RESEARCH ARTICLE

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Staging and Response Evaluation to Neo-Adjuvant Chemoradiation in Esophageal Cancers Using ^{18}FDG PET/CT with Standardized Protocol

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Abstract

Background: Precise staging of esophageal cancer (EC) is important for selection of optimal treatment option and prognostication. Aim of this study was to assess the role of ^{18}FDG PET/CT in staging and response evaluation to neoadjuvant chemoradiation (nCR) in EC patients using standardized imaging protocol. **Material and methods: T**his prospective study was conducted at PET/CT Section of Department of Radiology, Aga Khan University Hospital Karachi, Pakistan from July 2017 till February 2018. We included 34 biopsy proven EC patients who had ^{18}FDG PET/CT and CT of neck, chest and abdomen as part of initial staging. Eleven patients had post-nCR ^{18}FDG PET/CT using standardized imaging protocol as per EANM guidelines. CT and PET/CT based staging was compared. Based on PERCIST criteria, response evaluation was assessed using change in highest SUVmax (%ΔSUVmax) in baseline and follow-up scans (primary lesion, node or extra-nodal metastases). **Results:** Mean age of cohort was 57 ± 14 years (23 males and 11 females) having adenocarcinoma (AC) in 23 and squamous cell cancer (SCC) in 11 patients. Mean ^{18}FDG dose, uptake time and hepatic SUVmean for baseline scans were 169 ±54 MBq, 65 ±10 minute and 1.91 ± 0.49 which were within ± 10%, ± 15% and ± 20% for follow-up scans in 11 patients respectively. Mean size (craniocaudal dimension in mm) and SUVmax of primary tumor was 56 ±27 mm and 13.4 ± 4.7. Based on ^{18}FDG PET/CT findings, patients were categorized into N0 (10/34), N1 (09/34), N2 (11/34) and N3 (04/34) while 11/32 had stage IV disease. No significant difference was seen in AC and SCC groups. CT found stage IV disease in 3/34 (09%) while PET/CT found in 11/34 (32%; p value: 0.019) cases. PET/CT showed concordance with CT in 41% while discordance (all with upstaging) seen in 59%. On follow-up PET/CT, complete metabolic response was seen in 5/11 (45%) and partial metabolic response was noted in 6/11 (55% - p value non-significant) patients. Median %ΔSUVmax over primary lesions was 49.84% (-32.69 -100%) while over nodal sites it was 41.18% (-82.60 -100%). **Conclusion:** We conclude that ^{18}FDG PET/CT was found a sensitive tool in initial staging of EC. Compared with CT, it had higher diagnostic accuracy for distant nodal and extra-nodal metastasis. %ΔSUVmax between baseline and post-nCR studies acquired with standardized protocol had changed management in more than half of our patients. For response evaluation in EC more studies with standardized ^{18}FDG PET/CT imaging protocols are warranted.

Keywords: Esophageal cancer- staging- neoadjuvant chemoradiation- ^{18}FDG PET/CT and CT

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Introduction

Esophageal cancer (EC) is the 8th most common cancer and the 6th leading cause of cancer-associated fatalities worldwide (Montgomery et al., 2014). More than 50% of patients have un-resectable or metastatic disease at the time of presentation with an age-adjusted incidence rate of about 4.5 per 100,000 (Thomas et al., 2014). The 5-y relative survival for patients without nodal involvement is 37%, 18.4% with nodal disease and only 3.1% for stage IV disease (Thomas et al., 2014; Tan et al., 2014). Therefore, disease stage has profound prognostic implications as for patients with localized disease are offered surgery or definitive chemoradiation but those with locally aggressive disease have option of neoadjuvant chemoradiation (nCR) with or without surgery (Talsma et al., 2012).

