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Review Article

Diagnostic Imaging of Metastatic Cervical Lymph Nodes

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The presence of lymph node metastasis in the neck in patients with cancer of the oral cavity or other head and neck regions is an important prognostic determinant in staging cancers and in planning radiotherapy of the cancer patients. We review recent advances in diagnostic imaging of metastatic lymph nodes in the neck of patients with extracranial head and neck squamous cell carcinoma, with the main emphasis on diagnostic performances of CT, sonography, and MR imaging.

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Key Words: squamous cell carcinoma, neck, nodal metastasis, CT, sonography, MRI

Introduction

Staging of neck metastasis is a crucial step in managing patients with head and neck squamous cell carcinoma[1]. The presence of lymph node metastasis in the neck in patients with cancer of the oral cavity or other head and neck regions is an important prognostic determinant in staging cancers and in planning radiotherapy of the cancer patients. In this regard, the presence of a metastatic lymph node(s) in the ipsilateral or contralateral side of the neck, or both, reduces the 5-year survival rate by about 50%[2]. In general, a patient with head and neck squamous cell carcinoma and regional metastasis will be treated with irradiation of the neck, surgery, or both. Since nodal metastasis is a frequent event that impacts prognosis of patients, the necks of such patients will be treated electively when regional metastasis is likely, even if not detected clinically. Thus, if the probability of nodal metastasis is reduced (i.e. more accurately diagnosed), the number of elective treatment will be reduced. It is, therefore, important to assess as reliably as possible whether a patient has regional lymph node metastasis.

Several studies have attempted to establish diagnostic criteria for differentiation of metastatic from non-metastatic cervical lymph nodes in these patients[3,4]. The development of imaging techniques such as helical CT, MR imaging, and high resolution sonography[4,5] has improved the detection of metastatic cervical nodes in patients with head and neck cancer. Accordingly, several studies have attempted to determine reliable criteria for these techniques.

Increases in nodal size were found to be effective imaging criteria for detection of metastatic cervical nodes with CT and MR imaging[1,4]. However, size determination alone is not effective enough for detecting metastatic nodes. Thereby, several studies have attempted to improve the diagnostic accuracy by assessing the internal architecture of the node, and by using other tissue specific imaging techniques such as sonography-guided fine needle aspiration biopsy[6]. Here, we review imaging techniques and criteria for detection of metastatic cervical lymph nodes from head and neck cancer.

Structure of lymph node

The lymph node consists of four structural and functional components (Fig. 1): 1) the cortex with its germinal center, where the B cell system develops; 2) the medullary zone, in which most of the plasma cells reside and the B cell system exerts its secretory function; 3) the paracortex lying between the germinal centers, in which most T cells reside; and 4) the sinuses, which contain macrophages and other mononuclear phagocyte cells.

The capsule of the lymph node is interrupted at various parts by afferent lymphatics that bring lymph into the marginal sinus. The marginal sinus continues into cortical or trabecular sinuses that traverse the paracortex and then enter the medullary cords, where the sinus become wider and more tortuous (medullary sinus).

