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Long-term Results of a Pilot Study Comparing FLT-PET and FDG-PET in the Evaluation of Response to Treatment in Advanced Head and Neck and Esophageal Malignancies

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Abstract

Objective: We prospectively compared FDG-PET and FLT-PET in assessing patient responses to induction cetuximab and/or chemoradiotherapy (CRT) for advanced head and neck squamous cell carcinoma (HNSCC) and esophageal cancer (EC).

Methods: Sixteen patients were enrolled, 9 with HNSCC and 7 with EC. FDG-PET and FLT-PET scans were performed at baseline and two weeks into chemoradiotherapy (CRT) for patients with EC. Patients with HNSCC received two weeks of induction chemotherapy along with post-induction PET scans prior to starting CRT in addition to the baseline and intra-chemoradiotherapy PET scans. Changes in SUVmax and total lesion glycolysis/proliferation (TLG/TLP) were compared with baseline.

Results: Median follow-up for living patients was 6.0 years. Median overall survival (OS) was 3.3 years and progression-free survival (PFS) was 2.5 years. Patients with HNSCC had higher baseline SUVmax, TLG and TLP than those with EC. Changes in SUVmax, TLG and TLP after induction chemotherapy or during CRT did not correlate with PFS or OS. Those with >40% decline in SUVmax on FDG-PET six weeks after completing CRT had better PFS ($p<0.0001$) and OS ($p=0.0003$) than those with less of a response. In addition, >70% decrease in post-treatment TLG correlated with better PFS ($p=0.03$) and OS ($p=0.04$).

Conclusions: Functional imaging performed early during chemoradiotherapy for advanced HNSCC and EC is feasible. Changes on post-induction and intra-CRT FLT and FDG PET did not correlate with PFS or OS. However, better PFS and OS were seen in patients with >40% decline in SUVmax and >70% decrease in TLG on FDG-PET performed six weeks after completing CRT. Further research is needed to determine the prognostic impact of PET performed during chemotherapy and radiotherapy.

Keywords: Head and neck cancer; Esophageal cancer; FDG-PET; FLT-PET; Cetuximab; Radiotherapy

Introduction

In the United States each year, almost 40,000 people are diagnosed with advanced, potentially curable, head and neck squamous cell carcinoma (HNSCC) and 20,000 are diagnosed with esophageal cancer (EC) [1]. Treatment of HNSCC often includes definitive chemoradiotherapy, whereas EC is often treated with neoadjuvant chemoradiotherapy followed by surgical resection. Though overall survival is relatively high, local failure occurs in nearly 30% of HNSCC patients at three years [2-5]. Neoadjuvant chemoradiotherapy for EC results in a pathologic complete response in 30% to 40% of patients [6,7]. In contrast to HNSCC, survival is relatively poor at 40% at 5 years and treatment-related mortality can be as high as 14% [7-9]. Thus, risk stratification early in treatment could help stratify resistant and sensitive tumors to tailor subsequent treatment.

Positron emission tomography (PET) with 2-deoxy-2-18F-fluoro-d-glucose (FDG) and 3'-deoxy-3'-18F-fluorothymidine (FLT) tracers have been used in HNSCC to define extent of disease and assess response to treatment [10-15]. A series of EC patients scanned with FDG-PET before and after induction chemotherapy showed a doubling in two-year disease-free survival when the SUVmax declined by greater than 60% [16]. Because cellular uptake of FLT is a more specific marker for proliferation than FDG, it has theoretical advantages over FDG-PET. Overall uptake of FLT is typically lower than FDG, with similar tumor to background ratios [15]. While there is a paucity of data comparing FLT and FDG-PET with clinical outcomes, early changes in FLT-PET correlated better with progression-free survival (PFS) and local control (LC) than FDG-PET in a study of patients with squamous cell carcinoma EC [17]. As a result, FLT-PET remains a potentially promising risk stratification tool.

