

## Imaging of Nasopharyngeal Carcinoma

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### Abstract

**Nasopharyngeal cancer (NPC) is a unique disease that shows clinical behaviour, epidemiology and histopathology that is different from that of other squamous cell carcinomas of the head and neck. Magnetic resonance imaging (MRI) is now the preferred imaging modality in the assessment and staging of NPC, especially in relation to its superior soft tissue contrast, ability to demonstrate perineural tumour spread, parapharyngeal space, bone marrow involvement and its ability to show the involvement of adjacent structures, such as the adjacent paranasal sinuses and intracranial extension. An understanding of its patterns of spread and the criteria used in the AJCC TNM staging system is important to relay the relevant information to the referring clinician, so that appropriate treatment planning decisions may be made. In this article, the various features of NPC that are pertinent to staging and treatment planning will be discussed, inclusive of locoregional spread, nodal involvement and metastatic disease.**

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**Key words:** Magnetic resonance imaging, Staging

### Introduction

Nasopharyngeal cancer (NPC) is considered an Asian disease, particularly in the southern Chinese population; the incidence in Guangzhou is quoted to be up to 800 cases per million people.<sup>1</sup> It is rare in the rest of the world, although NPC has spread to other areas of the world due to immigration. Intermediate rates are recorded in areas such as Southeast Asia, Hong Kong, Taiwan and locations with large numbers of immigrant Chinese such as San Francisco and New York. A high incidence in non-Chinese populations has also been found, such as the indigenous Bidayuh people of Sarawak.<sup>2</sup>

There are 3 histologic subtypes of NPC, which vary in their clinical behaviour and prognostic significance. Type I (keratinising squamous cell carcinoma) is the least common, found in non-endemic areas, carries the least favourable prognosis, and is similar to squamous cell carcinomas of oropharyngeal origin with a relation to alcohol and tobacco use. Types II (non-keratinising squamous cell carcinoma) and III (undifferentiated carcinoma) are more common, carry a more favourable prognosis and are more sensitive to radiotherapy.

The elevated nitrosamine content in salted/preserved foods and fermented dietary items are thought to be a

causative factor, while the presence of HLA A2 and B Sin2, particularly on the same chromosome, is thought to confer an increased susceptibility to developing NPC. Epstein-Barr virus (EBV) infection is ubiquitous in the East Asian region and found in NPC cells of the type II and III varieties, and in dysplastic cells of precursor lesions, but not in normal nasopharyngeal cells.

### Anatomy

The nasopharynx is a fibromuscular sling whose shape is maintained by the pharyngobasilar fascia, which acts as a temporary barrier to the spread of NPC. The fossa of Rosenmuller is the most common site of origin. This variably-sized recess lies posterior and superior to the Eustachian tube on axial and coronal images respectively, separated by the torus tubarius overlying the Eustachian tube opening (Fig. 1a).<sup>3</sup>

The nasopharynx is related laterally to the fibrofatty parapharyngeal space, the pterygoid bodies and plates anterolaterally. The retropharyngeal structures, comprising mainly the prevertebral musculature, retropharyngeal nodes and clivus, lie posterior to the nasopharynx. They are separated from the nasopharynx by the deep layer of the deep cervical fascia. The sphenoid sinus floor and

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Fig. 1a.

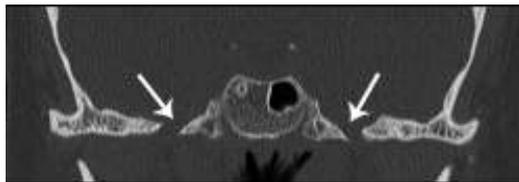


Fig. 1b.



Fig. 1c.

Fig. 1. Anatomy.

- (a) Axial T1W image showing Eustachian tube opening (A), torus tubarius (B) and fossa of Rosenmuller (C) on right. Note stage T1 NPC on the left.
- (b) Bilateral foramina ovale (white arrows) seen in coronal CT image.
- (c) Pterygopalatine fossae (arrows). Note normal hyperintense signal on T1W image.

basisphenoid are related superiorly, while the nasopharynx is contiguous with the posterior aspect of the nasal cavity.

