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Original article

Impact of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Scan on Initial Evaluation of Head and Neck Squamous Cell Carcinoma: Our Experience at a Tertiary Care Center in India

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Abstract

The efficacy of the whole body (WB) ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT) as a part of conventional initial staging in all cases of head and neck squamous cell carcinoma (HNSCC) is still controversial with various studies in literature giving contradictory reports. We conducted this study at a government tertiary care oncology center in India to identify the impact of WB ^{18}F-FDG PET-CT scan on HNSCC staging and treatment. A prospective clinical study of patients of HNSCC who were evaluated and treated at our center was performed. The patients included in the study were HNSCC of the oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, and carcinoma of unknown primary site (CUPS) with cervical metastasis. The study design was to evaluate the cases of HNSCC initially by staging with conventional investigations followed by staging with the information derived from WB ^{18}F-FDG PET-CT scan. At the end of the conventional investigations, a tumor, node, metastasis (TNM) staging as per AJCC 7th edition, and a detailed treatment plan as per NCCN 2012 guidelines was decided in consultation with the multidisciplinary oncology team of the hospital. WB ^{18}F-FDG PET-CT scan was carried out in all these patients. The findings of WB ^{18}F-FDG PET-CT were then interpreted with the staging with conventional investigations to identify the cases with change in staging and also those in whom the treatment protocol would be affected. Descriptive analysis of demographic data and analytical analysis of the sensitivity and specificity of WB ^{18}F-FDG PET-CT scan and also the change in staging and treatment plan after WB ^{18}F-FDG PET-CT scan was analyzed using SPSS version 18. A total of 131 patients met the inclusion criteria, which included 123 males and 8 females. The various sites involved among the study group are oral cavity 11 (8.3%), oropharyn × 39 (29.7%), hypopharyn × 31 (23.6%), laryn × 34 (25.9%), nasopharyn × 4 (3%), and CUPS 12 (9.1%). The majority of cases studied were of T2 and T3 stage, and changes in T staging after WB ^{18}F-FDG PET-CT scan were minimal and not statistically significant ($P > 0.5$). In the nodal staging after WB ^{18}F-FDG PET-CT scan, there was a statistically significant change in identification of nodal metastasis in N0 group and also identification of additional multiple/bilateral nodes (N2b and N2c). 3 (2.2%) patients had a change in M status with identification of distant metastasis in lungs (2 patients) and in the liver and lung (1 patient). Of the 131 patients, 75 (57.25%) underwent surgical management with or without adjuvant treatment (Group I) and 56 (42.74%) patients underwent nonsurgical management (Group II). There was no significant statistical difference in sensitivity and specificity of ^{18}F-FDG PET-CT scan in detecting cancer among the two groups. Considering all the patients in this study, WB ^{18}F-FDG PET-CT scan showed an overall sensitivity of 95.2% and specificity of 80%. In this study, change in TNM staging after WB ^{18}F-FDG PET-CT was seen in 22 (16.8%) patients and an alteration in the treatment in 21 (16.1%) patients, which were both found to be statistically significant ($P < 0.5$). In our study, WB ^{18}F-FDG PET-CT scan has shown to have an impact on initial staging of disease affecting the change in treatment protocol in a significant number of patients. The effect of this change in staging and treatment on the eventual morbidity and

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mortality rates is not known. In practice, the use of ^{18}F-FDG PET-CT scan is limited, owing to the high cost and low availability. A realistic evaluation of cost versus benefit needs to be undertaken to identify the impact of using ^{18}F-FDG PET-CT scan as a mode for initial evaluation of HNSCC.

Keywords: Head and neck squamous cell carcinoma, initial staging, whole body positron emission tomography-computed tomography scan

Introduction

Head and neck squamous cell carcinoma (HNSCC) may present with a variety of symptoms and signs depending on the site of the primary tumor, nodal spread, and distant metastasis. Despite advances in diagnosis and treatment, HNSCC remains an important cause of morbidity and mortality worldwide. The primary site in HNSCC is identified clinically and the tumor type and grade by pathology, but radiological imaging for an accurate staging is an integral part of initial management of patients. In the recent past whole body ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography scan (WB ^{18}F-FDG PET-CT scan) has been used as an effective tool in lung, breast and colorectal cancers.[1] In HNSCC, it is found to have a significant role in the evaluation of the primary in carcinoma of unknown primary site (CUPS) with neck metastasis and in detecting posttreatment recurrence. The efficacy of WB ^{18}F-FDG PET-CT scan as a part of conventional initial staging in all cases of HNSCC is still unclear. Our study evaluated the role of WB ^{18}F-FDG PET-CT scan in initial staging of HNSCC and its impact on treatment modality.

