Clinical Radiology 74 (2019) 818.e9–818.e15

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Imaging characteristics of nasopharyngeal carcinoma for predicting distant metastasis

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ARTICLE INFORMATION

Article history:
Received 14 December 2018
Accepted 28 June 2019

AIM: To determine the imaging characteristics of nasopharyngeal carcinoma (NPC) that may be associated with increased risk of distant metastasis.

MATERIALS AND METHODS: A total 164 patients with NPC were reviewed retrospectively. Patients were divided into the metastatic group ($n=110$) or the non-metastatic group ($n=54$). Non-metastatic was defined as no evidence of distant metastasis during at least 5 years of follow-up. Pretreatment images of the primary tumour and nodal involvement were analysed. Statistical analyses were performed to identify the factors that may predict distant metastasis.

RESULTS: The statistically significant sites of tumour extension in the metastatic group included: skull base bone ($p<0.001$), cervical spine (C-spine; $p=0.012$), parapharyngeal space ($p=0.003$), pterygopalatine fossae (PPF; $p=0.004$), prevertebral space ($p<0.001$), masticator space ($p=0.006$), carotid space ($p=0.001$), and intracranial extension ($p=0.004$). Statistically significant nodal involvement included bilateral involvement ($p=0.04$), size 3–6 cm ($p=0.011$), >10 pathological nodes ($p<0.001$), level IB ($p=0.013$), IIB ($p=0.011$), III ($p=0.001$), IV ($p<0.001$), VB ($p=0.001$), and supraclavicular ($p=0.003$) and intraparotid nodes ($p=0.004$). The mean number of significant involvement factors was significantly higher in the metastatic group (3.46 ± 2.24 tumour extension sites and 5.04 ± 2.51 nodal involvement factors) than in the non-metastatic group ($p<0.001$).

CONCLUSION: NPC patients with local extension at more than three sites and with more than five nodal involvement factors should be screened for distant metastasis.

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common head and neck cancers, with endemic distribution in Southern China, Southeast Asia, Africa, and the Middle East.[1] Magnetic resonance imaging (MRI) is preferred to computed tomography (CT) for primary and nodal staging of NPC. Staging of NPC according to the 8th edition of the American Joint Committee on Cancer TNM staging system relies on evaluation of the primary tumour (T category), the draining nodal groups (N category), and evidence or absence of metastatic disease (M category).

NPC has a higher incidence of distant metastasis compared to other head and neck cancers.[2] Distant metastasis is found in approximately 5% of patients at diagnosis.[3]

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https://doi.org/10.1016/j.crad.2019.06.031
0009-9260/

The most common sites of metastasis are bone (20%), lung (13%), and liver (9%).[4]

Parapharyngeal invasion is associated with an increased risk of distant metastasis and decreased survival rate.[5–7] Lee *et al.* showed that invasion of the prevertebral space was associated with an increased risk of distant metastasis.[8] King *et al.* reported that nodal metastases at the supraclavicular fossa increased the incidence of distant metastases.[9]

Several countries have their own national guidelines, which have been developed with consensus of multiple cancer centres for diagnosis, staging, treatment and follow-up recommendations for NPC. In the United States, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for head and neck cancers version 2018 recommends a complete imaging screening for distant metastasis at any N and any T stages of NPC. The suggested imaging methods for distant metastasis include combined 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-positron-emission tomography (PET)/CT and/or CT of the thorax with contrast medium; however, these imaging methods are not used in practice in Thailand due to the considerable cost and restricted access.[10] Chest radiography and ultrasonography of the liver are frequently used with individual adjustment to detect metastasis despite their lower sensitivity. Likewise, bone scintigraphy is also used despite its lower specificity.

The presence of distant metastasis alters the staging of the disease and it influences the treatment of NPC. Radiotherapy is the mainstay of treatment, whereas chemotherapy becomes the primary treatment in cases with distant metastasis or locoregional advanced disease (Table 1).

No imaging guideline or protocol has yet been developed for the early detection of distant metastasis. Identification of factors that predict distant metastasis on imaging may improve treatment outcome, quality of life, and patient survival. Accordingly, the aim of this study was to determine the imaging characteristics of NPC that may be associated with increased risk of distant metastasis.

