

¹⁸F-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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Abstract

Purpose: 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 (PDAC) 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 a baseline ^{18}F -FDG-PET/CT (PET1), early interim ^{18}F -FDG PET/CT (PET2) and late interim ^{18}F -FDG-PET/CT (PET3). ROC selected and established (mPERCIST / RECIST1.1) cut-offs for metabolic and radiographic tumor response assessment were applied. Patients were followed to collect data on further treatments and overall survival (OS).

Results: The study population consisted of 28 patients who underwent PET1. Twenty-three of these (82%) underwent PET2 and 21 (75%) PET3, respectively. Twenty-three deaths occurred during a median follow up period of 14 months (maximum follow up, 58.3 months). The median OS was 36.2 months (95%CI, 28-NYR) in early metabolic responders (6/23 (26%), $p=0.016$) and 25.4 months (95%CI, 19.6-NYR) in early radiographic responders (7/23 (30%), $p=0.16$). The median overall survival was 27.4 months (95%CI, 21.4-NYR) in late metabolic responders (10/21 (48%), $p=0.058$) and 58.2 months (95%CI, 21.4-NYR) in late radiographic responders (7/21 (33%), $p=0.008$).

Conclusion: ^{18}F -FDG PET may serve as early interim imaging biomarker (~ at 4 weeks) for evaluation of response to first-line chemotherapy in patients with PDAC.

Radiographic changes might be sufficient for response evaluation after the completion of first line chemotherapy.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) typically has a tumor microenvironment which is characterized by a dense desmoplastic stroma. Extensive desmoplasia results in decreased stromal vascularization and altered immune cell infiltration, but also represents an imaging challenge to differentiate 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 (NAT) / adjuvant setting and the first-line therapy for metastatic disease are FOLFIRINOX (or modified FOLFIRINOX) or gemcitabine / nab-paclitaxel (GnP). New second-line approaches and specific treatments, such as PARP-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 utilized 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 have been described as an imperfect predictor of response of PDAC to therapy in the white paper on pancreatic ductal adenocarcinoma from the society of abdominal radiology (6). Other imaging biomarkers, such as diffusion weighted (DW) MRI (7-9) and ¹⁸F-FDG-PET/CT (10-15) have been proposed for treatment response assessment

in PDAC but are not specifically supported by current society guidelines due to inconsistent and limited data, even more so when investigating early response.

In this exploratory prospective study, we assessed 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) in comparison to early radiographic size changes.

Patients 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 inability to tolerate a PET/CT scan or another concurrent malignant condition.

Patients were planned to undergo a 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 overall survival.

The study was approved by the University of California at Los Angeles (Los Angeles, CA) Institutional Review Board (08/01/2012), 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.

¹⁸F-FDG PET/CT imaging and analysis

Image acquisition was performed in accordance with ¹⁸F-FDG PET/CT guidelines (16). In total, 72 ¹⁸F-FDG PET/CT studies were conducted (Siemens Biograph 64 TruePoint (n=41), Siemens Biograph 64 mCT (n=27), Siemens Biograph 16 (n=4)). PET images were acquired from midhigh to vertex (whole-body scan) with a time-per-bed position of 2-4 min using a weight based protocol. All PET images were reconstructed using attenuation, dead-time, random events, and scatter corrections. PET images were reconstructed with an iterative algorithm (ordered-subset expectation maximization) in an axial 168×168 matrix (2D, 2 iterations, 8 subsets, Gaussian Filter 5.0) or 200×200 matrix (3D, 2 iterations, 24 subsets, Gaussian Filter 5.0).

