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ORIGINAL ARTICLE

Chemotherapy dose density is prognostic for overall survival in patients with resectable pancreas cancer: A landmark analysis of SWOG 1505

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Abstract

Background: Chemotherapy is required to improve the overall survival (OS) of patients with resectable pancreatic ductal adenocarcinoma (PDAC). Assessing the impact of chemotherapy dose density (DD) on survival is difficult as a result of confounding. The objective of this study was to determine the impact of chemotherapy DD on OS in patients with resectable PDAC.

Methods: This was a secondary analysis of SWOG 1505, a randomized phase 2 trial of perioperative chemotherapy in resectable PDAC. DD was defined as the percentage of chemotherapy dose received of the total planned. Two landmark time points for OS were used: after surgery and at 40 weeks (which encompassed the entire treatment period).

Results: Of the 102 eligible patients enrolled, 73 (71%) underwent surgery, and median preoperative chemotherapy DD was 89%. Patients with ≥85% DD had higher OS compared to those with <85% DD (median, 38.1 vs. 17.2 months; $p = .039$). Of the 82 patients who survived to 40 weeks postrandomization, 67

This trial was registered at ClinicalTrials.gov (NCT02562716).

underwent surgery, and median DD for all perioperative chemotherapy was 67%. In this cohort, DD ≥70% was associated with better OS (median, 32.2 vs. 14.0 months; $p = .017$). Perioperative DD was not significantly associated with pathologic response, margin status, or lymph node negativity.

Conclusions: This is the first study to identify a prognostic association of chemotherapy DD with OS in patients undergoing perioperative chemotherapy and surgery for resectable PDAC. Patients who received ≥85% DD preoperatively and/or ≥70% DD perioperatively survived longer than those receiving a smaller proportion of protocol therapy.

KEYWORDS
chemotherapy, dose density, pancreatic adenocarcinoma, surgery

INTRODUCTION

Systemic therapy is a critical component of the multidisciplinary treatment of solid gastrointestinal malignancies that frequently relapse at distant sites despite curative-intent surgery. Pancreatic ductal adenocarcinoma (PDAC) is one of the most notorious offenders, with many patients developing recurrences despite margin-negative resection. However, with the use of a multimodal approach of systemic chemotherapy alongside surgery, 5-year overall survival (OS) has improved to 44.3% for localized disease, with median OS exceeding 50 months.[1,2]

"How much" systemic chemotherapy a patient should receive is based on data from seminal clinical trials in PDAC (CONKO-001, ESPAC-4, JASPAC 01, and PRODIGE 24). For all these study designs, patients were assigned to receive 6 months of postoperative therapy.[2–5] This quantity or duration of therapy is considered to be an optimal amount needed to kill micrometastatic disease, and therefore provide a survival benefit. However, not every patient in these studies, or in clinical practice, is able to receive all assigned therapy as a result of a variety of patient and perioperative factors. The impact of missing doses of systemic chemotherapy or having dose reductions is not without consequence. We have previously examined the prognostic impact of these missing doses on OS via dose density (DD; the percentage of total chemotherapy received out of the total planned chemotherapy) in patients with resected PDAC.[6] This analysis demonstrated that patients who received <80% had significantly worse OS compared to patients who were able to receive more (median OS, 18.6 vs. 27.1 months; $p = .01$).[6] These findings of higher OS with a greater quantity of chemotherapy received have been supported by other retrospective studies but several of the major limitations are the heterogeneity in the type of chemotherapy regimen received, planned duration, and treatment sequence (preoperative, postoperative, or both). This makes the interpretation of the ideal threshold cutoff of DD challenging, and therefore evaluation in a prospective clinical trial, where there are standardized treatment arms, would be ideal.[7]

The aim of this study was to assess the prognostic value of reduced DD for survival via data from SWOG 1505 in patients with resectable PDAC.

SWOG 1505 (NCT02562716) was a randomized, phase 2 study of planned perioperative chemotherapy (12 weeks preoperative and 12 weeks postoperative) with either modified (m) oxaliplatin, irinotecan, 5-fluorouracil (FOLFIRINOX), or gemcitabine/nab-paclitaxel for resectable PDAC.

