Review Article

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CURRENT CONCEPTS IN IMAGING CERVICOFACIAL LYMPHADENOPATHY: A REVIEW

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ABSTRACT:

Imaging of the lymphatic system is clinically necessary during diagnosis or treatment of many conditions and diseases; it is used for identifying and monitoring lymphedema, for detecting metastatic lesions during cancer staging and for locating lymphatic structures so they can be spared during surgical procedures. Imaging lymphatic anatomy and function also plays an important role in experimental studies of lymphatic development and function. In this article, we review technologies for visualizing and imaging the lymphatic system for clinical applications.

Keywords: Lymphatic System, Lymphatic Vessels, Lymphedema, Neoplasm Staging

INTRODUCTION:

The lymphatic system is a part of the circulatory system and an essential part of the immune system, embracing a network of lymphatic vessels that transport a clear fluid called lymph. In the fourth century B.C., Aristotle incisively described lymphatic vessels as, ‘‘fibers which take a position between blood vessels and nerves and which contain a colorless liquid”.[1] The lymphatic system develops in conjunction with the blood vascular system through a process known as lymphangiogenesis.

It is not surprising that many infectious diseases produce symptoms associated with the lymphatic system, because the lymphatic system is involved with the production of lymphocytes that fight infectious disease, and the lymphatic system filters blood and lymph to remove microorganisms. Lymphadenitis- an inflammation of the lymph nodes, which causes them to enlarge and become tender, is an indication that microorganisms are being trapped and destroyed within the lymph nodes. If the microorganisms pass through the lymphatic vessels and nodes to reach the blood, it can result in septicemia. Therefore, disruption of lymphatic function may lead to lymphedema, condition which results in fluid accumulation in a tissue due to deficient lymphatic functions leading to immunocompromised state and significant morbidity.

The lymphatic system is also involved in cancer progression as there can be entry of metastatic cancer cells into the lymphatic system and result in lymph node metastases. Lymphoma for example is a neoplasm (tumor) of lymphatic tissue. Under such circumstances, the immune system is depressed, and the patient’s susceptibility to infections increases. Enlargement of the lymph nodes can also compress surrounding structures and produce complications.[4] In short, from

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inflammation to malignancies the human lymphatic system can be affected in a spectrum of diseases. As a result, visualization of the lymphatic system is clinically necessary during diagnosis or treatment of many conditions and diseases. Imaging techniques helps to visualize the lymphatic system, understand its anatomy, its functions and dysfunction during its involvement in maxillofacial diseases and disorders.

This review article is an overview of various conventional and advanced imaging modalities that can be utilized to investigate the lymphatic system. This paper also gives an insight into the possible functional changes that the lymphatic system undergoes and the interpretation of the same in terms of disease progression.

Lymphography: For decades, conventional lymphography was considered the benchmark of reference for diagnosing pathologic conditions of the lymphatic system. Currently technological innovations have severely curtailed its use but still it has a cornerstone role in diagnosis and management of lymphatic circulatory disorders.[5] Lymphography has the unique capability of demonstrating internal architectural disorganization within the diseased lymph nodes. This highly valuable advantage makes lymphography diagnostically more accurate than other imaging techniques. [6]

As for the technique, after cannulation of a lymphatic vessel, a contrast agent such as Direct Blue or Patent Blue is injected into the dermis. On being absorbed by initial lymphatics, the dye fills the lymphatic vessels that drain the injection site. Continuous x-ray imaging, or fluoroscopy, is then done to track the flow of dye through the lymphatic circulation. Infrequently, plain x-ray films are also obtained to record any abnormalities.[7]

The normal lymphographic appearance of lymph node is characterized by a homogeneous, even-textured, fine granularity that is due to the relationship between the opacified sinus system and the nonopacified lymphoid follicles. The margin of the node is well defined, with the hilar area usually demarcated by a smooth indentation (Figure 1). Whereas, conditions like Lymphomas are diagnosed when an alteration in appearances of the lymph nodes such as focal filling defects or a foamy, licelike appearance is seen in lymphograpy. Lymph node size is not the prime diagnostic criterion of any lymphatic disease.[5] Misselwitz et al studied Lymphographic effects in guinea pigs, dogs, and tumor-bearing rabbits after interstitial (subcutaneous or intracutaneous) injection and pronounced differentiation between normal and metastatic lymph nodes were achieved.[33]

