FDG-PET Predicts Neoadjuvant Therapy Response and Survival in Borderline Resectable/Locally Advanced Pancreatic Adenocarcinoma

Amro M. Abdelrahman, MBBS, MS[1]; Ajit H. Goenka, MD[2]; Roberto Alva-Ruiz, MD[1]; Jennifer A. Yonkus, MD[1]; Jennifer L. Leiting, MD[1]; Rondell P. Graham, MBBS[3]; Kenneth W. Merrell, MD[4]; Cornelius A. Thiels, DO, MBA[1]; Christopher L. Hallemeier, MD[4]; Susanne G. Warner, MD[1]; Michael G. Haddock, MD[4]; Travis E. Grotz, MD[1]; Nguyen H. Tran, MD[5]; Rory L. Smoot, MD[1]; Wen Wee Ma, MBBS[5]; Sean P. Cleary, MD[1]; Robert R. McWilliams, MD[5]; David M. Nagorney, MD[1]; Thorvardur R. Halfdanarson, MD[5]; Michael L. Kendrick, MD[1]; and Mark J. Truty, MD, MS[1]

ABSTRACT

Background: Neoadjuvant therapy (NAT) is used in borderline resectable/locally advanced (BR/LA) pancreatic ductal adenocarcinoma (PDAC). Anatomic imaging (CT/MRI) poorly predicts response, and biochemical (CA 19-9) markers are not useful (nonsecretors/nonelevated) in many patients. Pathologic response highly predicts survival post-NAT, but is only known postoperatively. Because metabolic imaging (FDG-PET) reveals primary tumor viability, this study aimed to evaluate our experience with preoperative FDG-PET in patients with BR/LA PDAC in predicting NAT response and survival. **Methods:** We reviewed all patients with resected BR/LA PDAC who underwent NAT with FDG-PET within 60 days of resection. Pre- and post-NAT metabolic (FDG-PET) and biochemical (CA 19-9) responses were dichotomized in addition to pathologic responses. We compared post-NAT metabolic and biochemical responses as preoperative predictors of pathologic responses and recurrence-free survival (RFS) and overall survival (OS). **Results:** We identified 202 eligible patients. Post-NAT, 58% of patients had optimization of CA 19-9 levels. Major metabolic and pathologic responses were present in 51% and 38% of patients, respectively. Median RFS and OS times were 21 and 48.7 months, respectively. Metabolic response was superior to biochemical response in predicting pathologic response (area under the curve, 0.86 vs 0.75; $P<.001$). Metabolic response was the only univariate preoperative predictor of OS (odds ratio, 0.25; 95% CI, 0.13–0.40), and was highly correlated ($P=.001$) with pathologic response as opposed to biochemical response alone. After multivariate adjustment, metabolic response was the single largest independent preoperative predictor ($P<.001$) for pathologic response (odds ratio, 43.2; 95% CI, 16.9–153.2), RFS (hazard ratio, 0.37; 95% CI, 0.2–0.6), and OS (hazard ratio, 0.21; 95% CI, 0.1–0.4). **Conclusions:** Among patients with post-NAT resected BR/LA PDAC, FDG-PET highly predicts pathologic response and survival, superior to biochemical responses alone. Given the poor ability of anatomic imaging or biochemical markers to assess NAT responses in these patients, FDG-PET is a preoperative metric of NAT efficacy, thereby allowing potential therapeutic alterations and surgical treatment decisions. We suggest that FDG-PET should be an adjunct and recommended modality during the NAT phase of care for these patients.

J Natl Compr Canc Netw 2022;20(9):1023–1032.e3
doi: 10.6004/jnccn.2022.7041

See JNCCN.org for supplemental online content.

Background

The current recommended neoadjuvant therapy (NAT) strategy in borderline resectable (BR) or locally advanced (LA) pancreatic ductal adenocarcinoma (PDAC) includes initial induction systemic chemotherapy often followed by subsequent consolidative chemoradiation, referred to as total NAT. The purpose of NAT relies on negative and positive selection principles: identifying patients likely to not benefit from resection, treatment of occult metastases, and potential downstaging to achieve margin-negative resection.[1–4] If we anticipate that NAT will improve outcomes over up-front resection, then we need to objectively show therapeutic responses.

Traditional cross-sectional imaging modalities such as CT and/or MRI poorly predict response, rendering NAT radiologic evaluations relatively ineffective.[3,5,6] In the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pancreatic Adenocarcinoma,[4] the criteria for surgery post-NAT in patients with BR/LA PDAC do not include post-NAT radiologic response as a metric, and the NCI does not consider tumor shrinkage as a clinically relevant endpoint for trials because it poorly predicts pathologic response and survival.[7] CA 19-9 levels are often used to determine biochemical responses[8]; however, 10% of patients lack fucosyl-transferase (nonsecretors), and up to one-third of patients have normal levels at presentation (ie, normo-secretors),[9–11] limiting CA 19-9 utility in a significant proportion of patients. Furthermore, the operations required for these advanced tumors confer potentially higher rates of perioperative morbidity and mortality compared with standard operations for anatomically resectable

[1]Division of Hepatobiliary and Pancreas Surgery, Department of Surgery; [2]Division of Nuclear Medicine Radiology, Department of Radiology; [3]Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology; [4]Department of Radiation Oncology; and [5]Division of Medical Oncology, Department of Oncology, Mayo Clinic, Rochester, Minnesota.

tumors,[12] hence the need to identify patients with long-term oncologic benefit to justify these increased risks. Studies have shown pathologic treatment response, a surrogate for demonstrably effective NAT, to be among the most significant independent predictors of survival after resection for BR/LA PDAC.[13–16] However, pathologic response is only known post–surgical resection; thus, methods to objectively determine the adequacy of NAT response preoperatively are critically needed.

Given the limitations of traditional cross-sectional imaging and biochemical tumor marker assessment to determine NAT response in BR/LA PDAC, we used serial FDG-PET metabolic imaging to increase the accuracy and objectivity of NAT response assessment, anticipate postoperative pathologic responses, and determine eligibility for complex resections. FDG-PET combined with either standard CT (PET/CT) or contrast-enhanced MRI (PET/MRI) has been shown to predict metastasis[17] and survival,[18,19] provide insight into tumor viability during NAT, and reveal metabolic changes earlier than changes in radiologic tumor size.[20] This study aimed to evaluate our experience with assessing the diagnostic accuracy of the FDG-PET metabolic response in predicting pathologic responses and survival compared with biochemical (CA 19-9) levels and responses in patients with BR/LA PDAC undergoing NAT pre-resection.

