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Article

FOLFIRINOX as Initial Treatment for Localized Pancreatic Adenocarcinoma: A Retrospective Analysis by the Trans-Atlantic Pancreatic Surgery Consortium

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Abstract

Background: Large pragmatic studies of patients who received 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin ([m]FOLFIRINOX) as initial treatment for localized pancreatic ductal adenocarcinoma (PDAC) are lacking. This study aimed to provide realistic estimates of oncologic outcomes in these patients. **Methods:** This international retrospective cohort study included all consecutive patients presenting with localized PDAC who received at least 1 cycle of (m)FOLFIRINOX as initial treatment in 5 referral centers from the United States and the Netherlands (2012-2019). Primary outcome was median overall survival (OS), calculated from the date of tissue diagnosis, assessed using Kaplan-Meier estimates. Log-rank test was used to compare OS between groups. A Cox proportional hazards regression model was used to assess prognostic baseline factors for OS. All statistical tests were 2-sided. **Results:** Overall, 1835 patients were included, of whom 958 (52.2%) had locally advanced (LA), 531 (28.9%) had borderline resectable (BR), and 346 (18.9%) had potentially resectable (PR) PDAC. The median number of (m)FOLFIRINOX cycles was 6 (interquartile range = 4-8). Subsequent treatment included second chemotherapy (12.9%), radiotherapy (49.0%), and resection (37.9%). The resection rate was 17.6% for LA, 53.1% for BR, and 70.5% for PR PDAC ($P < .001$). The margin-negative resection rate (>1 mm) was 55.2% for LA, 62.6% for BR, and 79.2% for PR PDAC ($P < .001$). The median OS was 18.7 months (95% confidence interval [CI] = 17.7 to 19.9 months) for LA, 23.2 months (95% CI = 21.0 to 25.7 months) for BR, and 31.2 months (95% CI = 26.2 to 36.6 months) for PR PDAC ($P < .001$). The median OS for 695 patients who underwent a resection was 38.3 months (95% CI = 36.1 to 42.0 months). Independent prognostic factors at baseline for worse OS were more advanced stage, worse performance status, baseline carbohydrate antigen (CA) 19-9 > 500 U/mL, and body mass index $\leq$18.5 kg/m^2. **Conclusions:** This large international cohort study provides realistic estimates of resection rates and survival in patients with LA, BR, and PR PDAC who started (m)FOLFIRINOX treatment in PDAC referral centers.

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal solid cancers. Even after curative-intent resection, the 10-year overall survival (OS) is only approximately 4% due to high rates of disease recurrence (1). PDAC could be considered a systemic disease even without evidence of distant metastases on initial imaging. Therefore, it has been suggested that systemic therapy should be the initial treatment modality for all patients diagnosed with PDAC, followed by surgery in selected patients (2).

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The multidrug combination regimen of 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin ([m]FOLFIRINOX) has been shown in 2 randomized controlled trials (RCTs) to be superior to gemcitabine in the metastatic and adjuvant settings (3,4). Extrapolating these data, guidelines recommend (m)FOLFIRINOX as the preferred initial treatment for patients with locally advanced (LA) or borderline resectable (BR) PDAC with a good performance status. For patients with potentially resectable (PR) PDAC, adjuvant mFOLFIRINOX is recommended and neoadjuvant (m)FOLFIRINOX can be considered, especially in patients with poor prognostic features (5). In the absence of RCTs, 2 patient-level meta-analyses of nonrandomized studies demonstrated favorable outcomes for patients with LA and BR PDAC treated with (m)FOLFIRINOX (6,7). Moreover, several cohort studies reported favorable survival in the subgroup of patients who underwent a resection after preoperative (m)FOLFIRINOX (8,9). However, that subgroup represents only a minority of all nonselected patients. International series including all patients who started (m)FOLFIRINOX regardless of subsequent treatment (ie, "denominator" data) are lacking.

Within this context, the Trans-Atlantic Pancreatic Surgery (TAPS) Consortium was assembled to investigate the treatment course and oncologic outcome after (m)FOLFIRINOX as initial treatment for localized PDAC. The TAPS consortium combined all consecutive patients to fill the gap in knowledge on real-world outcomes beyond RCTs with restrictive inclusion criteria and small retrospective series with inherent selection bias. The aim of this study was to provide realistic estimates of resection rates and OS after initial (m)FOLFIRINOX for localized PDAC to better inform clinicians and patients.

Methods

Consortium Creation and Study Design

This was an international retrospective cohort study, which was the first study from the TAPS Consortium including 5 high-volume pancreatic cancer referral centers from the United States (Memorial Sloan Kettering Cancer Center, New York City, NY; University of Pittsburgh Medical Center, Pittsburgh, PA; University of Texas MD Anderson Cancer Center, Houston, TX) and the Netherlands (Erasmus MC University Medical Center and Amsterdam UMC, location Academic Medical Center). The rationale behind this consortium was to create a large uniform database including patients from referral centers with comparable high-quality care and only minor differences in patient characteristics and treatment approaches. Consequently, several research questions regarding the treatment and outcomes of patients with localized PDAC can be addressed with generalizable results for other referral centers and benchmarks for community practices. Although diverse in geographic location, all TAPS centers share common features. These include high referral volumes for patients in need of both surgical and nonsurgical therapies, specialty-trained pancreatic surgeons, medical and radiation oncologists with experience in collaborative research studies, institutions recognized as comprehensive multimodality cancer care centers, and prospective databases run by surgeons monitoring data fidelity. The name and purpose of the TAPS Consortium were finalized at the 2020 Americas Hepato-Pancreato-Biliary Association meeting by principal investigators from all TAPS centers. All participating centers hence obtained ethical approval from local institutional review boards as well as legal approval of data sharing agreements for deidentified data to be uploaded and analyzed in a cloud-based digital research environment (Microsoft Azure DRE, Nijmegen, the Netherlands). The requirement to obtain informed consent was waived because of the retrospective nature of the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines (10).