Important skull base foramina and fissures include the foramen lacerum, which lies within the pharyngobasilar fascia, superolateral to the fossa of Rosenmuller; and the foramen ovale (Fig. 1b), which lies outside the pharyngobasilar fascia.

The fat-filled pterygopalatine fossa (Fig. 1c) is another important site, communicating with the foramen rotundum and Vidian canal; these canals can act as potential routes of tumour spread. Other important structures to note include the bony margins of the sinus cavities, the orbit and floor of the middle cranial fossa.

### Clinical Presentation and Evaluation

NPC presents most commonly as a unilateral neck lump in 50% to 70% of patients, from cervical lymph node metastases; the tumour may not be clinically apparent at the time of presentation.<sup>4</sup> Eustachian tube obstruction may produce persistent unilateral hearing loss or otitis media. Other presenting features include a bloody nasal discharge or less frequently, cranial nerve palsies. The peak incidence

Table 1. T Stage of Nasopharyngeal Carcinoma Using the AJCC TNM Staging System

Tis	In situ tumour
T1	Tumour confined to the nasopharynx
T2	Tumour extends to soft tissues
T2a	To oropharynx or nasal cavity but no parapharyngeal extension
T2b	Parapharyngeal extension beyond pharyngobasilar fascia
T3	Tumour involves bone or paranasal sinuses
T4	Intracranial extension or involvement of cranial nerves, orbit, hypopharynx, masticator space or infratemporal fossa

is usually in the 5th to 6th decades, also the peak years of economic productivity for individuals.

Endoscopic evaluation of the nasopharynx with biopsy is performed in patients suspected of having NPC, particularly if risk factors are present. However, tumours may be clinically occult. Imaging modalities include contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) for staging and evaluation. MRI, with its superior soft tissue contrast resolution and ability to detect perineural tumour spread, is currently preferred. Recent advances in both hardware and software MRI technology have also contributed to its role in the evaluation of NPC.

### Imaging Evaluation

When imaging patients for suspected or biopsy proven NPC, attention should be made to patterns of spread of the tumour, as well as features that assist in staging. Staging of the primary tumour is performed according to the American Joint Committee on Cancer (AJCC) TNM classification. T staging is based on the relationship of the primary tumour to anatomical structures; the AJCC has recommended MRI as the study of choice (Table 1).<sup>5</sup> The MRI features will be described, with reference to CT where appropriate.

#### A. Local Extension

##### 1. T-Staging

T1 lesions are wholly confined to the nasopharynx, causing thickening and asymmetry (Fig. 1a). Compared to normal mucosa, tumour enhances to a lesser degree and is less bright on T2W images. Lymphoid hyperplasia can be differentiated by a striped pattern on both T2W and post-contrast images.<sup>6</sup>

Lesions are classified as T2a once there is spread to the oropharynx or nasal cavity (Fig. 2a). Anterior spread to the nasal fossa occurs in up to 22% of patients.<sup>7</sup> Parapharyngeal space involvement, however, is classified as T2b, as this carries a worse prognosis, and concurrent chemotherapy

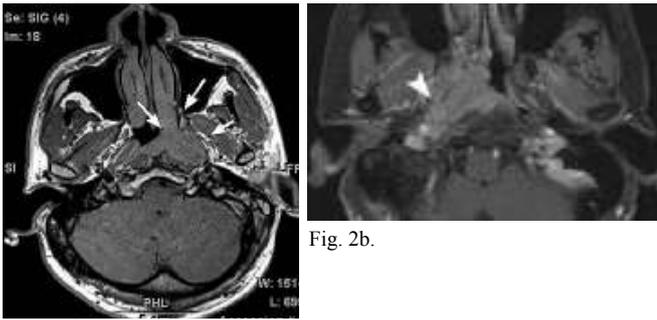


Fig. 2a.