Methods

This was an Institutional Review Board–approved retrospective cohort of patients diagnosed with BR/LA PDAC who underwent surgical resection at a single center after NAT, with at least one FDG-PET post-NAT within 60 days of resection. Serum CA 19-9 level was assessed at baseline and post-NAT, and considered elevated if ≥35 U/mL. CA 19-9 groups included those that were (1) elevated at baseline and normalized post-NAT, (2) elevated at baseline and stayed elevated post-NAT, (3) normal at baseline and post-NAT, and (4) nonsecretors (<1 U/mL). We analyzed the CA 19-9 levels for the entire cohort of patients ("CA 19-9 level") and then conducted subgroup analyses with only patients with elevated CA 19-9 at baseline ("CA 19-9 response"). For the entire cohort, CA 19-9 levels were dichotomized as follows: optimal (groups 1 and 3; ie, normal) and suboptimal (groups 2 and 4; ie, elevated or nonsecretors) per previous stratification.[13] Because biochemical responses are only useful in those with CA 19-9 elevation, we dichotomized a subgroup (excluding groups 3 and 4) with initially elevated CA 19-9 into major response (group 1: normalized post-NAT) and minor response (group 2: stayed elevated post-NAT). Consolidative chemoradiation therapy was composed of a photon/proton external beam with a 50-Gy dose delivered in 25 to 28 daily fractions over 5 weeks, or a 45-Gy dose delivered in 15 fractions over 3 weeks with concurrent radiosensitizing chemotherapy (capecitabine) and delivered using 3D conformal or intensity-modulated techniques.

Baseline and interval (post-NAT) FDG-PET (CT or MRI) parameters[21,22] were reviewed. Major metabolic (PET) response was defined as FDG uptake of the tumor below hepatic FDG uptake and indistinguishable from background pancreatic tissue as previously described.[23] Minor metabolic response was defined as persistent or higher FDG activity than adjacent background tissues and compared with baseline FDG-PET if available. Pathologic treatment response was scored according to the College of American Pathologists (0 = complete response; 1 = near-complete response; 2 = partial response; 3 = no response).[24] Pathologic response scores were dichotomized as follows: major pathologic response (scores 0 and 1) or minor pathologic response (scores 2 and 3). Overall survival (OS) was measured from time of diagnosis to death from any cause. Recurrence-free survival (RFS) was measured from surgery to recurrence or death from any cause.

Continuous variables are presented as mean and standard deviation if normally distributed; otherwise, they are presented as median and interquartile range. The 2-tailed Student *t* test or Wilcoxon rank sum test was used for statistical comparison. The Fisher exact test or Pearson chi-squared test was used for statistical comparison. We conducted univariate and multivariate binary logistic regression analyses looking for preoperative predictive factors of major pathologic response. Significant variables in univariate analysis were included in multivariate logistic regression after satisfying statistical assumption. Diagnostic accuracy measures were estimated for metabolic and biochemical responses in predicting pathologic response and receiver operating characteristic (ROC) curves with area under the curve. To compare ROC curves for factors, we conducted paired-sample (ie, same patient) area under the curve statistical tests using a nonparametric assumption of empirical methods as described by DeLong et al.[25] Kaplan-Meier method and Cox proportional hazard regression were used as appropriate. All analyses were performed using SPSS Statistics, version 27.0 (IBM Corp.) with a statistical significance threshold of <0.05.

Results

An initial cohort of 232 patients with BR/LA PDAC was screened, with 36 patients excluded (FDG-PET >60 days preoperatively). A total of 202 patients were included in the final cohort, with demographics and variables listed in eTable 1 (available with this article at JNCCN.org). This cohort comprised 117 (58%) men and 85 (42%) women, with a mean [SD] age of 64.7 [9.8] years at surgery. All patients received either mFOLFIRINOX (modified oxaliplatin/leucovorin/irinotecan/fluorouracil) or gemcitabine/nab-paclitaxel as first-line neoadjuvant chemotherapy,

with 94 (46.5%) undergoing chemotherapy switch and the majority (91%) undergoing preoperative chemoradiation post-NAT. There were 135 (67%) patients with an elevated CA 19-9 level at diagnosis, 46 (23%) with normal levels, and 21 (10%) nonsecretors. The median (interquartile range) CA 19-9 level at diagnosis and pre-NAT was 106 (33.3–318) U/mL, and the last median (interquartile range) pre-resection was 21 (11–52) U/mL, respectively. Of the entire cohort, 117 (58%) patients had normal CA 19-9 levels (optimal CA 19-9) post-NAT. Of the 135 patients who had a baseline CA 19-9 elevation, 71 (53%) had their levels normalize post-NAT (major CA 19-9 response).

All patients had at least 1 FDG-PET scan post-NAT and pre-resection, and 182 (90.1%) had ≥2 FDG-PETs during NAT. The specific FDG-PET modality was either PET/CT (n=35; 17%) or PET/MRI (n=167; 83%). We found that 122 (60%) patients had FDG-PET at baseline with a mean [SD] standardized uptake value (SUV) of 6.5 [2.4], and only 4 (3.3%) patients had treatment-naïve nonavid tumors. Among the 122 patients who had FDG-PET at baseline pre-NAT, 34 (16.8%) also had avid regional lymph node involvement. In the remaining 80 (40%) patients without pretreatment metabolic imaging undergoing first FDG-PET after initial NAT, the mean [SD] SUV was 3.9 [1.4], with 22 (27.5%) patients who had nonavid tumors. There were significant differences in mean tumoral SUV between patients who had baseline pretreatment FDG-PET and those undergoing FDG-PET after some initial NAT ($P<.0001$) and the proportion of nonavid tumors in each group, respectively ($P=.0002$), possibly suggesting an interval response, although this type of response cannot be proven with this dataset. Major metabolic response post-NAT was seen in 104 (52%) patients, with the remaining 98 (49%) having residual metabolic activity above background. The mean [SD] SUV differences between major and minor metabolic response groups was significant (1.5 [1.9] vs 3.8 [1.6]; $P<.001$, respectively). Among the 34 (17%) patients who had avid lymph node involvement on baseline FDG-PET pre-NAT, 21 (62%) had complete metabolic nodal responses.

Vascular (venous/arterial) resection was required in 134 (66%) patients. The margin-positive rate was 3%, with 42 (21%) patients having metastatic lymph nodes. Lymphovascular and perineural invasion were present in 21 (10%) and 76 (38%) specimens, respectively. Pathologic treatment response categories included complete response in 27 (13%) patients, near-complete response in 50 (25%), partial response in 108 (54%), and no response in 17 (8%), with a total of 77 (38%) patients having major (complete or near-complete) pathologic responses. A minority of patients (23%) received any postoperative chemotherapy: 17 (9%) received adjuvant chemotherapy, whereas 27 (14%) received palliative chemotherapy after subsequent recurrence.

At follow-up, 82 (41%) patients developed recurrence and 140 (69%) remained alive. Supplemental eTable 2 shows the univariate analysis for factors associated with RFS and OS. Although optimal CA 19-9 levels, major CA 19-9 response, and lymphovascular invasion were associated with RFS alone, chemoradiation was associated with OS alone. Perineural invasion (hazard ratio [HR], 2.41; 95% CI, 1.56–3.74 [RFS]; HR, 2.11; 95% CI, 1.2–3.71 [OS]), major metabolic response (HR, 0.32; 95% CI, 0.2–0.51 [RFS]; HR, 0.25; 95% CI, 0.13–0.48 [OS]), and major pathologic response (HR, 0.27; 95% CI, 0.15–0.45 [RFS]; HR, 0.37; 95% CI, 0.19–0.72 [OS]) were significantly associated with both RFS and OS. Of these factors, only biochemical (CA 19-9) and metabolic (FDG-PET) variables were known before resection. Figure 1 shows the RFS and OS curves for each preoperative factor.

