Nasopharyngeal Carcinoma (NPC) : The value of 18-Florine Fluorodeoxyglucose (FDG) Positron Emission Tomography Computed Tomography (PET / CT) in comparison to conventional imaging modalities Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

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Citation
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Abstract
PURPOSE: To evaluate the clinical usefulness of 18F FDG PET/CT in the management of NPC in comparison to conventional imaging modalities. METHODS: This retrospective study was done at Ospedale Niguarda, Milan, Italy. Data acquired from 24 NPC patients between May 2003 and December 2006. They had FDG PET/CT and CT or MRI during initial diagnosis and at follow up. Each findings was tabulated and compared with tissue biopsy at diagnosis and clinical status during follow up after therapy. Statistical calculation was done to derive the value of each modalities. RESULTS: The sensitivity and accuracy of PET / CT and CT / MRI are equally high at diagnosis. At follow up, a negative PET / CT finding suggests complete remission with sensitivity and negative predictive value of 100%. CONCLUSIONS: 18F FDG PET/CT is a potential modality to be utilized in following up NPC patients for evaluating response to therapy.

ACKNOWLEDGEMENT
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INTRODUCTION
NPC is common among the Chinese populations especially in the south China and South East Asia region with incidence of 20 to 50 per 100 000 individuals [1,2]. Despite being uncommon among other ethnic groups including the Europeans, incidence has been reported among the south Indian community as well as in the North African community [3].

Ebstein Barr Viral (EBV) infection is thought to play an important role in initiating the development of this tumour. Multiple literature review revealed coexistence between EBV infection and NPC [4,5,6,7,8,9,10]. Kenneth and colleagues suggested that EBV status can be a reliable predictor for overall survival of NPC patients[11].

Most NPC patients commonly manifest themselves with painless enlarged lymph nodes in the neck which are often bilateral. When these are in association with positive EBV’s DNA, they are highly suspicious for nodal disease from NPC primary [12]. Other clinical features include nasal obstruction and epistaxis which may occur as a result of local tumor infiltration. Patients may also present with hearing problems like hearing loss, tinnitus or recurrent otitis media. In advanced cases, there may be cranial nerve dysfunction. A more generalized presentation like sore throat and headache are not uncommon. These clinical presentations are looked for at diagnosis and follow up.
Besides histological typing, early detection and accurate staging at diagnosis and restaging at follow up are important prognostic determinants. Early and accurate staging at diagnosis will ensure proper treatment deliveries as prevalence of head and neck metastases is as high as 40% at the time of initial presentation. Accurate restaging after therapy is also important to determine treatment response and to answer the question whether the patient requires change in pre planned treatment regime.

In current practice, conventional imaging modalities like CT and MR are routinely employed to assist clinicians in staging NPC patients. Fused integrated morphological and functional imaging modality PET/CT is another possible useful new tool to be utilized in the assessment of NPC patients. This study was conducted in view to evaluate the role of fused Positron Emission Tomography/Computed Tomography (PET/CT) in the management of NPC patients.

MATERIALS AND METHODS

PATIENTS

This study was approved by the institutional review board of the hospital.

Retrospective data from 33 patients between May 2003 to December 2006, from Nuclear Medicine Department, Ospedale Niguarda, and Milan, Italy were reviewed. These are confirmed cases of nasopharyngeal carcinoma from histopathological tissue biopsy. The results were collected and tabulated.

Since this study is selective on comparison between PET / CT and conventional imaging tools, only paired PET/CT with CT or MRI imaging results were included. Patients with incomplete imaging data were excluded from this study. Finally, we select imaging results from 24 patients for analysis. There were 7 women and 17 men, age between 21-75 years included in our study. Our patients were grouped into three categories.

Group A patients had combination of examinations consisting of 18F-FDG PET/CT, CT and or MRI examinations at diagnosis and after treatment. These patients received radio or chemotherapy singly or in combination following confirmation of the diagnosis of NPC. Post therapy imaging was conducted at five to six months upon completion of last treatment.

Group B patients consisting only newly diagnosed NPC patients and had combination of examinations at initial staging process. These patients are still under follow up. They will be re assessed during their next follow up visit to the clinic. Thus there is only one PET/CT study performed at diagnosis.

Group C patients had their combined examinations done during post therapy. PET/CT was not performed at earlier stage before treatment as the facility was not accessible.

