Original Article

Should fluorodeoxyglucose positron emission tomography/computed tomography be the first-line imaging investigation for restaging the laryngeal carcinoma patients?

ABSTRACT

Posttreatment detection of residual/recurrence disease in the head and neck cancers is not an easy task. Treatment induces changes create difficulties in diagnosis on conventional imaging (computed tomography [CT], magnetic resonance imaging) as well as macroscopic inspection (direct laryngoscopy). Hence, we evaluate the diagnostic performance of contract-enhanced F-18 fluorodeoxyglucose positron emission tomography (FDG PET)/CT in restaging of laryngeal carcinoma Postchemotherapy-surgery and/or radiation therapy. We retrospectively analyzed patients of carcinoma larynx (n = 100) who has completed treatment and were referred for FDG PET/CT. Two reviewers performed image analysis to determine recurrence at primary site and/lymph nodes and distant metastases. Receiver operating characteristic (ROC) was used to determine the maximum standardized uptake value (SUV_{max}) cut off for disease detection. Histopathological examination and clinical or imaging follow-up were taken as gold standard for recurrence. One hundred laryngeal carcinoma patients with mean age of 57.2 years (range of 40–76) were included in the present study. Among the 100 patients, 96 were male and remaining 4 were female. The average interval between completion of treatment and FDG PET/CT scan was 8.5 months (minimum 6 months). Of the 100 patients, FDG PET/CT detected FDG avid lesions in 66 patients. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of FDG PET/CT for residual/recurrence disease detection was 90.3%, 73.7%, 84.8%, 82.3%, and 84.0%, respectively ($P < 0.05$). In addition, in 10 patients, metachronous primaries were detected (lung-4, thyroid-2, tongue, colon, esophagus, and lymphoma-one each). On ROC curve analysis, SUVmax >6.1 had sensitivity and specificity of 80.6% and 94.7% respectively for detection of recurrent/metastatic disease. FDG PET/CT demonstrates high diagnostic accuracy for detection of residual/recurrent disease in treated laryngeal cancer patients and our findings suggest that this imaging modality should be the first-line diagnostic investigation in this cohort of patients.

Keywords: Fluorodeoxyglucose positron emission tomography/contrast-enhanced computed tomography, laryngeal carcinoma, metabolic biopsy, metachronous second primary, receiver operating characteristic analysis

INTRODUCTION

The larynx is an anatomically complex organ involved in respiration and phonation. The most common tumor of the larynx (~90%) is squamous cell carcinoma (SCC).[1] Laryngeal cancers are usually managed with radiotherapy, surgery or chemotherapy, alone or in combination. No specific serum tumor markers are available for the assessment of disease in patients with laryngeal carcinoma.[2] Clinical assessment

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and imaging are the only currently available options for assessment of residual/recurrent disease. Contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) are conventionally used for detection of disease recurrence with/without direct laryngoscopy. The diagnosis of residual/recurrence disease is not an easy task because post treatment sequelae in the form of significant anatomic distortion, scarring, inflammation, fibrosis, edema, thickening, and abnormal enhancement in the laryngeal tissues which make the diagnosis difficult on conventional imaging methods (computed tomography [CT], MRI) or also macroscopic inspection (via direst Laryngoscopy). F-18 fluorodeoxyglucose positron emission tomography (FDG PET) has been utilized for the purpose of distinguishing benign versus malignant tumors and to assess the changes/recurrence after treatment.[3]

F-18 FDG PET/CECT might be superior to CECT and MRI for restaging patients with laryngeal carcinoma.[4] Currently, limited numbers of publications exist regarding the utility of F-18 FDG PET/CT in isolated laryngeal carcinoma, mostly in small patient groups showing conflicting results.[5,6] Further evidence pertaining to the usefulness of F-18 FDG PET/CT in laryngeal carcinoma is needed. The aim of the present study is to access the diagnostic performance of FDG PET/CT as a first-line diagnostic investigation in treated laryngeal cancer patients.

MATERIALS AND METHODS

We retrospectively analyzed data of patients with larynx cancer, who underwent F-18 FDG PET/CT for suspected recurrence between May 2017 and September 2019 at Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India.