Table 1
NCCN guidelines version 2.2018. Cancer of nasopharynx.[10]

Clinical staging	Treatment of primary head and neck
T1, N0, M0	- Definitive radiotherapy to nasopharynx and elective radiotherapy to neck
T1, N1–3; T2–4, any N	- Clinical trials (preferred) or - Concurrent chemo/radiotherapy followed by adjuvant chemotherapy or - Induction chemotherapy followed by chemo/radiotherapy or - Concurrent chemo/radiotherapy not followed by adjacent chemotherapy
Any T, any N, M1	- Clinical trials (preferred) or - Platinum-based combination chemotherapy → radiotherapy to primary and neck or chemo/radiotherapy as clinically indicated or - Concurrent chemo/radiotherapy

Materials and methods

Patients

Data from patients who were diagnosed with NPC at King Chulalongkorn Memorial Hospital during the January 2007 to November 2017 study period were reviewed retrospectively and recorded. Collected data included baseline characteristics, histology of the primary cancer, and imaging data. Patients with no pretreatment imaging of the primary tumour were excluded from the study. Pretreatment imaging of the primary cancer included CT, PET/CT and/or MRI, which were performed at King Chulalongkorn Memorial Hospital or at other hospitals. Patients with evidence of distant metastasis from imaging or histopathology were classified into the metastasis group and patients who did not have metastasis during at least a 5-year follow-up were classified into the non-metastasis group. The protocol for this study was approved by the Institutional Review Board (IRB) for retrospectively review, and informed consent was waived.

Image analysis

Patient imaging data from the picture archiving and communication system (PACS) were reviewed independently by a neuroradiologist with 8 years of experience in neuroimaging and a second-year fellow of diagnostic neuroimaging. Any disagreements in the interpretation were resolved in consensus. The primary site of NPC was staged using CT in 46 of 110 patients with metastasis (41.8%), and using MRI in the remaining 64 patients (58.2%). In the non-metastatic group, 32 of 54 patients (59.3%) were staged using CT, 20 of 54 patients (37%) were staged using MRI and two of 54 patients (3.7%) were staged using PET/CT.

Primary tumour extension

Areas of primary tumour extension included skull base (temporal, occipital, sphenoid and ethmoid bones), cervical spine (C-spine), parapharyngeal space, pterygopalatine fossae (PPF), prevertebral space, masticator space, carotid space, parotid space, intracranial extension (including extra-axial mass, Meckel's cave and cavernous sinus involvement), orbit, paraspinal region, skin/subcutaneous tissue and the nasal cavity.

Parapharyngeal space extension was defined when the tumour spread posterolaterally and then laterally penetrated through the levator palatini muscle and pharyngobasilar fascia, which involved the tensor palatini muscle and parapharyngeal fat space (Fig 1). The involvement of skull base bone and C-spine was defined as[1] loss of normal fatty marrow on the T1-weighted sequence on the MRI images or[2] permeative or erosive bone changes and sclerosis of the bone with increased attenuation of medullary cavity or thickening of cortical bone on CT images (Fig 2). Carotid space involvement was defined as the tumour internal carotid artery without fat plane separation

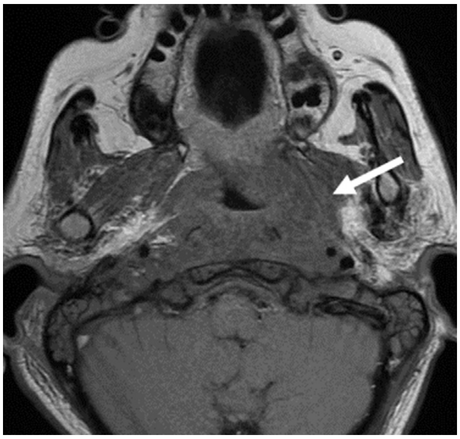

Figure 1 Parapharyngeal extension (arrow) of the NPC on Axial T1-weighted image showing posterolaterally and laterally penetration through the levator palatini muscle and pharyngobasilar fascia and involvement of the tensor palatini muscle and parapharyngeal fat space.

(Fig 3). Nasal cavity involvement was defined when the tumour extended anteriorly through the posterior choanae.

The apparent diffusion coefficient (ADC) of the primary tumour and pathological nodes was analysed using diffusion-weighted MRI sequences using b-values of 0 and 1,000 s/mm^2. Several regions of interest (ROIs; size <10 mm^2) were placed in the solid areas in several sections, and then the lowest mean ADC value was used to represent the ADC value of the lymph node.

