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Impact of Primary Tumor Size, SUVmax of Primary Tumor and the Most Avid Neck Node on Baseline ^{18}FDG PET/CT upon Disease Recurrence in Head and Neck Oropharyngeal SCC Using Standardized Imaging Protocol

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Abstract

Objective The purpose fo this prospective study was to find the impact of primary tumor size (Ts), standardized uptake values (SUVmax) of primary tumor, and the most avid neck node on disease recurrence in patients with head and neck oropharyngeal squamous cell carcinoma (HNOP-SCC).

Material and methods We included patients with HNOP-SCC (without distant metastasis—M0 disease) who had pre- and post-treatment F-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG PET/CT) using strict standardized imaging protocol from 2017 to 2019. Based on follow-up (^{18}FDG PET/CT) findings, patients were categorized as disease free (no or minimal ^{18}FDG uptake $\leq$ background over surgical bed and no distant metastasis) and disease recurrence (^{18}FDG uptake $>$ background over surgical bed with or without nodal and/or distant metastasis). Ts and SUVmax of primary tumor and the most avid neck node were compared and impact of these was studied upon disease recurrence.

Results Total 112 patients were included. No significant difference was seen in mean age (overall: 60 ± 14 years), gender distribution (overall M:F: 69:31%), body mass index (overall: 25.20 ± 5.82), and history of diabetes (overall: 19%) between disease-free and disease recurrence groups. Similarly, no significant difference was observed for fasting blood sugar (overall: 110 ± 28 mg%), ^{18}FDG dose (overall: 169 ± 37 MBq), and uptake period (overall: 70 ± 12 minutes) between two groups ensuring strict adherence to standardized imaging protocol. Significant difference ($p < 0.05$) was observed between disease-free and disease recurrence for Ts (25 ± 10 vs. 33 ± 14 mm), SUVmax of

Keywords
- head and neck cancer
- squamous cell cancer
- ^{18}FDG PET/CT
- primary tumor size
- SUVmax
- disease recurrence
- disease-free survival

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primary tumor (6.2 ± 6.8 vs. 9.3 ± 7.2) and the most avid neck node (2.1 ± 3.3 vs. 4.7 ± 5.9) and median follow-up (13 ± 12 vs. 08 ± 13 months), respectively. Using receiver operating characteristic analysis, Ts greater than 29 mm, baseline tumor SUVmax greater than 4.6, and nodal SUVmax greater than 6.2 were found independent predictors for disease recurrence. Nodal SUVmax greater than 6.2 was found an independent predictor of shortest disease-free survival (DFS) than Ts and tumor SUVmax.

Conclusion We conclude that in HNOP-SCC, primary Ts ($>$ 29 mm), SUVmax of primary tumor ($>$ 4.6), and the most avid neck node ($>$ 6.2) in baseline ^{18}FDG PET/CT using standardized imaging protocol are the independent predictors of disease recurrence. Furthermore, SUVmax greater than 6.2 of the most avid node predicts the shortest DFS than primary Ts and SUVmax of primary tumor.

Introduction

Globally head and neck cancer (HNC) accounts for more than 650,000 cases, 330,000 deaths annually and constitutes 3% and 4% of total cancer incidence in United States and Europe, respectively.[1] Most common histological type is squamous cell carcinoma (SCC) that accounts for 95% of cases (HN-SCC) and overall 5-year survival for all stages is approximately 60%.[2] Various prognostic markers indicating a dismal outcome include larger primary tumor size (Ts), greater tumor volume, higher histological grade, presence of nodal metastasis, negative human papillomavirus (HPV), and p-16 status.[3] F-18 fluorodeoxyglucose positron emission tomography computed tomography (^{18}FDG PET/CT) is an established modality for initial staging and restaging after treatment with higher diagnostic accuracy. Gathered data suggest that ^{18}FDG PET/CT may serve as a noninvasive method that can indirectly measure the expression of various biologic markers of tumor aggressiveness.[4] In many HN-SCC studies, various ^{18}FDG PET/CT metabolic markers (like standardized uptake value [SUV] of primary tumor and nodes, metabolic tumor volume [MTV], total lesion glycolysis [TLG]) and morphological parameters (likely primary tumor size; Ts and volume) have been identified as valuable imaging markers to assess treatment response and long-term survival.[5,6]

The purpose of this prospective study was to find the impact of primary Ts, SUVmax of primary tumor and the most avid neck node upon disease recurrence in patients with head and neck oropharyngeal squamous cell carcinoma (HNOP-SCC).