Materials and Methods

We conducted a prospective clinical study of patients of HNSCC who were evaluated and treated at our center from June 2010 to June 2012. The study was approved by the Ethical Committee. A total of 523 patients of HNSCC reported to our center during this period.

The patients included in the study were HNSCC of the oral cavity, oropharynx, hypopharynx, larynx, nasopharynx and CUPS. All patients who had prior surgical or adjuvant therapy before referral to our center, known metastatic disease at the time of presentation, WB ^{18}F-FDG PET-CT scan performed at earlier treatment facility and any condition causing inability to undergo WB ^{18}F-FDG PET-CT scan were excluded from the study.

The study design was to evaluate the cases of HNSCC initially by staging with conventional investigations followed by staging with the information derived from WB ^{18}F-FDG PET-CT scan. The staging with conventional investigations was based on evaluation by standard head and neck physical evaluation and neck palpation, rod lens telescope/flexible fiber optic examination, contrast enhanced computed tomography (CECT)/magnetic resonance imaging (MRI) of head and neck, chest radiograph (CECT chest in suspicious lesions), ultrasound abdomen, biochemical evaluation of hepatic and renal function followed by fine-needle aspiration cytology (FNAC) of suspected neck metastasis and biopsy of the primary lesion. At the end of the investigations, a tumor, node, metastasis (TNM) staging as per AJCC 7th edition guidelines, and a detailed treatment plan as per NCCN 2012 guidelines was decided in consultation with the multidisciplinary oncology team.

Whole body ^{18}F-FDG PET-CT scan was carried out in all these patients. Patients were instructed to fast and not consume beverages, except for water, for at least 4–6 h before the administration of the contrast. Oral hydration with water was encouraged. Random blood sugar of the patient undergoing the WB ^{18}F-FDG PET-CT was done routinely before the procedure. Since, we needed to evaluate the high cervical lymph nodes; scan was carried out from vertex to knee. Intravenous injection of 370 MBq of ^{18}FDG was given and patients were placed in an isolation room in a silent and dim lit atmosphere. Scan acquisition was done after 45 min of contrast administration using a WB full ring dedicated lutetium oxyorthosilicate PET-CT scanner. The patient was laid supine with arms down position so that there is no attenuation artifact. Noncontrast CT images were obtained using 130 kV and 90 mAs (mean). CT based attenuation correction was done and the images were reconstructed using standard iterative algorithm and reformatted into transaxial, coronal, and sagittal views. A three-dimensional image and fusion images of PET and CT were obtained.

Any additional findings of WB ^{18}F-FDG PET-CT scan were further evaluated by endoscopy, radiological evaluation, FNAC/biopsy to confirm the findings. The findings of WB ^{18}F-FDG PET-CT scan were then interpreted with the conventional staging to identify the cases with change in staging and also those in whom the treatment protocol would be affected. The patients after WB ^{18}F-FDG PET-CT scan were classified as Group A (no change in the treatment), Group B (change in staging affecting change within the same treatment modality or planned procedure) and Group C (change in staging affecting change in treatment modality and intent).

The patients were divided into two groups as per their initial treatment modality (surgical vs. nonsurgical) and the sensitivity and specificity of WB ^{18}F-FDG PET-CT scan was calculated. Group I: Initial surgical management with or without adjuvant treatment and hence availability of histopathology to confirm findings of WB ^{18}F-FDG PET-CT scan and Group II: Initial nonsurgical management. All patients who underwent nonsurgical management were followed up for a minimum of 6 months by clinical evaluation, imaging including WB ^{18}F-FDG PET-CT scan and biopsy/FNAC to identify residual or new disease. WB ^{18}F-FDG PET-CT scan in these cases was performed at 3 and 6 months after initial treatment. These posttreatment evaluation data were also used as a marker of efficacy of WB ^{18}F-FDG PET-CT scan in the initial evaluation in nonsurgical patients.