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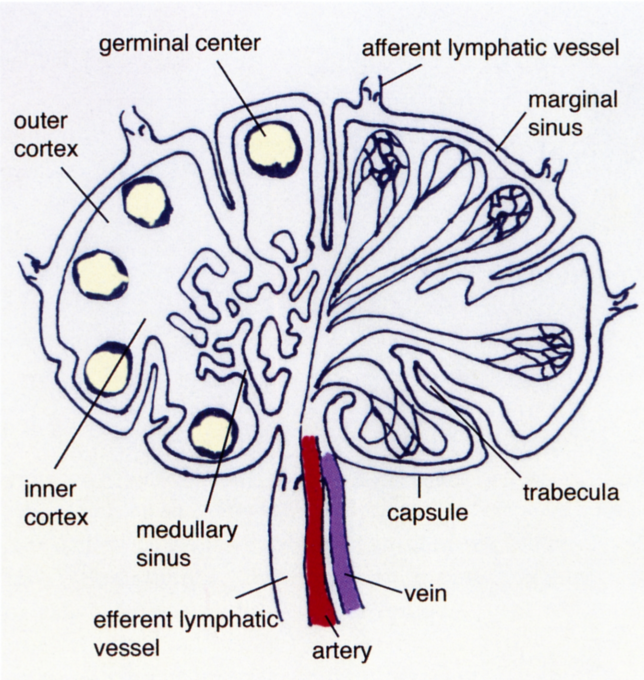
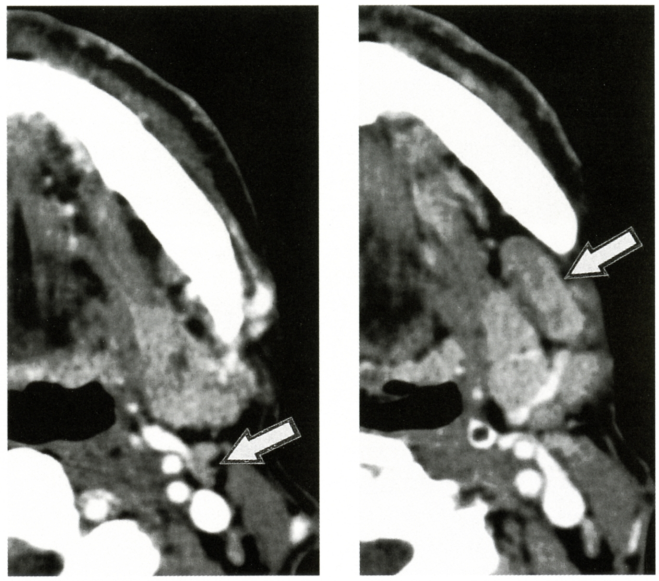


Fig. 1. Drawing of lymph node structures.



(A) (B)

Fig. 2. 70-year-old man with squamous cell carcinoma of lower gingival.
A, Axial CT shows reactive node (arrow) exhibiting hilar structure. Minimal axial diameter is 5 mm.
B, Axial CT shows fused metastatic nodes (arrow).

Fig. 3. 69-year-old man with squamous cell carcinoma of tongue. Axial CT shows homogeneously enhanced metastatic nodes (arrows). Minimal axial diameters are 10 mm (left) and 12 mm (right).

Almost all the blood vessels enter the lymph node through the hilum. The larger arterial branches initially run within the traneculae, and then they soon enter the medullary cords and supply their capillary networks. Then the arteries reach the cortex, where they distribute to capillary plexuses of the cortex parenchyma and germinal centers. In the paracortex, capillary branches give rise to the high endothelial venules, which are distinctive to this region and brings circulating lymphocytes, predominantly T cells, to the paracortex.

CT

Recent focus has been placed, at least in part, on the development of a diagnostic strategy to differentiate effectively the metastatic from reactive nodes in patients with cancer. Indeed, patients with head and neck cancer are associated with substantial numbers of reactive nodes along with metastatic nodes. CT imaging is most commonly used in surveying metastatic nodes in patients with head and neck cancer, since CT provides excellent information about the location, size and even internal architectures of the node[3-5].

The hallmarks for the metastatic nodes are increase in short (or minimal) axial diameter of the node and/or rim enhancement of the node (central nodal necrosis) after contrast enhancement (Figs. 2-4)[3]. Other criteria include the maximal axial diameter, the irregular enhancement due to tumor necrosis and the shape[4,7]. The difference in criteria used accounts, in part, for the difference in the reported overall error. van den Brekel, et al. showed that the minimal axial diameter was the most accurate size criterion for predicting metastatic cervical nodes[3]. They reported that a minimal axial diameter of 10 mm was the most effective size criterion. However, this criterion provided an atmost

Fig. 4. 87-year-old woman with squamous cell carcinoma of tongue. Axial CT shows metastatic node with rim enhancement (arrow). Minimal axial diameter is 14 mm.

moderate performance in detecting metastatic cervical nodes, with 42% sensitivity and 99% specificity for assessment per node and 89% sensitivity and 73% specificity per neck. More recent studies using the receiver operating characteristic curve (ROC) analysis demonstrated that the CT performance for detecting metastatic nodes was moderate, with the area under the ROC curve (Az value) at 0.80-0.87 for varying combinations of size and internal architecture criteria of the node[7,8]. These studies also showed that, when using a 10-mm size criteria, the CT had a negative predictive value of 0.83 and positive predictive value of 0.50, and had a accuracy of 0.80.

