CHAPTER 1

DIAGNOSIS AND CLINICAL EVALUATION OF NASOPHARYNGEAL CARCINOMA

Alan Soo-Beng Khoo*,[1] and Kin-Choo Pua[2]

[1]*Molecular Pathology Unit, Cancer Research Centre, Institute for Medical Research, Kuala Lumpur, Malaysia;*
[2]*Department of Otorhinolaryngology, Penang General Hospital, Penang, Malaysia*
**Corresponding Author: Alan Soo-Beng Khoo—Email: alankhoo@imr.gov.my*

Abstract: Nasopharyngeal carcinoma (NPC) is an epithelial malignant tumor which arises from the mucosa of the nasopharyngeal cavity. NPC usually presents as painless neck lumps. It can also present with nasal, aural and/or opthalmo-neurologic symptoms. Patients in early stage of the disease are often asymptomatic or present with apparently trivial symptoms. Diagnosis is based on histopathological examination of the biopsied tissue obtained through endoscopy of the nasopharynx. Delayed diagnosis remains a problem in NPC. The most common used staging system is the "tumor node metastasis (TNM)" system, jointly developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC).

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a unique entity among carcinomas of the upper respiratory and digestive tract, with distinct geographical distribution[1,2] and is strongly associated with Epstein Barr Virus.[3] The nasopharynx is the uppermost part of the pharynx that lies behind the nasal cavity (post nasal space). The Fossa of Rosenmüller (FOR) of the nasopharynx is the most common site of origin of NPC.[4,5] The tumor spreads anteriorly into the nasal cavity, inferiorly into the oropharynx, superiorly into the skull base, laterally into the parapharyngeal space and posteriorly into the retropharyngeal space (Fig. 1). When it spreads into the skull base, it leads to compression of cranial nerves. NPC commonly spreads by lymphatics to the cervical lymph nodes. Lymphatics of the FOR drain into the node of Rouvier within retropharyngeal space and subsequently to

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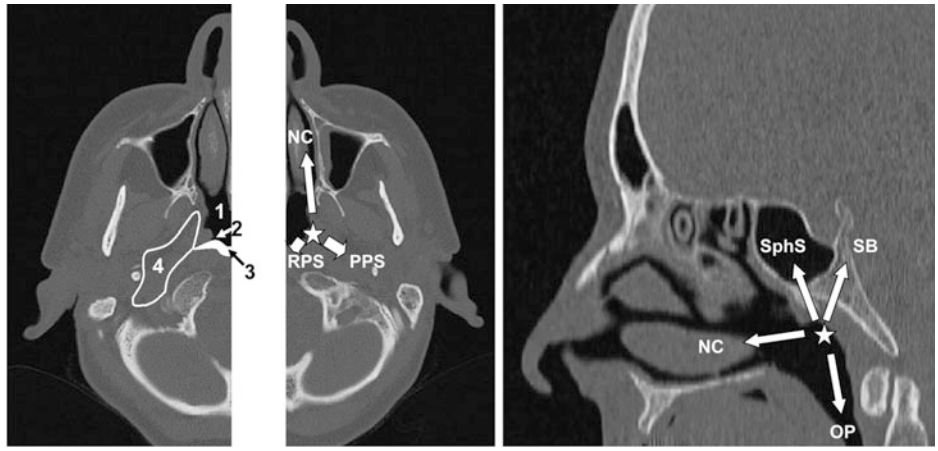

Figure 1. Anatomical relationship of the nasopharynx and preferential routes of local tumor spread. 1: nasopharynx; 2: fossa of Rosenmüller; 3: retropharyngeal space; 4: parapharyngeal space. NC: nasal cavity; RPS: retropharyngeal space; PPS: parapharyngeal space; SphS: sphenoid sinus; SB: skull base; OP: oropharynx; *: most common initial tumor site.

the upper deep cervical lymph nodes.[6] This explains why the neck lump is often the first presenting symptoms of NPC. NPC may spread through the blood stream (hematogenous route) to distant sites such as the bone, lung and liver.

CLINICAL DIAGNOSIS OF NPC

Clinicians need to be aware that NPC patients often present with nonspecific symptoms and signs in the head and neck region. A proper clinical workup begins with a detailed history of the presenting complaints. The next step is a thorough physical examination including endoscopic examination of the head and neck region. This should be followed by investigations to confirm the diagnosis and assess the extent of the disease prior to treatment.