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

¹⁸F-FDG-PET images were interpreted by three readers: two certified Nuclear Medicine physicians (JC, FC), and one dual certified Radiologist / Nuclear Medicine physician (MB). All three readers were aware of the PDAC diagnosis but blinded to the treatment regimen, other clinical and outcome data. The three readers independently quantified the FDG uptake of the primary pancreatic tumor site at each time point by placing a VOI to record the SUVmax. The size and the localization of the VOI was left to the reader choice. If there was agreement in SUVmax measurements between two readers but

disagreement with the 3rd reader, the SUV measurement of the 3rd reader was neglected. Tumor size was evaluated by one radiologist (MB) at each time point. Modified PET Response Criteria in Solid Tumors (mPERCIST) (19), the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (20), and ROC selected SUVmax and size cut-offs (see statistics section) for early and late metabolic and size response 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 interquartile range (IQR), or mean and standard deviation (SD) where appropriate. Statistics were performed using R 3.6.1 (R Core Team 2019).

The study was initially powered for a total of 70 patients with the following parameters: expected survival of responders 20 months, expected survival of non-responders 10 months, HR: 2.0, power 0.8.

Cut-offs for early and late metabolic tumor response assessment were delineated using optimally selected cut-offs and by mPERCIST ($\geq 30\%$ decrease in tumor SUVmax) (19). Receiver operating characteristic (ROC) analysis selected cut-offs, plotting SUVmax against OS dichotomized by median OS, were SUVmax decreases of $\geq 15\%$ and $\geq 38\%$ for early and late metabolic response, respectively. Cut-offs were increased to $\geq 20\%$ and $\geq 40\%$, respectively, for considerations of clinical relevance and reproducibility (21). The cut-off for early size response assessment was also optimally selected ($\geq 13\%$ decrease in size) but increased to $\geq 20\%$ for considerations of clinical relevance and

reproducibility. Late size response was defined according to RECIST1.1 ($\geq 30\%$ decrease in tumor size) (20).

Overall survival (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 less than 0.05 was considered to indicate statistical significance.

Results

Patient characteristics

Between February 2013 to February 2019, 33 patients with histologically proven PDAC were enrolled. Five patients were excluded: 3 patients never underwent PET1, in one patient chemotherapy was initiated prior to PET1, and one patient was enrolled in another trial investigating Nivolumab. Therefore, the study population consisted of 28 patients who underwent PET1, twenty-three of these (82%) underwent PET2 and 21 (75%) PET3, respectively (**Figure 1**).

The median time between PET1 and PET2, and PET1 and PET3 was 4.6 weeks (IQR, 3.8-5) and 12.6 (IQR, 11.4-14.9), respectively. The median time interval between PET1 and treatment initiation was 0.7 weeks (IQR, 0.5-1.3). PET2 and PET3 were performed 3.6 (IQR, 3-4.3) and 11.4 (IQR, 10.5-14.4) weeks after initiation of treatment respectively (**Figure 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 years (median, 65 years; range, 40-86 years). The primary tumor was located in the pancreatic head in 18 patients (64%). 22 patients (79%) had clinical stage ≥ 3 disease.

Treatment

First line treatments were FOLFIRINOX ($n = 12$; 43%), Gemzar/Abiraxane ($n = 7$; 25%), Folfirinox + Gemzar/Abiraxane ($n = 4$; 14%), Folfox ($n = 1$; 4%), and Gemzar ($n = 1$; 4%). 14 patients underwent second line chemotherapy and 8 patients received ≥ 3 lines of chemotherapy. Eight patients (29%) underwent curative surgical excision following

PET3. Thirteen patients (46%) received additional local radiation therapy. Three patients (11%) died after PET1 / before initiation of treatment.

Outcome assessment

The cut-off date for last follow up was 10/14/2020. 23 deaths occurred during a median follow up period of 14 months (maximum follow up, 58.3 months). The median follow up time in patients alive at last follow-up date was 25.4 months (IQR, 14.7-36.2). The median overall survival was 14 months (95%CI, 9.8-27.6) months.

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 ± 1.7 cm (median 3.8cm, range 2.0-8.4cm), 3.6 ± 1.5 cm (median, 3.6cm, range 1.6-8.7cm), and 2.8 ± 1.3 cm (median 2.7cm, range 0-5.6cm) at PET1, 2 and 3, respectively.

