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ORIGINAL REPORT

Optimal Duration and Timing of Adjuvant Chemotherapy After Definitive Surgery for Ductal Adenocarcinoma of the Pancreas: Ongoing Lessons From the ESPAC-3 Study

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ABSTRACT

Purpose
Adjuvant chemotherapy improves patient survival rates after resection for pancreatic adenocarcinoma, but the optimal duration and time to initiate chemotherapy is unknown.

Patients and Methods
Patients with pancreatic ductal adenocarcinoma treated within the international, phase III, European Study Group for Pancreatic Cancer–3 (version 2) study were included if they had been randomly assigned to chemotherapy. Overall survival analysis was performed on an intention-to-treat basis, retaining patients in their randomized groups, and adjusting the overall treatment effect by known prognostic variables as well as the start time of chemotherapy.

Results
There were 985 patients, of whom 486 (49%) received gemcitabine and 499 (51%) received fluorouracil; 675 patients (68%) completed all six cycles of chemotherapy (full course) and 293 patients (30%) completed one to five cycles. Lymph node involvement, resection margins status, tumor differentiation, and completion of therapy were all shown by multivariable Cox regression to be independent survival factors. Overall survival favored patients who completed the full six courses of treatment versus those who did not (hazard ratio [HR], 0.516; 95% CI, 0.443 to 0.601; $P < .001$). Time to starting chemotherapy did not influence overall survival rates for the full study population (HR, 0.985; 95% CI, 0.956 to 1.015). Chemotherapy start time was an important survival factor only for the subgroup of patients who did not complete therapy, in favor of later treatment ($P < .001$).

Conclusion
Completion of all six cycles of planned adjuvant chemotherapy rather than early initiation was an independent prognostic factor after resection for pancreatic adenocarcinoma. There seems to be no difference in outcome if chemotherapy is delayed up to 12 weeks, thus allowing adequate time for postoperative recovery.

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INTRODUCTION

Pancreatic ductal adenocarcinoma is a highly challenging disease with a 5-year survival rate of less than 5%.[1] Although most patients present with advanced disease, the best outcomes are seen in patients who undergo resection of their primary tumor at specialized centers.[2,3] Surgery alone achieves a 5-year survival rate of approximately 10%,[3] whereas a number of randomized studies have shown improved survival rates with the addition of adjuvant chemotherapy after potentially curative resection.[4-10] Thus, 5-year survival figures in the European Study Group for Pancreatic Cancer (ESPAC) –1 study were 8% for surgery alone versus 21% when adding fluorouracil (FU) and folinic acid after surgery.[5,6]

The ESPAC-3 trial,[8] the largest adjuvant study in this setting, was a prospective, randomized phase III chemotherapy study of FU and folinic acid (n = 551) versus gemcitabine (n = 537); a third, observation-alone arm was closed after the definitive results of

ESPAC-1.[6] The results of ESPAC-3 showed no significant differences between the two treatment arms with a median survival of 23.0 months in the FU arm and 23.6 months in the gemcitabine arm, and with no differences in global quality of life scores although gemcitabine had an improved safety profile.[8]

In practice, adjuvant chemotherapy is initiated within a few weeks from the date of surgery. Although survival rates have been shown not to be affected by postoperative complications,[8,11] it is unknown whether the use of adjuvant chemotherapy should still start as soon as possible after surgery or if it may be safely delayed to allow further postoperative recovery without compromising long-term survival. Also, it is not known whether the full six cycles of adjuvant chemotherapy need to be administered or whether fewer cycles may have a similar survival benefit.

A number of preclinical observations in cancer would support the concept of early initiation of adjuvant chemotherapy. Metastasis is an early event in the development of pancreatic cancer[12] and removal of a primary tumor may accelerate growth of micrometastases,[13] potentially causing the release of growth factors that may stimulate micrometastases at distant sites.[14] In addition, delay in starting treatment may result in the establishment of drug-resistant micrometastases[15] and an increase in angiogenesis in the vascular bed surrounding metastases.[16]

Within the ESPAC-3 protocol, patients were to start allocated adjuvant chemotherapy within 6 weeks of surgery, although patients with delayed postoperative recovery were allowed to wait up to 12 weeks.[8] Previous multivariable analysis had identified tumor grade, tumor size, nodal status, performance status, and smoking status as significant independent prognostic factors of overall survival.[8] We performed a further analysis to investigate the effect that the time between surgery and the start of chemotherapy, as well as the completion of planned chemotherapy, had on the long-term survival of patients in this trial.

PATIENTS AND METHODS

Patient Selection

Patients with pancreatic ductal adenocarcinoma were selected from the ESPAC-3 (version 2) trial, an open label, international, randomized phase III study to investigate whether gemcitabine was superior to FU and folinic acid (Trial Registration details: Old CTA Ref., 12155/0001/001; New CTA Ref., 12155/0207/001; Former DDX Ref., MF8000/9956: ISRCTN, 37494643). Patients initially randomly assigned to the observation arm are not included in this analysis. The study was performed after approval from relevant research ethics committees (MREC: 99/8/74).

Statistical Analysis

Analysis was carried out on the long-tem overall survival measured from the date of resection to the date of death from any cause. Patients who did not die during the course of the trial were censored at the date last seen alive. Survival estimates were calculated using the method of Kaplan and Meier[17] and were compared across biologic groups using log-rank tests.[18] Median and 95% CIs of 24-month and 60-month survival estimates were calculated. Multivariable Cox regression[19] techniques were used to adjust the overall treatment effect by all important prognostic variables on a complete case basis. Covariates were included in the multivariable model using forward stepwise selection based on the Akaike Information Criterion if they had an unadjusted log-rank significance of $P < .25$.[20] Initial exploratory analyses showed that the time to the start of treatment had a different effect depending on whether or not a patient completed therapy, which was therefore included as a nested effect. Here, the model allows separate terms to describe the effect of time to treatment, depending on whether or not a patient completed the planned six cycles of therapy.

Following analysis of the full data set, a subgroup sensitivity analysis was carried out using the landmark method[21] by removing from the data any patient who died within 8 months after surgery. This analysis was performed to remove any potential bias as a result of treatment-related deaths. As the choice of an 8-month landmark point was somewhat arbitrary, further sensitivity analyses using landmarks of 9 to 12 months were also considered. Time to treatment was primarily modeled as a continuous covariate, although sensitivity analyses also include time to treatment as a variable dichotomized at the median time from surgery until treatment. The median was 8.2 weeks (interquartile range [IQR], 6.7 to 9.7 weeks) rounded down to 8 weeks. The assumption of proportional hazards was satisfied via assessment of Schoenfeld residuals.[22]

Analyses were carried out using the statistical package R (version 2.13.1) on an intention-to-treat basis, retaining patients in their randomized treatment groups and including protocol violators and ineligible patients. A two-sided significance level of $P < .05$ was used throughout.

RESULTS

There were 985 patients in the analysis (Fig 1). Patients' clinical, surgical, and pathologic details are listed in Table 1; 486 patients (49%) were randomly assigned to the gemcitabine arm and 499 patients (51%) to the FU and folinic acid arm. Previous analyses indicating no significant overall survival difference between the two therapies was confirmed in this subset.[8] There were 674 patients (68%) who completed all six cycles of intended therapy, 294 patients (30%) received one to five cycles of therapy, and 17 patients (2%) had incomplete data regarding the number of cycles they received. There were similar proportions of patients receiving one to five cycles in each of the chemotherapy arms (FU, 32%; gemcitabine, 28%, respectively).

Overall Survival

The overall median follow-up period was 58.7 months (IQR, 49.1 to 65.3 months), 59.1 months (IQR, 50.0 to 68.9 months) for patients who completed all cycles of therapy and 56.0 months (IQR, 47.4 to 63.1 months) for those who did not. Seven hundred sixty-seven patients (78%) died; of the patients who died, 509 (75%) of 674 patients completed all cycles and 245 (84%) of 294 patients did not.

