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Response and Survival Associated With First-line FOLFIRINOX vs Gemcitabine and nab-Paclitaxel Chemotherapy for Localized Pancreatic Ductal Adenocarcinoma

Giampaolo Perri, MD; Laura Prakash, MD; Wei Qiao, PhD; Gauri R. Varadhachary, MD; Robert Wolff, MD; David Fogelman, MD; Michael Overman, MD; Shubham Pant, MD; Milind Javle, MD; Eugene J. Koay, MD; Joseph Herman, MD; Michael Kim, MD; Naruhiko Ikoma, MD; Ching-Wei Tzeng, MD; Jeffrey E. Lee, MD; Matthew H. G. Katz, MD

IMPORTANCE Fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and gemcitabine plus nanoparticle albumin-bound (nab)–paclitaxel (GA) are first-line chemotherapy regimens for pancreatic cancer. Their relative efficacy in the setting of localized disease is unknown.

OBJECTIVE To evaluate radiographic and serologic measures of responses associated with first-line chemotherapy with FOLFIRINOX or GA, and to determine the association between these drug regimens, putative measures of response, and survival.

DESIGN, SETTING, AND PARTICIPANTS This case series assessed 485 consecutive patients who were diagnosed as having previously untreated localized pancreatic ductal adenocarcinoma at The University of Texas MD Anderson Cancer Center between January 1, 2010, and December 31, 2017, and who received at least 3 cycles of first-line chemotherapy with FOLFIRINOX or GA. The median (range) follow-up duration was 33 (2-28) months.

EXPOSURES Administration of FOLFIRINOX (285 patients [59%]) or GA (200 patients [41%]) as first-line chemotherapy.

MAIN OUTCOMES AND MEASURES Resection rate, radiographic metrics (Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1, and change in tumor volume or anatomic staging), a serologic metric (serum cancer antigen 19-9 level), and overall survival after administration of first-line chemotherapy.

RESULTS In total, 485 patients (266 [55%] male) were included in the analysis. Patients treated with FOLFIRINOX were generally younger (median [range] age at diagnosis: 61 [30-81] vs 71 [36-89] years; $P = .001$) and had better performance status as indicated by the Eastern Cooperative Oncology Group scale (range 0-4, with lower numbers representing better performance) score of 2 or lower (274 patients [96%] vs 165 patients [82%] $P = .001$) but more invasive tumors than patients who received GA (91 [32%] vs 90 [45%] resectable tumors; $P = .01$). After propensity score matching to control for these biases, many objective serologic and radiographic metrics of response associated with administration of FOLFIRINOX or GA—including low rates of local tumor downstaging—did not differ. However, RECIST partial response was more common among patients treated with FOLFIRINOX (27 of 140 patients [19%]) than with GA (8 of 140 patients [6%]; $P = .001$). Moreover, (chemo)radiation (50% vs 34%; $P = .001$) was more commonly administered to and pancreatectomy (27% vs 16%; $P = .01$) was subsequently performed more frequently for patients initially treated with FOLFIRINOX. The overall survival duration of patients treated with either regimen was similar (hazard ratio, 1.48; 95% CI, 0.97-2.26; $P = .07$).

CONCLUSIONS AND RELEVANCE In this cohort of patients with localized pancreatic adenocarcinoma who received FOLFIRINOX or GA as their first line of therapy, FOLFIRINOX was associated with higher rates of RECIST partial response and subsequent pancreatectomy than GA, but the overall survival associated with these regimens was similar.

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Invited Commentary
Supplemental content

Author Affiliations: Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston (Perri, Prakash, Kim, Ikoma, Tzeng, Lee, Katz); Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston (Qiao); Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston (Varadhachary, Wolff, Fogelman, Overman, Pant, Javle); Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston (Koay, Herman).

Corresponding Author: Matthew H. G. Katz, MD, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1484, Houston, TX 77030-4009 (mhgkatz@mdanderson.org).

FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) and gemcitabine hydrochloride plus nanoparticle albumin-bound paclitaxel (GA) prolong the survival of patients with metastatic pancreatic ductal adenocarcinoma (PDAC).[1,2] These agents have increasingly been administered to patients with localized cancer, often prior to anticipated local treatment with (chemo)radiation, pancreatectomy, or both. For patients with locally advanced and borderline resectable tumors, these regimens are used to eradicate occult cancer, to select patients for whom local therapies might be most effective, and to reduce the anatomic extent of tumors to facilitate resection.[3] They are also recommended to patients with less invasive disease who are likewise thought to benefit from the early systemic and selective effects of chemotherapy despite having tumors that are otherwise surgically removable.[4,5]

Treatment with FOLFIRINOX is generally considered to be a more effective, but more toxic, systemic regimen than GA. In separate trials of patients treated for metastatic PDAC, FOLFIRINOX had a response rate of 31.6% and GA had a response rate of 23%; however, FOLFIRINOX was associated with higher rates of grade 3 and above adverse events.[1,2] Although clinical practice guidelines suggest that either regimen may be delivered as first-line therapy to patients with advanced PDAC, FOLFIRINOX has been favored in practice; GA is considered an alternative for patients who are not anticipated to tolerate FOLFIRINOX.[6]

Therapy with FOLFIRINOX is likewise generally favored when chemotherapy is administered as first-line treatment to patients with localized PDAC. In this setting, these regimens have primarily been studied in the context of their ability to allow subsequent pancreatectomy. Thus, they have they been considered primarily in anecdotal series reporting outcomes of patients who have received "neoadjuvant" therapy and have undergone resection, or in clinical trials of relatively robust patients with favorable oncologic and physiologic profiles.[7-10] In reality, however, many patients with localized cancers—such as older adults or those who are infirm or have clinical evidence suggestive of but not pathognomonic for synchronous metastatic disease—are treated with chemotherapy with little or no anticipation that surgery will ultimately follow. Expectations regarding the effects of FOLFIRINOX and GA in these patients cannot be extrapolated from existing studies of selected patients; data describing the efficacy of these agents in large, heterogeneous populations of patients with localized PDAC do not exist. Objective data to inform shared decision-making regarding the choice of FOLFIRINOX or GA as first-line therapy for localized PDAC are needed.

In the present study, we sought to evaluate and compare radiographic and serologic metrics of responses associated with first-line chemotherapy with FOLFIRINOX and GA in a consecutive, unselected series of patients who presented during a 7-year period for treatment of a new diagnosis of localized PDAC. We further sought to evaluate and compare survival rates of patients who received each of these regimens.

Key Points

Question What are the radiologic, serologic, and survival outcomes of patients associated with receipt of first-line chemotherapy with FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) or gemcitabine plus nab-paclitaxel for localized pancreatic cancer?

Findings Among 485 patients treated in this case series with first-line FOLFIRINOX or gemcitabine plus nab-paclitaxel, Response Evaluation Criteria in Solid Tumors partial response was more common and pancreatectomy was performed more often after FOLFIRINOX; however, other measures of response to therapy and overall survival were similar. Anatomic downstaging occurred in less than 10% of patients with borderline resectable or locally advanced tumors treated with each regimen.

Meaning Chemotherapy with FOLFIRINOX may have advantages relative to gemcitabine plus nab-paclitaxel and may be considered preferentially for patients without contraindications and who are anticipated to tolerate it, although known regimen toxicity profiles and patient clinical status should also be considered.

Methods

We used a prospectively maintained database to identify 619 consecutive patients who received a diagnosis of localized, previously untreated PDAC between January 1, 2010, and December 31, 2017, and who were prescribed chemotherapy with FOLFIRINOX or GA as the first line of therapy (eFigure 1 in the Supplement).[11] Of those 619 patients, 134 patients were excluded from analysis: 38 who received fewer than 3 cycles of chemotherapy; 10 who received FOLFIRINOX and GA consecutively; 6 who received a final diagnosis of PDAC arising in an intraductal papillary mucinous neoplasm; 3 who had a baseline computed tomography (CT) study that showed severe acute pancreatitis or no visible mass; 2 who underwent pancreatectomy elsewhere; and 75 who underwent imaging using a CT scanning protocol other than that described below or for whom CT images taken at baseline or restaging were not available for re-review. The Institutional Review Board at The University of Texas MD Anderson Cancer Center approved this study and waived the requirement for obtaining informed patient consent because the research involved no more than minimal risk to the patients, the waiver would not adversely affect the rights and welfare of the participants, and the research was retrospective and could not practicably be carried out without the waiver. No one received compensation or was offered any incentive for participating in this study.