Fig. 2b.



Fig. 2c.

Fig. 2d.

Fig. 2. T-staging.

- (a) Axial T1W+C images showing stage T2a (tumour involving nasal cavity, arrows).
- (b) T2b (parapharyngeal involvement, arrowhead) on axial T1W+C image.
- (c) Axial T1W image. T3 tumour (thin arrow). Clival involvement (thick arrow); note loss of normal fatty signal in this non-contrast T1 image.
- (d) Axial T1W+C images. T4 tumour showing cavernous sinus invasion (thin white arrow).

may be added to the treatment regimen. Parapharyngeal extension may be recognised by loss of the normal fat signal on T1W non-contrast images, with enhancement post-contrast administration (Fig. 2b). Care must be taken to distinguish the normal pterygoid venous plexus from tumour.

T3 tumours are characterised by paranasal sinus and bony involvement (Fig. 2c). Bone marrow involvement can be identified by loss of the normal hyperintense T1W fatty marrow signal on non-contrast images. While marrow involvement is better assessed on MRI (Fig. 3a), CT features suggesting involvement include cortical erosion and sclerosis.<sup>8</sup> Sclerosis is a non-specific sign, as this may reflect reactive change from irritation by tumour as much as direct infiltration. Adjacent sinus disease may produce a similar change, particularly in the sinus margins and the pterygoids. Nevertheless, sclerosis in a bony structure adjacent to the primary tumour, with no adjacent sinus disease, should alert the radiologist to the possibility of involvement by tumour. Up to 25% of patients have direct sphenoid sinus invasion.<sup>9</sup> Clival marrow can have a heterogeneous appearance, but normal marrow signal should not be less intense than the pons on T1-weighted images.<sup>10,11</sup>

Once intracranial (Fig. 2d), hypopharyngeal, orbital, maxillary sinus or cranial nerve involvement is seen, lesions are denoted as T4 tumours. MRI shows intracranial and cranial nerve involvement better than CT (Fig. 2c).

### 2. Orbital and Paranasal Sinus Involvement

Paranasal sinus involvement occurs as a result of direct extension. Maxillary sinus involvement occurs after nasal or infratemporal maxillary wall erosion (6%).<sup>12</sup> Sphenoid sinus extension (Fig. 3b) has been described above. The ethmoid sinuses are involved when direct invasion of the nasal cavity occurs. Sinus involvement is recognised by the loss of contiguity of the sinus walls. Intrasinus extension of tumour may be seen. Tumour can be differentiated from reactive mucosal thickening on CT, where the latter is seen to be hypodense, with enhancement less than that of tumour. On MRI, mucosal thickening is seen as uniform T2W signal greater than that of tumour, also enhancing to a lesser degree than tumour.

Direct extension from the pterygopalatine fossa (PPF) and inferior orbital fissure (IOF) represents the most common route of orbital involvement.<sup>11</sup> PPF infiltration (Fig. 4a) occurs as a result of direct extension from the nasal cavity, with 15% of patients having evidence of

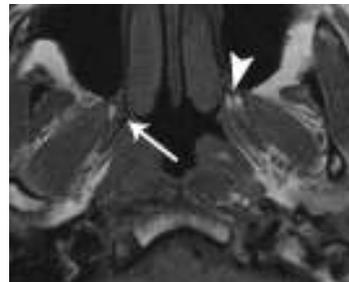


Fig. 3a.

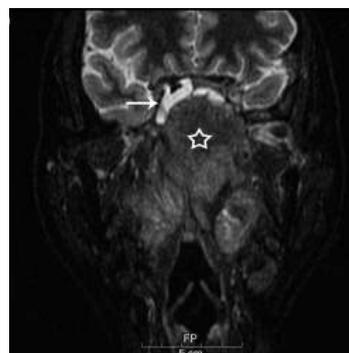


Fig. 3b.

Fig. 3.