Among cases of newly diagnosed NPC (totalling over 1200 cases), reported from the year 2007 to 2010 to the Malaysian Nasopharyngeal Carcinoma Database,[a] the most common presenting symptoms were neck lumps (40%), nasal symptoms (blood stained nasal discharge, blood stained saliva, or nasal blockage) (26%), aural symptoms (unilateral blocked ear, pressure sensation in the ears, mild hearing loss or tinnitus) (14%) and ophthalmo-neurologic symptoms (unilateral facial numbness, diplopia or unilateral headache) (10%). Similar spectrum of presenting symptoms are reported elsewhere in the world across time.[7-10]

[a] The Malaysian Nasopharyngeal Carcinoma Database (http://app.acrm.org.my/npc) was funded by the Ministry of Health Malaysia and set up by the Malaysian Nasopharyngeal Carcinoma Study Group, which comprise of a network of institutes including Penang Hospital, Kuala Lumpur Hospital, Queen Elizabeth Hospital, Sarawak General Hospital, University of Malaya Medical Centre, University Science Malaysia Hospital, Institute for Medical Research and Cancer Research Initiatives Foundation (CARIF).

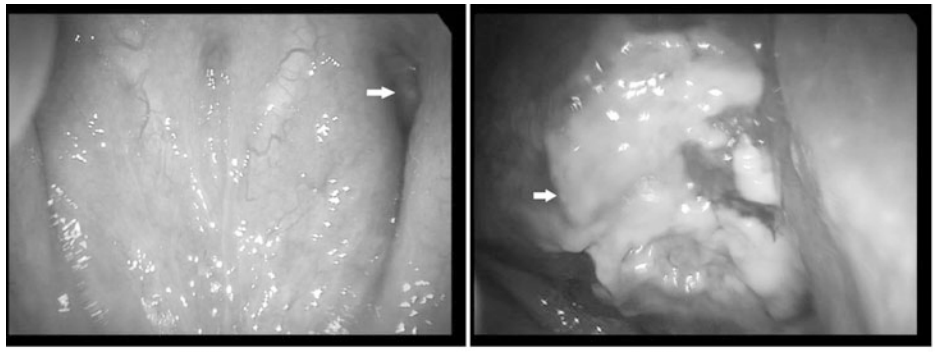

Figure 2. Nasopharynx as viewed through a fiberoptic endoscope. i) Normal nasopharynx showing the fossa of Rosenmüller (arrow). ii) Nasopharyngeal carcinoma (arrow).

As the nasopharynx is located in a confined space behind the nasal cavity, examination of this area is usually carried out using a flexible fiberoptic or rigid endoscope. The endoscope is connected to a camera system to allow the operator a close view of the nasopharynx. The NPC may appear as a mass in the nasopharynx (Fig. 2). Biospies are usually taken from this area to confirm the diagnosis. In certain instances, the nasopharygeal mucosa may appear normal although the tumor might be present under the mucosa (submucosal tumor). Magnetic resonance imaging (MRI) is useful to identify these submucosal tumors and to serve as a guide for biopsy.

The diagnosis of NPC is usually achieved by histopathological examination of the biopsied specimens. NPC is classified as keratinizing or nonkeratinizing (Table 1), the latter being the predominant type of NPC in endemic areas.[10] On the basis of electron microscopy, the NPC types are regarded as variants of squamous cell carcinomas (see Chapter 2 by Nicholls and Niedobitek).[11,12] This includes the undifferentiated type, which have morphological characteristics of undifferentiated epithelial cells upon examination by light microscopy.[11,13]

Table 1. WHO histopathological classification of NPC[10,16]

WHO Classification (2005)	Former Terminology (WHO 1998)
Keratinizing carcinoma	WHO Type 1
Nonkeratinizing carcinoma	
- differentiated	WHO Type 2
- undifferentiated	WHO Type 3
Basaloid squamous cell carcinoma	(no former terminology)

Adapted from reference 10 (Barnes L et al, eds. World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours Vol 9. Lyon, France: IARC Press 2005; 85-97); and from reference 16 (AJCC Cancer Staging Manual, 7th ed, (2010) published by Springer Science and Business Media LLC, www.springer.com. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois).

Since NPC has a high propensity to spread to the regional lymph nodes, it is imperative to examine the neck region to detect involvement of the cervical lymph nodes. Fine needle aspiration cytology of the enlarged cervical lymph nodes can be performed to confirm nodal involvement.