Baseline imaging biomarkers

Survival did not differ significantly in patients with tumors with high versus low SUVmax (dichotomized by median SUVmax ≥ 6.3 vs. < 6.3 : $n=15/28$ (54%) vs. ($n=13/28$ (46%)) at PET1: median OS 16.8 vs.14 months ($p = 0.62$).

Baseline primary tumor size did not affect survival (dichotomized by median size \geq 3.8cm vs. $<$ 3.8cm: n=14/28 (50%) vs. (n=14/28 (50%)): median OS 12 vs. 19.6 months ($p = 0.32$).

Early interim imaging biomarkers

Six / 23 patients (26%) were defined as early metabolic responders (**Figure 2a**) and 7/23 (30%) as early radiographic responders (**Figure 2b**). The median overall survival was 36.2 months (95%CI, 28-NYR) in early metabolic responders ($p=0.016$) (**Figure 3a**) and 25.4 months (95%CI, 19.6-NYR) in early radiographic responders ($p=0.16$) (**Figure 3b**).

Tumor metabolic response as defined by mPERCIST showed a strong trend but did not reach statistical significance at PET2 (median overall survival was 32.1 months (95%CI, 28-NYR) in early metabolic responders (5/23 (22%), $p=0.052$) (**supplemental Figure 1a**).

Late interim imaging biomarkers

Ten / 21 (48%) and 7/21 (33%) patients were defined as late metabolic (**Figure 2c**) and radiographic (**Figure 2d**) responders, respectively. The median overall survival was 27.4 months (95%CI, 21.4-NYR) in late metabolic responders ($p=0.058$) (**Figure 3c**) and 58.2 months (95%CI, 21.4-NYR) in late radiographic responders ($p=0.008$) (**Figure 3d**).

Five / 21 patients (24%) were classified as late metabolic and size responders (dual-modality responders) while 7/21 patients (33%) were either metabolic or size responder (uni-modality responders) (**Figure 4**). The median overall survival was not yet reached in dual-modality responders and 25.4 months (95%CI, 12.3-NYR) in uni-modality

responders ($p=0.108$). Dual-modality responders showed significantly improved survival when compared with non-responders (median overall survival NYR vs 10.5, $p=0.042$), while uni-modality responders showed trending improved survival (median overall survival 25.4 vs 10.5, $p=0.09$).

Tumor metabolic response as defined by mPERCIST was not predictive of survival (median overall survival was 26.1 months (95%CI, 19.6-NYR) in late metabolic responders (12/21 (57%) $p=0.18$) (**supplemental Figure 1b**).

Six / 6 early metabolic responders also classified as late metabolic responders.

Discussion

In this prospective study, SUVmax changes assessed 4 weeks after initiation of first-line chemotherapy served as an early interim imaging biomarker of overall survival in patients with PDAC. After 11 weeks from initiation of treatment, tumor size measurements by CT were superior to SUVmax in predicting survival. Dual-modality late responders (metabolic and size) trended towards a prolonged survival in comparison to uni-modality late responders (either metabolic or size); non-responders (neither metabolic nor size) exhibited the shortest survival.

According to the RECIST guidelines version 1.1 the frequency of tumor re-evaluation 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 early imaging biomarker. Therefore, the superiority of early SUVmax changes in comparison to early size changes in predicting overall survival are consistent with reports in other cancers (18, 22, 23). In fact, only 1 out of 23 patients

exhibited an early size response according to the RECIST1.1 cutoff of 30%. An early size cut-off of 20% which classified 7 / 23 patients as early size responders showed a trend towards 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) which is mainly explained by the challenge to differentiate 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 overall survival ($p=0.008$), 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 both hybrid imaging components for metabolic and radiographic responses (dual-modality vs. uni-modality vs. non-responder) warrants further investigation. This then could be expanded to investigate the role of changes in DW-MRI, size and metabolic changes using PET/MRI in response assessments of PDAC. DW MRI has been proposed as an imaging biomarker of therapy response however, previous studies lack data on progression free and overall survival (7, 8) or investigate post NAT changes (9).

