^{18}F-FDG PET/CT Imaging Biomarkers for Early and Late Evaluation of Response to First-Line Chemotherapy in Patients with Pancreatic Ductal Adenocarcinoma

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The purpose of this study was to evaluate ^{18}F-FDG PET/CT as an early and late interim imaging biomarker in patients with pancreatic ductal adenocarcinoma who undergo first-line systemic therapy. **Methods:** This was a prospective, single-center, single-arm, open-label study (IRB12-000770). Patient receiving first-line chemotherapy were planned to undergo baseline ^{18}F-FDG PET/CT, early interim ^{18}F-FDG PET/CT, and late interim ^{18}F-FDG PET/CT. Cutoffs for metabolic and radiographic tumor response assessment as selected and established by receiver-operating-characteristic analysis were applied (modified PERCIST/RECIST1.1). Patients were followed to collect data on further treatments and overall survival. **Results:** The study population consisted of 28 patients who underwent baseline ^{18}F-FDG PET/CT. Twenty-three of these (82%) underwent early interim ^{18}F-FDG PET/CT, and 21 (75%) underwent late interim ^{18}F-FDG PET/CT. Twenty-three deaths occurred during a median follow-up period of 14 mo (maximum follow-up, 58.3 mo). The median overall survival was 36.2 mo (95% CI, 28 mo to not yet reached [NYR]) in early metabolic responders (6/23 [26%], $P = 0.016$) and 25.4 mo (95% CI, 19.6 mo–NYR) in early radiographic responders (7/23 [30%], $P = 0.16$). The median overall survival was 27.4 mo (95% CI, 21.4 mo–NYR) in late metabolic responders (10/21 [48%], $P = 0.058$) and 58.2 mo (95% CI, 21.4 mo–NYR) in late radiographic responders (7/21 [33%], $P = 0.008$). **Conclusion:** ^{18}F-FDG PET may serve as an early interim imaging biomarker (at ~4 wk) for evaluation of response to first-line chemotherapy in patients with pancreatic ductal adenocarcinoma. Radiographic changes might be sufficient for response evaluation after the completion of first-line chemotherapy.

Key Words: ^{18}F-FDG PET; pancreas; adenocarcinoma; response

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Pancreatic ductal adenocarcinoma (PDAC) typically has a tumor microenvironment characterized by a dense desmoplastic stroma. Extensive desmoplasia results in decreased stromal vascularization and altered immune cell infiltration but also represents an imaging challenge in differentiating between viable tumor and desmoplasia. In addition, CT and MRI have been reported to be imperfect in discriminating between viable tumor, desmoplastic stroma, and dead scar tissue even after successful therapy (*1*).

The preferred chemotherapy regimens in the neoadjuvant or adjuvant setting and the first-line therapy for metastatic disease are FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin), modified FOLFIRINOX, or gemcitabine/nab-paclitaxel. New second-line approaches and specific treatments, such as poly(adenosine diphosphate-ribose) polymerase inhibitors in cancer related to BRCA1 or BRCA2 mutations, have broadened the spectrum of PDAC therapies. The considerable genetic heterogeneity among patients, however, results in a limited number of patients benefiting from a selected treatment.

Currently, multiple biomarkers are under investigation for their ability to predict treatment responses (*2*). The best validated and most widely used prognostic biomarker in PDAC is CA 19-9, which has shown value as a prognostic and predictive biomarker in PDAC in various settings (*3–5*).

Current imaging criteria for tumor response assessment focus on changes in tumor size, which were described as an imperfect predictor of response of PDAC to therapy in a white paper from the Society of Abdominal Radiology (*6*). Other imaging biomarkers, such as diffusion-weighted MRI (*7–9*) and ^{18}F-FDG PET/CT (*10–15*), have been proposed for treatment response assessment in PDAC but are not specifically supported by current society guidelines because of inconsistent and limited data, even more so when investigating early response.

In this exploratory prospective study, we investigated whether metabolic response assessment measured by ^{18}F-FDG PET can predict survival early after the start of first-line chemotherapy in patients with PDAC. The hypothesis was that early ^{18}F-FDG PET response is a better intermediate endpoint biomarker of overall survival (OS) than are early radiographic size changes.