As NPC may cause cranial nerve palsies, the cranial nerves should be examined. The patient should also be examined for distant metastasis to the bones, lungs and liver. The local and distant spread of the disease, are confirmed using diagnostic imaging modalities.

STAGING

Staging is a universal language used within the medical profession to communicate information about the extent of any cancer. This step is very important in order to make comparisons, to determine the prognosis and to assist in overall decisions on the choice of treatment modalities.

Staging may be carried out at several points during the care of the patient. Of these, the clinical stage (pretreatment stage) is the commonly used point. Clinical staging incorporates information obtained from symptoms, physical examination, endoscopic examinations as well as imaging of the tumor, regional lymph nodes and metastases.[14] It includes any information obtained about the extent of cancer before initiation of definitive treatment.[14]

Details of the presenting complaints would give an idea of the stage of the disease. Nasal and aural symptoms could be due to a tumour which is still confined to the primary site of the nasopharynx (i.e., may be as early as T1). The presence of a neck mass is a manifestation of disease spread to the cervical lymph nodes (N1-3) and is an indication that the tumor has already reached the next stage of spread to the regional lymph nodes. Ophthalmo-neurologic symptoms signify infiltration to the skull base (T4) which is considered as an advanced stage. The duration of the presenting complaints may give an idea of the aggressiveness of the tumor.

Staging is performed by clinical examination followed by imaging, such as, computerized tomography (CT), magnetic resonance imaging (MRI), chest X-ray, ultrasound, bone scintigraphy and ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (PET) scans. The exact combination of imaging modalities used depends on their availability and cost and may differ from one centre to another. For clinical staging of NPC, the National Comprehensive Cancer Network (NCCN) guidelines suggests CT with contrast or MRI with gadolinium (covering the region from the skull base to the clavicles), PET/CT for Stage III-IV disease[15] (see Table 2) and PET or PET/CT for detection of distant metastasis (lung, liver, bone) for N2-3 disease.[15]

The “tumor node metastasis” (TNM) staging system, jointly developed by The American Joint Committee on Cancer (AJCC)[14,16] and the International Union Against Cancer (UICC), is the most commonly used system. This staging system is primarily based on anatomy, in which, T refers to the local extent of the primary tumor, N refers to the extent of regional nodes involvement and M refers to the distant spread (metastasis) of the tumor. The TNM scores are then combined to determine the overall stage[14] (Table 2).

Rarely, NPC may be detected as pre-invasive carcinoma in situ[17,18] (Tis, N0, M0). This is classified as Stage 0.[16]

As the imaging modalities differ in their sensitivity, the stage determined could also differ depending on the modalities used. If there exist uncertainty in classifying or staging the disease, the lower category will be used.[14] This also means that centers which use

Table 2. TNM clinical classification for tumors of the nasopharynx (AJCC Staging, 7th Edition)

Primary Tumor (T)

- T1—Tumor confined to nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal extension
- T2—Tumor with parapharyngeal extension (posterolateral infiltration of tumor)
- T3—Tumor involves bony structures and/or paranasal sinuses
- T4—Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space

Regional Lymph Nodes (N)

- N0—No regional lymph node metastasis
- N1—Unilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, 6 cm or less, in greatest dimension
- N2—Bilateral metastasis in cervial lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
- N3—Metastasis in a lymph node(s) greater than 6 cm and/or to supraclavicular fossa
- N3a—Greater than 6 cm in dimension
- N3b—Extension to the supraclavicular fossa

Distant Metastasis (M)

- M0—No distant metastasis
- M1—Distant metastasis

Clinical Stage Groups (Anatomic Stage/Prognostic Groups)

Stage I: T1, N0, M0

Stage II: T1, N1, M0; T2, N0, M0; T2, N1, M0

Stage III: T1, N2, M0; T2, N2, M0; T3, N0, M0; T3, N2, M0

Stage IVA: T4, N0, M0; T4, N1, M0; T4, N2, M0

Stage IVB: Any T, N3, M0

Stage IVC: Any T, any N, M1

Adapted from Edge SB, DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer, 2010:44-46.[16] Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

less sensitive imaging modalities may under-stage their patients. This should be borne in mind when evaluating studies on the stage of disease, and, is of particular relevance in areas which may not have the state of the art imaging modalities for staging.

