Original Article

The Prognostic Role of Maximum Standardized Uptake Value of 18 F-FlouroDeoxy Glucose Positron Emission Tomography-Computed Tomography in Head and Neck Cancer Patients Undergoing Chemoradiotherapy

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ABSTRACT

Aims and Objectives: This retrospective study aims at correlating the pre- and post-therapy maximal standardized uptake values (SUV_{max}) of the whole-body 18-flourodeoxy glucose positron emission tomography (FDG-PET) scan with tumor response in patients with head and neck squamous cell cancer undergoing chemoradiotherapy.

Materials and Methods: Data for this retrospective study were taken from the clinical records of 20 evaluable head and neck cancer patients who had availed treatment and evaluation at our institute during the previous year (March 2017–April 2018). All these above-mentioned patients had undergone chemoradiation at our center for locally advanced squamous cell carcinoma of the head and neck and had undergone pre- and post-therapy whole-body FDG PET scan. The posttherapy PET-computed tomography (CT) was advised after 8 weeks' postcompletion of therapy. During the PET CT scan, images were acquired 1 h after injection of FDG. Pre- and post-therapy SUV_{max} were recorded and correlated with immediate treatment response.

Results: The mean pretherapy SUV_{Max} of the primary tumor was 10.27 ranging from 4.5 to 26.17. The mean pretherapy SUV_{Max} of the node was 5.34 ranging from 0 to 17.9. The mean time of recording the posttherapy SUV_{Max} was 3 months (range 2–5 months). The mean posttherapy SUV_{Max} of the primary tumor was 1.05 ranging from complete metabolic response to 6.4. The mean posttherapy SUV_{Max} of the node was 0.7 ranging from complete metabolic response to 5.43. The statistical analysis based on Wilcoxon–Signed Rank test revealed a statistically significant difference in the pre- and post-therapy SUV_{max} values for both primary tumor ($P < 0.001$) and regional node ($P = 0.001$). Majority of patients ($n = 15$) showed clinical remission; however, five patients had progressive disease at the time of evaluation.

Conclusion: Although the retrospective study revealed that complete responders had a statistically significant reduction in the posttherapy SUV_{max} in comparison

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to the pretherapy SUV_{max} it failed to identify a cutoff value for pretherapy SUV_{max} which could predict the probable outcome of therapy. In view of the same further prospective studies need to be conducted with larger patient numbers including various other tumor metabolic markers for greater clarity.

KEYWORDS: *Chemoradiotherapy, 18-flourodeoxy glucose positron emission tomography, head and neck cancer, squamous cell carcinoma*

INTRODUCTION

*H*ead and neck, squamous cell carcinomas constitute a major cause of cancer-related morbidity in India[1] accounting for nearly 30% of cancer cases in both genders together.[2] Locoregionally, advanced disease stage is commonly encountered in clinical practice,[2] and these patients are offered multimodality therapy. Although concurrent chemoradiation has improved locoregional control of inoperable locally advanced head and neck squamous cell carcinomas,[3] it has its own toxicity both acute and chronic which can negatively impact therapeutic outcome and affect quality of life. In addition, these locally advanced head and neck cancers are also associated with distant metastasis.[4] 18-fluorodeoxyglucose (FDG)-based positron emission tomography (PET) is gaining popularity today in the evaluation of squamous cell cancers of head and neck.[5] Although PET-computed tomography (CT) cannot replace tissue biopsy and the latter is still the gold standard for confirmation of malignancy, the application of PET CT in head and neck cancer staging is slowly but surely increasing.[5] Some of the common applications of FDG-PET CT in head and neck cancers are in the evaluation of secondary neck node with unknown primary, evaluation of recurrent cancers, and evaluation of locally advanced cancers to rule out distant metastasis and second primaries.[5] One of the areas of the current research focus is on the prognostic role of PET CT. There is evidence to state that indicators of FDG metabolism such as maximal and mean standardized uptake value (SUV_{max} and SUV_{mean}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) can predict disease-free survival.[6-8] Therefore, PET and measurements of FDG-related glucose metabolism may have prognostic benefit in these patients. Against this background and since available literature on prognostic evaluation of head and neck cancer using PET-CT in Indian population is sparse, available data in our institute were retrospectively analyzed to assess the prognostic value of PET-CT in locally advanced head and neck cancer patients, who had received concurrent chemoradiation. The study aimed at correlating the SUV_{max} of PET-CT with treatment response.