- (a) Pterygoid body sclerosis on right (arrow), with loss of normal fatty signal. Compare with normal appearance on left (arrowhead).
- (b) Sphenoid sinus invasion. Inversion recovery image showing intermediate signal tumour (star) invading sphenoid sinus. Note normal fluid signal of sinus secretions (white arrow).

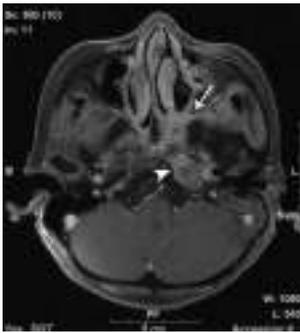


Fig. 4a.



Fig. 4b.



Fig. 4c.



Fig. 4d.

Fig. 4

- (a) Axial T1W+C image showing left pterygopalatine fossa invasion (thin arrow). Note left retropharyngeal node (arrowhead).  
 (b) CT image showing left orbital invasion (arrow).  
 (c) Coronal CT image showing right V3 perineural tumour spread (black arrow).  
 (d) Axial T1W+C. Bilateral XII nerve perineural tumour spread (arrowheads).

infiltration at diagnosis.<sup>13</sup> Extension from the ethmoid and/or sphenoid sinuses is the second most common route.<sup>14</sup> Orbital extension from the superior orbital fissure via the cavernous sinus is the least common route. Other orbital manifestations include nasolacrimal duct involvement (Fig. 4b), although the mechanism is uncertain (direct reflux has been postulated).<sup>15</sup> Optic neuritis has been described, possibly secondary to a paraneoplastic syndrome.

### 3. Perineural Tumour Spread and Intracranial Extension

As indicated, intracranial extension denotes T4, stage IV tumours. This may occur either from direct extension or perineural tumour spread (PTS). Features denoting intracranial extension include meningeal involvement (especially if seen as nodular enhancing masses), masses within the middle and/or posterior cranial fossa and PTS, for example, maxillary nerve and its branches (including auriculotemporal), mandibular and vidian nerves.

PTS may occur as small deposits or as large masses. It carries a worse prognosis and is commonly missed, as up to

40% of cases are asymptomatic. Recurrence is guaranteed if PTS is undetected and missed in radiation treatment fields. Once PTS has occurred, tumour involvement of sites distant from the primary tumour may occur, such as the facial nerve (after vidian nerve infiltration), and cavernous sinus (from maxillary and mandibular involvement). Symptoms related to PTS may present before the primary lesion, for example, hypoesthesia (50% of patients have hypoesthesia after PPF invasion).<sup>16</sup> PTS is recognised on fat-suppressed post-contrast T1W imaging by abnormal enhancement with nodular thickening of the affected nerve. Skip lesions may be seen. Expansion of the bony canals in which these nerves travel can be seen, albeit a late manifestation. Maxillary and mandibular nerve (Fig. 4c) involvement is best demonstrated on coronal T1W post-contrast MRI. Hypoglossal nerve involvement (Fig. 4d) may also occur.

### 4. Carotid Artery Encasement

Carotid artery encasement is defined as tumour tissue surrounding  $\geq 270^\circ$  of the vessel circumference (Fig. 5a). This becomes important in the follow-up setting, where surgical resection (e.g. nasopharyngectomy or lymph node dissection) may be contemplated. The patient is deemed inoperable if this is present, as the surgeon cannot remove all the tumour tissue. Other potential issues that may result from encasement include vascular invasion and potential carotid artery blow-outs post-radiotherapy.