Materials and Methods

This prospective study was conducted at PET/CT Section of Department of Radiology, Aga Khan University Hospital Karachi, Pakistan, from January 2017 till December 2019. Study was duly approved by ethical review committee (ERC-l2020–5555–14933). We included patients with biopsy-proven HNOP-SCC who were referred for ^{18}FDG PET/CT studies at baseline and follow-up for suspected recurrence. Based on baseline ^{18}FDG PET/CT studies, patient without distant metastases (M0) were enrolled. All patients had undergone surgery, local radiation therapy, and chemotherapy (some had neo-adjuvant as well). Patients with primary other than oropharynx, non-SCC, or distant metastasis (M1) at presentation were excluded. We strictly followed a standardized imaging protocol for ^{18}FDG PET/CT as per European Association of Nuclear Medicine (EANM) guidelines for both studies.[7] Based on follow-up ^{18}FDG PET/CT findings, patients were categorized as disease free (no or minimal ^{18}FDG uptake $\leq$ background over surgical bed and no distant metastasis) and disease recurrence (^{18}FDG uptake $>$ background over surgical bed with or without nodal and/or distant metastasis). Ts and SUVmax of primary tumor and the most avid neck node were compared and impact of these was studied upon disease recurrence.

^{18}FDG PET/CT Imaging

^{18}FDG PET/CT was performed as per institutional protocol adopted from EANM guidelines.[7] All patients had 4 to 6 hours 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 minutes), patients were requested to lie comfortably and allowed to take approximately 500 to 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 (midbrain to mid-thigh) followed by acquisition of PET imaging using 3 minutes/bed position from mid-thigh to head in all patients. Follow-up scans were performed with same protocols, keeping ^{18}FDG dose, uptake time, and hepatic SUV-mean of baseline and follow-up studies within $\pm$ 10%, $\pm$ 15% and 20% minutes, respectively, as per published recommendations.[8] On follow-up scan, disease-free status was defined as no or minimal ^{18}FDG uptake less than or equal to background over surgical bed and no distant metastasis. However, disease recurrence was defined as ^{18}FDG uptake greater than background over surgical bed with or without nodal and distant metastasis.

Statistical Analysis

Comparisons between patient groups were performed using Student's *t*-test for continuous variables and the $\chi 2$ test for categorical variables. Continuous variables were described by mean ± standard deviation. Receiver operating characteristic analysis was performed to calculate the area under the curve and cutoff values for highest SUVmax of primary tumor, SUVmax of neck node, and primary Ts with a corresponding 95% confidence interval were estimated as predictor for tumor recurrence. The Kaplan–Meier survival curve was plotted for recurrence-free survival. Statistical significance was defined as p less than 0.05. Commercially available packages Microsoft Excel 2010, Medcalc, and Statistical Package for Social Sciences (SPSS 19) were used.

Results

During study period, 112 patients with biopsy-proven HNOP-SCC without distant metastasis (M0) were included. No significant difference was seen in mean age (overall: 60 ± 14 years), gender distribution (overall M:F = 69:31%), body mass index (overall: 25.20 ± 5.82), and history of diabetes (overall: 19%) between disease-free and disease recurrence groups (►**Table 1**). Similarly, no significant difference was observed for fasting blood sugar (overall: 110 ± 28 mg%), ^{18}FDG dose (overall: 169 ± 37 MBq), and uptake period (overall: 70 ± 12 minutes) between two groups ensuring strict adherence to standardized imaging protocol (►**Table 1**). Significant difference ($p < 0.05$) was observed between disease-free and disease recurrence for Ts (25 ± 10 vs. 33 ± 14 mm), SUVmax of primary tumor (6.2 ± 6.8 vs. 9.3 ± 7.2) and the most avid neck node (2.1 ± 3.3 vs. 4.7 ± 5.9) and median follow-up (13 ± 12 vs. 08 ± 13 months), respectively (►**Table 1**). Using receiver operating characteristic analysis, Ts greater than 29 mm (95% confidence interval [CI]: 0.529–0.715; ►**Fig. 1**), baseline tumor SUVmax greater than 4.6 (95% CI: 0.502–0.690; ►**Fig. 2**), and nodal SUVmax greater than 6.2 (95% CI: 0.531–0.717; ►**Fig. 3**) were found independent predictors for disease recurrence (►**Fig. 4**). The Kaplan–Meier survival plots for time of recurrence (or disease-free survival; DFS) revealed an overall mean DFS of 24.6 months (95% CI: 16.2–33.0; $p < 0.05$). The Kaplan–Meier survival plots for Ts greater than 29 mm had a mean DFS of 17.5 versus 21.5 months for Ts less than or equal to 29 mm (Logrank test value = 12.79; $p < 0.0003$; ►**Fig. 5**). The Kaplan–Meier survival plots for primary tumor SUVmax greater than 4.6 had a mean DFS of 21.8 versus 23.6 months for SUVmax less than or equal to 4.6 (Logrank test

