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Evaluation of Adjuvant Chemotherapy in Patients With Resected Pancreatic Cancer After Neoadjuvant FOLFIRINOX Treatment

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IMPORTANCE The benefit of adjuvant chemotherapy after resection of pancreatic cancer following neoadjuvant combination treatment with folinic acid, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) is unclear.

OBJECTIVE To assess the association of adjuvant chemotherapy with overall survival (OS) in patients after pancreatic cancer resection and neoadjuvant FOLFIRINOX treatment.

DESIGN, SETTING, AND PARTICIPANTS This international, multicenter, retrospective cohort study was conducted from January 1, 2012, to December 31, 2018. An existing cohort of patients undergoing resection of pancreatic cancer after FOLFIRINOX was updated and expanded for the purpose of this study. All consecutive patients who underwent pancreatic surgery after at least 2 cycles of neoadjuvant FOLFIRINOX chemotherapy for nonmetastatic pancreatic cancer were retrospectively identified from institutional databases. Patients with resectable pancreatic cancer, borderline resectable pancreatic cancer, and locally advanced pancreatic cancer were eligible for this study. Patients with in-hospital mortality or who died within 3 months after surgery were excluded.

EXPOSURES The association of adjuvant chemotherapy with OS was evaluated in different subgroups including interaction terms for clinicopathological parameters with adjuvant treatment in a multivariable Cox model. Overall survival was defined as the time starting from surgery plus 3 months (moment eligible for adjuvant therapy), unless mentioned otherwise.

RESULTS We included 520 patients (median [interquartile range] age, 61 [53-66] years; 279 [53.7%] men) from 31 centers in 19 countries. The median number of neoadjuvant cycles of FOLFIRINOX was 6 (interquartile range, 5-8). Overall, 343 patients (66.0%) received adjuvant chemotherapy, of whom 68 (19.8%) received FOLFIRINOX, 201 (58.6%) received gemcitabine-based chemotherapy, 14 (4.1%) received capecitabine, 45 (13.1%) received a combination or other agents, and 15 (4.4%) received an unknown type of adjuvant chemotherapy. Median OS was 38 months (95% CI, 36-46 months) after diagnosis and 31 months (95% CI, 29-37 months) after surgery. No survival difference was found for patients who received adjuvant chemotherapy vs those who did not (median OS, 29 vs 29 months, univariable hazard ratio [HR], 0.99; 95% CI, 0.77-1.28; $P = .93$). In multivariable analysis, only the interaction term for lymph node stage with adjuvant therapy was statistically significant: In patients with pathology-proven node-positive disease, adjuvant chemotherapy was associated with improved survival (median OS, 26 vs 13 months; multivariable HR, 0.41 [95% CI, 0.22-0.75]; $P = .004$). In patients with node-negative disease, adjuvant chemotherapy was not associated with improved survival (median OS, 38 vs 54 months; multivariable HR, 0.85; 95% CI, 0.35-2.10; $P = .73$).

CONCLUSIONS AND RELEVANCE These results suggest that adjuvant chemotherapy after neoadjuvant FOLFIRINOX and resection of pancreatic cancer was associated with improved survival only in patients with pathology-proven node-positive disease. Future randomized studies should be conducted to confirm this finding.

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Supplemental content

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Pancreatic cancer has a poor 5-year survival rate of 9%.[1] After upfront surgical resection combined with adjuvant chemotherapy, which is the current standard of care, approximately 75% of patients develop disease recurrence within 2 years.[2] Several randomized trials have confirmed that adjuvant chemotherapy improves survival in patients after resection of pancreatic cancer.[3,4] None of these trials, however, included patients who received neoadjuvant therapy. A meta-analysis of nonrandomized studies and 3 recent multicenter randomized trials from South Korea, Japan, and the Netherlands suggested that neoadjuvant therapy in patients with resectable and borderline resectable pancreatic cancer (BRPC) improves disease-free survival and overall survival (OS).[5-8] Furthermore, 2 meta-analyses demonstrated improved R0 (microscopically no residual cancer) resection rates after pancreatic resection and neoadjuvant combined folinic acid, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) chemotherapy in both patients with BRPC (pooled R0 rate, 84%) and those with locally advanced pancreatic cancer (LAPC; pooled R0 rate, 78%).[9,10] Based on these results, increasing numbers of patients with nonmetastatic pancreatic cancer are treated with neoadjuvant therapy.