Inclusion criteria

- Histopathological confirmed laryngeal carcinoma
- Previous treatment by radiotherapy, chemotherapy, or surgery alone/in combination. Restaging PET/CT done for suspected recurrent disease based on the findings of clinical examination/conventional anatomical imaging or for posttreatment assessment. The definite reference standard was in the form of either histopathology or minimum 6 months of clinical/imaging follow-up after PET/CT
- A minimum gap between treatment and FDG PET/CT of at least 8 weeks.

The patients were excluded if patients had no previous treatment, nonavailability of a definite reference standard and FDG PET/CT performed within 8 weeks after definite treatment

A total of 134 histopathologically proven and treated cases of carcinoma larynx underwent F-18 FDG PET/CT examination. Out of 134 patients, 34 were ineligible or lost to follow-up during the post imaging period. A total of 100 patients were included in the study. In view of the retrospective study design, written informed consent was waived. This retrospective study was approved by institutional ethical committee.

F-18 fluorodeoxyglucose positron emission tomography/computed tomography acquisition

All the patients underwent F-18 FDG PET/CT examination after fasting for minimum of 6 h, had blood glucose levels 140 mg/dl (7.8 m mol/dl), did not do strenuous activity or exercise on or before day of examination.

After intravenous injection of 370MBq (10 mCi) of F-18 FDG, the patients rested in a quiet room. PET/CT imaging was performed 45–60 min later as recommended by Wahl *et al*.[7] PET/CT acquisition was performed on dedicated hybrid scanners (Discovery IQ 16; GE healthcare, Milwaukee). A low dose scout scan (120 kV, 10 mA) was acquired from head to mid-thigh region. Iodinated intravascular contrast was used in all patients. CECT of patient from head to mid of thigh in craniocaudal orientation were acquired. Venous phase CT from head to mid-thigh was acquired 55 s after beginning of intravenous injection of contrast media. Following CT acquisition, three-dimensional (3D)-PET acquisition was done in caudocranial direction with acquisition time of 2–3 min per bed position. The reconstructed attenuation-corrected PET images, CT images and fused PET/CT images were available for review in three orthogonal planes (axial, coronal, and sagittal) along with maximum intensity projection image and 3D cine mode.

Image analysis

The PET-CT images were evaluated by two experienced nuclear medicine physicians independently with more than 9 year's' experience in PET-CT and who were unaware of clinical/imaging findings at the time of review. Any focal nonphysiological FDG uptake with anatomical abnormal findings in CECT was considered positive except small subcentimetric lung lesions with characteristic CT findings for metastasis were considered positive even in the absence of focal tracer uptake. Based on this, PET/CT studies were interpreted as either positive or negative for disease. The abnormal findings on PET/CT were categorized into local disease, regional, and distant metastasis. Maximum standardized uptake value (SUVmax) was used for the purpose of semi-quantitative analysis. This

SUV measurement was carried out using the default body weight (SUV = mean region of interest activity [MBq g-] injected dose [MBq]/body weight [g]).

Possibility of second primary neoplasm was also reported in few cases. Reference standard in such cases was second neoplasm established by histology and each neoplasm being geographically separate and distinct. In the absence of definitive histological differences for both tumors, a second primary should be separate by >2 cm with the normal epithelium from the known laryngeal carcinoma.

Reference standard

The combination of clinical or imaging findings (contrast CT, follow-up PET/CT, and MRI) and/or histopathology (if available) was employed as the reference standard for validation of PET-CT findings. The minimum follow-up duration was 6 months (median 18.6 months; range 6–26 months). Lesions on FDG PET/CECT were considered as true positive (TP) when follow-up imaging, with and without treatment, showed increased in size and/or showed increased F-18 FDG uptake and/or after treatment PET/CECT positive lesion showed decrease in size. Deterioration of clinical condition or death on follow-up related to the disease was considered positive for the presence of disease. Lesions that did not show any change in size or showed decrease in size F-18 FDG uptake on follow-up or clinically improved without any intervening therapy were classified as false positive (FP). Histopathology was gold standard when available.