The overall median survival was 23.7 months (95% CI, 22.0 to 25.4). The effect on overall survival of the time between surgery and the start of treatment for patients who received all six cycles of planned therapy and those who received fewer than six cycles (including and excluding patients who died within 8 months of surgery) is shown in Figures 2 and 3 respectively. Statistical analyses of overall survival by clinical characteristics for the full patient set are listed in Appendix Table A1 (online only). Time to starting chemotherapy did not influence overall survival for the full study population. The unadjusted effect of time between surgery and the start of therapy as a continuous variable was not significant (hazard ratio [HR], 0.985; 95% CI, 0.956 to 1.015; $\chi^2_{LR(1DF)} = 0.99$, $P = .32$).

Median survival for patients commencing within 8 weeks of surgery was 22.6 months (95% CI, 21.3 to 25.5 months) compared with 24.2 months (95% CI, 22.3 to 26.4 months) for those commencing later than 8 weeks (HR, 0.946; 95% CI, 0.82 to 1.09; $\chi^2_{LR(1DF)} = 0.594$; $P = .441$; Appendix Fig A1 [online-only]). Median survival was 28.0 months (95% CI, 26.1 to 30.9 months) for patients who completed all cycles of therapy versus 14.6 months (95% CI, 12.5 to 16.9

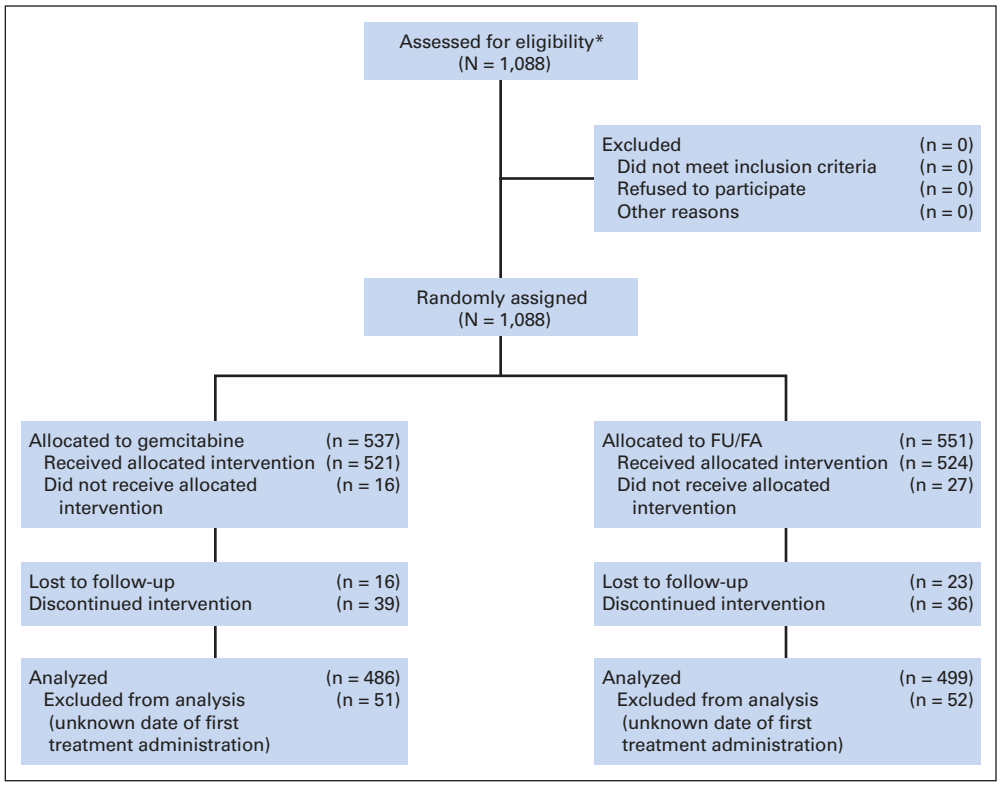

Fig 1. CONSORT diagram. (*) Screening data on number excluded and reasons not collected as part of the trial (pre 2000 set-up). FU/FA, fluorouracil and folinic acid.

months) for those who did not complete therapy (HR, 0.516; 95% CI, 0.443 to 0.601; $\chi^2_{LR(1DF)} = 74.627$; $P < .001$; Appendix Fig A2). Overall survival in six groups by the number of cycles received is shown in Appendix Figure A3. Considering only the cohort of patients that had fewer than six cycles of therapy, chemotherapy start time was an important survival factor, in favor of late start for treatment (HR, 0.919; 95% CI, 0.868 to 0.973; $\chi^2_{(1DF)} = 8.35$; $P = .004$).

There were no significant differences in the reasons for discontinuing treatment between the early and late start to chemotherapy groups (Table 2).

Smoking status, baseline performance status, tumor grade of differentiation, lymph node involvement, local invasion, tumor stage, and resection margins were all considered categoric variables; age and the proportion of therapy received were considered continuous variables. The assumption of proportional hazards was satisfied.[22] There was no evidence that there was a country effect (data not shown). The time between surgery and the start of therapy was not included as a main effect in the multivariable model ($P = .319$) but was included as an effect nested within the completion of therapy variable.

A model based on 949 patients (741 deaths) identified lymph node involvement, completion of therapy, resection margins, and tumor differentiation as important independent survival factors. Postoperative CA19-9 was not considered for inclusion in the Cox model because of the large number of missing values. The time to the start of therapy was only identified as an important factor for the subgroup of patients who did not complete therapy with reduced survival observed in patients starting chemotherapy early ($P = .004$).

Recurrence-Free Survival

The median recurrence-free survival rate for all patients was 14.29 months (95% CI, 13.47 to 15.14 months) and was not influenced by time to starting chemotherapy (Appendix Table A2). Median recurrence-free survival for patients commencing within 8 weeks of surgery was 13.83 months (95% CI, 12.41 to 15.46 months) compared with 14.82 months (95% CI, 13.62 to 16.34 months) for those starting later than 8 weeks (Appendix Figure A4). The unadjusted effect of time between surgery and the start of therapy as a continuous variable was not significant (HR, 0.988; 95% CI, 0.96 to 1.016; $\chi^2_{LR(1DF)} = 0.70$; $P = .40$; Appendix Table A3). Median recurrence-free survival was 16.56 months (95% CI, 15.14 to 17.94 months) for patients who completed all cycles of therapy versus 8.90 months (95%CI, 7.79 to 10.35 months) for those who did not (HR, 0.564; 95% CI, 0.49 to 0.66; $\chi^2_{LR(1DF)} = 58.541$; $P < .001$). When considering only the cohort of patients who had fewer than six cycles of therapy, chemotherapy start time was an important survival factor, in favor of late start for treatment (HR, 0.937; 95% CI, 0.885 to 0.992; $\chi^2_{(1DF)} = 5.08$; $P = .012$).

Factors with a log-rank significance of $P < .25$ were considered for inclusion in the multivariable Cox model.

A model based on 949 patients (797 deaths) identified lymph node involvement, completion of therapy, resection margins, and tumor differentiation as important independent survival factors. The assumption of proportional hazards was satisfied.[22] The time to the start of therapy was only identified as an important factor for the subgroup of patients who did not complete therapy with reduced recurrence-free survival observed in patients starting chemotherapy early ($P = .012$; Appendix Table A3).