Lymph node involvement

The number, size, lateralisation, and level of pathological nodes were recorded. Pathological nodes were diagnosed by imaging criteria as follows: (1) retropharyngeal lymph nodes (RLN) with a minimum axial diameter of 5 mm in the largest plane, cervical lymph nodes (CLN) in the jugulodigastric region with a minimum axial diameter of 11 mm and any other CLN with a minimum axial diameter of 10 mm, (2) the ratio of the maximum longitudinal nodal length to the maximum axial nodal length (L/T) <2 and (3) lymph nodes of any size with necrosis or extracapsular spread. The level of nodal involvement was classified according to the imaging-based nodal classification system published by Som *et al.*[11]

Distant metastasis

Distant metastasis was confirmed by bone scintigraphy, CT of the thorax and abdomen, MRI, or CT of the spine. The

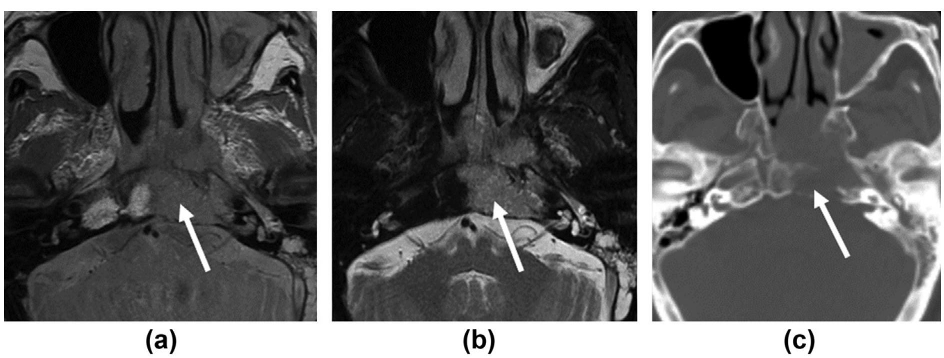

Figure 2 Skull base involvement of the NPC seen as loss of normal fatty marrow on Axial T1 and T2-weighted images (arrow in A and B) at clivus and bone erosion on Axial CT image (arrow in C).

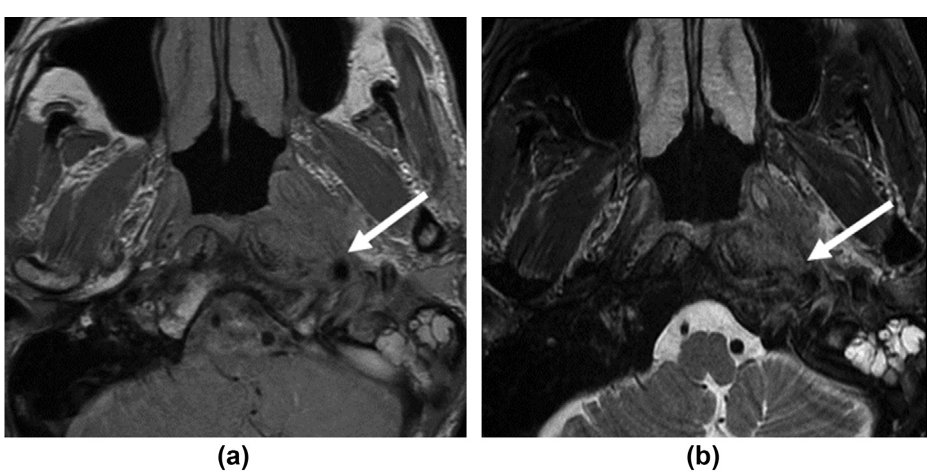

Figure 3 Carotid space involvement of the NPC on Axial T1 and T2-weighted image (arrow in A and B) showing loss fat separation plane with the left internal carotid artery.

sites of distant metastasis including bone, liver, lung, and other organs were recorded. The duration from the first imaging to the presence of metastasis was recorded. Synchronous metastasis was defined when the duration was $\leq$6 months. Metachronous metastasis was defined when the duration was >6 months. Early metastasis was defined when the duration was $\leq$12 months.