Endoscopic ultrasound (EUS) has good diagnostic accuracy to detect extent of mucosal involvement and peri-lesional nodal metastasis but could have limited access in locally advanced disease. Computerized tomography (CT) has good diagnostic accuracy for tumor

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staging (T-staging) but has lower sensitivity for nodal or distant metastasis (Chatterton et al., 2009). PET/CT using 18-Flourodeoxyglucose (^{18}FDG) is more accurate tool for staging, prognostication and can change management in more than one third of patients (Duong et al., 2006). However, it has limited value in the assessment of the primary tumor and detection of peri-tumoral nodal disease (Thomas et al., 2014). Reported sensitivity and specificity of ^{18}FDG PET/CT using maximum standardized uptake value (SUVmax) for response evaluation of nCR are 67% and 68% respectively (Leijenaar et al., 2015). However, published studies lack standardization in imaging protocols which could result in unknown biases and reproducibility of SUVs and SUV-based response assessment (Boellaard, 2011).

Aim of this study was to assess the role of ^{18}FDG PET/CT in staging and response evaluation to neoadjuvant chemoradiation in EC patients using standardized imaging protocol.

Materials and Methods

This prospective study was conducted at PET/CT Section of Department of Radiology, Aga Khan University Hospital Karachi, Pakistan from July 2017 till February 2018. We included patients with EC who were referred for ^{18}FDG PET/CT studies at baseline and those who had follow-up after completion of nCR during study period. All patients had endoscopic biopsies and contrast enhanced CT of neck, chest and abdomen as part of initial staging work-up. We strictly followed a standardized protocol for ^{18}FDG PET/CT as per European Association of Nuclear Medicine (EANM) guidelines for both studies (Boellaard et al., 2015). Staging of EC based on CT and baseline PET/CT scans were compared. In patients who had follow-up PET/CT studies, response evaluation was assessed using change in highest SUVmax (%ΔSUVmax) in baseline and follow-up scans (primary lesion, node or extra-nodal metastases).

Inclusion Criteria

Patients with biopsy proven EC who were referred for ^{18}FDG PET/CT imaging for staging and also had CT examination of neck, chest and abdomen as part of their initial staging work at our institute were included. Those without complete CT studies were not included.

CT Imaging

All patients had baseline contrast enhanced CT examinations done within 2 weeks prior to baseline ^{18}FDG PET/CT studies. CT scans were reported by our radiologists for primary tumor size and extent, peri-lesional nodal / visceral involvement and distant nodal and non-nodal metastasis. Staging was done using manual of American Joint Committee on Cancer 7th edition (AJCC 7th Ed) (Edge and Compton, 2010).

^{18}FDG PET/CT Imaging

^{18}FDG PET/CT was performed as per institutional protocol adopted from EANM guidelines (Boellaard et al., 2015). All patients had 4-6 hour fasting (only plain water was allowed) and a fasting blood sugar less than 200 mg% before receiving an intravenous ^{18}FDG dose of 3 MBq/Kg in the uptake room. During uptake period (55 -75 minute) patients were requested to lie comfortably and allowed to take about 500-1,000 ml of plain water. Bladder was emptied prior to call the patient for PET/CT imaging suite equipped with Celesteion, Toshiba, Japan. A low dose CT examination (mid brain to mid-thigh) from head to toe followed by acquisition of PET imaging using 3 minute/bed position from toe to head in all patients. Follow up scans were performed with same protocols, keeping ^{18}FDG dose, uptake time and hepatic SUVmean of baseline and follow-up studies within ± 10%, ± 15% and 20% minutes respectively as per PET response criteria in solid tumor (PERCIST) (Wahl et al., 2009). SUVmax of primary lesions and nodal disease were measured in both studies and also % change in highest SUVmax of baseline and follow-up studies for response evaluation as recommended by PERCIST criteria.

Statistical Analysis

Continuous variables were described by mean ± standard deviation (SD). Comparisons between patient groups of two histological types of CA esophagus were performed using Student's t test for continuous variables and the χ^2 test for categorical variables. Statistical significance was defined as $P<0.05$. Commercially available packages Microsoft excel 2010, Medcalc® and statistical package for social sciences (SPSS 19®) were used.