Subgroup Analysis, Excluding Early Deaths

A landmark analysis was carried out, excluding all patients who died within 8 months of surgery (n = 889). Of these, 449 patients (50%) were randomly assigned to gemcitabine and 440 patients (50%)

Table 1. Patient, Surgery, and Pathologic Characteristics at Randomization

Characteristic	Full Data Set						Subgroup of Patients Who Did Not Experience an Early Death					
	Early Treatment < 8 Weeks After Surgery (n = 457)		Late Treatment > 8 Weeks After Surgery (n = 528)		Total (n = 985)		Early Treatment < 8 Weeks After Surgery (n = 408)		Late Treatment > 8 Weeks After Surgery (n = 481)		Total (n = 889)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years												
Median	61		65		63		61		65		63	
IQR	55-68		58-70		56-70		55-68		58-70		56-69	
Sex												
Female	203	44	234	44	437	44	177	43	207	43	384	43
Male	254	56	294	56	548	56	231	57	274	57	505	57
Arm												
FU/FA	233	51	266	50	499	51	213	52	236	49	449	51
Gemcitabine	224	49	262	50	486	49	195	48	245	51	440	49
Baseline performance status												
0	177	39	175	33	352	36	161	39	163	34	324	36
1241	53	284	54	525	53	211	52	255	53	466	52	
2	39	9	69	13	108	11	36	9	63	13	99	11
Diabetic												
No	341	76	379	74	720	75	302	76	351	75	653	76
Yes	106	24	130	26	236	25	96	24	115	25	211	24
Smoking status												
Never	173	41	199	41	372	41	160	42	180	41	340	41
Past	173	41	211	44	384	42	150	40	197	44	347	42
Present	77	18	75	15	152	17	69	18	67	15	136	17
Surgery												
Distal panc	41	9	32	6	73	8	39	10	31	7	70	8
Pylorus Pres^{ng}	154	34	136	26	290	30	135	34	126	27	261	30
Total panc	16	4	22	4	38	4	14	3	17	4	31	4
Whipples	238	53	328	63	566	59	213	53	298	63	511	59
Extent of resection												
Standard	29	7	48	10	77	8	285	73	346	75	631	74
Radical	92	21	75	15	167	18	84	21	69	15	153	18
Extended radical	317	72	379	75	696	74	23	6	44	10	67	8
Maximum tumor diameter, mm												
Median	30		30		30		30		30		30	
IQR	22-40		23-40		23-40		22-39		23-39		22-39	
Tumor grade differentiation												
Poor	105	23	124	24	229	24	84	21	108	23	192	22
Moderate	284	63	323	63	607	63	260	64	298	64	558	64
Well	64	14	67	13	131	14	61	15	63	13	124	14
Lymph node involvement												
Negative	138	30	141	27	279	28	127	31	129	27	256	29
Positive	319	70	385	73	704	72	281	69	350	73	631	71

(continued on following page)

Table 1. Patient, Surgery, and Pathologic Characteristics at Randomization (continued)

Characteristic	Full Data Set						Subgroup of Patients Who Did Not Experience an Early Death					
	Early Treatment < 8 Weeks After Surgery (n = 457)		Late Treatment > 8 Weeks After Surgery (n = 528)		Total (n = 985)		Early Treatment < 8 Weeks After Surgery (n = 408)		Late Treatment > 8 Weeks After Surgery (n = 481)		Total (n = 889)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Resection margins												
Negative	303	66	327	62	630	64	275	67	295	61	570	64
Positive	154	34	201	38	355	36	133	33	186	39	319	36
Local invasion												
No	284	64	275	53	559	58	252	64	242	51	494	57
Yes	158	36	244	47	402	42	142	36	231	49	373	43
Tumor stage												
I	47	10	47	9	94	10	44	11	43	9	87	10
II	130	29	149	29	279	29	117	29	138	29	255	29
III	252	56	312	60	564	58	221	55	282	59	503	57
IVa	23	5	13	2	36	4	22	5	11	2	33	4
Postoperative complications												
No	371	83	357	69	728	75	331	83	320	68	651	75
Yes	78	17	159	31	237	25	69	17	150	32	219	25
Postoperative CA 19-9 level, KU/l												
Number	356		382		738		316		348		664	
Median	3		3		3		3		3		3	
IQR	2-4		2-4		2-4		2-4		2-4		2-4	
Percentage of therapy received												
Median	90		86		89		93		89		90	
IQR	65-100		57-100		61-100		74-100		66-100		67-100	
Disease recurrence within 12 months of surgery												
No	293	64	360	68	653	66	266	65	333	69	599	67
Yes	164	36	168	32	332	34	142	35	148	31	290	33
Completed six cycles of therapy												
No	123	27	171	33	294	30	85	21	135	28	220	25
Yes	327	73	347	67	674	70	323	79	346	72	669	75

Abbreviations: FU/FA, fluorouracil plus folinic acid; IQR, interquartile range; panc, pancreatectomy; Pres^{ng}, preserving.

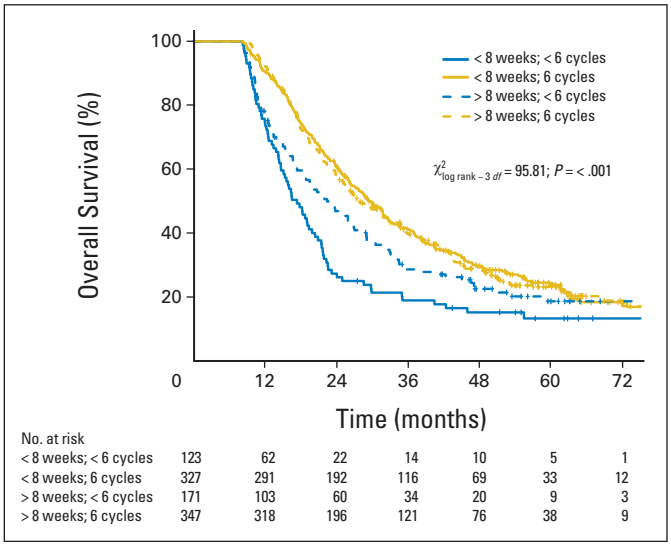

Fig 2. Kaplan-Meier plot of the effect of overall survival of the time between surgery and the start of treatment for all patients who received all planned therapies (six cycles) and those who did not (< six cycles), including patients who died within 8 months of surgery.

to FU plus folinic acid; 408 patients (46%) received adjuvant chemotherapy within 8 weeks after surgery and 481 patients (54%) received adjuvant chemotherapy later than 8 weeks (Table 1).

Overall median follow-up time was 59.1 months (IQR, 50.0 to 65.8 months); this was 57.8 months (IQR, 49.5 to 71.2 months) for the early-treatment group and 59.4 months (IQR, 50.0 to 65.0 months) for the late-treatment group. There were 685 patient deaths (77%), 316 (79%) in the early-treatment group and 369 (77%) in the late-treatment group. Statistical analyses of overall survival by clinical characteristics are listed in Appendix Table A4.

The median survival was 25.9 months (95% CI, 24.1 to 27.7 months). Survival was 25.5 months (95% CI, 22.9 to 28.6 months) for the early-treatment group and 25.9 months (95% CI, 23.9 to 28.9 months) for the late-treatment group, and the unadjusted analysis of the continuous variable was not significant (HR, 0.985; 95% CI, 0.95 to 1.02; $\chi^2_{\text{LR(1DF)}} = 0.831$; $P = .362$). Median survival was 28.35 months (95% CI, 26.1 to 31.0 months) for patients who completed all cycles of therapy versus 19.3 months (95% CI, 17.3 to 21.8 months) for those who did not complete therapy (HR, 0.667; 95% CI, 0.56 to 0.79; $\chi^2_{\text{LR(1DF)}} = 22.06$; $P < .001$). In patients who had fewer than six cycles of therapy, the median survival was 16.5 months (95% CI, 14.6 to 20.3 months) for the early-treatment group and 21.9 months (95% CI, 18.5 to 26.8 months) for the late-treatment group ($\chi^2_{\text{LR(1DF)}} = 4.33$; $P = .038$).