Radiographic Review

Disease staging was accomplished with multidetector CT using a 64-detector row scanner and a standard protocol.[12] Tumors were radiographically staged as potentially resectable, borderline resectable, or locally advanced.[13] The baseline and posttreatment CT images of all patients were re-reviewed for this study by a surgeon (G.P.) who was blinded to treatment and outcome.

The examiner measured the tumor size using the longest (L) and shortest (W) axial diameters and the craniocaudal diameter (H). The volume of each tumor was calculated according to the formula for a typical ellipsoid: Volume = $\pi/(6 \times L \times W \times H)$.[14] The change in tumor volume after preoperative treatment was calculated as a percentage of

the baseline volume. Changes were also described using the modified Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, guideline as progressive disease, partial response (PR), stable disease, or complete response.[15]

Serum Cancer Antigen 19-9 Level

Serum cancer antigen (CA) 19-9 levels (reference range, 0-37 U/mL; to convert to kilounits per liter, multiply by 1.0) were measured before and after treatment. Patients with a CA 19-9 level of less than 1 U/mL both before and after treatment were defined as nonproducers.

Therapy and Follow-up

The performance status of all patients was determined at baseline by using the Eastern Cooperative Oncology Group system (range of scores, 0-4, with lower numbers representing better performance).[16] First-line therapy was administered as part of a trial protocol in some patients. Systemic chemotherapy consisted of FOLFIRINOX or GA or both. In general, chemotherapy was administered for 2 to 4 months to patients with resectable or borderline resectable disease for whom surgery was anticipated. Comprehensive staging was conducted every 2 months during treatment.

Following systemic chemotherapy, treatment included 1 or more of the following: second-line chemotherapy, (chemo) radiation, pancreatectomy,[17] and observation/supportive care. (Chemo)radiation consisted either of external-beam radiation therapy (50.4 Gy over 5.5 weeks or 30 Gy over 2 weeks) with concurrent fluorouracil, capecitabine, or gemcitabine, or of stereotactic body radiation therapy over 5 days without a radiosensitizer. (Chemo)radiation administered later than the second line of therapy was not recorded. After surgery, patients were evaluated on a routine schedule.[18]

Statistical Analysis

Clinical, demographic, and pathologic variables were compared between patients who received FOLFIRINOX or GA as first-line treatment. Continuous variables were compared using a *t* test if normally distributed and a nonparametric Mann-Whitney test if not. Categorical variables were compared using the Pearson χ^2 test (or the Fisher exact test when appropriate). Overall survival (OS) was calculated from the date of tissue diagnosis to the date of death or last follow-up using the Kaplan-Meier method; OS was compared between groups using the Mantel-Cox log-rank test. Median follow-up was calculated using the reverse Kaplan-Meier method. Kaplan-Meier curves were also used to estimate OS distribution among different categories of responses associated with administration of first-line chemotherapy. A stratified Cox proportional hazards regression model was used to evaluate the association of variables with OS. Clinical factors that had $P < .20$ on univariable analysis and those perceived to have potential clinical importance were included in the multivariable models.

Propensity score matching was performed to control for potential selection bias in the delivery of either FOLFIRINOX or GA. We used 5 to 1 digit greedy 1:1 matching for the clinical variables given in **Table 1** with $P \leq .05$. The absolute standard difference (ASD) for the variables used to compute the propensity score was evaluated before and after the match. An ASD value lower than 0.1 would suggest a substantial reduction of bias between the 2 regimens. Based on the matched data, outcomes were compared between the 2 regimens using stratified logistic regression, paired *t* tests, generalized McNemar tests, and stratified Cox models.