It remains unclear, however, whether patients who underwent pancreatectomy for pancreatic cancer after neoadjuvant FOLFIRINOX still benefit from adjuvant chemotherapy. In some retrospective studies, no survival benefit of adjuvant chemotherapy was found in this setting (E. van Veldhuisen, MD, personal communication, 2020),[11] whereas in a comprehensive analysis of the National Cancer Database, adjuvant therapy remained associated with improved survival after adjustment for treatment and tumor characteristics in multivariable analyses.[12] Randomized data to answer this question are still lacking.

This study aimed to assess the association of adjuvant chemotherapy with OS in a large retrospective cohort of patients who underwent resection of pancreatic cancer after neoadjuvant FOLFIRINOX chemotherapy.

Key Points

Question Do patients who underwent resection of pancreatic cancer after neoadjuvant combination folinic acid, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) chemotherapy benefit from adjuvant chemotherapy?

Findings This international cohort study of 520 patients with resected pancreatic cancer found that adjuvant chemotherapy was significantly associated with improved survival in 254 patients with pathology-proven node-positive disease but not in 256 patients with node-negative disease.

Meaning Adjuvant chemotherapy after neoadjuvant FOLFIRINOX and resection of pancreatic cancer was associated with improved survival only in patients with pathology-proven node-positive disease.

Methods

Study Design and Patients

This international, multicenter, retrospective cohort study was initiated by the scientific committee of the European-African Hepato-Pancreato-Biliary Association. Institutions that performed pancreatectomy for pancreatic ductal adenocarcinoma (referred to as pancreatic cancer in this study) after neoadjuvant FOLFIRINOX were invited to participate. An existing cohort of patients undergoing resection of pancreatic cancer after FOLFIRINOX was updated and expanded for the purpose of this study.[13] The local institutional review board at the Amsterdam University Medical Center approved this study and issued a waiver of the requirement to obtain informed consent due to the retrospective nature of the study.

All consecutive patients who underwent pancreatic surgery (ie, pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy) after at least 2 cycles of neoadjuvant FOLFIRINOX chemotherapy for nonmetastatic pancreatic cancer between January 1, 2012, and December 31, 2018, were retrospectively identified from institutional databases. Patients with resectable pancreatic cancer, BRPC, and LAPC were deemed eligible for this study. Patients with in-hospital mortality or those who died within 3 months after surgery were excluded from analyses to reduce guarantee-time bias (ie, in order to start adjuvant chemotherapy within 3 months after surgery, the patient needs to survive this amount of time).[14] This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Collection and Definitions

Data on baseline, treatment, tumor characteristics, and survival were locally collected and shared anonymously using predefined electronic case report forms (Castor EDC).[13,15] FOLFIRINOX cycles consisted of oxaliplatin (85 mg/m^2 body surface area), irinotecan (150 or 180 mg/m^2), leucovorin (400 mg/m^2), and fluorouracil (2400 mg/m^2 over a 46-hour period) whether or not preceded by a fluorouracil bolus (400 mg/m^2) every 2 weeks, as described before.[4,16] Resectability status was classified according to the National Comprehensive Cancer Network 2018 criteria, determined after neoadjuvant therapy.[17] Cancer within 1 mm of the resection margin was considered microscopically positive (R1) according to the Royal College of Pathologists definition.[18] Pathological tumor, node, metastasis (TNM) staging was performed according to the 8th edition of the *American Joint Committee on Cancer Staging Manual*.[19] Adjuvant therapy was defined as at least 1 cycle of postoperative chemotherapy, with or without additional radiotherapy. OS was calculated as time in months between the date of surgery plus 3 months (moment eligible for adjuvant therapy) and date of death, unless mentioned otherwise. Survival was also reported (but not used in comparative analyses) from the date of diagnosis and from the date of surgery. Vital status was collected based on last follow-up visit, follow-up phone calls, or nationwide registry depending on the country of origin.

