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The value of ^{18}F-fluorodeoxyglucose –positron emission tomography/ computed tomography (^{18}F- FDG PET/CT) in the staging and impact on the management of patients with nasopharyngeal carcinoma

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ABSTRACT

This study sought to prospectively evaluate the influence of contrasted fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDGPET/CT) in the staging of and impact on the management plan for treatment in patients with nasopharyngeal carcinoma (NPC). A total of 14 histologically proven NPC patients (mean age: 44.64±4.01years) were included in the study. These patients underwent contrasted Computed Tomography (CT) as well as ^{18}F-FDGPET/CT imaging. Staging was based on the 7th edition of the American Joint Committee on Cancer Tumor Node Metastases (AJCC-TNM) recommendations.The oncologist was asked to prospectively assign a treatment plan for all patients being evaluated by CT and ^{18}F-FDGPET/CT. The treatment plans were compared with the incremental information supplied by the FDG-PET/CT. The maximum standardised uptake value (SUV_{max}) and the widest dimension of the primary tumour, cervical lymph nodes size and the distant metastatic lesions were quantified on the co-registered PET/CT images by two experienced nuclear radiologists. The contrasted ^{18}F-FDGPET/CT changed the management intent in nine patients (64.7%). A univariate analysis showed that there were significant correlations between SUV_{max} and the size of the metastatic lymph nodes (R2 =0.0761, $p<0.01$), lymph node volume ($R^2=0.695$, $p<0.01$) and the T-stage ($R^2=0.647$, $p<0.01$). Multiple linear regression analysis revealed the tumour SUV_{max} to be the independent predictor of the T-stage (adjusted $R^2=0.889$, $p<0.05$). The SUV_{max} may potentially be a surrogate marker for the T-stage in the NPC patients. The use of the combined imaging modality, ^{18}F-FDGPET/CT, substantially impacted on the management strategy for treatment of NPC patients.

Keywords: ^{18}F-FDG PET/CT, nasopharyngeal carcinoma, AJCC-TNM staging), $SUV_{max,}$ impact

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is unique and distinguished from other head and neck malignant tumours because of its epidemiology, histopathological spectrum, clinical characteristics, therapy and biological behavior (Vokes et al., 2000; Yang et al., 2015). Distinct geographic variation in the incidence of NPC indicates an influence of genetic and environmental factors. Various reports revealed that the southern Chinese are an ethnically distinct and high-risk group for this particular tumour.The environmental factor is the ingestion of Cantonese-style salted fish especially in childhood. NPC presents most commonly as a neck lump in 50% to 70% of patients as a result of cervical lymph node metastases. The tumour may not be clinically apparent at the time of presentation (Goh et al., 2009). The symptoms are usually protracted and the disease manifests late in its course.

Positron Emission Tomography (PET) imaging has been reported to be the more sensitive imaging technique in detecting clinically occult metastatic disease, retropharyngeal lymph nodes, small volume lesions and distant metastases (Chang et al., 2005; Fathinul et al., 2009). The use of a glucose analogue (fluorodeoxyglucose, FDG) underpins the cancer cell reprogramming on the altered glycolytic metabolism, seen as areas of increased tracer uptake on the PET images. The standardised uptake value (SUV) is a measure of the FDG-intensity on the PET image and appears to be a reliable parameter in evaluating correlation with factors that determine the tumour's aggressiveness (Fathinul et al., 2013). All NPC cases in this study were regrouped into two histological types according to the WHO 1991 classification, namely keratinising squamous cell carcinoma (equivalent to WHO Type I) and non-keratinising carcinoma (pooling together WHO Type II non-keratinising and Type III undifferentiated carcinoma in the old terminology (Shanmugaratnam et al., 1991).

Although the five-year survival rate for overall NPC patients is high, around 90% of patients with distant metastases will die within one year (King et al., 2000). Thus, accurate staging and restaging of NPC are important for improving treatment and prognosis. As outlined by the AJCC (American Joint Committee on Cancer), the TNM staging system is the most important prognostic factor for appropriate treatment planning and survival prediction of NPC patients (Li et al., 2014). A revised AJCC-TNM staging 7th edition was released in 2009. There were several revisions in the new edition staging system compared to 6th edition. Li et al. compared the prognostic value of the TNM 6th edition and the TNM 7th edition for NPC patients. Their study demonstrated that the TNM 7th staging system is superior to the TNM 6th staging system in predicting the frequency of overall survival and distant metastases free survival (Li et al., 2014).

