Imaging of Neck Metastases

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Awareness of the presence of cervical node metastasis is important in treatment planning and in prognostic prediction for patients with head and neck cancer. Currently, MRI and CT are commonly used to evaluate the primary tumor and the neck status. They characterize the cervical lymph nodes dependent on morphological criteria. However, metastases may be missed in some morphologically normal nodes. Conversely, it is difficult to discriminate reactive hyperplasia from metastasis in some enlarged nodes. Doppler ultrasound with fine-needle aspiration can overcome some of these limitations, but it is dependent on the sonographer's skill level and may be impractical in some cases due to too many questionable nodes. Positron emission tomography (PET) is a functional imaging that can detect metastasis lesions by pinpointing regions of high metabolism. It is better suited for assessing metastases to lymph nodes that appear morphologically normal. The main drawback of PET is its poor anatomical resolution. Side-by-side visual correlation of PET and CT/MRI can help determine the anatomical location of abnormal PET uptake and eliminate some false-positive PET findings caused by spatial errors. Fused PET/CT is considered to be the most accurate imaging modality for detecting nodal metastases, because it simultaneously provides prompt and accurate coregistration of functional and anatomical images. However, it is expensive, less-often available, and still constrained by technical resolution limits for tiny nodal metastases. Diffusion-weighted MRI, dynamic contrast-enhanced MRI, and nanoparticle-enhanced MRI are novel imaging technologies that have been exploited to enhance the detection of metastatic nodes. The initial results have been promising; however, micrometastases can still not be detected, and the extra costs and logistical burdens associated with these techniques prevent them from gaining wider acceptance. To date, neck dissection with detailed pathological examination is the gold standard. There is always a need for further refinement of the imaging techniques that can provide accurate information that approaches this gold standard. *(Chang Gung Med J 2006;29:119-29)*

Key words: cancer staging, lymph node imaging, lymph node metastasis, nodal morphology, MRI, CT, PET, ultrasound.

Introduction

Accurate evaluation of primary tumors and the cervical lymph node status of head and neck tumors is important for treatment planning and prognosis prediction.[1-3] The incidence of neck metastases depends mainly on the site and size of the primary

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Received: Oct. 11, 2005; Accepted: Dec. 2, 2005
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tumor, varying from as low as 1% for early glottic cancers to as high as 80% for nasopharyngeal carcinomas.[1] As a general rule, the larger the primary tumor, the more posterior its location in the mouth, and the lower degree of differentiation, the more likely neck metastasis occurs.[2] However, the associations between primary tumor size and the likelihood of nodal disease may not be found for some primary sites, such as the nasopharynx. Of note, tumors arising in Waldeyer's ring are most likely to exhibit metastatic adenopathy and to involve the neck bilaterally.[3]

Imaging has a great impact on treatment of head and neck cancers if it discloses an unexpected metastatic node, especially when that node is located outside of the planned treatment field. Among oropharyngeal, hypopharyngeal, and laryngeal carcinomas that are often treated nonsurgically, identification of metastatic nodes may change the treatment mode from radiation alone to chemotherapy and radiation. Regarding the prognosis, when compared to a patient with no nodal metastases, the overall 4-year survival is reduced by 50% in the presence of a solitary cervical node, and is further reduced by another 50% if extracapsular nodal spread has occurred.[4] The number of histologically positive nodes (more than 3), extranodal spread, and lymph node metastases at multiple neck levels have been shown to be significant determinants for distant metastases.[5,6]

Most tumors originating from the mucosal lining of the upper aerodigestive tract have a predictable pattern of neck metastasis.[3,7-9] Although skip metastases do occur, their incidence is only about 5%.[7,8] Detection of cervical nodal metastasis is more accurately performed with imaging than with clinical palpation; therefore, imaging is widely used in pretreatment staging and in the detection of nodal recurrence. Cross-sectional imaging, including computed tomography (CT), and magnetic resonance imaging (MRI), are routinely performed to assess the primary tumor and to display the lymph nodes along the drainage pathways of the tumor. Other imaging modalities currently used are ultrasound (US) and positron emission tomography (PET). Recently, some novel imaging techniques have been developing in attempts to improve the accuracy of the detection of nodal metastasis. This review article addresses the clinical usefulness of various imaging methods from conventional anatomic modalities to functional techniques in assessing lymph nodes of the neck.