Patients

All consecutive patients diagnosed with localized biopsy-confirmed PDAC between January 1, 2012, and December 31, 2019, who received at least 1 cycle of (m)FOLFIRINOX as initial treatment were included. Inherently, patients not eligible for (m)FOLFIRINOX were not included, although no direct selection was made on performance score or age. Patients who started with a modified regimen were included if the primary intention was to give the complete 4-drug regimen of (m)FOLFIRINOX and they received at least 1 cycle of this complete regimen for localized PDAC. For patients who received part of their treatment outside the 5 TAPS centers, at least 1 follow-up visit and consultation before initiating (m)FOLFIRINOX were required. Patients with all subtypes of PDAC, including PDAC arising from precursor lesions, were included.

Primary and Secondary Outcomes

The primary outcome was OS from the date of tissue diagnosis. Secondary outcomes included resection rate and postoperative outcomes such as margin-negative (R0) resection rate, pathological TNM staging, lymphovascular invasion, perineural invasion, and histologic differentiation grade. Furthermore, details and sequence of treatment after (m)FOLFIRINOX were evaluated, including surgery, second chemotherapy, radiotherapy, adjuvant therapy, and cancer-directed palliative therapy.

Data Collection and Definitions

Predefined data on baseline, radiologic, treatment, and pathological characteristics in addition to survival data were collected locally. Demographics on sex were based on self-report. No data on race and ethnicity were collected. The stage at diagnosis (ie, PR, BR, or LA PDAC) was based on radiographic imaging before initiating (m)FOLFIRINOX, as assessed by the local multidisciplinary team. The MD Anderson Cancer Center (MDACC) Clinical Classification System was used by the MD Anderson Cancer Center (11). The other 4 centers used the National Comprehensive Cancer Network (NCCN) criteria applicable at the time of diagnosis. The main difference is that PR PDAC requires venous contact less than 180° without contour irregularity for NCCN criteria, whereas the MDACC system allows for any degree of venous contact in the absence of occlusion. Tumor marker levels (ie, carbohydrate antigen [CA] 19-9 and carcinoembryonic antigen) closest to the start of FOLFIRINOX were included, preferably measured at the time of normalized bilirubin levels (ie, <1.2 m/dL). If no measurement was conducted simultaneously with normalized bilirubin levels, the value at the time of the lowest bilirubin level within 4 weeks before initiating (m)FOLFIRINOX was used.

Full-dose FOLFIRINOX consisted of oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2), irinotecan (180 mg/m^2), and fluorouracil (2400 mg/m^2) with or without bolus (400 mg/m^2) over 46 hours every 2 weeks. Dosage modifications were allowed. The number

of (m)FOLFIRINOX cycles was defined as all continuous cycles with or without modifications until metastatic disease, change in chemotherapy regimen, or change of treatment modality. Second chemotherapy was defined as any change in the chemotherapy regimen because of toxicity or local progression before radiotherapy or surgery.

R0 resection was defined as the absence of tumor within 1 mm of any resection or dissection margin, including the pancreatic neck, common bile duct, superior mesenteric artery and vein, enteric margins, and the posterior and anterior surfaces (12). All centers used the axial slicing or bivalve dissection technique for pancreatoduodenectomy specimens (13,14). Pathological TNM staging was converted to the 8th edition of the American Joint Committee on Cancer Staging Manual based on pathological tumor size, the number of positive lymph nodes, and arterial involvement (15). Histologic differentiation grade was categorized into 3 levels (grade 1, well differentiated; grade 2, moderate differentiation; and grade 3, poor differentiation). Adjuvant therapy was defined as at least 1 cycle of postoperative chemotherapy. Palliative therapy included any cancer-directed therapy (eg, chemotherapy, immunotherapy, or radiotherapy for local recurrent disease) for metastatic or recurrent disease after start of neoadjuvant or induction treatment. OS was defined as the time between the date of tissue diagnosis and the date of death. To enable comparison with resection cohort studies, a secondary analysis was performed for the subgroup who underwent resection with OS calculated from the date of surgery. The date of final follow-up was December 31, 2020. Patients still alive were censored at their last follow-up date.

