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research article

Imaging in nasopharyngeal carcinoma: the value of 18-Florine Fluorodeoxyglucose PET/CT in comparison to conventional imaging modalities CT and MRI

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Background. *The aim of the study was to evaluate the clinical usefulness of 18F Fluorodeoxyglucose (FDG) positron emission tomography / computed tomography (PET/CT) in the management of nasopharyngeal carcinoma (NPC) in comparison to conventional imaging modalities.*

Methods. *This retrospective study was done at Ospedale Niguarda, Milan, Italy. Data were acquired from 24 NPC patients between May 2003 and December 2006. They had FDG PET/CT and CT or MRI during the initial diagnosis and at follow-up. Each finding was tabulated and compared with tissue biopsy at diagnosis and clinical status during the follow up after the therapy. A statistical calculation was done to derive the value of each modality.*

Results. *The sensitivity and accuracy of PET/CT and CT/MRI were equally high at diagnosis. At the follow up, a negative PET/CT finding suggested a 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 a response to therapy.*

Key words: positron emission tomography; computed tomography; magnetic resonance imaging; nasopharyngeal carcinoma; follow-up

Introduction

Nasopharyngeal carcinoma (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, a higher incidence

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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 the coexistence between EBV infection and NPC.[4-10] There is a huge clinical value of the data about EBV infection, because no factor in a wide spectrum of biochemical and histological candidate-markers has yet been identified to predict reliably the natural course of the disease or its response to the therapy to be used in the routine clinical practice,[11] but, Kenneth *et al.* suggested that EBV status could be a reliable predictor for the overall survival of NPC patients.[12]

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.[13] Other clinical features include nasal obstruction and epistaxis which may occur as a result of the local tumour infiltration. Patients may also suffer from hearing problems like hearing loss, tinnitus or recurrent *otitis media*. In advanced cases, the cranial nerve dysfunction may occur. 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, the 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 the prevalence of head and neck metastases is as high as 40% at the time of the initial presentation. Accurate restaging after therapy is also important to determine the treatment response and to answer the question whether the patient requires a change in the pre planned treatment regime.

In the current practice, conventional imaging modalities like CT and MR are routinely employed to assist clinicians in staging NPC patients. A fused integrated morphological and functional imaging modality of positron emission tomography / computed tomography (PET/CT) is another possible useful new tool to be utilized in the assessment of NPC patients like in other oncological patients.[14] This study was conducted in view to evaluate the role of fused PET/CT in the management of NPC patients.

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

Patients and methods

Patients

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

Since this study was selective for 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 selected imaging results from 24 patients for the analysis. There were 7 women and 17 men, age between 21-75 years included in the study. Patients were grouped into three categories.

Group A patients had a combination of examinations consisting of 18F-FDG PET/CT, CT and or MRI examinations at diagnosis and after the treatment. These patients received radio or chemotherapy singly or in combination following the confirmation of the diagnosis of NPC. Post therapy imag-