Computed tomography (CT) and magnetic resonance imaging (MRI)

CT and MRI are noninvasive cross-sectional imaging modalities which enjoy high patient acceptance. The assessment of lymph nodes using these modalities relies on lymph node anatomy. On cross-sectional imaging, a normal lymph node usually measures < 1 cm in diameter, has a smooth, well-defined border, shows homogeneous density or signal intensity, and tends to have an oval or cigar shape. Most benign nodes have a central fatty hilum, which is a distinctive feature on CT and MRI. Nodes are considered to be metastatic if central necrosis or extracapsular spread is present irrespective of size, if their shortest axial diameter reaches 11 mm in the jugulodigastric region and 10 mm in other cervical regions (Fig. 1), or if there is a group of 3 or more

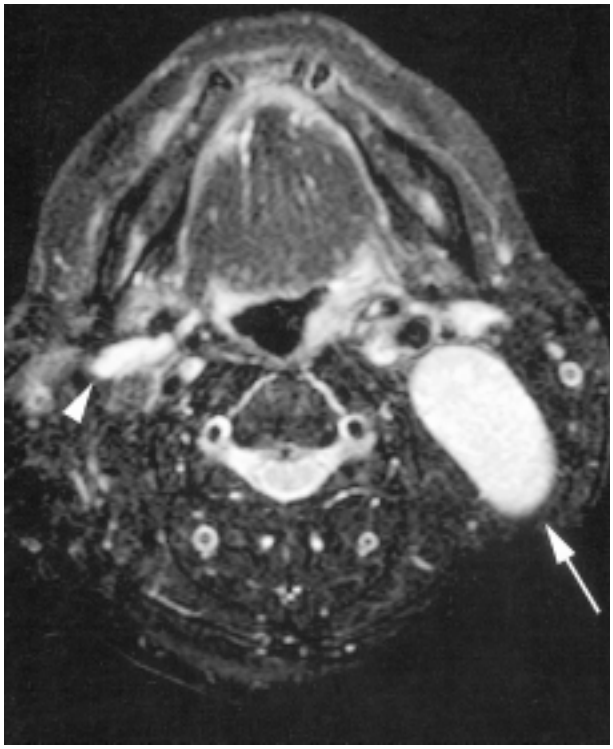

Fig. 1 Neck metastasis presenting with significantly increased nodal size. The T2-weighted MRI shows an enlarged left level II metastatic node with an axial diameter substantially greater than 10 mm (arrow). Note the small, flattened, benign node in the right subgastric region (arrowhead) for comparison.

nodes that are borderline in size. Round nodes are also more likely to harbor metastases than oval nodes (Table 1).[10,11]

MRI, by virtue of its high contrast resolution and multiplanar capacity, has advantages over CT for staging primary tumors of the head and neck region, while CT is faster, cheaper, and marginally more accurate than MRI in staging cervical nodes.[12] The reported sensitivity of CT and MRI for detecting lymph node metastases ranges from 36% to 94%, while the calculated specificity ranges from 50% to 98%.[1,7,10-17] Although the size of the cervical adenopathy is most frequently used to determine nodal metastasis, the accuracy of this criterion is insufficient, resulting in the occurrence of false-positive and false-negative results. The accuracy of CT based on size measurements of the lymph node has been reported to be 45%, while those based on central necrosis, extracapsular spread, configuration (round shape) were 95%~100%, 90%, and < 40% respectively.[11] With advanced innovations of multidetector CT technology, the scan speed, spatial resolution, size of the examination field, and facilities for multiplanar re-formation continue to improve. A large-scale study is warranted to revise the accuracy of multidetector CT in detecting neck metastases.

Central nodal necrosis is the most reliable radiologic criterion for diagnosing nodal metastases. It typically manifests as an intranodal focal area of low attenuation with or without a surrounding rim of contrast enhancement on CT. Such an area may represent true necrosis, residual lymphoid elements, or tumor deposits. On T2-weighted MR images, a focal area of both high and intermediate signal intensities is characteristically shown. Indeed, nodal necrosis can also be either hyperintense (indicating cystic necrosis) or hypointense (indicating keratinization).[7] Detection of necrosis in small nodes is of the utmost importance, because these small malignant nodes may be overlooked if their internal architectures are not closely scrutinized (Fig. 2). Apart from being used as a radiologic criterion for metastasis, central nodal necrosis may also be an important prognostic feature if the patient is treated with chemotherapy or radiotherapy. In cases of extensive necrosis, poor tumor oxygenation is probably the cause of resistance to chemotherapy and radiotherapy.[7,15]

Macroscopic extranodal tumor spread can be indicated on contrast-enhanced CT or MRI when the affected node exhibits an irregularly enhanced rim or infiltration of the adjacent fat planes (Fig. 3).