In our previous report, we demonstrated that functional imaging early during definitive therapy for HNSCC was feasible. Distinct changes were seen after induction cetuximab therapy, but follow-up was too short to correlate with clinical outcomes [18]. In the current

study, we extended inclusion criteria to allow patients with EC and expanded follow-up to assess the potential for early FLT and FDG-PET to identify patients at highest risk for progression and mortality after therapy.

Methods

Patients

This prospective study was approved by the Mayo Clinic Institutional Review Board. Written informed consent was obtained from all patients. Eligible patients had biopsy-proven HNSCC or EC requiring treatment with chemoradiotherapy and an ECOG performance status of 0 or 1. All HNSCC patients had squamous cell carcinoma and EC patients could have either adenocarcinoma or squamous cell carcinoma. Patients were required to be at least 18 years old, with ≤ 10% weight loss in the past three months and a negative serum pregnancy test for women of childbearing potential. Patients with uncontrolled infections, poorly controlled diabetes, New York Heart Association class III or IV heart failure, major surgery within two weeks of registration, grade 2 or greater peripheral neuropathy or other major comorbidities were excluded. All patients underwent pre-treatment laboratory evaluation (complete blood count, creatinine, total bilirubin, and aspartate aminotransferase), baseline staging FDG-PET scan, and evaluation by radiation, medical, and surgical oncologists. Patients were enrolled between October 2008 and June 2011.

Study design

The study schema is shown in Figure 1. All HNSCC patients were treated with chemoradiotherapy with curative intent. Weekly intravenous cetuximab infusions were initiated two weeks prior to radiotherapy with a loading dose of 400 mg/m^2 and subsequent weekly doses of 250 mg/m^2 during concomitant radiotherapy, which began with the third dose of cetuximab. Concurrent cisplatin chemotherapy (30 mg/m^2/week) was also given with radiotherapy at the discretion of the treating physician. Radiation was delivered as intensity-modulated radiotherapy using 70 Gy in 35 daily 2 Gy fractions to the gross tumor plus a 1.5 cm margin for the primary tumor and 1.0 cm margin for gross nodal disease and 63 Gy in 35 daily 1.8 Gy fractions to clinically and radiographically negative areas at risk.

Treatment for EC patients included chemoradiotherapy and was consistent with standard of care therapy at Mayo Clinic. Concurrent chemotherapy consisted of weekly carboplatin (doses titrated to achieve an area under the curve of 2 mg per milliliter per minute) and paclitaxel (50 mg/m^2) or 5-fluorouracil (1000 mg/m^2/day, four-day continuous infusion) and cisplatin (1000 mg/m^2) given every three weeks. Patients were required to have treatment delivered with curative intent with a cumulative radiation dose of at least 45 Gy. There were no restrictions on the treatments delivered following completion of chemoradiotherapy and 5 of the 7 with EC underwent surgical resection following chemoradiotherapy.

Baseline FLT and FDG-PET scans were obtained after registration but prior to induction cetuximab. Staging FDG-PET scans obtained at Mayo Clinic within 14 days of registration were used when available. FLT and FDG-PET scans were repeated after the second dose of cetuximab before initiation of chemoradiotherapy in HNSCC patients. Intra-chemoradiotherapy scans were performed on both HNSCC and EC patients between during the third week of radiation treatment. Follow-up FDG-PET scans were performed six weeks after completion of chemoradiotherapy. Those with HNSCC received an FDG-PET scan six months after completion of chemoradiotherapy.