Statistical analysis

(IBM SPSS, Turkey) programme was used for all statistical analysis. Mean and standard deviation was used to present continuous quantitative data. Numerals and percentage were used to present categorical data. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated with 95% confidence interval for F18 FDG PET-CT on a per study basis. Continuous variables were compared among groups using Mann–Whitney test with two-tail probability. For comparison of proportions, Chi-square test was used. The relationship between SUV_{max} and reference standard was assessed by Pearson correlation coefficient. Receiver operating characteristic (ROC) curve analysis of significant parameters was performed to calculate the area under the curve (AUC) values with sensitivity and specificity determined using Youden's index as the cut off point. A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 100 carcinoma larynx patients with mean age of 57.2 years (range of 40–76) were included in the present study. All patients had histopathological diagnosis of SCC of larynx based on biopsy or postsurgery examination. All the patients had undergone treatment by surgery, chemotherapy, and radiotherapy alone or in combination. The demographic and clinical characteristics of all patients are shown in Table 1.

On the basis of the reference standard, after a median follow-up of 18.6 months, 62/100 (62%) patients were positive and rest 38/100 (38%) patients were negative for recurrent/residual disease. A diagnosis was established with histopathology/fine needle aspiration cytology in 38 patients (40 lesions). Since pathological confirmation of all lesions was not technically or ethically feasible, the diagnosis was established with clinical/imaging follow-up for the remaining 72 patients. The follow-up imaging included contrast-enhanced CT ($n = 46$), ultrasound ($n = 12$), MRI ($n = 28$), bone scan ($n = 12$), and repeat PET/CECT ($n = 42$). A combination of these was available in many patients. In follow-up PET/contrast-enhanced CT ($n = 42$) imaging, we used the CECT part as an imaging reference standard.

F-18 fluorodeoxyglucose positron emission tomography/computed tomography results

F-18 FDG PET/CT was interpreted as positive for recurrence/residual disease in 66/100 (66.0%) and negative

Table 1: Patient characteristics

Parameter	Patients Number (%)
Number of patients	100
Age (years)	
Mean	57.2
Range	40-76
Sex	
Male	96
Female	4
Risk factors	
Smoker	84
Alcohol	78
Others	4
Indication of PET/CT	
Clinical suspicion of disease recurrence	20
Radiological suspicion of disease recurrence	36
Post treatment surveillance	44
Treatment (%)	
Surgery only	6/100 (6)
Chemotherapy only	2/100 (2)
Radiotherapy only	52/100 (52)
Surgery and radiotherapy	10/100 (10)
Surgery and chemotherapy	0/100 (0)
Radiotherapy and chemotherapy	24/100 (24)
Surgery, chemotherapy and radiotherapy	6/100 (6)

in 34/100 (34%) patients [Table 2]. When compared with the reference standard, PET/CT was TP in 56 [Figure 1a-g], true negative in 28 [Figure 2a-g], FP in 10 and false negative (FN) in six patients. Sensitivity, specificity, PPV, and NPV of F-18 FDG PET/CT for detection of residual/recurrent disease was 90.3%, 73.7%, 84.8%, and 82.3% respectively with diagnostic accuracy 84.0% [Table 3].

Patient and lesion based analysis

F-18 FDG PET/CT detected abnormal FDG uptake in 66 patients. Uptake at the primary site was detected in 56/66 (85%) patients with eight of them having uptake in the regional lymph nodes and eighteen in distant lesions. Ten (10/100, 10%) patients had only metastatic disease. The primary lesions in these 56 patients were distributed in supra-glottic, glottis, and infra-glottic areas in 48, 34, and 10 patients respectively (few patients showing involvement of more than one of these sites). These patients with primary disease has additional local infiltration in the form of muscle, cartilage or bony involvement in eight patients, vocal cord involvement in eighteen patients, epiglottis involvement in 20 patients and tracheostomy site involvement or fistula formation in twenty patients (either in isolation or combination).

Table 2: F-18 fluorodeoxyglucose positron emission tomography/computed tomography findings

Parameter	Patients number (%)
FDG PET/CT	
Positive for malignancy	66/100 (66)
Negative for malignancy	34/100 (34)
Distribution of recurrent disease (n=66)	
Only primary site	30/66 (45)
Primary + lymph node sites	8/66 (12)
Primary + distant metastasis	18/66 (27)
Only localized lymphnodes	0/66 (0)
Only distant metastasis	10/66 (15)
Additional findings (related to local recurrence)	
Adjacent muscles and bone invasion	8
Vocal cord involvement	18
Epiglottic involvement	20
Tracheostomy site involvement or fistula formation	20
Additional metachronous second malignancy detection	
Lung	4
Thyroid	2
Others (tongue, colon, esophagus and lymphoma)	4 (1 each)