Table 1. Criteria for Cervical Nodal Metastasis on CT and MRI

Criterion	Description
Size	Minimal axial diameter greater than 11 mm in the subdigastric area or greater than 10 mm in other areas
Shape	Longitudinal length/transaxial width radio < 2 (round shape vs. lima bean shape)
Grouping	A group of 3 of more nodes of 8~10 mm in the drainage area of the tumor
Central nodal necrosis	A central area of low "water" attenuation with an enhanced rim on CT or of high and intermediate signal intensity on T2-weighted MRI
Extracapsular spread	Irregular nodal margin with infiltration around and obliteration of the adjacent fat plane

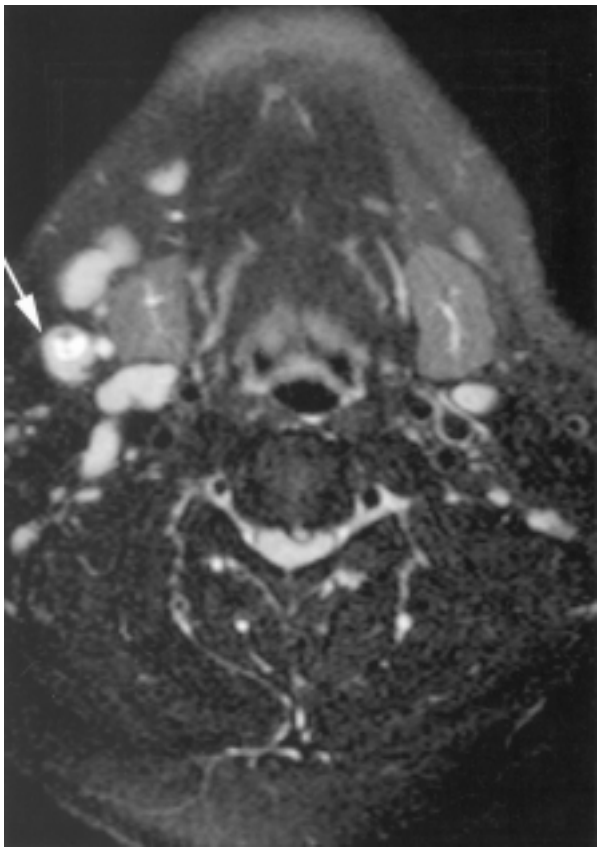

Fig. 2 Neck metastasis presenting as central necrosis in a small node. The T2-weighted MRI shows mixed high and intermediate signal intensities in the central portion of the right non-enlarged submandibular node (arrow).

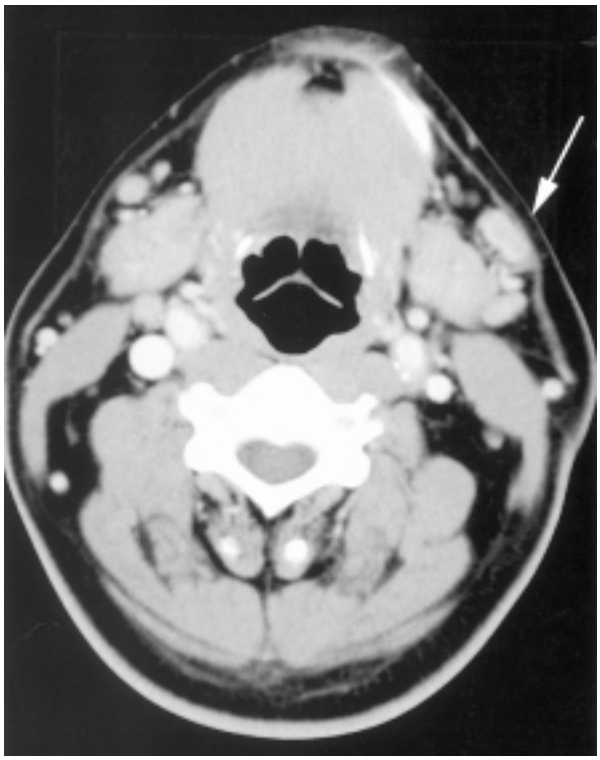

Fig. 3 Neck metastasis presenting as extracapsular spread in a normal-sized node. CT shows an oval left submandibular node with infiltration in the surrounding area (arrows).