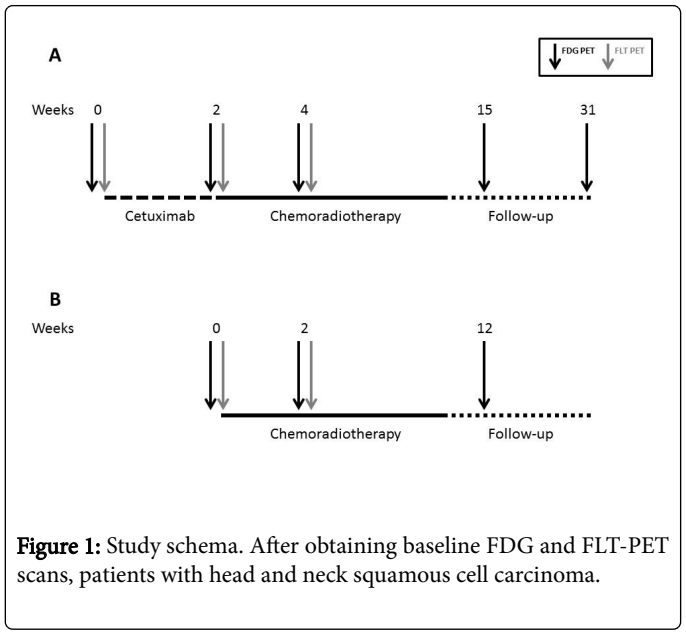

Figure 1: Study schema. After obtaining baseline FDG and FLT-PET scans, patients with head and neck squamous cell carcinoma.

A received two weeks of induction cetuximab followed by post-induction FDG and FLT-PET scans. They then received FDG and FLT-PET scans during week three of chemoradiotherapy. Patients treated for esophageal cancer. B received baseline FDG and FLT-PET scans along with intra-chemoradiotherapy FDG and FLT-PET scans during week three of radiation treatments. Post-treatment FDG-PET scans were obtained six weeks following completion of radiation therapy for all patients and six months following completion of radiation therapy for head and neck cancer patients.

PET synthesis and acquisition

Methods for producing PET tracers was completed as previously described [18]. To briefly summarize, 18F was produced using a PET trace Cyclotron (GE Medical Systems, Inc, Milwaukee, Wisconsin), and 18F labeled FDG was synthesized with the standard Hamacher method. Patients were fasting as verified by pre-injection blood glucose levels. 18F-FLT was synthesized as previously described using 5'-O-[4,4'dimethoxytriphenylmethyl]-2,3'-anhydrothymidine precursor [18,19]. PET image acquisition was performed on a GE RX or 690 PET/CT scanner (GE Medical Systems, Inc) as previously described [18].

PET image analysis

All FLT and FDG-PET images were analyzed in transverse, coronal, and sagittal planes by a clinical investigator and nuclear medicine specialist blinded to clinical data. Qualitative image evaluation consisted of a slice-by-slice comparison of FLT and FDG-PET scans at each time interval. Quantitative evaluation was performed using the PET Edge Contour tool on a MIMvista workstation (MIM Software, Inc, Cleveland, OH). A three-dimensional region of interest (ROI) was generated using a gradient-based algorithm and placed around all areas of focally increased radiotracer uptake including the primary tumor and regional lymph nodes. SUV maximum (SUVmax), SUV mean, total lesion glycolysis (TLG; FDG-PET), total lesion

proliferation (TLP; FLT-PET), and functional tumor volume (FTV) were calculated. TLG and TLP were defined as SUVmean multiplied by FTV as is considered standard [20].

PET Response Criteria in Solid Tumors (PERCIST) version 1.0 was used to quantify tumor response, where a partial metabolic response (PMR) was defined as a >30% reduction in SUVmax, progressive metabolic disease (PMD) was a >30% increase in SUVmax and stable metabolic disease (SMD) was between the two [21]. Outcomes were also assessed using TLG/TLP response, where PMR was >45% decrease in TLG/TLP, PMD was a >75% increase in TLG/TLP, and SMD was between the two [21,22].

Statistical considerations

The primary study endpoints were changes in FLT and FDG-SUVmax compared to baseline on scans obtained after induction cetuximab (for HNSCC) and during chemoradiotherapy (for all patients). Other endpoints included changes in TLG/TLP, progression, and survival. All treatment outcomes were defined from the time of initial biopsy. All statistical analysis was performed using JMP 10.0 (SAS Institute, Inc, Cary, NC). Survival curves were compared using the Kaplan-Meier method with the Log-Rank test.