Statistical analysis

Statistical analyses were performed to compare data between the metastasis and non-metastasis groups using SPSS software, version 22.0 (SPSS, Chicago, IL, USA). Subgroup analyses in the metastatic group were performed. Chi-square test and independent *t*-test were used to compare categorical and continuous data, respectively. Categorical data are shown as number and percentage, and continuous data are presented as mean ± standard deviation (SD). A difference between groups with a *p*-value of <0.05 was considered statistically significant.

Tumour extension factors included skull base, C-spine, parapharyngeal space, PPF, prevertebral space, masticator space, carotid space, and intracranial extension. Nodal involvement factors included bilateral involvement, size 3–6 cm, >10 nodes, level IB, IIB, III, IV, VB supraclavicular and intraparotid nodes. The number of significant involvement factors for each patient was calculated. Prevalence rate ratios (PRRs) of the number of significant factors were calculated. The mean ± SD of the number of significant involvement factors in each group was calculated.

Results

There were 110 NPC patients in the metastasis group and 54 patients in the non-metastasis group. The mean age at diagnosis between the metastasis group (50.7 years) and non-metastasis group (49.4 years) was not significantly different. Synchronous metastasis was found in 38.2% of patients in the metastasis group, and metachronous metastasis was found in 61.8%. The mean duration of metastasis in the metachronous group was approximately 23 months. The metastatic-free period of the patients in the non-metastatic group ranged from 60 to 133 months (mean ± SD 87.8±21.6). Undifferentiated non-keratinising carcinoma was the most common tumour histology in both the metastasis and the non-metastasis group; however, differentiated non-keratinising carcinoma was significantly more common in the metastasis group than in the non-metastatic group (p=0.04). The demographic and clinical characteristics of patients are shown in Table 2.

Significant extension of the primary tumour and significant nodal involvement between groups are shown in Tables 3 and 4, respectively. The mean number of significant involvement factors in the metastatic group was significantly higher than in the non-metastatic group (p<0.001). In the metastatic group, the total number of significant involvement factors was 8.50±3.20 (tumour extension 3.46±2.24 sites plus nodal involvement 5.04±2.51 factors). In the non-metastatic group, the total number of significant involvement factors was 4.57±2.70 (tumour extension 1.61±1.76 sites plus nodal involvement 2.96±1.63 factors). There were 10 cases of diffusion-weighted MRI sequences that included both the metastasis group (n=7) and the non-metastasis group (n=3). The ADC value of the primary tumour showed no statistically significant difference between groups ($706.68\pm76.51\times10^{-6}$ mm^2/s in the metastasis group versus $612.74\pm242.17\times10^{-6}$ mm^2/s in the non-metastasis group; p=0.573). The most common site of distant metastasis was bone (n=82, 74.5%), followed by lung (n=57, 51.8%) and liver (n=57, 51.8%). Other sites of metastasis were pleura (n=6, 5.5%), kidney (n=2, 1.8%) and spleen (n=1, 0.9%).

Subgroup analysis of metastasis occurring within 12 months showed nodal classification level IV (p=0.003), level VA (p=0.001), level VB (p=0.01), supraclavicular node (p=0.03), and >10 pathological nodes (p=0.002) to be significantly different when compared to the group of patients that developed metastasis after 12 months (Table 5). In contrast, lymph nodes of <1 cm and fewer than five lymph nodes were significantly more evident in patients who developed late metastasis after 24 months (p=0.014 and p=0.001, respectively). Carotid space involvement was the only significant extension factor for metastasis occurring of earlier than 24 months (p=0.018).

Subgroup analysis of the site of metastasis revealed the following findings. A comparison between the liver

Table 2
Patient demographic and clinical characteristics.

	Non-metastatic group (n=54)		Metastatic group (n=110)		p-Value
	n	%	n	%	
Age					
Mean±SD	54	49.43±12.84	110	50.69±12.92	0.556
Gender					
Male	33	61.1%	88	80%	
Female	21	38.9%	22	20%	
Histology					
Keratinising squamous cell carcinoma	2	3.7%	2	1.8%	0.616
Non-keratinising carcinoma, differentiated type	5	9.3%	25	22.7%	0.042*
Non-keratinising carcinoma, undifferentiated type	34	63%	60	54.5%	0.067
Mixed non-keratinising differentiated and undifferentiated type	1	1.9%	1	0.9%	

A p-value of <0.05 indicates statistical significance.

Table 3
Extension of primary tumour involvement.