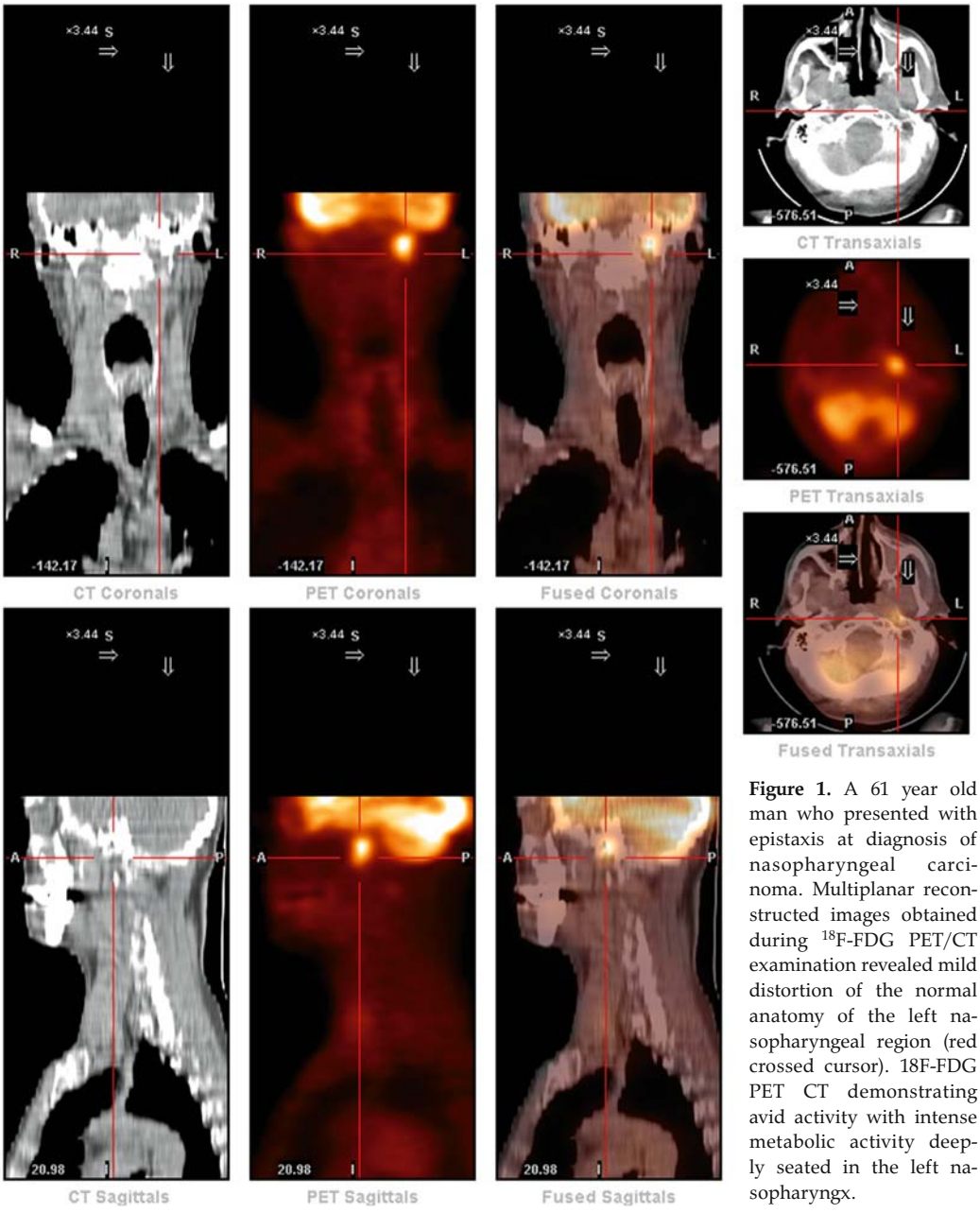

Figure 1. A 61 year old man who presented with epistaxis at diagnosis of nasopharyngeal carcinoma. Multiplanar reconstructed images obtained during ^{18}F-FDG PET/CT examination revealed mild distortion of the normal anatomy of the left nasopharyngeal region (red crossed cursor). 18F-FDG PET CT demonstrating avid activity with intense metabolic activity deeply seated in the left nasopharyngx.

ing was conducted at 5 - 6 months upon the completion of the last treatment.

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

Table 1. Clinical, histopathological and imaging results

		At diagnosis			Following treatment		
Group A	**Age/Sex**	**PET/CT**	**CT/MR**	**HPE**	**PET/CT**	**CT/MR**	**Disease status**
1	64/M	pos	pos	und	neg	neg	remission
2	63/M	pos	pos	und	pos	pos	persistent
3	61/M	pos	pos	few diff	pos	pos	persistent
4	53/M	pos	pos	N/A	pos	pos	persistent
5	48/M	pos	pos	few diff	pos	pos	persistent
6	39/F	pos	pos	und	pos	pos	remission
7	51/M	pos	pos	und	pos	pos	persistent
8	62/M	pos	pos	und	pos	pos	persistent
9	75/M	pos	pos	few diff	pos	pos	persistent
10	47/F	pos	pos	und	neg	neg	remission
11	37/F	pos	pos	und	pos	pos	persistent
12	63/F	pos	pos	und	pos	neg	persistent
13	21/F	pos	pos	und	pos	pos	persistent
Group B							
14	61/F	pos	pos	und	n/a	n/a	n/a
15	64/M	pos	pos	und	n/a	n/a	n/a
16	52/M	pos	pos	und	n/a	n/a	n/a
17	45/M	pos	pos	und	n/a	n/a	n/a
18	63/M	pos	pos	und	n/a	n/a	n/a
Group C							
19	54/M	n/a	n/a	und	neg	neg	remission
20	45/M	n/a	n/a	und	pos	pos	persistent
21	46/M	n/a	n/a	und	neg	neg	remission
22	44/F	n/a	n/a	und	pos	pos	persistent
23	60/M	n/a	n/a	und	pos	neg	persistent
24	60/M	n/a	n/a	und	neg	neg	remission

F=female, M=male, pos=positive, neg=negative, und=undifferentiated, diff=differentiated, n/a=not available