Statistical Analysis

Baseline characteristics were presented as frequencies and proportions for categorical variables. Continuous variables were

presented as medians with interquartile ranges (IQRs). Unadjusted OS was assessed using Kaplan-Meier estimates and presented as median OS with corresponding 95% CIs. Two-sided *P* values of less than .05 were considered statistically significant. All analyses were performed between September 8, 2019, and May 23, 2020, using R statistical software, version 3.4.3 (R Foundation). All Kaplan-Meier estimates and survival curves were constructed using the original data.

The association between clinicopathological parameters and OS was evaluated with a Cox proportional hazards model in univariable analysis. The association of adjuvant chemotherapy with OS was also assessed in a multivariable analysis and adjusted for all available potential confounders (baseline and tumor characteristics). All potential confounders to be adjusted for were evaluated and visualized in a directed acyclic graph (eFigure 1 in the Supplement). These confounders were all included in the multivariable model. The proportional hazard assumption was assessed visually by Schoenfeld residuals. Multiple imputation was used to account for missing data (eAppendix in the Supplement).

The heterogeneous treatment effect of adjuvant therapy (different effect on OS in different subgroups, ie, effect modification) was assessed by creating interaction terms for each clinicopathological predictor with potential interaction with adjuvant treatment in a multivariable Cox model. A statistically significant interaction term indicates that the association of adjuvant therapy with OS differs depending on the value of the covariate.[20] All interaction terms were fitted in a single model (adjusted for covariates). The Wald test statistic was used to evaluate statistical significance.

Multiple sensitivity analyses were performed. All patients who died within 6 and 12 months were subsequently excluded (to minimize guarantee-time bias), and outcomes were assessed within subgroups according to resectability status (resectable pancreatic cancer, BRPC, and LAPC group), number of preoperative FOLFIRINOX cycles (<4 cycles, 4-6 cycles, and >6 cycles), and type of adjuvant therapy.

Results

Baseline Characteristics

In total, 536 patients underwent pancreatectomy after neoadjuvant FOLFIRINOX at 31 centers in 19 countries. Of those, 16 (3.0%) patients were excluded owing to death within 3 months. The final cohort consisted of 520 patients (median [IQR] age, 61 [53-66] years; 279 men [53.7%] and 241 women [46.3%]); the pancreatic cancer was staged as resectable in 243 patients (48.4%), as BRPC in 208 patients (41.4%), and as LAPC in 51 patients (10.2%) (stage unknown in 18 patients) after receiving neoadjuvant FOLFIRINOX. The median number of neoadjuvant FOLFIRINOX cycles was the same for patients who received adjuvant therapy (median [IQR], 6 [5-8] patients) and for those who did not (median [IQR], 6 [5-9] patients). Of all patients, 343 (66.0%) received adjuvant chemotherapy. A total of 201 patients received gemcitabine-based adjuvant chemotherapy (58.6% of those who received adjuvant chemotherapy), followed by FOLFIRINOX (68 patients [19.8%]), capecitabine (14 patients [4.1%]), and a combination or other chemotherapeutic agents (45 patients [13.1%]) as adjuvant therapy. Fifteen patients (4.4%) received an unknown type of adjuvant chemotherapy. Patients who received adjuvant chemotherapy were more likely to undergo pancreatoduodenectomy (272 [79.3%] vs 122 [68.9%]), more often had an R1 resection (144 [42.4%] vs 55 [31.8%]), and more often had node-positive (ypN+) disease (114 [33.5%] with ypN1 disease and 75 [22.1%] with ypN2 disease vs 43 [25.3%] and 22 [12.9%], respectively) compared with those who did not receive adjuvant chemotherapy. All baseline characteristics are presented in **Table 1**. The ypN0 rate was 46%, 51%, and 53% within the groups who received less than 4 cycles, 4 to 6 cycles, and greater than 6 cycles of neoadjuvant FOLFIRINOX, respectively (χ^2 analysis, $P = .51$).