Computations were carried out in SAS, version 9.4 (SAS Institute Inc), R, version 3.6.2 (The R Foundation), and SPSS, version 24.0 (SPSS Inc). All *P* values were 2-sided, and $P < .05$ was considered statistically significant.

Results

In total, 485 patients (219 [45%] female; 266 [55%] male) were included in the analysis (eFigure 1 in the Supplement). Among them, 285 (59%) were treated with FOLFIRINOX as the first line of therapy and 200 (41%) were treated with GA.

Clinical Profile

The clinical profiles of all evaluated patients are reported in Table 1. Patients treated with FOLFIRINOX were generally younger (median [range] age at diagnosis: 61 [30-81] vs 71 [36-89] years; $P = .001$) and had more favorable performance status as indicated by an Eastern Cooperative Oncology Group score of 2 or lower (274 patients [96%] vs 165 patients [82%] $P = .001$) but had more invasive primary tumors than patients treated with GA (91 [32%] vs 90 [45%] resectable tumors, $P = .01$). Patients treated with FOLFIRINOX received fewer cycles of chemotherapy than did those treated with GA (median [range] number of cycles, 5 [3-13] vs 5 [3-21]; $P = .001$).

The ASDs for age, performance status, stage, and chemotherapy cycles before and after propensity score matching are given in eTable 1 in the Supplement. A propensity-matched cohort was generated that consisted of 280 patients, of whom 140 were treated with GA and 140 with FOLFIRINOX.

Radiographic and Serologic Measures of Responses After Administration of First-line FOLFIRINOX or GA

Measures of responses observed in all patients after administration of FOLFIRINOX or GA are reported in **Table 2**. The volume of the tumor in 324 patients (67%) decreased following receipt of first-line chemotherapy, with a median (range) reduction in tumor volume of 20% (−297% to 92%). Of 485 patients, 55 (11%) had RECIST PR, 382 (79%) had stable disease, and 48 (10%) had progressive disease; no patients had RECIST complete response. Local tumor downstaging was observed in 17 of 304 patients (6%) who had a borderline resectable or locally advanced tumor at baseline.

Of 378 patients who had CA 19-9 levels above the reference range at presentation, the levels in 95 (25%) decreased to within reference ranges following FOLFIRINOX or GA treatment. Of 80 patients (16%) whose CA 19-9 levels were within the reference ranges at presentation, 9 (11%) had CA 19-9 levels above the reference range after receiving FOLFIRINOX or GA.

There were no differences in any of these putative radiographic or serologic measures of response between all patients treated with first-line FOLFIRINOX or GA. In the matched

Table 1. Clinical Profile of All 485 Included Patients

Characteristic	No. (%) of patients			*P* value
	All (N = 485)	First-line chemotherapy regimen		
		FOLFIRINOX (n = 285)	GA (n = 200)	
Sex				
Female	219 (45)	125 (44)	94 (47)	.50
Male	266 (55)	160 (56)	106 (53)	
Age at diagnosis				
Median (range), y	65 (30-89)	61 (30-81)	71 (36-89)	.001
≥75 y				
Yes	67 (14)	11 (4)	56 (28)	.001
No	418 (86)	274 (96)	144 (72)	
BMI, median (range)	27 (16-56)	27 (16-56)	27 (18-50)	.20
ECOG performance status				
2	439 (91)	274 (96)	165 (82)	.001
≥2	46 (9)	11 (4)	35 (18)	
Baseline CA 19-9 level, median (range), U/mL	256 (1-39 800)	256 (1-15 290)	248 (1-39 800)	.90
Tumor site				
Head or neck	367 (76)	211 (74)	156 (78)	.30
Body or tail	118 (24)	74 (26)	44 (22)	
Baseline radiographic stage				
Resectable	181 (37)	91 (32)	90 (45)	.01
Borderline resectable	133 (28)	88 (31)	45 (23)	
Locally advanced	171 (35)	106 (37)	65 (32)	
No. of chemotherapy cycles				
Mean	6	5	6	.01
Median (range)	5 (3-21)	5 (3-13)	5 (3-21)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CA 19-9, cancer antigen 19-9; ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; GA, gemcitabine plus nanoparticle albumin-bound paclitaxel.

