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REVIEW

Ultrasound of malignant cervical lymph nodes

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Abstract

Malignant lymph nodes in the neck include metastases and lymphoma. Cervical nodal metastases are common in patients with head and neck cancers, and their assessment is important as it affects treatment planning and prognosis. Neck nodes are also a common site of lymphomatous involvement and an accurate diagnosis is essential as its treatment differs from other causes of neck lymphadenopathy. On ultrasound, grey scale sonography helps to evaluate nodal morphology, whilst power Doppler sonography is used to assess the vascular pattern. Grey scale sonographic features that help to identify metastatic and lymphomatous lymph nodes include size, shape and internal architecture (loss of hilar architecture, presence of intranodal necrosis and calcification). Soft tissue oedema and nodal matting are additional grey scale features seen in tuberculous nodes or in nodes that have been previously irradiated. Power Doppler sonography evaluates the vascular pattern of nodes and helps to identify the malignant nodes. In addition, serial monitoring of nodal size and vascularity are useful features in the assessment of treatment response.

Keywords: *Cervical lymph nodes; metastases; lymphoma; ultrasound.*

Introduction

Assessment of nodal status is essential in patients with head and neck carcinomas as it predicts prognosis and helps in the selection of treatment options[1,2]. In patients with proven head and neck carcinomas, the presence of a unilateral metastatic node reduces the 5-year survival rate by 50%, whereas the presence of bilateral metastatic nodes reduces the 5-year survival rate to 25%[3]. Metastatic cervical lymph nodes from head and neck carcinomas are usually site specific with respect to the location of the primary tumour. Therefore, assessment of the distribution of metastatic nodes in patients with unknown primary may provide a clue to the site of the primary tumour. Moreover, metastatic nodes in an unexpected site indicates that the primary tumour is biologically more aggressive[4].

Besides metastases, lymphoma is also a common malignant disease and head and neck involvement is relatively common[5]. Clinically, lymphomatous cervical lymph nodes are difficult to differentiate from other causes of lymphadenopathy including metastatic nodes. As the treatment options differ, accurate identification of the nature of the diseases is essential.

The role of ultrasound in the assessment of cervical lymphadenopathy is well established. It is particularly sensitive compared to clinical examination (96.8% and 73.3% respectively) in patients with previous head and neck cancer with post-radiation neck fibrosis[6]. When combined with guided fine needle aspiration cytology (FNAC), the specificity of ultrasound is as high as 93%[7]. Although computed tomography (CT) and magnetic resonance imaging (MRI) are also used to evaluate cervical lymph nodes, the nature and internal architecture of small lymph nodes (<5 mm) may not be readily assessed. In addition, MRI may not identify intranodal calcification which is a useful feature in predicting metastatic nodes from papillary carcinoma of

the thyroid[1,3,8,9]. On contrast-enhanced CT, the reported sensitivity and specificity in the evaluation of metastatic cervical lymph nodes are 90.2% and 93.9% respectively[10]. On high resolution MRI, the sensitivity and specificity in assessing metastatic nodes are 86% and 94% respectively, whereas those in evaluating lymphomas are 85% and 95% respectively[11]. Positron emission tomography (PET) has a relatively lower sensitivity (80.3%) and specificity (92.8%) in the evaluation of metastatic nodes, but the sensitivity (91.8%) and specificity (98.9%) are higher when PET/CT is used[10]. Among different imaging modalities, ultrasound has the highest sensitivity in the assessment of malignant cervical nodes, whereas PET/CT has the highest specificity in the diagnosis.

This article reviews the grey scale and Doppler sonographic features in the assessment of metastatic and lymphomatous cervical lymph nodes. In the sonographic assessment of cervical lymph nodes, grey scale ultrasound assesses the nodal site, size, shape, border, internal architecture (echogenicity, echogenic hilus, calcification and necrosis), matting and adjacent soft tissue oedema. The vascular pattern of lymph nodes is evaluated with colour or power Doppler ultrasound, whilst the blood flow velocity and vascular resistance are measured using spectral Doppler ultrasound.