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MATERIALS AND METHODS

Study Design and Patients

This was a single-center, single-arm, open-label, prospective exploratory study. Patients with biopsy-proven PDAC who were scheduled to undergo first-line chemotherapy were offered participation in this study. Exclusion criteria were an inability to tolerate a PET/CT scan or the presence of another concurrent malignant condition.

Patients were planned to undergo baseline ^{18}F-FDG PET/CT (PET1), early interim ^{18}F-FDG PET/CT (PET2), and late interim ^{18}F-FDG PET/CT (PET3) during first-line treatment. Patients were then followed to obtain further clinical data and OS.

The study was approved by the UCLA Institutional Review Board (August 1, 2012), and all patients provided written informed consent for their participation (IRB12-000770). The study was initiated, planned, funded, conducted, analyzed, and published by the investigators.

^{18}F-FDG PET/CT Imaging and Analysis

Images were acquired in accordance with ^{18}F-FDG PET/CT guidelines (*16*). In total, 72 ^{18}F-FDG PET/CT studies were conducted (on a Siemens Biograph 64 TruePoint [$n = 41$], Siemens Biograph 64 mCT [$n = 27$], or Siemens Biograph 16 [$n = 4$]). PET images were acquired from mid thigh to vertex (whole-body scan) with a time of 2–4 min per bed position using a weight-based protocol. All PET images were reconstructed using attenuation, dead-time, random-event, and scatter corrections. PET images were reconstructed with an iterative algorithm (ordered-subset expectation maximization) in an axial 168 × 168 matrix (2-dimensional, 2 iterations, 8 subsets, gaussian filter of 5.0) or 200 × 200 matrix (3-dimensional, 2 iterations, 24 subsets, gaussian filter of 5.0).

Patients fasted for a minimum of 6 h. The median serum glucose level was 104 mg/dL (interquartile range [IQR], 97–118 mg/dL). Patients received 7.77 MBq (0.21 mCi)/kg of ^{18}F-FDG intravenously. The median injected activity of ^{18}F-FDG was 372 MBq (IQR, 308–424.6 MBq). The median uptake time was 60 min (IQR, 57–67 min). Intravenous and oral contrast media were administered in 71 of 72 and 71 of 72 scans, respectively. The PET and CT image acquisition was performed as reported previously (*17*,*18*)

^{18}F-FDG PET images were interpreted by 3 readers: 2 certified nuclear medicine physicians and 1 dual-certified radiologist/nuclear medicine physician. All 3 readers were aware of the PDAC diagnosis but not of the treatment regimen, other clinical data, or outcome data. The 3 readers independently quantified the ^{18}F-FDG uptake of the primary pancreatic tumor site at each time point by placing a volume of interest to record the SUV_{max}. The choice of the size and location of the volume of interest was left to the reader. If there was agreement in SUV_{max} measurements between 2 readers but disagreement with the third reader, the SUV measurement of the third reader was neglected. Tumor size was evaluated by 1 radiologist at each time point.

For early and late metabolic and size response, SUV_{max} and size cutoffs as selected by modified PERCIST (mPERCIST) (*19*), RECIST1.1 (*20*), and receiver-operating-characteristic analysis were evaluated.

Statistics

The primary objective of the study was to assess metabolic and radiographic response during first-line chemotherapy as early and late imaging biomarkers of OS in patients with PDAC. Quantitative variables are presented as median and IQR or as mean and SD. Statistics were performed using R, version 3.6.1 (R Core Team).

The study was initially powered for a total of 70 patients with the following parameters: expected survival of responders, 20 mo; expected survival of nonresponders, 10 mo; hazard ratio, 2.0; power, 0.8.

Cutoffs for early and late metabolic tumor response assessment were delineated using optimally selected cutoffs and by mPERCIST (≥30% decrease in tumor SUV_{max}) (*19*). Receiver-operating-characteristic analysis–selected cutoffs, plotting SUV_{max} against OS dichotomized by median OS, were SUV_{max} decreases of at least 15% and at least 38% for early and late metabolic response, respectively. Cutoffs were increased to at least 20% and at least 40%, respectively, because of considerations related to clinical relevance and reproducibility (*21*).

