**Introduction**

Nasopharyngeal carcinoma (NPC) is an epithelial neoplasm that shows endemic distribution. The highest prevalence rates are in the South-Eastern Asia including Malaysia, Indonesia, Singapore, and South-Eastern China. It is considered a rare tumor of head and neck occurring in 10–30 persons per 100,000 people per year. The etiology of the disease is linked with the Epstein–Barr virus (EBV). NPC has the highest rate of lymph node and/or distant metastasis among the head and neck tumors with distant metastasis most commonly affecting the bones (approaching 70–80%) followed by the liver (30%) then the lungs (18%). Bone metastases are reported to be
the most frequent site of distant failure causing 30% of
deaths in advanced disease with studies suggesting that
the sites and number of bone metastasis may be prognostic
indicators for survival.[7] Growing evidence shows
that long-term survival and complete response can be
obtained among a small proportion of patients with bone
metastasis, especially those patients with a solitary lesion
who received aggressive treatment.[8] Hence, the detection
of distant metastases including bone metastasis is crucial
in the management and prognosis of NPC patients.

NPC is usually investigated by physical examination and
direct nasopharyngeal endoscopy with biopsy. Locoregional
involvement is evaluated by computed tomography (CT)
or magnetic resonance imaging (MRI) scans. Distant
metastases are assessed by plain chest radiographs,
ultrasonography of the liver and bone scintigraphy.[9]
Recently, positron emission tomography (PET)/CT with
18F-fluorodeoxyglucose (18F-FDG) is performed as a routine
procedure for diagnosing, staging, recurrence, and
follow-up of NPC patients. In addition, it is used to assess
local residual disease and response to treatment.

The aim of this study is to evaluate the imaging of the
distribution of bone metastases in NPC with 18F-FDG
PET/CT.

Materials and Methods

The patients
We reviewed the reports of 18F-FDG PET/CT scans of
histologically proven NPC patients performed in the
Nuclear Medicine and PET Department, Singapore
General Hospital, Singapore, between 2003 and 2009
using the Nuclear Medicine Information System. The
study was approved by the SingHealth Centralized
Institutional Review Board. The scans were interpreted
by nuclear medicine physicians.

We excluded all patients with additional second
malignancies from the study. We analyzed the reports
of patients with more than one PET/CT scan between
2003 and 2009 individually. We analyzed the data from
the reports for the following:
• Study indication (staging, response to treatment,
  recurrence, and follow-up)
• Locoregional nodal involvement
• Distant metastases, if any and their sites
• Sites of any bone lesions were carefully assessed and
  further analyzed for distribution.

18F-fluorodeoxyglucose positron emission
tomography/computed tomography scan
All patients fasted overnight or at least 6 h prior
to the scan and received between 333 and 518
MBq (9 and 14 mCi) of 18F-FDG calculated based on
body weight. PET/CT system (Biograph, Siemens, LSO
crystals) was utilized for image acquisition. A low dose
single slice CT with a slice thickness of 5 mm, KVp
from 80 to 130, and mAs range 200–400 was done from
the vertex of the skull to mid-thigh followed by PET
acquisition in the same area at 3 min per bed position.
The CT data were utilized for attenuation correction
and anatomical correlation. The PET data underwent
iterative reconstruction (24 subsets, 3 iterations).
Intravenous contrast was given when requested by the
referring physician.

Metastases determination
We considered all metastasis to be present if noted on
the report. We considered all the equivocal lesions as
negative though follow-up reports within the targeted
period were reassessed and were used to upgrade the
equivocal lesions if later turn to be positive.

Results

Patient demographics
A total of 722 reports of 18F-FDG PET/CT scans
performed on NPC patients imaged between 2003
and 2009 were reviewed. Five patients with additional
concurrent primary malignancies were excluded, and a
total of 717 reports (628 patients) were included in the
final analysis. Five hundred and fourteen patients were
male and 203 were female [Table 1]. The majority were
between 45 and 55 years of age.

The ethnic groups of the patients are listed in [Table 2].

The noted indications for the FDG PET/CT studies are
listed in [Table 3].