Given the significance of the association between NAT pathologic response and survival known only postoperatively, we then assessed the associations of preoperatively known biochemical (CA 19-9) and metabolic (PET) response factors to subsequent NAT pathologic responses (Table 1). Major pathologic response was more likely in patients with optimal CA 19-9 levels (82% vs 43%; $P<.0001$), major CA 19-9 responses (86% vs 36%; $P<.0001$), and major metabolic responses (94% vs 21%; $P<.0001$). A small cohort of 19 (9%) patients who received NAT without subsequent chemoradiation were identified. Even in this smaller cohort, there was still a significant association between metabolic response and pathologic response ($P=.004$), as opposed to CA 19-9 levels ($P=.52$) or CA 19-9 responses ($P=1.00$). Relative contributions of various combinations of biochemical and metabolic responses were assessed (Table 1). Biochemical response in the absence of an associated major metabolic response did not correlate with a subsequent major pathologic response (major pathologic response among patients with optimal CA 19-9 level and minor metabolic response, 7.1%; among patients with major CA 19-9 response and minor metabolic response, 3.8%), suggesting that CA 19-9 alone is insufficient in determining the adequacy of NAT response. In contrast, major metabolic response was highly associated with major pathologic response regardless of biochemical response (major pathologic response among patients with major metabolic response and any CA 19-9 level or response, 73.5%). Furthermore, when both factors were present, pathologic response was even more predictive.

Table 2 reveals diagnostic testing measures for major metabolic response, optimal CA 19-9 level, and major CA 19-9 response in predicting major pathologic response. Major metabolic response was superior compared with biochemical assessments in all measures. Figure 2 shows the superior performance of metabolic response on ROC analyses in predicting pathologic response. On multivariate regression, both biochemical and metabolic responses were independently associated with major pathologic

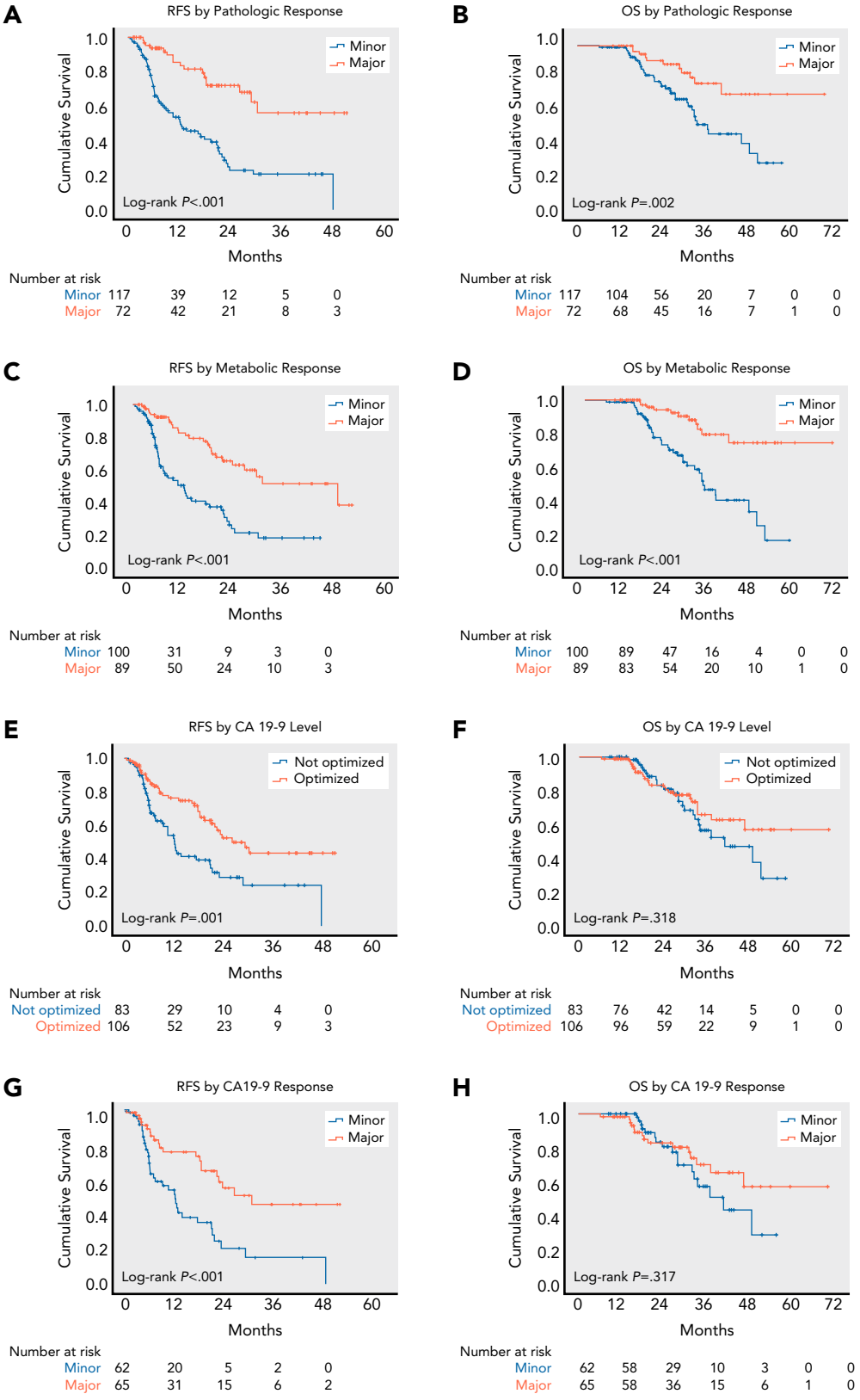


Figure 1. RFS and OS, respectively, stratified by **(A, B)** pathologic response, **(C, D)** metabolic response, **(E, F)** CA 19-9 level, and **(G, H)** CA 19-9 response.
Abbreviations: OS, overall survival; RFS, recurrence-free survival.