The MRI currently provides the most sensitive and accurate evaluation of the primary tumor (T classification) and is preferable to CT for this purpose.[19] In comparison to CT, MRI was reported to be more precise in detecting the extent of the tumor, resulting in changes in the T classification for almost 50% of cases, as well as changes in the N classification and clinical stage in 11 and 39% of cases respectively.[20] As MRI is superior

to CT for soft tissue discrimination, it is able to differentiate retropharyngeal lymph node (RLN) metastasis from parapharyngeal extension of the primary tumor. This is important because the presence of RLN metastasis correlates with prognosis[21-23] and is now included in the AJCC Staging (7th Edition).[16]

While MRI is superior to PET/CT in demonstrating tumor invasion in the parapharyngeal space, base of the skull, intracranial area, sphenoid sinus and retropharyngeal lymph nodes, PET/CT is superior in demonstrating spread to the cervical lymph nodes.[24,25] PET/CT is the most sensitive, specific and accurate modality for detection of distant metastasis.[24-26] PET/CT has been reported to be superior, and able to replace conventional investigations such as chest radiography, abdominal ultrasound and skeletal scintigraphy for staging of distant metastases (M staging).[27] While MRI is superior to PET/CT to detect recurrence/residual disease at the primary site, combination of MRI and PET/CT is superior to either modality alone for restaging.[28]

The staging system undergoes periodic revisions in order to improve the classification of the extent of the tumor. In evaluating the AJCC Staging (6th Edition), Mao et al found that survival curves of the different T/N subsets showed a better segregation when Stage T2a was downstaged to T1, T2b and T3 were incorporated into T2, and the nodal greatest dimension was not used as a criteria for N staging.[29] In line with this, in the AJCC 7th Edition,[16] changes were made to staging of the cancer of the nasopharynx. T2a lesions is now designated T1. Stage IIA is now classified as Stage I. Lesions previously staged as T2b is designated as T2 and Stage IIB is now designated as Stage II. Retropharyngeal lymph node(s), regardless of unilateral or bilateral location, is now considered N1 in the AJCC Staging (7th Edition).[16] The criteria which was used in the AJCC Staging (7th Edition) was found to be superior to the AJCC Staging (6th Edition). Edition as the revised criteria provided better segregation of survival curves.[30]

It is important to take note of the version of staging when comparing cancers staged in studies at different time points. In some instances when comparing studies across time, it is possible that the apparent overall decrease in stage could be due to revisions of the staging criteria rather than actual differences in the extent of the cancer.

DELAYED DIAGNOSIS OF NPC

Delayed diagnosis remains a major issue in NPC.[7-9] Although NPC may be curable in the early stages, most patients present to the clinicians at late stages. In our series from the Malaysian Nasopharyngeal Carcinoma Database,[a] majority of cases (75%) presented at Stage III/IV. Symptoms such as blood stained nasal discharge, blood stained saliva and unilateral nasal/aural symptoms (such as unilateral nasal blockage, unilateral middle ear effusion symptoms such as blocked ear, pressure sensation in the ears, mild hearing loss or tinnitus) could be dismissed by patients and even doctors, as trivial, missing the chance of early diagnosis.[7]

Owing to the hidden location of the tumor and their indirect manifestations, diagnosis can be delayed for as much as six months in 70% of patients.[31] Up to 13% of patients may also present with neck lumps without a visible primary tumor (a situation known as ‘occult primary’).[32] Serial and multiple biopsies are sometimes necessary due to submucosal disease, and false negative histopathological examination. Fine-needle aspiration cytology of neck metastases at best has an accuracy of 82.6%.[33]

Table 3. ECOG* performance scale/Zubrod score[16,35]

ECOG Score	Performance	Karnofsky Score[34]
0	Fully active, able to carry on all predisease activities without restriction.	90-100
1	Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature.	70-80
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	50-60
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	30-40
4	Completely disabled. Cannot carry on self-care. Totally confined to bed.	10-20
5	Death	0

*Eastern Co-operative Oncology Group, Robert Comis, M.D., Group Chair.
Adapted from Edge SB, DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer, 2010:44. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Currently, diagnosis is made by endoscopic examination followed by biopsy of the suspected tumor. This procedure requires skill and is usually carried out by ENT specialists. Diagnosis of NPC at an early stage would require detection of the tumor prior to the appearance of metastatic lymph nodes in the neck or other local extension.

Other than clinical staging, the overall health of the patient prior to treatment is evaluated using the Karnofsky General Performance Status[34] or Eastern Co-operative Oncology Group (ECOG) Performance Status, (also known as the WHO score or Zubrod Score).[16] The ECOG Performance Status is a set of scales and criteria used to assess how the disease affects the activities of daily living abilities of the patient. (Table 3).[35] In NPC, most patients have minimal impairment of performance status, even though they may be at a late stage of the disease. This lack of general symptoms and the feeling of general wellbeing further clouds the patient's decision to seek medical advice and delays the time of diagnosis.