Extranodal spread is generally thought to occur in large nodes with clinical fixation, but it does occur in small nodes as well.[1] Therefore, close scrutiny of the nodal margin is mandatory for assessing the presence of extranodal spread. It has been reported that when macroscopic extracapsular tumor spread is present, the patient has a nearly 10-fold greater risk of recurrence compared with patients with either microscopic tumor spread or no extracapsular spread.[18]

Ultrasound (US)

Due to its wide availability and ease of use, US has been shown to be helpful in assessing cervical lymph nodes in patients with various head and neck carcinomas.[19-21] Normal cervical nodes appear sonographically as somewhat flattened hypoechoic structures with varying amounts of hilar fat (Fig. 4).[22] They may show hilar vascularity but are usually hypovascular.[23] Malignant infiltration alters the US features of the lymph nodes, resulting in enlarged nodes that are usually round and heterogeneous (Fig. 5), and show peripheral or mixed vascularity.[24] Using these features, US has been reported to have an accuracy of 89%~94% in differentiating malignant from benign cervical lymph nodes.[25] The main limitations of US are that it can only visualize superficial tissue to a depth of 4~6 cm and its results are dependent on the expertise and experience of the sonographer.

Ultrasound-guided fine-needle aspiration can provide cytologic analysis from nodes as small as 5 mm in diameter. It is a very accurate method for determining cervical metastasis, with a reported sensitivity of 90% and specificity of 100%.[26] However, it is also dependent on the skill levels of the investigator and pathologist, and may be impractical in

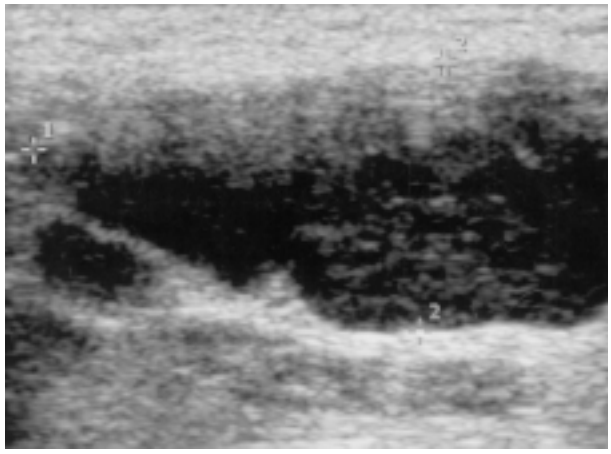

Fig. 4 US appearance of a normal lymph node. The image shows a hypoechoic oval-shaped structure.

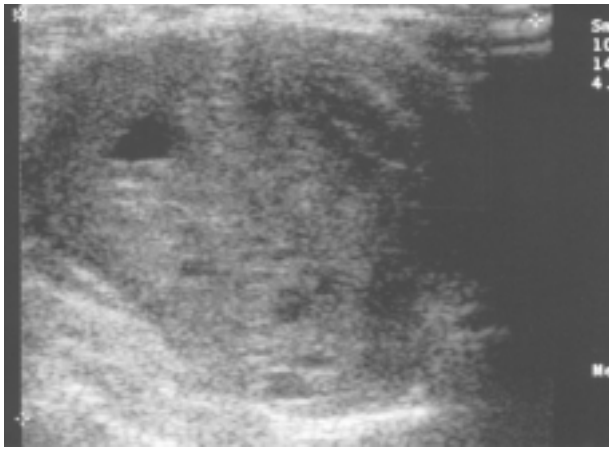

Fig. 5 US appearance of a malignant lymph node. The image shows an enlarged, round lymph node with mixed cystic and solid components.

some cases because of the large number of nodes in question.

Positron emission tomography (PET)

^{18}F-Fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is a functional imaging technique that provides information about tissue metabolism and has been successfully applied to the evaluation of head and neck cancers.[9,27-44,46] ^{18}F-FDG PET is based on identifying increased glycolytic activity in malignant cells, in which radiolabeled FDG is preferentially concentrated due to increases in membrane glucose transporters as well as in hexokinase, an enzyme which phosphorylates glucose. After phosphorylation, radiolabeled FDG continues to accumulate in cancer cells instead of glycolysis, allowing imaging by PET.[27]

^{18}F-FDG PET is more sensitive than CT or MRI in detecting cervical node metastases. It can help identify metastatic nodes which are morphologically normal (Fig. 6). Currently available data from 16 studies[28-43] demonstrate large variations in the sensitivity and specificity of ^{18}F-FDG PET in the detection of cervical lymph node metastases in head and neck cancers. These ranged from 67% to 96% for sensitivity and 82% to 100% for specificity (Table 2). In our previous study examining 124 patients with oral carcinomas,[43] the sensitivity of ^{18}F-FDG PET for the identification of nodal metastases on a level-by-level basis was 22.1% higher than that of CT/MRI (74.7% vs. 52.6%). The technical resolution limitation of ^{18}F-FDG PET of about 5 mm, and its difficulty in detecting small-volume disease contributes to false-negative results (Fig. 7). Thus, intranodal tumor deposits play a determinate role in the sensitivity of ^{18}F-FDG PET, and those malignant nodes with a mean tumor deposit of less than 5 mm would likely be missed.[27,43] Other false-negative outcomes may arise in metastatic nodes that are largely necrotic, are derived from well-differentiated tumors, or are locat-

