margin involvement as well as the outcome of stud-

ies of new agents in advanced pancreatic cancer. The German Lilly phase III trial²⁰ compared adjuvant gemcitabine treatment with observation in 368 pancreatic cancer patients, with disease-free survival as the primary end point. Preliminary results indicated an advantage for gemcitabine treatment,²⁰ but the results are unlikely to demonstrate superiority over fluorouracil and folinic acid, as demonstrated in ESPAC-1, given an overall median survival of 21.6 months and a 5-year survival of 29%.⁹ The ESPAC-3 trial, an adjuvant trial of nearly 1000 patients, directly compares gemcitabine treatment with fluorouracil and folinic acid (the trial was close to achieving target accrual at the time of manuscript preparation).

The Radiation Therapy Oncology Group recently reported on the phase III adjuvant trial comparing gemcitabine treatment with fluorouracil-based chemoradiotherapy (with fluorouracil radiosensitization in both arms) in 442 analyzable patients of 538 randomized patients.²¹ There was no overall difference in survival; however, in further subgroup analysis among 330 patients with tumors in the head of the pancreas, there was better survival in the gemcitabine-based chemoradiotherapy group.²¹ With a median survival of only 18.8 months,²¹ however, this result is clearly inferior to the median survival achieved with chemotherapy alone in the ESPAC-1 trial.⁹ There is further disappointment for chemoradiotherapy in locally advanced pancreatic cancer from a recent phase III French trial,²² which had to be abandoned, because after 119 patients had been randomized, the survival was significantly worse for patients who had had chemoradiotherapy compared with gemcitabine alone.

Two agents, however, have shown great promise when combined with gemcitabine in locally advanced and meta-

static pancreatic cancer, resulting in significantly improved survival compared with gemcitabine alone.^{23,24} Of these, capecitabine,²³ an orally active fluoropyrimidine, is particularly attractive in the adjuvant setting because it has a higher tumor response rate compared with erlotinib,²⁴ an orally active tyrosine kinase inhibitor, and has a manageable toxicity. Thus, it is envisaged that the combination of gemcitabine and capecitabine must feature as the next major arm for a large adjuvant trial. With such a recent increase in patients involved in such trials, future meta-analyses should be able to further dissect the specific roles of adjuvant chemoradiotherapy and chemotherapy for patients with R1 tumors in a manner that is, at present, not feasible.

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Author Contributions: The principal investigator (Dr Neoptolemos) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Neoptolemos, Büchler, Dervenis, and Bassi are the lead ESPAC investigators who, along with Ms Stocken (biostatistician), were responsible for initiating the meta-analysis project and developing the protocol. In addition to the data from the ESPAC-1 trial, individual patient data were provided by the lead investigators of the European Organisation for Research and Treatment of Cancer trial (Drs Jeekel and Klinkenbijl), the Norwegian Pancreatic Trials Group (Dr Bakkevoid), and the Japanese Pancreatic Group (Drs Takada and Amano). **Study concept and design:** Butturini, Stocken, Wentz, Jeekel, Takada, Dervenis, Bassi, Büchler, and Neoptolemos. **Acquisition of data:** Butturini, Stocken, Jeekel, Klinkenbijl, Bakkevoid, Takada, Dervenis, Bassi, and Neoptolemos. **Analysis and interpretation of data:** Butturini, Stocken, Wentz, Jeekel, Klinkenbijl, Bakkevoid, Takada, Amano, Bassi, and Neoptolemos. **Drafting of the manuscript:** Butturini, Stocken, Wentz, Jeekel, Bakkevoid, Takada, Amano, Bassi, and Neoptolemos. **Critical revision of the manuscript for important intellectual content:** Butturini, Stocken, Jeekel, Klinkenbijl, Bakkevoid, Dervenis, Büchler, and Neoptolemos. **Statistical analysis:** Stocken, Wentz, Takada, and Amano. **Obtained funding:** Stocken and Neoptolemos. **Administrative, technical, and material support:** Stocken, Jeekel, Bakkevoid, and Neoptolemos. **Study supervision:** Butturini, Jeekel, Klinkenbijl, Bakkevoid, Bassi, Büchler, and Neoptolemos.

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INVITED CRITIQUE

Cancer of the pancreas is no disease for wimps. Carcinoma of the pancreas is increasing in incidence and ranks as the fourth leading cancer death in the United States. Indeed, this is one of the more deadly diseases, as can be seen by the close similarity of incidence and death statistics for the disease: in the United States in 2006 there were 33 730 new cases of the disease and 32 300 deaths.¹

The article by Butturini et al details the interaction of postoperative adjuvant therapy on survival in 875 patients with pancreatic cancer at various TNM stages. Patients were found to have either no disease (R0) or microscopic residual disease (R1) at the resection margin. This is a follow-up statistical analysis of a meta-analysis from 4 major study groups² and was organized to decide whether R1 patients should be included in a subgroup of R0 patients or whether they should be a separate category for purposes of treatment. In other words, do positive margins make a difference in postsurgical treatment or outcomes?

The authors found that the 2- and 5-year survival rates for R0 and R1 patients were virtually identical, that microscopic involvement of the margin was not a significant factor for survival, and that chemotherapy was better than chemoradiation in treating pancreatic cancer. While the authors should be commended for attempting to answer these critical questions, we should be cautious of stretching the science of statistical meta-analysis to a limit that begins to make alchemy look respectable. The scientific reader, like the buyer, must always beware.

The authors have combined a widely disparate group of patients, ranging all the way from those with tumors smaller than 2 cm in diameter and no nodal disease (TNM stage IA) to those patients with tumors larger than 2 cm in diameter and positive nodes (TNM stage IIB) into one group. They then divided this large heterogeneous group into those who did and did not have microscopic disease

at the resection margin. It is not unusual, therefore, to anticipate results that make one pause and reflect on whether or not these groups are truly comparable. For instance, looking at Table 3 and examining all patients with no further therapy, there appears to be relatively large differences in survival at 2 and 5 years between those allocated as controls to the various groups (range, 19%-38% at 2 years; 8%-20% at 5 years). Also, in that same category of patients, it appears that there is a survival advantage to having residual tumor in the patients (R0 patients with no chemotherapy had a 10% 5-year survival vs R1 patients with no chemotherapy who had a 17% 5-year survival). Obviously, this does not make biologic sense, but it does illustrate the danger of attempting to conclude too much from aggregated data and questions the overall conclusions drawn from this meta-analysis.

However, this study does emphasize the critical need for a large, carefully controlled, randomized trial to answer the question of which cancer patients will not benefit from additional chemotherapy and/or irradiation. As American health care costs continue to skyrocket, we need valid data to help redirect precious resources to use for those areas in which true benefit has been established. We are running out of money and cannot afford to do otherwise.

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