FDG PET: F-18 Fluorodeoxyglucose positron emission tomography, CT: Computed tomography

Table 3: Analysis of F-18 fluorodeoxyglucose positron emission tomography/computed tomography results

Parameter	Results (CI)
Sensitivity (%)	90.32 (74.25-97.96)
Specificity (%)	73.68 (48.80-90.85)
PPV (%)	84.85 (68.10-94.89)
NPV (%)	82.35 (56.57-96.20)
Diagnostic accuracy (%)	84

CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

On lesion-based analyses, 28 (28%) patients has evidence of distant metastases-lymph nodes, lung, liver, skeleton, and brain metastases were present in 10, 6, 6, 2 and 4 patients respectively. In addition, 16 patients had FDG PET/CT findings suspicious for second primary and 10 of these patients were detected to have metachronous second primaries with histopathology confirmation (lung-4 [Figure 3], thyroid-2, tongue, colon, esophagus, and lymphoma-one each). The imaging interpretation or suspicion for second metachronous primary was based on abnormal pattern of the disease presentation was unlikely to be metastatic disease. The second primary in lung cancers was SCC in two patients, small cell lung cancer (SCLC), and undifferentiated non-SCLC in one patient each. All suspected second primary cancers were detected more than 6 months after laryngeal carcinoma was diagnosed.

Ten patients with 14 suspicious lesions had FP results including 8 lesions at primary site and two lesions in lung and four lesions in cervical lymph nodes, which were later found to be benign lesions. Six of these eight lesions at primary site were found to be residual posttherapy inflammation by histopathology (n = 2) and follow-up (n = 4). The remaining two lesions at primary sites were tubercular and fungal infection in etiology on biopsy and follow-up. The lung lesions and cervical lymph nodes disappeared on follow-up CT without any treatment and were interpreted as nonspecific inflammation.

Six patients had FN PET/CT results in the present study, of which two had had small residual tumor at primary site and two had non FDG avid subcentimetric lung nodule (largest dimension in lung window ~5 mm) and one had non FDG avid subcentimetric cervical lymph node and one had non FDG avid mediastinal lymph node. All of the FN lesions were confirmed either on histopathology and clinical follow-up. These lung findings are not unusual or uncommon in countries where tuberculosis and smoking-related lung injury/infection are endemic.

In the present study, over the conventional and macroscopic (laryngoscope) methods, PET-CT has changed the management in 32 patients (32%). Of these 32 patients, 12 for primary site characteristic, 10 for distant metastasis