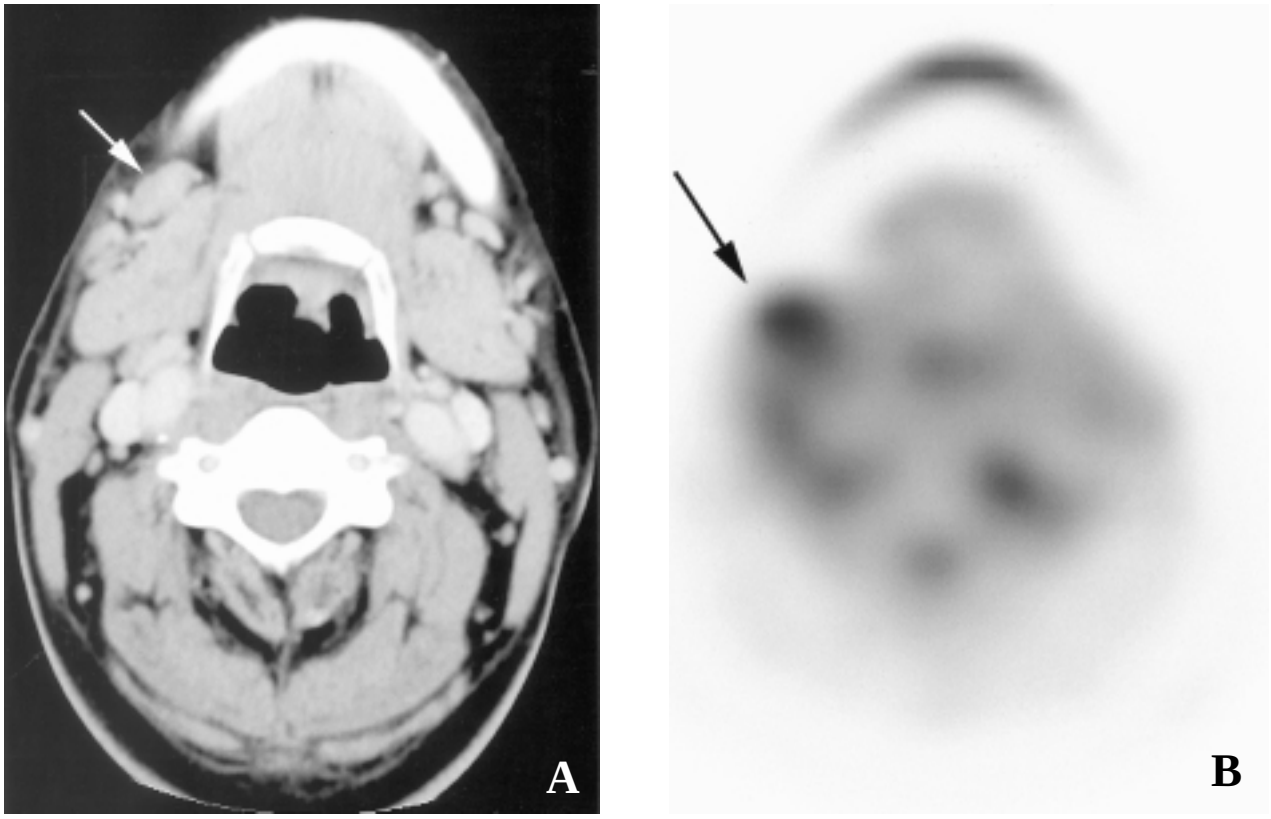

Fig. 6 Metastatic node with normal morphology detected by ^{18}F-FDG PET. (A) CT shows a morphologically benign right submandibular node (arrow). (B) ^{18}F-FDG PET shows positive FDG uptake in the corresponding area (arrow). A histopathologic examination revealed that this node harbored a metastatic carcinoma.