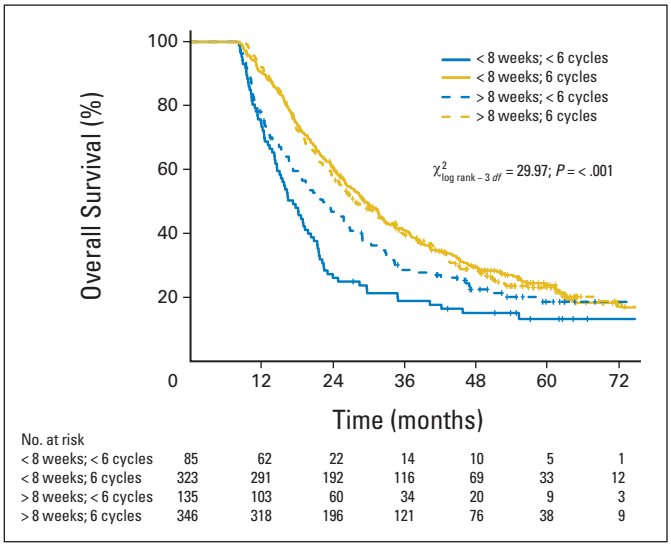

Fig 3. Kaplan-Meier plot of the effect of overall survival of the time between surgery and the start of treatment for patients who receive all planned therapies (six cycles) and those who did not (< six cycles), after excluding any patients who died within 8 months of surgery.

A model based on 872 patients (674 deaths) identified lymph node involvement, the completion of therapy, tumor grade differentiation, and resection margins as independent survival factors. The assumption of proportional hazards was satisfied.[22] There was no significant difference in overall survival with respect to the time between surgery and randomization (data not shown). A further subgroup analysis was carried out to investigate only the group of patients who did not complete therapy. Again, earlier therapy was shown to be detrimental to long-term survival ($_{\text{adj}}$HR, 0.934; $P = .046$; analysis not included).

Further analyses of overall survival were carried out using 9 to 12 months as additional landmark points. These show that there are no major changes in the interpretation of the multivariable analyses owing to the choice of landmark used or for which time to the start of treatment was considered as a dichotomized variable (Appendix Table A5).

Inclusion of Postoperative CA19-9 in Analysis

CA19-9 levels were missing in 247 patients as this test was not routinely available at all institutions. Multivariable Cox models were fitted both with and without this variable and confirmed that CA19-9 was an independently significant variable (data not shown).

Subgroup Analysis of the Early-Deaths Group

There were 96 patients who died within 8 months after surgery (early death) of whom 58 (60%) had disease progression before death compared with 747 (76%) of 985 patients in the full data set. The 30-day chemotherapy mortality rate was eight (0.8%) of 985 patients, suggesting that early deaths were not chemotherapy-related. The cause of death for patients with an early death was not significantly different to other patients (Appendix Table A4). The overall survival of the early-death group of patients was not affected by when patients started therapy (Appendix Fig A5). The effects of including the early-death group of patients in the full analysis produced similar conclusions at the 5% level of significance.

DISCUSSION

Surgical resection followed by chemotherapy with FU and folinic acid, gemcitabine, or *S*-1 (oral fluoropyrimidine-tegafur/gimeracil/oteracil combination capsule) offers the best chance of long-term cure for patients with pancreatic cancer.[4-10] In keeping with other adjuvant strategies for most solid tumors, treatment is usually planned to start as soon as possible postoperatively. Pancreas cancer surgery is however associated with a high morbidity so patients do not all recover at

Table 2. Reasons for Discontinuing Treatment by Time to Start of Therapy and Details of Cause of Death Comparing Early and Later Deaths

	Time Between Surgery and Start of Therapy					
	< 8 Weeks (n = 457)		> 8 Weeks (n = 528)		Total (n = 985)	
Reason for Discontinuation	No. of Patients	%	No. of Patients	%	No. of Patients	%
Toxicity	153	33	198	38	351	36
Consultant decision	43	9	47	9	90	9
Patient decision	27	6	51	10	78	8
Recurrent disease	28	6	43	8	71	7
Death	4	1	3	1	7	1
Missing	202	44	186	35	388	39
	Early Death (within 8 months of surgery)					
	No (n = 889)		Yes (n = 96)		Total (n = 985)	
Cause of Death	No. of Patients	%	No. of Patients	%	No. of Patients	%
Recurrent disease	524	59	50	52	574	58
Other cause with recurrent disease	30	3	4	4	34	4
Other cause without recurrent disease	23	3	11	11	34	4
Missing	108	12	17	18	125	13
Censored	204	23	14	15	218	22

the same rate. Before surgery, many patients may already be nutritionally compromised from main pancreatic duct and main bile-duct obstruction and may also be recovering from obstruction jaundice and related sepsis. It is not known whether delaying treatment to allow for a full postoperative recovery before starting adjuvant chemotherapy affects long-term survival.

Computational modeling of pancreatic cancer therapy has predicted that aggressive full-dose systemic therapy was needed to suppress tumor proliferation and that earlier initiation had a better survival than a later start.[23] This model was developed on a group of 101 pancreatic patients who had consented for autopsy and then validated on another set of 127 patients who underwent adjuvant radiation therapy and chemotherapy after their resections.[23] Nevertheless, such a study based on retrospective cohorts has underlying biases in patient selection and biases in the choice of adjuvant treatments that will influence survival. To better test these hypotheses, the intrinsic biases can be minimized by appropriate statistical modeling and sensitivity analyses of data from prospective randomized controlled trials.

This study was an intention-to-treat analysis of 985 eligible patients randomly assigned to one of two equally effective chemotherapy arms with exclusion of surgery-alone patients. The best recurrence-free and overall survival was observed in patients who had received all of the planned six cycles of treatment compared with those who had received between one and five cycles only. For patients who had completed all six cycles of chemotherapy, there was no difference in overall survival whether treatment was started early, namely within 8 weeks of surgery, or later, at 8 to 12 weeks after surgery. In patients who completed fewer than six cycles of chemotherapy, there was reduced recurrence-free and overall survival when starting treatment early, which may be related to insufficient time-dependent recovery from postoperative immune suppression.[24-26]

These findings held true after adjusting for independent survival factors, including lymph node involvement, resection margin status, and tumor differentiation, with completion of therapy remaining an independent predictor of survival. In the multivariable analysis, the time to the start of therapy was only identified as an important factor for the subgroup of patients who did not complete all six cycles of chemotherapy, with reduced recurrence-free and overall survival when starting treatment early. CA19-9 levels, in keeping with previous studies, was again shown to be an independent prognostic variable,[27-31] but was not included in the final model in order to focus on the primary questions and extend the number of sensitivity analyses.

A further potential bias could arise by including patients who experience early death as a result of disease progression and, hence, might not complete all six cycles of chemotherapy. Thus, a further sensitivity analysis was undertaken after excluding patients who had died within 8 months after surgery. Analysis of this subgroup of the remaining 889 patients again showed the improved overall and recurrence-free survival effects of fully completing the planned chemotherapy was maintained. The requirement for completing all six cycles of adjuvant chemotherapy after pancreatic cancer resection to obtain the best survival may have contributed to the lack of randomized phase III data to support the use of adjuvant chemoradiotherapy as the total dose of adjuvant systemic chemotherapy is reduced in this context,[5,6,32-34] although there may be other reasons.[35,36]

Completion of all six cycles of adjuvant chemotherapy was an independent favorable prognostic variable. There was no survival disadvantage from delaying the start of treatment for up to 12 weeks after surgery. Conversely, there was no survival advantage for starting early treatment, within 8 weeks of surgery. In routine clinical practice, though it is not possible to know in the immediate postoperative setting whether a patient will go on to complete the full course of treatment, ensuring adequate postoperative recovery is likely to maximize this chance. Patients who feel stronger after a slightly longer period of postoperative convalescence may be more likely to stay the full course of adjuvant chemotherapy. Thus, the

key message from this study is to delay the start of adjuvant chemotherapy until the patient is fully recovered and aim to give them the full six cycles of treatment.