The cutoff for early assessment of size response was also optimally selected to be at least a 13% decrease in size but was increased to at least a 20% decrease because of considerations related to clinical relevance and reproducibility. Late size response was defined according to RECIST1.1 (≥30% decrease in tumor size) (*20*).

OS was calculated from the date of subject consent to the date of death or last follow-up. All deaths included in the survival analysis were cancer-related. OS was estimated using the method of Kaplan and Meier. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Patient Characteristics

Between February 2013 and February 2019, 33 patients with histologically proven PDAC were enrolled. Five patients were excluded: 3 patients never underwent PET1, in 1 patient chemotherapy was initiated before PET1, and 1 patient was enrolled in another trial investigating nivolumab. Therefore, the study population consisted of 28 patients who underwent PET1; 23 of these (82%) underwent PET2, and 21 (75%) underwent PET3, (Fig. 1).

The median time between PET1 and PET2 and between PET1 and PET3 was 4.6 wk (IQR, 3.8–5 wk) and 12.6 wk (IQR, 11.4–14.9 wk), respectively. The median interval between PET1 and treatment initiation was 0.7 wk (IQR, 0.5–1.3 wk). PET2 and PET3 were performed 3.6 wk (IQR, 3–4.3 wk) and 11.4 wk (IQR, 10.5–14.4 wk) after initiation of treatment, respectively (Fig. 1).

The baseline characteristics are summarized in Table 1. The study cohort consisted of 11 men (39%) and 17 women (61%), with a mean age of 65 ± 12 y (median, 65 y; range, 40–86 y). The primary tumor was located in the pancreatic head in 18 patients (64%). Twenty-two patients (79%) had at least clinical stage 3 disease.

Treatment

First-line treatments were FOLFIRINOX ($n = 12$; 43%), gemcitabine/nab-paclitaxel ($n = 7$; 25%), FOLFORINOX plus gemcitabine/nab-paclitaxel ($n = 4$; 14%), FOLFOX (folinic acid, fluorouracil, and oxaliplatin) ($n = 1$; 4%), and gemcitabine ($n = 1$; 4%). Fourteen patients underwent second-line chemotherapy, and 8 patients received at least 3 lines of chemotherapy. Eight patients (29%) underwent curative surgical excision after PET3. Thirteen patients (46%) received additional local radiation therapy. Three patients (11%) died after PET1 before initiation of treatment.

Outcome Assessment

The cutoff for the last follow-up was October 14, 2020. Twenty-three deaths occurred during a median follow-up of 14 mo (maximum follow-up, 58.3 mo). The median follow-up time in patients alive at the last follow-up date was 25.4 mo (IQR, 14.7–36.2 mo). The median OS was 14 mo (95% CI, 9.8–27.6 mo).

Imaging Characteristics

Primary tumor SUV_{max} averaged 6.9 ± 3 (median, 6.3; range, 3.5–17.7), 6.3 ± 3.4 (median, 5.7; range, 2.6–15.1), and 4.7 ± 3.2 (median, 4.2; range, 0–15.2) at PET1, PET2, and PET3, respectively.