OBJECTIVES OF THE STUDY

This retrospective study aims at correlating the pre- and post-therapy SUVmax of whole-body FDG-PET scan with tumor response in patients with head and neck squamous cell cancer undergoing chemoradiotherapy (RT).

MATERIALS AND METHODS

Nature of study - This study was a single arm retrospective study which analyzed the data of patients with locally advanced head and neck cancer who had undergone radical chemo-RT as well as pre- and post-therapy whole-body FDG PET CT at our institute.

STUDY DURATION

Data collection and analysis was done in September 2018. Data of patients who received treatment in the 8 months' period between April 2017 (when the institute started PET CT services) and December 2017 were analyzed. The latter endpoint was fixed as the posttherapy PET CT for the patients treated in December 2017 would be done in March 2018 and at the time of data analysis, all patients would have a minimum of 6 months' follow-up data.

The inclusion criteria for the retrospective study were as follows:
a. Patients with locally and regionally advanced head and neck squamous cell carcinomas without visceral metastasis
b. Patients who had received a complete course of concurrent chemoradiotherapy as treatment
c. Patients who had undergone evaluation with pre- and post-therapy ^{18}F FDG PET CT.

The exclusion criteria for the retrospective study were as follows:
a. Patients who had histological presentation other than squamous cell carcinoma
b. Patients who did not receive radical concurrent chemoradiation as treatment (either not fit due to medical comorbid conditions or those who had received primary surgery)
c. Patients who had not undergone pre- and post-therapy FDG PET CT.

DETERMINATION OF SAMPLE SIZE

A total of 76 patients with head and neck cancer received treatment in our institute in the above-mentioned period. Of these patients, 69 patients fulfilled histopathology and stage criteria for inclusion. Of these 69 patients, 21 had undergone primary surgery and were excluded. Of the remaining 48 patients, 13 patients were unfit for

chemotherapy and received radical RT and remaining 35 patients underwent chemoradiation. Of these 35 patients, three patients had discontinued treatment midway through while four patients did not return for evaluation. Of the remaining 28 patients, only 20 had undergone pre- and post-therapy PET CT as a part of the evaluation, and hence, the total number of patients whose data were analyzed in the study was 20.

RANDOMIZATION

The study was a single-arm retrospective study, where only data of patients who received similar investigative and treatment modalities were taken up for evaluation. All patients were aware of the evaluation and treatment modalities to which they were subjected, and there was no control arm included. Hence, randomization or masking was not feasible.

INFORMED CONSENT

Informed consent for RT and chemotherapy treatment and undergoing PET-CT and using their data for subsequent research were taken from each patient. As the study was a retrospective study analyzing data of patients who had already undergone the standard recommended protocol for evaluation and therapy for their disease a Formal Ethical Committee approval was deemed not necessary.

TREATMENT PROTOCOL

All the patients received Platin (Cisplatin/Carboplatin), and Taxol (Paclitaxel/Docetaxel)-based chemotherapy concurrent with intensity-modulated RT. RT was delivered using 6 MV Linear Accelerator Photons. The radiation dose delivered was 66 Gy to gross tumor volume and 54–60 Gy to clinical tumor volume in 1.8 Gy/fraction. All patients received a minimum of three cycles of chemotherapy along with RT.

POSITRON EMISSION TOMOGRAPHY-COMPUTED TOMOGRAPHY PROTOCOL

PET-CT was taken before the commencement of treatment and 8 weeks after completion of treatment. Patients underwent the FDG-PET-CT scan in fasting state with blood glucose level below 180 mg/dl. These patients were administered iv injection of FDG at a dose of 0.22 mCi (8.14 MBq)/kg (10–15 mCi/370–555 MBq) FDG. One hour after, the injection of isotope patients was imaged from vertex to thigh with 120 kV, 50 mA, CT scanner with slice thickness of 3 mm. Immediately after CT, patients were subjected to PET scan (Siemens Biograph Horizon) involving seven to eight-bed positions totally lasting 7 min. After attenuation correction and reconstruction, CT and PET images were fused and evaluated in transaxial, sagittal, and coronal planes.