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Table A1. Univariable and Multivariable Regression Analysis of Survival Factors

Factor	No. of Patients	No. of Deaths	Survival Rates (%)		Survival Median	95% CI	Hazard Ratio	95% CI	Log-Rank Test	
			24 Months	60 Months					χ^2	*P*
Univariable Analyses (n = 985)										
Age	Continuous variable						0.998	0.991 to 1.007	0.14	.711
Sex										
Female	437	327	51	21	25.39	22.8 to 27.83				
Male	548	440	47	17	22.11	20.76 to 24.84	1.161	1.006 to 1.34	4.19	**.041**
Arm										
FU/FA	499	392	49	18	23.72	21.48 to 25.85				
Gemcitabine	486	375	49	20	23.69	21.68 to 26.41	0.969	0.841 to 1.116	0.19	.663
Baseline performance status										
0	352	265	55	22	25.85	23.85 to 29.01				
1	525	416	47	16	23.00	21.39 to 25.53	1.147	0.983 to 1.338		
2	108	86	40	18	20.93	17.44 to 24.01	1.285	1.007 to 1.639	5.18	.075
Diabetic										
No	720	564	51	19	24.28	22.47 to 26.08				
Yes	236	183	43	17	21.16	18.89 to 23.92	1.103	0.934 to 1.303	1.33	.249
Smoking status										
Never	372	283	54	22	26.48	23.65 to 30.95				
Past	384	302	47	18	22.80	21.16 to 25.85	1.18	1.003 to 1.388		
Present	152	124	43	15	21.09	17.81 to 24.97	1.331	1.078 to 1.645	8.14	**.017**
Surgery										
Distal panc	73	53	48	22	23.52	20.34 to 32.65				
Pylorus Pres[ng]	290	228	53	18	25.85	23 to 27.73	1.107	0.821 to 1.492		
Total Panc	38	31	39	16	20.70	15.44 to 38.21	1.342	0.862 to 2.091		
Whipples	566	444	47	18	22.47	20.93 to 24.97	1.142	0.859 to 1.518	1.86	.601
Extent of resection										
Standard	77	57	49	24	23.77	20.86 to 34.4				
Radical	167	131	49	19	23.75	20.83 to 29.89				
Ext radical	696	545	49	19	23.65	21.68 to 25.85	1.066	0.811 to 1.4	0.23	.890
Median and IQR maximum tumor diameter, mm	Continuous variable						1.001	0.998 to 1.004	0.65	.420
Tumor grade differentiation										
Poor	229	190	37	14	17.9	15.83 to 21.29				
Moderate	607	468	52	19	24.7	22.6 to 26.81	0.755	0.638 to 0.893		
Well	131	98	58	24	28.02	24.18 to 36.37	0.616	0.483 to 0.786	17.74	**< .001**
Lymph node involvement										
Negative	279	174	63	33	34.92	29.73 to 42.02				
Positive	704	591	44	13	21.39	19.84 to 22.8	1.841	1.553 to 2.182	51.03	**< .001**
Resection margins										
Negative	630	462	52	23	25.2	23.52 to 27.83				
Positive	355	305	44	10	20.07	17.81 to 23.72	1.433	1.239 to 1.657	23.84	**< .001**
Local invasion										
No	559	428	51	20	24.34	22.27 to 26.48				
Yes	402	323	46	16	22.34	20.83 to 25.16	1.144	0.99 to 1.322	3.31	.069

(continued on following page)

Table A1. Univariable and Multivariable Regression Analysis of Survival Factors (continued)

Factor	No. of Patients	No. of Deaths	Survival Rates (%) 24 Months	Survival Rates (%) 60 Months	Survival Median	95% CI	Hazard Ratio	95% CI	Log-Rank Test χ^2	Log-Rank Test *P*
Univariable Analyses (n = 985)										
Tumor stage										
I	94	53	56	41	33.08	21.68 to NA				
II	279	206	58	23	28.09	25.16 to 32.16	1.445	1.068 to 1.955		
III	564	469	43	13	21.09	19.28 to 22.8	2.004	1.507 to 2.664		
IVa	36	29	47	18	23.74	16.39 to 42.9	1.636	1.04 to 2.574	33.36	**< .001**
Postoperative complications										
No	728	575	48	17	23.00	21.52 to 24.97				
Yes	237	181	50	21	24.01	21.02 to 29.2	0.917	0.776 to 1.084	1.03	.31
Postoperative CA 19-9 level, KU/l			Continuous variable				1.221	1.16 to 1.286	53.20	**< .001**
Percentage of therapy received, median (IQR)			Continuous variable				0.994	0.991 to 0.996	27.99	**< .001**
Start of therapy after surgery			Continuous variable				0.985	0.956 to 1.015	0.99	.319
Completed therapy										
No	294	245	29	12	14.62	12.55 to 16.92				
Yes	674	509	58	22	28.02	26.05 to 30.88	0.516 (0.443 to 0.601)		74.63	**< .001**

	Parameter Est	SE	Multivariable Analyses (n = 949; No. of events = 741) χ^2 Statistic	HR	95% CI	*P*
Lymph node involvement						
Negative						
Positive	0.593	0.089	44.08	1.809	1.518 to 2.155	**< .001**
Completion of therapy (six cycles received)						
No						
Yes	−1.327	0.313	17.98	0.265	0.144 to 0.490	**< .001**
Tumor grade differentiation						
Poor						
Moderate	−0.331	0.087	14.52	0.718	0.605 to 0.851	**< .001**
Well	−0.511	0.128	15.99	0.600	0.467 to 0.771	**< .001**
Resection Margins						
No						
Yes	0.338	0.077	19.47	1.402	1.207 to 0.629	**< .001**
Completed therapy						
Yes; time to start of therapy	−0.022	0.197	1.25	0.978	0.941 to 1.017	.264
No; time to start of therapy	−0.090	0.031	8.41	0.914	0.860 to 0.971	**.004**

NOTE. Boldfaced *P* values are statistically significant.

Abbreviations: Est, estimate; Ext, extended; FU/FA, fluorouracil plus folinic acid; HR, hazard ratio; IQR, interquartile range; mo, months; NA, not applicable; Neg, negative; Panc, pancreatectomy; Pos, positive; Pres^{ng}, preserving.

Table A2. Patient Characteristics at Random Assignment by Whether or Not Patients Had Disease Recurrence Within 12 Months of Surgery

	Full Data Set					
	No Recurrence Within 12 Months (n = 653)		Recurrence Within 12 Months (n = 332)		Total (n = 985)	
Characteristic	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	64		62		63	
IQR	57-70		56-69		56-70	
Sex						
Female	303	46	134	40	437	44
Male	350	54	198	60	548	56
Arm						
Gemcitabine	327	50	172	52	499	51
FU/FA	326	50	160	48	486	49
Baseline performance status						
0	237	36	115	35	352	36
1	347	53	178	54	525	53
2	69	11	39	12	108	11
Diabetic						
No	479	76	241	74	720	75
Yes	151	24	85	26	236	25
Smoking status						
Never	252	42	120	40	372	41
Past	258	43	126	42	384	42
Present	95	16	57	19	152	17
Surgery						
Distal panc	46	7	27	8	73	8
Pylorus Pres^{ng}	193	30	97	29	290	30
Total panc	26	4	12	4	38	4
Whipples	372	58	194	59	566	59
Extent of resection						
Standard	462	74	234	74	696	74
Radical	113	18	54	17	167	18
Extended radical	50	8	27	9	77	8
Maximum tumor diameter, mm						
Median	30		30		30	
IQR	22-36		25-40		23-40	
Tumor grade differentiation						
Poor	132	21	97	30	229	24
Moderate	416	65	191	58	607	63
Well	92	14	39	12	131	14
Lymph node involvement						
Negative	211	32	68	21	279	28
Positive	441	68	263	79	704	72
Resection margins						
Negative	436	67	194	58	630	64
Positive	217	33	138	42	355	36
Local invasion						
No	393	62	166	51	559	58
Yes	243	38	159	49	402	42
Tumor stage						
I	72	11	22	7	94	10
II	201	31	78	24	279	29
III	345	54	219	67	564	58
IVa	26	4	10	3	36	4
Postoperative complications						
No	480	76	248	75	728	75
Yes	155	24	82	25	237	25
Postoperative CA 19-9 level, KU/l						
Median	3		4		3	
IQR	2-4		3-5		2-4	