Metastases

Metastatic cervical nodes from head and neck primaries are site-specific[4,12]. Common nodal metastatic sites for head and neck primaries are[1,12–29]:

- pharynx, larynx, oesophagus, papillary carcinoma of thyroid metastasize along internal jugular chain
- tumours in the oral cavity metastasize to the submandibular and upper cervical regions, although carcinoma of the tongue may give rise to skip metastases in the lower neck.
- infraclavicular primaries from breast and lung metastasize to supraclavicular fossa and posterior triangle.
- nasopharyngeal carcinoma commonly spreads to upper cervical and posterior triangle nodes.

Grey scale evaluation of metastatic nodes

Size

Nodal size is one of the criteria used to differentiate reactive from metastatic nodes[15,30]. Although larger nodes tend to have a higher incidence of malignancy, reactive nodes can be as large as metastatic nodes. Therefore, different cut-offs of the nodal size to differentiate reactive and metastatic nodes have been reported (5 mm, 8 mm and 10 mm)[30–32]. However, when a lower cut-off of nodal size is used, the diagnostic sensitivity increases while the specificity decreases and vice versa[33]. Therefore, nodal size alone cannot be used to distinguish reactive from metastatic lymph nodes. However, the size of lymph nodes is useful in two clinical situations: (1) increase in nodal size on serial examinations in a patient with a known carcinoma is highly suspicious for metastatic involvement; (2) serial reduction in nodal size is a useful indicator in monitoring patient's response to treatment[34].

Shape

Metastatic nodes tend to be round with a short to long axes ratio (S/L ratio) greater than 0.5, while reactive or benign lymph nodes are elliptical in shape (S/L ratio <0.5)[18,32,35–37]. Although the round shape helps to identify a metastatic lymph node, it should not be used as the sole criterion of nodal assessment as normal submandibular and parotid nodes are also round[36]. Irrespective of size, eccentric cortical hypertrophy, which is due to focal tumour infiltration within the lymph node, is a useful sign to identify metastatic nodes[37].

Border

Contrary to common belief, metastatic lymph nodes tend to have sharp borders (Fig. 1), whilst benign lymph nodes usually show unsharp borders[31]. This sharp border in metastatic nodes is due to intranodal tumour infiltration which causes an increase in the acoustic impedance difference between intranodal and surrounding tissues[31]. However, metastatic nodes in advanced stages may demonstrate ill-defined borders, indicating extracapsular spread[38]. Nodal border alone is therefore not a reliable criterion in distinguishing normal from abnormal nodes in routine clinical practice. However, the presence of ill-defined borders in a proven metastatic
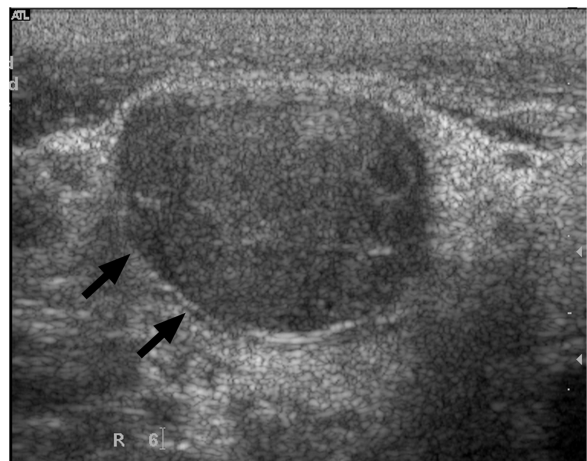

Figure 1 **Grey scale sonogram showing a metastatic lymph node which is enlarged, hypoechoic, well-defined and without an echogenic hilus (arrows).**

node indicates extracapsular spread and is useful in predicting patient prognosis.

Echogenicity

Metastatic lymph nodes are predominantly hypoechoic relative to the adjacent musculature[18,19,24,39]. However, metastatic nodes from papillary carcinoma of the thyroid are usually hyperechoic (Fig. 2), and this is believed to be related to the intranodal deposition of thyroglobulin originating from the primary tumour[8,26].