Table 1 Demographic comparison of head and neck cancer patients labeled as responders and nonresponders on metabolic response in their follow up PET/CT studies

Variables	Total $n = 112$	Disease free $n = 46$ (41%)	Disease recurrence $n = 66$ (59%)	Test/X^2 values	*p*-Values
Age, median ± SD (range)	60 ± 14 (27–85) years	64 ± 17 (27–85) years	60 ± 12 (28–81) years	−1.461	0.1470
BMI (kg/m^2) (mean ± SD)	25.20 ± 5.82	25.08 ± 5.56	25.29 ± 6.03	0.187	0.8519
Gender (male: female)	77:35 (69: 31%)	31:15 (67: 33%)	46:20 (70: 30%)	0.113	0.7372
Obesity (≥ 30 kg/m^2)	22 (20%)	10 (22%)	12 (18%)	0.272	0.6018
DM	21 (19%)	08 (17%)	13 (20%)	0.159	0.6905
FBS (mg/dL) (mean ± SD)	110 ± 28	115 ± 32	107 ± 25	−1.484	0.1408
FDG dose (MBq) (mean ± SD)	169 ± 37	171 ± 41	168 ± 35	−0.416	0.6784
Uptake period (mean ± SD)	70 ± 12	70 ± 10	70 ± 14	0.000	1.0000
Highest SUVmax primary tumor Average ± SD Range	6.1 ± 7.5 (0–31)	6.2 ± 6.8 (00–24)	9.3 ± 7.2 (00–31)	2.293	[a]0.0238
Highest SUVmax node Average ± SD Range	3.7 ± 5.2 (0–28)	2.1 ± 3.3 (0–12.7)	4.7 ± 5.9 (0–28)	2.706	[a]0.0079
Primary tumor size Average ± SD Range	27 ± 13 (9–74) mm	25 ± 10 (10–52)mm	33 ± 14 (0–74)mm	3.327	[a] < .0012
Median follow-up in months	07 ± 12 (02–96)	13 ± 12 (02–52)	08 ± 13 (02–96)	−2.066	[a]0.0412

Abbreviations: BMI, body mass index; DM, diabetes mellitus; FBS, fasting blood sugar; FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; SD, standard deviation; SUV, standardized uptake value.
[a]$p < 0.05$.

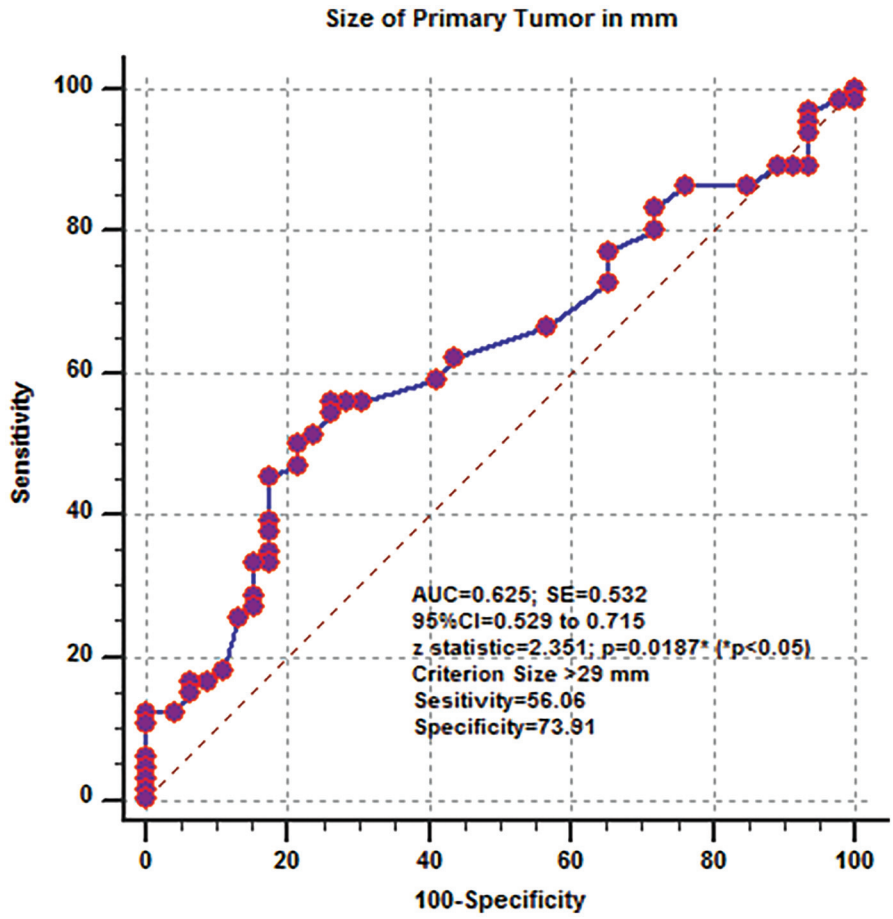

Fig. 1 Receiver operating characteristic analysis of primary tumor size (in mm) on baseline ^{18}FDG PET/CT as predictor for disease free and disease recurrence on metabolic response in SCC of head and neck in follow up studies. AUC, area under curve; CI, confidence interval; SE, standard error; SUV, standardized uptake value.