(continued on following page)

Table A2. Patient Characteristics at Random Assignment by Whether or Not Patients Had Disease Recurrence Within 12 Months of Surgery (continued)

Characteristic	Full Data Set					
	No Recurrence Within 12 Months (n = 653)		Recurrence Within 12 Months (n = 332)		Total (n = 985)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Percentage of therapy received						
Median	90		83		89	
IQR	65-100		50-98		61-100	
Time to start of therapy						
Median	8		8		8	
IQR	7-10		6-10		7-10	
Completed six cycles of therapy						
No	163	25	131	40	294	30
Yes	477	75	197	60	674	70

Abbreviations: FU/FA, fluorouracil plus folinic acid; IQR, interquartile range; panc, pancreatectomy; Pres^{ng}, preserving.

Table A3. Univariable and Multivariable Regression Analysis of Survival Factors for Disease-Free Survival

Variable	No. Of Patients	No. of Patients With Disease Recurrence	Disease-Free Survival Rates (%)		Survival Median (95% CI)	Hazard Ratio	95% CI	Log-Rank Test	
			24 Months	60 Months				χ^2	*P*
Age			Continuous variable			0.996	0.988 to 1.004	1.09	.298
Sex									
Female	437	354	33	16	15.14 (13.8 to 17.31)				
Male	548	471	27	12	13.53 (12.75 to 14.82)	1.139	0.992 to 1.307	3.41	.065
Arm									
FU/FA	499	417	31	14	14.55 (12.81 to 16.06)				
Gemcitabine	486	408	28	14	14.16 (13.44 to 15.7)	0.995	0.868 to 1.141	0.01	.946
Baseline performance status									
0	352	287	33	17	14.82 (13.3 to 16.98)				
1	525	444	29	12	14.52 (13.5 to 15.7)	1.114	0.96 to 1.293		
2	108	94	23	10	12.68 (10.87 to 14.78)	1.272	1.007 to 1.606	4.58	.101
Diabetic									
No	720	608	29	14	14.29 (13.47 to 15.51)				
Yes	236	193	30	17	13.53 (12.02 to 16.29)	0.992	0.844 to 1.167	0.01	.926
Smoking status									
Never	372	310	33	16	16.29 (14.55 to 18.82)				
Past	384	320	28	13	13.8 (12.88 to 15.47)	1.101	0.941 to 1.287		
Present	152	132	23	12	12.65 (11.47 to 14.29)	1.272	1.037 to 1.559	5.44	.066
Surgery									
Distal panc	73	57	25	20	15.64 (11.96 to 19.48)				
Pylorus Pres^{ng}	290	246	30	13	14.52 (13.27 to 16.72)	1.064	0.798 to 1.42		
Total panc	38	32	34	14	13.47 (9.3 to 26.45)	1.116	0.724 to 1.721		
Whipples	566	477	29	14	13.96 (13.04 to 15.11)	1.087	0.826 to 1.431	0.42	.935
Extent of resection									
Standard	696	585	29	14	14.26 (13.34 to 15.28)				
Radical	167	140	33	16	14.87 (13.47 to 17.12)	0.947	0.788 to 1.139		
Ext radical	77	65	30	10	13.39 (11.2 to 19.81)	0.995	0.77 to 1.286	0.34	.846
Maximum tumor diameter (mm), median and IQR			Continuous variable			1.002	0.999 to 1.004	1.14	.286
Tumor grade differentiation									
Poor	229	199	24	11	11.6 (10.09 to 13.34)				
Moderate	607	505	29	15	14.85 (13.63 to 16.29)	0.81	0.687 to 0.955		
Well	131	108	41	14	17.18 (14.52 to 22.96)	0.709	0.56 to 0.896	9.87	**.007**
Lymph node involvement									
Negative	279	195	44	28	20.86 (18.33 to 24.31)				
Positive	704	628	24	8	13.01 (12.19 to 13.67)	1.861	1.582 to 2.188	58.15	**< .001**
Resection margins									
Negative	630	502	34	18	15.74 (14.52 to 17.25)				
Positive	355	323	22	7	12.45 (11.4 to 13.63)	1.448	1.258 to 1.667	26.87	**< .001**
Local invasion									
No	559	454	33	16	16.1 (14.55 to 17.44)				
Yes	402	354	24	10	13.01 (11.93 to 13.67)	1.261	1.097 to 1.45	10.68	**.001**

(continued on following page)

Table A3. Univariable and Multivariable Regression Analysis of Survival Factors for Disease-Free Survival (continued)

Variable	No. Of Patients	No. of Patients With Disease Recurrence	Disease-Free Survival Rates (%)		Survival Median (95% CI)	Hazard Ratio	95% CI	Log-Rank Test	
			24 Months	60 Months				χ^2	*P*
Tumor stage									
I	94	60	45	36	19.56 (16.98 to 36.24)				
II	279	228	35	17	16.75 (14.68 to 19.48)	1.516	1.14 to 2.015		
III	564	497	24	9	12.81 (11.83 to 13.67)	2.052	1.568 to 2.685		
IVa	36	30	36	17	16.34 (10.78 to 25.92)	1.508	0.972 to 2.339	37.22	**< .001**
Postoperative complications									
No	728	613	29	14	13.9 (13.21 to 15.14)				
Yes	237	200	30	14	14.22 (12.84 to 16.89)	0.958	0.816 to 1.123	0.28	.594
Postoperative CA 19-9 level, KU/l			Continuous variable			1.215	1.157 to 1.276	55.39	**< .001**
Percentage of therapy received, median and IQR			Continuous variable			0.589	0.465 to 0.745	19.53	**< .001**
Start of therapy after surgery			Continuous variable			0.988	0.96 to 1.016	0.70	.401
Completion of therapy									
No	294	256	19	10	8.9 (7.79 to 10.35)				
Yes	674	556	35	16	16.56 (15.14 to 17.94)	0.564	0.486 to 0.655	58.54	**< .001**

	Parameter Est (SE)	χ^2 Statistic	HR	95% CI	*P*
Lymph node involvement					
Negative					
Positive	0.567 (0.085)	44.72	1.764	1.493 to 2.083	**< .001**
Completion of therapy (six cycles received)					
No					
Yes	−1.080 (0.301)	12.84	0.340	0.188 to 0.613	**< .001**
Tumor grade differentiation					
Poor					
Moderate	−0.224 (0.085)	6.99	0.800	0.678 to 0.944	**.008**
Well	−0.322 (0.123)	6.91	0.724	0.570 to 0.921	**.009**
Resection margins					
No					
Yes	0.321 (0.074)	18.66	1.378	1.192 to 1.594	**< .001**
Completed therapy					
Yes; time to start of therapy	−0.021 (0.018)	1.33	0.979	0.945 to 1.015	.248
No; time to start of therapy	−0.075 (0.030)	6.32	0.923	0.875 to 0.984	**.012**

NOTE. Boldfaced *P* values are statistically significant.
Abbreviations: Est, estimate; Ext, extended; FU/FA, fluorouracil plus folinic acid; HR, hazard ratio; IQR, interquartile range; panc, pancreatectomy; Pres^{ng}, preserving.