Survival Outcomes of Entire Cohort

At the end of the follow-up period, 253 patients (48.7%) were still alive. The median follow-up of patients was 35 months (IQR, 22-44). Median OS of the entire cohort was 38 months (95% CI, 36-46 months) after diagnosis and 31 months (95% CI, 29-37 months) after surgery. Patients who received adjuvant therapy had a median OS of 29 months (95% CI, 26-36 months) vs 29 months (95% CI, 24-45 months) for patients who did not (**Figure**, A). Adjuvant therapy was not associated with improved survival (univariable HR, 0.99; 95% CI, 0.77-1.28; $P = .93$).

Interaction Analysis

Only the interaction term of nodal status and adjuvant chemotherapy was statistically significant: On multivariate analysis, adjuvant therapy was associated with improved survival in patients with pathology-proven ypN+ disease (HR, 0.41; 95% CI, 0.22-0.75; $P = .004$) but not in patients with node-negative (ypN–) disease (HR, 0.85; 95% CI, 0.35-2.10; $P = .73$) **Table 2**.

Post Hoc Subgroup Analysis by Nodal Status

Within the ypN– subgroup (n = 256, 50.2%), median OS was 38 months (95% CI, 31 months to not reached) in the adjuvant therapy group vs 54 months (95% CI, 34 months to not reached) in the no adjuvant therapy group (Figure, B). Within the ypN+ subgroup (n = 254 patients, 49.8%), median OS was 26 months (95% CI, 22-32 months) in the adjuvant group vs 13 months (95% CI, 9-20 months) in the no adjuvant therapy group (Figure, C). For the subgroups of patients with ypN1, OS was 28 months (95% CI, 23-38 months) with adjuvant chemotherapy and 17 months (95% CI, 10-29 months) without adjuvant chemotherapy (eFigure 2 in the Supplement). For the subgroups of patients with ypN2, OS was 22 months with and 10 months without adjuvant chemotherapy (eFigure 3 in the Supplement). When patients were stratified for different types of adjuvant therapy, a benefit was found for both adjuvant gemcitabine and adjuvant FOLFIRINOX in the ypN+ group, with a larger benefit of adjuvant FOLFIRINOX. Median OS of the ypN+ group with no adjuvant therapy was 13 months (95% CI, 9-20 months) compared with 27 months (95% CI, 21-34 months) for gemcitabine and 28 months (23 months to not reached) for FOLFIRINOX (eFigure 4 and eFigure 5 in the Supplement).

Table 1. Baseline Characteristics

Characteristic	No. (%)[a]		
	Entire cohort (N = 520)	Adjuvant therapy (n = 343)	No adjuvant therapy (n = 177)
Clinical characteristics			
Age, median (IQR), y[b]	61 (53-66)	61 (54-66)	61 (52-66)
Male sex	279 (53.7)	192 (56.0)	87 (49.2)
ASA status[c]			
ASA 1	118 (22.9)	69 (20.4)	49 (27.7)
ASA 2	299 (58.1)	212 (62.7)	87 (49.2)
ASA 3-4	98 (19.0)	57 (16.9)	41 (23.2)
Resectability status[d]			
Resectable	243 (48.4)	172 (52.0)	71 (41.5)
Borderline resectable	208 (41.4)	131 (39.6)	77 (45.0)
Locally advanced	51 (10.2)	28 (8.5)	23 (13.5)
Treatment characteristics			
No. of neoadjuvant FOLFIRINOX cycles, median (IQR)[e]	6 (5-8)	6 (5-8)	6 (5-9)
Surgical procedure			
Pancreatoduodenectomy	394 (75.8)	272 (79.3)	122 (68.9)
Distal pancreatectomy	76 (14.6)	44 (12.8)	32 (18.1)
Total pancreatectomy	42 (8.1)	24 (7.0)	18 (10.1)
Other	8 (1.5)	3 (0.9)	5 (2.8)
Tumor characteristics			
Tumor diameter, median (IQR), mm[f]	25 (15-32)	25 (18-31)	22 (13-34)
Margin status (1-mm definition)[g]			
R0	314 (61.2)	196 (57.6)	118 (68.2)
R1	199 (38.8)	144 (42.4)	55 (31.8)
Pathological T stage (AJCC, 8th ed)[h]			
ypT1/ypT2	382 (80.6)	262 (82.4)	120 (76.9)
ypT3/ypT4	92 (19.4)	56 (17.6)	36 (23.1)
Pathological N stage (AJCC, 8th ed)[i]			
ypN0	256 (50.2)	151 (44.4)	105 (61.8)
ypN1	157 (30.8)	114 (33.5)	43 (25.3)
ypN2	97 (19.0)	75 (22.1)	22 (12.9)
Tumor differentiation[j]			
Well differentiated	69 (21.2)	50 (22.5)	19 (20.7)
Moderately differentiated	159 (50.0)	116 (52.3)	43 (46.7)
Poorly differentiated	86 (28.8)	56 (25.2)	30 (32.6)