The selected early and late metabolic response cut-offs of $\geq 20\%$ and $\geq 40\%$ decreases in SUVmax, respectively, improved outcome predictions in comparison to the mPERCIST cut-off of 30%. A single cut-off, as proposed by PERCIST, to longitudinally assess cytotoxic treatment effects might not entirely reflect the treatment induced metabolic tumor changes of a responding or non-responding 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 non-responders could lead to improved outcomes in PDAC (24).

Several potential limitations of our study merit consideration. First, the statistically powered patient accrual target, $n=70$, was not met. While the study was designed as a two-center study, enrollment primarily occurred 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 cut-off of $\geq 20\%$ fell within the early partial metabolic response criteria evaluated after one cycle of chemotherapy given by EORTC (25, 26).

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

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

Key points.

Questions: Is metabolic response, assessed by ^{18}F -FDG-PET, a better intermediate endpoint biomarker of overall survival in comparison to radiographic response early and late after the start of first-line chemotherapy in patients with PDAC?

Pertinent findings: Metabolic response assessed 4 weeks after initiation of first-line chemotherapy served as an early interim imaging biomarker of overall survival in patients with PDAC. After 11 weeks from initiation of treatment, tumor size measurements by CT were superior to SUVmax in predicting survival. Dual-modality late responders (metabolic and size) trended towards a prolonged survival in comparison to uni-modality late responders (either metabolic or size); non-responders (neither metabolic nor size) exhibited the shortest survival.

Implication 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 early interim endpoint biomarker in research and clinic.

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Table 1. Characteristics (n=28)	
Characteristics	All patients
Age, years	
Mean	65
Range	40-86
Sex	
Male	11
Female	17
Site	
Head	18
Body	6
Tail	4
Clinical stage	
Ib	2
II	4
III	16
IV	6
DOD	23
Lost FU	1
AWD	4
CA 19.9 (n=28)	
Median, IQR range	101, 5.95-592 5-1432
CEA (n=13)	
Median, IQR range	3.7, 2.7-59.1 1.4-39.7
Surgery	
Yes	8
No	20
RT	
Yes	13
No	15
Initial chemotherapy	
Folfinox	12
Gemzar/Abraxane	7
Folfox	1
Folforinox + Gemzar/Abraxane	4
Gemzar	1
No treatment	3
Initial treatment - average number of cycles	6.0 (2-12)
Additional treatments (patients / average cycles)	
Second line	14 / 4.9 (1 - 16)
Third line	8 / 2.5 (1 - 4)
Forth line	6 / 3.3 (1 - 7)
Fifth line	2 / 1 and N/A