### B. Nodal Involvement

Identification of nodal disease is important as it increases the risk of local recurrence and is associated with a higher risk of metastatic disease, affecting management. Imaging studies suggest that nodal metastases are seen in 60% to 90% of cases, suggesting N0 disease is seen in only 10% to 40% of cases, behaving in an orderly fashion beginning with the retropharyngeal nodes (RPN) (Fig. 5a), and thence to levels II, III and IV.<sup>17</sup> Although King et al found that the RPN were bypassed in only 6% of cases, Ng et al found the RPN were bypassed in 17 of 89 patients, postulating a separate pathway allowing direct spread of NPC to level II nodes.<sup>18,19</sup> This group also noted skip metastases in lymph node levels in the lower neck and supraclavicular fossa in 7.9% of cases, and distant spread to thoracic and abdominal nodes in 3% to 5% of cases, associated with supraclavicular metastases. Chong et al also noted the absence of RPN involvement in up to 1/3 of patients.<sup>20</sup> Level 1 lymph nodes may also be involved after radiotherapy.<sup>21</sup> Facial lymphadenopathy is also a rare feature.<sup>22</sup> Lymphadenopathy is more commonly bilateral, compared to other pharyngeal squamous cell cancers (SCCs).

As the prognostic significance of nodal disease in NPC differs from that of other head and neck SCCs, a different

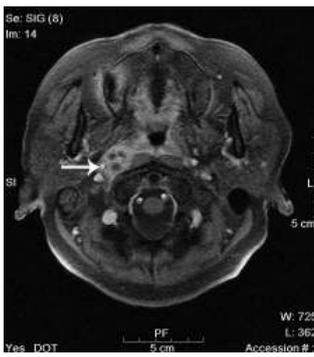


Fig. 5a.

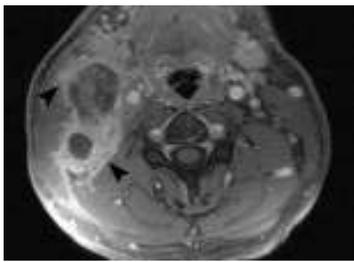


Fig. 5b.

Fig. 5. Nodes.

- (a) Carotid artery encasement (arrowed) by necrotic right retropharyngeal nodes.  
 (b) Necrotic level 2 nodes with extranodal spread (arrowheads) invading adjacent muscles.

N staging is used in the TNM classification (Table 2). While N0 and Nx are identical to that of other head and neck SCCs, N1-3 have different criteria. A higher N stage indicates more extensive disease with a poorer prognosis. N1 and N2 disease in NPC refer to unilateral nodes  $\leq 6$  cm and bilateral nodes  $\geq 6$  cm, respectively, above the supraclavicular fossa. Once supraclavicular fossa nodes are affected, the patient has N3b disease, which upstages the patient and indicates more extensive disease. Nodes  $>6$  cm in size are considered N3a disease. Supraclavicular nodes include level IV and Vb nodes, and currently are identified as supraclavicular nodes when lymph nodes are seen on the same axial cross-sectional slice with a portion of the clavicle.

Several criteria are used in the evaluation of lymph nodes. Size is the most commonly used. The measurements are taken using the shortest transaxial diameter. Upper limits of normal are 1.5 cm for levels I and II and 1 cm for levels IV to VII.<sup>23</sup> For retropharyngeal nodes, a maximal diameter of 8 mm and minimum transverse diameter of 5 mm have been proposed.<sup>23</sup> However, nodes may still be of normal size and harbour malignant cells, and the other criteria detailed below should also be sought. The ratio of the longest longitudinal to axial dimensions has also been proposed; if the ratio is less than 2, this suggests metastatic carcinoma. Normal nodes should have a ratio

greater than 2. Clustering of  $>3$  nodes of borderline size is a suspicious feature. A group of  $>3$  nodes with maximal diameters of 8 to 15 mm, or minimum axial diameters of 9 to 10 mm and 8 to 9 mm (for the jugulodigastric region and other regions of the neck, respectively) is considered suggestive of metastatic disease, provided these nodes are in the drainage area of the primary tumour. Rounded nodes, coupled with loss of the fatty hilum, are another feature that may suggest lymphadenopathy. However, this feature should not be taken in isolation when assessing the neck nodes. Nevertheless, there is no one size criterion that can actually predict metastatic disease with an error rate less than 15% to 20% and often the longest dimension is used, as this is the dimension used by the referring clinician.