SI conversion factor: To convert CA 19-9 levels to kU/L, multiply by 1.

Table 2. Metrics of Response to Chemotherapy Among All 485 Included Patients

Characteristic	No. (%) of patients			*P* value
	All (N = 485)	First-line chemotherapy regimen		
		FOLFIRINOX (n = 285)	GA (n = 200)	
Radiographic measures after treatment				
Reduction in primary tumor volume				
Yes	324 (67)	189 (66)	135 (67)	.80
No	161 (33)	96 (34)	65 (33)	
%Δvol, Median (range)	20 (−297 to 92)	21 (−297 to 90)	15 (−227 to 92)	.50
RECIST 1.1				
CR	0	0	0	.40
PR	55 (11)	37 (13)	18 (9)	
SD	382 (79)	219 (77)	163 (82)	
PD[a]	48 (10)	29 (10)	19 (9)	
Local tumor downstaging[b]				
Yes[c]	17 (6)	10 (5)	7 (6)	.60
No[c]	287 (94)	181 (95)	103 (94)	
Serologic measures after treatment				
Posttreatment CA 19-9 level, median (range), U/mL	63 (1-24 390)	59 (1-24 390)	72 (1-11 570)	.40
Change in CA 19-9				
Not expressed	27 (6)	18 (6)	9 (5)	.60
Normal to normal	71 (14)	46 (16)	25 (12)	
Elevated to normal	95 (20)	56 (21)	39 (20)	
Elevated to elevated	283 (58)	161 (56)	122 (61)	
Normal to elevated	9 (2)	4 (1)	5 (2)	

Abbreviations: CA 19-9, cancer antigen 19-9; CR, complete response; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; GA, gemcitabine plus nanoparticle albumin-bound paclitaxel; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease; %Δvol, percentage of volume change in primary tumor.

SI conversion factor: To convert CA 19-9 levels to kU/L, multiply by 1.

[a] Of 485 patients with PD, 24 (5%) had isolated or local disease, and 24 (5%) had distant disease with or without local disease.

[b] Downstaging was defined as any change from locally advanced disease to either borderline resectable or resectable disease or from borderline resectable to resectable disease.

[c] Percentage of patients with borderline resectable or locally advanced disease at baseline (n = 304).

Table 3. Metrics of Response to Chemotherapy Among 280 Matched Patients

Characteristic	No. (%) of patients			P value
	All (n = 280)	First-line chemotherapy regimen		
		FOLFIRINOX (n = 140)	GA (n = 140)	
Radiographic measures after treatment				
Reduction in primary tumor volume				
Yes	197 (70)	100 (71)	97 (69)	.70
No	83 (30)	40 (29)	43 (31)	
%Δvol, Median (range)	20 (−240 to 90)	30 (−240 to 90)	10 (−150 to 90)	.10
RECIST 1.1				
CR	0	0	0	.001
PR	35 (13)	27 (19)	8 (6)	
SD	219 (78)	102 (73)	117 (83)	
PD	26 (9)	11 (8)	15 (11)	
Local tumor downstaging[a]				
Yes[b]	13 (8)	7 (8)	6 (7)	.70
No[b]	154 (92)	79 (92)	75 (93)	
Serologic measures after treatment				
Posttreatment CA 19-9 level, median (range), U/mL	59 (1 to 11 570)	59 (1 to 5813)	63 (1 to 11 570)	.70
Change in CA 19-9				
Not expressed	14 (5)	7 (5)	7 (5)	.90
Normal to normal	41 (15)	22 (16)	19 (14)	
Elevated to normal	59 (21)	31 (22)	28 (20)	
Elevated to elevated	161 (58)	78 (56)	83 (59)	
Normal to elevated	5 (2)	2 (1)	3 (2)	

Abbreviations: CA 19-9, cancer antigen 19-9; CR, complete response; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; GA, gemcitabine plus nanoparticle albumin-bound paclitaxel; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease; %Δvol, percentage of volume change in primary tumor.