In a comparative study by kosuda et al using mice, the results of radiocolloid SPECT/CT lymphoscintigraphy were superior to those of interstitial MR lymphography, while both have a potential of being employed for

sentinel node navigation surgery in the head and neck region.[34]

The major complications of lymphography are caused by the vital dye and contrast materials rather than the technique. Among all complications, pulmonary oil embolization is the most common and frequently occurring.[5,6] Apart from this, clinical symptoms appear if there is an underlying cardiopulmonary disorder, or excess amounts (>20 mL) of contrast material is given, or the patient is hypersensitive to the oil.[6] The technique per se requires multiple injections into the tissue and microcannulation of vessels; hence is an invasive procedure. To overcome these limitations newer imaging modalities have evolved.

Lymphoscintigraphy (LSG): LSG is the radionuclide technique of imaging the lymphatic system using interstitially injected radiopharmaceutical particles. It was first introduced in 1953 and has emerged as the gold standard for assessing the lymphatics.[10] Depending on the type of tissue examined, the radiotracer is either injected into the body, swallowed or inhaled as a gas and eventually accumulates in the organ or area of the body being examined. Radioactive emissions from the radiotracer are detected by a special camera or imaging device such as the gamma camera or single-photon emission-computed tomography (SPECT) that produces pictures and provides molecular information. The gamma camera, also called a scintillation camera, detects radioactive energy that is emitted from the patient's body and converts it into an image. Single-photon emission-computed tomography (SPECT) involves the rotation of the gamma camera heads around the patient's body to produce more detailed, three-dimensional images. Several radiotracers in the range of 50-70nm in size are in use for lymphoscintigraphy.[11] These tracers are usually bound to technetium-99m (99mTc), which is an ideal radioisotope for imaging.[8,9] Lymph nodes are usually visualized 15 to 20 mins after injection with these radiotracers (Figure 2). The normal pattern of LSG is symmetric movement of the tracer in the extremities, discrete lymphatic channels, early visualization of regional lymph nodes: within 15-20min, and visualization of liver in 1hour.[9]

This method is currently used for imaging lymphatics to identify the sentinel lymph node (first node to receive the lymph drainage from a malignant tumor), plan a biopsy or surgery that will help assess the stage of cancer and formulate a treatment plan, identify points of blockage in the lymphatic system (such as lymph flow or lymphedema).[8] Abnormal findings in LSG are reported to be asymmetric visualization of the regional lymph nodes, non-visualization in severe cases, dermal backflow (due to small collateral lymph vessels), interrupted/ dilated and/or collateral lymph channels, and decreased number of regional nodes.[8] The thoracic duct is not usually well seen on the LSG images, however this technique has been

used to evaluate thoracic duct abnormalities with some limited success. Lymphatic leakage can also be seen easily by LSG. Muhle et al conducted a study on computed tomography (CT)-guided lymphoscintigraphy on 13 patients with squamous cell carcinoma of the hypopharynx and larynx, the technique was found to be feasible and minimally invasive diagnostic tool for sentinel lymph node detection.[35] Klutmann et al in their study showed that using lymphoscintigraphy accurate correlation of lymphatic drainage and cervical compartments yields re-evaluation of its impact in preoperative planning of different procedures of neck dissection in tumors of head and neck.[36]

Lymphoscintigraphy examinations provide unique information, including details on both function and anatomic structure of the lymphatic system that is often unattainable using other imaging procedures. Doses of radiotracer administered are small resulting in relatively low radiation exposure to the patient that is acceptable for diagnostic examinations. However, limitations such as poor spatial resolution, additional expense to the patients when combined with CT, and the exposure of the patient and clinician to radioactive compounds, necessitating special protection equipment and waste handling have to be considered prior to choosing the technique for investigation. Rarely, mild Allergic reactions to radiopharmaceuticals may occur. For these reasons other techniques have emerged to replace lymphoscintigraphy.