Results

Study included 34 patients with biopsy proven EC, having a mean age of 57 ± 14 years (23 males and 11 females) and a mean BMI (kg/m^2) of 23.92 ± 4.81. Twenty three patients had adenocarcinoma (AC) while 11 had squamous cell cancer (SCC). All patients had baseline ^{18}FDG PET/CT prior to nCR and only 11 had follow-up studies during study period for response evaluation. Mean ^{18}FDG dose, uptake time and hepatic SUVmean for baseline scans were 169 ±54 MBq, 65 ±10 minute and 1.91 ± 0.49 (Table 1). These values were within ± 10%, ± 15% and ± 20% for follow-up scans in 11 patients respectively. Mean size (craniocaudal dimension in mm) and SUVmax of primary tumor was 56 ±27 mm and 13.4 ± 4.7. Based on ^{18}FDG PET/CT findings, patients were categorized into N0 (10/34), N1 (09/34), N2 (11/34) and N3 (04/34) while 11/32 had stage IV disease (Table 1).

Histopathology revealed AC in 23/34 and SCC in 11/34 patients. No significant difference was seen in both groups for mean age, gender, BMI, mean tumor size or mean tumor SUVmax. Similarly no significant difference was noted for nodal involvement (N0-N3) or stage IV disease between AC and SCC groups (Table 2).

CT found stage IV disease in 3/34 (09%) while PET/CT found in 11/34 (32%; p value: 0.019) cases (Figure 1). A concordance in staging between CT and PET/CT was seen in 14/34 (41%) patients. However, in 20/34 (59%) patients PET/CT upstaged the disease due to new lesions seen in nodes (12/20) and distant metastasis (08/20). ^{18}FDG PET/CT was not found to downstage the disease

Table 1. Study Demographics

Variables	N=34
Age in years	57 ± 14
Mean ± SD (range)	(26-85 yrs)
Gender (Male: Female)	23: 11 (68: 32%)
BMI (Kg/m2) Mean ± SD	23.92 ± 4.81
FDG Dose (MBq) Mean ± SD	169 ± 54
FBS (mg/dl) Mean ± SD	101 ± 26
Duration (minutes) Mean ± SD	65 ± 11
CTDI (Mean ± SD)	5.17 ± 0.92
DLP (Mean ± SD)	570.62 ± 103.59
Mean Liver uptake (Mean ± SD)	1.91 ± 0.49
SD of mean liver uptake (Mean ± SD)	0.26 ± 0.11
Adenocarcinoma: SCC	23: 11 (68:32%)
SUVmax of tumor (Mean ± SD)	13.4 ± 4.7
Size of tumor in mm (Mean ± SD)	56 ± 27
Nodal involvement (N0:N1:N2:N3)	10: 09:11:04 (29:27:32:12%)
Stage IV	11 (32%)

BMI, Body Mass Index; SD, Standard Deviation; FDG, Flurodeoxy Glucose; FBS, Fasting Blood Sugar; CTDI, CT dose index; DLP, Dose Length Product; SUV, Standardized Uptake Value; SCC, Squamous Cell Carcinoma

in any patient (Table3).

Eleven patients had a follow-up ^{18}FDG PET/CT for response evaluation to nCR. Using PERCIST criteria, complete metabolic response (disappearance of all abnormal ^{18}FDG uptake; CMR) was seen in 5/11 (45%) (Figure 2) while partial metabolic response (>30% decline in highest SUVmax; PMR) was noted in 6/11 (55% - p value non-significant) patients (Figure 3,4). Median %ΔSUVmax over primary lesions was 49.84% (-32.69 -100%) while over nodal sites it was 41.18% (-82.60 -100%) (Figure 5).

Discussion

Esophageal cancer (EC) is one of the most aggressive tumors with higher recurrence rate even after radical surgery. Therefore precise pretreatment staging is important to determine appropriate stage-specific treatment options. CT based staging has limited sensitivity (30-60%) and specificity (60-80%) for nodal metastasis as it relies on anatomic criteria (Napier et al., 2014) and also for distant metastasis due to delayed appearance of appreciable morphological changes over those sites. However, in recent years ^{18}FDG PET/CT has shown a better diagnostic accuracy for nodal and distant