Statistical Analysis

Outcomes were presented for the complete cohort and by stage at diagnosis. Baseline characteristics were presented as medians with interquartile ranges (IQRs) for continuous variables and frequencies with proportions for categorical variables. Differences between groups were calculated using the χ^2 test for categorical variables and Mann-Whitney U test for continuous variables. OS was assessed using Kaplan-Meier estimates and presented as median with corresponding 95% confidence interval (CI). Difference in survival outcomes between groups was tested using the log-rank test. The median follow-up time of patients alive at last follow-up was calculated using the reverse Kaplan-Meier method. A Cox proportional hazards regression model was used to assess the potential prognostic baseline factors for OS. Known prognostic factors and factors with a $P < .20$ in univariate analysis were included in the multivariable model (16). The proportional hazards assumption was assessed by visualization of the Schoenfeld residuals and the log[-log(survival)] vs log of survival time plot. The proportional hazards assumption was not violated for any of the factors. Multiple imputation was used to account for missing data in multivariable analysis, including World Health Organization (n = 7), body mass index (BMI) (n = 23), tumor size (n = 61), and CA 19-9 (n = 102). All tests were 2-sided, and $P < .05$ was considered statistically significant. All analyses were performed using R software, version 3.4.3.

Results

Baseline Characteristics

From 2012 through 2019, 1835 patients were diagnosed with localized PDAC and started (m)FOLFIRINOX as initial treatment. At diagnosis, 958 (52.2%) were staged as LA, 531 (28.9%) as BR, and 346 (18.9%) as PR PDAC. Patient and treatment characteristics are summarized in Table 1. Most patients were men (54.6% male, 45.4% female), median age was 64 years, and 95.6% had a performance score of 0 or 1. Initial FOLFIRINOX was started at centers other than the 5 TAPS centers in 106 patients (5.8%), and 35 patients (1.9%) received initial (m)FOLFIRINOX after aborted upfront surgery.

Treatment Characteristics

Figure 1 shows the flow chart of subsequent treatments after (m)FOLFIRINOX for all patients. A separate flow chart for each stage (ie, LA, BR, and PR) is included in the Supplementary Figure 1, A-C (available online). The median number of initial (m)FOLFIRINOX cycles was 6 (IQR = 4-8). Second chemotherapy was administered to 236 patients (12.9%). Furthermore, systemic chemotherapy was followed by radiotherapy (ie, excluding adjuvant radiotherapy) in 888 patients (49.0%), including 546 patients with LA (57.7%), 222 with BR (42.7%), and 120 with PR (34.9%) PDAC (Table 1).

Treatment Evaluation

At multidisciplinary evaluation after all systemic treatment with or without radiotherapy, 51.5% of patients were ineligible for surgery. This was due to anatomy (definitively unresectable disease on imaging in 504 patients [27.5%]), biology (metastases in 351 patients [19.1%]), or condition (clinical decline without metastases or other medical conditions precluding surgery in 90 patients [4.9%]). The remaining 868 patients (47.3%) were considered for surgical exploration (Figure 1; Table 1). Fourteen patients (1.6%) ultimately did not undergo surgery because of the patient's preference (n = 7) or unknown reason (n = 7).

Surgical Cohort

Overall, 854 patients (46.5%) underwent surgical exploration, of whom 159 (8.7%) did not undergo resection because of occult metastatic disease in 77 (4.2%), unresectable disease in 78 (4.3%), or other reasons encountered during surgical exploration (eg, unrecognized cirrhosis) in 8 (0.1%) (Figure 1, A). The remaining 695 patients (81.4%; 37.8% of the total cohort) underwent resection. Resection rates were 17.6% for LA, 53.1% for BR, and 70.5% for PR PDAC ($P < .001$) (Table 1). Median time from diagnosis to resection was 175 (IQR = 135-225) days. Vascular resection was performed in 292 of 695 patients (42.0%). Arterial resection and reconstruction was performed in 128 of 695 (18.4%) patients. The 30- and 90-day postoperative mortality rates were 1.0% and 2.0%, respectively.

Following resection, 411 patients (59.1%) received adjuvant therapy, of whom 149 of 411 (36.3%) received (m)FOLFIRINOX with a median of 6 (IQR = 4-6) cycles (data not shown). Other adjuvant regimens included gemcitabine-based therapy in 203 of 411 patients (49.4%), 5-fluorouracil–based therapy other than (m)FOLFIRINOX in 27 of 411 patients (6.6%), and (chemo)radiotherapy in 66 of 411 patients (16.1%).

Pathology Outcomes

Pathology outcomes for patients who underwent a resection are shown in Table 2. The R0 resection rate was 405 of 613 (66.1%)

Table 1. Baseline characteristics of included patients and treatment specifications