The total number of FDG avid metastatic lesions in
these reports was 709. Of these, 357/709 (50.35%) were

| Table 1: Age distribution of patients |
| Age | Number of reports | Percentage of total (%) |
|------|------------------|--------------------------|
| >35  | 41               | 5.72                     |
| 35-44 | 181              | 25.24                    |
| 45-55 | 291              | 40.59                    |
| >55  | 204              | 28.45                    |
| Total | 717              | 100.00                   |

| Table 2: The patient ethnic groups |
| Ethnic group | Number of reports | Percentage of total (%) |
|--------------|------------------|--------------------------|
| Chinese      | 614              | 85.63                    |
| Malay        | 13               | 1.81                     |
| Indians      | 1                | 0.14                     |
| Others       | 89               | 12.41                    |
| Total        | 717              | 100.00                   |
locoregional nodal metastases (retropharyngeal 115, cervical 226, and supraclavicular 16) [Table 4].

Distant metastases represented 352 (49.65%) of the 709 lesions. Of these, 192 were bone lesions (27.08%).

The distribution of bone lesions is cervical spine (13/192, 6.77%), clavicles (7/192, 3.65%), ribs (23/192, 11.98%), sternum (8/192, 4.17%), scapulae (15/192, 7.77%), humerus (6/192, 3.13%), thoracic spine (26/192, 13.54%), lumbar spine (27/192, 14.06%), sacrum (28/192, 14.58%), pelvic bones (28/192, 14.58%), and femora (13/192, 6.77%) [Table 5].

Discussion

NPC is an epidermoid-origin malignant neoplasm classified by the World Health Organization in two histological types of differentiated nonkeratinizing carcinoma (type II) and undifferentiated carcinoma (type III). It is a squamous cell carcinoma with very aggressive behavior, high incidence of locoregional lymph node, and distant metastasis at presentation.

Although that NPC is considered radiosensitive and curable, the 1-year mortality rate can reach 90% when distant metastasis is present at the presentation.[9] In patients with NPC, the presence of distant metastasis influences prognosis and treatment, so accurate evaluation of distant metastases is essential for the management.

Our study showed that about half of the metastatic lesions are at distant sites and that 192 (27%) of the 709 FDG avid metastases were in the bones.

Our incidence of bone metastases is slightly higher than other existing studies, for example, 15% by Liu et al.[6] and 11% (230 patients) by Caglar et al.[10]

The majority of the bone lesions 125/192 (65%) are in the axial skeleton with 109/192 (57%) in the lower skeleton (thoracolumbar spine, sacrum, and pelvis) Figure 1.

Bone metastases have even been reported in the femora and the feet[11] and as such some metastases in our study may have been outside the field of view of the scans.

FDG PET/CT is reported as useful in imaging NPC bone metastases[3,12] though there is controversy when comparing its usefulness relative to other modalities.

Vellayappan et al. conclude that for newly diagnosed NPC, 18F-FDG PET/CT is accurate in N and M staging but not T staging. They recommend using 18F-FDG PET/CT, together with MRI of the nasopharynx, in routine staging of NPC.[13]

A study comparing 18F-FDG PET/CT with 18F-sodium fluoride (18F-NaF) PET/CT and bone scintigraphy showed that 18F-NaF PET/CT is superior in detecting bone metastases followed by 18F-FDG PET/CT which was superior to technetium-99m based bone scintigraphy.[14]

Yang et al. showed that although 18F-FDG PET/CT is superior at lesion level, there was no statistical difference between 18F-FDG PET/CT and planar bone scintigraphy in detecting bone metastases in NPC.[12]
Recent meta-analysis by Wei et al. comparing 18F-FDG PET/CT, MRI, and single photon emission computed tomography (SPECT) in the diagnosis of local residual/recurrent NPC showed that SPECT and PET/CT are superior to MRI for the detection of local residual/recurrent NPC, and the addition of CT to PET will not significantly improve the diagnostic accuracy. They also concluded that 201TI-SPECT and MIBI-SPECT have the same diagnostic accuracy.[10]

Huang et al. evaluated the differences in prognostic values of static and dynamic PET/CT in NPC. The study concluded that the tumor volume from the static scan is useful in NPC prognosis, but they could not justify the role of dynamic scanning in their small study population.[16]