Ultrasonography (USG): Ultrasonography is the visualization of deep structures of the body by recording the echoes of ultrasonic pulses directed into the tissues. Ultrasound was first used for clinical purposes in 1956 in Glasgow. Use of ultrasound for imaging or diagnostic purposes employs frequencies ranging from 1.6 to 10 megahertz.[12] High-resolution ultrasonography has been used extensively in the assessment of cervical lymphadenopathy. Ultrasonographic features like shape, border sharpness, echogenicity, presence or absence of matting, intra nodal necrosis are significant in differentiating normal nodes from affected ones.

Normal lymph node are oval in shape, the short axis/long axis (S/L) ratio is found to be less than 0.5, borders are unsharp and there is absence of echogenic hilus. Neck nodes with a maximum transverse diameter greater than 5mm show an echogenic hilus. The incidence of echogenic hilus increases with age due to increased fatty deposition in the lymph node of elderly individuals. Benign and reactive nodes are usually oval in shape, S/L ratio is less than 0.5, with unsharp borders due to edema and inflammation of surrounding tissues. Benign nodes tend to be hypoechoic, which is related to intranodal cystic necrosis, and largely appear to have hyperechoic hilum with no visible cortex (Figure 3 a).[12,13] Malignant nodes are round in shape and S/L ratio greater than 0.5, tend to have sharp borders due to the fact that tumor infiltration causes an increase in difference

of acoustic impedence between intranodal region and surrounding tissue. Some malignant nodes in advanced stages show an ill-defined border. Malignant nodes are predominantly hypoechoic (Figure 3 b) when compared to adjacent soft tissues except in case of metastatic lymph nodes of papillary carcinoma of thyroid which are commonly hyperechoic. Malignant nodes do not show echogenic hilus, as a result of tumor infiltration and apparent narrowing and displacement of the hilum.[12-14] Lakshmi et al in their study stated ultrasonographic features of lymph nodes with round shape, absence of hilar echo, sharp nodal borders, hyperechoic internal echogenicity, and presence of intranodal necrosis were highly suggestive of metastatic cervical lymph nodes and ultrasound can be used accurately to assess the status of lymph nodes.[43]

Application of USG in the examination of lymph nodes is further enhanced by utilizing additional facilities such as the ones described below.

a) Colour Doppler ultrasonography

It has been reported that Doppler ultrasonographic evaluation of the vascular pattern of cervical nodes is highly reliable.[16] Ultrasound images of flow are essentially obtained from measurements of movement. In ultrasound scanners, a series of pulses is transmitted to detect movement of blood. Echoes from stationary tissue are the same from pulse to pulse. Echoes from moving scatterers exhibit slight differences in the time for the signal to be returned to the receiver. These differences can be measured as a direct time difference or, more usually, in terms of a phase shift from which the 'Doppler frequency' is obtained.[16] They are then processed to produce either a color flow display or a Doppler sonogram. About 90% of normal neck nodes with maximum transverse diameter greater than 5 mm show hilar vascularity. Normal and reactive lymph nodes tend to demonstrate hilar vascularity or appear apparently avascular. However, metastatic lymph nodes usually have a peripheral or mixed (hilar + peripheral) vascularity.[16,17] Unlike metastatic nodes, lymphomatous nodes tend to have mixed vascularity and isolated peripheral vascularity is uncommon. The presence of peripheral vascularity in malignant nodes is thought to be related to tumor angiogenesis and the associated recruitment of capsular vessels. Because peripheral vascularity is common in malignant nodes, its presence, regardless of the presence or absence of hilar vascularity, is highly suggestive of malignancy.[16-18]

b) **Ultrasound Elastography:** Elastography is a type of ultrasonography that maps the elastic properties of soft tissue to know whether the tissue examined is hard or soft, which will give diagnostic information about the presence or status of disease. In ultrasound elastography, a compression force is applied to the region of interest (ROI) and the stiffness of the ROI is estimated by evaluating the degree of local