Central nodal necrosis is considered to be a pathognomonic feature for metastatic nodes from head and neck squamous cell carcinomas. Central nodal necrosis occurs as cancer cells infiltrate into the medullary portion of the node to surpass the blood supply. Central nodal necrosis was reported to occur in 32% of metastatic nodes[3]. CT was shown to have a sensitivity of 74% and specificity of 94% for detecting central nodal necrosis. Another study showed that CT was more effective than MR imaging in detecting central nodal necrosis[9].

One of the most commonly accepted classifications of cervical nodes is that of the International Union Against Cancer (UICC)[10]. However, the classification adopted by the Academy of Otolaryngology Head and Neck Surgery, where the nodes are classified into level I through level VI[11], appears to be readily acceptable for clinicians, since such numeric classification is simple and useful for understanding recent management of selective neck dissections. The image-based classification originally proposed by Som, et al.[12] is basically similar to this classic, pulpation-based numerical classification (Fig. 5). However, in the image-based classification, nodes are classified with more in-deep definition, allowing reproducible identification of nodes using precise anatomical landmarks. Thus, except for nodes in the lowest levels of the neck, such as those in level VI and the subclavicular fossa, where CT imaging is disturbed by artifacts from the bone, the image-based classification may be relevant to the management of patients and dispensable for the palpation-based classification.

Introduction of helical CT can improve diagnostic performance for detection of malignant nodes in the neck. In this context, Steinkamp, et al reported preliminarily that size criterion using the ratio of the maximum longitudinal diameter to maximum axial diameter yielded 97% sensitivity and 97% specificity for metastatic lymph nodes from head and neck tumors[13]. Helical CT technique allows displaying coronal, sagittal, axial, and paraxial images of the node without increasing extra examination time. Therefore, helical CT technique could permit more precise assessment of topographical relationships of the node to vessels as well as volumetric assessment of enlarged nodes in the neck.

It was documented that metastatic and non-metastatic nodes in the subdigastric and submandibular regions,

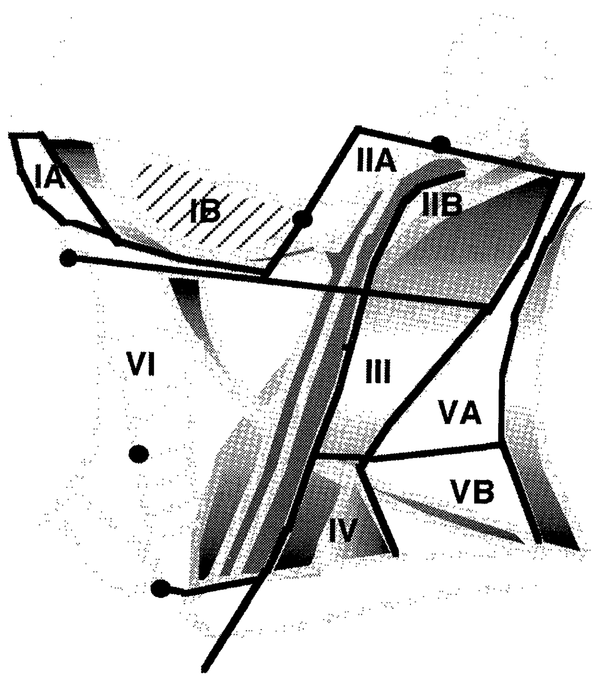


Fig. 5. Drawing shows image-based classification by Som, et al.[12]

which correspond to levels I and II of the neck, had axial diameters that were on average 1-2 mm larger than nodes in other levels[3,4]. This could affect size criteria that yield compromising sensitivity and specificity in detecting metastatic nodes. Sumi, et al. showed that metastatic nodes in level II were on average 2-3 mm larger in minimal axial diameter than those in other levels (I, III, and IV) of the neck, but non-metastatic nodes were similar in size among these levels[8]. Consistent with the notion proposed by preceding reports, they showed that the diagnostic performance of CT in detecting metastatic nodes was higher with nodes at level II than those at other levels.