Table 1. Metabolic and Biochemical Factor Associations With Pathologic Response

Variable	Major Pathologic Response n (%)	Minor Pathologic Response n (%)	*P* Value
Total, n	77 (38.1)	125 (61.9)	
Biochemical (CA 19-9)			
CA19-9 level			
Optimal CA 19-9 level	63 (81.8)	54 (43.2)	**<.0001**
Suboptimal CA 19-9 level	14 (18.2)	71 (56.8)	
CA19-9 response			
Major CA 19-9 response[a]	38 (86.4)	33 (36.3)	**<.0001**
Minor CA 19-9 response[a]	6 (13.6)	58 (64.7)	
Metabolic (PET)			
Major metabolic response	72 (93.5)	26 (20.8)	**<.0001**
Minor metabolic response	5 (6.5)	99 (79.2)	
Biochemical (CA 19-9) and metabolic (PET)			
Optimal CA 19-9 level and major metabolic response	60 (80.0)	15 (20.0)	**<.0001**
Optimal CA 19-9 level and minor metabolic response	3 (7.1)	39 (92.9)	**<.0001**
Optimal CA 19-9 level	63 (53.8)	54 (46.2)	.4
Suboptimal CA 19-9 level and major metabolic response	12 (52.2)	11 (47.8)	.17
Suboptimal CA 19-9 level and minor metabolic response	2 (3.2)	60 (96.8)	**<.0001**
Suboptimal CA 19-9 level	14 (16.5)	71 (83.5)	**<.0001**
Major CA 19-9 response[a] and major metabolic response	37 (82.2)	8 (17.8)	**<.0001**
Major CA 19-9 response[a] and minor metabolic response	1 (3.8)	25 (96.1)	**.0003**
Major CA 19-9 response[a]	38 (53.5)	33 (46.5)	.55
Minor CA 19-9 response[a] and major metabolic response	5 (35.7)	9 (64.3)	.79
Minor CA 19-9 response[a] and minor metabolic response	1 (2)	49 (98)	**<.0001**
Minor CA 19-9 response[a]	6 (9.4)	58 (90.6)	**<.0001**
Major metabolic response	72 (73.5)	26 (26.5)	**<.0001**
Minor metabolic response	5 (4.8)	99 (95.2)	**<.0001**

Bold indicates statistically significant *P* value.
[a]Included only those with initial CA 19-9 elevation.

responses, although with a significantly higher OR for metabolic response (Table 3). Finally, multivariate Cox proportional hazard analyses for preoperatively known factors associated with RFS and OS on univariate analyses revealed that metabolic response was the only significant independent preoperative predictor of survival (Table 4).

Discussion

If we intend NAT to be of benefit in patients with BR/LA PDAC, then we must show treatment efficacy objectively. Standard radiologic and biochemical assessments provide insufficient predictions about NAT effectiveness in PDAC. Anatomic imaging has not been useful in BR/LA PDAC,[5,6,13,26–28] and NCI and NCCN Guidelines for Pancreatic Adenocarcinoma do not include, and discourage, radiologic responses as relevant treatment endpoints because they do not predict survival.[4,7] Biochemical responses (CA 19-9) are not assessable in at least 40% of patients (10% nonsecretors, 30% with normal CA 19-9 levels), and variability exists regarding what constitutes an appropriate NAT response (ie, stability, partial stability, or normalization).[13,29–31] Therefore, biochemical responses to NAT, although helpful in some (ie, baseline elevated),[8] are generally inadequate in patients with BR/LA PDAC. Given these limitations, the absence of metastatic disease alone is an indication for proceeding with resection post-NAT, a strategy with possible suboptimal oncologic and potentially devastating surgical outcomes given the increased risks with these operations. Thus, current standards of NAT response assessment are inadequate.

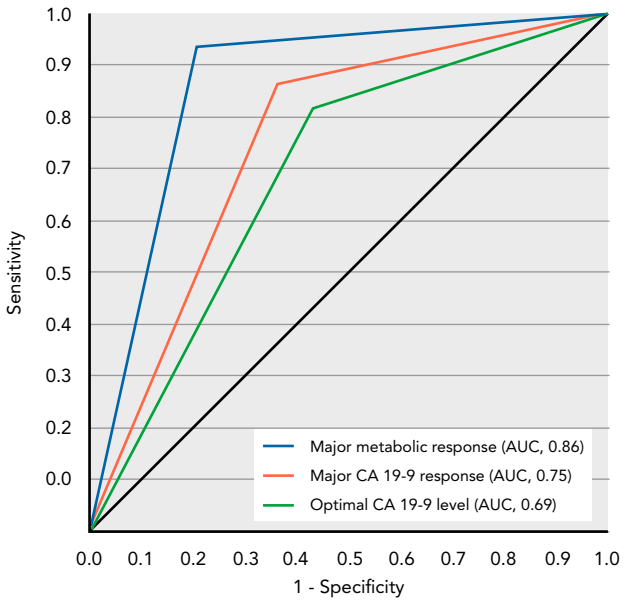
Determining the optimal response to initial induction chemotherapy in BR/LA PDAC presents a therapeutic dilemma. A multidisciplinary team needs to determine whether chemotherapeutic benefit has been maximized

Table 2. Diagnostic Testing Accuracy Measures of Major Metabolic Response, Optimal CA 19-9 Level, and Major CA 19-9 Response in Predicting Major Pathologic Response

Diagnostic Accuracy	Metabolic (PET) Major Response	Biochemical (CA 19-9)	
		Optimal CA 19-9 Level	Major CA 19-9 Response[a]
Sensitivity	93.5 (85.49–97.86)	81.8 (71.38–89.69)	86.4 (72.65–94.83)
Specificity	79.2 (71.01–85.94)	56.8 (47.64–65.63)	63.7 (52.99–73.56)
PPV	73.5 (63.59–81.88)	53.8 (44.39–63.1)	53.5 (41.29–65.45)
NPV	95.2 (89.14–98.42)	83.5 (73.91–90.69)	90.6 (80.7–96.48)
LR+	4.5 (3.18–6.36)	1.89 (1.51–2.38)	2.38 (1.77–3.2)
LR−	0.08 (0.04–0.19)	0.32 (0.2–0.53)	0.21 (0.1–0.46)
Accuracy	84.7	66.34	71.11
AUC (95% CI)	0.86 (0.81–0.9)	0.69 (0.63–0.75)	0.75 (0.67–0.82)
P value (model)	<.001	<.001	<.001
P value (AUC)	ref	<.001	.004

Abbreviations: AUC, area under the curve; LR+, positive likelihood ratio; LR–, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.
[a]This model included only those with initial CA 19-9 elevation. Estimated prevalence is the proportion of the sample with a positive major pathologic response. The estimated prevalence has been used as a valid estimate of the population prevalence because the entire sample is a random sample of the population and is comparable to what have been reported previously in the literature including Truty et al.[13] The AUC is calculated from the predicted values generated from the adjusted binary logistic regression analysis controlling for the chemoradiation effect.

and either proceed to chemoradiation[2] and/or surgery,[32] extend the duration of the same chemotherapeutic regimen, or consider a chemotherapeutic switch.[33] Having highly predictive preoperative data is critical for decision-making, with a substantial influence on patient outcomes. Most NAT studies have identified pathologic treatment response—a postoperative metric—as the most independent predictor of survival. This retrospective study assessed preoperative FDG-PET in determining the adequacy of NAT response in relation to pathologic response and survival. The current approved role of FDG-PET in PDAC is to assess metastatic disease when



- AUC difference of major metabolic response vs optimal CA 19-9 level: 0.17 (95% CI, 0.1–0.24); *P*<.0001
- AUC difference of major metabolic response vs major CA 19-9 response: 0.11 (95% CI, 0.04–0.19); *P*=.0041
- AUC difference of major CA 19-9 response vs optimal CA 19-9 level: 0.06; *P*>.05

Figure 2. ROC curves and AUC to compare how metabolic response, optimal CA 19-9 level, and major CA 19-9 response predict major pathologic response.
Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