MATERIALS AND METHODS

Data set

Data from the 102 eligible patients enrolled in SWOG 1505 were used for this study. SWOG 1505 (NCT02562716) was a randomized, "pick the winner" phase 2 study of two perioperative chemotherapy regimens for patients with radiographically resectable PDAC.[8] Patients were randomized 1:1 to two chemotherapy regimens. In arm 1, patients received mFOLFIRINOX: oxaliplatin 85 mg/m^2, followed by irinotecan 180 mg/m^2, and then a FOLFIRINOX 2400 mg/m^2 infusion over 46 h. The treatment was twelve 2-week cycles (six preoperative and six postoperative). In arm 2, patients were treated with nab-paclitaxel 125 mg/m^2, followed by gemcitabine 1000 mg/m^2. This was given for a total of six 4-week cycles (three preoperative and three postoperative).

In order to simplify the terminology for "cycles" that is applicable to both mFOLFIRINOX and gemcitabine/nab-paclitaxel, cycles 1–3 will refer to the preoperative component and cycles 4–6 will refer to the postoperative portion.

Data variables

Patient- and disease-specific clinicopathologic variables, including demographics, clinical characteristics, and radiographic resectability,

were obtained from the SWOG 1505 data set. Patients were deemed "resectable" on the basis of the absence of tumor-arterial involvement, venous involvement of less than or equal to 180°, patent portal–splenic confluence, and the absence of any metastatic disease.[8] Clinical staging was reported according to the American Joint Committee on Cancer *Cancer Staging Manual*, Eighth Edition.

DD was defined as the amount of chemotherapy received divided by the amount of chemotherapy planned, which was expressed as a percentage. This was calculated for each patient on the basis of their assigned treatment per the protocol.

Statistical analysis

OS was examined with landmark analyses to reduce immortal time bias; namely the outcome was OS from each landmark time, and only patients alive at the designated landmark time were included in the analysis. Two time points were chosen: (1) after completion of surgery (surgery cohort), and (2) at 40 weeks, when all patients could have completed their assigned systemic therapy (total treatment cohort). Disease-free survival (DFS), defined as from the time of surgery to the earlier of recurrence or death, was assessed in the surgery cohort as a function of preoperative DD. Only patients with no recurrence before surgery were included in the analysis. Survival time was set as the time of last patient contact for surviving patients. All eligible patients with follow-up data were included in the analyses, regardless of receiving the assigned treatment (including surgery), according to a modified intention-to-treat approach. Probabilities of OS and DFS were estimated via the Kaplan–Meier method, with differences in event rates between groups assessed via the log-rank test. Cox regression models were applied to estimate associations between DD and OS while adjusting for other factors. Preoperative and postoperative DD were compared within patients via a paired Wilcoxon signed-rank test. Statistical analyses were performed with SAS, version 9.4 (SAS Institute) and R, version 3.6.1 (R Project). Statistical significance was declared for $p < .05$.

RESULTS

Patient demographics and trial outcomes

Of the 102 eligible patients registered in SWOG 1505, 55 received mFOLFIRINOX and 47 received gemcitabine/nab-paclitaxel. Median patient age was 64 years, and 59% were male. For the 73 patients who underwent resection, 81% received a pancreaticoduodenectomy, 15% received a distal pancreatectomy, and 3% received a total pancreatectomy. OS did not significantly differ by treatment arm: 2-year OS was 47% (95% confidence interval [CI], 31%–61%) for the mFOLFIRINOX arm and 48% (95% CI, 31%–63%) for the gemcitabine/nab-paclitaxel arm.

The surgery cohort included 73 patients who received surgery and may have received preoperative therapy. The total treatment cohort included 82 patients who survived at least 40 weeks after randomization and may have received surgery and perioperative chemotherapy. The surgery and total treatment groups were evaluated separately, although 67 patients contributed data to both cohorts (Figure 1).