Results

Patient characteristics

Clinical characteristics are shown in Table 1. A total of 16 patients were enrolled, 9 with HNSCC and 7 with EC. Baseline FDG scans were obtained for all 16 patients and baseline FLT scans for 15 patients. Post-induction chemotherapy FDG and FLT scans were available in 7 of 9 HNSCC patients. Intra-chemoradiotherapy FDG scans were available in 12 and intra-chemoradiotherapy FLT scans were available in 11 patients. FDG-PET scans were performed six weeks after RT in 13 and six months after RT in 8 patients.

		Overall		Head and Neck		Esophagus	
		n=16		n=9		n=7	
		n	%	n	%	n	%
Age	mean (range)	59.7 (41-79)		61.5 (43-78)		57.0 (41-79)	
Gender	Male	11	69%	8	89%	3	43%
	Female	5	31%	1	11%	4	57%
Location	Tonsil	4	25%	4	44%	N/A	N/A
	Base of tongue	2	13%	2	22%	N/A	N/A
	Larynx	2	13%	2	22%	N/A	N/A
	Hypopharynx	1	6%	1	11%	N/A	N/A
	Esophagus	7	44%	N/A	N/A	7	100%
Histology	Squamous	12	75%	9	100%	3	43%
	Adenocarcinoma	4	25%	0	0%	4	57%
T-stage	T2	3	19%	1	11%	2	29%
	T3	10	63%	5	56%	5	71%
	T4	3	19%	3	33%	0	0%
N-stage	N0	2	13%	1	11%	1	14%
	N1	4	25%	1	11%	3	43%
	N2	10	63%	7	78%	3	43%
	N3	0	0%	0	0%	0	0%
Stage	II	3	19%	0	0%	3	43%
	III	4	25%	1	11%	3	43%
	IV	9	56%	8	89%	1	14%
Surgery	Yes	5	71%	N/A	N/A	5	71%
	No	2	29%	N/A	N/A	2	29%

Margins	R0	4	80%	N/A	N/A	4	80%
	R1	0	0%	N/A	N/A	0	0%
	R2	1	20%	N/A	N/A	1	20%
pCR	Yes	1	20%	N/A	N/A	1	20%
	No	4	80%	N/A	N/A	4	80%
R0, negative margin; R1, microscopically positive margin; R2, gross residual disease; pCR, pathologic complete response							

Table 1: Patient characteristics.

Clinical outcomes

Oncologic outcomes were prospectively assessed with no patients being lost to follow-up. Median follow-up for living patients was 6.0 years. Median overall survival (OS) was 3.3 years and progression-free survival (PFS) was 2.5 years. Median OS was 1.2 years for EC patients and not reached for HNSCC patients (p=0.004). Median PFS was 0.9 years for EC patients and not reached for HNSCC patients (p=0.006). Kaplan-Meier plots are shown in Figure 2.