Table 3. Multivariate Regression Analysis on Preoperative Factors Predicting Major Pathologic Response

Multivariate Cohort	Variable	OR (95% CI)	*P* Value
n=202	Chemoradiation	1.29 (0.24–8.11)	.77
	Optimal CA 19-9 level	3.27 (1.35–8.07)	**.009**
	Major metabolic response	43.20 (16.88–135.16)	**<.0001**
n=135[a]	Chemoradiation	0.49 (0.04–12.29)	.61
	Major CA 19-9 response	6.91 (2.09–25.40)	**.001**
	Major metabolic response	76.25 (18.61–571.15)	**<.0001**

Bold values indicate a statistically significant *P* value.
Abbreviation: OR, odds ratio.
[a]This model included only those with initial CA 19-9 elevation.

standard imaging is indeterminate. FDG-PET is not formally recommended to assess NAT responses in BR/LA PDAC, in contrast to many other malignancies in which it is the standard of care.[34] We found that post-NAT metabolic response is the preoperative metric superior to biochemical responses alone in predicting pathologic response and the most significant independent predictor of survival. FDG-PET results increase the likelihood of making accurate treatment decisions beyond biochemical responses alone by shifting major pathologic response probability to more accurate estimates. Although both biochemical and metabolic response factors are individually distinct, our findings logically suggest that they together likely potentiate the likelihood of compatible pathologic response, with metabolic responses having a greater probability of predicting pathologic responses than biochemical responses alone. These data support their dual role during NAT given the rarity (n=2) of patients with major pathologic response when both major biochemical and metabolic responses were absent. Most relevant, FDG-PET precisely categorized pathologic responses in patients in whom formal biochemical responses could not be assessed (ie, nonsecretors/nonelevated)—a significant proportion of patients with PDAC. If we cannot achieve optimal FDG-PET response despite NAT alterations, then we assume chemoresistance and suboptimal postoperative survival. In these circumstances, patients should be counseled appropriately, with the risks of planned operation weighed against predicted survival benefit.

Our findings align with previous reports showing that FDG-PET predicts chemotherapy response in BR/LA PDAC.[35] However, some previous studies showing the FDG-PET utility of NAT response in PDAC did not compare metabolic parameters with pathologic responses.[24,36–38] One trial terminated due to low accrual and too small a size to draw meaningful conclusions.[37] Another compared metabolic responses with radiologic responses[38]; however, RECIST has previously established low correlation to pathologic response. Lee et al[39] did not detect FDG-PET metabolic activity and pathologic response associations, likely explained by small sample size and very low overall major pathologic response rates. We found that FDG-PET responses are independently predictive of survival outcomes, similar to previous studies,[38–41] which are explained by the association between metabolic response and post-NAT tumor viability. Tumor viability within the resected specimen is the only direct NAT response test with true findings; therefore, any test to predict NAT response should be compared with the standard reference, pathologic treatment response, as performed in this series. Others have looked at the correlation between NAT response and percentage change in FDG-PET parameters, such as the SUV maximum.[21,42,43] Although partial metabolic responses are encouraging, they only indicate

Table 4. Multivariate Cox Proportional Hazard Analyses on Preoperative Factors Predicting RFS and OS

	RFS (n=202)		RFS (n=135)[b]		OS (n=202)		OS (n=135)[b]	
Variable[a]	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* value	HR (95% CI)	*P* Value
Chemoradiation	—	—	—	—	0.33 (0.15–0.87)	**.03**	0.36 (0.12–1.55)	.15
Optimal CA 19-9 level	0.64 (0.4–1.02)	.06	—	—	1.39 (0.76–2.54)	.28	—	—
Major CA 19-9 response	—	—	0.56 (0.3–1.02)	.06	—	—	1.46 (0.6–3.21)	.35
Major metabolic response	0.37 (0.22–0.6)	**<.0001**	0.43 (0.22–0.8)	**.01**	0.21 (0.1–0.42)	**<.0001**	0.26 (0.1–0.61)	**.002**

Bold values indicate a statistically significant *P* value.
Abbreviations: HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival.
[a]Only significant variables on univariate RFS or OS have been used for the multivariate Cox proportional hazards RFS or OS as appropriate.
[b]This model included only those with initial CA 19-9 elevation.

incomplete pathologic response and likely incomplete systemic efficacy. Tumors with any residual metabolic activity post-NAT, regardless of degree, will likely still harbor significant viable tumors with associated worse survival. Thus, the goal of NAT before any higher-risk interventions should be complete or near-complete metabolic responses. The concept of tumor viability and consequences of high stakes treatment support FDG-PET dichotomization of metabolic response into either major or minor response for better prognostication. Although it is difficult to contextualize FDG-PET without baseline FDG-PET, and some patients underwent first FDG-PET after initial NAT (treated elsewhere), serial FDG-PET throughout NAT duration is still possible and useful. We conducted subgroup analysis by excluding the 40% of patients without pretreatment PET. All of the measures (ie, metabolic, CA 19-9 level, and CA 19-9 response) had identical results to the full cohort analysis, showing that metabolic PET response associates with pathologic response far better than biochemical response (CA 19-9).

Although data from prospective clinical trials of FDG-PET utility in assessing NAT response in PDAC would be optimal (a current R01-funded trial is underway at our center), the feasibility and benefits of such FDG-PET studies have already been established in many other cancers.[44,45] For a test to be mandated, we need to show that without it, a potential target disorder is dangerous if left undiagnosed, and that results change management with the potential for additional treatment being available and rendered.[12,13,46] Given the high correlation of FDG-PET in predicting post-NAT pathologic response and survival, FDG-PET serves as an optimal preoperative assessment of NAT response, thus stratifying patients into specific downstream options (ie, proceed to surgery, continue current NAT, or chemotherapy switch).[33,47]

This study has significant limitations due to its retrospective cohort design with selection bias that likely may overestimate the prognostic ability compared with unselected populations. However, our sample was very representative of all patients with PDAC who received surgical resection at our institute, where FDG-PET has become more standardized in our practice; however, we cannot exclude selection bias in general. We included patients referred from other centers to enhance sample representativeness, although this inclusion may still impact the generalizability of our findings. Both BR and LA in our practice are grouped together because they are treated identically; the only difference is the magnitude and complexity of any possible subsequent operation, so we do not typically stratify between these 2 types. Our criteria for surgery are more liberal, and thus a higher proportion of patients underwent resection, many of whom may have been deemed unresectable elsewhere. We do not use RECIST criteria in making surgical decisions, given low specificity with minimal survival prediction[21] and the fact that they are not included in the NCCN Guidelines criteria for surgery post-NAT in patients with BR/LA PDAC.[4] Radiologic downstaging is not relevant in our practice because patients are either anatomically reconstructable or they are not. Metabolic nodal activity and response were not suitable to address in this study for the following reasons: (1) early NAT was administered before some FDG-PET scans were performed, and (2) FDG-PET may have low sensitivity for detecting lymph node metastasis. In addition, we included patients who underwent both standard PET/CT and PET/MRI and did not find any significant differences between modalities; thus, we feel that the results translate to any FDG-PET modality that is available at any center. Our FDG-PET protocols may differ and require standardization to enhance agreement beyond chance; however, the outcomes measured were reproducible and sufficient to answer the study question about evaluating the diagnostic accuracy of the FDG-PET metabolic response in predicting pathologic responses and survival compared with biochemical response in patients with BR/LA PDAC undergoing NAT pre-resection. Finally, our metabolic and pathologic response rates may differ from those of other centers because we generally use total NAT (chemotherapy + chemoradiation) with extended-duration NAT and consideration of chemotherapy switch.[33]