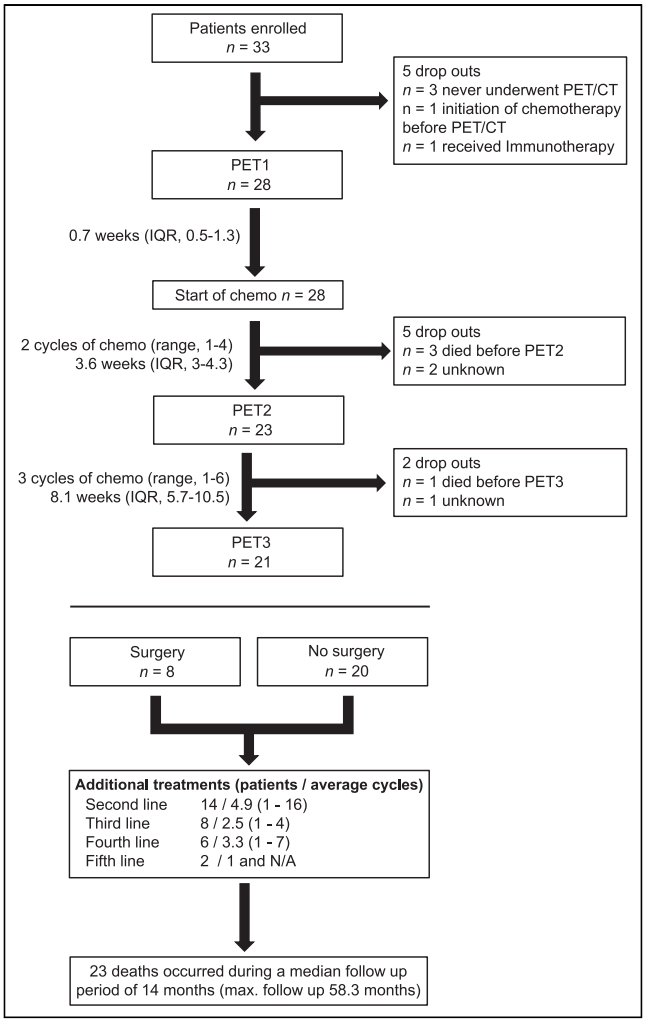

FIGURE 1. Flowchart.

Primary tumor size averaged 4.1 ± 1.7 cm (median, 3.8 cm; range, 2.0–8.4 cm), 3.6 ± 1.5 cm (median, 3.6 cm; range, 1.6–8.7 cm), and 2.8 ± 1.3 cm (median, 2.7 cm; range, 0–5.6 cm) at PET1, PET2, and PET3, respectively.

Baseline Imaging Biomarkers

Survival did not differ significantly in patients with tumors with high versus low SUV_{max} (dichotomized by median $SUV_{max} \geq 6.3$ vs. < 6.3: $n = 15/28$ [54%] vs. $n = 13/28$ [46%] at PET1; median OS, 16.8 mo vs.14 mo [$P = 0.62$]).

Baseline primary tumor size did not affect survival (dichotomized by median size ≥ 3.8 cm vs. < 3.8 cm: $n = 14/28$ [50%] vs. $n = 14/28$ [50%]); median OS 12 mo vs. 19.6 mo [$P = 0.32$]).

PET2 Imaging Biomarkers

Six of 23 patients (26%) were defined as early metabolic responders (Fig. 2A), and 7 of 23 (30%), as early radiographic responders (Fig. 2B). The median OS was 36.2 mo (95% CI, 28 mo–not yet reached [NYR]) in early metabolic responders ($P = 0.016$) (Fig. 3A) and 25.4 mo (95% CI, 19.6 mo–NYR) in early radiographic responders ($P = 0.16$) (Fig. 3B).

Tumor metabolic response as defined by mPERCIST showed a strong trend but did not reach statistical significance at PET2 (median OS was 32.1 mo (95% CI, 28 mo–NYR) in early

TABLE 1
Patient Characteristics ($n = 28$)

Characteristic	Data
Age (y)	
Mean	65
Range	40–86
Sex	
Male	11
Female	17
Site	
Head	18
Body	6
Tail	4
Clinical stage	
Ib	2
II	4
IIII	16
IV	6
Died of disease	23
Lost to follow-up	1
Alive with disease	4
CA 19-9	
Median	101 (IQR, 5.95–592)
Range	5–1,432
Carcinoembryonic antigen ($n = 13$)	
Median	3.7 (IQR, 2.7–59.1)
Range	1.4–39.7
Surgery	
Yes	8
No	20
Radiation therapy	
Yes	13
No	15
Initial chemotherapy	
FOLFIRINOX	12
Gemcitabine/nab-paclitaxel	7
FOLFOX	1
FOLFORINOX+	4
Gemcitabine/nab-paclitaxel	
Gemcitabine	1
No treatment	3
Initial treatment, average cycles	6.0 (range, 2–12)
Additional treatments	
Second line	14 (average cycles, 4.9; range, 1–16)
Third line	8 (average cycles, 2.5; range, 1–4)
Fourth line	6 (average cycles, 3.3; range, 1–7)
Fifth line	2 (average cycles, 1; range, NA)

NA = not applicable.
Qualitative data are number of patients; continuous data are as individually indicated.