SI conversion factor: To convert CA 19-9 levels to kU/L, multiply by 1.

[a] Downstaging was defined as any change from locally advanced disease to either borderline resectable or resectable disease or from borderline resectable to resectable disease.

[b] Percentage of patients with borderline resectable or locally advanced disease at baseline (n = 167).

cohort, however, a significant difference with respect to RECIST rates was observed ($P = .001$), and the rate of RECIST PR was higher for patients treated with FOLFIRINOX (27 of 140 patients [19%]) than with GA (8 of 140 patients [6%]). No differences were observed in the median change in tumor volume, the rate of local tumor downstaging, or CA 19-9 levels (**Table 3**).

Local Therapy After First-line Chemotherapy

Overall, 211 patients (44%) were treated with (chemo) radiation immediately following systemic chemotherapy, and 108 patients (22%) ultimately underwent pancreatectomy following chemotherapy or (chemo)radiation. Patients treated with FOLFIRINOX were immediately treated with (chemo) radiation (50% vs 34%; $P = .001$) and ultimately underwent pancreatectomy (27% vs 16%; $P = .01$) more commonly than patients who received GA (eTable 2 and eFigure 2 in the Supplement). Similarly, in the matched cohort, patients treated with FOLFIRINOX were immediately treated with (chemo) radiation (53% vs 34%; $P = .001$) and ultimately underwent pancreatectomy more commonly than patients who received GA (29% vs 18%; $P = .02$) (eTable 3 in the Supplement).

Overall Survival

After a median (range) follow-up of 33 (2-88) months, the median OS duration of the entire population of 485 patients was 20 months (95% CI, 18-23 months). The median OS duration of patients who ultimately underwent pancreatectomy was longer than that of patients who did not (55 months [95% CI, 38 to not reached] vs 17 months [95% CI, 16-18 months]; $P < .001$). However, the median OS duration of patients who were treated with FOLFIRINOX was similar to that of patients who were treated with GA (all patients: 21 months [95% CI, 18-24 months] vs 20 months [95% CI, 17-25 months]; $P = .30$; patients with resection: 48 months [95% CI, 37 months to not reached] vs not reached [95% CI, 31 months to not reached]; $P = .80$; patients without resection: 18 months [95% CI, 16-20 months] vs 17 months [95% CI, 15-18 months]; $P = .20$).

The results of the multivariable model constructed to evaluate potential variables associated with survival for all 485 patients following receipt of FOLFIRINOX or GA are presented in **Table 4**. Performance status (hazard ratio [HR], 1.47; 95% CI, 1.01-2.13; $P = .04$), baseline CA 19-9 level (HR, 1.01; 95% CI, 1.00-1.01; $P = .001$), radiographic stage (HR, 0.60; 95% CI, 0.45-0.80; $P = .001$), and number of chemotherapy cycles (HR, 0.92; 95% CI, 0.88-0.96; $P = .001$) were each independently associated with OS. The first-line chemotherapy regimen administered was not (HR, 1.14 [95% CI, 0.89-1.44]; $P = .30$). In the propensity-matched cohort, none of these variables, including chemotherapy regimen, was associated with OS (**Table 5**).

Discussion

We evaluated and compared rates of radiographic and serologic responses and duration of survival associated with administration of first-line FOLFIRINOX or GA in a consecutive series of patients treated for localized pancreatic cancer at The University of Texas MD Anderson Cancer Center during 7 years.