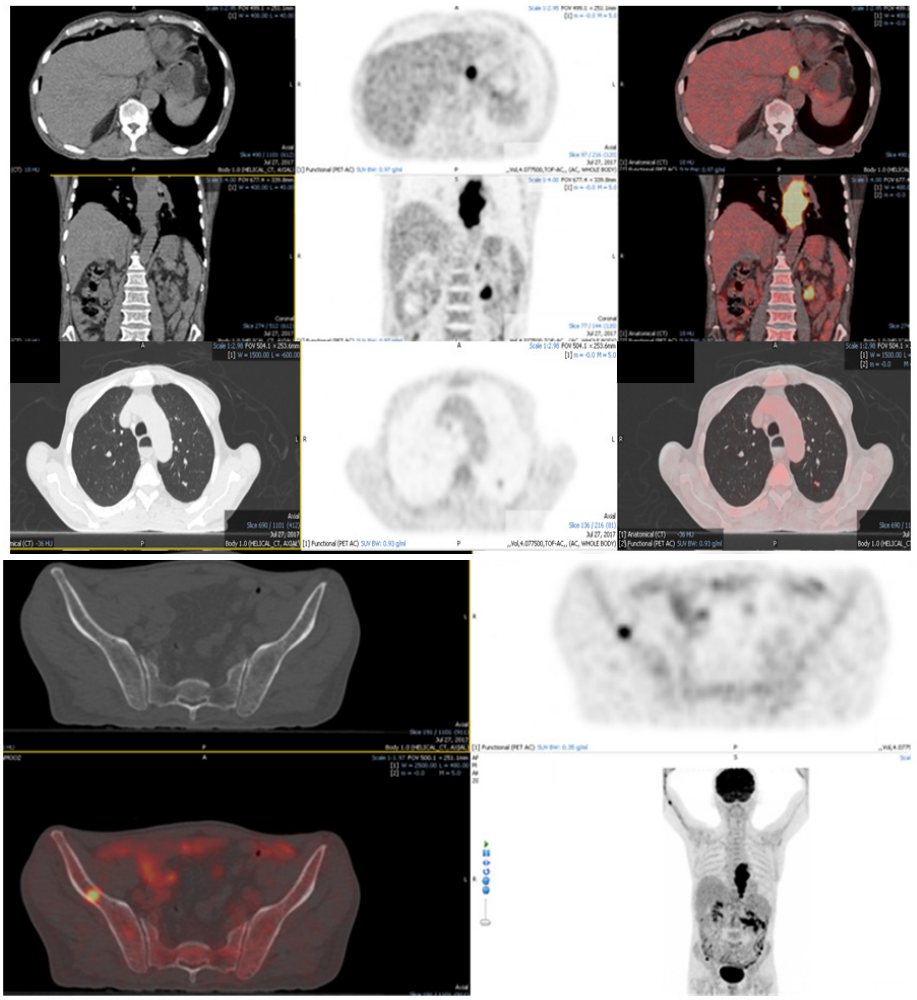

Figure 1. 70 Years Old Male, Known Case of Esophageal Cancer, Baseline ^{18}FDG PET/CT for Staging Showing Hypermetabolic Circumferential Soft Tissue Mass Involving Esophagus from Carina to GE Junction (2nd and 5th rows), a hypermetabolic gastrohepatic lymph node (1st row), 18FDG avid left pulmonary nodules (3rd row) and hypermetabolic left adrenal (2nd row) and solitary bony metastasis in right iliac blade (4th and 5th rows; Stage IV).

Table 2. Demographic Comparison of Adenocarcinoma and Squamous Cell Carcinoma of Esophagus on Baseline PET/CT Scan