Echogenic hilus

On ultrasound, the echogenic hilus appears as an echogenic intranodal linear structure which is continuous with the adjacent perinodal fat[40–42]. The echogenic
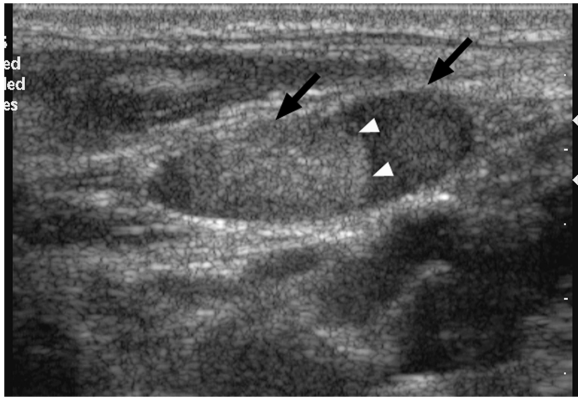

Figure 2 **Grey scale sonogram showing a metastatic lymph node from papillary carcinoma of the thyroid (arrows). Note the hyperechoic component within the node which may be related to intranodal deposition of thyroglobulin (arrowheads).**
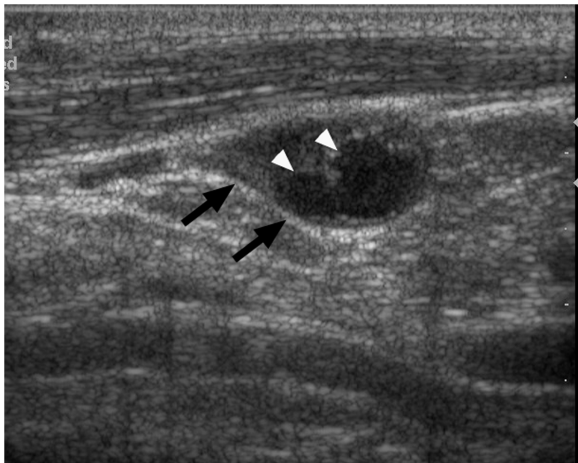

Figure 3 **Longitudinal grey scale sonogram showing a metastatic cervical node (arrows) with intranodal cystic necrosis which appears ill-defined and echolucent (arrowheads).**

hilus is mainly the result of multiple medullary sinuses, which act as acoustic interfaces and partially reflect the ultrasound waves to produce an echogenic structure[2,40,42]. In the normal neck, about 90% of nodes with a maximum transverse diameter greater than 5 mm will demonstrate an echogenic hilus on high resolution ultrasound[43]. Metastatic lymph nodes usually do not show an echogenic hilus (Fig. 1), and the presence of an echogenic hilus within lymph nodes was previously considered a sign of benignity[44]. However, studies have shown that echogenic hilus may also be found in malignant nodes[2,18,19,40]. Therefore, the presence/absence of echogenic hilus cannot be used as the sole criterion in the evaluation of cervical lymph nodes.

Intranodal necrosis

Intranodal necrosis may be seen as a cystic (cystic or liquefaction necrosis) or echogenic (coagulation necrosis) area within the node. Cystic necrosis is the more common form of intranodal necrosis which appears as an echolucent area within the nodes (Fig. 3). Coagulation necrosis is a less common sign, and appears as an echogenic focus within lymph nodes but is not continuous with the surrounding fat and does not produce acoustic shadowing[41,42]. Intranodal necrosis may be found in metastatic and tuberculosis nodes[4,19,24,26], and regardless of nodal size, the presence of intranodal necrosis should be considered pathologic[4].