At presentation, the diagnosis of each patient was confirmed through histopathological examination of tissue biopsy at Ospedale Niguarda in Milan or elsewhere and referred to the centre for further evaluation and follow up.

Upon completion of full course of radiotherapy or combined chemotherapy, group A and Group C patients were reassessed by the clinicians during follow up visit at the clinic when they returned for clinical assessment. Clinical signs and symptoms of recurrence like pain, epistaxis, neurological deficit or evidence of hearing impairment were sought for. Endoscopic examination looking for direct evidence of recurrent disease performed prior to imaging studies. In routine practice, during follow up, close monitoring for tumor recurrence or progression were accomplished using CT or MRI. In doubtful imaging findings, other than undergoing PET/CT examination, patients underwent biopsy. Eventually, the final diagnosis of the patient was made based upon clinical evaluation as stated in the ‘Disease Status’ column in Table 1.

18F-FDG PET/CT IMAGING

Whole body FDG PET/CT scan was done at The Department of Nuclear Medicine, Ospedale Niguarda, Milan, Italy using integrated PET / CT system (Biograph, Siemens) combine dual slice spiral CT with a dedicated full-ring Bismuth Germanate (BGO) crystal for the PET scanner.

Following overnight fasting, PET / CT image acquisition was accomplished after 60 minutes waiting time following intravenous FDG injection. All examinations performed without intravenous contrast administration using the following protocol:

CT Scanogram performed for planning the CT and PET study.

Low dose CT acquisition was done first with parameters of
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2.5 mm slices, spiral mode at 50 mAs and 130 kV for anatomical correlation and attenuation correction of PET images. Immediately after CT acquisition, the table was positioned for PET acquisition. PET image acquisition was done at 5 min per bed position.

First acquisition was performed from the lung to the thighs in 3-dimensional mode. Second acquisition was performed from the vertex of the skull to the thoracic inlet.

Reconstruction of the emission data was performed by using an iterative algorithm with software Somaris/5 VA40C and stored in a 128 matrix. CT-data were used for attenuation correction. Volume projected images (transaxial, coronal and sagittal slices) and fusion images were generated for interpretation.

In post therapy patients, PET / CT imaging was done 20-24weeks post treatment, to avoid false positive results.

.IMAGE INTERPRETATION AND DATA ANALYSIS

In our study, we include 37 paired imaging examinations. These consist of PET / CT with CT or with MRI. Each method was interpreted separately and independently to assess primary tumour and cervical node status at two different stages, at initial diagnosis and following therapy by three experienced PET CT specialists. Observation also includes evidence for distant metastasis.

On PET CT images, results were derived from visual analysis. Areas of increased uptake other than the normal physiological distribution are considered pathological. This is further confirmed through semi quantitative analysis on the region of interest using Standardized Uptake Value (SUV). A value of more than 2.5 is pathological.

On CT or MR images, any pathological alterations to the normal anatomical boundaries as evident by distorted outline or presence of enhancing lesions in the studied areas are considered as pathological. Observations also include abnormal neck lymphadenopathies exceeding 10 mm in diameter. Lymph nodes of any size with central necrosis are also regarded as pathological.

STATISTICAL ANALYSIS

All the findings were tabulated to calculate the sensitivity, specificity and accuracy of the imaging modules. The negative and positive predictive values derived from these data.

RESULTS

PATIENTS

From selected 24 patients in our study, we include 37 paired examinations of PET / CT and CT or MRI. At diagnosis, the imaging results were compared with histo pathological findings. At follow up, the standard was taken as final clinical conclusion of disease status done by the clinicians following clinical assessment. The summary of the findings of all enrolled patients are summarized in table 1.