	Adenocarcinoma N=23	SCC N=11	χ2/ or t-test values	p-values
Age in years	56 ± 12	59 ± 17	0.595	0.556
Mean ± SD (range)	(33-77)	(26-85)		
Gender (Male: Female)	17: 06 (74:26%)	06:05 (55:45%)	1.195	0.274
BMI (Kg/m2) Mean ± SD	24.09 ± 5.05	23.56 ± 4.49	-0.296	0.769
SUVmax of tumor (Mean ± SD)	12.8 ± 4.4	15.3 ± 5.0	1.484	0.148
Size of tumor in mm (Mean ± SD)	56 ± 29	56 ± 23	0	1
Nodal involvement				
N0	07 (30%)	03 (27%)	0.032	0.859
N1	05 (22%)	04 (36%)	0.726	0.394
N2	08 (35%)	03 (27%)	0.211	0.646
N3	03 (13%)	01 (10%)	0.061	0.804
Stage IV	09 (39%)	02 (18%)	1.459	0.227
Upstaging	14 (60%)	06 (55%)	0.074	0.785
Nodal	08 (57%)	04 (67%)	0.102	0.749
Distant	06 (43%)	02 (33%)	0.102	0.749

SD, Standard Deviation; BMI, Body Mass Index; SUV, Standardized Uptake Value; SCC, Squamous Cell Carcinoma

Table 3. Change in Staging by Comparing Baseline ^{18}FDG PET/CT with CT

Change in Staging based on PET/CT	PET/CT vs. CT
UNCHANGED	14 (41%)
UPSTAGING	20 (59%)
Nodes	12 (60%)
Distant	08 (40%)
(Liver: Bone: Lungs: Adrenals)	03:01:03:01 (38%: 12%: 38%: 12%)
DOWNSTAGING	0%

metastasis compared to contrast enhanced CT (Lu et al., 2016). In our study, we had a higher prevalence of AC than SCC (primary lesion in distal esophagus and at gastroesophageal junction) which is significantly higher than South America but in concordance with Western Europe and North America which is possibly due to the increase of obesity and gastroesophageal reflux disorder (GERD) incidence in these regions (Thomas et al., 2014; Tustumi et al., 2016). In our study, GERD could be the possible reason for higher incidence of AC as BMI of our total cohort was not high. In this study no significant difference was seen in BMIs of patients with SCC and AC which is in concordance with published study (Lu et al., 2016)

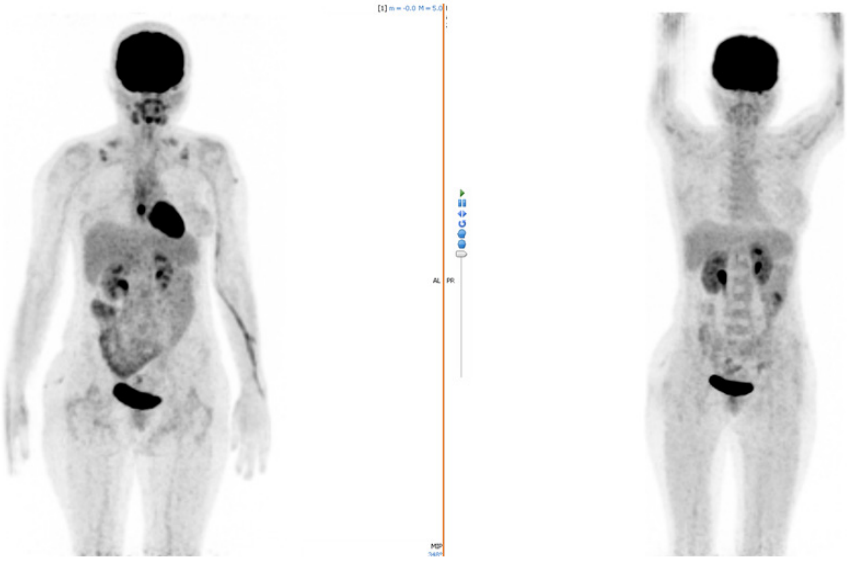

Figure 2. 34 Years Old Female, Known Case Distal Esophageal Cancer, ^{18}FDG PET/CT MIP Images at Baseline (Left) and Follow-up (Right) Showing Complete Metabolic Response (CMR) Over Primary Site after Neoadjuvant Chemoradiation. Brown adipose tissue uptake seen in bilateral supraclavicular baeline MIP scan (Responder).