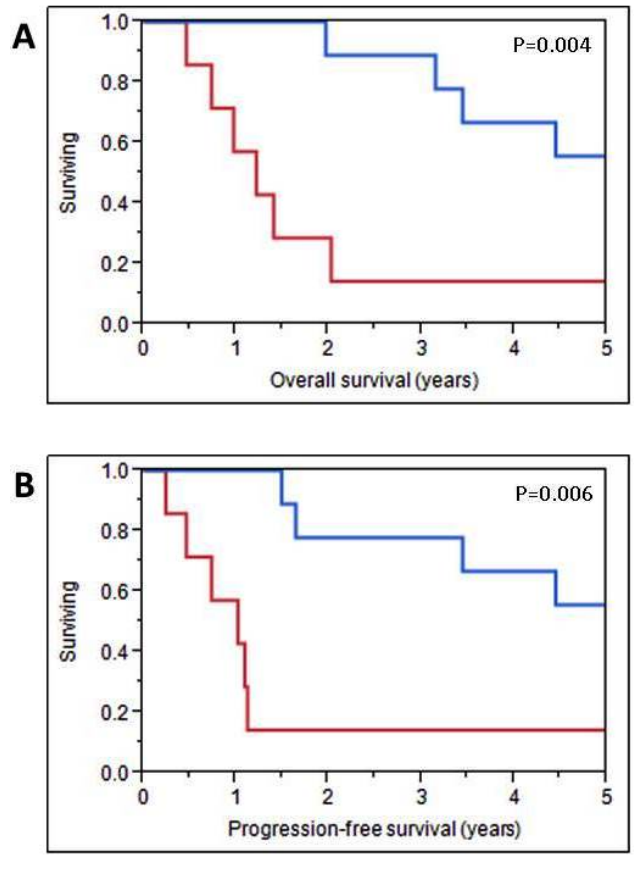

Figure 2: Overall survival (A, p=0.004) and progression-free survival (B, p=0.006) for patients with esophageal cancer (red) and head and neck squamous cell carcinoma (blue).

Baseline imaging

Characteristics of baseline FDG and FLT PET scans were quantified and analyzed for prognostic significance. Baseline SUVmax, SUVmean, TLG and TLP values are shown in Table 2. Mean baseline FDG SUVmax was 18.3 for HNSCC and 10.9 for EC (p=0.02), TLG was 157 for HNSCC and 125 for EC (p=0.69) and TLP was 61 for HNSCC and 77 for EC (p=0.49). A baseline FDG SUVmax greater than 10 was associated with better PFS (p=0.0004) and OS (p=0.002). A borderline significant correlation between better PFS (p=0.049) and OS (p=0.048) and a baseline TLG greater than 85 was noted. However, more patients with HNSCC (7 of 9) had baseline TLG greater than 85 (p=0.15) compared with EC (3 of 7). A baseline TLP greater than 70 was associated with better PFS (p=0.012) and OS (p=0.016). Still, more patients with HNSCC (8 of 9) had a baseline TLP greater than 70 (p=0.14) compared with EC (4 of 7). No correlation was seen between PFS and baseline FLT SUVmax (p=0.89), FDG SUVmean (p=0.40), FLT SUVmean (p=0.98), FDG FTV (p=0.41), or FLT FTV (p=0.88). Similarly, there was no correlation between OS and baseline FLT SUVmax (p=0.80), FDG SUVmean (p=0.91), FLT SUVmean (p=0.46), FDG FTV (p=0.39), or FLT FTV (p=0.81). Stratification by primary tumor type did not change these results (all comparisons p>0.05).

	Baseline	PI	Intra-CRT	6 week	6 months
Median FDG SUVmax	14.5	13.5	7.2	4.4	3.1
% decrease	-	7%	51%	70%	79%
Median FLT SUVmax	8	6.9	3.5	-	-
% decrease	-	14%	56%	-	-
Median FDG SUVmean	9.3	9.3	4.5	3.2	2.3
% decrease	-	0%	52%	66%	75%
Median FLT SUVmean	5.2	4.3	2.8	-	-
% decrease	-	17%	45%	-	-
Median FDG TLG	93.8	59.7	55.4	13.6	4.1
% decrease	-	36%	41%	85%	96%
Median FLT TLP	59.1	36.4	12.3	-	-
% decrease	-	38%	79%	-	-

Table 2: Changes in PET parameters with time.

Post-induction imaging

All HNSCC patients were treated with two weeks of induction cetuximab, and changes in radiotracer uptake were compared with baseline. The post-induction SUVmax, SUVmean, TLG and TLP values are shown in Table 2. After induction chemotherapy, FDG-PET revealed a partial metabolic response (PMR) in 1 and stable metabolic disease (SMD) in 6 patients, whereas FLT-PET revealed PMR in 2 and SMD in 5 patients. The single patient with PMR by FDG-PET experienced progression and subsequent death, whereas only 1 of the 6 with SMD experienced progression and/or death (p=0.01). Post-induction changes in FDG-PET were not associated with OS (p=0.18). Post-induction changes in FLT-PET were not significantly associated with PFS (p=0.35) or OS (p=0.56). Using TLG-S criteria, there was no correlation between FDG (p=0.12) or FLT (p=0.45) PET outcomes and PFS or OS (p=0.12 and p=0.15). Ultimately, changes in radiotracer uptake after induction chemotherapy did not correlate with oncologic outcomes.