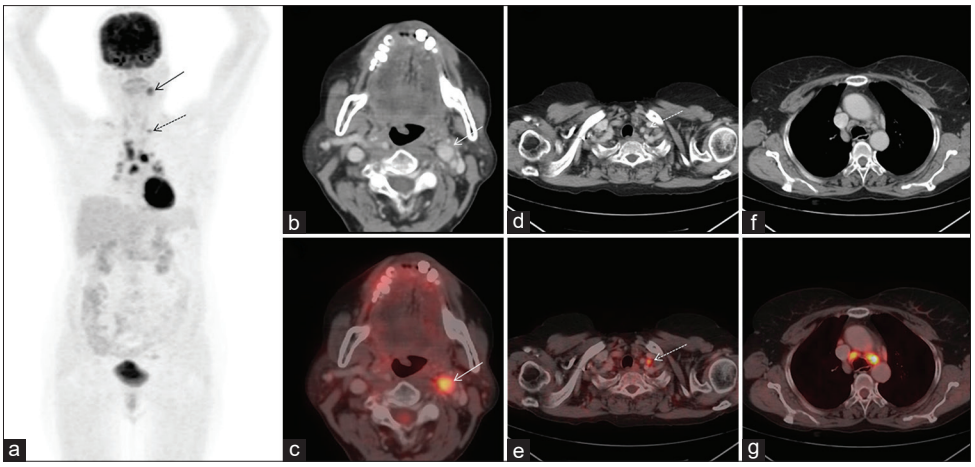

Figure 1: A 48-year-old female with squamous cell carcinoma of left pyriform sinus underwent concurrent chemoradiotherapy. She presented with clinical palpable left sided neck swelling after 6 months. 18F fluorodeoxyglucose positron emission tomography/computed tomography was done due to suspicion of disease recurrence. Positron emission tomography maximum intensity projection image (a) reveals focal areas of increased fluorodeoxyglucose uptake in left cervical and mediastinal regions. Transaxial computed tomography and positron emission tomography/computed tomography images revealed fluorodeoxyglucose avid left level II cervical (maximum standardized uptake value 5.9, arrow b and c), left supraclavicular (maximum standardized uptake value 4.3, arrow d and e) and mediastinal lymphnodes (f and g) indicating nodal metastases. Fine needle aspiration cytology from left cervical lymph node revealed metastatic squamous cell carcinoma

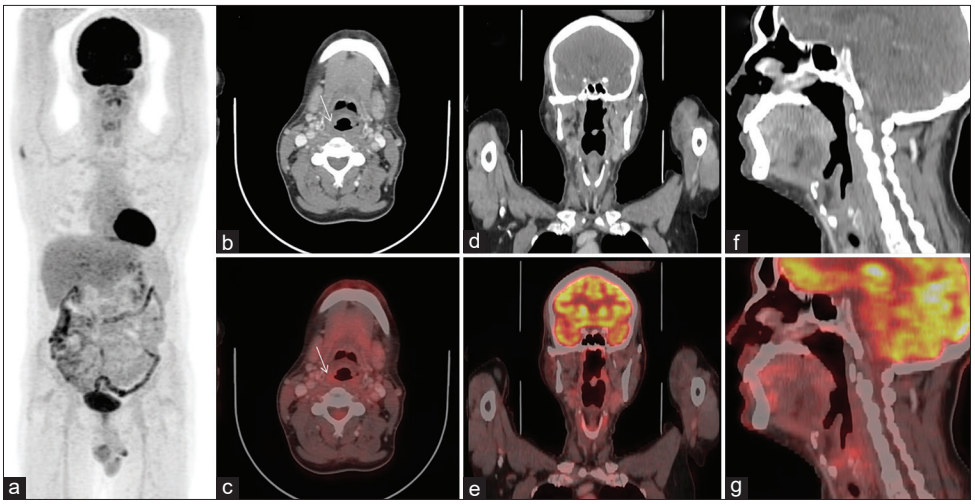

Figure 2: A 45-year-old male diagnosed with squamous cell carcinoma of supraglottic larynx underwent concurrent chemoradiotherapy. Posttreatment CECT of head-neck region were suspicious for residual disease. fluorodeoxyglucose positron emission tomography/computed tomography was done for further evaluation. PET maximum intensity projection image reveals (a) physiological radiotracer distribution throughout the body. Orthogonal computed tomography and fused positron emission tomography computed tomography images (b-g) revealed non fluorodeoxyglucose avid edematous swelling of the bilateral aryepiglottic folds (arrow) and epiglottis indicating no evidence of residual/recurrent disease. The patient was followed-up clinically/radiologically for 2 years and remains asymptomatic

and 10 for metachronous second primary. Out of 12 patients with abnormal findings at primary site, PET-CT showed post treatment sequelae and small residual disease in 8 and 4 patients, respectively; which was confirmed by follow-up/microscopic examination.

Semi-quantitative analysis

The lesion with the maximum SUVmax value on each PET/CT study was used for semi-quantitative analysis. On semi-quantitative analysis, the overall mean lesion SUVmax was 12.24 ± 2.36 (median 11.5 and range 2.3–40.3). The mean SUV_{max} of lesions at primary site was 10.42 ± 2.95 (median 9.2 and range 2.9–40.3), regional nodes was 8.42 ± 1.37 (median 7.05 and range 2.9–15.2) and distant organ metastasis was 13.34 ± 5.2 (median 12.8 and range 4.5–26.3).

On ROC curve analysis [Figure 4], SUV_{max} >6.1 had sensitivity and specificity 80.6% and 94.7% respectively; area under the ROC AUC for lesion detection on FDG PET/CT was 0.883 (95% confidence interval 0.760–0.956 and $P = 0.0001$).