STATISTICAL ANALYSIS

The pre- and post-treatment SUVmax values of the primary site and nodal disease which were measured as continuous variables were recorded as arithmetic mean for comparison and statistical analysis. The values obtained did not follow normality. As the study involved repeated measurements on a single sample to assess whether their population mean ranks differ Wilcoxon signed-rank test was used for analysis. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) software version 16.0 (IBM, SPSS statistics, USA).

RESULTS

This study was carried out among 20 participants with head and neck cancer, of which the different sites included were nasopharynx ($n = 5$), tongue ($n = 4$), buccal mucosa ($n = 3$), hypopharynx ($n = 3$), oropharynx ($n = 4$), and larynx ($n = 1$) [Figure 1]. The stage and distribution of the site of the tumor are given in Tables 1, 2 and Figures 2, 3 describes respective pre- and post-therapy SUV$_{max}$ values as recorded in the primary tumor site and the involved lymph node. The mean pretreatment SUV$_{Max}$ of the primary tumor was 10.27 ranging from 4.5 to 26.17. The mean pretreatment SUV$_{Max}$ of the node was 5.34 ranging from 0 to 17.9. The mean time of recording the SUV$_{Max}$ from completion of chemoradiotherapy was 3 months (range 2–5 months). The mean posttreatment SUV$_{Max}$ of the primary tumor was 1.05 ranging from complete metabolic response to 6.4. The mean posttreatment SUV$_{Max}$ of the node was 0.7 ranging from complete metabolic response to 5.43. The comparison of pre- and post-treatment values of the primary tumor as given in Figure 2 shows a considerable reduction in the posttreatment SUV$_{max}$ values when compared to pretreatment values, which is consistent across all the tumors. However, in Figure 3, on comparing the pre-and post-treatment SUV$_{max}$ values of the regional nodes, four patients did not show any uptake in the node before and after treatment while 15 patients had lower posttreatment
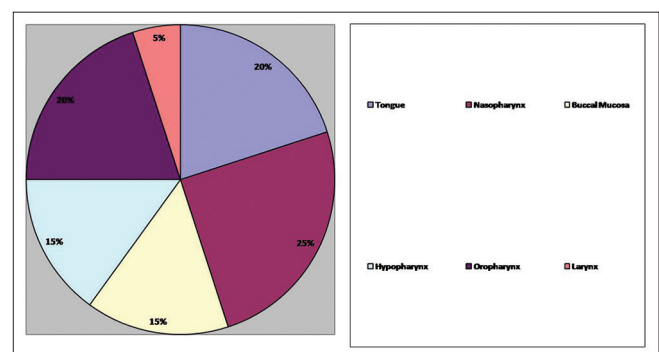

Figure 1: Site of the tumor among the study participants

uptake values and one patient showed increase in the posttreatment uptake value. The statistical analysis based on Wilcoxon signed-rank test revealed a statistically significant difference in the pre- and post-treatment SUV$_{max}$ values for both primary tumor ($P < 0.001$) and regional node ($P = 0.001$) [Table 3]. All patients underwent clinical examination at the time of posttherapy PET CT, and majority of patients ($n = 15$) were found to be in clinical remission while the remaining five patients had residual disease. Figures 4 and 5 depict the pre and post treatment PET CT images of two patients with oro pharyngeal disease who attained complete response.

DISCUSSION

^{18}F-FDG PET-CT has an important role to play in staging, treatment planning and follow-up evaluation of locally advanced head and neck squamous cell carcinomas.[9] Although its application in the evaluation of head and neck cancers suffers from some inherent limitations such as false positivity in inflammatory conditions and physiological uptake[9] it is considered as the gold standard in detecting second primaries and ruling out recurrence by virtue of its high negative predictive value.[8,9] In addition, PET-CT facilitates
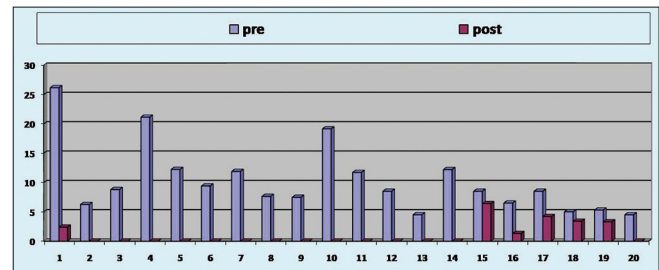
Table 1: Stage and tumor characteristics of study participants