Intra-chemoradiotherapy imaging

Changes in FDG and FLT-PET after three weeks of radiotherapy were compared with baseline. Median intra-chemoradiotherapy SUVmax, SUVmean, TLG and TLP are shown in Table 2. During chemoradiotherapy, FDG-PET revealed PMR in 9 and SMD in 3, whereas FLT-PET revealed PMR in 9, SMD in 1 and progressive metabolic disease (PMD) in 1. Intra-chemoradiotherapy changes in FDG and FLT-PET were not significantly associated with PFS (p=0.81 and p=0.58) or OS (p=0.87 and p=0.58). No correlation was seen between TLG-S changes via FDG (p=0.22) or FLT (p=0.49) PET and PFS. Similarly, no significant correlation could be established between FDG (p=0.32) or FLT (p=0.64) PET and OS. When stratified by primary tumor type, no significant correlations between FDG or FLT-PET and outcomes were seen (p>0.05). Thus, changes in PET uptake after three weeks of chemoradiotherapy did not correlate with oncologic outcomes.

Post-treatment imaging

FDG-PET scans were performed six weeks and six months following completion of radiotherapy and changes were compared with baseline. Median post-treatment SUVmax, SUVmean and TLG are shown in Table 2. Six weeks after completion of therapy, FDG-PET showed PMR in 11 and SMD in 2. Patients with a post-treatment PMR had better PFS (p=0.002) and marginally better OS (p=0.06) than those with SMD (Figure 3A-B). Patients with a greater than 40% decline in SUVmax six weeks after completion of therapy had better PFS (p<0.0001) and OS (p=0.003) than those with less of a response (Figure 3C-D). TLG-S outcomes did not correlate with PFS (p=0.27) or OS (p=0.42). However, a threshold of at least a 70% decrease in TLG resulted in better PFS (p=0.03) and OS (p=0.04), as noted in Figure 3E-F. Because of limited numbers when analyzing by site treated, no significant correlations between PET changes after completion of radiotherapy and oncologic outcomes could be elucidated (all p>0.05). However, it is notable that HNSCC patients were more likely to meet the threshold for SUVmax (p=0.01) and TLG (p=0.002) decline. Six months after completion of therapy, FDG-PET showed PMR in all 8 scans performed. Because all patients had PMR, no statistical correlations could be performed with oncologic outcomes. While changes on imaging performed during active treatment did not correlate with outcomes, patients with a substantial response on early post-treatment FDG PET had better PFS and OS.