Conclusions

Among patients with BR/LA PDAC undergoing NAT, FDG-PET is superior in predicting pathologic treatment response versus biochemical assessments alone, with those metabolic responses independently predictive of survival. Such preoperative metabolic data may either support or refute the adequacy of NAT pre-resection. Further validity evidence on the use of PET in assessing treatment responses in PDAC should be actively collected through other centers' studies and clinical trials (a current R01-funded clinical trial is underway at our center). Although prospective studies are warranted, the results of FDG-PET for BR/LA PDAC in this study may be sufficient to recommend FDG-PET as an approved adjunct modality in assessing NAT efficacy in addition to the currently approved but poorly predictive metrics (CT/MRI and CA 19-9 level). We recommend that providers combine all available response measures (ie, clinical, radiologic, biochemical, and metabolic) to make suitable decisions regarding NAT alterations and final decisions for surgery or no surgery on a case-by-case basis.

Submitted November 29, 2021; final revision received June 2, 2022; accepted for publication June 3, 2022.

Author contributions: *Study concept and design:* Abdelrahman, Truty. *Data acquisition:* Abdelrahman, Alva-Ruiz, Yonkus, Truty. *Data analysis:* Abdelrahman, Truty. *Data interpretation:* All authors. *Writing – original draft:* Abdelrahman, Truty. *Writing – review and editing:* All authors.

Disclosures: Dr. Halfdanarson has disclosed receiving grant/research support from Thermo Fisher Scientific, Turnstone Biologics, Advanced Accelerator Applications, Basilea, and Agios; and serving as an advisory board member for Terumo, Ipsen, Advanced Accelerator Applications, TerSera, ITM Isotopen Technologien Muenchen, Crinetics, and Viewpoint Molecular Targeting. The remaining authors have not received any financial consideration from any person or organization to support the preparation, analysis, results, or discussion of this article.

Correspondence: Mark J. Truty, MD, MS, Division of Hepatobiliary and Pancreas Surgery, Department of Surgery, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55902. Email: Truty.Mark@mayo.edu

References

1. Zakem SJ, Mueller AC, Meguid C, et al. Impact of neoadjuvant chemotherapy and stereotactic body radiation therapy (SBRT) on R0 resection rate for borderline resectable and locally advanced pancreatic cancer. HPB (Oxford) 2021;23:1072–1083.
2. Hue JJ, Dorth J, Sugumar K, et al. Neoadjuvant radiotherapy is associated with improved pathologic outcomes and survival in resected stage II-III pancreatic adenocarcinoma treated with multiagent neoadjuvant chemotherapy in the modern era. Am Surg 2021;87:1386–1395.
3. Choi M, Heilbrun LK, Venkatramanamoorthy R, et al. Using ^{18}F-fluorodeoxyglucose positron emission tomography to monitor clinical outcomes in patients treated with neoadjuvant chemo-radiotherapy for locally advanced pancreatic cancer. Am J Clin Oncol 2010;33:257–261.
4. Tempero MA, Malafa MP, Al-Hawary M, et al. NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 2.2021. Accessed October 1, 2021. To view the most recent version, visit NCCN.org
5. Wagner M, Antunes C, Pietrasz D, et al. CT evaluation after neoadjuvant FOLFIRINOX chemotherapy for borderline and locally advanced pancreatic adenocarcinoma. Eur Radiol 2017;27:3104–3116.
6. Okada KI, Kawai M, Hirono S, et al. Diffusion-weighted MRI predicts the histologic response for neoadjuvant therapy in patients with pancreatic cancer: a prospective study (DIFFERENT trial). Langenbecks Arch Surg 2020;405:23–33.
7. Philip PA, Mooney M, Jaffe D, et al. Consensus report of the National Cancer Institute clinical trials planning meeting on pancreas cancer treatment. J Clin Oncol 2009;27:5660–5669.
8. Diaz CL, Cinar P, Hwang J, et al. CA 19-9 response: a surrogate to predict survival in patients with metastatic pancreatic adenocarcinoma. Am J Clin Oncol 2019;42:898–902.
9. van Veldhuisen E, Vogel JA, Klompmaker S, et al. Added value of CA19-9 response in predicting resectability of locally advanced pancreatic cancer following induction chemotherapy. HPB (Oxford) 2018;20:605–611.
10. Reni M, Zanon S, Balzano G, et al. Selecting patients for resection after primary chemotherapy for non-metastatic pancreatic adenocarcinoma. Ann Oncol 2017;28:2786–2792.
11. Bergquist JR, Puig CA, Shubert CR, et al. Carbohydrate antigen 19-9 elevation in anatomically resectable, early stage pancreatic cancer is independently associated with decreased overall survival and an indication for neoadjuvant therapy: a National Cancer Database study. J Am Coll Surg 2016;223:52–65.
12. Tee MC, Krajewski AC, Groeschl RT, et al. Indications and perioperative outcomes for pancreatectomy with arterial resection. J Am Coll Surg 2018;227:255–269.
13. Truty MJ, Kendrick ML, Nagorney DM, et al. Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. Ann Surg 2021;273:341–349.
14. Macedo FI, Ryon E, Maithel SK, et al. Survival outcomes associated with clinical and pathological response following neoadjuvant FOLFIRINOX or gemcitabine/nab-paclitaxel chemotherapy in resected pancreatic cancer. Ann Surg 2019;270:400–413.
15. Zhao Q, Rashid A, Gong Y, et al. Pathologic complete response to neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma is associated with a better prognosis. Ann Diagn Pathol 2012;16:29–37.
16. Chun YS, Cooper HS, Cohen SJ, et al. Significance of pathologic response to preoperative therapy in pancreatic cancer. Ann Surg Oncol 2011;18:3601–3607.
17. Wilson JM, Mukherjee S, Brunner TB, et al. Correlation of ^{18}F-fluorodeoxyglucose positron emission tomography parameters with patterns of disease progression in locally advanced pancreatic cancer after definitive chemoradiotherapy. Clin Oncol (R Coll Radiol) 2017;29:370–377.
18. Pergolini I, Crippa S, Salgarello M, et al. SUVmax after (18)fluoro-deoxyglucose positron emission tomography/computed tomography: a tool to define treatment strategies in pancreatic cancer. Dig Liver Dis 2018;50:84–90.
19. Yeh R, Dercle L, Garg I, et al. The role of 18F-FDG PET/CT and PET/MRI in pancreatic ductal adenocarcinoma. Abdom Radiol (NY) 2018;43:415–434.
20. Higashi T, Sakahara H, Torizuka T, et al. Evaluation of intraoperative radiation therapy for unresectable pancreatic cancer with FDG PET. J Nucl Med 1999;40:1424–1433.
21. Panda A, Garg I, Truty MJ, et al. Borderline resectable and locally advanced pancreas cancer: FDG PET/MRI and CT tumor metrics for assessment of pathologic response to neoadjuvant therapy and prediction of survival. AJR Am J Roentgenol 2021;217:730–740.
22. Panda A, Garg I, Johnson GB, et al. Molecular radionuclide imaging of pancreatic neoplasms. Lancet Gastroenterol Hepatol 2019;4:559–570.
23. Wahl RL, Jacene H, Kasamon Y, et al. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med 2009;50(Suppl 1):122S–150S.
24. Kakar S, Shi C, Adsay NV, et al. Protocol for the examination of specimens from patients with carcinoma of the pancreas. Accessed June 10, 2022. Available at: https://documents.cap.org/protocols/cp-pancreas-exocrine-17protocol-4001.pdf
25. DeLong ER, DeLong DM, Clark-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1998;44:837–845.
26. Takaori K. "International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017": will this pull us up out of the quagmire of confusing definitions and criteria? Pancreatology 2018;18:1.
27. Kuwatani M, Kawakami H, Eto K, et al. Modalities for evaluating chemotherapeutic efficacy and survival time in patients with advanced pancreatic cancer: comparison between FDG-PET, CT, and serum tumor markers. Intern Med 2009;48:867–875.
28. Yin L, Miao Y, Yu J. Advances of pathological complete response after neoadjuvant therapy for pancreatic cancer. J Pancreatol 2019;2:11–15.
29. Al Abbas AI, Zenati M, Reiser CJ, et al. Serum CA19-9 response to neoadjuvant therapy predicts tumor size reduction and survival in pancreatic adenocarcinoma. Ann Surg Oncol 2020;27:2007–2014.
30. Rose JB, Edwards AM, Rocha FG, et al. Sustained carbohydrate antigen 19-9 response to neoadjuvant chemotherapy in borderline resectable pancreatic cancer predicts progression and survival. Oncologist 2020;25:859–866.
31. Liu H, Zenati MS, Rieser CJ, et al. CA19-9 change during neoadjuvant therapy may guide the need for additional adjuvant therapy following resected pancreatic cancer. Ann Surg Oncol 2020;27:3950–3960.
32. Fong ZV, Ferrone CR. Surgery after response to chemotherapy for locally advanced pancreatic ductal adenocarcinoma: a guide for management. J Natl Compr Canc Netw 2021;19:459–467.
33. Alva-Ruiz R, Yohanathan L, Yonkus JA, et al. Neoadjuvant chemotherapy switch in borderline resectable/locally advanced pancreatic cancer. Ann Surg Oncol 2022;29:1579–1591.
34. Centers for Medicare & Medicaid Services. Medicare national coverage determinations (NCD) manual. Accessed June 10, 2022. Available at: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS014961
35. Evangelista L, Zucchetta P, Moletta L, et al. The role of FDG PET/CT or PET/MRI in assessing response to neoadjuvant therapy for patients with borderline or resectable pancreatic cancer: a systematic literature review. Ann Nucl Med 2021;35:767–776.
36. Myssayev A, Myssayev A, Ideguchi R, et al. Usefulness of FDG PET/CT derived parameters in prediction of histopathological finding during the surgery in patients with pancreatic adenocarcinoma. PLoS One 2019;14:e0210178.
37. Zimmermann C, Distler M, Jentsch C, et al. Evaluation of response using FDG-PET/CT and diffusion weighted MRI after radiochemotherapy of pancreatic cancer: a non-randomized, monocentric phase II clinical trial-PaCa-DD-041 (Eudra-CT 2009-011968-11). Strahlenther Onkol 2021;197:19–26.