value = 6.01; $p < 0.0014$; ►**Fig. 6**). The Kaplan–Meier survival plots for most avid node SUVmax greater than 6.2 had a mean DFS of 8.6 versus 31.4 months for SUVmax less than or equal to 6.2 (Logrank test value = 12.75; $p < 0.0004$; ►**Fig. 7**). Importantly, SUVmax of the most avid node at baseline ^{18}FDG PET/CT was found an independent predictor of the shortest DFS than Ts and SUVmax of primary tumor.

Discussion

In Pakistan, head and neck SCC (HN-SCC) is the second most common malignancy in both genders, after breast cancer in females and lung cancer in males.[9] Like other cancers, prognosis of HN-SCC depends largely on the stage of presentation, with nodal metastasis being the single most important factor that reduces long-term survival by 50%.[10] In our studied population, no significant difference was seen between disease-free and disease recurrence group for age, male gender predominance, body mass index, and diabetes. This indeed increases the statistical strength of our data. Similarly, lack of significance in acquisition parameters between two PET/CT studies in two groups also minimizes the impact these confounding factors on SUVmax calculations.[8] This also highlights the importance of adherence to a standardized imaging protocol.[8]

Our study found positive impact of primary Ts on recurrence in studied population with a cutoff value of greater than 29 mm (≥ T2 stage). Possible explanation for this correlation is higher odds of positive margins with increasing Ts[11] and involved surgical margin is an established independent risk factor for higher recurrence.[12] This finding is in concordance with another study published from our institute revealing a poor outcome with tumor volume greater than 23.1 cm^3 in patients with HN-SCC.[9] However, there are some published studies that reported no significant association between recurrence and Ts but the depth of primary tumor invasion.[13] This finding again draws attention of multidisciplinary team toward a meticulous and wide local resection of primary tumor (≥T2) to minimize odds of recurrence.

In this study, we have also evaluated the most commonly used metabolic matrix SUVmax of primary tumor and the most avid neck node. We found that higher SUVmax of primary tumor (cutoff: > 4.6) is an independent risk factor for recurrence. SUVmax of primary tumor is one of the frequently reported metrics showing significant prognostic impact on overall survival, progression-free survival, and locoregional control.[14,15] One of the pioneer studies in this regard was published by Min et al in 1997 and they also found a cutoff SUVmax greater than 9.0 was associated with lower

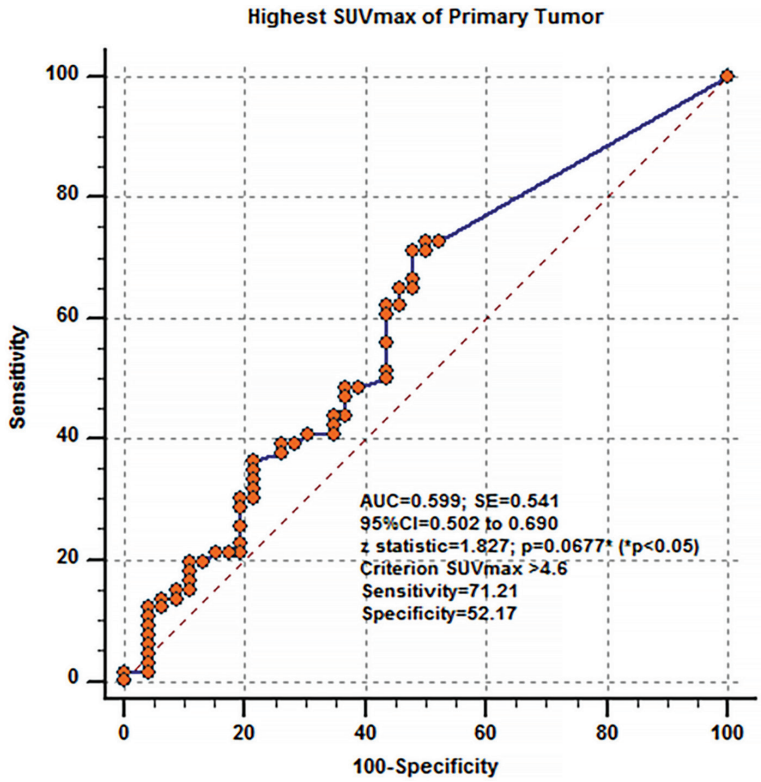

Fig. 2 Receiver operating characteristic analysis of highest SUVmax of primary tumor on baseline ^{18}FDG PET/CT as predictor for disease free and disease recurrence on metabolic response in SCC of head and neck in follow up studies. AUC, area under curve; CI, confidence interval; SE, standard error; SUV, standardized uptake value.