Table 2. Reported Diagnostic Accuracy of PET in Detecting Neck Metastases of Head and Neck Cancers

First author (ref. no.)	Year	No. of patients	Sensitivity	Specificity
Bailet (28)	1992	16	86%	98%
Jabour (29)	1993	12	74%	98%
Rege (30)	1994	34	94%	no data
Braam (31)	1995	12	91%	88%
Laubenbacher (32)	1995	22	90%	96%
McGuirt (33)	1995	49	83%	82%
Benchaou (34)	1996	48	7%	99%
Wong (35)	1997	16	67%	100%
Adam (36)	1998	60	90%	94%
Kau (37)	1999	70	87%	94%
Nowak (38)	1999	71	80%	92%
Stokkel (39)	2000	54	96%	90%
Stuckensen (40)	2000	106	70%	82%
Hannah (41)	2002	35	82%	94%
Hlawitschka (42)	2002	38	93%	83%
Ng (43)	2005	142	75%	93%
Range		12~142	67%~96%	82%~100%

ed in close proximity to the primary tumor.[27,37,45,46] False positives of ^{18}F-FDG PET are mainly due to its inherent inability to discriminate inflammatory processes and reactive hyperplasia from tumor infiltration, because high metabolic changes occur in both instances. Spatial inaccuracies have also contributed to a portion of the false-positive results.[43]

The main drawback of PET remains its relatively poor anatomic resolution. It provides inadequate information necessary for surgical planning of primary tumor resection, such as information regarding the depth of penetration of the tumor and any involvement of neighboring structures. It also cannot accurately assess the size, number, location, or the presence of extracapsular spread of lymph nodes. Therefore, it cannot be used in isolation in the pretreatment staging of head and neck tumors. CT and MRI, by virtue of their better anatomical resolutions, remain the methods of choice for evaluating primary tumors with reliable T-staging.[13,14] PET, nevertheless,

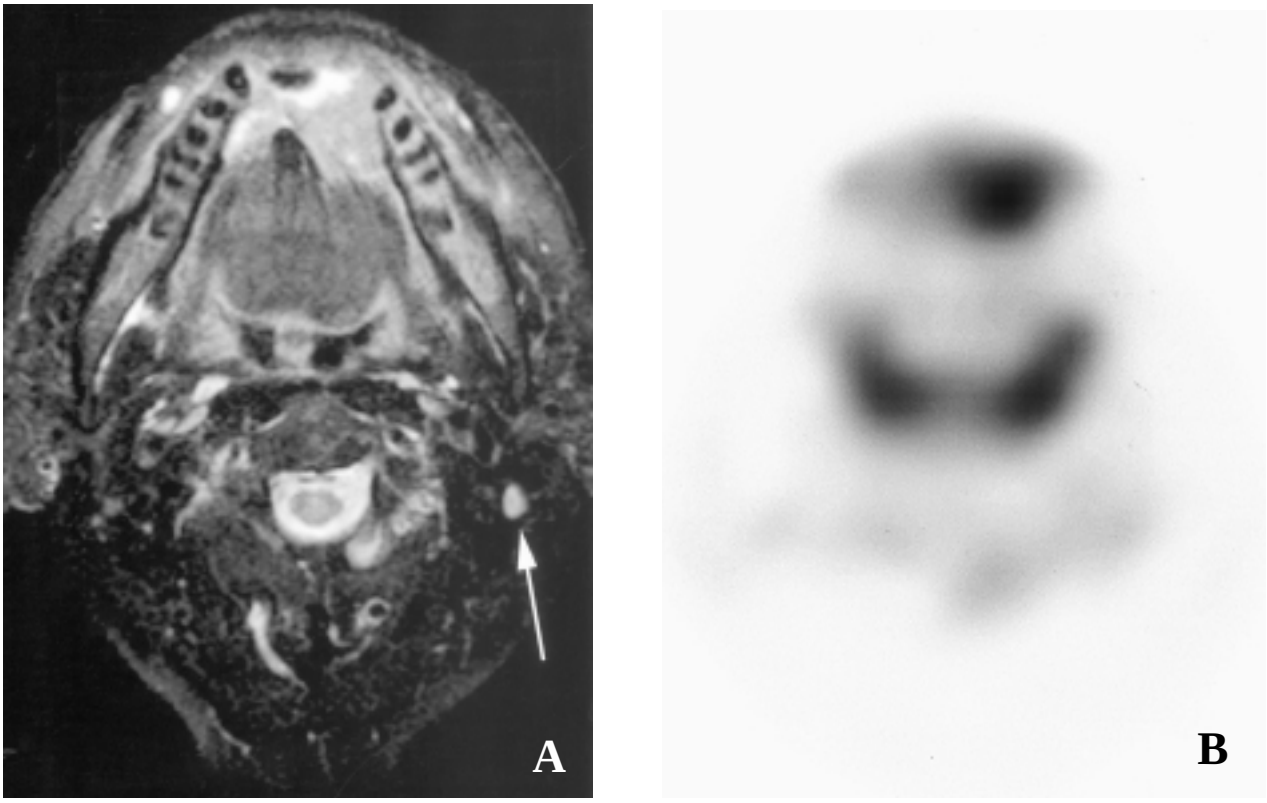

Fig. 7 Small-node metastasis missed by both MRI and ^{18}F-FDG PET. (A) T2-weighted MRI shows a small left neck level II node (arrow), suggesting a benign node. (B) ^{18}F-FDG PET shows no increased metabolism in the corresponding area. A histopathologic examination revealed that this node was a metastatic node.