The PET/CT is also having a role in the management of NPC patients who develop distant metastasis after initial radiation therapy. Chang et al. showed that combining 18F-FDG PET/CT with aggressive treatment approach using locoregional modalities could be of benefit to NPC patients with favorable prognostic factors, even after distant metastasis.[17]

The role of PET in evaluating NPC is growing through the use of new PET radiotracers, for example, 68Ga-DOTA-TOC,[18] 68Ga-DOTA-NOC,[19] 11C-Choline,[20] and 18F-FLT[21] which can evaluate bone metastases from different aspects.

Prognostic biomarkers, for example, osteopontin[22] can have a crucial role in imaging and the management of bone metastases in NPC patients as well.

The study had few limitations as it is a retrospective study. Moreover, we did not account for the number of patients instead of the number of scans, albeit a minority did have multiple scans. Furthermore, the distant metastases were not proven histologically and we did not consider the SUV_\text{max} measurements. A recent study done by Xiao et al. showed that SUV_\text{max} at the primary site can be helpful biomarker in predicting distant metastasis of NPC patients treated with intensity modulated radiation therapy. Furthermore, combining SUV_\text{max} of the primary site with the overall tumor stage could be more precise to predict treatment outcome.[23]

Another limitation for the study is not considering the ethnicity of the patients and other factors in regards to bone metastases distribution.

Future prospective study with a large sample size is recommended to correlate metastases with the EBV titers and the treatment modality which will be of great benefit in the management of patients with NPC.

**Conclusion**

18F-FDG PET/CT has a role in the management of NPC and in evaluating bone metastases. A prospective study may help further assess the evolving role of PET/CT in NPC bone metastases particularly in light of the development of new PET/CT scanners, advances in scanning/processing technology, and the growing use of new PET tracers and prognostic biomarkers.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Yang Z, Shi Q, Zhang Y, Pan H, Yao Z, Hu S, et al. Pretreatment (18) F-FDG uptake heterogeneity can predict survival in patients with locally advanced nasopharyngeal carcinoma – A retrospective study. Radiat Oncol 2015;10:4.
2. Yen RF, Hong RL, Tzen KY, Pan MH, Chen TH. Whole-body 18F-FDG PET in recurrent or metastatic nasopharyngeal carcinoma. J Nucl Med 2005;46:770-4.
3. Liu FY, Lin CY, Chang JT, Ng SH, Chin SC, Wang HM, et al. 18F-FDG PET can replace conventional work-up in primary M staging of nonkeratinizing nasopharyngeal carcinoma. J Nucl Med 2007;48:1614-9.
4. Chang JT, Chan SC, Yen TC, Liao CT, Lin CY, Lin KJ, et al. Nasopharyngeal carcinoma staging by [18] F-fluorodeoxyglucose positron emission tomography. Int J Radiat Oncol Biol Phys 2005;62:501-7.
5. Bensouda Y, Kaikani W, Aboeddou N, Rahhali R, Jabri M, Mrabti H, et al. Treatment for metastatic nasopharyngeal carcinoma. Eur Ann Otorhinolaryngol Head Neck Dis 2011;128:78-95.
6. Liu FY, Chang JT, Wang HM, Liao CT, Kang CJ, Ng SH, et al. [18F] fluorodeoxyglucose positron emission tomography is more sensitive than skeletal scintigraphy for detecting bone metastasis in endemic nasopharyngeal carcinoma at initial staging. J Clin Oncol 2006;24:599-604.
7. Kapoor A, Kalwar A, Kumar N, Maharia S, Nirban RK, Kumar HS. Detection of bone metastasis in nasopharyngeal carcinoma by bone scintigraphy: A retrospective study in perspective of limited resource settings. Clin Cancer Invest J 2015;4(1):17.
8. Shen L, Dong J, Li S, Wang Y, Dong A, Shu W, et al. M1 stage subdivision and treatment outcome of patients with bone-only metastasis of nasopharyngeal carcinoma. Oncologist 2015;20:291-8.
9. Yen TC, Chang JT, Ng SH, Chang YC, Chan SC, Lin KJ, et al. The value of 18F-FDG PET in the detection of stage M0 carcinoma of the nasopharynx. J Nucl Med 2005;46:405-10.
10. Caglar M, Ceylan E, Ozyar E. Frequency of skeletal metastases in nasopharyngeal carcinoma after initiation of therapy: Should bone scans be used for follow-up? Nucl Med Commun 2003;24:1231-6.
11. Zhao CL, Qian GQ, Chen XY, Chen C. Retrograde analysis of clinical characteristics of bone metastasis in 1,031 cases of preliminarily diagnosed nasopharyngeal carcinoma. Asian Pac J Cancer Prev 2014;15:3785-8.
12. Yang Z, Zhang Y, Shi W, Zhu B, Hu S, Yao Z, et al. Is 18F-FDG PET/CT more reliable than 99mTc-MDP planar bone scintigraphy in detecting bone metastasis in nasopharyngeal carcinoma? Ann Nucl Med 2014;28:411-6.

