The purpose of this study was to evaluate ¹⁸F-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 (R8B12-000770). Patient receiving first-line chemotherapy were planned to undergo baseline ¹⁸F-FDG PET/CT, early interim ¹⁸F-FDG PET/CT, and late interim ¹⁸F-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 ¹⁸F-FDG PET/CT. Twenty-three of these (82%) underwent early interim ¹⁸F-FDG PET/CT, and 21 (75%) underwent late interim ¹⁸F-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 [NRY]) in early metabolic responders (6/23 [26%], \( P = 0.016 \)) and 25.4 mo (95% CI, 19.6 mo–NRY) in early radiographic responders (7/23 [30%], \( P = 0.16 \)). The median overall survival was 27.4 mo (95% CI, 21 mo–NRY) in late metabolic responders (10/21 [48%], \( P = 0.058 \)) and 58.2 mo (95% CI, 21.4 mo–NRY) in late radiographic responders (7/21 [33%], \( P = 0.008 \)). **Conclusion:** ¹⁸F-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:** ¹⁸F-FDG PET; pancreas; adenocarcinoma; response

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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 min per bed position using a weight-based protocol. All PET images were reconstructed with an iterative algorithm of 5.0) or 200 matrix (3-dimensional, 2 iterations, 24 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 SUVmax. The choice of the size and location of the volume of interest was left to the reader. If there was agreement in SUVmax 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, SUVmax 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 SUVmax) (19). Receiver-operating-characteristic analysis–selected cutoffs, plotting SUVmax against OS dichotomized by median OS, were SUVmax 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%), FOLFIRINOX plus gemcitabine/nab-paclitaxel (n = 4; 14%), FOLFOX (folinic acid, fluorouracil, and oxaliplatin) (n = 1; 4%), and gemcitabine (n = 1; 4%). Seventeen 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 SUVmax 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.
Primary tumor size averaged $4.1 \pm 1.7$ cm (median, 3.8 cm; range, 2.0–8.4 cm), 3.6 $\pm$ 1.5 cm (median, 3.6 cm; range, 1.6–8.7 cm), and 2.8 $\pm$ 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$_{\text{max}}$ (dichotomized by median SUV$_{\text{max}}$ $\leq 6.3$ vs. $> 6.3$: $n = 15/28$ [54%] vs. $n = 13/28$ [46%] at PET1; median OS, 16.8 mo vs. 14.0 mo [$P = 0.62$]). Baseline primary tumor size did not affect survival (dichotomized by median size $\leq 3.8$ cm vs. $> 3.8$ cm: $n = 14/28$ [50%] vs. $n = 14/28$ [50%]; median OS 12.0 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

FIGURE 1. Flowchart.
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).

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).

DISCUSSION

In this prospective study, \( SUV_{\text{max}} \) 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 \( SUV_{\text{max}} \) 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 18F-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 18F-FDG tumor uptake differently, were included in this study (Supplemental Table 1).

**CONCLUSION**

The current study suggests that 18F-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 18F-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:** 18F-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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