Figure 1: Flow chart

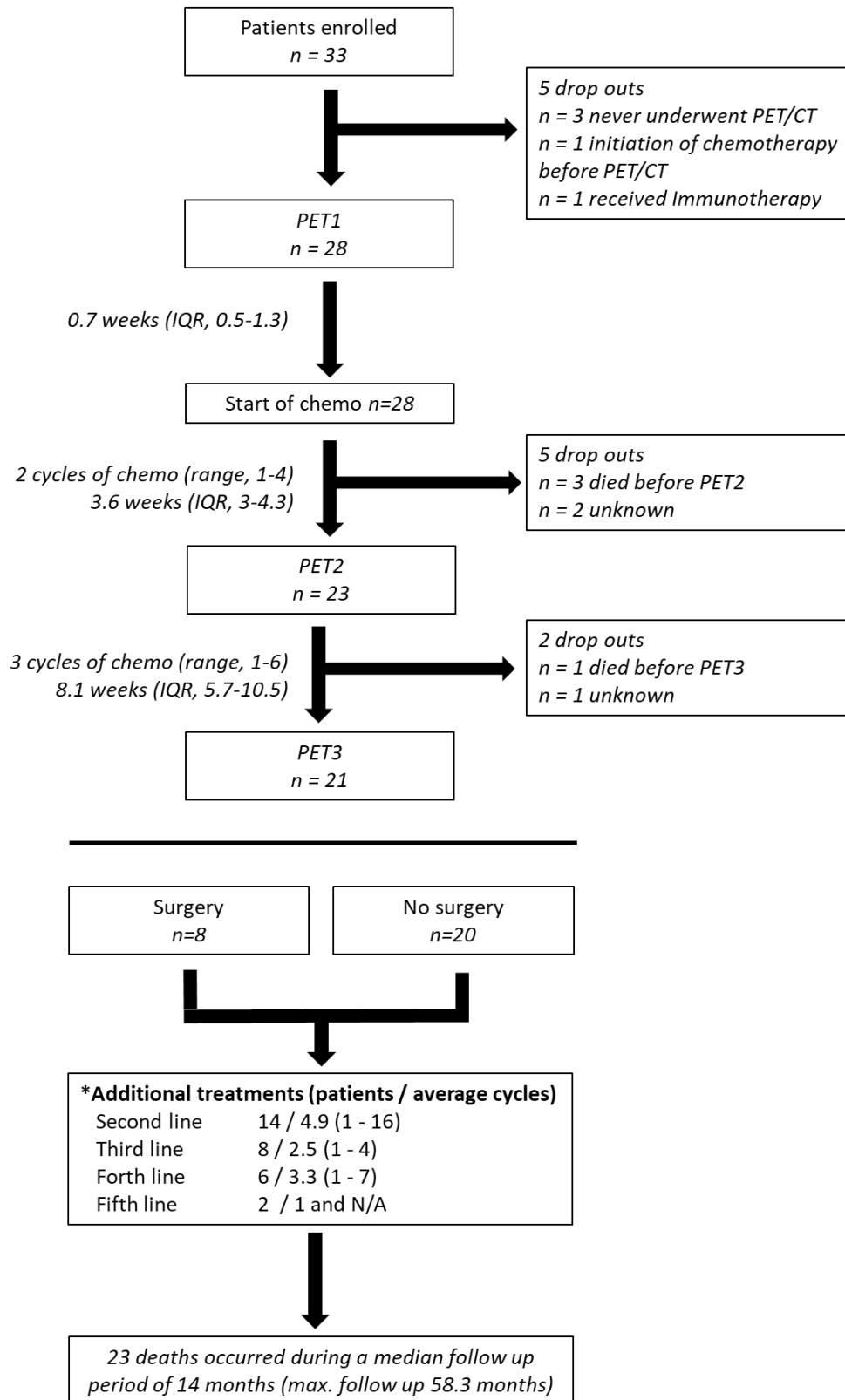


Figure 2: The waterfall plot depicts the per patient changes in (a) early metabolic responders, (b) early size responders, (c) late metabolic responders, and (d) late size responders.