13. Vellayappan BA, Soon YY, Earnest A, Zhang Q, Koh WY, Tham IW, et al. Accuracy of [18] F-fluorodeoxyglucose-positron emission tomography/computed tomography in the staging of newly diagnosed nasopharyngeal carcinoma: A systematic review and meta-analysis. Radiol Oncol 2014;48:331-8.

14. Iagaru A, Mittra E, Dick DW, Gambhir SS. Prospective evaluation of [99mTc] MDP scintigraphy, [18]F NaF PET/CT, and [18]F FDG PET/CT for detection of skeletal metastases. Mol Imaging Biol 2012;14:252-9.

15. Wei J, Pei S, Zhu X. Comparison of 18F-FDG PET/CT, MRI and SPECT in the diagnosis of local residual/recurrent nasopharyngeal carcinoma: A meta-analysis. Oral Oncol 2016;52:11-7.

16. Huang B, Wong CY, Lai V, Kwong DL, Khong PL. Prognostic value of [18]F-FDG PET-CT in nasopharyngeal carcinoma: Is dynamic scanning helpful? Biomed Res Int 2015;2015:582614.

17. Chang JH, Ahn YC, Park H, Oh D, Noh JM, Sun JM, et al. Fate of patients with nasopharyngeal cancer who developed distant metastasis as first failure after definitive radiation therapy. Head & neck 2014. [DOI: 10.1002/hed.23980].

18. Schartinger VH, Dudás J, Url C, Reinold S, Virgolini IJ, Kroiss A, et al. 68Ga-DOTA-Tyr3-octreotide positron emission tomography in nasopharyngeal carcinoma. Eur J Nucl Med Mol Imaging 2015;42:20-4.

19. Khor LK, Loi HY, Sinha AK, Tong KT, Goh BC, Loh KS, et al. (68) Ga-DOTA-peptide: A novel molecular biomarker for nasopharyngeal carcinoma. Head Neck 2016;38:76-80.

20. Jiang J, Wu H, Huang M, Wu Y, Wang Q, Zhao J, et al. Variability of gross tumor volume in nasopharyngeal carcinoma using 11C-choline and 18F-FDG PET/CT. PLoS One 2015;10:e0131801.

21. Zheng Y, Yang Z, Zhang Y, Shi Q, Bao X, Zhang J, et al. The preliminary study of 18F-FLT micro-PET/CT in predicting radiosensitivity of human nasopharyngeal carcinoma xenografts. Ann Nucl Med 2015;29:29-36.

22. Hou X, Wu X, Huang P, Zhan J, Zhou T, Ma Y, et al. Osteopontin is a useful predictor of bone metastasis and survival in patients with locally advanced nasopharyngeal carcinoma. Int J Cancer 2015;137:1672-8.

23. Xiao W, Xu A, Han F, Lin X, Lu L, Shen G, et al. Positron emission tomography-computed tomography before treatment is highly prognostic of distant metastasis in nasopharyngeal carcinoma patients after intensity-modulated radiotherapy treatment: A prospective study with long-term follow-up. Oral Oncol 2015;51:363-9.