Necrosis, though considered 100% specific if present, can only be reliably identified in tumour foci larger than 3 mm. Tumour foci  $\leq 2$  mm in size cannot be resolved by any imaging method at present. When greater than 3 mm in size, nodal necrosis has been observed in approximately one-third of metastatic nodes.<sup>23,24</sup> Necrosis is hypointense on T1W images with rim enhancement post-contrast administration, and hyperintense on T2W images (Fig. 5b). In CT images, necrosis is seen as a focal area of hypoattenuation with or without rim enhancement. Caveats are a) prominent fatty hila, which have normal hyperintense fatty signal on pre-contrast T1W images and show loss of this normal signal in fat saturated sequences, and b) suppurative nodes in the setting of lymphadenitis. Although CT has long been considered superior to MRI in detecting necrosis, King et al found both techniques to be comparable, with an accuracy of 92% versus 91% for CT and MRI, respectively.<sup>25,26</sup> Although surface coils were utilised in King's study, necrosis can now be depicted using standard head and neck coils, given the advancements seen in both MR software and hardware. Ultrasound performed less well in King's study compared to CT and MRI, with an accuracy of only 85%.

Extranodal spread carries a grave prognostic significance. Patients with nodes showing necrosis and extranodal spread have a 50% less rate of 5-year survival.<sup>27</sup> Extranodal spread can also occur in normal-sized nodes in up to 23% of cases.<sup>28</sup> In extranodal spread, there is extension beyond

Table 2. N Stage of NPC Using the AJCC TNM Staging System

Nx	Nodes cannot be assessed
N0	No regional nodal metastases
N1	Unilateral nodes $\leq 6$ cm in greatest dimension
N2	Bilateral nodes $\leq 6$ cm in greatest dimension
N3	N3a Nodes $\geq 6$ cm in dimension
	N3b Nodal metastasis in supraclavicular fossa

the capsule into the adjacent soft tissues. It is recognised radiologically as loss or irregularity of the nodal margins, and/or streakiness of the adjacent fat, although the latter may occur in the context of inflammation. Invasion of adjacent structures may occur, for example, sternocleidomastoid muscle or carotid artery encasement.

### C. Metastatic Spread

Distant metastases presenting at initial diagnosis are seen in 5% to 11% of NPC patients.<sup>29,30</sup> The likelihood of metastasis increases with increasing T and N stage. In Teo's study, approximately 26% (247 out of 945 patients) developed metastases within 3 years of radiotherapy. Approximately 90% of patients with distant metastases pass away within a year.<sup>31</sup> In descending order, the most common sites are skeletal, thoracic (mediastinal lymph nodes and pulmonary deposits), hepatic, distant lymph nodes other than mediastinal, and other distant sites including bone marrow and soft tissue metastases. Ghaffarian reported 4 cases of soft tissue metastases to the forehead in 4 patients in 1980.<sup>32</sup> Hypertrophic pulmonary osteoarthropathy is a rare manifestation of intrathoracic metastatic disease.<sup>33</sup> M staging is performed as for other head and neck carcinomas (Table 3). M0 indicates no metastasis, M1 the presence of metastatic disease while Mx indicates that metastatic disease cannot be, or has not been, assessed. The presence of metastatic disease immediately makes the patient a Stage IVc patient.

### Positron Emission Tomography (PET) Imaging

PET imaging has emerged in recent years and is a sensitive technique in detecting clinically occult metastatic disease. The technique works on the premise that cancer cells are more metabolically active, have a higher rate of glucose metabolism, with concomitant increased glucose uptake. The most commonly used radiopharmaceutical, fluorine-18-labeled 2-deoxyglucose (<sup>18</sup>F-FDG) is a glucose analogue that is accumulated by metabolically active cells, including cancer cells, seen as areas of increased tracer uptake.