Table 4. Univariate and Multivariate Cox Proportional Hazards Regression Analysis of Overall Survival for All 485 Patients

	Univariable		Multivariable	
Characteristic	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Female sex	1.08 (0.86-1.35)	.50	NA	NA
BMI	1.01 (0.98-1.02)	.60	NA	NA
Age ≥75 y	0.98 (0.69-1.37)	.90	NA	NA
ECOG PS ≥2	1.37 (0.95-1.97)	.09	1.47 (1.01-2.13)	.04
First-line chemotherapy regimen				
FOLFIRINOX	1 [Reference]	NA	NA	NA
GA	0.91 (0.72-1.15)	.50	1.14 (0.89-1.44)	.30
Baseline CA 19-9 level	1.01 (1.00-1.01)	.001	1.01 (1.00-1.01)	.001
Tumor site		NA	NA	
Body or tail	1 [Reference]	NA	NA	
Head or neck	0.96 (0.74-1.25)	.50	NA	
Baseline radiographic stage		NA	NA	
Resectable	0.70 (0.54-0.91)	.001	0.60 (0.45-0.80)	.001
Borderline resectable	0.86 (0.65-1.15)	.30	0.79 (0.59-1.06)	.10
Locally advanced	1 [Reference]	NA	NA	NA
No. of chemotherapy cycles	0.95 (0.91-0.99)	.03	0.92 (0.88-0.96)	.001

Abbreviations: BMI, body mass index; CA 19-9, cancer antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; GA, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; NA, not applicable.

Table 5. Univariate and Multivariate Cox Proportional Hazards Regression Analysis of Overall Survival for 280 Matched Patients

	Univariable		Multivariable	
Characteristic	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Female sex	1.19 (0.67-2.13)	.50	NA	NA
BMI	1.01 (0.96-1.07)	.70	NA	NA
First-line chemotherapy regimen				
FOLFIRINOX	1 [Reference]			
GA	1.50 (1.00-2.26)	.05	1.48 (0.97-2.26)	.07
Baseline CA 19-9 level, U/mL	1.01 (0.99-1.03)	.30	NA	NA
Tumor site				
Head or neck	1 [Reference]			
Body or tail	0.78 (0.39-1.56)	.50	NA	NA
No. of chemotherapy cycles	0.72 (0.52-1.01)	.06	0.73 (0.52-1.02)	.06

Abbreviations: BMI, body mass index; CA 19-9, cancer antigen 19-9; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; GA, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; NA, not applicable.

Patients who were prescribed FOLFIRINOX were younger and physiologically more robust, but had more advanced cancer than patients who were prescribed GA. Following propensity matching to control for those biases, many objective serologic and radiographic metrics of responses associated with administration of FOLFIRINOX and GA—including low rates of local tumor downstaging—were similar. However, RECIST PR was more common among, (chemo)radiation was more commonly administered to, and pancreatectomy was subsequently performed more frequently for, patients initially treated with FOLFIRINOX. Ultimately, the median OS durations of patients treated with FOLFIRINOX and GA were similar.

FOLFIRINOX and GA are the favored first-line chemotherapeutic regimens for patients with advanced PDAC. In 2 randomized trials,[1,2] each regimen was found to prolong survival relative to gemcitabine. Patients in those 2 distinct studies who received FOLFIRINOX had a longer median OS duration and higher radiographic response rate than those who received GA, but they also had higher rates of associated adverse events. On the basis of these results, these 2 regimens have been increasingly used as the first-line treatment for patients with localized disease, typically with "preoperative" intent.[3,8-10,19,20] In this setting, most studies of these regimens have reported on the use of FOLFIRINOX, likely owing to a perception that the higher toxicity reported with this regimen is warranted given what appears to be greater systemic activity and potential to "downstage" locally invasive tumors. The belief that FOLFIRINOX may be more effective among patients with localized PDAC may have been further strengthened by the recently reported results of separate studies that showed that adjuvant FOLFIRINOX, but not GA, definitively prolonged disease-free survival following pancreatectomy relative to gemcitabine.[21,22]

Here, we compared objective metrics of responses associated with therapy in an attempt to provide further insight into the relative efficacy of these regimens in the setting of localized PDAC. Despite differences in patients' profiles in terms of age, comorbidity, and cancer stage, most metrics of radiographic and serologic responses to first-line FOLFIRINOX and GA that we evaluated were similar. In addition, although

RECIST PR appeared to be more common following FOLFIRINOX than GA, rates of local tumor downstaging were equivalently low—approximately 5%—with both regimens. The extent to which the higher resection rate identified among patients treated with FOLFIRINOX in this study is due to its greater activity or a simple artifact of patient selection based on factors we did not control is therefore unclear.