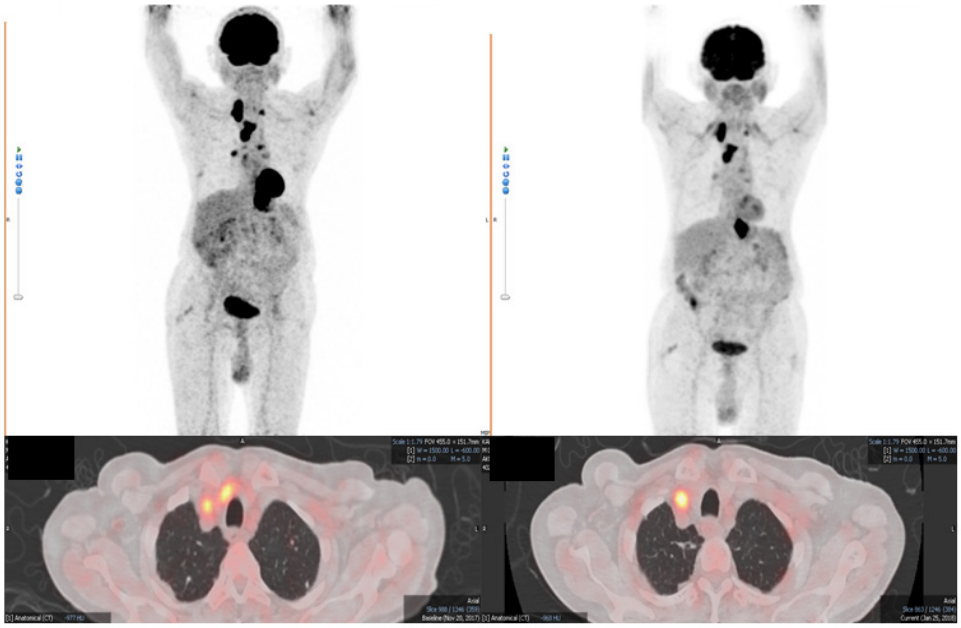

Figure 3. 75 Years Old Male with Known Case of Mid Esophageal Cancer, ^{18}FDG PET/CT MIP Images at Baseline (Left) and Follow-up (Left) Showing Partial Metabolic Response (PMR) Over Primary and Loco- Regional Nodes and Resolution of ^{18}FDG Non-Avid Bilateral Pulmonary Nodules (Non-Responder).

In our study nodal involvement was seen in about two third cases at initial staging (no difference between SCC and AC groups) which could be explained by dual lymphatic drainage of esophagus (one plexus arising within mucosal and other within muscular layers) (Napier et al., 2014). In our study incidence of nodal metastasis was similar in AC and SCC which is in contradiction to published fact that submucosal AC has lower prevalence of nodal and skip metastasis than SCC (Cho et al., 2014). This could be explained by a significantly higher sensitivity (up to 90%) of ^{18}FDG PET/CT for distant nodal metastasis than locoregional nodes (Napier et al., 2014). A meta-analysis of 12 previous studies revealed that sensitivity of ^{18}FDG PET/CT for regional nodal metastasis was significantly lower than that of CT (51% vs 63%–87%), but the specificity was higher than CT (84% vs. 14%–43%) (Cho et al., 2014). The lower sensitivity of ^{18}FDG PET/CT might result from the difficulty in differentiating the primary tumor from peri-tumoral lymph nodes because of intense ^{18}FDG uptake by the tumor, as well as from false-positive findings due to inflammatory enlarged nodes (Hing et al., 2014). The overall incidence of distant metastasis in this study was 32% (liver > lung > bone > adrenal) which is in concordance with published data (Napier et al., 2014). In this study incidence of distant metastasis was higher in AC (39%) than SCC (18%) which is also reported in other demographic studies (Tavirani et al., 2017). However, it was statistically not significant which is likely due to small sample size. However, this might raise the possible higher hematogenous spread in AC than SCC which needs to be explored.