Patient and treatment characteristics[a]	Overall (N = 1835)	LA (n = 958)	BR (n = 531)	PR (n = 346)	P[b]
Sex, No. (%)					.06
Male	1002 (54.6)	502 (52.4)	293 (55.2)	207 (59.8)	
Female	833 (45.4)	456 (47.6)	238 (44.8)	139 (40.2)	
Median age (IQR), y	64 (57, 69)	63 (56, 68)	64 (57, 70)	65 (58, 70)	.003
Performance status, No. (%)					<.001
WHO 0	718 (39.3)	305 (32.1)	254 (47.8)	159 (46.0)	
WHO 1	1036 (56.7)	605 (63.6)	261 (49.2)	170 (49.1)	
WHO 2-3	74 (4.0)	41 (4.3)	16 (3.0)	17 (4.9)	
Median BMI, kg/m^2 (IQR)	26 (23, 29)	26 (23, 29)	26 (23, 30)	27 (24, 30)	<.001
Location, No. (%)					<.001
Head/uncinated	1223 (66.6)	555 (57.9)	422 (79.5)	246 (71.1)	
Body/tail	612 (33.4)	403 (42.1)	109 (20.5)	100 (28.9)	
Median tumor size on CT (IQR), mm	36 (28, 46)	39 (32, 49)	34 (27, 42)	30 (24, 38)	<.001
Median pretreatment CA 19-9 (IQR), U/mL	208 (46, 774)	236 (51, 858)	219 (48, 720)	148 (42, 490)	.003
Median pretreatment CA 19-9, No. (%)					.004
Nonsecretor (<5 U/mL)	124 (7.3)	64 (7.2)	42 (8.6)	18 (5.6)	
5-500 U/mL	1016 (59.8)	508 (57.4)	285 (58.0)	223 (69.0)	
>500 U/mL	559 (32.9)	313 (35.4)	164 (33.4)	82 (25.4)	
Median pretreatment CEA (IQR), ng/mL	3.8 (2.2, 7.3)	3.9 (2.2, 8.2)	3.5 (2.1, 6.4)	3.7 (2.4, 6.3)	.17
Median no. of cycles (IQR)	6 (4, 8)	7 (4, 8)	6 (4, 8)	5 (4, 8)	<.001
Cycles, No. (%)					<.001
1-4 cycles	646 (35.2)	295 (30.8)	203 (38.2)	148 (42.8)	
5-8 cycles	868 (47.3)	423 (44.2)	265 (49.9)	180 (52.0)	
>8 cycles	320 (17.4)	239 (25.0)	63 (11.9)	18 (5.2)	
Second chemotherapy, No. (%)	236 (12.9)	126 (13.2)	77 (14.6)	33 (9.5)	.09
Radiotherapy[c], No. (%)	888 (49.0)	546 (57.7)	222 (42.7)	120 (34.9)	<.001
Multidisciplinary recommendation after systemic treatment with or without radiotherapy, No. (%)					<.001
Surgical exploration	868 (47.9)	252 (26.7)	340 (64.4)	276 (81.2)	
Pall. tx/BSC for metastases	351 (19.4)	219 (23.2)	93 (17.6)	39 (11.5)	
Pall. tx/BSC for unresectable disease	504 (27.8)	418 (44.2)	71 (13.4)	15 (4.4)	
BSC for clinical decline/comorbidities	90 (5.0)	56 (5.9)	24 (4.5)	10 (2.9)	
Surgery with intent of resection, No. (%)	854 (46.5)	247 (25.8)	335 (63.1)	272 (78.6)	<.001
Resection, No. (%)	695 (37.9)	169 (17.6)	282 (53.1)	244 (70.5)	<.001
Surgical procedure, No. (%)					<.001
Pancreatoduodenectomy	514 (74.3)	98 (58.7)	238 (84.7)	178 (73.0)	
Distal pancreatectomy	145 (21.0)	57 (34.1)	30 (10.7)	58 (23.8)	
Central pancreatectomy	27 (3.9)	9 (5.4)	12 (4.3)	6 (2.5)	
Total pancreatectomy	6 (0.9)	3 (1.8)	1 (0.4)	2 (0.8)	
Adjuvant treatment, No. (% of resections)	411 (59.2)	73 (43.5)	177 (62.8)	161 (66.0)	<.001
Palliative cancer-directed treatment[d], No. (%)	1022 (58.6)	575 (62.8)	279 (55.1)	168 (51.9)	<.001

[a]Missing data: age (n = 1), WHO (n = 7), BMI (n = 21), size (n = 61), CA 19-9 (n = 113), CEA (n = 761), cycles (n = 1), second chemotherapy (n = 9), radiotherapy (n = 24), recommendation (n = 22), procedure (n = 3), adjuvant (n = 1), palliative (n = 90). BMI = body mass index; BR = borderline resectable; BSC = best supportive care; CA 19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; IQR = interquartile range; LA = locally advanced; Pall. tx = palliative treatment; PR = potentially resectable; WHO = World Health Organization.

[b]Differences between groups were calculated using the χ^2 test for categorical variables and Mann-Whitney U test for continuous variables. All tests were 2-sided.

[c]Preoperative radiotherapy only.

[d]Any cancer-directed treatment (eg, chemotherapy, immunotherapy, or radiotherapy for local recurrent disease) for metastatic or recurrent disease after start of neoadjuvant or induction treatment.

for patients with known margin status: 55.2% for LA, 62.6% for BR, and 79.2% for PR PDAC (P < .001). In total, 33 of 597 (5.5%; 1.8% of the total cohort) patients with known pathologic response had a complete response, and 302 of 684 (44.2%; 16.5% of the total cohort) patients with known nodal status had node-negative disease.

Survival Outcomes

After a median follow-up time of 36.5 months, 1202 patients (65.6%) had died. The median OS for all patients was 21.4 months (95% CI = 20.1 to 22.7) (Supplementary Figure 2, A, available online). The median OS was 18.7 months (95% CI = 17.7 to 19.9) for LA, 23.2 months (95% CI = 21.0 to 25.7) for BR, and 31.2 months (95% CI = 26.2 to 36.6) for PR PDAC (P < .001) (Figure 2, A). The 5-year OS rate was 15.8% (95% CI = 13.6% to 18.4%) for all patients, including 9.5% (95% CI = 7.2% to 12.6%) for LA, 18.4% (95% CI = 14.1% to 23.9%) for BR, and 33.7% (95% CI = 27.1% to 42.0%) for PR PDAC.