Nodes in levels I and II of the neck receive lymphatic drainage from anterior facial structures and skin, the floor of the mouth, and the anterior oral cavity[14]. Nodes in level II-IV receive lymphatic drainage from the parotid, retropharyngeal, and nodes in level IB. The nodal chain in levels II-IV serves as a common pathway for all lymphatics of the upper aerodigestive tract and neck. Thus, these drainage patterns result in different incidences of metastatic nodes in different levels of the neck. The incidence of adenopathic or enlarged nodes was higher in patients with pharyngeal cancer than those with oral cancer. Metastatic nodes from the oral cavity appear predominantly in levels IB and IIA. Level IA is a common site for metastasis from cancers in the lower gingiva, oral floor, and tongue. Cancers in the oral floor and tongue can metastasize to nodes in levels III and IV, but metastatic nodes in this level were uncommon from other oral cancers. In contrast, laryngeal and esophageal cancers rarely metastasize to nodes in levels IA and IB. Levels VA, VB, and VI are uncommon sites for metastasis from head and neck cancers.

Sonography

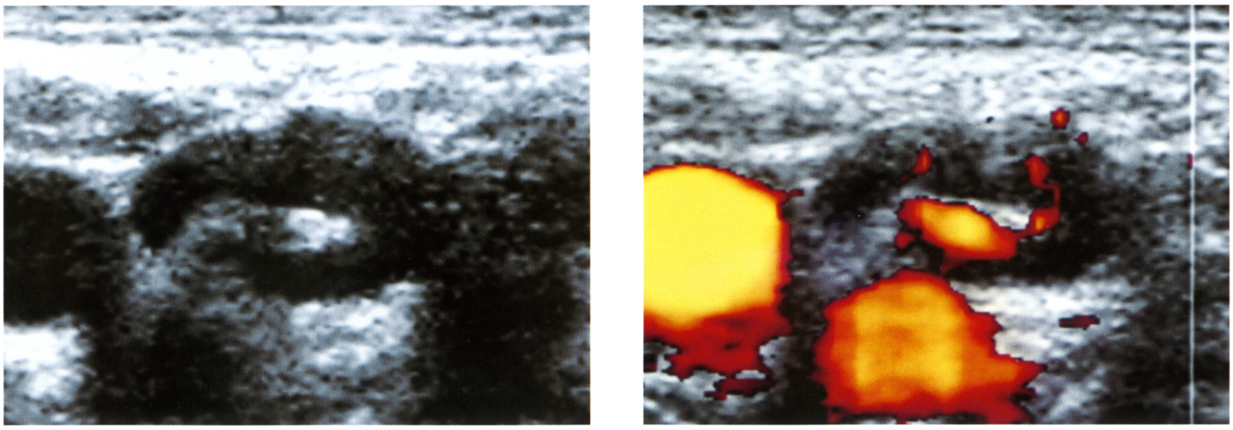
Sonographic evaluation of metastatic nodes is also based on assessment of the internal architecture of the node and size determination of the node, and abnormalities in the metastatic node may be reflected by increased parenchymal echogenicity or loss of hilar echogenicity[5,15]. In addition, the recent development of Doppler sonographic technology has shed light on the diagnostic significance of changes in nodal blood flow when differentiating metastatic from non-metastatic nodes[16-19].