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

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

Upon completion of the full course of radiotherapy or combined chemotherapy, group A and Group C patients were reassessed by the clinicians during the follow up visit at the clinic when they returned for the clinical assessment. Clinical signs and symptoms of recurrence like pain, epistaxis, neurological deficit or evidence of hearing impairment were sought for. The endoscopic examination looking for a direct evidence of the recurrent disease performed prior to

imaging studies. In the routine practice, during the follow up, close monitoring for tumour 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 the 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.
- A low dose CT acquisition was done first with parameters of 2.5 mm slices, spiral mode at 50 mAs and 130 kV for the 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.
- A first acquisition was performed from the lung to the thighs in 3-dimensional mode. The second acquisition was performed from the vertex of the skull to the thoracic inlet.
- The 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 the attenuation correction. Volume projected images (transaxial, coronal and sagittal slices) and fusion images were generated for the 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 the initial diagnosis and the following therapy by three experienced PET/CT specialists. Observation also includes evidence for distant metastasis.

On PET/CT images, results were derived from the visual analysis. Areas of the increased uptake, other than the normal physiological distribution, were considered as pathological. This was further confirmed through the semi quantitative analysis on the region of interest using Standardized Uptake Value (SUV). A value of more than 2.5 was 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 included 37 paired examinations of PET/CT and CT or MRI. At diagnosis, the imaging results were compared with histopathological findings. At follow up, the standard was taken as the final clinical conclusion of disease status done by the clinicians following the clinical assessment. The summary of the findings of all enrolled patients are summarized in Table 1.

There were 17 (65%) males and 7 (35%) female patients. The age distribution was between 21 to 70 year-old with the highest frequency of patients aged at 61 years and above (Table 2).

Table 2. Age distribution

Age (years)	Frequency	Percentage
<30	1	4
31-40	2	8.5
41-50	6	25
51-60	6	25
61 and above	9	37.5
Total	24	100

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.

Comparing results between imaging modalities for the assessment of the treatment response

At imaging after the 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 4). Overall, PET/CT provides a higher sensitivity in detecting the local recurrence disease as compared to the conventional imaging modality.

Discussion

Accuracy in staging NPC is most crucial during the post therapy evaluation at the follow up study. Centrally necrotic cervical nodes following the therapy may resemble the disease progression. The 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 the post treatment evaluation with a good statistical consensus at diagnosis.