Table A4. Univariable and Multivariable Regression Analysis of Survival Factors After Excluding Patients Who Died Within 8 Months of Surgery (excluding 96 patients and 82 patient deaths)

Variable	No. of Patients	No. of Deaths	Survival Rates (%)		Survival Median (95% CI)	Hazard Ratio (95% CI)	Log-Rank Test	
			24 Months	60 Months			χ^2	*P*
Age			Continuous variable			0.997 (0.988 to 1.005)	0.57	.449
Sex								
Female	384	282	57	23	28.02 (25.76 to 32.16)			
Male	505	403	50	18	24.11 (21.75 to 26.35)	1.245 (1.069 to 1.45)	7.92	**.005**
Arm								
FU/FA	449	349	53	19	25.2 (23.72 to 28.52)			
Gemcitabine	440	336	54	21	26.22 (23.65 to 29.57)	0.97 (0.835 to 1.126)	0.16	.687
Baseline performance status								
0	324	243	58	24	27.2 (25.16 to 31.57)			
1	466	364	52	18	25.76 (23.52 to 28.65)	1.111 (0.945 to 1.308)		
2	99	78	43	19	22.47 (18.82 to 26.22)	1.293 (1.001 to 1.669)	4.22	.121
Diabetic								
No	653	505	55	21	26.18 (24.8 to 28.98)			
Yes	211	164	46	18	22.34 (20.34 to 26.22)	1.13 (0.947 to 1.347)	1.84	.175
Smoking status								
Never	340	255	58	23	29.76 (25.76 to 33.34)			
Past	347	270	52	19	25.2 (22.47 to 27.73)	1.179 (0.993 to 1.399)		
Present	136	112	45	15	21.39 (18.82 to 25.85)	1.393 (1.115 to 1.74)	9.19	**.010**
Surgery								
Distal panc	70	52	48	22	23.52 (20.34 to 32.65)			
Pylorus Pres^{ng}	261	201	59	20	26.87 (25.53 to 31.57)	0.973 (0.717 to 1.32)		
Total panc	31	25	45	17	21.81 (17.77 to 41.23)	1.142 (0.709 to 1.84)		
Whipples	511	398	51	20	24.8 (22.47 to 27.69)	1.024 (0.767 to 1.367)	0.74	.863
Extent of resection								
Standard	631	489	54	20	25.85 (23.78 to 27.83)			
Radical	153	119	52	20	24.97 (21.62 to 31.04)	1.027 (0.840 to 1.255)		
Ext radical	67	49	54	26	26.35 (22.31 to 35.48)	0.914 (0.681 to 1.226)	0.48	.788
Maximum tumor diameter (mm), median and IQR			Continuous variable			1.001 (0.997 to 1.004)	0.11	.739
Tumor grade differentiation								
Poor	192	156	44	16	21.52 (18.5 to 26.22)			
Moderate	558	427	55	20	26.08 (24.67 to 28.91)	0.826 (0.688 to 0.992)		
Well	124	93	59	24	29.73 (24.28 to 38.3)	0.709 (0.548 to 0.917)	7.54	.023
Lymph node involvement								
Negative	256	157	67	35	38.21 (32.72 to 44.84)			
Positive	631	526	48	14	23.03 (21.62 to 25.16)	1.87 (1.563 to 2.237)	48.42	**< .001**
Resection margins								
Negative	570	413	56	25	27.73 (25.2 to 31.11)			
Positive	319	272	48	11	23.13 (20.07 to 25.89)	1.441 (1.236 to 1.681)	22.01	**< .001**
Local invasion								
No	494	371	57	23	27.73 (24.97 to 31.24)			
Yes	373	300	49	17	23.49 (21.68 to 26.35)	1.231 (1.057 to 1.434)	7.17	**.007**
Tumor stage								
I	87	46	61	44	35.74 (25.39 to NA)			
II	255	188	62	24	30.22 (26.51 to 35.81)	1.521 (1.101 to 2.101)		
III	503	416	48	15	22.83 (21.16 to 25.49)	2.105 (1.551 to 2.857)		
IVa	33	26	52	20	24.18 (20.83 to 44.84)	1.684 (1.041 to 2.725)	32.12	**< .001**
Postoperative complications								
No	651	510	52	19	25.39 (23.65 to 27.2)			
Yes	219	165	54	23	26.45 (22.31 to 31.7)	0.949 (0.796 to 1.131)	0.34	.560
Postoperative CA 19-9 level, KU/l			Continuous variable			1.193 (1.128 to 1.262)	35.35	**< .001**
Percentage of Therapy Received, Median and IQR			Continuous variable			0.806 (0.61 to 1.066)	2.29	.130
Start of therapy after surgery			Continuous variable			0.985 (0.954 to 1.017)	0.83	.362
Completion of therapy								
No	220	180	38	15	19.32 (17.25 to 21.81)			
Yes	669	505	58	22	28.35 (26.12 to 31.04)	0.667 (0.562 to 0.79)	22.06	**< .001**

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Table A4. Univariable and Multivariable Regression Analysis of Survival Factors After Excluding Patients Who Died Within 8 Months of Surgery (excluding 96 patients and 82 patient deaths) (continued)

	Parameter Est (SE)	χ^2 Statistic	HR (95% CI)	*P*
Lymph node involvement				
Negative				
Positive	0.596 (0.093)	41.08	1.816 (1.513 to 2.179)	**< .001**
Completion of therapy (six cycles received)				
No				
Yes	−1.044 (0.354)	8.70	0.352 (0.176 to 0.705)	**.003**
Tumor grade differentiation				
Poor				
Moderate	−0.230 (0.094)	6.01	0.794 (0.661 to 0.955)	**.014**
Well	−0.359 (0.133)	7.32	0.698 (0.538 to 0.906)	**.007**
Resection margins				
No				
Yes	0.324 (0.080)	16.32	1.383 (1.182 to 0.1619)	**< .001**
Completed therapy				
Yes; time to start of therapy	−0.019 (0.020)	0.91	0.981 (0.944 to 1.020)	.34
No; time to start of therapy	−0.082 (0.036)	5.22	0.921 (0.858 to 0.988)	**.022**

NOTE. Boldfaced *P* values are statistically significant.
Abbreviations: Est, estimate; Ext, extended; FU/FA, fluorouracil plus folinic acid; HR, hazard ratio; IQR, interquartile range; NA, not applicable; panc, pancreatectomy; Pres^{ng}, preserving.