The median OS from diagnosis for patients who did not undergo a resection was 16.3 months (95% CI = 15.6 to 17.2 months) (Figure 2, B). Median OS from diagnosis for patients who underwent a resection was 38.3 months (95% CI = 36.1 to 42.0 months). From the date of surgery, the median OS was 32.6 months (95% CI = 29.2 to 37.0 months). The 5-year OS rate for patients who

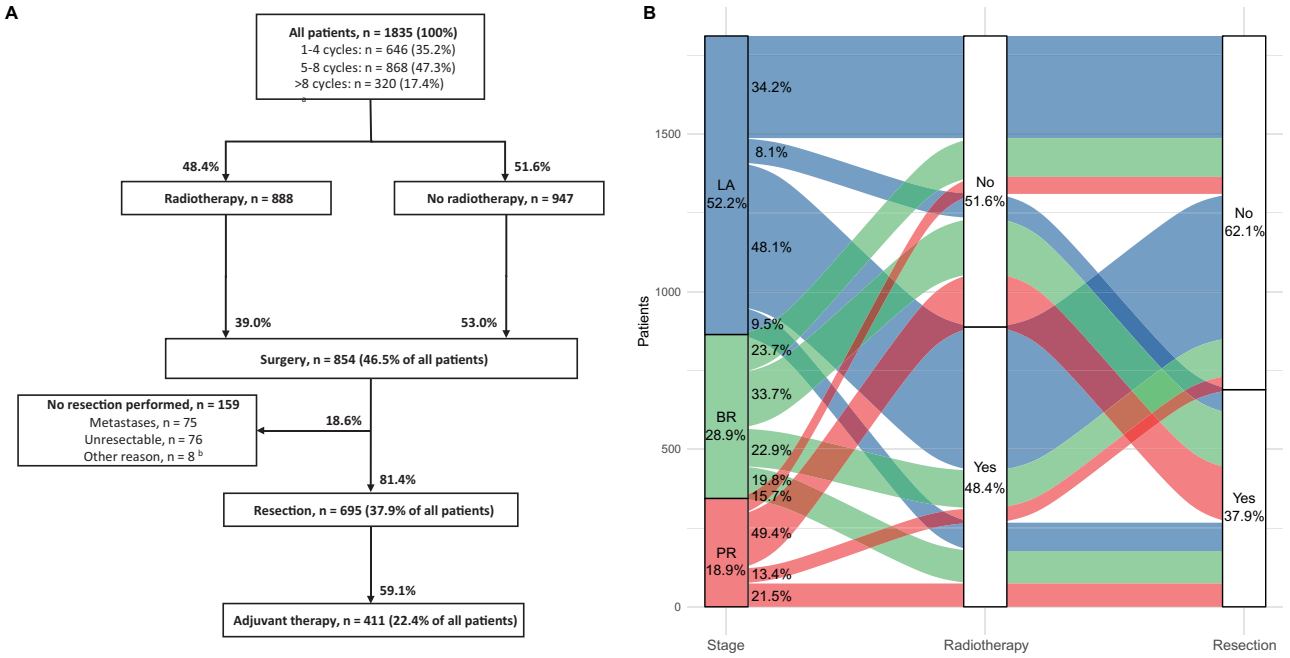

Figure 1. Flow chart and alluvial diagram of treatment for all patients with localized pancreatic adenocarcinoma who started treatment with (m)FOLFIRINOX. **A)** A flow chart of treatment for all patients with localized pancreatic adenocarcinoma treated with (m)FOLFIRINOX is shown.

[a]236 patients (13%) also received second chemotherapy.

[b]Other reasons for not performing a resection were a cirrhotic liver in 3, peripancreatic fibrosis in 3, and an unknown reason for not performing a resection in 2 patients. **B)** In the alluvial diagram, the first column shows the stage at baseline before start of (m)FOLFIRINOX, the second column shows whether patients received radiotherapy to the primary tumor after initial (m)FOLFIRINOX, and the last column shows whether patients underwent a surgical resection. Percentages in columns represent the percentages of the total cohort. Percentages in the **blue**, **green**, and **red stream fields** represent the stage-specific percentages for subsequent radiotherapy and surgery. For example, 52.2% of the total cohort was diagnosed with locally advanced pancreatic ductal adenocarcinoma (LA PDAC). Of those LA PDAC patients, 34.2% received radiotherapy and did not undergo resection after start of (m)FOLFIRINOX, 8.1% did not receive radiotherapy but did undergo a resection, 48.1% received radiotherapy but did not undergo a resection, and 9.5% received both radiotherapy and resection. Due to rounding, total stage-specific percentages may not exactly add up to 100%. BR = borderline resectable; LA = locally advanced; (m)FOLFIRINOX = 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin, with or without modifications; PR = potentially resectable.

underwent a resection was 33.4% (95% CI = 28.7% to 39.0%) for all patients, including 24.9% (95% CI = 16.9% to 36.5%) for LA, 31.5% (95% CI = 24.6% to 40.3%) for BR, and 44.6% (95% CI = 36.3% to 54.9%) for PR PDAC. The 5-year OS rate for patients who did not undergo a resection was 4.8% (95% CI = 3.3% to 7.2%) and the 2-year OS rate was 27.6% (95% CI = 24.9% to 30.6%). The median OS from diagnosis for 888 patients (49.0%) who received radiotherapy after initial (m)FOLFIRINOX (ie, excluding adjuvant radiotherapy) was 23.6 months (95% CI = 22.4 to 25.7 months); the median OS from diagnosis for 923 patients who did not receive additional radiotherapy was 18.4 months (95% CI = 17.5 to 20.1 months) (hazard ratio = 0.77, 95% CI = 0.69 to 0.87, $P < .001$).