Calcification

Calcification within lymph nodes is uncommon, however, metastatic cervical nodes from papillary carcinoma of the thyroid tend to show calcification (Fig. 4)[4,8,26]. The calcification in these lymph nodes is usually punctate, peripherally located with acoustic shadowing using a high resolution transducer[26]. The relatively higher
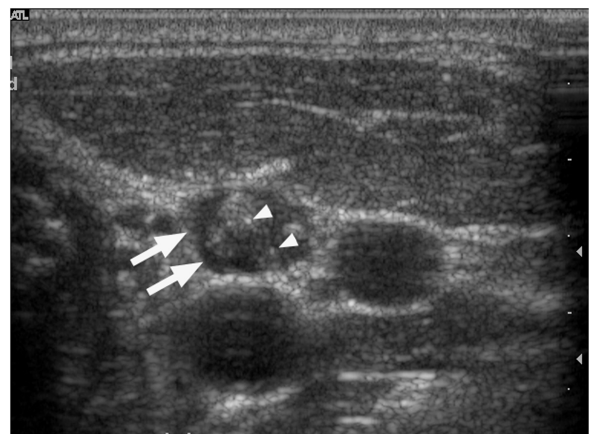

Figure 4 **Transverse grey scale sonogram of a metastatic lymph node from papillary carcinoma of the thyroid (arrows) with echogenic, punctate calcification (arrowheads).**

incidence of calcification in metastatic nodes from papillary carcinoma of the thyroid makes this a useful feature in predicting the nature of the adenopathy and directing a search for the primary tumour in the thyroid gland. Although metastatic lymph nodes from medullary carcinoma of the thyroid may also show calcification, the incidence is substantially lower than metastatic nodes from papillary carcinoma of the thyroid.

Ancillary features

On grey scale ultrasound, the presence/absence of ancillary features such as matting of lymph nodes and adjacent soft tissue oedema should also be evaluated. Although matting and adjacent soft tissue oedema are common in tuberculous nodes, metastatic nodes with extracapsular spread can invade adjacent soft tissues and cause oedema, and patients with previous radiation therapy of the neck may also show post-radiation soft tissue oedema and nodal matting[24,25,45].

Doppler evaluation of metastatic nodes

Vascular distribution

Evaluation of the vascular pattern of cervical lymph nodes has been reported to be highly reliable, with a repeatability of 85%[46]. On power Doppler ultrasound, approximately 90% of normal lymph nodes with a maximum transverse diameter greater than 5 mm will show hilar vascularity[43]. Normal and reactive nodes usually show hilar vascularity, or appear apparently avascular[47−50]. However, peripheral or mixed vascularity (the presence of both hilar and peripheral vascularity) are common in metastatic nodes[47−49,51,52]. Therefore, the presence of peripheral vessels in lymph nodes is a useful indicator of malignancy (Fig. 5). The peripheral vascularity in metastatic nodes is believed to be related to tumour infiltration of the lymph nodes in which the tumour cells produce tumour angiogenetic factor (TAF), which causes angiogenesis and recruitment of peripheral vessels[47−49,51]. Mixed vascularity is seen in malignant nodes because angiogenesis occurs and peripheral vessels are induced, but the pre-existing hilar vessels are preserved until they are destroyed by the tumour cells at a later stage[48].

Vascular resistance

With the use of spectral Doppler ultrasound, the vascular resistance in terms of resistive index (RI) and pulsatility index (PI) can be evaluated (Fig. 6). However, the value of vascular resistance in differentiating malignant from benign lymph nodes remains unclear. Some reports have shown that the vascular resistance of metastatic nodes is higher than that of reactive nodes[48,49,51,53,54], whereas others have suggested that metastatic nodes have a lower or similar vascular resistance compared to benign nodes[55,56]. Different cut-off values of RI
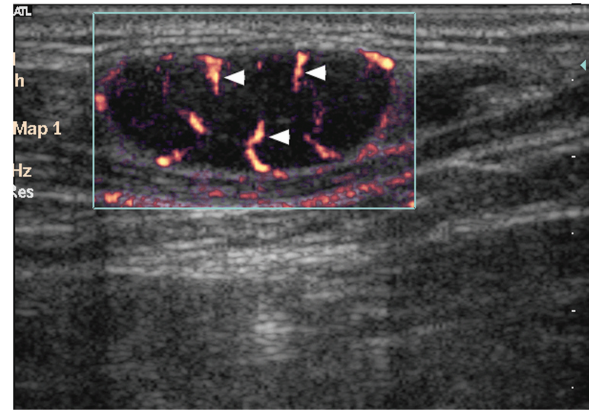