Abbreviations: AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; FOLFIRINOX, folinic acid, fluorouracil, irinotecan, oxaliplatin; IQR, interquartile range; N, nodal; T, tumor.

[a] Values are given as No. (%) unless otherwise indicated.

[b] Three patients had a missing age.

[c] Five patients had missing ASA status.

[d] National Comprehensive Cancer Network 2018 resectability criteria were used after neoadjuvant therapy; 18 patients had missing data to determine resectability status.

[e] Eight patients had a missing number of neoadjuvant FOLFIRINOX cycles.

[f] Forty-eight patients had missing tumor size.

[g] Seven patients had missing margin status.

[h] Forty-six patients had missing T stage.

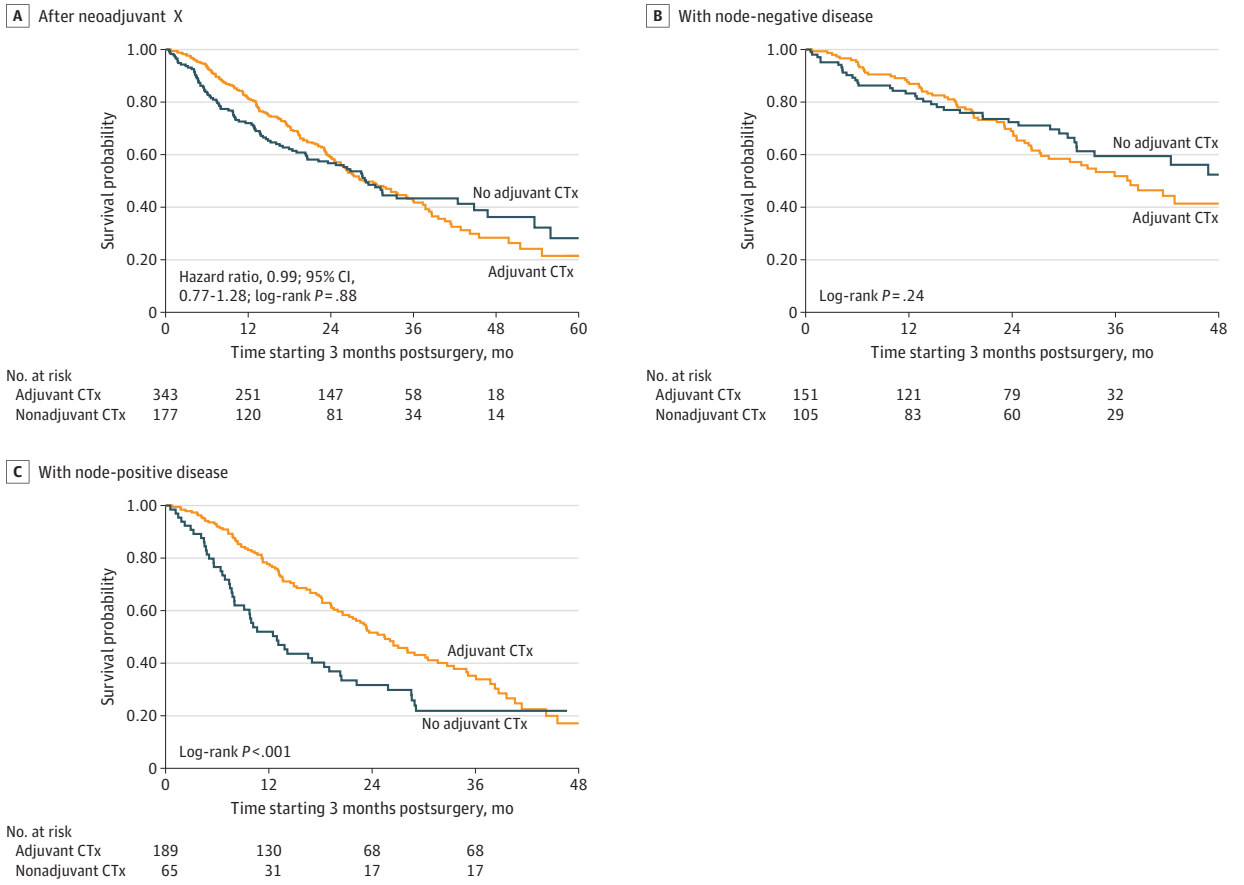
[i] Ten patients had missing N stage.