In the present study, only 22% of patients ultimately underwent pancreatectomy. This resection rate may seem low when compared with reports of surgical resection rates of 60% or more among patients with localized PDAC who received "neoadjuvant" FOLFIRINOX or GA.[9,10] However, such high resection rates have generally been reported in selected retrospective series of otherwise favorable operative candidates. Similarly, the results from existing prospective studies, in which enrollment was generally limited to patients with favorable physiologic and oncologic profiles, are difficult to generalize to patients who are typically excluded from enrollment in such studies. Nonetheless, such excluded patients—those with poor physiologic status or clinical findings (eg, CA 19-9 levels higher than the reference range) suggestive of a high burden of occult metastatic disease—represent a substantial proportion of patients who present with newly diagnosed PDAC.[23] To limit bias and improve the generalizability of the data reported here, we evaluated all patients initially treated with at least 3 cycles of chemotherapy. Notably, the resection rates reported in this context are consistent with those reported in another pragmatic analysis of 614 patients with borderline resectable and locally advanced PDAC, among whom 15% ultimately underwent pancreatectomy.[20]

We evaluated the serologic response by using serial measurements of CA 19-9 levels and the radiographic response by using the RECIST, version 1.1, guideline. Because RECIST is limited—it relies on 2-dimensional measurement of maximum tumor diameter and uses a fixed cutoff of 30% to discriminate between stable disease and PR—we also evaluated 3-dimensional change in tumor volume. Some members of our team recently explored the biological value of each of these metrics and showed that serum CA 19-9 level and changes in tumor size and volume represent robust clinical signals associated with chemotherapeutic effect as measured histopathologically.[24] The clinical importance of these associated metrics justifies both their use as end points in the present study as well as their periodic evaluation during therapy.

Limitations

The strengths of this study notwithstanding, it has several limitations. First, it may have biases associated with its retrospective, single-institution design. However, we attempted to minimize such biases through the use of a large, heterogeneous data set that accurately represents real-world practice, and we actively tried to control for major bias through propensity matching. Furthermore, we evaluated objective radiographic and serologic metrics that members of our team have previously found to be associated with clinical significance. Those metrics are less subject to bias than resection rate or even survival, which can be affected by treatments delivered long after the first-line therapies being studied have been administered. We also had one, unbiased investigator conduct a re-review of all CT images. Second, we did not evaluate patient-reported outcomes or quality of life in this study, and we did not evaluate adverse events associated with FOLFIRINOX or GA administration. Consideration of these parameters is clearly important in selecting between potential regimens. Although we compared the number of cycles administered to account for such differences, we did not account for the extent to which dose modifications may have been made. Finally, we did not consider the extent to which other factors, such as genomics, may have affected the response associated with each of these regimens.[25]

Conclusions

In conclusion, RECIST PR was more common following FOLFIRINOX than GA administration, but other objective metrics of therapeutic response associated with FOLFIRINOX and GA, including the rate of local tumor downstaging, were similar in this unselected population of patients who were treated with first-line chemotherapy for localized PDAC. Although pancreatectomy was performed more frequently following FOLFIRINOX, the median OS duration associated with these regimens did not differ. Taken together, these data suggest that certain advantages may be associated with FOLFIRINOX in this setting. FOLFIRINOX should thus be considered preferentially for patients without contraindications and who are anticipated to tolerate it. However, the choice between these regimens should also take into account their known toxicity profiles and each patient's clinical status.

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Drafting of the manuscript: Perri, Prakash, Javle, Koay, Herman, Katz.
Critical revision of the manuscript for important intellectual content: Perri, Prakash, Qiao, Varadhachary, Wolff, Fogelman, Overman, Pant, Koay, Herman, Kim, Ikoma, Tzeng, Lee, Katz.
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