Figure 5   **Power Doppler sonogram of a metastatic lymph node with peripheral vascularity (arrowheads).**
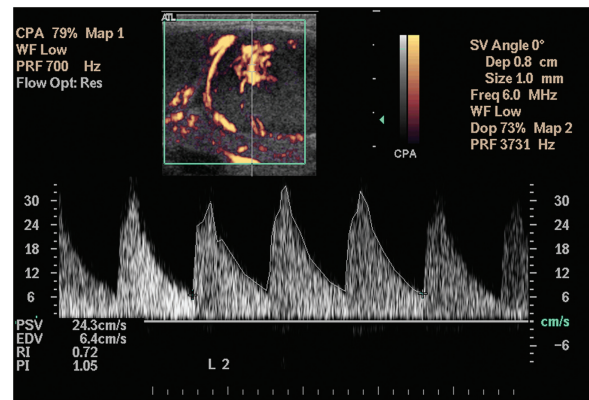

Figure 6   **Spectral Doppler sonogram showing measurement of the resistive index (RI) and pulsatility index (PI) of a metastatic lymph node. Measurement of the peak systolic velocity (PSV) and end diastolic velocity (EDV) is also demonstrated. Note the measurements are obtained from three consecutive waveforms.**

(0.6, 0.7 and 0.8) and PI (1.1, 1.5 and 1.6) with different sensitivities (RI, 47−81%; PI, 55−94%) and specificities (RI, 81−100%; PI, 97−100%) in differentiating metastatic and reactive lymph nodes have been reported[48,49,51,55]. In our experience the optimum cut-off values for RI and PI are 0.7 and 1.4, with a sensitivity of 86% and 80%, and a specificity of 70% and 86%, respectively[52]. In view of the inconsistency between various reports and the technical difficulties involved in obtaining suitable/repeatable values, the role of intranodal vascular resistance in routine clinical practice is limited.

Lymphoma

Lymphoma in the head and neck region can be classified into Hodgkin's, and the more common non-Hodgkin's type. Involved lymph nodes are usually found in the submandibular, upper cervical chain and posterior triangle regions[5,57,58].
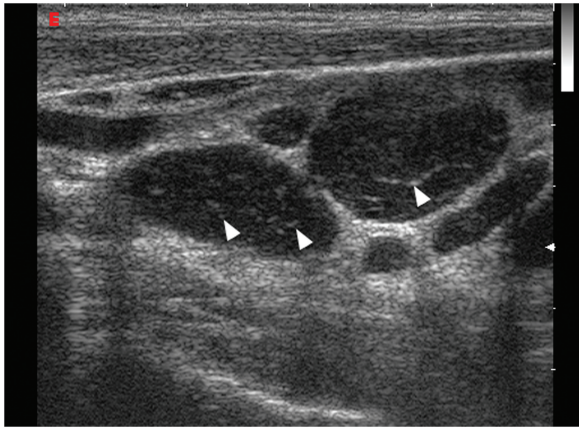
Figure 7 **Grey scale sonogram showing multiple hypoe-
choic lymphomatous nodes. Arrowheads indicate the intra-
nodal reticulation, commonly seen in lymphomatous nodes
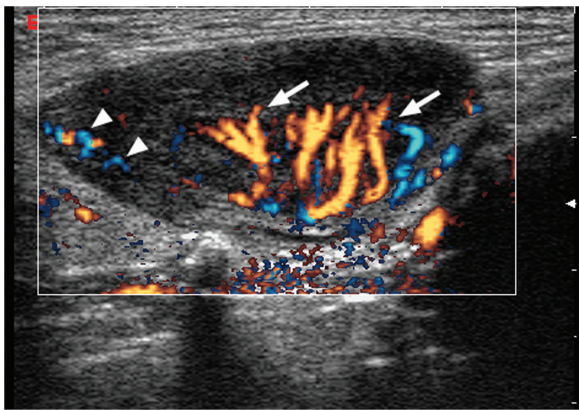using high-resolution transducers.**

Figure 8 **Directional power Doppler sonogram showing a
lymphomatous lymph node with both hilar (arrows) and
peripheral (arrowheads) vascularity, which are commonly
seen in lymphoma.**

Grey scale evaluation of lymphomatous nodes

Size

The size of lymphomatous lymph nodes varies signifi-
cantly[58]. Although lymphomatous nodes tend to be
enlarged with a minimum transverse diameter of 10 mm
or larger[5,6,59], nodal size alone is not an accurate crite-
rion for differentiating lymphomatous nodes from
normal or other pathologic lymph nodes. Nevertheless,
similar to metastatic lymph nodes, progressive and
substantial reduction in nodal size is a useful parameter
to indicate good treatment response[60].