tissue displacements before and after the application of compressive force.[19,20] In qualitative real time US elastography, the lymph nodes and other soft tissues are color coded and the colors represent degree of stiffness of the tissues. To evaluate the stiffness of lymph node, elastograms are usually classified into 4 to 5 grades according to proportion of hard area. On conventional strain elastography, the strain of the soft tissues can be estimated by customized software. When examining neck lymph nodes, the strain index/ ratio is calculated as the ratio of the strain of neck muscle to the strain of lymph node.[19] On conventional strain elastography, benign lymph nodes tend to have a lower strain index, whereas malignant nodes usually have a higher strain index. Shear wave elastography (SWE) is a recent development in soft tissue elasticity imaging. Using a focused ultrasound beam, acoustic radiation force impulses are applied to the soft tissues and shear waves are generated. SWE allows absolute quantification of the soft tissue stiffness presented in kilopascals or measured as the shear wave in metres per second.

c) **Contrast enhanced ultrasonography:** This allows more accurate evaluation of nodal vascularity and provides information on lymph node parenchymal perfusion. Studies have reported that contrast-enhanced ultrasonography improves the accuracy in differentiating benign and malignant nodes because it increases the sensitivity of detecting intranodal vascularity. Although contrast enhancement may provide additional information in the evaluation of cervical lymph nodes, the value of this technique in routine clinical practice is limited because it is expensive, time consuming and does not obviate the need for FNAC.[21,22]

Pitsfalls of ultrasonography:

Ultrasonography cannot assess the retropharyngeal lymph nodes, which lie behind the air-filled pharynx. Retropharyngeal lymph nodes are common sites of metastases in some head and neck cancers such as nasopharyngeal carcinoma. Similar to other imaging modalities, ultrasonography cannot detect micrometastasis in lymph nodes leading to false-negative findings.[23] Coagulation necrosis show same echogenicity as that of lymph node hilum. However, the two can be distinguished by noting that the hilus is a linear echogenic structure continuous with the surrounding fat, whereas coagulation necrosis appears as an echogenic focus and is not continuous with the surrounding fat.

Diffusion weighted MRI:

Diffusion-weighted magnetic resonance imaging (DWMRI) is an imaging technique that shows molecular diffusion. Diffusion is the net movement of molecules or atoms from a region of high concentration to a region of low concentration. Cell size, density and integrity influence the signal intensity seen on diffusion-weighted

images. This technique is a helpful complementary tool to distinguish tumors from normal tissue, and has several interesting applications in the evaluation of head and neck lymphadenopathy.[25]

Diffusion weighted imaging (DWI) has shown its potential to be a reliable non-invasive imaging technique for tissue characterization. DWI exploits the random motion of water in the targeted tissue, which reflects the tissue specific diffusion capacity. In biologic tissues, the diffusivity of water molecules is confined by the intra-cellular and inter-cellular spaces.[24]

Hyper cellular tissue, such as malignant tumors, show decreased mobility of water protons and restrict the diffusion capacity of the tissue. Therefore, tumors show increased signals on DWI and low apparent diffusion co-efficient (ADC) values (Figure 4). Non-tumoral tissues such as edema, inflammation, fibrosis, and necrosis show low cellularity in contrast to tumors. This results consecutively in a signal loss on DWI and in a high ADC. The evaluation of cervical adenopathies is important as they serve as an excellent clue to underlying problems due to infections, autoimmune disorders or malignancies (metastatic or lymphomas).[24,26] King et al., reported that Diffusion-weighted MR imaging shows significant differences among malignant nodes of differentiated carcinoma, lymphoma, and undifferentiated carcinoma.[37]

Promising results with DW imaging to help detect cervical lymph node metastases and differentiate between benign and malignant enlarged nodes have been reported. Thoeny et al[38]. reported that after chemotherapy or radiation therapy, residual changes or even masses are commonly observed at the primary or nodal site, and conventional morphologic MR imaging currently encounters difficulty in helping distinguish between benign post treatment alterations and residual cancer. The poor spatial resolution and sensitivity are limitations of MRI.[26] Choi et al. stated that false-positive readings in DW imaging may be due to restricted diffusion in recent hemorrhage or hematoma. Therefore, DW imaging probably should not be performed directly after biopsy. Further improvements to the methodology, including new probes, show promise in increasing spatial resolution and the utility of this method.[39]

Positron Emission Tomography–Computed Tomography (PET/CT):

Positron emission tomography–computed tomography (PET–CT) is an imaging device which combines both PET and an X-ray computed tomography in a single gantry system. While a CT scan provides anatomical detail (size and location of the tumor), a PET scan provides metabolic detail (cellular activity of the tumor). Hence, combined PET/CT is more accurate than PET or CT alone.