RECURRENT NASOPHARYNGEAL CANCER

After completion of treatment for NPC, patients would need to be followed up and evaluated for the possibility of recurrence. The latency for recurrence vary widely.[36] Recurrence may occur within the nasopharynx (local recurrence), regional lymph nodes (regional/nodal recurrence) or at distant metastatic sites. The clinical workup is similar to that of the primary disease. Staging may be carried out prior to treatment of the recurrent tumor using the same classification with the r prefix (rTNM).[14]

It should also be noted that early recurrence of NPC could be due to geographical miss during radiotherapy, in which part of the cancer was not included in the irradiated volume. This may be clinically indistinguishable from true recurrence. Recurrence may have a long latency in NPC. In a series of over 800 patients with nasopharyngeal carcinoma, recurrence could occur even after 5 years in 9% of cases.[36] However, local recurrence of NPC (i.e., in the nasopharynx) may be clinically indistinguishable from newly formed radiation-induced tumor from the same site.

CONCLUSION

The most common presenting symptom of NPC is a neck lump. The neck lump is actually a regional metastatic lymph node, which, is a sign that the cancer had already spread. Nasal and aural symptoms, which may be present at the early stage of the disease, are trivial and may be disregarded by the patient or even the professionals, thus reducing the chance of early diagnosis. In addition, most NPC patients have minimal impairment of their general performance status. Definitive diagnosis requires endoscopic guided biopsy of the nasopharynx. All these pose major challenges to early diagnosis of NPC, especially if patients are to wait for significant clinical symptoms or poor general health before seeking treatment. Thus, screening procedures, which can be carried out on patients with trivial symptoms or even asymptomatic individuals, would be very helpful. Newer ways to predict the risk of recurrence are also eagerly awaited.

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REFERENCES

1. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev 2006; 15(10):1765-1777.
2. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 International Agency for Research on Cancer, Lyon, France; 2010. http://globocan.iarc.fr.
3. Pathmanathan R, Prasad U, Chandrika G et al. Undifferentiated, nonkeratinizing, and squamous cell carcinoma of the nasopharynx. Variants of Epstein-Barr virus-infected neoplasia. Am J Pathol 1995; 146(6):1355-1367.
4. Prasad U. Cancer of the nasopharynx. A clinical analysis with anatomicopathological orientation. J R Coll Surg Edinb 1972; 17(2):108-117.
5. Prasad U. Fossa of Rosenmuller and nasopharyngeal carcinoma. Med J Malaysia 1979; 33(3):222-225.
6. Prasad U. Nasopharyngeal carcinoma in man. In: Reznik G, Stinson SF, eds. Nasal Tumors in Animals and Man. Boca Raton: CRC Press, 1983:151-185.
7. Prasad U, Pua KC. Nasopharyngeal carcinoma: a delay in diagnosis. Med J Malaysia 2000; 55(2):230-235.
8. Skinner DW, Van Hasselt CA, Tsao SY. Nasopharyngeal carcinoma: modes of presentation. Ann Otol Rhinol Laryngol 1991; 100(7):544-551.
9. Pua KC, Khoo AS, Yap YY et al. Nasopharyngeal Carcinoma Database. Med J Malaysia 2008; 63 Suppl C: 59-62.