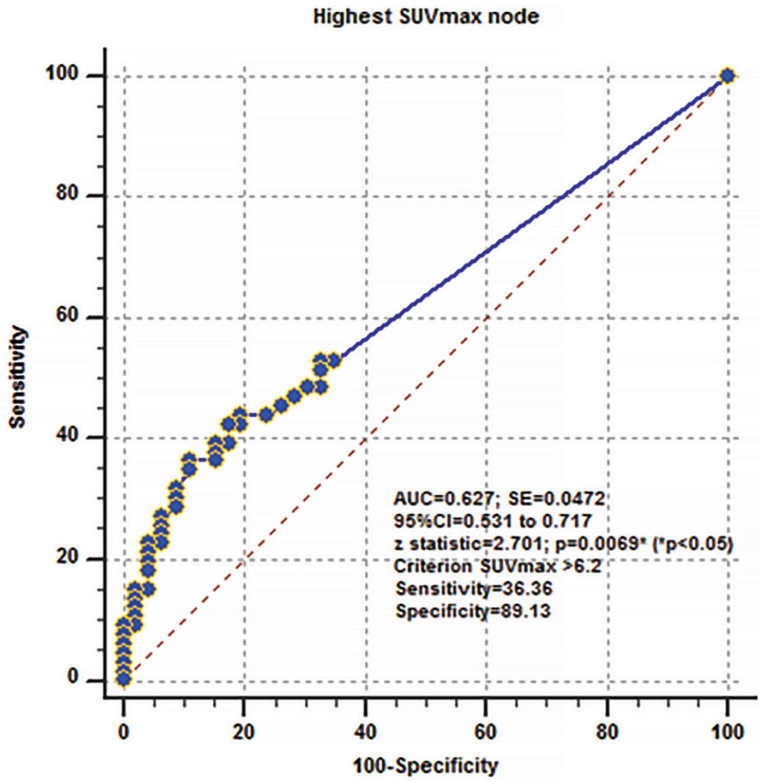

Fig. 3 Receiver operating characteristic analysis of size of SUVmax of the most avid node on baseline ^{18}FDG PET/CT as predictor for disease free and disease recurrence on metabolic response in SCC of head and neck in follow up studies. AUC, area under curve; CI, confidence interval; SE, standard error; SUV, standardized uptake value.