Descriptive analysis of demographic data and analytical analysis of the pre- and post-WB ^{18}F-FDG PET-CT scan data were analyzed by SPSS (Statistical package for the social sciences) developed by IBM corporation version 18. The sensitivity and specificity of WB ^{18}F-FDG PET-CT scan and also the change in staging and treatment plan was analyzed.

Results

A total of 131 patients met the inclusion criteria, which included 123 males and 8 females. The mean patient age was 58.2 years for male (range: 21-76) and 56.2 years for female (range: 50-59). The various sites involved among the study group are oral cavity 11 (8.3%), oropharyn × 39 (29.7%), hypopharyn × 31 (23.6%), laryn × 34 (25.9%), nasopharyn × 4 (3%), and CUPS 12 (9.1%).

The change in T staging before and after WB ^{18}F-FDG PET-CT is described in Table 1. The majority of cases studied were T2/T3 and changes in T staging after WB ^{18}F-FDG PET-CT scan in all the stages were minimal and was found to be statistically not significant ($P > 0.5$). The initial nodal status and the changes after WB ^{18}F-FDG PET-CT are described in Table 2. In the nodal staging after WB ^{18}F-FDG PET-CT scan, there was a statistically significant change in identification of nodal metastasis in N0 group and also identification of additional multiple/bilateral nodes (N2b and N2c). 3 (2.2%) patients had a change in M status with identification of distant metastasis in lungs (2 patients) and in the liver and lung (1 patient). Primary disease in patients with CUPS with neck secondaries were identified in 3 (25%) of the 12 patients in nasopharynx, tonsil, and base of tongue.

The changes in TNM staging as per site are depicted in Table 3. There was a mean change of 20.13% (range: 5.8-27.27) among all the sites. Of the 131 patients in the study, change in TNM staging after WB ^{18}F-FDG PET-CT was seen in 22 (16.8%) patients and an alteration in the treatment in 21 (16.1%) patients, which were both found to be statistically significant ($P < 0.5$). The treatment plan of the 22 patients who had a change in TNM staging after WB ^{18}F-FDG PET-CT are enumerated in Table 4. In the 22 patients with change in staging, 1/22 (4.5%) patient was of Group A, 11/22 (50%) were of Group B and 10/22 (45.5%) patients were of Group C. Among the 11 patients of Group B, change in the staging resulted in modified radiation fields in 7 patients and modified surgical fields in 4 patients. In the 10 patients of Group C, 4 patients had additional modality of CT added to radiotherapy (RT), 3 patients had a change from surgical treatment with adjuvant therapy to concurrent chemo-radiotherapy and in 3 patients with distant metastasis the intent of treatment was changed. A significant change in treatment was seen in 21 patients due to change in N status in 17 patients (12.9%), T status in 3 patients (2.2%) and M status in 3 patients (2.2%).

Of the 131 patients, 75 (57.25%) patients underwent surgical management with or without

Table 1: Change in T status after PET-CT

T stage	Before PET	After PET
T0	12	10
T1	16	18
T2	32	32
T3	49	50
T4a	16	15
T4b	06	06

PET-CT: Positron emission tomography-computed tomography

Table 2: Change in nodal status after PET-CT

N stage	Before PET	After PET
N0	23	19
N1	16	10
N2a	09	11
N2b	07	05
N2c	07	18
N3	04	03

PET-CT: Positron emission tomography-computed tomography

Table 3: Change in TNM staging after PET-CT as per site

Site	Number of patients with change in TNM	% change
Oral cavity (*n*=11)	03	27.27
Oropharynx (*n*=39)	06	15.38
Hypopharynx (*n*=31)	07	22.5
Larynx (*n*=34)	02	5.8
Nasopharynx (*n*=04)	01	25
CUPS (*n*=12)	03	25
Total	22	16.79

PET-CT: Positron emission tomography-computed tomography; TNM: Tumor, node, metastasis; CUPS: Carcinoma of unknown primary site