The superiority of the PET/CT to whole-body MRI in overall TNM staging supports the usefulness of ^{18}F-FDG PET/CT as a possible first-line modality for whole-body tumour staging (Antoch et al., 2003). The N stage was found to be prognostically significant even among patient groups stratified for the size and degree of fixation of the neck nodes involved (Antoch et al., 2003; Chen et al., 2007). Though irrelevant to the N staging of NPC, the SUV_{max} was correlated to the size of the lymph nodes and also related to the degree of differentiation of NPC

(Liu et al., 2012). Analysing the prognostic factors for nasopharyngeal carcinoma (Iacovelli et al., 2014) demonstrated that the most significant prognostic factors in nasopharyngeal carcinoma were patient age, T-stage of the primary tumour, presence of cervical lymphadenopathy and certain technical factors of irradiation. This study was set to evaluate the clinical application of FDG PET/CT in predicting the staging of NPC using SUV on the latest AJCC 7th edition and to determine its potential impact on the management strategy for treatment.

MATERIALS AND METHODS

Patient Accrual

This study was approved by the institutional ethical committee and obtained written consent from all the patients .We prospectively analysed the contrasted CT and ^{18}F-FDGPET/CT findings from 14 consecutive patients (mean age: 44.64±4.01) with histologically proven NPC. The exclusion criteria were children, acute or chronic inflammatory disease, pregnant patients, lactating mothers, terminally ill patients and any previous malignancy. Staging of the disease was done based on the 7th edition AJCC-TNM (American Joint Committee on Cancer-Tumor size, Lymph Nodes, Metastases) staging system based on both imaging modalities. The oncologist was asked to outline the patients' treatment management intent based on CT as well after PET/CT. The change in management intent and incremental information obtained after PET/CT imaging were compared and analysed.

^{18}F-FDG-PET/CT

All the subjects were required to fast for at least 6 hours prior to PET/CT, although oral hydration with glucose-free water was allowed. After verification of a normal blood glucose level in the peripheral blood (mean FBS), patients received an IV injection of 370 MBq (10 mCi) of FDG and then rested for approximately 60 minutes prior to the PET/CT imaging. Image acquisition was performed with an integrated PET/CT device (Siemens Biograph-64) consisting of a PET scanner (lutetium oxyorthosilicate) 64-MDCT scanner. The axes of both systems were aligned such that the patient could be moved from the CT scanner to the PET scanner with a movement of the examination table of up to 68 cm. Patients were allowed normal shallow respiration during acquisition of CT scan. The CT was performed with IV contrast (Iopamidol 300) at 5.0-mm spiral acquisition from base of skull to the proximal thigh for the purpose of anatomical localisation and attenuation correction to rescale the FDG-PET image attenuation. The PET emission was performed contemporaneously at 3 minutes per bed position acquisition. CT data were resized from a 512 × 512 matrix to a 128 × 128 matrix to match the PET data to allow image fusion and CT transmission maps were generated. PET image data sets were reconstructed iteratively with the ordered-subsets expectation maximisation algorithm with segmented measured attenuation correction (two iterations, 28 subsets) with the CT data. Co-registered images were displayed on the Siemens-Leonardo workstation.

Image Analysis

The SUV_{max} and the widest dimension of the primary tumour, size of the cervical lymph nodes and the distant metastatic lesions were quantified on the co-registered PET/CT images by two experienced nuclear radiologists who were blinded to the diagnosis. As for the CT, nodes with a short-axis diameter greater than 10 mm were defined as abnormal, and the presence of necrosis within a lymph node was considered a sign of malignancy, regardless of node size.

STATISTICS

Mean, SD, range and frequencies were used to describe the data. Differences in the mean of the variables were analysed via a non-parametric test (Kruskal Wallis) The clinical risk factors i.e. age, sex, SUV_{max} and tumour size were evaluated for independent predictors for the TNM staging (AJCC 7th edition) using the univariate and multivariate analysis. A two-sided p value of <0.05 was considered significant.

RESULTS

Patients Characteristics

Fourteen patients with nasopharyngeal carcinoma were included in this study with the mean age of 44.64± 4.01 years. They comprised four females and 10 males. Biopsy results were available for all patients with WHO (type 1) noted in one patient and WHO (type II) in the 13 others (Table 1). All the patients had pre-treatment CT and ^{18}F-FDG PET/CT for the purpose of TNM staging disease stratification for the intended management plan (Table 2).