Baseline Factors Prognostic for OS

Independent prognostic factors at baseline for worse OS were more advanced stage, worse performance status, baseline CA 19-9 level greater than 500 U/mL, and BMI of 18.5 kg/m^2 or less (Table 3). All factors were measured before start of (m)FOLFIRINOX. Supplementary Figure 2, B-D (available online), show the survival curves of the 3 prognostic factors besides stage.

Discussion

This large, international, multicenter, retrospective cohort study assessed the treatment course and outcomes of 1835 patients who received (m)FOLFIRINOX as initial treatment for localized PDAC. Following (m)FOLFIRINOX, 49.0% received radiotherapy and 37.9% underwent a resection, of whom 59.2% started adjuvant treatment. The resection rate was 17.6% for LA, 53.1% for BR, and 70.5% for PR PDAC. The median OS was 18.7 months for LA, 23.2 months for BR, and 31.2 months for PR PDAC. In a multivariable analysis of baseline factors, more advanced stage, worse performance status, baseline CA 19-9 level greater than 500 U/mL, and BMI of 18.5 kg/m^2 or less were independently associated with worse OS.

To our knowledge, this study is the largest reported series on (m)FOLFIRINOX for localized PDAC to date. In the past decade, 2 patient-level meta-analyses of small cohort studies and several phase II trials investigated (m)FOLFIRINOX as initial treatment for LA, BR, and/or PR PDAC (6,7,17–30). In Supplementary Table 1 (available online), the resection rate and median OS of some key studies are presented. The broad range of outcomes across studies is partly explained by the small sample size of most studies. In addition, heterogeneity reflects differences in patient characteristics, staging, whether all consecutive patients were captured, the duration of systemic treatment, and subsequent treatments. Based on the large number of patients, the inclusion of all "denominator" data, and the international group of centers, our results are generalizable to pancreatic cancer referral centers. The results can be used as reference data for other experienced centers treating patients with localized PDAC with initial (m)FOLFIRINOX.

Table 2. Pathological outcomes of patients who underwent a resection

Pathological outcomes[a]	Overall (N = 695)	LA (n = 169)	BR (n = 282)	PR (n = 244)	P[b]
Tumor size, No. (%)					.17
0-20 mm	231 (34.1)	45 (28.5)	98 (35.0)	88 (36.7)	
21-40 mm	333 (49.1)	77 (48.7)	140 (50.0)	116 (48.3)	
>40 mm	114 (16.8)	36 (22.8)	42 (15.0)	36 (15.0)	
T stage[c], No. (%)					.04
ypT0	33 (4.9)	9 (5.7)	9 (3.2)	15 (6.2)	
ypT1-2	493 (72.5)	102 (64.2)	215 (76.8)	176 (73.0)	
ypT3-4	154 (22.6)	48 (30.2)	56 (20.0)	50 (20.7)	
N stage[c], No. (%)					.92
ypN0	302 (44.2)	75 (46.6)	119 (42.3)	108 (44.6)	
ypN1	245 (35.8)	56 (34.8)	105 (37.4)	84 (34.7)	
ypN2	137 (20.0)	30 (18.6)	57 (20.3)	50 (20.7)	
Resection margin status[d], No. (%)					<.001
R0	405 (66.1)	85 (55.2)	164 (62.6)	156 (79.2)	
R1	208 (33.9)	69 (44.8)	98 (37.4)	41 (20.8)	
Tumor differentiation, No. (%)					.11
Well (G1)	21 (3.4)	7 (4.9)	8 (3.1)	6 (2.9)	
Moderate (G2)	402 (65.8)	81 (57.0)	182 (70.3)	139 (66.2)	
Poor (G3)	188 (30.8)	54 (38.0)	69 (26.6)	65 (31.0)	
Perineural invasion, No. (%)	512 (75.6)	111 (70.7)	219 (78.2)	182 (75.8)	.21
Lymphovascular invasion, No. (%)	370 (55.2)	80 (51.3)	157 (56.5)	133 (56.4)	.53
Pathologic response, No. (%)					.23
Complete response	33 (5.5)	9 (6.9)	9 (3.6)	15 (6.9)	
<5% viable tumor cells	58 (9.7)	17 (13.1)	24 (9.6)	17 (7.8)	
≥5% viable tumor cells	506 (84.8)	104 (80.0)	216 (86.7)	186 (85.3)	

[a]Missing data: tumor size (n = 17), ypT (n = 15), ypN (n = 11), margin (n = 82), differentiation (n = 84), perineural (n = 18), lymphovascular (n = 25), pathologic response (n = 98). BR = borderline resectable; LA = locally advanced; PR = potentially resectable.
[b]Differences between groups were calculated using the χ^2 test. All tests were 2-sided.
[c]Eighth edition of the American Joint Committee on Cancer Staging.
[d]One-mm definition of the Royal College of Pathologists.