10. Chan JKC, Bray F, McCarron P et al. Nasopharyngeal carcinoma. In: Barnes L, Eveson JW, Reichart P, Sidransky D, eds. World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours Vol 9. Lyon: IARC Press, 2005:85-97.
11. Prasad U. Cells of origin of nasopharyngeal carcinoma: an electron microscopic study. J Laryngol Otol 1974; 88(11):1087-1094.
12. Nicholls J, Niedobitek G. Histopathological diagnosis of nasopharyngeal carcinoma—Looking beyond the blue book. In: Busson P, ed. Nasopharyngeal Carcinoma : Keys for Translational Medicine and Biology. Austin/New York: Landes Bioscience/Springer Science+Business Media, 2012:10-22.
13. Taxy JB, Hidvegi DF, Battifora H. Nasopharyngeal carcinoma: antikeratin immunohistochemistry and electron microscopy. Am J Clin Pathol 1985; 83(3):320-325.
14. Purposes and Principles of Cancer Staging. In: Edge S, Byrd D, Compton C, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer, 2010:3-14.
15. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Head and Neck Cancers. 2011. www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
16. Pharynx. In: Edge S, Byrd D, Compton C, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer, 2010:41-56.
17. Pathmanathan R, Prasad U, Sadler R et al. Clonal proliferations of cells infected with Epstein-Barr virus in preinvasive lesions related to nasopharyngeal carcinoma. N Engl J Med 1995; 333(11):693-698.
18. Pak MW, To KF, Lo YM et al. Nasopharyngeal carcinoma in situ (NPCIS)—pathologic and clinical perspectives. Head Neck 2002; 24(11):989-995.
19. King AD, Vlantis AC, Tsang RK et al. Magnetic resonance imaging for the detection of nasopharyngeal carcinoma. AJNR Am J Neuroradiol 2006; 27(6):1288-1291.
20. Liao XB, Mao YP, Liu LZ et al. How does magnetic resonance imaging influence staging according to AJCC staging system for nasopharyngeal carcinoma compared with computed tomography? Int J Radiat Oncol Biol Phys 2008; 72(5):1368-1377.
21. Ma J, Liu L, Tang L et al. Retropharyngeal lymph node metastasis in nasopharyngeal carcinoma: prognostic value and staging categories. Clin Cancer Res 2007; 13(5):1445-1452.
22. Tang L, Li L, Mao Y et al. Retropharyngeal lymph node metastasis in nasopharyngeal carcinoma detected by magnetic resonance imaging: prognostic value and staging categories. Cancer 2008; 113(2):347-354.
23. Tham IW, Hee SW, Yap SP et al. Retropharyngeal nodal metastasis related to higher rate of distant metastasis in patients with N0 and N1 nasopharyngeal cancer. Head Neck 2009; 31(4):468-474.
24. Lin XP, Zhao C, Chen MY et al. Role of 18F-FDG PET/CT in diagnosis and staging of nasopharyngeal carcinoma. Ai Zheng 2008; 27(9):974-978.
25. Ng SH, Chan SC, Yen TC et al. Staging of untreated nasopharyngeal carcinoma with PET/CT: comparison with conventional imaging work-up. Eur J Nucl Med Mol Imaging 2009; 36(1):12-22.
26. Chua ML, Ong SC, Wee JT et al. Comparison of 4 modalities for distant metastasis staging in endemic nasopharyngeal carcinoma. Head Neck 2009; 31(3):346-354.
27. Liu FY, Lin CY, Chang JT et al. 18F-FDG PET can replace conventional work-up in primary M staging of nonkeratinizing nasopharyngeal carcinoma. J Nuclear Med 2007; 48(10):1614-1619.
28. Comoretto M, Balestreri L, Borsatti E et al. Detection and restaging of residual and/or recurrent nasopharyngeal carcinoma after chemotherapy and radiation therapy: comparison of MR imaging and FDG PET/CT. Radiology 2008; 249(1):203-211.
29. Mao YP, Liang SB, Liu LZ et al. The N staging system in nasopharyngeal carcinoma with radiation therapy oncology group guidelines for lymph node levels based on magnetic resonance imaging. Clin Cancer Res 2008; 14(22):7497-7503.
30. Chen L, Mao YP, Xie FY et al. The seventh edition of the UICC/AJCC staging system for nasopharyngeal carcinoma is prognostically useful for patients treated with intensity-modulated radiotherapy from an endemic area in China. Radiother Oncol 2011.
31. Prasad U. Problems in the early diagnosis of nasopharyngeal carcinoma: A review of 40 cases. In: Prasad U, ed. Nasopharyngeal Carcinoma. Kuala Lumpur: University of Malaya Press, 2000:233-239.
32. Prasad UAD, Prathap K et al. Problem of occult primary in nasopharyngeal carcinoma. In: Prasad U, ed. Nasopharyngeal Carcinoma: Current Concepts. Kuala Lumpur: University of Malaya Press, 1983:11-15.
33. Kaur A, Chew CT, Lim-Tan SK. Fine needle aspiration of 123 head and neck masses—an initial experience. Ann Acad Med Singapore 1993; 22(3):303-306.
34. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. Evaluation of Chemotherapeutic Agents: Columbia Univ Press, 1949:196.
35. Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5(6):649-655.
36. Lee AW, Foo W, Law SC et al. Recurrent nasopharyngeal carcinoma: the puzzles of long latency. Int J Radiat Oncol Biol Phys 1999; 44(1):149-156.