In this study concordance between CT and ^{18}FDG PET/CT for initial staging was found in 41% which is in concordance with a published study (45% concordance) having almost a similar patient population (40 patients) (Tan et al., 2016). However, concordance in our study is well below another study published study (60% concordance) having a higher patient population (139

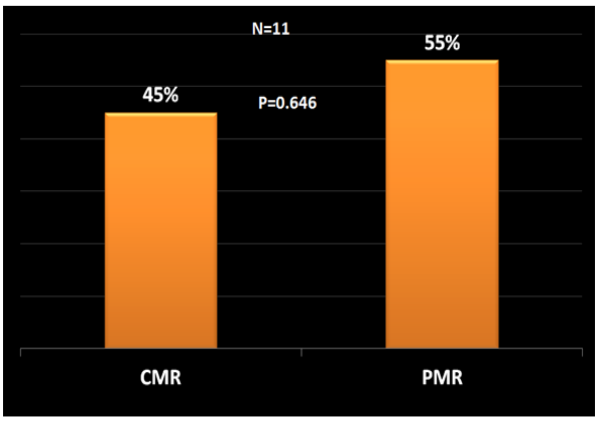

Figure 4. Metabolic response on Follow-up ^{18}FDG PET/CT in Esophageal Cancer Patients who Underwent Neoadjuvant Chemoradiation (nCR).

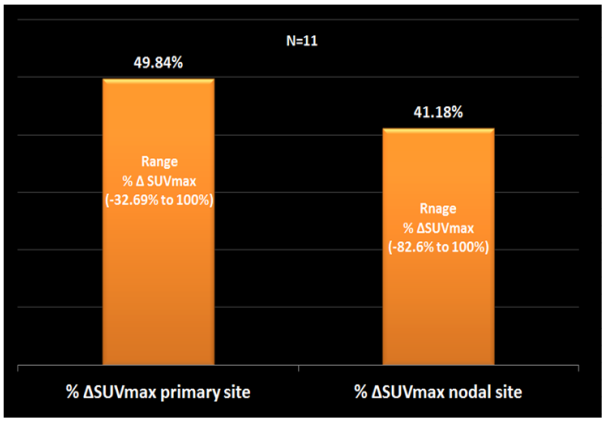

Figure 5. Median % Change in SUV_{max} Over Primary and Nodal Sites of Esophageal Cancer Patients between Baseline and Post-nCR ^{18}FDG PET/CT Studies

patients) (Thomas et al., 2014). This could be explained by strict CT reporting criteria in our study particularly about size of nodes (abnormal nodes = >10 mm in short axis). Similarly discordance between CT and ^{18}FDG PET/CT for initial staging was found in 59% and all led to upstaging (no down staging) which is not in concordance with published results (Thomas et al., 2014; Tan et al., 2016). This could be explained by established higher diagnostic accuracy of ^{18}FDG PET/CT than CT for distant metastasis (Napier et al., 2014) and stringent CT reporting criteria adopted by our radiologists.

In EC accurate response evaluation to nCR is imperative to omit surgery in complete responders or prevent unjustified nCR in non-responders. ^{18}FDG PET/CT using SUVmax for evaluation of response to nCR has a sensitivity of 67% and specificity of 68% (Beukinga et al., 2017). We found clinical CMR in 45% and clinical PMR in 55% to nCR in 11 patients who had a post-treatment study. Our CMR rate is in concordance with recently published studies having rates of 61% (Elimova et al., 2015) and 46% (Gunther et al., 2015) respectively.

Our study has some limitations. First it has a small sample size which increases uncertainty and relatively less precision. However, like other small sample sized published studies, this could always be used for meta-analysis in future. Second, we had used only SUVmax and no other parameters like total lesion glycolysis or texture for response evaluation. Third, we did not validate our results with pathology; instead we used % change in ^{18}FDG uptake as validation criterion which is a major limitation. However, we had used a standardized imaging protocol for ^{18}FDG PET/CT for baseline and follow-up which significantly improves precision of %ΔSUVmax by minimizing the impact of various confounding factors associated with non-standardized protocols.

We conclude that ^{18}FDG PET/CT was found a sensitive tool in initial staging of EC. Compared with CT, it had higher diagnostic accuracy for distant nodal and extra-nodal metastasis. %ΔSUVmax between baseline and post-nCR studies acquired with standardized protocol had changed management in more than half of our patients. For response evaluation in EC more studies with standardized ^{18}FDG PET/CT imaging protocols are warranted.

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