High-resolution sonography could be a tool for the detection of metastatic lymph nodes, and this was partly substantiated by the observation of Vassallo, et al., who showed that an increased transverse to longitudinal ratio and eccentric widening of the nodal cortex were useful structural parameters for differentiating benign and malignant nodes[5]. van den Brekel, et al.[3] and, later, Chikui, et al.[20] demonstrated that the minimal axial diameter was the most accurate size criterion compared to the maximal axial diameter and the longitudinal diameter. Similar to the assessment by CT, the best size criterion for metastatic nodes differed among levels of the neck; van den Brekel, et al.[21] and Yonetsu, et al.[22] postulated that a minimal axial diameter of 7 mm for level II and 6 mm for the remainder of the neck provide the optimal compromise between sensitivity (67-87%) and specificity (72-89%).

Color Doppler sonography provides information about blood flow and morphology. The use of higher frequency transducers improves the ability to detect low-velocity signals from superficial organs. By analyzing the spectral waveform, Steinkamp, et al.[23] and, more recently, Choi, et al.[19] appraised the clinical usefulness of color Doppler sonography for differentiating superficial lymph nodes involved in metastasis from those affected by benign diseases. They showed that the resistive index was significantly higher in the metastatic lymph nodes than in the benign lymph nodes, and they proposed that this difference was due to compression by tumor cells of vessels in the lymph node and/or tumor-evoked angiogenesis. However, vessels were dilated in the non-metastatic lymph nodes.

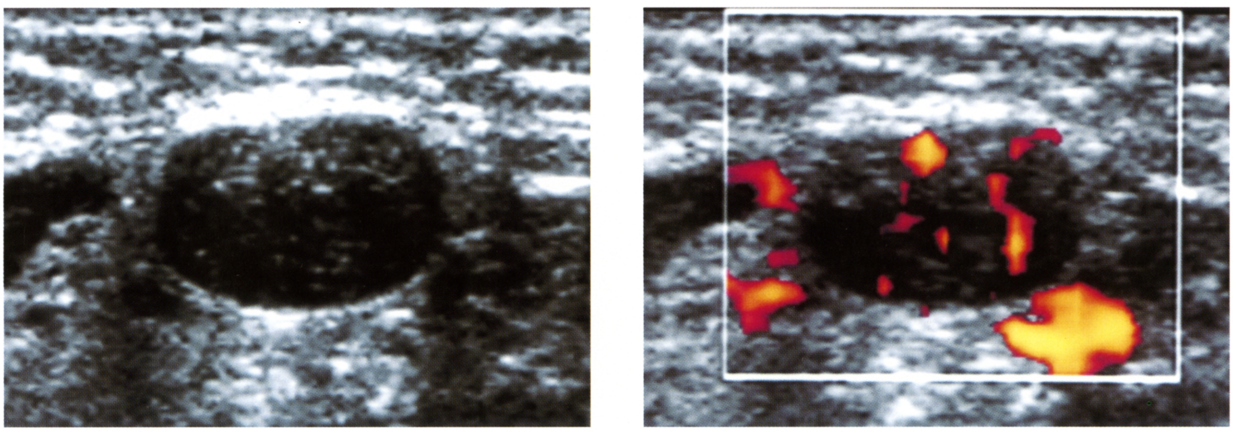
Power Doppler sonography was first introduced by Rubin, et al.[24]. It is essentially angle-independent and has a greater dynamic range than conventional color Doppler sonography, thus increasing sensitivity. This extended dynamic range enhances visualization of the microvascularity of the lymph nodes. Ariji, et al. was among the first who described the importance of abnormal blood flow patterns in differentiating metastatic from non-metastatic nodes in patients with head and neck cancer[17]. They classified nodal flows into three major types; 1) hilar, 2) parenchymal, and 3) no blood flow signals (Figs. 6-9). Power Doppler sonography was found to provide high levels of sensitivity (83%) and specificity (98%) in depicting metastatic lymph nodes, which was superior to those by lymph node size criteria (transverse to longitudinal ratio, T/L ratio). Furthermore, they showed that a combination of the two sonographical criteria (parenchymal color signal and T/L ratio) improved the diagnostic accuracy (92% sensitivity and 100% specificity).