Shape, border, echogenicity, echogenic hilus

On grey scale ultrasound, lymphomatous nodes tend to
be round in shape, well-defined, appear hypoechoic and

are usually without an echogenic hilus[29,57,59,61], features
which are similar to most metastatic lymph nodes.
Therefore, nodal shape, border sharpness, echogenicity
and the presence/absence of an echogenic hilus may not
be useful sonographic criteria to differentiate lymphoma
from metastases.

Intranodal reticulation

Previous studies have suggested that pseudo-cystic
appearance and posterior acoustic enhancement are
characteristic features of lymphomatous nodes,
especially in non-Hodgkin's lymphoma[29,57,59,61,62]. It
was believed that the pseudo-cystic appearance was
related to the homogeneous and diffuse histologic pattern
of non-Hodgkin's lymphoma, which allows easy propaga-
tion of ultrasound resulting in a hypoechoic echopattern
and posterior enhancement (67–90%)[6,18,25,29,57,63].
However, with the use of newer high-resolution transduc-
ers, the pseudocystic appearance in non-Hodgkin's
lymphoma is not often seen, whilst intranodal reticula-
tion (micronodular echopattern) is commonly found in
lymphomatous nodes (Fig. 7)[64].

Intranodal necrosis and calcification

Lymphomatous nodes seldom show cystic necrosis
unless the patient has received previous radiation therapy
or chemotherapy, or has advanced disease[5,25]. Similarly,
intranodal calcification is uncommon in lymphomatous
lymph nodes. However, calcification may be found
in lymphomatous nodes after treatment, and the calcifi-
cation in these nodes is usually dense with posterior
acoustic shadowing.

Doppler evaluation of lymphomatous nodes

Vascular distribution

On power Doppler ultrasound, lymphomatous lymph
nodes tend to have both hilar and peripheral vessels
(62–90%, Fig. 8)[48,51,54,65,66]. Unlike metastatic nodes,
the presence of peripheral vascularity alone is not
common in lymphomatous nodes (5%)[66]. The high inci-
dence of hilar vascularity in lymphomatous nodes is
thought to be related to the fact that intranodal necrosis
or keratinisation is not common in lymphoma, and there-
fore the hilar vessels of the nodes are preserved[65,66].

Vascular resistance

Similar to metastatic lymph nodes, the role of vascular
resistance in the assessment of lymphomatous nodes is
not clear because of insufficient information in the liter-
ature and inconsistent findings[9,48,51]. The reported RI
and PI of lymphomatous nodes varies from 0.64 to 0.84
and from 1.2 to 2.2, respectively[48,51,54,66]. Nevertheless,
it is generally believed that the RI and PI of lymphoma-
tous nodes are higher than those of reactive, tuberculous

and normal nodes, and are lower than those of metastatic nodes[48,51,66].

Doppler sonographic assessment is useful in monitoring the treatment response of lymphomatous lymph nodes. On colour/power Doppler sonography, rapid reduction of nodal vascularity is a sensitive sign of positive treatment response, and is useful in predicting patient prognosis. Patients with lymph nodes of rapidly diminishing vascularity tend to remain in remission, whereas patients with lymph nodes with prolonged high vascularity following chemotherapy tend to have subsequent relapse after chemotherapy[60]. Since the RI and PI do not significantly correlate with the response to chemotherapy, evaluation of the vascular resistance in post-chemotherapy lymphomatous nodes has limited prognostic value[60].