Out of the 14 patients, five had early-stage disease (Stage I and Stage II) and of them, two were put on an altered treatment plan based on the PET-CT results. Nine patients were initially classified as having advanced stage disease (Stage III and Stage IV) and seven of these patients had their treatment altered following the findings of the PET-CT inaging. The PET-CT imaging accurately identified that the extension of the primary tumour and T staging had changed in the four patients. The PET-CT imaging had correctly identified the nodal stage in three patients and these patients benefitted by being having neoadjuvant chemotherapy added. Distant metastases were identified in four patients and thus, the management intent was changed from definitive to palliative intent. Nine (64.3%) patients had stage migration i.e. upstaging of the disease as shown in Table 3.There was no change in disease staging among five of the (35.3%) patients.

Table 1
Patient Characteristics

Parameter	Characteristic	n	%
Age	44.64±4.01 (years)		
Sex	Male	10	71.42
	Female	4	28.57
Histology	WHO (Type 1)	1	7.14
	WHO (Type 1I)	13	92.85

Table 2
Management Intent Based On CT and PET-CT

No	age	sex	CT staging	PET/CT staging	Management Intent	
					CT	PET/CT
P1	44	M	T1N3M0 IVB	T1N3bM0 IVB	3 cycles neoadj Ct then CtRT	3 cycles neoadj Ct then CtRT
P2	56	F	T1N2M0 III	T1N3bM0 IVB	CtRT	3 cycles neoadj Ct then CtRT
P3	50	M	T2N1M0 II	T4N1M0 IVA	CtRT	3 cycles neoadj Ct then CtRT
P4	70	M	T1N0M0 I	T1N0M0 I	RT alone	RT alone
P5	39	M	T2N2M0 III	T4N2M0 IVA	CtRT	3 cycles neoadj Ct then CtRT
P6	22	M	T1N1M0 I	T1N1M0 I	CtRT	CtRT
P7	65	M	T3N2M0 III	T3N3M0 IVB	CtRT	3 cycles neoadj Ct then CtRT
P8	46	M	T3N0M0 III	T4N0M1 IVC	CtRT	Chemotherapy – 6 cycles
P9	42	M	T3N3M0 IVB	T4N1M0 IVA	3 cycles neoadj Ct then CtRT	3 cycles neoadj Ct then CtRT
P10	55	F	T3N0M0 III	T4N0M1 IVC	CtRT	Chemotherapy – 6 cycles
P11	54	M	T2N2M0 III	T2N2M1 IVC	CtRT	Chemotherapy – 6 cycles
P12	22	M	T1N1M0 I	T2N1M0 II	CtRT	CtRT
P13	26	F	T2N2M0 III	T2N2M0 III	CtRT	CtRT
P14	34	F	T3N3M0 IVB	T3N3M1 IVC	3 cycles neoadj Ct then CtRT	Chemotherapy – 6 cycles

Note. NPC: Nasopharyngeal Carcinoma; CT: Computed Tomography;
PET/CT: Positron Emission Tomography/Computed Tomography;
RT: Radiotherapy; Ct: Chemotherapy; neoadj: neoadjuvant
CtRT: Chemoradiotherapy
M-male, F-Female

Table 3
Influence of PET-CT Findings on the Impact of Management Intent

Number of patients	Stage Migration/ shift	Management intent with CT	Management intent with PET/ CT	Impact on management intent
2	11 -1VA	CtRT	Neoadj Ct &CtRT	High
3	111-1V B	CtRT	Neoadj CT &CtRT	High
3	111 -1VC	CtRT	Chemotherapy alone	High
1	1VB-1VC	Neoadj Ct &CtRT	Chemotherapy alone	High

CT: Computed Tomography; PET/CT: Positron Emission Tomography/Computed Tomography; RT: Radiotherapy; Ct: Chemotherapy neoadj: neoadjuvant; CtRT: Chemoradiotherapy

Correlation of SUV_{max} and the Clinical Risk Parameters

As shown in Table 4, the univariate analysis showed significant correlations between SUV_{max} of the primary tumour and the widest diameter of metastatic lymph nodes (R^2=0.0.761, $p<0.01$) and the lymph node volume (R^2=0.695, $p<0.01$). There was no significant correlation with other continuous clinical risk parameters pertaining to the primary tumour with the SUV_{max}.

Table 4
Univariate Analysis of SUVmax Primary Tumour for Clinical Risk Variables

SUVmax mean 14.28±2.43 Clinical parameter/R^2	Mean	P value
Lymph node size (d/cm)	1.14±0.09	<0.01
Lymph node volume (cm^3)	3.05±0.47	<0.01

SUV_{max} as a Predictive Marker

Multiple linear regression analysis revealed the tumour SUV_{max} to be the independent predictor of the T-stage (adjusted R^2=0.889, $p<0.05$). There was no influence of the other clinical parameters on the SUV_{max}. The details of these are shown in the Table 5.