[j] Two hundred six patients had missing tumor differentiation.

Sensitivity Analyses

After subsequently excluding all patients who died between 6 and 12 months after surgery, the interaction term for ypN stage with adjuvant therapy remained statistically significant ($P = .003$ and $P = .03$, respectively). In the subgroup of patients with resectable disease (n = 242, 47%), adjuvant therapy was not associated with improved OS in patients with ypN- disease (39 months [95% CI, 27-not reached] vs 47 months [95% CI, 31 months to not reached]; eFigure 6 in the Supplement) or in patients with ypN+ disease (27 months [95% CI, 23-36 months] vs 18 months [95% CI, 10 months to not reached]; eFigure 7 in the Supplement; $P = .23$ for interaction). In the subgroup of patients with BRPC or LAPC (n = 250, 48%), adjuvant therapy was not associated with improved OS in patients with ypN- disease (eFigure 8 in the Supplement), whereas it was associated with improved OS in patients with ypN+ disease (22 months [95% CI, 18-32 months] vs 10 months [95% CI, 8-20 months]; eFigure 9 in the Supplement; $P = .009$ for interaction). Effect modification by nodal status was most evident in patients who received less than 4 cycles of neoadjuvant FOLFIRINOX (111 patients, $P = .006$ for interaction), followed by patients who received 4 to 6 cycles (212 patients, $P = .09$ for interaction) and more than 6 cycles (189 patients, $P = .32$ for interaction). Also, adjuvant FOLFIRINOX selectively was associated with a survival benefit in patients with ypN+ disease, but not with ypN- disease (eFigure 10 and eFigure 11 in the Supplement, $P = .05$ for interaction).

Figure. Overall Survival Outcomes Stratified by Receipt of Adjuvant Therapy



CTx indicates chemotherapy.

Table 2. Univariable and Multivariable Cox Analyses of the Association of Adjuvant Therapy With Overall Survival, Including Interaction Terms

	Univariable analysis		Multivariable analysis	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Adjuvant therapy				
No	1 [Reference]	.93	1 [Reference]	.73
Yes	0.99 (0.77-1.28)		0.85 (0.35-2.10)	
Interaction terms with adjuvant chemotherapy[a]				
Adjuvant therapy (yes)				
No. of neoadjuvant FOLFIRINOX cycles	NA		1.03 (0.95-1.12)	.43
Margin status (R1)	NA		0.79 (0.43-1.47)	.46
Differentiation (G2)	NA		1.68 (0.68-3.47)	.16
Differentiation (G3)	NA		1.26 (0.55-2.79)	.57
Pathological T stage (T3/4)	NA		0.93 (0.56-1.74)	.81
Pathological N positive (ypN+)	NA		0.41 (0.22-0.75)	.004

Abbreviations: ASA, American Society of Anesthesiologists; FOLFIRINOX, folinic acid, fluorouracil, irinotecan, oxaliplatin; HR, hazard ratio; N, nodal; NA, not available; T, tumor.