Table 4: Summary of treatment change after PET-CT

Patient no.	Primary tumor site	TNM before WB ^{18}F-FDG PET-CT	TNM after WB ^{18}F-FDG PET-CT	Treatment alteration
1	Oral cavity	T2N1M0	T2N2CM0	Ipsilateral to bilateral neck dissection
2	Oral cavity	T3N2BM0	T3N2CM0	Ipsilateral to bilateral neck dissection
3	Oral cavity	T4AN3M0	T4AN3M1	Changed to palliative intent
4	Oropharynx	T2N0M0	T2N1M0	Change in gross tumor volume and dose
5	Oropharynx	T1N1M0	T1N2CM0	RT to CCRT
6	Oropharynx	T2N1M0	T2N2CM0	RT to CCRT
7	Oropharynx	T3N0M0	T3N2AM0	Change in gross tumor volume and dose
8	Oropharynx	T3N2BM0	T3N2CM0	Ipsilateral to bilateral neck dissection
9	Oropharynx	T4AN2CM0	T4AN2CM1	Changed to palliative intent
10	Hypopharynx	T2N0M0	T2N1M0	RT to CCRT
11	Hypopharynx	T2N1M0	T2N2CM0	RT to CCRT
12	Hypopharynx	T3N1M0	T3N2BM0	Change in gross tumor volume and dose
13	Hypopharynx	T3N1M0	T3N2CM0	Change in gross tumor volume and dose
14	Hypopharynx	T4AN1M1	T3N1M1	No change
15	Hypopharynx	T3N2AM0	T3N2CM1	Changed to palliative intent
16	Hypopharynx	T3N1M0	T3N2CM0	Change in gross tumor volume and dose
17	Larynx	T3N1M0	T3N2CM0	Change in gross tumor volume and dose
18	Larynx	T4AN2BM0	T4AN2CM0	Ipsilateral to bilateral neck dissection
19	Nasopharynx	T2N1M0	T2N2CM0	Change in gross tumor volume and dose
20	CUPS	T0N2AM0	T1N2AM0	Surgery with adjuvant therapy to CCRT (primary in BOT)
21	CUPS	T0N2AM0	T1N2AM0	Surgery with adjuvant therapy to CCRT (primary in tonsil)
22	CUPS	T0N3M0	T1N3M0	Surgery with adjuvant therapy to CCRT (primary in nasopharynx)

PET-CT: Positron emission tomography-computed tomography; TNM: Tumor, node, metastasis; FDG: Fluorodeoxyglucose; CUPS: Carcinoma of unknown primary site; RT: Radiotherapy; CCRT: Concurrent chemo-radiotherapy; BOT: Base of tongue; WB: Whole body

adjuvant treatment (Group I) and 56 (42.74%) patients underwent nonsurgical management (Group II). Of the 75 patients of Group I, WB ^{18}F-FDG PET-CT scan had a sensitivity of 94.8% and specificity of 88.2%. In the 56 patients of Group II, after incorporating data of post treatment follow-up, WB ^{18}F-FDG PET-CT scan had a sensitivity of 95.8% and specificity of 87.5%. There was no significant statistical difference in sensitivity and specificity among the two groups. Considering all the patients in this study, WB ^{18}F-FDG PET-CT scan showed an overall sensitivity of 95.2% and specificity of 80%.

Discussion

Head and neck squamous cell carcinoma is the 6th most common cancer worldwide. The initial evaluation of HNSCC is based on examination protocol which includes physical examination, fiberoptic and endoscopic examination, radiological evaluation by ultrasound scan and CT scan and histological evaluation by biopsy and FNAC. The successful management of HNSCC depends on appropriate staging of the local, regional, and distant disease. Radiological imaging is an integral part of the initial evaluation and CECT scan is a well-established diagnostic imaging tool. Despite technical improvements in CT and MRI, the number of false-negative and false-positive findings is still high. PET-CT scan provides additional information about the molecular and metabolic changes associated with disease. In the past few decades, PET-CT scan has rapidly become an integral part of oncology practice in the initial evaluation and treatment of lung, breast, and colorectal cancers.

In HNSCC, PET-CT has been found to be of value in detecting post treatment recurrence, evaluation of pre RT staging,[2] detecting primary in CUPS,[3] and detecting distant metastasis. The use of PET scan in the initial evaluation of HNSCC is still not clear owing to its limited availability and high cost. In India, there is limited data in the literature of the use of WB ^{18}F-FDG PET-CT scan for initial staging. We conducted this study at a government tertiary care oncology center in India to identify the impact of WB ^{18}F-FDG PET-CT scan on HNSCC staging and treatment.

The advantage of PET scan over conventional radiology in determining primary lesion has been low due to the functional uptake by various structures in the head and neck causing high number of false-positive results. The advent of hybrid PET-CT scan has improved the visualization and delineation of structures. Various studies have indicated PET scan to have an equal sensitivity[4,5] as compared to CT/MRI, whereas others have shown a higher sensitivity in staging primary disease.[6] In our study, we found equivocal results with only few cases (2.2%) with change in T staging as compared with conventional radiology.