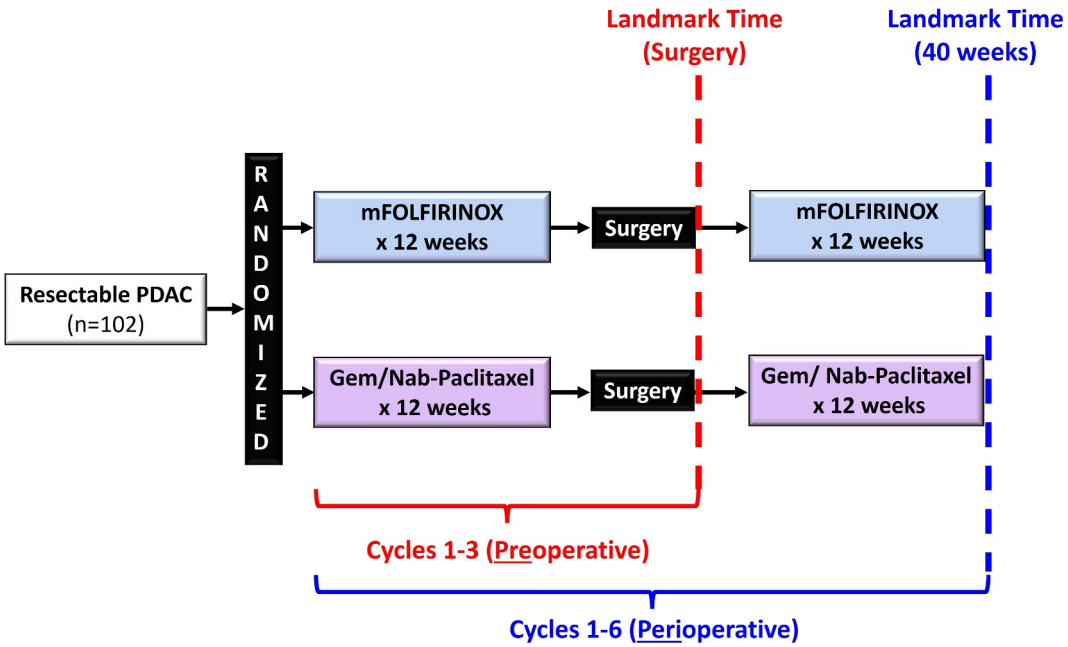

FIGURE 1 SWOG 1505 trial schema and landmark times. Gem indicates gemcitabine; mFOLFIRINOX, modified 5-fluorouracil; PDAC, pancreatic ductal adenocarcinoma.

DD

Median DD was 89% for the surgery group (cycles 1–3) and 67% for the total treatment group, which included cycles 1–6.

In the total treatment cohort, median DD was 83% for the preoperative period and 58% in the postoperative period ($p < .001$).

We then compared DD on the basis of chemotherapy regimens. In the surgery cohort, median DD for mFOLFIRINOX was 94% versus 78% for gemcitabine/nab-paclitaxel ($p = .015$). In the total treatment group, median DD for mFOLFIRINOX was 69% versus 66% for gemcitabine/nab-paclitaxel ($p = .56$).

In the total treatment cohort, median DD was greater for both regimens when received in the preoperative period compared with the postoperative period (mFOLFIRINOX: preoperative, 87.5% vs. postoperative, 59.6%; $p < .001$; gemcitabine/nab-paclitaxel: preoperative, 77.3% vs. postoperative, 51.7%; $p < .001$).

Reasons for patients coming off of treatment are provided in Table S1.

Landmark survival analysis: Surgery

The preoperative DD threshold of 85% was chosen to stratify patient outcomes on the basis of published analyses, power, and statistical significance. Patients with ≥85% DD preoperatively had higher OS from time of surgery compared to patients with <85% DD (median, 38.1 vs. 17.2 months; $p = .039$) (Figure 2). The same did not hold true for the outcome of DFS ($p = .67$) (Figure S1).

Patient- and tumor-related factors for patients receiving ≥85% DD versus <85% DD are listed in Table 1. These characteristics and outcomes varied little according to DD subgroups, except that the proportion of patients with grade ≥3 adverse events was higher in the <85% DD group compared to the ≥85% DD group (96.9% vs. 73.2%; $p = .02$).