Contrast enhanced ultrasound of lymph nodes

Contrast enhancement in the evaluation of superficial nodes appears it to be more sensitive in characterizing lymph node pathology[67,68]. Contrast-enhancement demonstrates more lymph node vessels, which allows more accurate characterization of nodal vascularity. Real-time sonography during contrast administration (dynamic contrast enhancement) adds a new, time-dependent dimension to the evaluation of lymph node vascularity, and has been shown to provide information on lymph node parenchymal perfusion[68]. Dynamic contrast scanning using ultrasound is advantageous over similar techniques using CT or MRI in that it is radiation-free, has a high spatial resolution yet maintains a high frame rate, and can be performed repeatedly during the same examination.

Our preliminary experience with dynamic sonographic contrast enhancement in Hodgkin's and non-Hodgkin's lymphoma[69] showed a delay in the time to peak enhancement after treatment (Figs. 9–11). On the other hand, the change in the magnitude of peak enhancement was variable after treatment (nodes in some patients had more enhancement and some had less enhancement after treatment). This delay to peak enhancement may be due to arteriolar constriction,
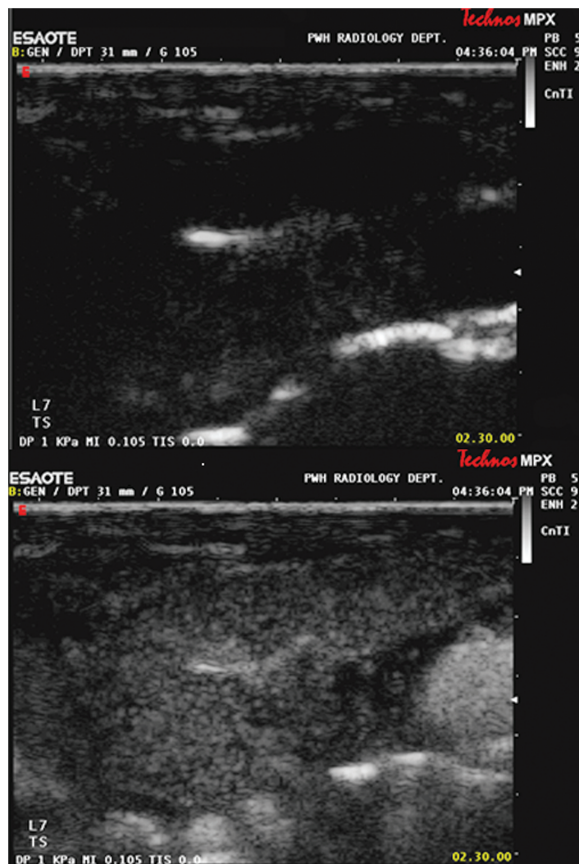

Figure 9 **Grey scale ultrasound images of a lymphomatous cervical lymph node at the start (top) and at peak enhancement (bottom) of contrast administration. The lymph node parenchyma enhances uniformly with contrast. A region of interest is drawn to include the lymph node to calculate a time-enhancement curve.**
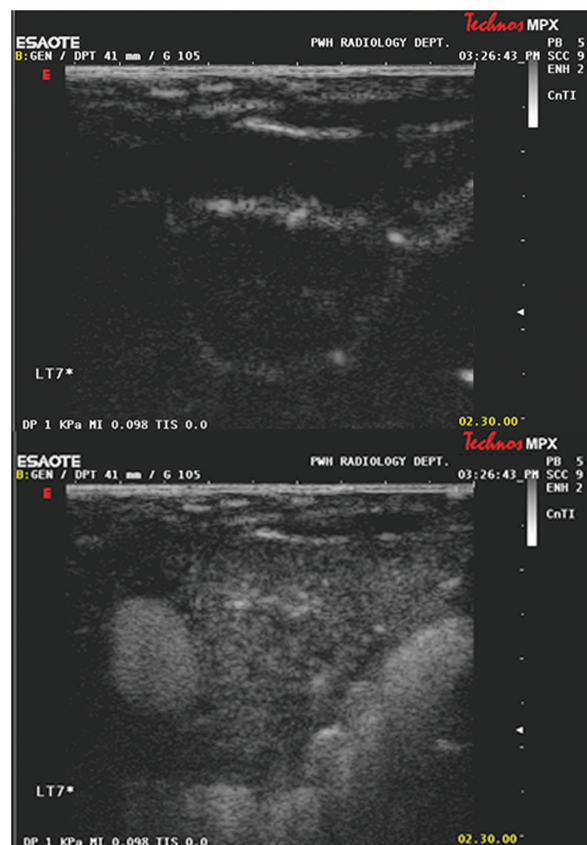