One of the most important applications of PET scan in initial staging of HNSCC is in identifying

metastatic disease in cervical nodes. At the time of initial presentation, metastatic disease to cervical nodes is present in a significant number of cases.[7] The presence of nodal disease in HNSCC indicates a higher disease load with change in management and prognosis. PET-CT scan due to its higher sensitivity and specificity is useful in identifying nodal disease leading to change in initial staging, which modifies the overall treatment plan affecting survival rates.[2,8-10] PET-CT scan can identify metastatic deposit in nonenlarged nodes, nodes with no morphological change and also in nodes like retropharyngeal and supraclavicular which are difficult to evaluate in conventional studies. In our study, WB ^{18}F-FDG PET-CT scan was found to be affective in identifying nodal disease in N0 neck and also in identifying multiple or bilateral nodal disease in patients. This led to upstaging of disease and change in the treatment in 17 (12.9%) of the study group.

Head and neck squamous cell carcinoma metastasizes to the cervical lymph nodes from an unknown primary in the range of 3-7%.[11,12] Up to 80% of the primary lesion is known to be from the tonsils and base of tongue and may be missed on conventional radiology. Various studies show a detection rate of the primary in 22–57% of cases with the use of PET scan.[3,13,14] PET scan also facilitates directed biopsies at the site of increased SUV uptake during panendoscopy providing better yield during biopsies. Our study also mimics the findings of the literature with the primary identified in 25% of cases of CUPS with neck secondaries. The primaries identified were in tonsil, nasopharynx and base of tongue. This led to a change of treatment from surgical excision followed by adjuvant therapy to neck to concurrent chemotherapy and RT to neck with additional RT dosage to the site of primary.

The presence of distant metastasis from a primary in HNSCC suggests advanced disease with a poor outcome. The treatment modality also in these cases changes from a curative intent to a palliative treatment protocol. WB ^{18}F-FDG PET-CT is an excellent tool in identification of distant metastasis as compared with routine initial workup.[15-17] Our results showed an additional identification of distant metastasis in 3 (2.2%) patients with change in treatment modality.

Various reviews have indicated the sensitivity of PET-CT is 72-98% and specificity of 92–100% for the identification of malignancy in HNSCC, which is higher than CT/MRI or PET alone.[18-20] In our study, the sensitivity was 95.8% and 94.8% and specificity of 87.5% and 88.2%, respectively for patients who underwent surgical or nonsurgical modality of treatment, which is similar to the published literature.

The initial evaluation of HNSCC by WB ^{18}F-FDG PET-CT in our study changed the TNM staging in 22 (16.8%) patients, which was primarily due to nodal upstaging and to a lesser extent due to detection of primary and distant metastasis. Other studies in the literature have identified the change in TNM staging after PET-CT scan to be in the range of 20-30%.[21-23] Our results are different from the published literature as our study was a prospective one which included patients of HNSCC of various sites as compared to other studies which evaluated only a specific site. Furthermore, we evaluated our patients by a hybrid system of PET and CT scan providing better delineation and reducing false-positive, which was seen in earlier studies evaluated by PET alone. A few limitations of our study would be that all patients did not undergo surgical treatment and hence had to be further evaluated by biopsy, aspiration cytology or surrogate markers like clinical and radiological follow-up as reference standards as compared to studies in the literature where all cases were operated and histopathology was the gold standard. Although, it was seen that no difference in sensitivity and specificity among the surgical and nonsurgical cases were observed in our study.

It is a well-known fact that a significant change in the perceived risk in a disease would alter the management of the disease. In our study, WB ^{18}F-FDG PET-CT scan has shown to have an impact on initial staging of disease affecting the change in treatment protocol. Although the study does not evaluate the impact of WB ^{18}F-FDG PET-CT scan on mortality and survival rates as compared to patients who have not undergone WB ^{18}F-FDG PET-CT scan as initial evaluation. In practice, the use of WB ^{18}F-FDG PET-CT scan in India is limited, owing to the high cost and low availability. A realistic evaluation of cost versus benefit needs to be undertaken to identify the impact of using PET-CT scan as a mode for initial evaluation of HNSCC.

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