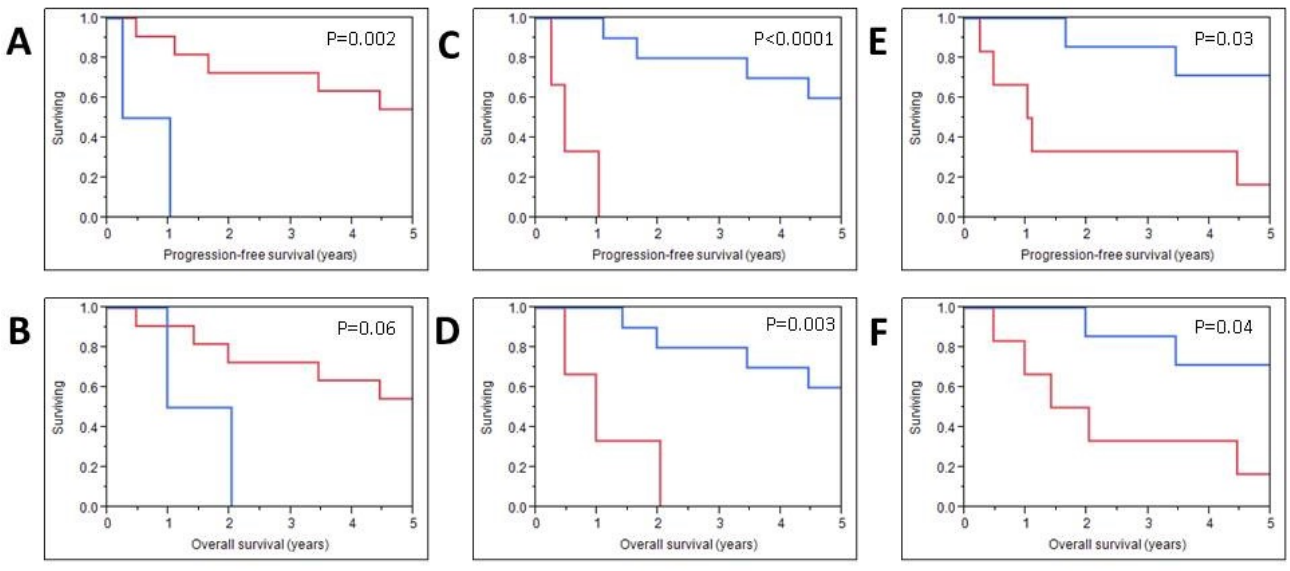

Figure 3: Better PFS (A) and borderline significant OS (B) for patients with a partial metabolic response (red) compared with stable metabolic disease (blue) six weeks following completion of chemoradiotherapy. A decline in SUVmax greater than 40% (blue) compared with less than or equal to 40% (red) correlated with better PFS (C) and OS (D) six weeks after completing chemoradiotherapy. At the same timepoint, a decrease in total lesion glycolysis of at least 70% (blue) was associated with better PFS (E) and OS (F) than a small decrease.

Discussion

In this study, we report the results from a prospective trial evaluating changes in PET during and after treatment for EC and HNSCC. FDG and FLT-PET scans performed after induction chemotherapy and during concurrent chemoradiotherapy did not reveal early changes with prognostic value. However, FDG-PET performed six weeks after treatment revealed better outcomes when at least a 40% reduction in SUVmax and 70% reduction in TLG were achieved. This highlights the potential prognostic value of post-treatment PET for risk stratification in patients with HNSCC and EC.

A baseline PET is often obtained for accurate staging of locally advanced EC and HNSCC. The ability to use baseline PET scans to risk stratify based on tumor kinetics would be very appealing. In the current study, PFS and OS were higher with an FDG SUVmax above 10, TLG above 85 and TLP above 70. This is confounded by the finding that baseline SUVmax, TLG and TLP values were higher for patients with HNSCC compared with EC. Patients with HNSCC had better PFS and OS in this study, consistent with historic data [3,4,7]. In contrast to the current study, larger prior studies in patients with HNSCC and EC have correlated worse outcomes with higher baseline SUVmax [14,23-25]. Similarly, larger prior studies suggest that higher TLG values correlated with worse oncologic outcomes [24-27]. When analyzed by disease site in this study, no baseline PET characteristics correlated with outcomes. Thus, it seems probable that the small sample size of this study limited reliable detection of baseline PET characteristics with true prognostic significance.

While baseline PET characteristics may offer a single snapshot of tumor biology, the ability to predict PFS and OS based on early responses to chemotherapy and radiotherapy would be quite useful. Early prognostication could identify patients where treatment de-escalation could be safely performed and select patients at highest risk of recurrence for treatment intensification. Most patients in the present study had a modest decrease in SUVmax after induction chemotherapy with only 2 of 7 having a slight increase in SUVmax on FLT or FDG-PET. The two patients with an initial increase in SUVmax were alive without disease at the time of last follow-up. The limited number of patients in this study, coupled with the generally favorable PET responses to induction chemotherapy, precluded our ability to detect a correlation between PET changes and long-term oncologic outcomes. In contrast, several prior studies showed that post-induction FDG-PET responses correlated with subsequent PET responses and PFS [28-30]. The utility of FLT-PET in assessing responses after induction chemotherapy in HNSCC has only been evaluated by a small number of studies. A study of five HNSCC patients treated with induction cetuximab followed by chemoradiotherapy did not find any relationship between changes in FLT-PET and post-induction EGFR or Ki-67 expression [31]. A randomized phase II trial of preoperative concurrent chemoradiotherapy with or without induction chemotherapy in patients with esophageal cancer evaluated changes in FLT-PET after two cycles of induction chemotherapy [32]. In this study, changes in SUVmax were more prominent in patients with a final tumor response. However, no correlations were made between early PET response and PFS or OS. Ultimately, the current report did not find a difference between FDG and FLT-PET in assessing responses to induction chemotherapy, and similarly could not establish a relationship between changes on post-induction PET and oncologic outcomes.