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

In the 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

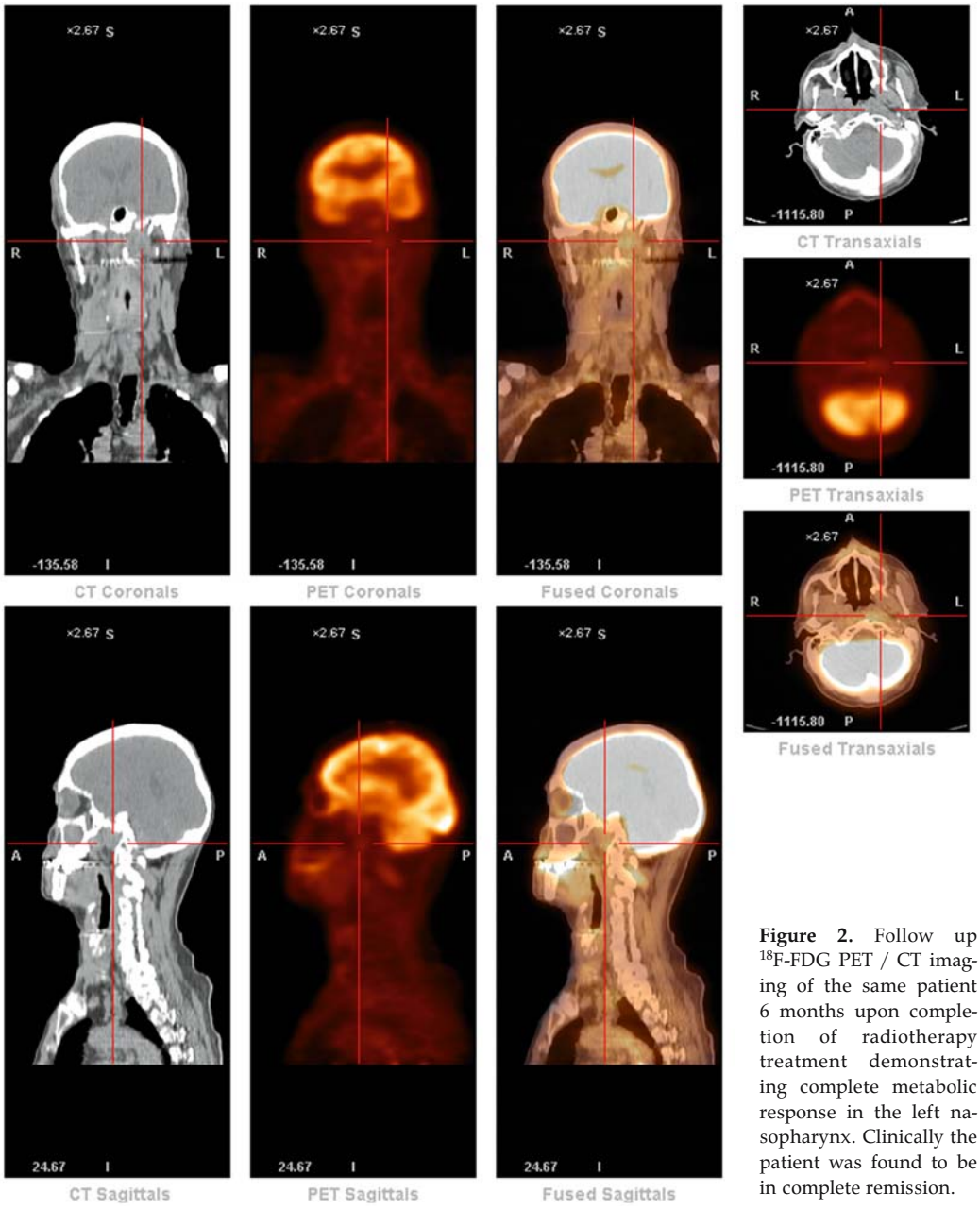

Figure 2. Follow up ^{18}F-FDG PET / CT imaging of the same patient 6 months upon completion of radiotherapy treatment demonstrating complete metabolic response in the left nasopharynx. Clinically the patient was found to be in complete remission.

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 the search by the direct endoscopic visualization were the imaging findings confirmed. However, PET/CT evaluation demonstrated the lesion with a high metabolic activity indicating recurrent NPC. This particular clinical ex-

Table 3. Comparative evaluation results between imaging modalities at diagnosis

Modality	TP	TN	FP	FN	Sensitivity %	Specificity %	Accuracy %
CT/MR	18	0	0	0	100	null	100
PET/CT	18	0	0	0	100	null	100

TP=true positive, TN=true negative, FP=false positive, FN=false negative

Table 4. Evaluation results for treatment response assessment between imaging modalities

Modality	TP	TN	FP	FN	Total exam	Sensitivity %	Specificity %	Accuracy %	PPV %	NPV %
CT/MR	11	5	1	2	19	84	83	84	92	71
PET/CT	13	5	1	0	19	100	83	84	93	100

TP=true positive, TN=true negative, FP=false positive, FN=false negative, PPV=positive predictive value, NPV=negative predictive value

ample has been described previously where 15.4% prevalence of residual or recurrent tumours are found to be beyond the reach of the routine nasopharyngeal biopsy.[15] Therefore, the clinical assessment via endoscopic examination may missed deeply seated tumours whilst early tumour development may not manifest themselves clinically. Since conventional imaging modalities like CT or MRI are much dependent on anatomical alterations to be readily identified at imaging, this clinical example may have resulted in understaging or missed tumour lesions.

We also performed the 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 the disease recurrence, the patient underwent biopsy of the nasopharynx which result was later found to be negative. The remission state was later confirmed at the subsequent follow-up. Thus, our reviewers came to an agreement that the altered anatomical landmark with reactivity following radio- and radio/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.[16,17] In addition, the possibility of a brief episode of the local inflammatory reaction at the time of imaging as a result of the infection cannot be totally segregated from the fact that there is a high metabolic activity in PET image acquisition.

The literature search suggested 18F-FDG PET was 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%.[18-22] 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 the functional metabolic activity of tumour 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 give better results.[14,23-25] Furthermore, useful information can be obtained during a single seating and also time saving for the patient's convenience.

Within our small study population, we also demonstrated a higher negative predictive value of PET/CT in comparison to conventional imaging methods (Table 4). This finding signifies a more reliable negative PET/CT imaging result in circumstances when the actual disease is absent where the conventional imaging modality may have 29% chances of the false negative interpretation.

Our study encourages the use of PET/CT in the post therapy management of NPC patients. We demonstrated the ability of PET/CT in correcting tumour under staging in two of our patients whose results were found to be falsely negative using the conventional imaging modality (patient 12 and 23). Aside from the treatment response assessment, PET/CT findings can also lead the clinicians in decision making on the choices of the 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.[26,27]

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

Conclusions

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

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