Figure 2a and b: Early metabolic and radiographic changes

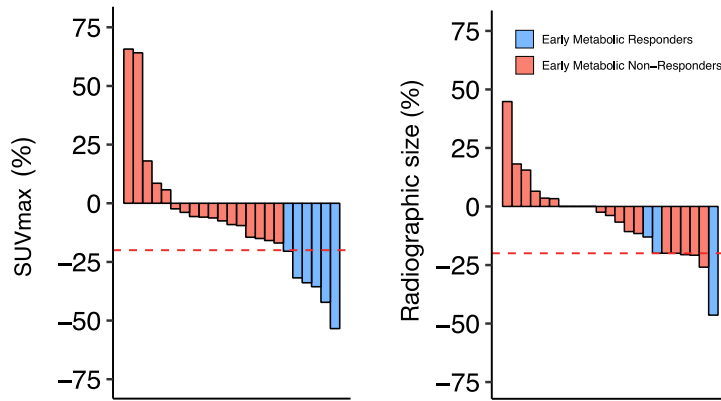


Figure 2c and d: Late metabolic and radiographic changes

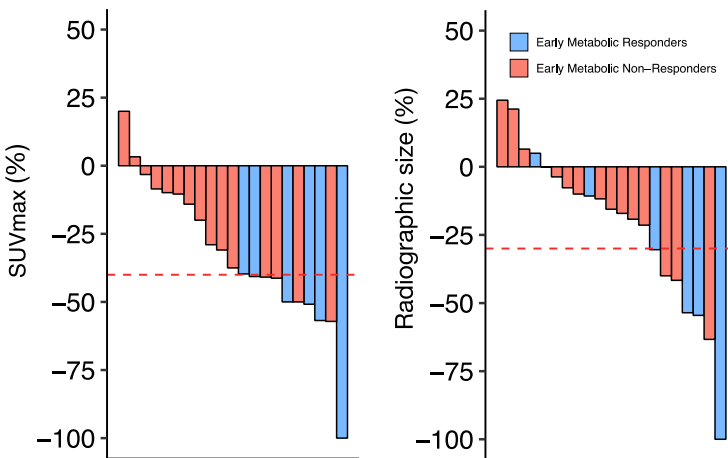


Figure 3: Kaplan Meier curves show the overall survival in (a) early metabolic responders ($\geq 20\%$ decrease in SUVmax), (b) early size responders ($\geq 20\%$ decrease in tumor size), (c) late metabolic responders ($\geq 40\%$ decrease in SUVmax), and (d) late size responders ($\geq 30\%$ decrease in tumor size).