Chikui, et al.[20] compared in a multivariate feature study the grey-scale and power Doppler sonographic parameters to show that, of the sonographic criteria advocated for metastatic or non-metastatic nodes, the presence or absence of hilar echogenicity, increases in short axis diameter, and the presence of normal hilar blood flow were the only sonographic features that



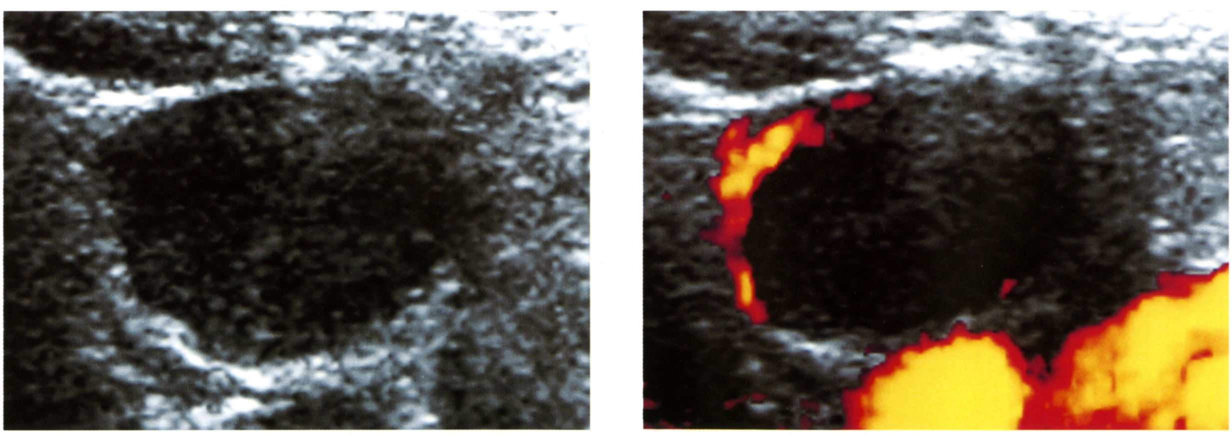
(A) (B)

Fig. 6. 57-year-old man with squamous cell carcinoma of buccal mucosa.
A, Grey-scale sonography of reactive node shows homogeneous echogenicity of the nodal parenchyma with hilar echogenicity. Minimal axial diameter is 8 mm.
B, Power Doppler sonoography of the same node as that shown in panel **A** exhibits hilar blood flow signal.



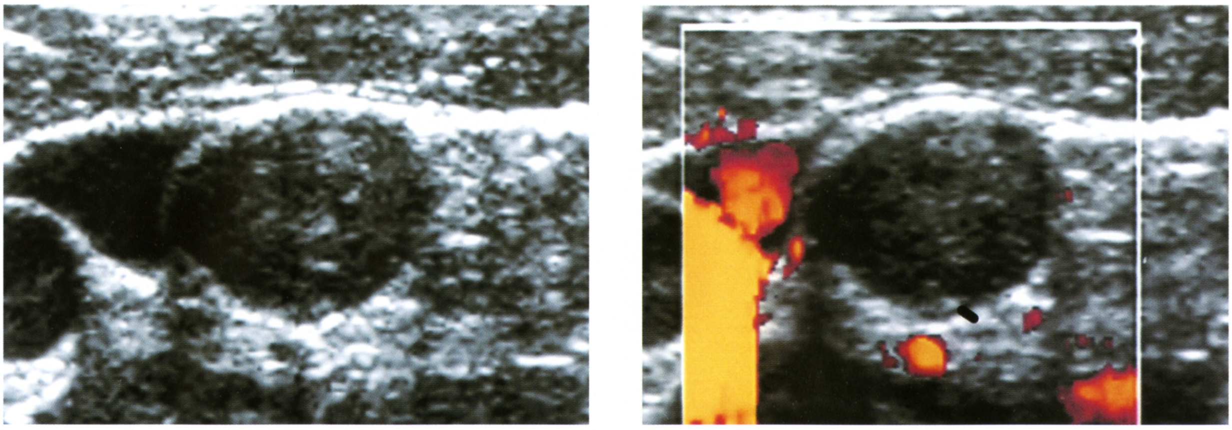
(A) (B)

Fig. 7. 63-year-old woman with squamous cell carcinoma of lower gingiva.
A, Grey-scale sonography of metastatic node shows heterogeneous echogenicity of the nodal parenchyma. Note that no hilar echogenicity is detected. Minimal axial diameter is 8 mm.
B, Power Doppler sonography of the same node as that shown in panel **A** exhibits multiple parenchymal blood flow signals.