Primary tumour	Stage
Nasopharynx	T4N0M0
Anterior tongue	T4 N1M0
Hypopharynx	T2N3M0
Oropharynx	T2 N2c M0
Nasopharynx	T2N2b M0
Nasopharynx	T3 N2c M0
Nasopharynx	T2N2cM0
Hypopharynx	T3N0 M0
Anterior tongue	T4 N2b M0
Oropharynx	T2 N3 M0
Oropharynx	T2 N2b M0
Oropharynx	T2N2bM0
Larynx	T3N1M0
Hypopharynx	T2N2cM0
Buccal mucosa	T3 N1M0
Buccal mucosa	T2 N2b M0
Tongue	T4 N2a M0
Buccal mucosa	T4b N0 M0
Tongue	T4 N0M0
Nasopharynx	T3N2cM0

Figure 2: Comparison of pre- and post-treatment values of the primary tumor

Table 2: Pre- and post-treatment maximal standardized uptake value values of the study participants

Primary tumour	Pretreatment SUV$_{max}$		Posttreatment SUV$_{max}$		Disease status at 6 months
	Primary	Node	Primary	Node	
Nasopharynx	26.17	Nil	2.39	Nil	CR
Anterior tongue	6.24	3.02	CMR	CMR	CR
Hypopharynx	8.8	1.5	CMR+AZ	CMR	CR
Oropharynx	21.14	17.9	CMR	2	CR
Nasopharynx	12.23	12.78	CMR	2.11	CR
Nasopharynx	9.4	6.2	CMR	CMR	CR
Nasopharynx	11.89	3.75	CMR	2.43	Progressive disease
Hypopharynx	7.63	Nil	CMR	Nil	CR
Anterior tongue	7.47	Nil	CMR	Nil	CR
Oropharynx	19.14	16.69	CMR	CMR	CR
Oropharynx	11.71	12.91	CMR	CMR	CR
Oropharynx	8.5	9.9	CMR	CMR	CR
Larynx	4.5	2.1	CMR	CMR	CR
Hypopharynx	12.2	4.5	CMR	1.4	CR
Cheek	8.5	4.6	6.4	2.4	Progressive disease
Cheek	6.5	3.4	1.3	CMR	CR
Tongue	8.5	3.6	4.2	1.3	Progressive disease
Cheek	5	Nil	3.4	Nil	Progressive disease
Tongue	5.3	2.3	3.3	CMR	Progressive disease
Nasopharynx	4.5	2.7	CMR	CMR	CR

CMR=Complete metabolic response, CR=Clinical remission, SUV$_{max}$=Maximal standardized uptake value
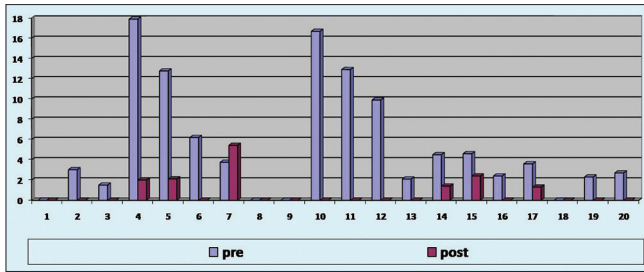
Figure 3: Comparison of pre- and post-treatment values of the node

Table 3: Comparison of pre- treatment and post-treatment Maximal standardized uptake value values using Wilcoxon-Signed rank test

	Median (IQR)		P
	Pretreatment	**Posttreatment**	
Tumor	8.5	0.0	<0.001
	6.30	0.00	
	8.50	0.00	
	12.12	2.11	
Node	4.12	0.00	= 0.001
	2.47	0.00	
	4.12	0.00	
	12.06	1.85	

IQR=Inter quartile range

guided biopsy with a sensitivity of 88% and specificity of 78%.[9] Modern research is directed toward improving the prognostic potential of FDG PET in head and neck cancers particularly in analyzing the response to treatment and predicting treatment outcome. Numerous indicators of FDG metabolism such as SUV$_{max}$ and SUV$_{mean}$, MTV and TLG are estimated in clinical practice.[8]