Sites	Non-metastasis (*n*=54)		Metastasis (*n*=110)		*p*-Value	PRR (95%CI)
	n	%	*n*	%		
Skull base bone	24	44.4%	79	71.8%	<0.001*	1.51 (1.15,1.97)
Sphenoid	23	42.6%	75	68.2%	0.002*	1.44 (1.12, 1.86)
Occipital	13	24.1%	62	56.4%	<0.001*	1.53 (1.23, 1.91)
Temporal	12	22.2%	59	53.6%	<0.001*	1.52 (1.23, 1.87)
C-spine	0	0%	12	10.9%	0.012*	1.55 (1.38, 1.75)
Parapharyngeal space	16	29.6%	60	54.5%	0.003*	1.39 (1.12, 1.72)
PPF	11	20.4%	48	43.6%	0.004*	1.38 (1.13, 1.68)
Prevertebral space	21	38.9%	87	79.1%	<0.001*	1.96 (1.41, 2.72)
Masticator space	1	1.9%	18	16.4%	0.006*	1.49 (1.27, 1.76)
Intracranial extension	6	11.1%	35	31.8%	0.004*	1.4 (1.16, 1.69)
Carotid space	7	13%	43	39.1%	0.001*	1.46 (1.21, 1.77)

A *p*-value of <0.05 indicates statistical significance.
PRR, prevalence rate ratio; CI, confidence interval; PFF, pterygopalatine fossae.

Table 4
Characteristics of nodal involvement.

Characteristics	Non-metastasis (*n*=54)		Metastasis (*n*=110)		*p*-Value	PRR (95%CI)
	n	%	*n*	%		
Bilateral	40	74.1%	94	85.5%	0.040*	1.32 (0.92, 1.87)
Size						
3–6 cm	8	14.8%	37	33.6%	0.011*	1.34 (1.1, 1.63)
Number						
>10	7	13%	62	56.4%	<0.001*	1.78 (1.44, 2.2)
Level						
IB	2	3.7%	19	17.3%	0.013*	1.42 (1.18, 1.71)
IIB	46	85.2%	104	94.5%	0.011*	1.62 (0.88, 2.99)
III	32	59.3%	89	80.9%	0.001*	1.51 (1.09, 2.08)
IV	12	22.2%	59	53.6%	<0.001*	1.52 (1.23, 1.87)
VB	11	20.4%	52	47.3%	0.001*	1.44 (1.17, 1.76)
Supraclavicular	0	0%	16	14.5%	0.003*	1.57 (1.39, 1.78)
Intraparotid	2	3.7%	23	20.9%	0.004*	1.47 (1.24, 1.75)

A *p*-value of <0.05 indicates statistical significance.
PRR, prevalence rate ratio; CI, confidence interval.

Table 5
Early metastasis compared between 12 months or earlier and longer than 12 months.

Factors	Time from 1st image to metastasis		*p*-Value	PRR (95%CI)
	≤12 months (*n*=61), *n* (%)	>12 months (*n*=49), *n* (%)		
Node				
>10	43 (70.5%)	19 (38.8%)	0.002*	2.04 (1.32, 3.13)
Level				
IV	41 (67.2%)	18 (36.7%)	0.003*	2.0 (1.28, 3.13)
VA	41 (67.2%)	17 (34.7%)	0.001*	2.08 (1.33, 3.33)
VB	36 (59%)	16 (32.7%)	0.010*	1.85 (1.16, 2.94)
Supraclavicular	13 (21.3%)	3 (6.1%)	0.030*	2.63 (0.92, 7.14)

A p-value of <0.05 indicates statistical significance.
PRR, prevalence rate ratio; CI, confidence interval.

metastasis subgroup (*n*=57, 51.8%) and the non-liver metastatic subgroup showed the tumour extension to be significantly involved in the parapharyngeal space (*n*=38, 66.7%, *p*=0.008), sphenoid bone (*n*=44, 77.2%, *p*=0.035), occipital bone (*n*=38, 66.7%, *p*=0.024), temporal bone (*n*=37, 64.9%, *p*=0.014), ethmoid bone (*n*=9, 15.8%, *p*=0.036), intracranial extension (*n*=25, 43.9%, *p*=0.005), and nasal cavity (*n*=23, 40.4%, *p*=0.046). A comparison between the lung metastasis subgroup (*n*=57, 51.8%) and the non-lung metastatic subgroup revealed significantly more involvement in the carotid space (*n*=28, 49.1%, *p*=0.025). In the bone metastasis subgroup (*n*=82, 74.5%), there was no significant difference in tumour extension compared to non-bone metastasis group.