Figure 10 **Grey scale ultrasound images of the same lymph node (as in Fig. 9) after chemotherapy, at the start (top) and at peak enhancement (bottom) of contrast administration. The lymph node is smaller in size, the parenchyma enhances less (lower peak enhancement) and enhancement is more heterogeneous.**
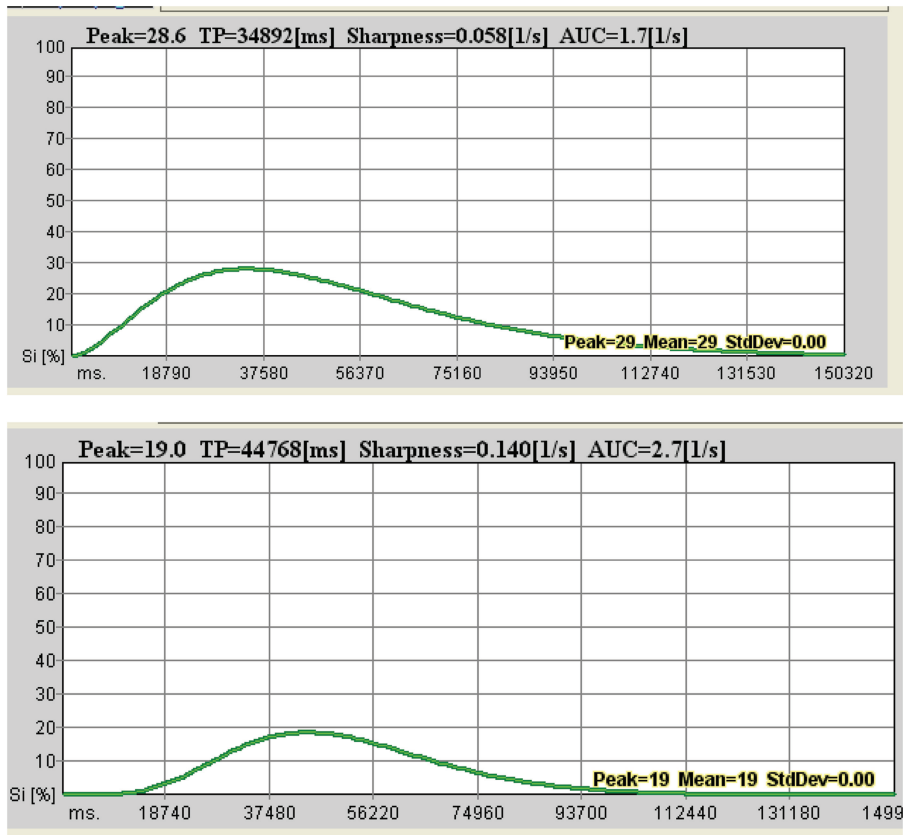
Figure 11 **Dynamic time-enhancement curves before (top) and after chemotherapy (bottom) for the same affected cervical lymph node as in Figs. 9 and 10. The time to peak contrast enhancement has lengthened from 34.9 s to 44.8 s. The peak and total (area under curve) contrast enhancement are both lower after treatment.**

an increase in capillary resistance, of a decrease in capillary density after treatment.

Dynamic contrast enhancement appears to provide a new, time-dependent dimension in the assessment of lymph node pathology and supplements the morphological information provided by grey scale and Doppler sonographic interrogation.

Conclusion

Ultrasound is a useful examination in the evaluation of malignant nodes in the neck. It helps in identifying the abnormal nodes, confirms the nature (with guided FNAC) and objectively assesses the response to treatment.

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