Multivariate analysis of OS in the surgery cohort showed that lower DD was significantly associated with worse OS after adjusting for poor pathologic response (College of American Pathologists criteria 2 and 3),[9] positive margins, and lymphovascular invasion (hazard ratio [HR], 2.7; 95% CI, 1.4–5.2; $p = .004$) (Table 2).

Landmark survival analysis: Total treatment

A threshold of 70% was chosen to stratify patient outcomes for the total treatment cohort via the same methods as for the surgery cohort. Of the 82 patients who survived to 40 weeks post-randomization, DD ≥70% compared to DD <70% was associated with better OS (median, 32.2 vs. 14.0 months; $p = .017$) (Figure 3). Comparison of clinicopathologic factors of patients receiving ≥70% DD versus <70% DD showed no significant differences between groups (Table 3).

Multivariate analysis of OS in the total treatment cohort showed that lower DD was significantly associated with worse OS after adjusting for poor pathologic response, positive margins, and lymphovascular invasion (HR, 2.1; 95% CI, 1.1–4.9; $p = .03$) (Table 4).

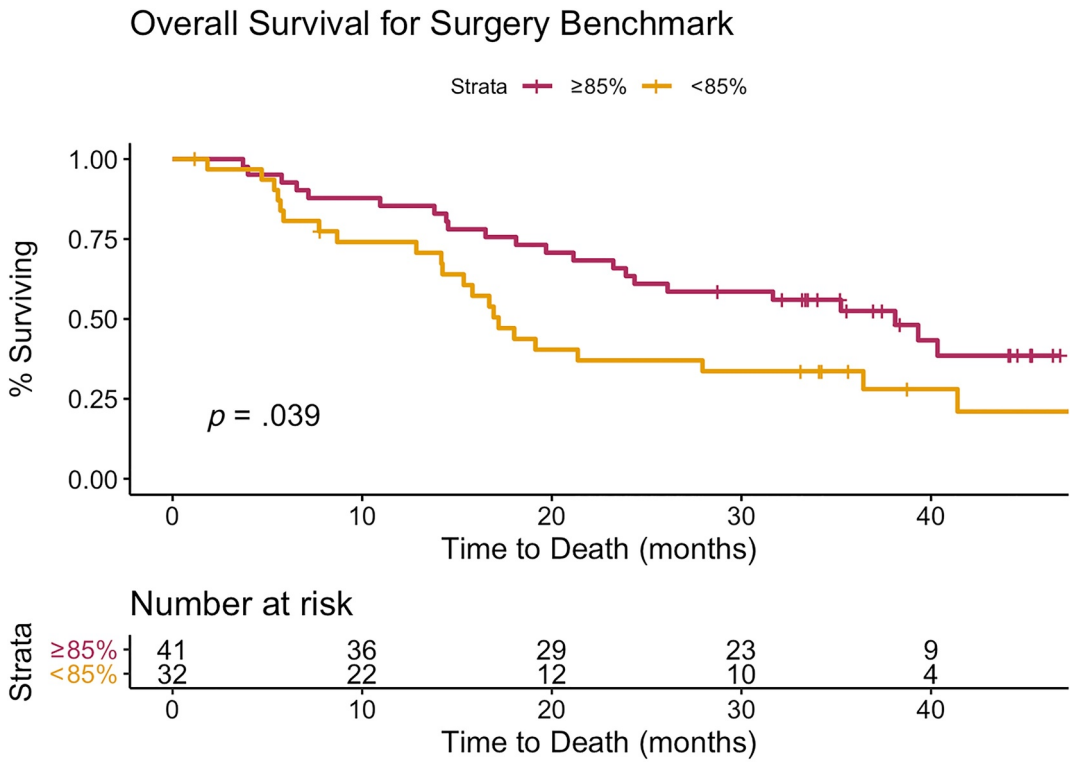

FIGURE 2 Kaplan–Meier curve for overall survival for the surgery cohort based on preoperative chemotherapy dose density.

TABLE 1 Patient, disease, and treatment characteristics in the surgery cohort.