(A) (B)

Fig. 8. 77-year-old woman with squamous cell carcinoma of lower gingiva.
A, Grey-scale sonography of metastatic node shows homogeneous echogenicity of the nodal parenchyma. Minimal axial diameter is 12 mm.
B, Power Doppler sonography of the same node as that shown in panel **A** exhibits blood flow signals in the periphery of the node.



(A) (B)

Fig. 9. 49-year-old woman with squamous cell carcinoma of lower gingiva.
A, Grey-scale sonography of metastatic node shows heterogeneous echogenicity of the nodal parenchyma. Minimal axial diameter is 9 mm.
B, Power Doppler sonography of the same node as that shown in panel **A** exhibits no blood flow signal from the node.

were predictive of metastatic (increases in short axis length) or reactive nodes (the presence of normal hilar blood flow or hilar echoes, or both).

Compared with the single use of short axis diameter criteria, the combined use of the size and Doppler blood flow pattern criteria increased the diagnostic accuracy of sonography at all levels in the neck. Accordingly, the best cut-off values were improved to 6, 7, and 5 mm for nodes at levels I, II, and III plus IV, respectively. In addition, the combined criteria yielded high sensitivities ($\geq$ 89%) and specificities ($\geq$ 94%)[22].

Most recently, Sumi, et al. compared the ability of sonography and CT to differentiate benign from malignant cervical lymph nodes in patients with head and neck squamous cell carcinomas[8]. ROC curve analysis showed that sonography provided greater diagnostic performance (power Doppler plus grey-scale, 0.97 and grey-scale, 0.95) than CT (0.87). ROC curve analysis also demonstrated that the greater ability of sonography to depict the internal architecture of the nodes compared with CT significantly contributed to the better performance of sonography compared to CT in diagnosing metastatic nodes in the neck. However, size criteria (minimal axis diameter) were equally predictive in sonography and CT.

Assessment of the intranodal blood flow patterns is also useful in monitoring malignant nodes after radiation therapy. Ahuja et al showed, in their preliminary study, that a reduction in intranodal vascularity was detected and color Doppler sonographic parameters, such as resistive and pulsatility indices, had returned to levels observed in benign nodes as early as 8 weeks after completion of treatment[25].

The lack of requirement for radiation and low cost may be major advantages of sonographic examination. Accumulating evidence indicates that sonography performs better than CT in detecting metastatic nodes in patients with head and neck squamous cell carcinoma. Nevertheless, since sonographic examination takes much more time than CT, it may greatly diminish the value of sonography; in general, sonographic examination of the bilateral neck requires on average 10-fold much examination time[8]. In addition, the CT examination is necessary for the detection of deep cervical nodes such as those in the retropharyngeal space. Therefore, it may be reasonable to perform sonographic examination for detailed study of suspected nodes in the neck, following CT surveillance.

Sonography-guided fine-needle aspiration biopsy (FNAB) may be another adjunctive tool for a further increase in reliability and accuracy for the diagnosis of metastatic cervical nodes. A fundamental concept for sonography-guided FNAB is to combine the high sensitivity of sonography and the high specificity of cytology. However, sonography-guided FNAB has been reported to have relatively low sensitivity (less than 77%), while the reported specificity is 100%[26,27]. A combination of grey-scale and Doppler sonographic criteria may be helpful in selecting nodes for sonography-guided FNAB. Contrast-enhanced sonography, which has not yet been extensively studied, may also be helpful for increasing the reliability of sonographic diagnosis of metastatic nodes.