is helpful in detecting distant lymph node, soft-tissue, and skeletal metastases and is still a satisfactory adjuvant imaging modality for tumor staging. In addition, it is more accurate than CT or MRI in detecting residual or recurrent nodes.[44]

Recent attempts to coregister PET and MRI/CT images have yielded promising results. Side-by-side visual correlations of PET and CT/MRI show a slightly increased diagnostic accuracy over PET alone in detecting neck metastases.[9,43,47] The improvement is mainly due to correction of false PET results resulting from either spatial inaccuracies or largely necrotic nodes. This technique is simple, but is occasionally unfeasible due to a failure to match the abnormal PET uptake with CT/MRI. Coregistration of PET images with CT or MRI scans can also be performed with a computer algorithm which combines the images in a single display using either anatomical landmarks or an automatic algorithm based on matching the pattern of signals from individual voxels. However, in clinical practice, it is time consuming and may be difficult to accomplish due to variations in neck position.[48] Recently, the dual-acquisition PET/CT system has been developed.[48-52] It provides intrinsic alignment of functional data from PET and morphologic detail of CT, and can be very useful in differentiating physiologic from abnormal uptake. In head and neck tumors, PET/CT appears to be superior to PET alone and probably also to visual correlation of PET and CT in the detection of regional nodal metastases and distant metastases, and, thus, is likely to result in accurate tumor staging.[48-51] It can be used to identify the most active tumor regions, which allows biological radiotherapy planning using intensity-modulated radiotherapy (IMRT). FDG-PET/CT-guided IMRT planning can selectively target and intensify treatment of head and neck tumors while reducing critical normal tissue doses.[52] However, it has problems of high cost, limited availability, and the inability to identify micrometastases.

Other novel techniques

Dynamic contrast-enhanced MRI

Dynamic contrast-enhanced MRI has been applied for differentiating normal from metastatic lymph nodes.[53,54] This approach measures the amount of contrast medium accumulating within a node versus time after bolus intravenous contrast administration, and evaluates alterations in nodal microcirculation. Compared with a normal node, a metastatic node has a longer time-to-peak accumulation of contrast medium, a reduced peak enhancement, a reduced slope of accumulation, and a reduced washout slope. However, it is difficult to standardize the acquisition parameters to obtain reproducible data, and this new technique has not stood up to large-scale testing.

Diffusion-weighted MRI

Diffusion-weighted MRI has been investigated for characterizing cervical adenopathies based on the hypothesis that nodal metastases may be associated with alterations in water diffusivity and microcirculation.[55,56] The apparent diffusion coefficient (ADC) for cancerous nodes is reported to be greater than that for benign nodes, which in turn is greater than that for lymphomas. The ADC of highly or moderately differentiated cancers was greater than that of poorly differentiated cancers.[56] This technique has a positive predictive value of 93% and a negative predictive value of 71%.[55] However, relatively large nodes are required to obtain reliable ADC values with high signal-to-noise ratios. Therefore, its application is restricted to considerably enlarged nodes. Another problem with this technique is its relative lack of reproducibility.

Nanoparticle-enhanced MRI

A novel MR contrast agent, known as ultrasmall superparamagnetic particles of iron oxide (USPIO), is classified as a nanoparticle (with a mean diameter of 30 nm) composed of an iron oxide core. These nanoparticles have been employed to improve the ability of MRI to differentiate metastatic from benign nodes.[57-61] Evaluation with USPIO requires 2 MR scans performed 24 h apart. The first scan is used to identify the location of the lymph nodes. Twenty-four hours after injection of USPIO, a second MR scan is performed to evaluate the patterns of contrast enhancement of the identified lymph nodes.