Characteristic	Entire cohort (n = 73)	Dose density, ≥85% (n = 41)	Dose density, <85% (n = 32)	p
Age, median (range), years	64.4 (43.7–76.0)	64.2 (45.8–75.8)	65.4 (43.7–76.0)	.681
Race, No. (%)				.795
White	87.7 (64)	85.4 (35)	90.6 (29)	
Black	8.2 (6)	9.8 (4)	6.2 (2)	
Other	4.1 (3)	3.1 (1)	4.9 (2)	
Male, No. (%)	61.6 (45)	61.0 (25)	62.5 (20)	.999
Zubrod PS, No. (%)				
0	67.1 (49)	75.6 (31)	562 (18)	
1	32.9 (24)	24.4 (10)	43.8 (14)	
Chemotherapy, No. (%)				.335
Gemcitabine/nab-paclitaxel	45.2 (33)	39.0 (16)	53.1 (17)	
mFOLFIRINOX	54.8 (40)	61.0 (25)	46.9 (15)	
Body surface area, median (range), m^2	1.95 (1.56–2.56)	1.96 (1.56–2.56)	1.92 (1.56–2.54)	.521
Grade ≥3 adverse events, No. (%)	83.6 (61)	73.2 (30)	96.9 (31)	.017
Time to surgery, median (range), days	113 (85–142)	113 (85–132)	113 (94–142)	.509
Pancreatectomy, No. (%)				.383
PD–pylorus preserving	30.1 (22)	31.7 (13)	28.1 (9)	
PD–classic	50.7 (37)	51.2 (21)	50.0 (16)	
Distal pancreatectomy	15.1 (11)	12.5 (4)	17.1 (7)	
Total pancreatectomy	2.7 (2)	6.2 (2)	0 (0)	
Estimated blood loss, median (range), mL	300 (0–2500)	300 (50–1000)	300 (20–2500)	.704
Vascular resection, No. (%)	28.8 (21)	26.8 (11)	31.2 (10)	.878
Pathologic response,[9] No. (%)				.832
Complete/moderate	31.5 (23)	29.3 (12)	34.4 (11)	
Minor/poor	68.5 (50)	70.7 (29)	656 (21)	
Positive lymph nodes, No. (%)	57.5 (42)	70.7 (29)	40.6 (13)	.019
Positive margin, No. (%)	20.5 (15)	24.4 (10)	15.6 (5)	.530
Lymphovascular invasion, No. (%)	28.8 (21)	26.8 (11)	31.2 (10)	.878

Abbreviations: mFOLFIRINOX, modified 5-fluorouracil; PD, pancreaticoduodenectomy; PS, performance status.

TABLE 2 Multivariate analysis of overall survival in the surgery cohort.

Variable	Unadjusted HR (95% CI)	HR (95% CI)	p
Poor pathologic response	1.4 (0.7–2.7)	1.3 (0.7–2.7)	.42
Positive margin	1.5 (0.8–2.7)	1.5 (0.7–2.9)	.29
Positive lymph nodes	1.5 (0.7–2.9)	2.1 (1.0–4.2)	.05
Preoperative chemotherapy dose density <85%	1.9 (1.0–3.4)	2.7 (1.4–5.2)	.004

Abbreviations: CI, confidence interval; HR, hazard ratio.

Finally, we evaluated the prognostic impact of DD in the preoperative versus postoperative component of therapy with the total treatment cohort. A DD cutoff of ≥85% was used for the preoperative portion and ≥70% was used for the postoperative portion, and four scenarios were created. Patients who received DD ≥85% in the preoperative period and ≥70% postoperatively had a median OS of 34.8 months. Those who received DD ≥85% in the preoperative period but <70% postoperatively had a median OS of 32.2 months. If