Figure 1

Table 1- Clinical, histopathological and imaging results

<table>
<thead>
<tr>
<th>Group</th>
<th>Age / Sex</th>
<th>At Diagnosis</th>
<th>Following treatment</th>
<th>Disease Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 1</td>
<td>64M</td>
<td>PET/CT</td>
<td>CT/MR</td>
<td>HPE</td>
</tr>
<tr>
<td>2</td>
<td>61M</td>
<td>pos</td>
<td>pos</td>
<td>Neg</td>
</tr>
<tr>
<td>3</td>
<td>61M</td>
<td>pos</td>
<td>pos</td>
<td>neg</td>
</tr>
<tr>
<td>4</td>
<td>53M</td>
<td>pos</td>
<td>pos</td>
<td>neg</td>
</tr>
<tr>
<td>5</td>
<td>48M</td>
<td>pos</td>
<td>pos</td>
<td>neg</td>
</tr>
<tr>
<td>6</td>
<td>39F</td>
<td>pos</td>
<td>pos</td>
<td>neg</td>
</tr>
<tr>
<td>7</td>
<td>51M</td>
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<td>neg</td>
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<td>8</td>
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<td>47M</td>
<td>pos</td>
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<td>neg</td>
</tr>
<tr>
<td>11</td>
<td>37F</td>
<td>pos</td>
<td>pos</td>
<td>neg</td>
</tr>
<tr>
<td>12</td>
<td>58F</td>
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<tr>
<td>16</td>
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<td>neg</td>
</tr>
<tr>
<td>17</td>
<td>45M</td>
<td>pos</td>
<td>pos</td>
<td>neg</td>
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<td>neg</td>
</tr>
<tr>
<td>19</td>
<td>54M</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>20</td>
<td>45M</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>21</td>
<td>46M</td>
<td>n/a</td>
<td>n/a</td>
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</tr>
<tr>
<td>22</td>
<td>48F</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>23</td>
<td>60M</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>24</td>
<td>60M</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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</table>

There are 17 males and 7 female patients (table 2). Age distribution between 21 to 70 years old with highest frequency of patients aged 61 years and above (table 3).

Figure 2

Table 2 - Sex distribution

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Male</td>
<td>17</td>
<td>65%</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>35%</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>100%</td>
</tr>
</tbody>
</table>
Nasopharyngeal Carcinoma (NPC) : The value of 18-Florine Fluorodeoxyglucose (FDG) Positron Emission Tomography Computed Tomography (PET / CT) in comparison to conventional imaging modalities Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

Figure 3
Table 3 - Age distribution

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>31-40</td>
<td>2</td>
<td>8.5</td>
</tr>
<tr>
<td>41-50</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>51-60</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>61 and above</td>
<td>9</td>
<td>37.5</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>100</td>
</tr>
</tbody>
</table>

Comparing results between imaging modalities at diagnosis

All 18 results at diagnosis were found to be concordant between PET / CT and CT or MRI. When these results were compared with standard (tissue biopsy) the calculated sensitivity and accuracy were found to be equally high (table 4).

Since there were no false negative or false positive results, the specificity is statistically void.

Figure 4
Table 4 - Comparative evaluation results between imaging modalities at diagnosis

<table>
<thead>
<tr>
<th>Modality</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Total</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/MRI</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>100</td>
<td>null</td>
<td>100</td>
</tr>
<tr>
<td>PET/CT</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>100</td>
<td>null</td>
<td>100</td>
</tr>
</tbody>
</table>

Comparing results between imaging modalities for assessment of treatment response

In imaging after therapy, both methods are found to be equally accurate with high positive predictive values. The negative predictive value for PET / CT is found to be higher than the conventional imaging modalities (100.0% for PET and 71.0% for conventional imaging) (Table 5). Overall, PET / CT provides a higher sensitivity in detecting local recurrence disease as compared to conventional imaging modality.

Figure 5
Table 5 - Evaluation results for treatment response assessment between imaging modalities

<table>
<thead>
<tr>
<th>Modality</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Total</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TP: true positive; TN: true negative; FP: false positive; FN: false negative; PPV: positive predictive value; NPV: negative predictive value

Figure 6
Figure 1. A 61 year old man who presented with epistaxis at diagnosis of nasopharyngeal carcinoma. Multiplanar reconstructed images obtained during 18F-FDG PET/CT examination revealed mild distortion of the normal anatomy of the left nasopharyngeal region (red crossed cursor). 18F-FDG PET CT demonstrating avid activity with intense metabolic activity deeply seated in the left nasopharynx.
Figure 7
Figure 2. Follow up 18F-FDG PET / CT imaging of the same patient 6 months upon completion of radiotherapy treatment demonstrating complete metabolic response in the left nasopharynx. Clinically the patient was found to be in complete remission.

DISCUSSION
Accuracy in staging NPC is most crucial during post therapy evaluation at follow up study. Centrally necrotic cervical nodes following therapy may resemble disease progression. Situation can be further complicated with the presence of reconstructive surgical procedures using graft and flap in this region.

While conducting this study, we found more significant variations in imaging results during post treatment evaluation with good statistical consensus at diagnosis.