Table A5. Sensitivity Analysis Showing the Results of the Multivariable Models Considering Time-To-Treatment As a Dichotomized Variable and Investigating the Differing Landmarks for the Subgroup Analysis

Variable	Time to Start of Therapy Included As a Dichotomized Variable						Using Different Landmarks									
	Full Dataset (n = 949; No. of events = 741)			8-Month Landmark Analysis (n = 872; No. of events = 674)			9 Months (n = 853; No. of events = 655)			10 Months (n = 819; No. of events = 622)			11 Months (n = 788; No. of events = 591)			12 Months (n = 758; No. of events = 562)		
	Parameter Est	SE	*P*	Parameter Est	SE	*P*	Parameter Est	SE	*P*	Parameter Est	SE	*P*	Parameter Est	SE	*P*	Parameter Est	SE	*P*
Lymph node involvement																		
Negative																		
Positive	0.610	0.090	**< .001**	0.610	0.093	**< .001**	0.598	0.094	**< .001**	0.619	0.097	**< .001**	0.599	0.098	**< .001**	0.591	0.1	**< .001**
Completion of therapy (six cycles received)																		
No																		
Yes	−0.997	0.118	**< .001**	−0.707	0.134	**< .001**	−0.961	0.366	**.009**	−0.937	0.383	**.014**	−1.106	0.4	**.006**	1.114	0.414	**.007**
Tumor grade differentiation																		
Poor																		
Moderate	−0.347	0.087	**< .001**	−0.242	0.094	**.010**	−0.225	0.096	.019	−0.161	0.1	.108	−0.156	0.103	.128	−0.158	0.106	.135
Well	−0.540	0.128	**< .001**	−0.380	0.133	.004	−0.324	0.134	**.015**	−0.259	0.138	.061	−0.252	0.141	.074	−0.229	0.144	.112
Resection margins																		
No																		
Yes	0.318	0.077	**< .001**	0.308	0.08	**< .001**	0.337	0.081	**< .001**	0.296	0.084	**< .001**	0.284	0.086	**.001**	0.238	0.089	**.008**
Completed therapy																		
Yes; time to start of therapy > 8 weeks	−0.073	0.090	.418	−0.048	0.091	.601	−0.013	0.020	.497	−0.009	0.020	.671	−0.008	0.020	.697	−0.004	0.021	.859
No; time to start of therapy > 8 weeks	−0.475	0.130	**< .001**	−0.380	0.153	**.013**	−0.073	0.037	.052	−0.070	0.039	.074	−0.100	0.042	**.018**	−0.097	0.043	**.025**

NOTE. Boldfaced *P* values are statistically significant.
Abbreviation: Est, estimate.

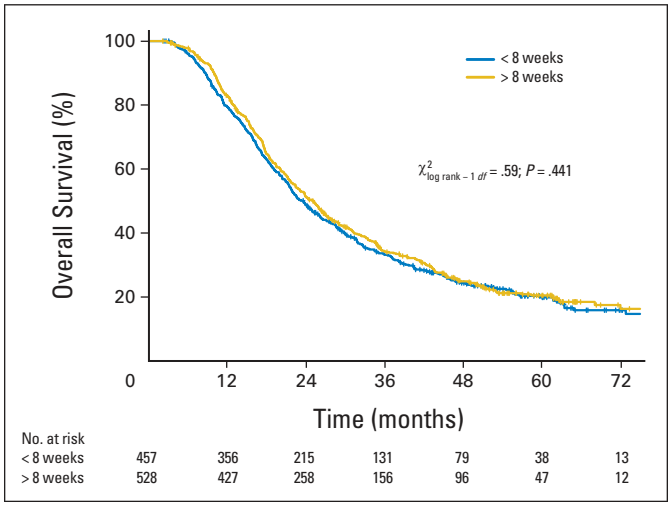

Fig A1. Kaplan-Meier plot of overall survival by the time to first administration of therapy.

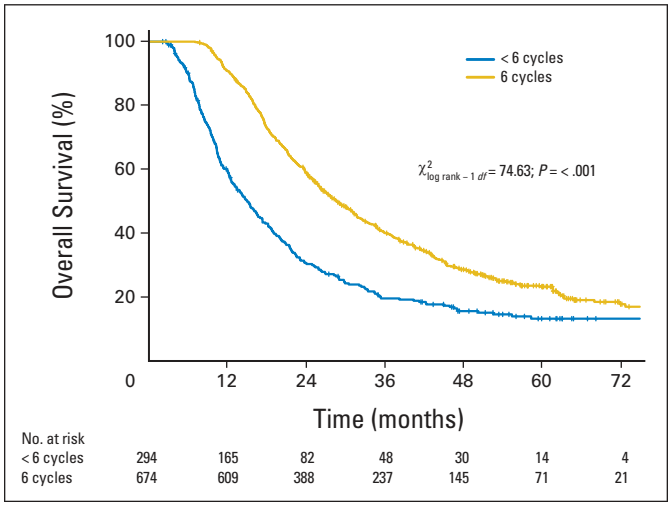

Fig A2. Kaplan-Meier plot of overall survival by completion of therapy.

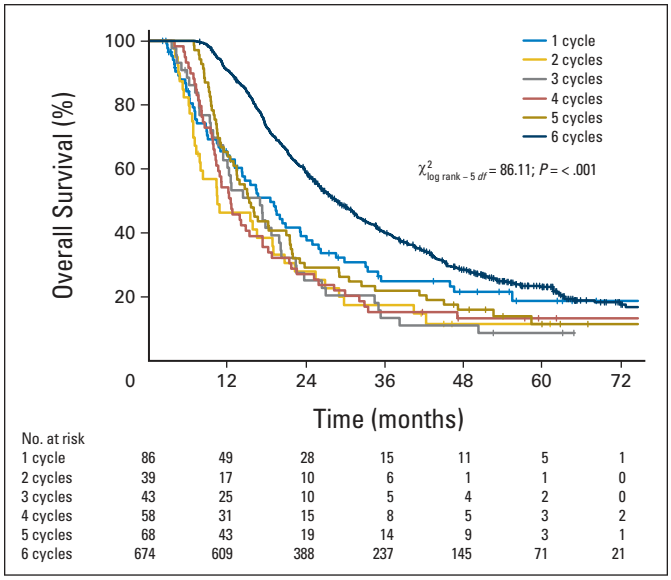

Fig A3. Kaplan-Meier plot of overall survival by the number of cycles.

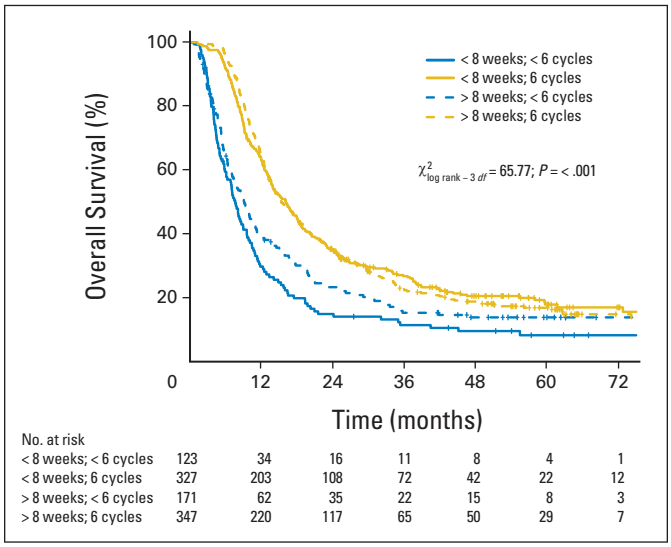

Fig A4. Recurrence-free survival by completion of chemotherapy and time to first administration.

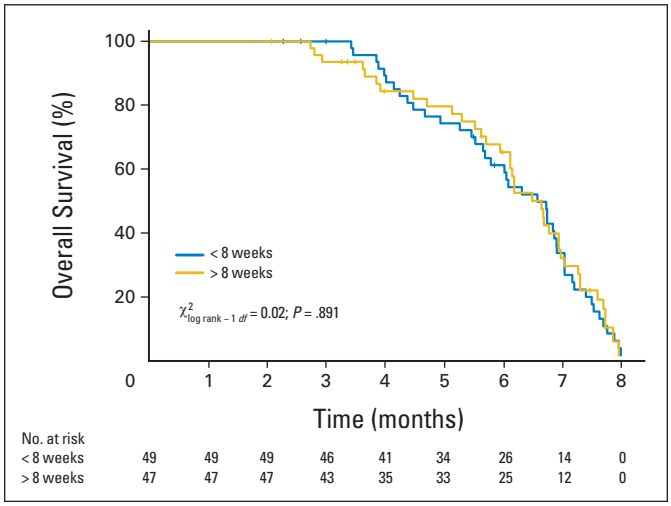

Fig A5. Kaplan-Meier plot of the effect of the start time of chemotherapy for patients who died within 8 months of surgery.