MR imaging

Since the early 1990s, MR imaging has been extensively applied to diagnostic imaging of metastatic cervical lymph nodes[28]. Despite the superior contrast resolution of MR over CT, the signal intensity of metastatic nodes does not differ significantly from that of benign nodes. Central nodal necrosis appears high in signal intensity on T2-weighted images and low in signal intensity on T1-weighted images. In general, however, the performance of MR imaging does not exceed that of CT in this aspect; for instance, MR imaging criteria regarding the presence or absence of central nodal necrosis yielded an accuracy of 86-87% with T1- or T2-weighted images, which was lower than that of CT (91-96%)[9]. Gadolinium-enhanced fat-suppression techniques did not improve detection of central nodal necrosis.

A more recent study showed that CT performed slightly better than MR imaging, when size criteria and/or information on internal architectural abnormalities of the node on MR images was used for highlighting positive nodes[7]; they reported that Az values for combined information on size and internal architectural abnormalities were 0.80 for CT and 0.75 for MR imaging. Information on extranodal cancer spread did not improve the performance of MR imaging for detecting metastatic nodes[9]. Use of specific techniques, such as diffusion-weighted imaging[29] and magnetization transfer imaging[30], may improve the performance.

Use of superparamagnetic contrast agents may be an alternative way for improving the performance of MR imaging in detecting metastatic nodes in the neck. Ultrasmall ion particles less than 20 nm in diameter are able to traverse across the capillary wall, enter the lymphatics, and subsequently are trapped by macrophages in the lymph node[31]. Normal nodes that have taken up ion particles reduce signal intensity, while metastatic nodes remain high in signal intensity due to replacement by cancer cells. Anzai, et al. reported in their preliminary study, that dextran-coated ultrasmall superparamagnetic ion oxide (USPIO) differentiated effectively metastatic from benign nodes in the neck of patients with extracranial head and neck cancer[31]. More recent studies on patients with cancer in head and neck as well as other regions have extended the previous findings to show that sensitivity was 95-100%, and specificity was 38-97% with USPIO[32-34]

Miscellaneous modalities

Lastly, we should comment on recent advances of single photon emission CT (SPECT) and positron emission CT (PET) for detection of metastatic nodes. Thallium 201 (201Tl) and technetium-99m (^{99m}Tc) hexakis-2-methoxy-isobutyl-isonitrile (MIBI) are major SPECT agents. Uptake of 201Tl depends on blood flow in the interstitial spaces and on the sodium-potassium pump in the cell membrane. Valdes Olmos reported that 201Tl-SPECT yielded 71% sensitivity and 92% specificity for detection of metastatic cervical nodes in patients with head and neck squamous cell carcinoma and concluded that 201Tl-SPECT alone was not sensitive enough for staging of the neck[35]. To date, no extensive study using MIBI-SPECT has been reported with cervical lymph nodes, while MIBI-SPECT provided low sensitivity in detecting axillary lymph nodes metastatic from breast cancer[36].

PET using 2-[18F]fluoro-2-deoxy-d-glucose (FDG) could be another functional imaging modality for detection of metastatic nodes. Malignant nodes have higher glucose utilization than normal nodes. Accordingly, FDG-PET might detect metastatic nodes that are negative with size criteria by MR imaging[37]. However, metastatic nodes that contain large necrotic area are negative with FDG-PET criteria due to the low glycolytic activity of the necrotic material. FDG-PET criteria has not been well established, and poor accuracy of FDG-PET in visual interpretation of a lesion is frequently a problem. Other disadvantages of FDG-PET are limited clinical availability, low spatial resolution, and high cost. FDG-PET provided better performance in detecting metastatic pelvic nodes in patients with cervical cancer compared to MR imaging, with a patient-based nodal staging by FDG-PET resulting in 91% sensitivity and 100% specificity, while 73% sensitivity and 83% specificity with MR imaging[38]. Further studies are necessary to facilitate clinical application of FDG-PET for head and neck imaging.

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