Subgroup analysis of patients with one site versus those with multiple sites of distant metastasis revealed that the patient with multiple sites of distant metastasis had significantly more involvement of the prevertebral space

(p=0.008), intracranial extension (p=0.009), carotid space (p=0.026), parapharyngeal space (p=0.031), and orbit (p=0.036).

Discussion

The results of this study revealed factors that were significantly associated with distant metastasis in NPC. Those factors were identified from two broad groups of factors that were investigated, including the sites of tumour extension and lymph node characteristics. The sites of tumour extension included the following eight factors: skull base bones, C-spine, parapharyngeal space, PPF, prevertebral space, masticator space, carotid space, and intracranial extension. The characteristics of nodal involvement included the following 10 factors: bilateral involvement, node size 3–6 cm, >10 pathologic nodes, nodal level IB, IIB, III, IV, VB, supraclavicular nodes and intraparotid nodes.

The mean total number of significant involvement factors in the metastasis group and non-metastasis group was 8.50±3.20 and 4.57±2.70, respectively. This finding suggests that patients with a total factor number over five may be at increased risk for distant metastasis. In the metastasis group, the mean number of tumour extension factors was 3.46±2.24, and the mean number of nodal involvement factors was 5.04±2.51. Therefore, the authors suggest a guideline for whole-body imaging screening such as CT, PET/CT, or MRI for early detection of and surveillance for metastasis in NPC patients who have more than three sites with local extension and more than five nodal factors. This finding is consistent with the evidence-based indications for the use of PET/CT in the UK 2016[12] that a complete search for distant metastasis using PET/CT is recommended in patients with advanced locoregional disease.

More than 10 pathological nodes, node levels IV, VA, VB and supraclavicular node involvement were significantly more common in patients with early metastasis within 12 months from the first imaging study than in the later than 12 months subgroup (Table 4). These findings might suggest the use of early imaging screening for metastasis, especially in the first year after diagnosis. Early metastasis was more commonly detected in all of the uncommon lymph nodes including level I node, intraparotid, occipital, subpectoral, paratracheal, and axilla nodes, at ≤12 or ≤24 months; however, not at a significant level. This might be due to the fact that such nodes are few in number; however, it is likely that these uncommon nodes will be significant predictors of early metastasis if larger studies are undertaken with a larger cohort of patients.

Smaller-sized nodes and fewer nodes were not found to be significant factors for metastasis of NPC; however, these findings did not entirely exclude the likelihood of metastasis. In contrast, larger-sized nodes and a greater number of nodes were significant factors and were also associated with early spread after diagnosis. Based on the present study, no metastasis was observed in patients with small-sized nodes <1 cm within the first 12 months, but metastasis was detected later. This supports the NCCN guideline 2018 version 2, which suggests imaging for distant metastasis in any T and N stage[10]; however, the present findings may improve the ability to identify patients at increasing or greater risk of developing distant metastasis so they can be referred for screening earlier. The only significant extension factor for early metastasis during ≤24 months was carotid space involvement. This may be explained by the richness of vascular and lymphatic structures in this space and the anatomical location where the skull base is connected to the mediastinum.

Several studies have investigated for factors that predict metastasis in NPC. Teo *et al.*[5] reported parapharyngeal tumour involvement to be a significant predictor of determining distant metastasis and survival. Cheng *et al.*[6] found invasion into the parapharyngeal space and marrow of skull base to be associated with a higher incidence of distant metastasis. Ho *et al.*[7] identified and reported parapharyngeal invasion to be associated with increased risk for distant metastasis. Lee *et al.*[8] found prevertebral space invasion to be significantly associated with increased risk for distant metastasis. The results of this study were consistent with these aforementioned previous studies. In our study, the highest PRR among the evaluated tumour extension factors was prevertebral space (PRR=1.96) and the highest PRR among the nodal involvement factors was the supraclavicular node (PRR=2.63). The previous studies mentioned here mainly studied patient prognosis and survival. In contrast, the present study also evaluated extension sites of primary tumour and nodal involvement that might be significantly associated with distant metastasis. The present study also included a larger number of patients with metastasis than the numbers of metastatic patients enrolled in similar previous studies.