Among these parameters, SUV which is a measure of the radioactivity in a tumor or lesion is most commonly used as an indicator of tumor metabolism.[8] The SUV is defined as the ratio of radioactivity concentration measured in tissue and the injected activity divided by the body weight.[9] Although studies have high shown poorer treatment outcomes with higher FDG uptake and thereby higher pretreatment SUV values[10,11] the benefit of SUV as a predictor of treatment response and survival has not been categorically established as on date.[9] SUV of the tumor or node is measured in two ways namely SUVmax and SUVmean. SUVmax reflects the highest voxel value within the volume of interest, and it is the most widely used parameter to measure metabolic tumor activity in oncologic FDG-PET/CT imaging.[9] Zhang *et al.*[12] in his meta-analysis of 7 studies involving 674 head and neck cancer patients identified poorer survival in patients with higher SUVmax values at primary tumor sites. On the contrary, there are other studies which claim that the SUVmax at the nodal site[13] and in particular the distal node[14]

is the main prognostic marker. In addition, there is no consensus on the probable cutoff value for SUVmax above which a poorer outcome is associated with values ranging from 7 to 13 being described.[9]

Against this background, keeping in mind the fact that literature on the prognostic benefit of PETCT in Indian population is sparse, available data in our institute were retrospectively analyzed to assess the prognostic benefit if any of ^{18}F FDG PET CT in locally advanced squamous cell carcinoma head and neck cancer patients, who had received concurrent chemoradiation. In our study, we recorded the pre- and post-treatment SUVmax at the primary and nodal sites of disease for all patients. In addition, at the time of posttherapy PET-CT patients also underwent clinical evaluation of response. The clinical response was then correlated with the pretreatment SUVmax at tumor and nodal sites to analyze whether these values had any bearing on outcome and if possible to identify a possible cutoff value of SUVmax which would predict treatment response.

In comparison to the pretreatment SUV$_{max,}$ the present study demonstrated a significant reduction in the posttreatment SUV$_{max}$ values at both primary tumor and nodal sites for most patients. A total of 14 patients (70%) had a complete metabolic response (CMR) at the primary tumor site which was confirmed by clinical evaluation. Among these 14 patients, 9 patients (45%) had a (CMR) at the nodal site, while 3 patients (15%) had N0 disease in both scans while in the remaining 2 patients (10%) a 60% reduction in posttherapy SUVmax at nodal site on comparison with pretherapy SUVmax node value. One patient with nasopharyngeal cancer with N0 disease had a 90% reduction in posttherapy SUVmax at the primary site and was found to have a complete clinical response. All these 15 patients (75%) were found to be in remission at 6 months of follow-up. Five patients (25%) had residual disease on clinical examination of which 4 patients (20%) had a posttherapy SUVmax primary tumor value ≥50% of pretherapy value while one patient had a posttherapy SUVmax nodal site value ≥50% of pretherapy value. All these five patients had progressive disease local and distal at 6 months' follow-up.

In our study, the mean and median pretreatment SUV$_{Max}$ of the primary tumor was 10.27 and 8,5, respectively with values ranging from 4.5 to 26.17. The mean and median pretreatment SUV$_{Max}$ of the nodal site was 5.34 and 4.12, respectively, ranging from 0 to 17.9. Unlike other studies which have correlated poorer outcomes with higher pretreatment SUVmax values, our patients with high pretreatment SUVmax at primary and nodal sites did not have an adverse outcome. These findings are in concordance with the study by Moeller *et al.*[15]
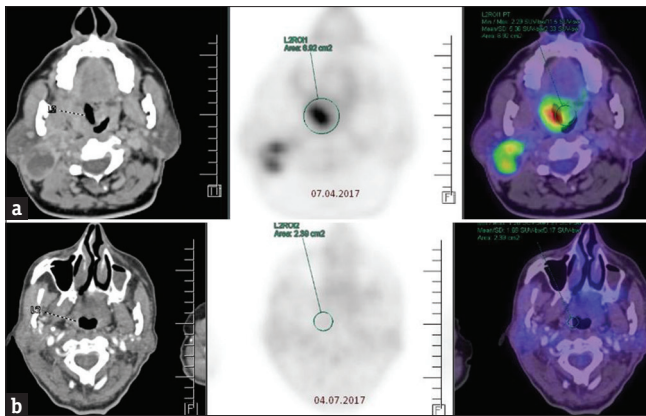
Figure 4: (a) Pretherapy 18 F-flouradeoxy glucose positron emission tomography-computed tomography showing metabolically active lesion in soft palate with right cervical node. (b) Posttherapy 18 F-flourodeoxy glucose positron emission tomography-computed tomography showing complete metabolic response at primary and nodal site

who showed that a significant association was not found between pretreatment SUVmax and prognosis. On the contrary in our study, higher posttreatment SUVmax values at the primary and nodal site (posttherapy SUVmax value ≥50% of pretherapy value) was found to be associated with higher relapse rates. Our study shows that a single arbitrary value of SUVmax measured before treatment may not predict the extent of treatment-related metabolic change, but it is the serial change in the SUVmax before and after treatment which can predict response and survival. The results of our study were found to be statistically significant.