Figure 3a and b: Early metabolic and size response at 4 weeks

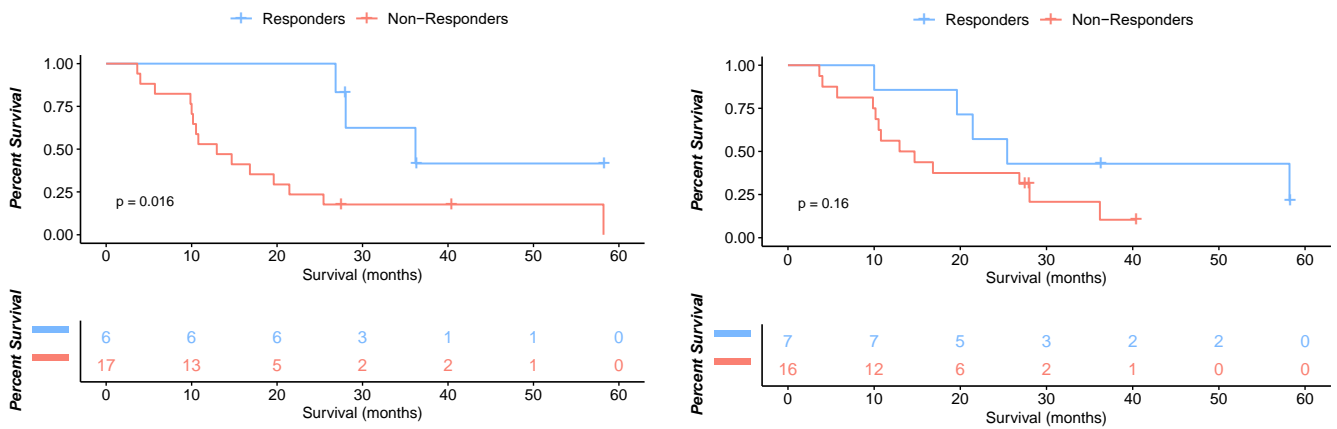


Figure 3c and d: Late metabolic and size response at 11 weeks

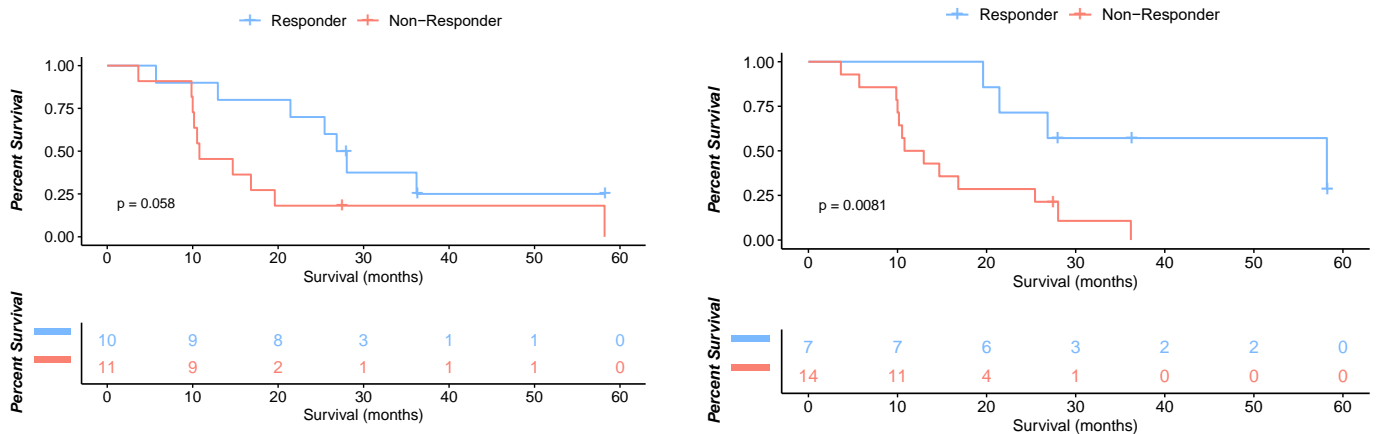
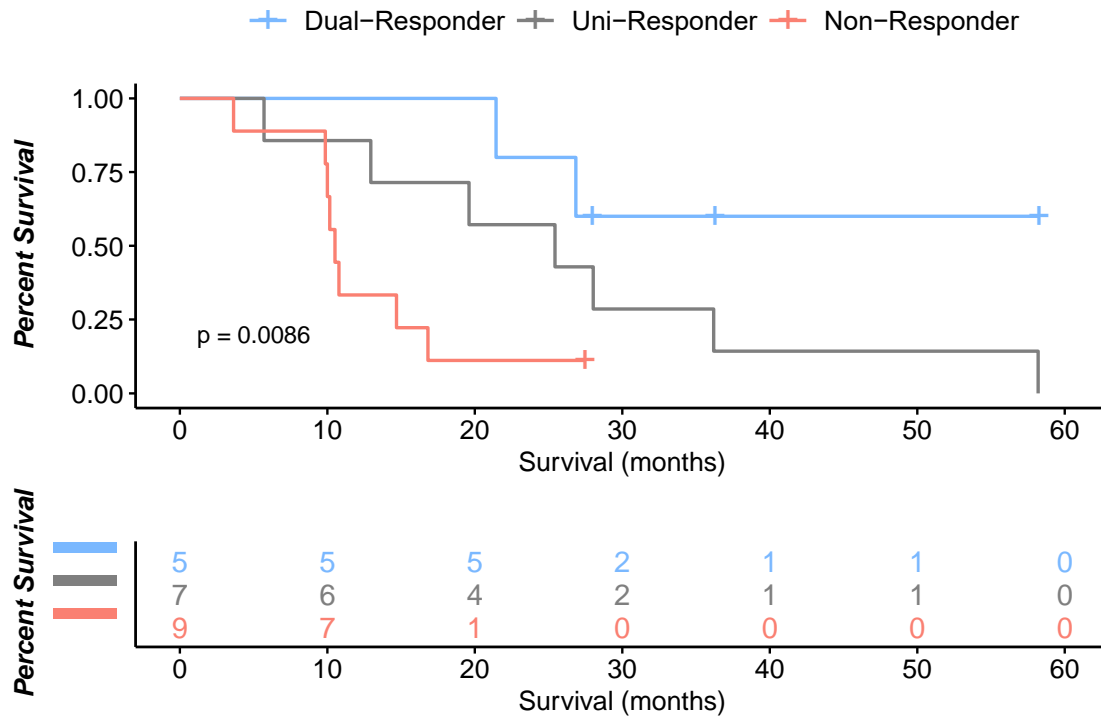