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Initial (m)FOLFIRINOX was the focus of this study; however, no RCT has been published that shows superiority of (m)FOLFIRINOX over other regimens beyond the metastatic and adjuvant setting. Several ongoing RCTs compare initial FOLFIRINOX with gemcitabine-based regimens. For the Dutch PREOPANC-2 trial, comparing neoadjuvant FOLFIRINOX with neoadjuvant gemcitabine-based chemoradiotherapy for BR and PR PDAC, accrual was completed in January 2021 (31). A Chinese RCT compared initial mFOLFIRINOX with gemcitabine plus nab-paclitaxel for LA and BR PDAC (NCT04617821).

The available evidence on neoadjuvant (m)FOLFIRINOX for PR PDAC is limited. The phase II SWOG S1505 trial is the largest prospective study to date, including 102 patients (18). This study compared 12 weeks of pre- and postoperative mFOLFIRINOX (n = 55) with gemcitabine plus nab-paclitaxel (n = 47), showing a resection rate of 73% and median OS of 23.2 months for mFOLFIRINOX, with no difference in outcomes between the treatment arms. This study included 346 patients with PR PDAC, showing a similar resection rate of 70.5% and a median OS of 31.2 months. In comparison, the PRODIGE24/CCTG PA.6 trial found a median OS of 54.4 months for patients who received adjuvant mFOLFIRINOX. An adjuvant trial, however, includes only the selected subgroup of patients who underwent a resection, without evidence of early recurrence on CT, a low postoperative CA 19-9 level, and a good performance score within 3 months after resection. Currently, 4 RCTs directly compare neoadjuvant with adjuvant (m)FOLFIRINOX, including the NorPACT-1 (32), ALLIANCE A021806 (NCT04340141), PREOPANC-3 (NCT04927780), and PANACHE01-PRODIGE48 (33).

Almost one-half of all patients received radiotherapy after initial (m)FOLFIRINOX, whereas no RCT has been published to support radiotherapy after (m)FOLFIRINOX in LA, BR, or PR PDAC. Recently, the ALLIANCE A021501 trial did not demonstrate a benefit in OS of stereotactic body radiation therapy (SBRT) after initial mFOLFIRINOX for BR PDAC (25). A recent meta-analysis comparing neoadjuvant (m)FOLFIRINOX alone or followed by radiotherapy for BR and PR PDAC showed an improved R0 resection rate but no difference in OS (34). In this study, patients who received additional radiotherapy following systemic treatment showed superior OS compared with those who did not. However, both selection bias and guarantee-time bias may have influenced this comparison (35). Future studies are needed to further elucidate the role of radiotherapy for PDAC. Ongoing trials investigating the role of radiotherapy after multidrug systemic treatment include the CONKO-007 trial (36) for LA PDAC and the PANDAS-PRODIGE44 trial (NCT02676349) for BR PDAC. With the literature available to date, no strong recommendation for or against radiotherapy after initial (m)FOLFIRINOX is possible at this time.

Four factors at diagnosis were independently associated with worse OS: radiographic stage (ie, LA, BR, PR), baseline CA 19-9 level greater than 500 U/mL, performance status, and BMI of 18.5 kg/m^2 or less. Conventional staging systems (eg, NCCN) are based only on the radiographic stage determined by the apparent abutment of the tumor to the vasculature (5). The difference in anatomical tumor-vessel contact may also represent a biological difference. In addition, the poor prognostic value of serum CA 19-9 level greater than 500 U/mL has been

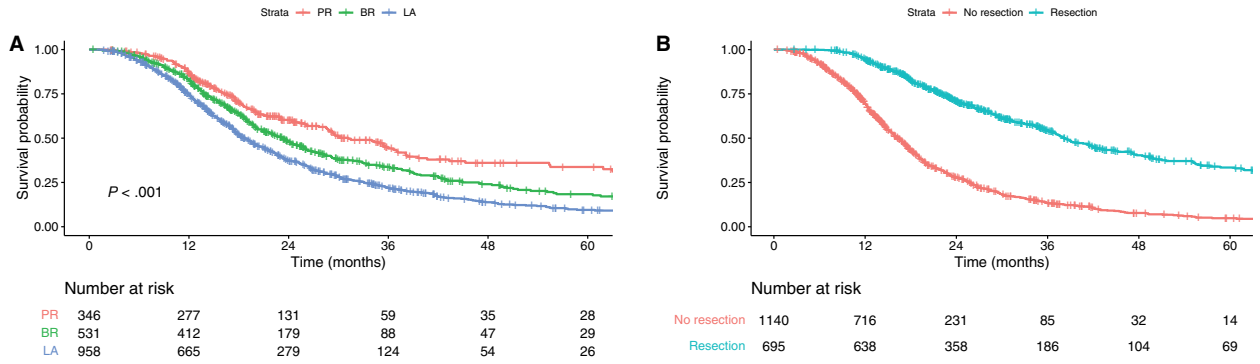

Figure 2. Overall survival of patients with localized pancreatic adenocarcinoma treated with (m)FOLFIRINOX as initial treatment by radiographic stage at diagnosis and by resection status. **A)** MD Anderson Cancer Center (MDACC) classification was used for patients from MDACC. National Comprehensive Cancer Network (NCCN) classification applicable at time of diagnosis was used for patients from the other centers. Difference in survival outcomes between groups was tested using the log-rank test. The test was 2-sided. $P < .001$. **B)** Survival was measured from the time of diagnosis in patients who did and did not undergo resection. BR = borderline resectable; LA = locally advanced; (m)FOLFIRINOX = 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin, with or without modifications; PR = potentially resectable.