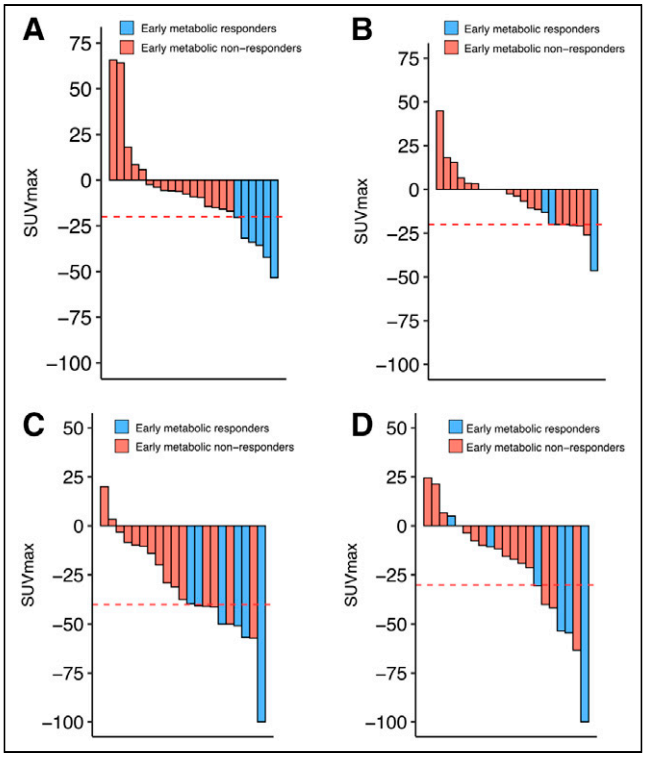

FIGURE 2. Waterfall plot depicting per-patient changes in early metabolic responders (A), early size responders (B), late metabolic responders (C), and late size responders (D).

metabolic responders (5/23 [22%], $P = 0.052$) (Supplemental Fig. 1A; supplemental materials are available at http://jnm.snmjournals.org).

PET3 Imaging Biomarkers

Ten of 21 (48%) and 7 of 21 (33%) patients were defined as late metabolic (Fig. 2C) and radiographic (Fig. 2D) responders, respectively. The median OS was 27.4 mo (95% CI, 21.4 mo–NYR) in late metabolic responders ($P = 0.058$) (Fig. 3C) and 58.2 mo (95% CI, 21.4 mo–NYR) in late radiographic responders ($P = 0.008$) (Fig. 3D).