With intravenous administration of USPIO, a normal node will phagocytize the particles and the entire node "blackens" on T2- and T2*-weighted images obtained 24 h later. If a part of the node is infiltrated with tumor, such an intranodal area does not uptake USPIO and, hence, does not blacken. Thus, the extent of the darkened area in the delayed

MR scan is inversely proportional to the nodal tumor burden. If less than 50% of the node blackens, there is an 80% chance that the node contains a tumor.[61] As this can occur in a lymph node that is morphologically normal on conventional MRI, it represents a step forward in diagnosis. Reported false-negative results were mainly due to microscopic intranodal tumor deposits that were below the spatial resolution of the current MR scanners, while the false-positive results were due to reactive hyperplasia, granulomatous disease, and localized nodal lipomatosis.[57,61] Although this technique can increase the accuracy of detecting nodal metastases, the cost of USPIO and logistical problems associated with the requirement to obtain delayed imaging at 24 h may prevent it from gaining wide acceptance.

Conclusions

In clinical practice, CT and MRI are commonly used to detect neck metastases, because they can delineate the extent of the primary head and neck tumors in the same session. Determination of the neck status by these cross-sectional imaging modalities relies on size and morphological criteria. Since metastases can occur in non-enlarged lymph nodes and not all enlarged nodes are malignant, their accuracies are not sufficiently high to be fully accepted by radiologists and clinicians. US and US-guided fine-needle aspiration cytology can improve the diagnostic accuracy, but good results are dependent on the expertise and experience of the examiners, and may be impractical in some cases because of numerous nodes in question.

PET is a functional imaging technique that is more sensitive than CT and MRI in detecting neck metastases. However, it lacks anatomical detail and is seldom used alone. Side-by-side visual correlation of PET and CT/MRI is a simple technique that can increase the diagnostic accuracy of PET. The combined PET/CT device is an advance in PET technology that can simultaneously provide precise integrated functional and anatomical information. It is considered to be the most accurate imaging modality to date, but it still has problems of high cost, lower availability, and the inability to detect micrometastases.

Some novel imaging technologies, including, dynamic contrast-enhanced MRI, diffusion-weighted MRI, and nanoparticle-enhanced MRI, have recently been exploited to improve the detection of neck metastases. The initial results have been encouraging; however, micrometastases can still not be detected, while the extra costs and logistical burdens associated with these techniques prevent them from gaining wide acceptance. At present, neck dissection with detailed pathological examination is still the gold standard for assessing cervical metastases. Further refinement of imaging techniques is mandatory to improve their accuracy until it approaches that of the gold standard.

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頸部轉移的影像學

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對於頭頸癌病患，頸部淋巴結的轉移情形對治療計劃與預後評估是極爲重要。目前，磁振造影 (MRI) 與電腦斷層掃瞄 (CT) 是最普遍被用來評估原發腫瘤與頸部淋巴結狀況。此兩種檢查工具都以淋巴結的形態作爲界定準則。然而，有些移轉發生在形態正常之淋巴結則會被疏漏掉；另一方面，對於一些已擴大的淋巴結，有時很難去識別是來自於腫瘤轉移或是反應增殖。超音波術加上彩色杜卜勒與細針穿刺檢查可以克服部份上述的難題，但這些超音波檢查必需仰賴於檢查人員的技巧水準；而且有時由於超音波可看到太多的不明確淋巴結，若要全面確實診斷，卻有實際執行上的困難。正子斷層掃瞄 (PET) 是一種功能性影像，藉顯示出高新陳代謝的區域來偵測轉移病灶。它較能鑑定那些形態正常之淋巴結有否轉移，但不良之解剖解析度是其主要缺點。並排視覺對照 PET 及 CT/MRI 可幫忙判定異常吸取處之解剖位置及幫忙排除 PET 因空間誤差所造成的僞陽性。目前PET/CT被認爲是探測淋巴結轉移之最佳影像工具，因它可準確地同時合成解剖性與功能性影像。然而，PET/CT 是相當昂貴且不易取得，並受技術解析度的局限，且對偵測微小之淋巴結轉移仍有所不足。在近年來，一些新興的影像技術，包含 nanoparticle-enhanced MRI、dynamic contrast-enhanced MRI 與 diffusion-weighted MRI 已經開發利用於提昇頸部淋巴結轉移的偵測效能。初步結果是令人鼓舞的，然而微小轉移仍舊無法被偵測出來，而且這些新興的技術所需額外的成本與繁複的後續處理卻阻礙它們被廣泛應用。至今，頸部切割術加上精細病理學檢查仍是最佳診斷標準，所以影像技術需要更進一步改良，俾使其提供資料之準確度能近乎這最佳診斷標準。(長庚醫誌 2006;29:119-29)

關鍵字：癌症分期，淋巴結影像，淋巴結轉移，磁振造影，電腦斷層掃瞄，正子斷層掃瞄，超音波術。

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受文日期：民國94年10月11日；接受刊載：民國94年12月2日
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