Table 3. Univariate and multivariable Cox proportional hazards regression analysis of overall survival using baseline factors for all patients[a]

Baseline factors	No. of patients	Univariate analysis		Multivariable analysis	
		HR (95% CI)	P[b]	HR (95% CI)	P[b]
Sex					
Male	1002	1 [Referent]	NA	–	–
Female	833	0.95 (0.85 to 1.07)	.41		
Age, y					
<65	990	1 [Referent]	NA	–	–
65-74	711	1.04 (0.92 to 1.17)	.57		
≥75	133	1.15 (0.91 to 1.45)	.24		
Location					
Head/uncinate	1223	1 [Referent]	NA	–	–
Body/tail	612	0.97 (0.86 to 1.09)	.58		
Performance status					
WHO 0	718	1 [Referent]	NA	1 [Referent]	NA
WHO 1	1036	1.39 (1.23 to 1.56)	<.001	1.31 (1.16 to 1.48)	<.001
WHO 2-3	74	1.74 (1.31 to 2.32)	<.001	1.78 (1.33 to 2.37)	<.001
BMI, kg/m^2					
18.5-30	1374	1 [Referent]	NA	1 [Referent]	NA
≤18.5	53	1.66 (1.21 to 2.27)	.002	1.46 (1.06 to 2.01)	.02
>30	387	0.98 (0.85 to 1.13)	.77	1.03 (0.90 to 1.19)	.67
Radiographic stage at baseline					
PR PDAC	346	1 [Referent]	NA	1 [Referent]	NA
BR PDAC	531	1.44 (1.19 to 1.73)	<.001	1.43 (1.18 to 1.72)	<.001
LA PDAC	958	1.94 (1.63 to 2.30)	<.001	1.81 (1.20 to 2.16)	<.001
Tumor size on baseline CT					
0-20 mm	97	1 [Referent]	NA	1 [Referent]	NA
21-40 mm	1036	1.33 (0.98 to 1.79)	.06	0.99 (0.73 to 1.35)	.97
>40 mm	641	1.56 (1.15 to 2.11)	.004	1.05 (0.77 to 1.44)	.75
Pretreatment CA 19-9					
5-500 U/mL	1016	1 [Referent]	NA	1 [Referent]	NA
Nonsecretor (<5 U/mL)	124	1.19 (0.95 to 1.49)	.13	1.16 (0.93 to 1.44)	.19
>500 U/mL	559	1.42 (1.25 to 1.61)	<.001	1.39 (1.23 to 1.58)	<.001

[a]Imputed data for multivariable analysis: WHO (n = 7), BMI (n = 21), tumor size (n = 61), and CA 19-9 (n = 136). BMI = body mass index; BR = borderline resectable; CA 19-9 = carbohydrate antigen 19-9; CI = confidence interval; CT = computed tomography; HR = hazard ratio; LA = locally advanced; NA = not applicable; PR = potentially resectable; WHO = World Health Organization.

[b]A Cox proportional hazards regression model was used to assess the potential prognostic baseline factors for OS. Known prognostic factors and factors with *P* less than .20 in univariate analysis were included in the multivariable model (16).

acknowledged in the biological definition of BR PDAC of the MDACC classification introduced in 2008 and subsequently adapted by the International Association of Pancreatology (11,37,38). These classifications upstaged patients with a performance status greater than or equal to 2. This study found that even a performance status of 1 (compared with 0) was associated with worse OS. Although not common, underweight (BMI ≤ 18.5 kg/m^2) at diagnosis, another measure of

poor clinical condition, was one of the worst prognostic factors.

This international, multicenter, retrospective cohort study has some inherent limitations. First, no centralized histopathological or radiologic review was conducted, and the staging criteria (eg, NCCN, MDACC) differed somewhat across centers. Moreover, the NCCN criteria have changed slightly over time. Second, the participating centers varied in terms of subsequent treatment after (m)FOLFIRINOX. All centers, however, are experienced referral centers, and heterogeneity in subsequent treatment makes the study results more generalizable to everyday patients in pancreatic cancer referral centers. Third, community practices may care for a patient population that differs from this study and consequently may have different outcomes. Finally, no detailed data on radiographic treatment response or timing and site of disease progression (eg, local vs distant, primary site of distant progression) were collected.

The results of this TAPS cohort allow for improved discussion between patients and clinicians regarding resection rates and survival outcomes by clinical stage after initial (m)FOLFIRINOX for localized PDAC. Moreover, the results can be used as robust real-world estimates for sample size calculations for studies investigating new treatments for PDAC when initial (m)FOLFIRINOX is the standard arm. Future research should determine the optimal number of cycles of (m)FOLFIRINOX treatment before definitive local therapy. Moreover, future studies may investigate which patients benefit from subsequent treatments, including second systemic regimens, radiotherapy, surgical resection, and adjuvant chemotherapy.

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Data Availability

The data that support the findings of this study are available from the corresponding author, B. Groot Koerkamp, upon reasonable request.

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