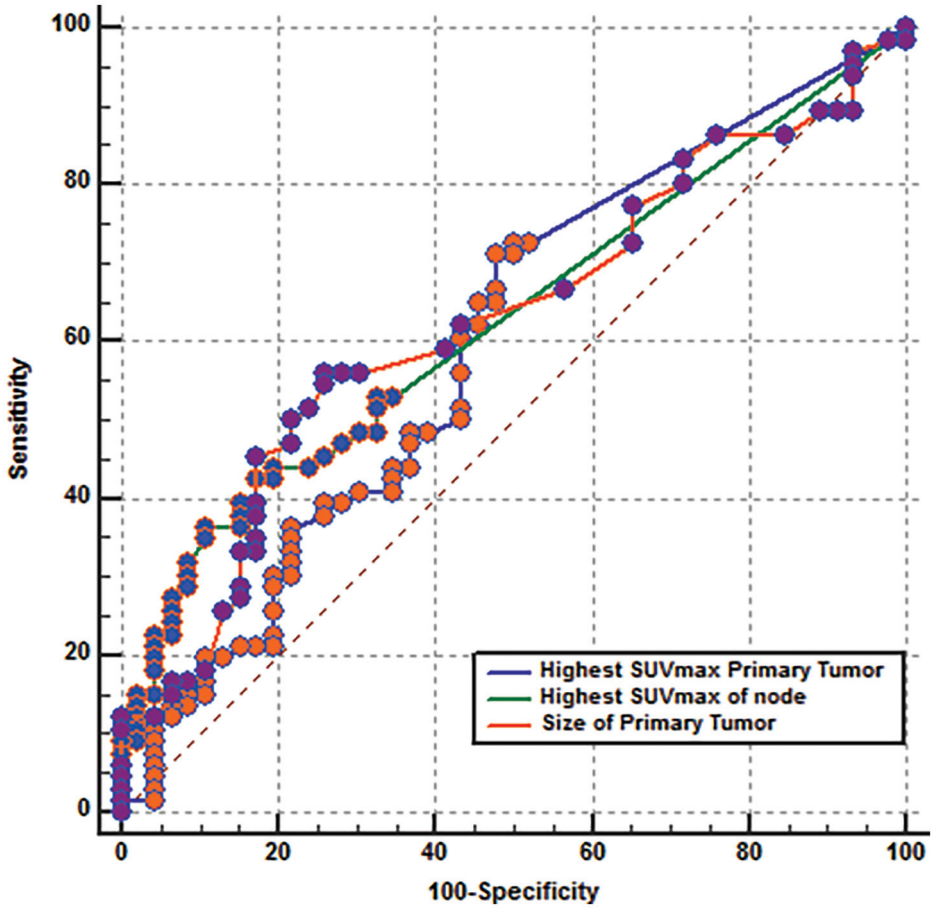

Fig. 4 Comparison of Receiver operating characteristic curves of highest SUVmax of primary tumor, largest tumor size and highest SUVmax of node on baseline ^{18}FDG PET/CT as disease free and disease recurrence on metabolic response in SCC of head and neck in follow up studies. AUC, area under curve; CI, confidence interval; SE, standard error.

3 years DFS (< 24%).[16] The difference between their cutoff value (> 9.0) with current study (> 4.6) might be due to variation in histological tumor grading and/or imaging protocols. Another study reported significantly lower DFS in patients with higher SUVmax of primary HN-SCC.[5] However, a recent study did not find a significant correlation between high ^{18}FDG uptake in the primary tumor and T-site recurrence using same acquisition protocol in a competing risk scenario.[6] The authors suspected that the effect of a high ^{18}FDG uptake may already be accounted for by inclusion of T-stage in their model.[6] We have also found that SUVmax of the most avid neck node at baseline is an independent risk factor for recurrence with a cutoff greater than 6.2. This indicates higher metastatic tumor burden in the involved node and presence of nodal metastasis at baseline reduces long-term survival by 50%.[9] Our data are in concordance with a recent study that reveals that high nodal FDG uptake (SUVmax) increases risk of distant metastasis in patients with HNOP-SCC.[6] They found that model including ^{18}FDG uptake (SUVmax) had a significantly better absolute risk prediction (Brier score) for M-site recurrence compared with the model without SUVmaxN.[6] Another published study revealed that baseline SUVmax of neck node is a poor prognostic marker.[17] However, a recent study from India failed to find a significant influence of baseline SUVmax of node on overall survival or DFS.[18]

Our study also revealed that SUVmax greater than 6.2 of the most avid node was the strongest predictor of early tumor recurrence and the shortest DFS (8.6 months) compared with Ts and SUVmax of primary tumor in baseline ^{18}FDG PET/CT study. This finding is in concordance with a recently published Danish study which also showed that high nodal FDG uptake increases the risk of N- and M-site recurrence in oropharyngeal SCC in a competing risk scenario.[6] We are cognizant that presence of nodal metastasis in HN-SCC reduces the long-term survival by 50%[10] and using a SUVmax greater than 6.4 of the most avid node at baseline ^{18}FDG PET/CT would help the multidisciplinary team to plan treatment strategy accordingly.

Strength of our studies are its prospective design, reasonably good sample size, no significant difference in patients' demographic in disease-free and disease recurrence groups, and strict adherence to standardized ^{18}FDG PET/CT acquisition protocol. Our study has some limitations like we did not describe TNM staging explicitly as we had selected patients with M0-disease only (lenient criterion). We also did not mention p-16 and HPV status as these were available in only few patients. Another limitation is that we did not use other ^{18}FDG PET/CT based metabolic markers (like TLG, MTV) as we