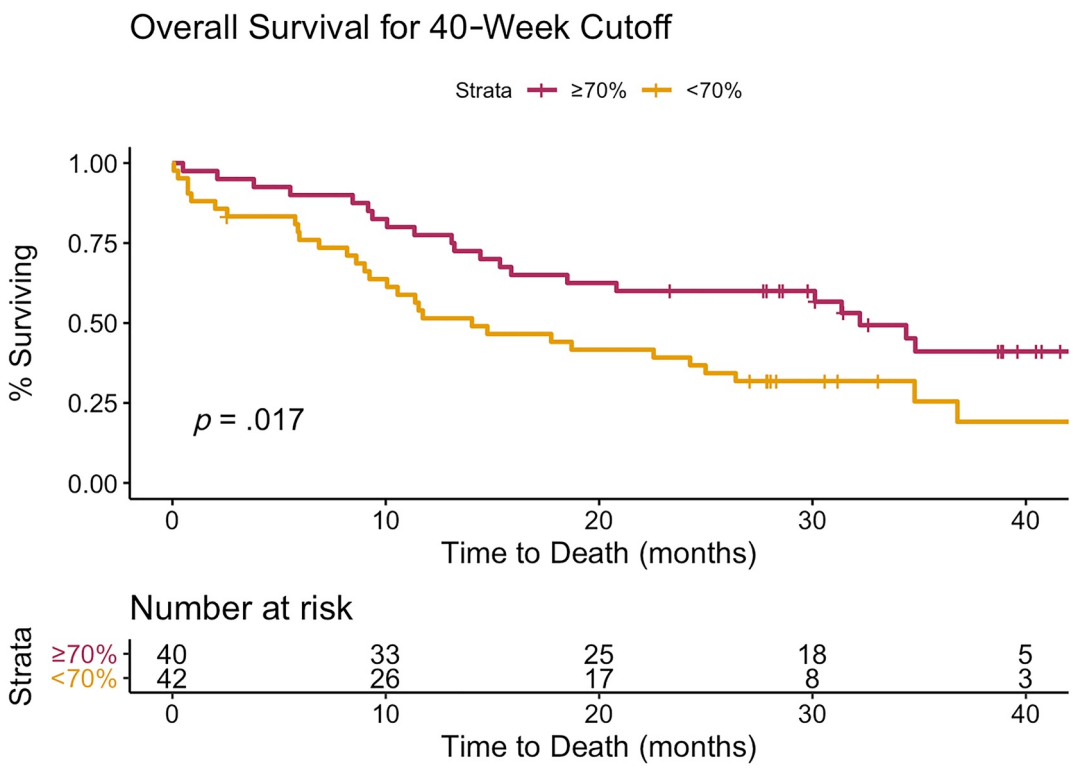

FIGURE 3 Kaplan–Meier curve for overall survival for the total treatment cohort based on perioperative chemotherapy dose density.

patients received DD <85% in the preoperative period and ≥70% in the postoperative period, median OS was 23.6 months. Finally, if patients received DD <85% in the preoperative period and <70% in the postoperative period, median OS was 11.7 months. Although the median OS estimates show a decreasing pattern across these ad hoc categories, the variability was not statistically significant (Table 5).

Figures S2 and S3 provide survival analyses based on chemotherapy regimens for the surgery and total treatment cohorts, respectively.

DISCUSSION

In this study, we evaluated DD as a metric to quantify the proportion of chemotherapy patients receive as part of a previously set treatment plan. Dose intensity, which is the amount of drug delivered over time, is different from DD. With limitations in the level of detail of the chemotherapy administration schedule, dose intensity was not used.

In patients with resectable PDAC, we demonstrate that chemotherapy DD is an important prognostic factor for OS. Data from SWOG 1505 showed that patients with a higher DD had significantly better OS in both the preoperative and combined perioperative time periods. These associations were consistent for both the mFOLFIRINOX and gemcitabine/nab-paclitaxel regimens.

Furthermore, lower DD (<85% compared to ≥85%) in the preoperative period was significantly associated with worse OS after adjusting for other known adverse pathologic factors.

SWOG 1505 was the first perioperative trial for resectable PDAC with modern combination therapy regimens. This study was ideal to examine DD as a prognostic factor for OS because the uniform patient population, where all patients had a tissue diagnosis of PDAC, were anatomically resectable on the basis of a systematic radiologic review, and were randomized to receive standard doses and durations of systemic therapy. In SWOG 1505, all patients were assigned to a standardized regimen of 3 months of chemotherapy pre- and postoperatively (six cycles pre- and postoperatively for mFOLFIRINOX and three cycles pre- and postoperatively for gemcitabine/nab-paclitaxel).