38. Kurahara H, Maemura K, Mataki Y, et al. Significance of ^{18}F-fluorodeoxyglucose (FDG) uptake in response to chemoradiotherapy for pancreatic cancer. Ann Surg Oncol 2019;26:644–651.
39. Lee W, Oh M, Kim JS, et al. Metabolic activity by FDG-PET/CT after neoadjuvant chemotherapy in borderline resectable and locally advanced pancreatic cancer and association with survival. Br J Surg 2021;109:61–70.
40. Ramanathan RK, Goldstein D, Korn RL, et al. Positron emission tomography response evaluation from a randomized phase III trial of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas. Ann Oncol 2016;27:648–653.
41. Maemura K, Takao S, Shinchi H, et al. Role of positron emission tomography in decisions on treatment strategies for pancreatic cancer. J Hepatobiliary Pancreat Surg 2006;13:435–441.
42. Mellon EA, Jin WH, Frakes JM, et al. Predictors and survival for pathologic tumor response grade in borderline resectable and locally advanced pancreatic cancer treated with induction chemotherapy and neoadjuvant stereotactic body radiotherapy. Acta Oncol 2017;56:391–397.
43. O JH, Lodge MA, Wahl RL. Practical PERCIST: a simplified guide to PET response criteria in solid tumors 1.0. Radiology 2016;280:576–584.
44. Borggreve AS, Mook S, Verheij M, et al. Preoperative image-guided identification of response to neoadjuvant chemoradiotherapy in esophageal cancer (PRIDE): a multicenter observational study. BMC Cancer 2018;18:1006.
45. Borggreve AS, Goense L, van Rossum PSN, et al. Preoperative prediction of pathologic response to neoadjuvant chemoradiotherapy in patients with esophageal cancer using ^{18}F-FDG PET/CT and DW-MRI: a prospective multicenter study. Int J Radiat Oncol Biol Phys 2020;106:998–1009.
46. Truty MJ, Colglazier JJ, Mendes BC, et al. En bloc celiac axis resection for pancreatic cancer: classification of anatomical variants based on tumor extent. J Am Coll Surg 2020;231:8–29.
47. JAMAevidence: using evidence to improve care. In: Guyatt G, Rennie D, Meade MO, Cook DJ, eds. Users' Guide to the Medical Literature: A Manual for Evidence-Based Clinical Practice, 3rd ed. New York, NY: McGraw Hill Education; 2015.

See JNCCN.org for supplemental online content.