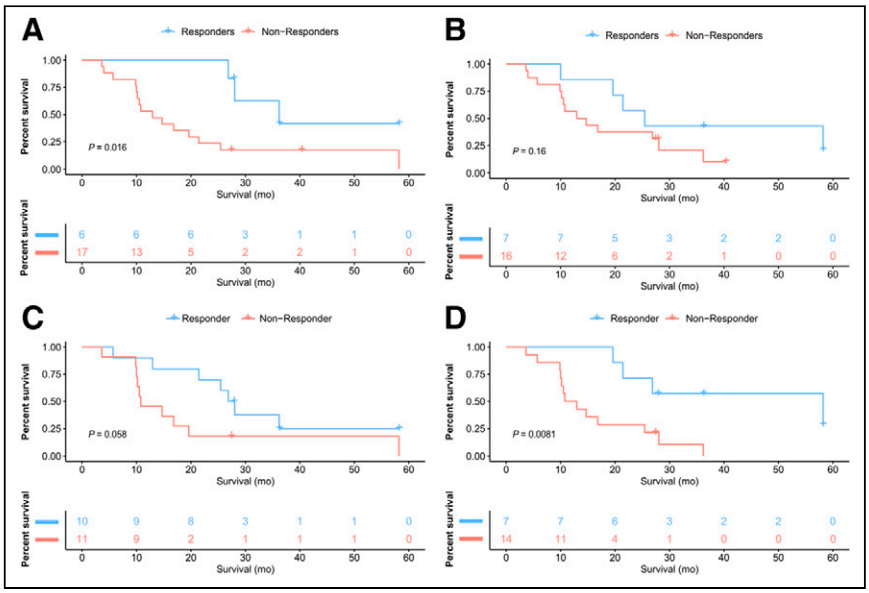

FIGURE 3. Kaplan–Meier curves showing OS in early metabolic responders (≥20% decrease in SUV_{max}) (A), early size responders (≥20% decrease in tumor size) (B), late metabolic responders (≥40% decrease in SUV_{max}) (C), and late size responders (≥30% decrease in tumor size) (D).

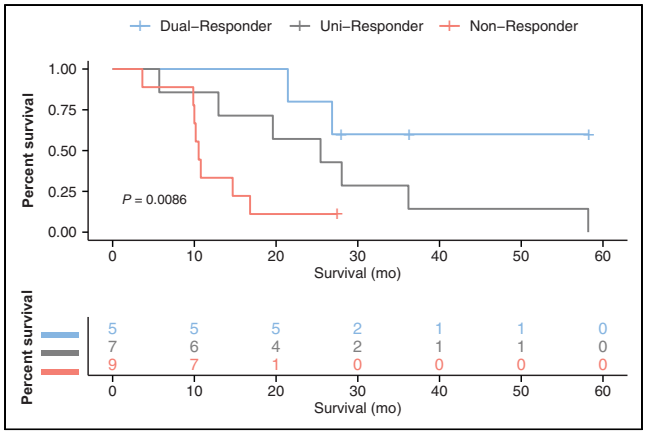

FIGURE 4. Kaplan–Meier curves showing OS in dual-modality responders (metabolic and size response), unimodality responders (either metabolic or size response), and nonresponders (neither metabolic nor size response) at PET3 (11 wk).

Five of 21 patients (24%) were classified as late metabolic and size responders (dual-modality responders), whereas 7 of 21 patients (33%) were either metabolic or size responders (unimodality responders) (Fig. 4). The median OS was not yet reached in dual-modality responders and was 25.4 mo (95% CI, 12.3 mo–NYR) in unimodality responders ($P = 0.108$). Dual-modality responders showed significantly improved survival when compared with nonresponders (median OS, NYR vs. 10.5; $P = 0.042$), whereas unimodality responders showed a trend toward improved survival (median OS, 25.4 vs. 10.5, $P = 0.09$).

Tumor metabolic response as defined by mPERCIST was not predictive of survival (median OS was 26.1 mo [95% CI, 19.6 mo–NYR]) in late metabolic responders (12/21 [57%], $P = 0.18$) (Supplemental Fig. 1B).

Six of 6 early metabolic responders were also classified as late metabolic responders.

DISCUSSION

In this prospective study, SUV_{max} changes assessed 4 wk after initiation of first-line chemotherapy served as a PET2 imaging biomarker of OS in patients with PDAC. After 11 wk from initiation of treatment, tumor size measurements by CT were superior to SUV_{max} in predicting survival. Dual-modality late responders (metabolic and size) trended toward a prolonged survival in comparison to unimodality late responders (either metabolic or size); nonresponders (neither metabolic nor size) exhibited the shortest survival.

According to RECIST1.1, the frequency of tumor reevaluation while on treatment should be protocol-specific and adapted to

the type and schedule of treatment (*20*). However, since tumor metabolic changes precede changes in tumor size in response to cytotoxic treatments (*18*), there is a broad consensus that tumor size measurements are not suitable as an early imaging biomarker. Therefore, the superiority of early SUV_{max} changes in comparison to early size changes in predicting OS are consistent with reports in other cancers (*18*,*22*,*23*). In fact, only 1 of 23 patients exhibited an early size response according to the RECIST1.1 cutoff of 30%. An early size cutoff of 20%, which classified 7 of 23 patients as early size responders, showed a trend toward improved survival ($P = 0.16$).