A key finding of SWOG 1505 was that there were no significant differences in survival or toxicity outcomes between mFOLFIRINOX and gemcitabine/nab-paclitaxel. FOLFIRINOX is often considered a more toxic regimen, and would be expected to have a greater number of dose reductions or missed cycles than gemcitabine/nab-paclitaxel. However, in this study, we found a similar median DD received for both regimens when examined over the entire perioperative period, and no difference in thresholds associated with survival. Interestingly, in the preoperative period (surgery group), patients who were receiving mFOLFIRINOX were able to tolerate a higher DD compared to gemcitabine/nab-paclitaxel (95% vs. 78%). These findings are consistent with the literature showing that patients can tolerate preoperative mFOLFIRINOX without higher complication rates.[10,11] However, the impact of the actual chemotherapy drugs versus timing (every 2 weeks with mFOLFIRINOX vs. 3 weeks on and 1 week off for gemcitabine/nab-paclitaxel) on tolerability is not clear.

TABLE 3 Patient, disease, and treatment characteristics for the total treatment cohort (dose density ≥70% vs. <70%).

Characteristic	Entire cohort (n = 82)	Dose density, ≥70% (n = 40)	Dose density, <70% (n = 42)	p
Age, median (range), years	64.6 (43.7–76.0)	66.2 (45.8–75.8)	63.9 (43.7–76.0)	.603
Race, No. (%)				.621
White	87.8 (72)	90.0 (36)	85.7 (36)	
Black	7.3 (6)	7.5 (3)	7.1 (3)	
Other	4.9 (4)	2.5 (1)	7.1 (3)	
Male, No. (%)	58.5 (48)	65.0 (26)	52.4 (22)	.350
Zubrod PS, No. (%)				.931
0	68.3 (56)	70.0 (28)	66.7 (28)	
1	31.7 (26)	30.0 (12)	33.3 (14)	
Chemotherapy, No. (%)				.978
Gemcitabine/nab-paclitaxel	43.9 (36)	42.5 (17)	45.2 (19)	
mFOLFIRINOX	56.1 (46)	57.5 (23)	54.8 (23)	
Body surface area, median (range), m^2	1.97 (1.51–2.52)	1.96 (1.56–2.31)	1.98 (1.51–2.52)	.298
Grade ≥3 adverse events, No. (%)	86.6 (71)	85.0 (34)	88.1 (37)	.931
Time to surgery, median (range), days	113 (85–142)	113 (94–128)	113 (85–142)	.932
Pancreatectomy, No. (%)				.565
PD–pylorus preserving	25.6 (21)	35.0 (14)	16.7 (7)	
PD–classic	41.5 (34)	50.0 (20)	33.3 (14)	
Distal pancreatectomy, No. (%)	13.4 (11)	15.0 (6)	11.9 (5)	
Total pancreatectomy, No. (%)	1.2 (1)	0 (0)	2.4 (1)	
Estimated blood loss, median (range), mL	300 (0–2500)	300 (0–2500)	275 (25–1000)	.383
Vascular resection, No. (%)	24.4 (20)	27.5 (11)	21.4 (9)	.886
Pathologic response, No. (%)				.494
Complete/moderate	24.4 (20)	25.0 (10)	23.8 (10)	
Minor/poor	58.5 (48)	75.0 (30)	42.9 (18)	
Positive lymph nodes, No. (%)	47.6 (39)	57.5 (23)	38.1 (16)	.999
Positive margin, No. (%)	18.3 (15)	17.5 (7)	19.0 (8)	.432
Lymphovascular invasion, No. (%)	24.4 (20)	27.5 (11)	21.4 (9)	.886

Abbreviations: mFOLFIRINOX, modified 5-fluorouracil; PD, pancreaticoduodenectomy; PS, performance status.

TABLE 4 Multivariate analysis of overall survival in the total treatment cohort.

Variable	Unadjusted HR (95% CI)	HR (95% CI)	p
Poor pathologic response	1.5 (0.7–3.2)	1.7 (0.8–3.6)	.19
Positive margin	1.6 (0.8–3.1)	1.3 (0.6–2.7)	.45
Positive lymph nodes	1.5 (0.8–2.8)	1.5 (0.8–2.9)	.25
Total chemotherapy dose density <70%	2.0 (1.1–3.4)	2.1 (1.1–4.0)	.03

Abbreviations: CI, confidence interval; HR, hazard ratio.