[a] All interaction terms are tested in 1 model, adjusted for age, sex, ASA status, resectability status, number of neoadjuvant FOLFIRINOX cycles, surgical procedure, margin status, tumor differentiation, pathological T stage, pathological N stage, and adjuvant therapy. Shown *P* values are for the Wald statistic of the interaction coefficient.

Discussion

This international, multicenter, retrospective cohort study assessed the value of adjuvant therapy for OS in 520 patients who underwent pancreatectomy for pancreatic cancer after neoadjuvant FOLFIRINOX chemotherapy. Although adjuvant therapy did not improve survival in the entire cohort, a differential treatment effect was found based on lymph node status. Within the subgroup of patients with ypN+ resected pancreatic cancer (n = 254, 49%), patients receiving adjuvant therapy demonstrated a median OS of 26 months, compared with 13 months for those who did not. Adjuvant therapy remained associated with improved survival in subgroup analy-

ses of patients with ypN1 or ypN2 disease and for both FOLFIRINOX and gemcitabine-based adjuvant therapy. This effect modification by nodal status was most expressed in BRPC and LAPC and diminished after an increasing number of preoperative cycles of FOLFIRINOX.

There is strong evidence that patients with pancreatic cancer may benefit from chemotherapy during the course of their treatment. Randomized clinical trials have demonstrated that FOLFIRINOX is the most potent treatment regimen in the metastatic and adjuvant setting.[4,21] It is still unclear, however, whether and to what extent the timing of treatment (ie, neoadjuvant or adjuvant), the number of cycles, and dose density are relevant for survival. The present study suggests that only the subgroup of patients with ypN+ resected pancreatic cancer after neoadjuvant FOLFIRINOX benefited from adjuvant treatment. A nationwide register study from Denmark in 623 patients also found that adjuvant therapy after upfront surgery for pancreatic cancer improved survival only in patients with ypN+ disease.[22] Another study by the MD Anderson Cancer Center, including 245 patients who received preoperative therapy and pancreatectomy, concluded that adjuvant therapy was marginally associated with a longer OS in the entire cohort (HR, 0.55; 95% CI, 0.29-1.01; P = .05).[23] The authors did not assess the association of adjuvant therapy in different subgroups.

To our knowledge, no other large series of patients who underwent resection after neoadjuvant FOLFIRINOX are available. Two patient-level meta-analyses for resection of BRPC and LAPC after FOLFIRINOX included 313 and 355 patients, respectively.[9,10] However, these studies did not present data on adjuvant therapy. The relatively large multicenter AGEO-FRENCH cohort included 80 patients who underwent surgery for BRPC or LAPC after a median of 6 cycles of neoadjuvant FOLFIRINOX.[24] Approximately half of these patients (54%) received adjuvant chemotherapy, but no association with improved survival was found (HR, 0.85; 95% CI, 0.45-1.61; P = .62). Patients of this study were also included in the present study.[24] Recently, another large series reported on 110 patients who underwent surgery for BRPC or LAPC after neoadjuvant FOLFIRINOX at Massachusetts General Hospital, Boston, United States.[25] Unfortunately, the authors did not report on adjuvant therapy.

It is possible that the most fit patients received adjuvant therapy (ie, confounding by indication) in this international cohort. In the present study, medical oncologists were more likely to administer adjuvant therapy to patients with resectable pancreatic cancer and American Society of Anesthesiologists 1/2 status, whereas patients with BRPC or LAPC or American Society of Anesthesiologists 3/4 status were less likely to receive adjuvant therapy (potentially overestimating the effect of adjuvant therapy). However, patients who received adjuvant therapy more often had unfavorable tumor characteristics on pathology, reflected by a higher R1 rate and a higher proportion of patients with ypN+ disease (potentially underestimating the effect of adjuvant therapy). The effect of confounding by indication, however, would be expected in patients with both ypN- and ypN+ disease, but we found no difference in OS in patients with ypN- disease. The improved survival with adjuvant chemotherapy observed in patients with ypN+ disease remained after landmark analyses by excluding patients who died both 6 and 12 months after surgery, controlling for guarantee-time bias. Moreover, when separately assessing patients with ypN1 and ypN2 disease, the association with adjuvant therapy remained (eFigures 4 and 5 in the Supplement). However, the differential association of adjuvant chemotherapy in resectable pancreatic cancer needs to be further studied, as the interaction term within this subgroup was not statistically significant. This may be due either to a type II error or to absence of effect modification in patients with resectable pancreatic cancer.