Table 5
Multivariate Analysis of the SUVmax for the Clinical Risk Variables (n=14)

Clinical parameter	HR (95% CI)	p
Age	0.433 ± 0.315	0.711
Sex	22.217± 11.19	0.450
Lymph node size	44.420± 10.23	0.177
No of lymph node	1.808± 1.94	0.931
T stage	11.564± 0.17	*0.045
N stage	6.167± 7.38	0.833
M stage	18.085± 13.14	0.712

* Statistical significant value ($p<0.05$)

DISCUSSION

Nasopharyngeal carcinoma is a progressive epithelial malignancy that is often under-staged by clinical examination (Chen et al., 2006). Accurate timely diagnosis of TNM staging is of paramount importance for appropriate treatment planning and prognosis (Zeng et al., 2014). The main effective method of treatment for NPC is radiotherapy and a good outcome is indicated if the disease is detected early in its course. The five-year overall survival rate is about 50% to 70% (Phua et al., 2013).

As shown in our study, the SUV_{max} for this diseases is significantly correlated with the size and the volume of the metastatic lymph nodes. These indicate that SUV_{max} as a marker for an altered glucose metabolism is an important signalling marker of the PET that reflects the tumour aggressiveness. This evidence clearly shows that the prevalence of the nodal metastasis is proportionally associated with tumour aggressiveness as reflected on the TNM staging. Information gathered from PET imaging complements the questionable sub-centimeter lymph node that is vastly imperceptible on the CT. This was reflected in our study and is seen in Table 2 (P2, P7& P9) which shows that the patients were upstaged based on the N-stage. This is in line with previous reports that stated that FDG PET-CT has higher accuracy in detecting cervical Lymph nodes than conventional imaging (Chang et al., 2005).

SUV_{max} was determined to be the only independent parameter for the T-staging. The finding further emphasised that the aggressiveness of the primary tumour was reflected by the intensity of the SUV_{max} concentration of the primary tumour. In this context, SUV_{max} plays a potential role in T-staging as determined in our study. This is in accordance with other reports that established the association of ^{18}F-FDG PET/CT on the T staging of NPC (Phua et al., 2013). Chen et al. compared ^{18}F-FDG PET/CT, PET and CT in the detection of the primary site of NPC and reported that the T stage was accurately determined in 18 out of 20 cases with ^{18}F-FDG PET/CT. Both PET alone and CT alone correctly assessed the T-stage in 15 out of 20 cases (Chen et al., 2006).

The SUV_{max} was found to be a statistically insignificant marker for the M staging in our cohort of patients compared with those in other reports, which stated the contrary in other cancer cell lines. The explanation for this is that our study cohort included a small number of patients, in whom the PET findings were positive for metastatic disease. There were only four patients (P8, P10, P11 and P14) who were found to have positive metastatic deposits on PET but none was discerned from the CT. Although no correlation was found between the SUV_{max} and the M-staging, it is noteworthy to highlight that PET had accurately detected two patients with skeletal metastasis on the FDG-PET. This is supported by the study by Liu et al., whose report showed that ^{18}F-FDG PET was more sensitive in detecting bone metastases compared to skeletal scintigraphy (Liu et al., 2006). Two patients in our study group were detected to have mediastinal nodal metastases by PET/CT. The treatment for all four patients with distant metastases was subsequently altered to palliative intent.

Our ^{18}F FDG PET/CT study findings had altered the management intent of 64.7% [9/14] patients based on the TNM-AJCC 7th edition. Among them, the PET /CT findings disclosed further evidence of distant metastases in 28% [4/14] patients. This study suggested ^{18}F-FDG uptake as measured by SUV_{max} in the PET-CT could potentially play a significant role in providing appropriate staging and adequate treatment planning.

Limitations

There were some limitations to our study. Some of the influence of the SUV_{max} did not seem to influence clinical parameters as stated in other studies. The potential attribute for this may be due to the small sample size calculated for a significant statistical test. A more cohesive method in preparing the patients for the PET-CT scanning and the scanning procedures should be adopted as to minimise factors that lead to image degradation. This was observed when the scanning time varied from 45 minutes to 90 minutes and some of the suboptimal images were not repeated to yield an image of better quality. It would also have had been better to include an MRI study in the comparative analysis with the CT imaging as the former is known to have better soft tissue resolution than the latter, thus providing better image interpretation.

CONCLUSION

While the SUV_{max} may potentially be a surrogate marker for the T-stage in NPC patients based on the 7th edition of AJCC-TNM staging, the use of the contrasted ^{18}[F]-FDGPET/CT substantially impacted on the management strategy for treatment of the disease.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

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