Figure 4: Kaplan Meier curves for overall survival in dual-modality responders (metabolic and size responds), uni-modality responders (either metabolic or size response) and non-responders (neither metabolic nor size response) at late interim PET.

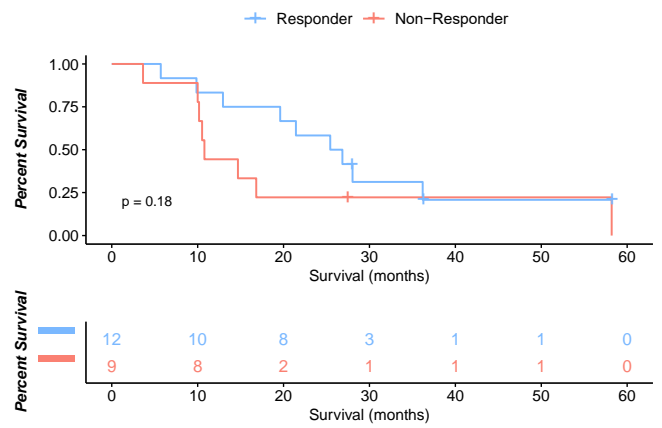
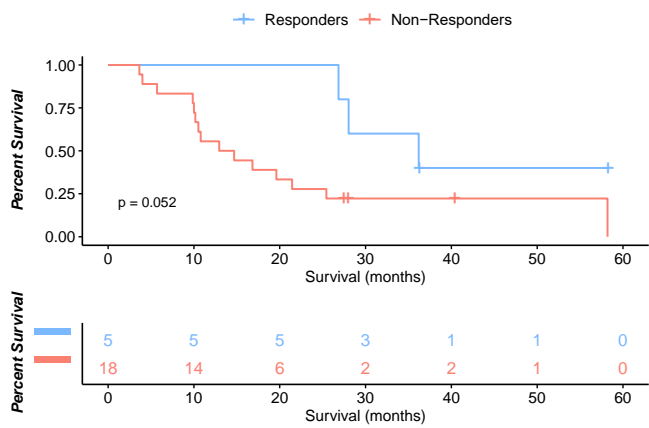
Figure 4: Dual modality response at 11 weeks



Supplemental Figures

Figure 1: Kaplan Meier curves show the overall survival in (a) early metabolic responders, and (b) late metabolic responders dichotomized by modified PET Response Criteria in Solid Tumors (mPERCIST; partial response $\geq 30\%$ decrease in SUVmax).

Supplemental Figure 1a and b.



Supplemental Table 1.

Supplemental Table 1.					
Stage	Early MR / MNR	Late MR / MNR	Early RR / RNR	Late RR / RNR	DMR / UMR / NR
Ib	2 / 0	2 / 0	1 / 1	1 / 1	1 / 1 / 0
II	1 / 3	1 / 3	3 / 1	2 / 2	1 / 1 / 2
III	2 / 11	4 / 8	2 / 11	3 / 9	2 / 3 / 7
IV	1 / 3	3 / 0	1 / 3	1 / 2	1 / 2 / 0
DMR, dual modality responder; MNR, metabolic non-responder; MR, metabolic responder; NR, non-responder; RNR, non-responder; RR, radiographic responder; UMR, uni-modality responder					

Graphical abstract.