JNCCN

National Comprehensive Cancer Network®

JOURNAL OF THE NATIONAL COMPREHENSIVE CANCER NETWORK

Supplemental online content for:

FDG-PET Predicts Neoadjuvant Therapy Response and Survival in Borderline Resectable/Locally Advanced Pancreatic Adenocarcinoma

Amro M. Abdelrahman, MBBS, MS; Ajit H. Goenka, MD; Roberto Alva-Ruiz, MD; Jennifer A. Yonkus, MD; Jennifer L. Leiting, MD; Rondell P. Graham, MBBS; Kenneth W. Merrell, MD; Cornelius A. Thiels, DO, MBA; Christopher L. Hallemeier, MD; Susanne G. Warner, MD; Michael G. Haddock, MD; Travis E. Grotz, MD; Nguyen H. Tran, MD; Rory L. Smoot, MD; Wen Wee Ma, MBBS; Sean P. Cleary, MD; Robert R. McWilliams, MD; David M. Nagorney, MD; Thorvardur R. Halfdanarson, MD; Michael L. Kendrick, MD; and Mark J. Truty, MD, MS

J Natl Compr Canc Netw 2022;20(9):1023–1032.e3

eTable 1: Descriptive Cohort Demographics and Variables

eTable 2: Univariate RFS and OS Models

eTable 1. Descriptive Cohort Demographics and Variables

Variable	n (%)
Total, N	202
Sex	
Male	117 (58)
Female	85 (42)
Ethnicity	
Non-Hispanic or Latino	190 (94.1)
Hispanic or Latino	3 (1.5)
Other/Unknown/Chose not to disclose	9 (4.4)
Race	
White	187 (92.6)
Black/African American	2 (1)
Asian	7 (3.4)
Other	4 (2)
Unknown	2 (1)
Age at surgery	
Mean [SD], y	65 [9.8]
Median (range), y	65 (24.2–85.6)
≥65 y	101 (50)
CA 19-9 at diagnosis	
Mean [SD], U/mL	563 [1,829]
Median (range), U/mL	106 (0–20,860)
>500 U/mL	62 (31)
>1,000 U/mL	44 (22)
CA 19-9 elevated at diagnosis	
Yes	135 (67)
No	42 (23)
Nonsecretors	21 (10)
NAT type	
Any FOLFIRINOX	179 (89)
Any GA	117 (58)
Chemotherapy switch	94 (47)
Total chemotherapy cycles	
Mean [SD]	8.8 [3.6]
Median	8
Range	2–28
Days between end of NAT and preoperative FDG-PET scan	
Mean [SD]	34.8 [13.8]
Median	32.5
Range	7–128
CA 19-9 response categories	
1: Elevated and normalized	71 (35)
2: Elevated and stayed elevated	64 (32)
3: Normal and stayed normal	46 (23)
4: Nonsecretors	21 (10)

(*continued in next column*)

eTable 1. Descriptive Cohort Demographics and Variables (cont.)

Variable	n (%)
Optimal CA 19-9 levels post-NAT	
Yes	117 (58)
No	85 (42)
Major CA 19-9 response (only those with initial CA 19-9 elevation)	
Yes	71 (53)
No	64 (47)
Chemoradiation	
Yes	183 (91)
No	19 (9)
FDG-PET scan type	
PET/CT	35 (17)
PET/MRI	167 (83)
>1 PET before surgery	
Yes	182 (90)
No	20 (10)
Pre-NAT baseline PET	
Yes	122 (60)
No	80 (40)
Avid tumor at first baseline PET (chemotherapy-naïve)	118 (97)
SUV at first baseline PET (chemotherapy-naïve), mean [SD]	6.5 [2.4]
Avid tumor at first baseline PET (previous chemotherapy)	58 (73)
SUV at first baseline PET (previous chemotherapy), mean [SD]	3.9 [1.4]
Days from last PET to surgery, mean [SD]	11.5 [13]
Avid regional lymph nodes on PET	
Avid	40 (19.8)
Nonavid	162 (80.2)
Metabolic (PET) response	
Major	104 (52)
Minor	98 (49)
Surgery	
Whipple	100 (49.5)
Total pancreatectomy	56 (27.7)
Distal pancreatectomy	46 (22.8)
Vascular resection	
Yes	134 (66)
No	68 (34)
Resection margin status	
Positive	5 (3)
Negative	197 (97)
Positive lymph nodes	
Yes	42 (21)
No	160 (79)

(*continued on next page*)

eTable 1. Descriptive Cohort Demographics and Variables (cont.)

Variable	n (%)
Lymphovascular invasion	
Yes	21 (10)
No	181 (90)
Perineural invasion	
Yes	76 (38)
No	126 (62)
Pathologic treatment response	
Score 0: complete	27 (13)
Score 1: near-complete	50 (25)
Score 2: partial	108 (54)
Score 3: none	17 (8)
Major pathologic response (0 or 1)	
Yes	77 (38)
No	125 (62)
90-day operative mortality	
Yes	13 (6)
No	189 (94)
Postoperative chemotherapy	
Adjuvant (before progression and/or recurrence)	17 (9)
Palliative (after progression and/or recurrence)	27 (14)
No	145 (77)
Any recurrence	
Yes	82 (41)
Distant recurrence	63 (77)
No	120 (59)
Alive at last follow-up	
Yes	140 (69)
No	62 (31)

Abbreviations: FOLFIRINOX, fluorouracil/leucovorin/irinotecan/oxaliplatin; F/U, follow-up; GA, gemcitabine/nab-paclitaxel; NAT, neoadjuvant therapy; SUV, standardized uptake value.

eTable 2. Univariate RFS and OS Models

	Univariate RFS Analysis		Univariate OS Analysis	
Variable	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Sex, female	0.7 (0.44–1.08)	.11	0.88 (0.50–1.56)	.67
Age at surgery, y	1.01 (0.99–1.04)	.36	1.02 (0.99–1.05)	.31
Age at surgery, y	1.23 (0.8–1.9)	.35	1.22 (0.69–2.13)	.5
CA 19-9 at diagnosis >500 U/mL	1.4 (0.88–2.17)	.15	1.23 (0.68–2.21)	.49
CA 19-9 at diagnosis >1,000 U/mL	1.52 (0.91–2.45)	.11	1.38 (0.73–2.60)	.32
CA 19-9 elevated at diagnosis	1.29 (0.74–2.24)	.38	1.02 (0.50–2.08)	.96
Optimal CA 19-9 level	0.47 (0.3–0.73)	**<.001**	0.75 (0.43–1.32)	.32
Major CA 19-9 response[a]	0.38 (0.22–0.65)	**<.001**	0.70 (0.35–1.41)	.32
Chemoradiation	0.56 (0.29–1.2)	.13	0.36 (0.15–0.84)	**.02**
Neoadjuvant therapy duration, mo	1.04 (0.99–1.09)	.13	0.99 (0.92–1.07)	.86
Major metabolic (PET) response	0.32 (0.2–0.51)	**<.001**	0.25 (0.13–0.48)	**<.001**
Vascular resection	1.28 (0.8–2.16)	.32	1.19 (0.63–2.24)	.56
Positive margin	2.25 (0.55–6.08)	.22	1.53 (0.37–6.33)	.56
Positive lymph nodes	1.29 (0.75–2.12)	.34	1.2 (0.63–2.28)	.58
Lymphovascular invasion	2.13 (1.16–3.65)	**.02**	1.08 (0.46–2.55)	.86
Perineural invasion	2.41 (1.56–3.74)	**<.001**	2.11 (1.20–3.71)	**.009**
Major pathologic response	0.27 (0.15–0.45)	**<.001**	0.37 (0.19–0.72)	**.004**
Adjuvant chemotherapy	0.56 (0.22–1.19)	.14	0.43 (0.13–1.41)	.12

Bold values indicate statistically significant *P* values.
Abbreviations: HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival.
[a]Included only those with initial CA 19-9 elevation.