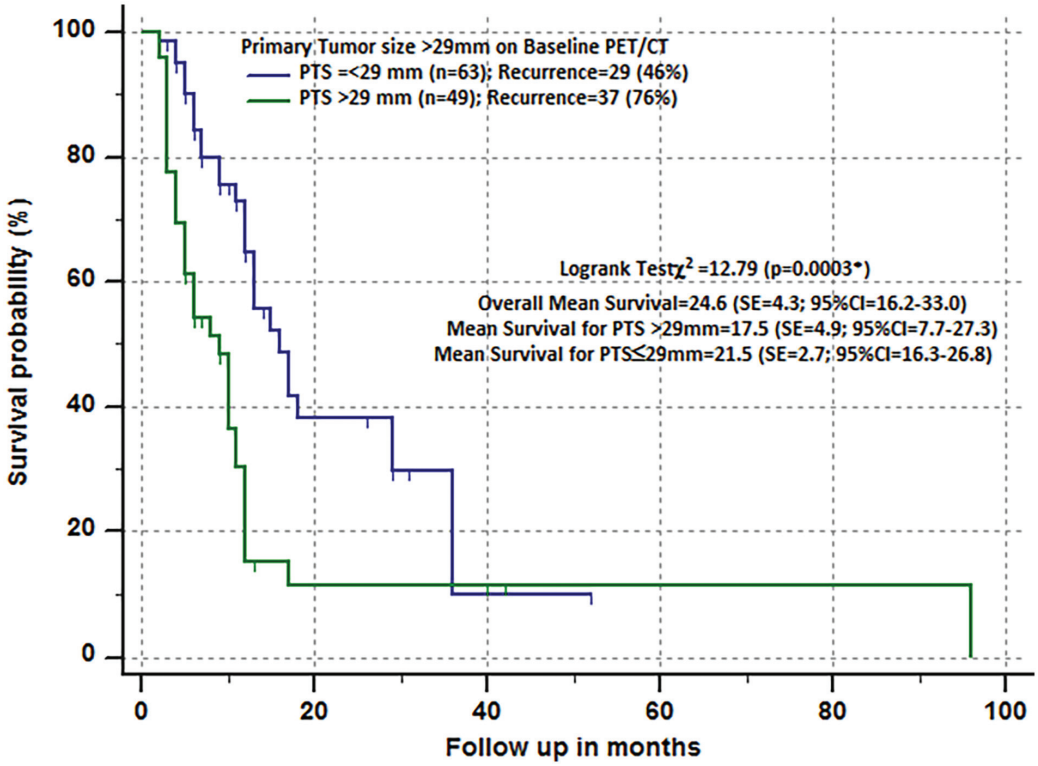

Fig. 5 Comparative analysis for Kaplan Meier Survival plots for primary tumor size $>$ 29 mm and $\leq$ 29 mm in baseline ^{18}FDG PET/CT studies as predictor for recurrence in SCC of head and neck in follow up studies. $^{*}p < 0.05$; CI, confidence interval; PTS, primary tumor size; SE, standard error.

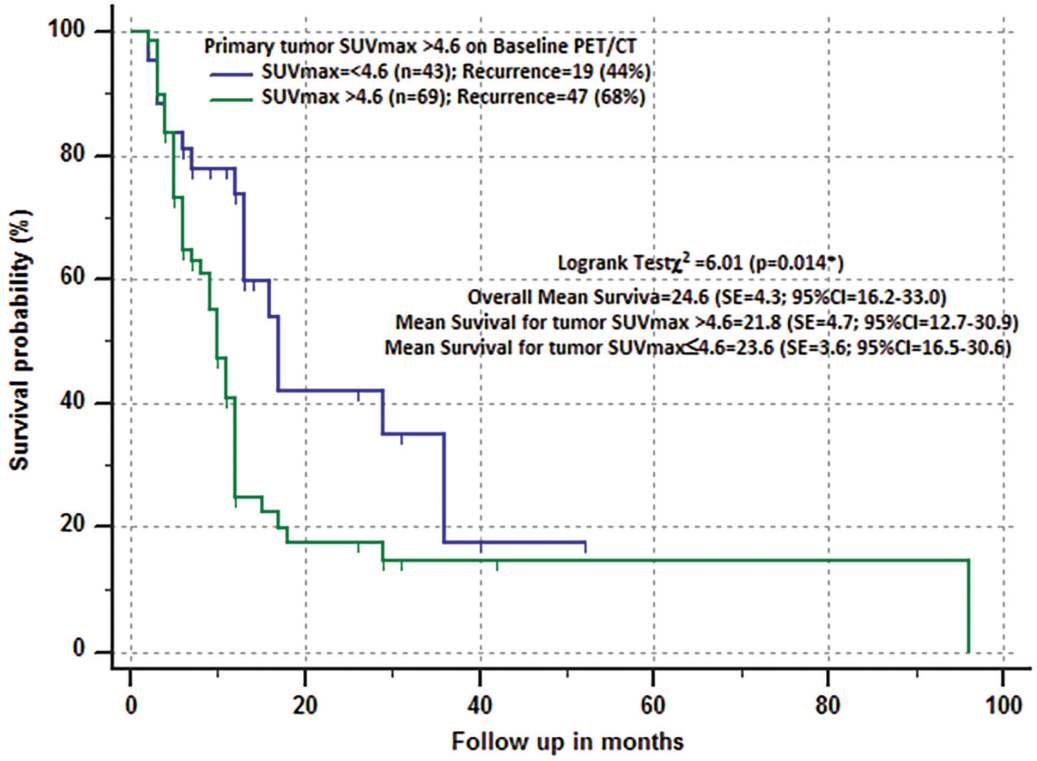

Fig. 6 Comparative analysis for Kaplan Meier Survival plots for primary tumor SUVmax $<$ 4.6 and SUVmax $\leq$ 4.6 in baseline ^{18}FDG PET/CT studies as predictor for recurrence in SCC of head and neck in follow up studies. $^{*}p < 0.05$; CI, confidence interval; SE, standard error.