There are no significant indifferences in the results at diagnosis since our study comprised of small number of patient. Furthermore, this retrospective selection of cases did not reflect the actual progress of clinical work flow for patients investigated for suspicious NPC. This includes identification of infected neck nodes or other nearby pathology at imaging which may resemble the clinical presentation of NPC. These are major contribution towards variation in statistic analysis.

In post therapy evaluation of both imaging modalities at follow up, we found two false negative results on conventional imaging modalities (patient 12 and 23) and 1 false positive result on both imaging modalities including PET/CT (patient 6).

We re-evaluated the retrospective false negative results of the two patients on conventional imaging modalities and reach to an agreement that there were no significant anatomical disruption noted in the nasopharyngeal areas. Furthermore, no loco regional nodal involvement demonstrated in these patients. Thorough search by direct endoscopic visualization confirmed the imaging findings. However, PET / CT evaluation demonstrated lesion with high metabolic activity indicating recurrent NPC. This particular clinical example has been described previously where 15.4% prevalence of residual or recurrent tumors are found to be beyond the reach of routine nasopharyngeal biopsy[13].Therefore, clinical assessment via endoscopic examination may missed deeply seated tumors whilst early tumor development may not manifest themselves clinically. Since conventional imaging modalities like CT or MRI dependent much on anatomical alterations to be readily identified at imaging, this clinical example may have resulted in understaging or missed tumor lesions.

We also performed re-evaluation study on the imaging results of the other patient. Because of doubtful positive imaging findings in the absence of signs and symptoms of disease recurrence, the patient underwent biopsy of the nasopharynx which result was later found to be negative. The remission state was later confirmed at subsequent follow-up. Thus, our reviewers came to an agreement that altered anatomical landmark with reactivity following radio and/ chemotherapy may have been the cause for the false positive interpretation. Although we follow standard recommendations to perform imaging studies after 6 to 8 weeks post therapy period, variations in the rate of recovery and body response towards injury events caused by radiation or chemotherapy may differ from one patient to another[14,15]. In addition, possibility of a brief episode of local inflammatory reaction at the time of imaging as a result of infection cannot be totally segregate from the fact that there is high metabolic activity in PET image acquisition.

Literature search suggested 18F-FDG PET is more specific
than conventional imaging modalities in detecting residual or recurrent nodal metastasis in head and neck malignancies. The sensitivities in these articles cited ranging from 67% to 100% and specificities ranging from 77% to 100% (16, 17, 18, 19, and 20). Our results are comparable with these findings (sensitivity 100% and specificity 83%) supporting the assertion that 18F-FDG PET should be a sensitive tool in detecting residual or recurrent nodes in NPC. In fact, by incorporating CT into functional PET imaging, the percentage is expected to be higher as compared to PET imaging alone. The ability of PET in providing functional metabolic activity of tumor infiltrated structures including small nodes is being utilized to enhance the superior capability of CT in demonstrating the precise anatomical location of these lesions. Thus, they are readily detectable on PET imaging and independent on the morphological changes in CT or MR images. The fusion of both imaging modalities in an integrated PET / CT machine should gives better result [21, 22, 23]. Furthermore, useful informations can be obtained during a single seating and also time saving for patient’s convenience.

Within our small study population, we also demonstrated higher negative predictive value of PET / CT in comparison to conventional imaging methods (table 5). This finding signify a more reliable negative PET / CT imaging result in circumstances when actual disease is absent where conventional imaging modality may have 29% chances of false negative interpretation.

Our study encourages the use of PET / CT in post therapy management of NPC patients. We demonstrated the ability of PET / CT in correcting tumor under staging in two of our patients whose results were found to be falsely negative using conventional imaging modality (patient 12 and 23). Aside from treatment response assessment, PET / CT findings can also lead the clinicians in decision making on the choices of clinical approach to be adopted. In the absence of clinical findings, a positive PET / CT result can be used as a general indicator for a more aggressive approach like biopsy in order to confirm the final diagnosis (patient number 6). This modality should be recommended as a preferable tool at follow up [24, 25].

Even though our findings at post therapy assessment are relatively relevant, we suggest more research being granted for assessment of actual value of PET / CT in therapy response within a larger cohort group of NPC patients.

CONCLUSION

Our study found 18F-FDG PET / CT a suitable imaging modality to be utilized in managing patients with NPC especially at post therapy follow-up. Further evidence is required to seek the actual value of this imaging modality at initial stage of diagnosis and follow up within larger cohort group.

References

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