In addition to quantifying PET changes after induction chemotherapy, this study captured changes in FDG and FLT-PET after two weeks of concurrent chemoradiotherapy. During chemoradiotherapy, no patient had an increase in SUVmax on FDG-PET although one had an increase on FLT-PET. This patient was alive without disease at the end of follow-up. There was no clear threshold beyond which a reduction in SUVmax, TLG or TLP correlated with PFS or OS. While there was no difference in the accuracy of FLT compared with FDG-PET reported here, Kishino et al. found higher specificity and accuracy of FLT-PET in patients with HNSCC during and after completion of chemoradiotherapy [33]. Though they reported a statistically significant correlation between post-treatment PET changes and oncologic outcomes, there was no clear relationship between intra-chemoradiotherapy PET changes and prognosis. In contrast, a study of 48 patients with HNSCC who underwent FLT-PET during the second and fourth weeks of RT or chemoradiotherapy showed that a decrease of at least 45% in SUVmax correlated with better 3-year locoregional control [34]. The current study, while limited by size, further adds to the literature with our reported lack of correlation between any intra-treatment imaging and outcomes.

While changes during treatment did not correlate with oncologic outcomes in this study, there was a significant improvement in PFS and OS when at least a 40% decrease in SUVmax and at least a 70% improvement in TLG were observed. This is consistent with the Kishino report along with several additional small studies correlating SUVmax with oncologic outcomes [35-37]. The value of post-treatment, pre-operative FDG-PET in predicting pathologic response to chemoradiotherapy in EC has been a subject of debate, with several studies reporting no clear relationship [38-41]. Because the present study contained only a small number of patients undergoing surgical resection for EC after chemoradiotherapy, assessing the utility of FDG or FLT-PET in predicting pathologic tumor response was not possible. However, our correlation between post-treatment PET with long-term outcomes is consistent with multiple prior studies including a systematic review and meta-analysis [42-44]. Thus, while early FDG and FLT-PET performed during treatment did not correlate with outcomes, the prognostic value of post-treatment PET was confirmed by the present study.

This trial has several strengths. First, patients were prospectively enrolled and treated with chemotherapy and radiotherapy at a single institution with standardized timing of PET scans. In addition, follow-up is very mature in comparison to many similar studies. FDG and FLT-PET scans were performed within close temporal proximity to one another, so as to allow for the most accurate comparison of the modalities. Lastly, the requirement for post-treatment scans allowed for long-term follow-up. Despite its strengths, this study has several limitations. Only 67% of eligible patients received both post-induction scans, and 69% received both intra-chemoradiotherapy scans. While a limited analysis of PET changes and outcomes for patients with a single disease site (i.e. solely EC) was unremarkable, the small sample size of individual disease sites limited the validity of such analyses. In addition, it is notable but not surprising that patients with HNSCC were more likely to meet the thresholds for post-treatment SUVmax and TLG decline. Because HNSCC outcomes are generally superior to EC, this could potentially confound the prognostic significance of such thresholds. Thus, it is conceivable that a larger sample size might result in a greater statistical ability to detect a benefit for intra-therapy PET scans and solidify the reliability of post-treatment scans for prognostication.

In conclusion, functional imaging early during therapy for advanced HNSCC and EC is feasible. Changes on post-induction and intra-

chemoradiotherapy FLT and FDG-PET did not correlate with oncologic outcomes. However, patients with >40% decline in SUVmax or >70% reduction in TLG on post-treatment FDG-PET had better PFS and OS. Further research is needed to determine the value of PET performed during chemotherapy and chemoradiotherapy.

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