The role of PET is evolving. Liu et al showed PET as being more sensitive in detecting skeletal metastases compared to skeletal scintigraphy (70% compared with 37%) in 30 of 202 patients; in this study, nodal staging was the only significant factor for bone metastasis.<sup>34</sup> In another study by Chang et al, 81 of 95 patients without evidence of metastatic disease with conventional workup (including fiberoptic nasopharyngoscopy, chest X-ray, bone scan, abdominal ultrasound and MRI of the head and neck) were imaged with PET at staging and 3 to 4 months after treatment. While conventional studies identified 4 patients with distant metastases, PET identified another 10. Again, nodal stage was found to be a significant factor

Table 3. Final Tumour Stage Using the AJCC Staging System for NPC

Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II A	T2a N0 M0
Stage II B	T2b N0 M0
	T1/T2a/T2b N1 M0
Stage III	T1/T2a/T2b N2 M0
	T3 N0/N1/N2 M0
Stage IV A	T4 N0/N1/N2 M0
Stage IV B	Any T N3 M0
Stage IV C	Any T Any N M1

for metastasis.<sup>35</sup> However, PET alone suffered from a low specificity, as indicated by Chang. Also, the poor spatial resolution in conventional PET makes it difficult to localise anatomically the areas of increased FDG uptake. Integrated PET-CT offers a higher specificity; Lardinois showed that integrated PET-CT was able to show additional information in 20 out of 49 patients as compared to visual correlation between unfused PET-CT images.<sup>36</sup> Another study of 33 patients by Gordin showed that while PET-CT, PET and conventional CT had sensitivity rates of 92%, the specificity was 90%, 65% and 15%, respectively, with 5 of 7 false positive conventional PET scans being diagnosed as areas of physiological uptake by PET-CT.<sup>37</sup> The role of PET-CT remains to be resolved, although it may have a role in patients with lesions that are difficult to identify on conventional imaging; in patients with bulky nodal disease and in patients with suspected bone metastases.

### Staging and Treatment

Taking into account the various TNM features, NPC patients are then staged accordingly from Stage 0 to Stage IV. Several features of note are:

- T3 disease indicates a patient is at least Stage III
- T4 disease places the patient at Stage IV
- N3 disease (i.e. single node >6 cm in size; supraclavicular nodes) indicates a patient is at least Stage IVb
- M1 disease places the patient at stage IVc.

Correct staging enables the clinician to determine which treatment modality is best for the patient. A detailed discussion of the treatment options is beyond the scope of this paper. In brief, radiotherapy (RT) is the mainstay of treatment for NPC, as type II and III tumours are very radiosensitive. Conventional external beam RT was the traditional method of treatment. However, the tumour could not be maximally irradiated without damaging adjacent structures such as the parotid glands. With the advent of conformal techniques,

and in particular, intensity-modulated radiotherapy (IMRT), doses of up to 70 Grays may be delivered with relative sparing of the adjacent soft tissues. Limitations still remain with very large tumours, for example, T4 tumours, where NPC may be so close to vital structures such as the optic chiasm that the latter cannot be spared if the full RT dose were to be administered.

Combined chemotherapy using platinum-based drugs and radiotherapy (CRT) is given for patients with T3 disease and nodal disease >N1. Patients with T4 and N3 disease may receive neoadjuvant chemotherapy with platinum-based combination chemotherapy followed by definitive RT with concurrent chemotherapy.<sup>38</sup> Patients with T1/T2 N1 disease are also treated with CRT although this is a controversial topic and beyond the scope of this article.

## Conclusion

Understanding of the unique clinical behaviour, epidemiologic pattern and histopathologic nature of NPC, together with its pattern of spread, is important when performing imaging for NPC. MRI is the preferred imaging modality, particularly with regard to its (a) superior soft tissue contrast and resolution, (b) ability to show PTS, parapharyngeal space involvement and bone marrow infiltration, and (c) superior ability to demonstrate involvement of adjacent sites such as the orbit, masticator space and sinuses. Accurate detailing of the structures involved is required to convey a clear picture to the referring clinician so that appropriate treatment planning may be performed.

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