This study has several mentionable limitations. First, the retrospective nature of this study renders it vulnerable to missing or incomplete data. Second, as 95% of distant metastasis occurs within 5 years,[13] patients in the non-metastatic group can still develop metastasis in the future; however, most metastasis occurs during the first 2 years and the mean metastasis-free period in the non-metastatic group was approximately 7 years. Third, the imaging data in this study were from several techniques including CT, PET/CT, and MRI. Different techniques have different imaging resolution and criteria for determining tumour involvement. The CT and MRI images from other hospitals had different thickness and image quality, which adversely impacted image interpretation. Fourth, there were two cases with pretreatment imaging of the primary tumour only with no pretreatment imaging of cervical node involvement. Local extension of the primary tumour was determined by imaging without histological confirmation, which could lead to false-positives and false-negatives in data categorisation, especially in osseous involvement. Fifth, approximately 22% (12 of 54) of patients in the non-metastasis group and 20% (22 0f 110 patients) of the metastasis group did not have histopathological results in the hospital's computer databases. This may be due to the biopsy being performed at another hospital or because the diagnosis was based solely on the imaging data. Sixth, some nodal metastases were located across the imaginary lines drawn from anatomical landmarks for nodal classification. Therefore, the levels of these lymph nodes were classified according to the location of the major part of the lymph nodes. Seventh and last, although the ADC value of primary tumour and pathologic nodal involvement in this study showed no significant difference in ADC value of primary tumour, the number of patients who had pretreatment MRI with DWI sequences was small. Further study using MRI with DWI sequence as the only imaging method may more accurately demonstrate the factors that predicting metastasis in patients with NPC.

In conclusion, the present study revealed significant imaging characteristics of NPC for predicting distant metastasis. The results of this study suggest that NPC patients with local extension at more than three sites and that have more than five nodal involvement factors should receive an imaging screening for distant metastasis.

Conflict of interest

The authors declare no conflict of interest.

References

1. Chang ET, Adami H. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* 2006;**15**(10):1765–77.
2. Wei WI, Sham JST. Nasopharyngeal carcinoma. *Lancet* 2005;**365**:2041–54.
3. Teo PM, Kwan WH, Lee WY, *et al*. Prognosticators determining survival subsequent to distant metastasis from nasopharyngeal carcinoma. *Cancer* 1996;**77**:2423–31.
4. Razek A, King A. MRI and CT of nasopharyngeal carcinoma. *AJR Am J Roentgenol* 2012;**198**:11–8.
5. Teo P, Lee WY, Yu P. The prognostic significance of parapharyngeal tumour involvement in nasopharyngeal carcinoma. *Radiother Oncol* 1996;**39**:209–21.
6. Cheng SH, Tsai SY, Yen KL. Prognostic significance of parapharyngeal space venous plexus and marrow involvement: potential landmarks of dissemination for stage I-III nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2005;**61**:456–65.
7. Ho HC, Lee MS, Hsiao SH. Prognostic influence of parapharyngeal extension in nasopharyngeal carcinoma. *Acta Otolaryngol* 2008;**128**:790–8.
8. Lee CC, Chu ST, Chou P, *et al*. The prognostic influence of prevertebral space involvement in nasopharyngeal carcinoma. *Clin Otolaryngol* 2008;**33**:442–9.
9. King A, Bhatia KS. Magnetic resonance imaging staging of nasopharyngeal carcinoma in the head and neck. *World J Radiol* 2010;**2**:159–65.
10. NCCN guidelines version 2. *Cancer of the nasopharynx*. March 14, 2019. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
11. Som PM, Curtin HD, Mancuso AA. Imaging-based nodal classification for evaluation of neck metastatic adenopathy. *AJR Am J Roentgenol* 2000;**174**:837–44.
12. The Royal College of Radiologists, Royal College Of Physicians Of London; Royal College Of Physicians And Surgeons Of Glasgow; Royal College Of Physicians Of Edinburgh; British Nuclear Medicine Society; Administration Of Radioactive Substances Advisory Committee. Evidence-based indications for the use of PET-CT in the United Kingdom, 2016. *Clin Radiol* 2016;**71**:e171–88.
13. Hsu MM, Tu SM. Nasopharyngeal carcinoma in Taiwan clinical manifestations and results of therapy. *Cancer* 1983;**52**:362–8.