DISCUSSION

In the present study, we analyzed 100 patients with carcinoma

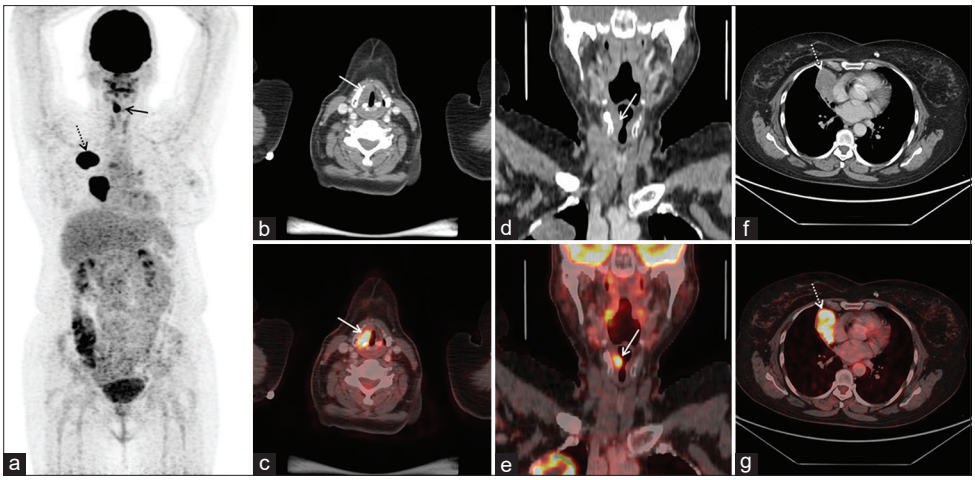

Figure 3: A 56-year-old female presented with respiratory distress after one year of treatment of squamous cell carcinoma in supraglottic region. Fluorodeoxyglucose positron emission tomography maximum intensity projection image reveals (a) focal areas of increased fluorodeoxyglucose uptake in cervical and thoracic regions. Transaxial and coronal computed tomography and positron emission tomography/computed tomography images (b-e) revealed fluorodeoxyglucose avid lesion in right false vocal cord (maximum standardized uptake value 11.6; arrow) indicating local recurrence. Additional images (f and g) showed fluorodeoxyglucose avid masses in right lung (largest maximum standardized uptake value 13.5; 6.7 cm × 5.4 cm; broken-arrow). Lung mass biopsy revealed adenocarcinoma. She was planned for chemotherapy (for lung) and radiotherapy (for larynx)

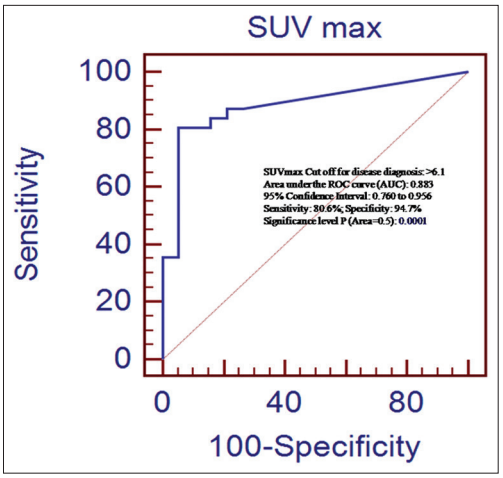

Figure 4: Receiver operating characteristic curve of maximum standardized uptake value value in the present study group

of larynx, who underwent F-18 FDG PET/CT following treatment for suspected recurrence or for posttherapy monitoring. FDG PET/CT showed sensitivity, specificity, PPV, NPV of 90.3%, 73.7%, 84.8%, and 82.3%, respectively for residual/recurrence detection ($P < 0.05$) with diagnostic accuracy of ~84%. These results are well in correlation with results by Oe *et al.* and Terhaard *et al*.[3,8] The reason for the relatively lower specificity was possibly because of the higher prevalence of infective/inflammatory pathologies in our patient population. Kim *et al*.[9] showed F-18 FDG PET scan could detect earlier the persistent or recurrent laryngeal cancer after treatment and avoided the need of biopsies, which would traumatize the post treatment tissues.[10] Early diagnosis of treatment failure can help in better second-line management. The need for an early, cost-effective and sensitive modality for the detection of recurrent or residual disease in laryngeal carcinoma is becoming increasingly important especially in the current era of organ-preserving.[11]