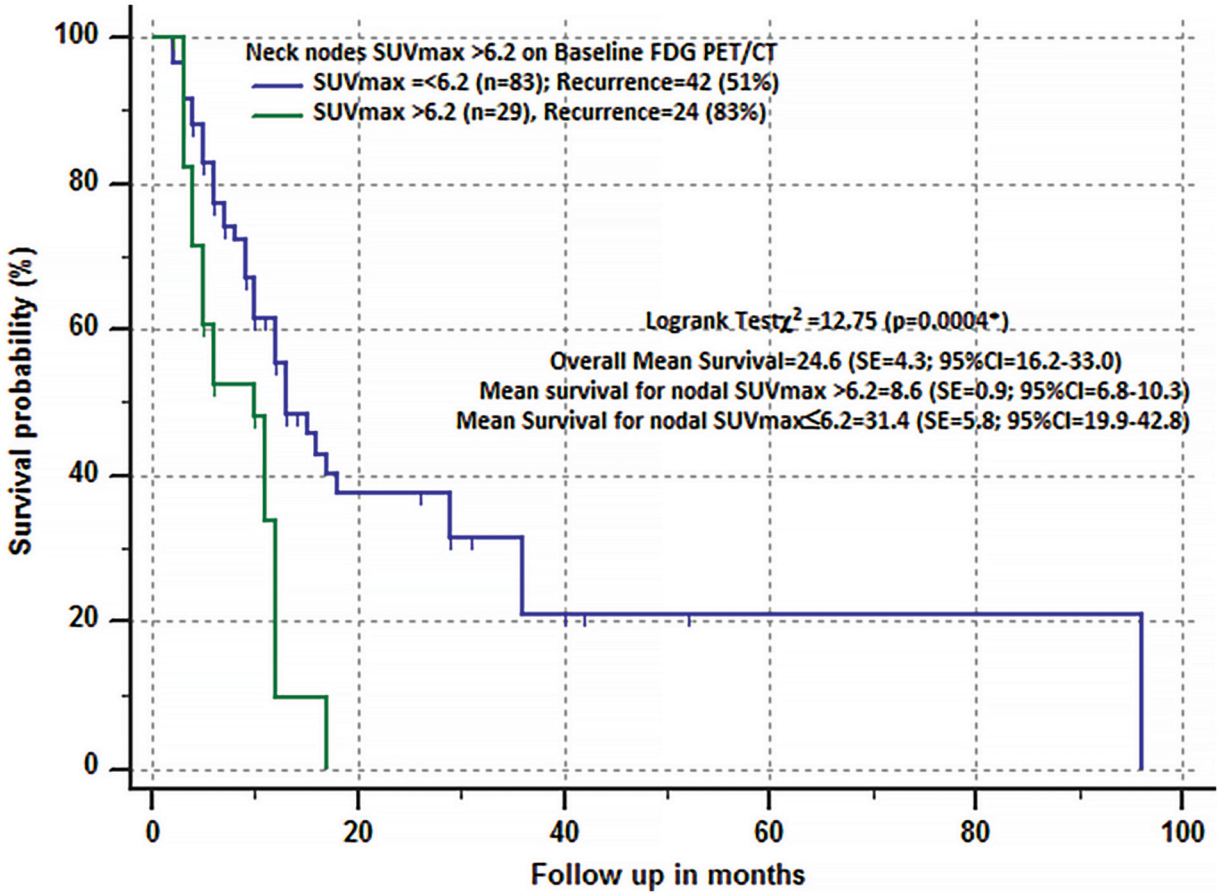

Fig. 7 Comparative analysis for Kaplan Meier Survival plots for nodal SUVmax $>$ 6.2 and SUVmax $\leq$ 6.2 in baseline ^{18}FDG PET/CT studies as predictor for recurrence in SCC of head and neck in follow up studies. $^{*}p < 0.05$; CI, confidence interval; SE, standard error.

know that SUVmax is the most common parameter used worldwide in oncological imaging. Follow-up of our cohort was short, but this is an ongoing study and a subsequent study with larger sample size with longer follow-up will be shared.

We conclude that in HNOP-SCC, primary Ts ($>$ 29 mm), SUVmax of primary tumor ($>$ 4.6), and the most avid neck node ($>$ 6.2) in baseline ^{18}FDG PET/CT using standardized imaging protocol are the independent predictors of disease recurrence. Furthermore, SUVmax greater than 6.2 of the most avid node predicts the shortest DFS than primary Ts and SUVmax of primary tumor.

Conflict of Interest

Authors declared no financial or institutional conflict of interest.

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