Node-positive status is most likely dependent on a combination of disease stage (time related) and tumor biology (mutation related), with aggressive tumors causing earlier nodal metastasis. It is, at this stage, not possible to determine whether patients with ypN- disease achieved this status as a result of preoperative FOLFIRINOX or whether they had ypN- disease initially. The finding that the N0 rate did not increase with an increasing number of preoperative cycles of chemotherapy may suggest the latter. The ypN- ratio in this study (50.2%) is, however, considerably higher than that in large series without neoadjuvant therapy. It remains difficult to exclude the possibility that optimal adjuvant therapy (eg, FOLFIRINOX) could improve survival in patients with ypN0 disease. In our sensitivity analysis, however, FOLFIRINOX was associated with a survival benefit in patients with ypN+ disease but not ypN0 disease.

Certain findings in this study vary somewhat from the current literature. First, the proportion of patients with ypN+ disease after neoadjuvant treatment in our study was relatively high (50%) compared with other series (44% and 33% ypN+).[5,8] Second, the R0 rate after neoadjuvant therapy in our study was lower (61%) than that previously reported in 2 systematic reviews in patients with BRPC (pooled R0 rate, 84%) and LAPC (pooled R0 rate, 78%).[9,10] The lower R0 rate and N0 rate might also be related to a lower rate of preoperative radiotherapy used in this study (21%), as was recently hypothesized by Pietrasz et al,[26] who demonstrated higher R0 and N0 rates after preoperative radiotherapy. Last, only 13% of patients in our cohort received FOLFIRINOX in the adjuvant setting, yet adjuvant FOLFIRINOX was associated with superior OS compared with all other regimens in patients with ypN+ disease.

Strengths and Limitations

The present study should be interpreted in the light of some limitations. First, the retrospective nature of this study is associated with increased risk of bias. Confounding by indication may introduce bias when interpreting nonrandomized data to evaluate treatment outcomes. Many parameters were adjusted for by multivariable analyses, and a landmark analysis was performed to assess and reduce guarantee-time bias. However, unmeasured confounders (eg, World Health Organization status) could not be adjusted for. Second, data were retrospectively collected by 31 centers from 19 countries. We strived to achieve uniformity of variables by providing clear definitions and explanations in the electronic case report forms and the study protocol,[13] but heterogeneity of data cannot be

ruled out. Although this heterogeneity would not necessarily result in a bias in any particular direction, it might have impaired the quality of the data. Third, this cohort only included the highly selected group of patients who eventually underwent a resection after neoadjuvant FOLFIRINOX. Patients who progressed on neoadjuvant chemotherapy or those who underwent surgical exploration but not resection were not included. Also, patients who died within 3 months after surgery were excluded. Although this excluded only a few patients, this inevitably caused further selection bias. These choices in study design were made to maximize internal validity in an attempt to approach a valid assessment of the effect of adjuvant therapy. Therefore, the favorable median OS of 38 months after diagnosis applies only to patients who underwent pancreatic resection after neoadjuvant FOLFIRINOX without postoperative mortality rather than to all patients who start neoadjuvant chemotherapy. As the current study is mostly hypothesis-generating (at least regarding secondary outcomes), it underlines the need for large, randomized studies on the outcome of adjuvant therapy after neoadjuvant therapy, in particular in patients with ypN+ disease.

Conclusions

In conclusion, adjuvant chemotherapy was not associated with improved OS in this large, international, multicenter cohort of 520 patients who underwent resection of pancreatic cancer after neoadjuvant FOLFIRINOX. Adjuvant chemotherapy was associated with 13 months of improved survival only in the subgroup of patients with ypN+ disease (median OS, 26 vs 13 months). In the future, these findings should be confirmed in randomized clinical trials.

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