This study is not without limitations. As a post hoc analysis, it needs to be emphasized that the associations between OS and DD do not imply causation. It is often assumed that the therapeutic effect of systemic therapy is directly proportional to the amount of chemotherapy received and that patients who receive more chemotherapy will likely have better outcomes as a result of increased cancer cell cytotoxicity. However, this may not be accurate because the ideal quantity of chemotherapy patients should

TABLE 5 Impact of preoperative versus postoperative dose density on overall survival in the total treatment cohort ($n = 82$).

Group	Preoperative, %	Postoperative, %	No. (%)	Median OS, months	*p*
1	≥85	≥70	23 (28)	34.8	.11
2	≥85	<70	17 (21)	32.2	
3	<85	≥70	8 (10)	23.6	
4	<85	<70	34 (41)	11.7	

Abbreviation: OS, overall survival.

receive and the direct therapeutic effects are not known. Chemotherapy drug tolerance may also be a marker of host or tumor biology. One might assume that patients who can tolerate a higher DD are more likely physiologically fit and less susceptible to drug toxicities, and therefore will have better survival regardless of treatment. DD may simply be another surrogate for performance status. However, when we examined Zubrod performance status between DD <85% versus ≥85% in the surgery group and <70% versus ≥70% in the total treatment group, there were no differences. This suggests that tumor biology and response to chemotherapy may have more impact than patient performance status in this study.

In our study, it may be inferred that patients who were able to tolerate a higher DD were more likely to be physiologically fitter and more tolerant to drug toxicities, and therefore had better survival regardless of the DD of the treatment received.

In conclusion, this is the first study to explore the association of chemotherapy DD with OS in patients undergoing perioperative chemotherapy and surgery for resectable PDAC. These findings suggest that greater survival is seen in patients receiving a higher chemotherapy DD, and higher DD is more likely to be delivered and tolerated in the preoperative versus postoperative period. Thus, these data further support consideration of a preoperative approach for resectable PDAC. A clinical trial with randomization to a variety of treatment doses and schedules is required to investigate the optimal amounts of chemotherapy patients should receive both preoperatively and in the postoperative setting.

AUTHOR CONTRIBUTIONS

Sameer H. Patel: Conceptualization; formal analysis; methodology; investigation; project administration; supervision; visualization; writing—original draft; writing—review and editing. **Sarah Colby**: Data curation; formal analysis; investigation; methodology; validation; writing—original draft; writing—review and editing. **Davendra Sohal**: Conceptualization; methodology; project administration; supervision; visualization; writing—original draft; writing—review and editing. **Katherine A. Guthrie**: Data curation; formal analysis; investigation; methodology; validation; writing—original draft; writing—review and editing. **Lisa A. Kachnic**: Conceptualization; methodology; supervision; writing—original draft; writing—review and editing. **Gabriela Chiorean**: Methodology; project administration; supervision; writing—original draft; writing—review and editing. **Andrew M. Lowy**: Methodology; supervision; writing—original draft; writing—review and editing. **Flavio G. Rocha**: Conceptualization; methodology; supervision; writing—original draft; writing—review and editing. **Howard S. Hochster**: Supervision; writing—original draft; writing—review and editing. **Philip A. Philip**: Methodology; project administration; supervision; writing—original draft; writing—review and editing. **Syed A. Ahmad**: Conceptualization; methodology; project administration; supervision; visualization; writing—original draft; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

Davendra Sohal reports consulting for Revolution Medicines and Incyte. Lisa A. Kachnic reports receiving grants from Varian Medical Systems, serving on the data and safety monitoring board for New Beta Innovation, and intellectual property. Gabriela Chiorean reports consulting for G1 Therapeutics, Ipsen Biopharmaceuticals, Pfizer, IGM Biosciences, Merus, Regeneron Pharmaceuticals, Purple Biosciences, BPGbio, and Bristol-Myers Squibb. Andrew M. Lowy reports consulting for Steba Biotech, Silexion, and Revolution Medicines. Syed A. Ahmad reports consulting for AbbVie. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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