Support for the findings of our study can be drawn from the study by Matoba[16] *et al.* who analyzed both pre- and post-therapy PET CT in 40 head and neck cancer patients undergoing chemoradiation and found the posttherapy SUVmax value at 3 months' posttherapy to be a stronger indicator of relapse and progressive disease than the pretreatment value. In addition, Kikuchi *et al.*[17] in their study on nasopharyngeal cancer patients undergoing neoadjuvant chemotherapy also showed that a reduction in posttherapy SUVmax (>50%) predicted better outcome while Hentschel *et al.*[18] showed similar findings in head and neck cancer patients on chemoradiation who underwent serial weekly PET CT during the first 2 weeks of therapy.

Apart from the research work on the prognostic potential of pre- and post-therapy SUV max, research work in head and neck PET CT is also focusing on other markers of tumor metabolism in PET CT such as MTV and TLG.[19] In addition, the benefit of PET/magnetic resonance imaging fusion and its prognostic potential is also being explored.[20]
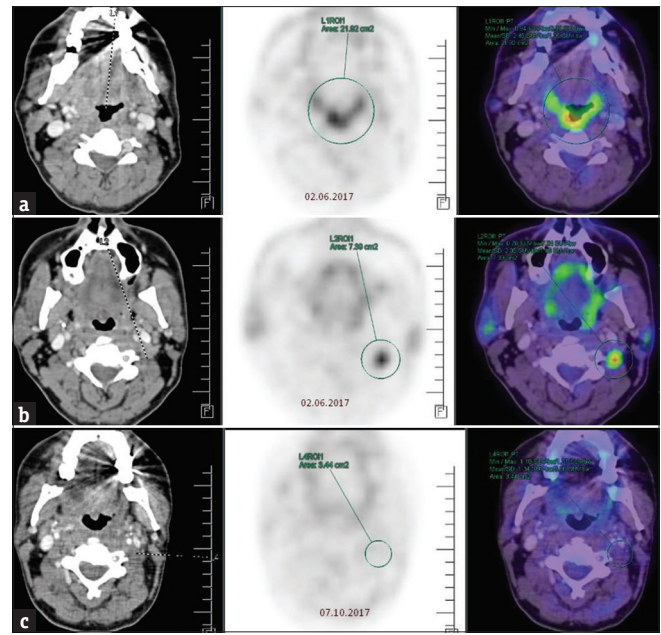

Figure 5: (a) Pretherapy 18 F-flourodeoxy glucose positron emission tomography-computed tomography showing metabolically active lesion in posterior pharyngeal wall of oropharynx (b) Pretherapy scan showing uptake in left level V cervical node. (c) Posttherapy 18 F-flourodeoxy glucose positron emission tomography-computed tomography scan showing complete resolution of disease

CONCLUSION

The retrospective study reveals that higher values of the posttherapy SUV$_{max}$ and smaller reductions in the value of posttherapy SUV$_{max}$ correlated with higher risk of relapse in head and neck cancer patients undergoing concurrent chemoradiation, and that high pretherapy SUV$_{max}$ values alone could not be taken as a prognostic tool. However, our study had its own inherent flaws in that it was retrospective in nature with limited data and included various head and neck subsites. In addition, the HPV and EBV status of patients particularly with oropharyngeal and nasopharyngeal sites of involvement was not analyzed the positivity of which could have favorably influenced the chemoradiation response thereby leading to bias. Furthermore, the follow-up period was short at 6 months, and hence, these survival values might have changed with longer periods of follow-up. Thus, the need of the hour is to conduct a prospective randomized study on head and neck cancer patients which would be subsite-specific with statistically powered number of participants with serial FDG PET CT done pre and post therapy for a minimum duration of 2 years' follow-up. Such a study might shed more conclusive proof on the findings of this study as well as change the treatment dynamics of head and neck squamous cell carcinoma in the near future.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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