Even late changes in tumor size have been described as an imperfect predictor of response of PDAC to therapy (*6*), as is explained mainly by the challenge in differentiating between viable tumor, the desmoplastic stroma, and dead scar tissue as a result of the treatment. However, a cutoff of 30% for late size response, as suggested by RECIST1.1, significantly predicted OS ($P = 0.008$), whereas a selected cutoff of 40% for late metabolic response only tended to be predictive ($P = 0.058$).

Although our patient cohort was too small for a robust statistical analysis, a response classification system that considers hybrid imaging components for both metabolic and radiographic responses (dual-modality vs. unimodality vs. nonresponder) warrants further investigation. This then could be expanded to investigate the role of changes in diffusion-weighted MRI findings, and size and metabolic changes using PET/MRI, in response assessments of PDAC. Diffusion-weighted MRI has been proposed as an imaging biomarker of therapy response; however, previous studies lack data on progression-free survival and OS (*7*,*8*) or investigate post–neoadjuvant therapy changes (*9*).

The selected early and late metabolic response cutoffs of at least a 20% and at least a 40% decrease in SUV_{max}, respectively, improved outcome predictions in comparison to the mPERCIST cutoff of 30%. A single cutoff, as proposed by PERCIST, to longitudinally assess cytotoxic treatment effects might not entirely reflect the treatment-induced metabolic changes of a responding or nonresponding tumor. Therefore, future guidelines might need to address the need for subcategorization of metabolic response criteria depending on time of assessment.

Our findings support the notion that ^{18}F-FDG PET/CT may be used as an early predictive imaging biomarker to assess the effectiveness of new cytotoxic or potentially specific treatments in phase II clinical trials. Further studies will be needed to determine whether adaptive treatment protocols in early nonresponders could lead to improved outcomes in PDAC (*24*).

Several potential limitations of our study merit consideration. First, the statistically powered patient accrual target—70 patients—was not met. Although the study was designed as a 2-center study, enrollment occurred primarily at UCLA. Even though the statistical sample size was small and reduced the power of this study, we still observed significance and trends in our analysis, in line with our hypothesis. Second, cutoffs for early and late metabolic response were not predefined but optimally selected. However, the optimally selected early metabolic response cutoff of at least 20% fell within the early partial metabolic response criteria evaluated after 1 cycle of chemotherapy given by the European Organization for Research and Treatment of Cancer (*25*,*26*).

Third, patients with various tumor stages and therefore outcomes and treatment regimens, which might have affected ^{18}F-FDG tumor uptake differently, were included in this study (Supplemental Table 1).

CONCLUSION

The current study suggests that ^{18}F-FDG PET allows survival predictions early after the initiation of first-line therapy (~4 wk) in patients with PDAC and might, therefore, potentially serve as an early interim endpoint biomarker in research and the clinic. At approximately 11 wk, radiographic changes might be sufficient for response evaluation after the completion of first-line therapy.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is metabolic response, assessed by ^{18}F-FDG-PET, better than radiographic response as an intermediate endpoint biomarker of OS early and late after the start of first-line chemotherapy in patients with PDAC?

PERTINENT FINDINGS: Metabolic response assessed 4 wk after initiation of first-line chemotherapy served as a PET2 imaging biomarker of OS in patients with PDAC. After 11 wk from the initiation of treatment, tumor size measurements by CT were superior to SUV_{max} in predicting survival. Dual-modality late responders (metabolic and size) trended toward a prolonged survival in comparison to unimodality late responders (either metabolic or size); nonresponders (neither metabolic nor size) exhibited the shortest survival.

IMPLICATIONS FOR PATIENT CARE: ^{18}F-FDG PET allows survival predictions early after the initiation of first-line therapy in patients with PDAC and might therefore potentially serve as an early interim endpoint biomarker in research and the clinic.

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