Primary tumor bed was the most common site for detection of suspicious lesion in 85% patients having positive F-18 FDG PET/CT. Most of the detected primary lesions involved supra-glottic region as isolated involvement or as one of the involved regions. The information on involvement of adjacent structures was helpful in arriving at decision for further management. F-18 FDG PET/CT detected involvement of isolated or multiple sites with the involvement of adjacent local muscle, cartilage or bone, vocal cord, epiglottis, and tracheostomy site or fistula formation. With regards to distant metastases, lymph nodes (10%) followed by lung (6%) and liver (6%) are commonly involved sites as described by Haerle *et al*.[11] FP findings on PET/CT were seen in 10% (10 patients) patients in our study which could be explained due to the nonspecific accumulation of F-18 FDG in infective/inflammatory lesions leading to FP results and is not an unusual finding. Furthermore, microscopic disease or small sized tumor can also be the reason for FN results (6%).

In addition, 10 out of 16 patients (~62.5%) were found to have metachronous second primary on histopathology (lung-4, thyroid-2, tongue, colon, esophagus, and lymphoma-one each). The second primary lung cancers were the commonest second primary followed by thyroid carcinoma as also described in literature.[12,13] A second primary cancer in conjunction with laryngeal carcinoma is associated with poor survival due to the advanced stage at time of diagnosis.[14] Hence, early detection of a second

primary with help of FDG PET/CT may be important. Until now, clinical assessment and conventional radiological imaging are used routinely for detection of second primary.[15,16] Six FP patients in the present study who were suspected to have second primary lung carcinoma showed pulmonary tuberculosis in 4 and pulmonary metastasis in two patients on histopathological evaluation. The common risk factor association (smoke and alcohol) might be the probable cause of detected second primary in our patient group.[17,18]

A major advantage of F-18 FDG PET/CT study is whole body imaging, which can detect or exclude viable tumors at different sites in a single examination. We found no significant difference in the F-18 FDG uptake (SUV_{max}) of lesion at various sites in the present study. On ROC curve analysis, SUV_{max} >6.1 had sensitivity and specificity of 80.6% and 94.7% respectively for detection of the recurrent disease at the local site. There are some studies which have shown that patient with high FDG avid lesion in carcinoma larynx had poor prognosis as compared to other patients.[19,20]

Various treatment modalities for laryngeal cancer, especially Surgery and radiotherapy, individually or in combination, lead to significant anatomic distortion, edema, thickening, and abnormal enhancement in the laryngeal tissues.[21] These changes make the diagnosis of local recurrence extremely difficult on CT/MRI. PET-CT may overcome these problems if performed after 2–3 months of treatment. For these reasons, FDG PET/CT has better diagnostic accuracy in detecting tumor recurrence.[22-24] In the present study, PET-CT lead to change of the management strategy in 32 patients (32%) as compare to conventional and macroscopic examination.

As per the result of our study, we could like to suggest that the PET/CT should be used as the first re-evaluation modality and this may be able to reduce futile routine evaluation by examination under general anesthesia as specified by de Bree *et al*.[25]

Limitations

The retrospective design of the present study is an important limitation. It might have introduced selection bias. Second, the lack of a pathological reference standard in all of the patients is also a limitation. Using clinical/imaging follow-up in place of the pathological reference standard can bias the diagnostic accuracy of test results. Although ideal, histopathology is difficult to obtain for all lesions, especially for distant sites because of ethical and technical reasons. Finally, conventional imaging (CT/MRI) was not available for all patients, and hence no comparison between F-18 FDG PET/CT and CT/MRI was attempted. Other limitation of the present study is that we have not mentioned TNM stage of enrolled patients due to nonavailability of the M part in all initial recruited patients. Although results favor PET/CT over conventional imaging but no definite comments could be made in the absence of systematic analysis. Prospective multi-center studies addressing these shortcomings of the present study are warranted.

CONCLUSION

F-18 FDG PET/CT demonstrates high diagnostic accuracy for the detection of residual/recurrent disease in laryngeal cancer patients posttreatment. F-18 FDG PET/CT scanning should be considered as the preferred first-line diagnostic investigation in patients suspected of residual/recurrent disease in treated laryngeal carcinoma patients. Incidental detection of metachronous second primary malignancy may be an important added benefit of the procedure.

Research involving human participant

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from individual participants included in the study.

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Conflicts of interest

There are no conflicts of interest.

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