PET is based on positron-emitting radionuclides, which synthesize

radiopharmaceuticals that are part of biochemical pathways in the human body, such as FDG in glucose metabolism and C-11–labeled methionine and choline in protein metabolism and membrane biosynthesis, respectively. Fluorodeoxyglucose (18F-FDG) is an analog of glucose, administered intravenously and is then transported into cells by glucose transporter proteins in a fashion similar to that for unlabeled glucose.[27]

Many malignant tumors express higher numbers of specific membrane transport proteins, with greater affinity for glucose than normal cells, which permits increased glucose flow into the cancerous cells. The rate of uptake of FDG by the tumor cells is proportional to their metabolic activity. Like glucose, it undergoes phosphorylation to form FDG-6-phosphate; however, unlike glucose, it does not undergo further metabolism, thereby becoming trapped in metabolically active tumor cells. Thus, PET provides images of quantitative uptake of the radionuclide injected by giving the concentration of radiotracer activity in kilobecquerels per milliliter.[27,28]

Pieterman et al.[40] demonstrated that the radiologic sensitivity and specificity of 18F-FDG PET was superior to CT in detecting malignant lymph nodes and staging of lung cancer. In their study, the sensitivity and specificity of PET was 91% and 86% compared with that of CT at 75% and 66% in detecting mediastinal metastases. Filmont et al.[41] reported that 18F-FDG PET altered the clinical management of 35% of their patients with non- Hodgkin's lymphoma. They also reported that PET was significantly better at predicting disease-free survival than conventional imaging.

PET is limited by poor anatomic detail, and correlation with some other form of imaging, such as CT, is desirable for differentiating normal from abnormal radiotracer uptake. It is highly useful in detection of unknown primary in patients presenting with metastatic cervical lymphadenopathy following conventional work-up. PET/CT application in diagnosis of malignancy is limited due to its false positive result in inflammatory conditions (caused by the metabolism of activated macrophage) and false negative results due to limited sensitivity or spatial resolution. Further, patient motion in PET-CT imaging can produce significant artifacts on the fused images and may cause confusion as to the correct position of the origin of the detected photon.[27]

Near-infrared (NIR) fluorescence imaging

Near infrared (NIR) fluorescence imaging of the lymphatics is an evolving technology for imaging lymphatic system that facilitates to study the structure, anatomy and function of lymphatic system with the help of low volumes and microdosages of contrast agents. It has been used currently to characterize lymphedema (LE) of the head and neck.

Near-infrared (NIR) imaging technologies light resides in the optimal wavelength

range, where light absorption and scattering are low in biological tissue and there is minimal autofluorescence hence it provides the ideal solution to functional lymphatic imaging in both as a research tool and a disease diagnostic tool. NIR imaging with an FDA-approved fluorescent dye, indocyanine green (ICG), has recently emerged as a novel method for quantitative assessment of lymphatic function in animals and humans; a technique in which ICG is injected intradermally, excited with a laser diode, and imaged with an NIR-sensitive detector as it is taken up by the lymphatic system. [29,32]

NIR imaging thus affords deeper penetration and excellent contrast and spatial resolution, all of which are vital for measuring lymphatic contractile properties. Currently, NIR lymphatic imaging technology has been quite successful at demonstrating differences in lymphatic function and architecture in patients who have already been diagnosed with lymphedema, differences in lymphatic function in response to manual lymphatic drainage and pneumatic pressure devices, as well as a decline in lymphatic pumping pressure in response to aging.[30,32]

Maus et al[42] conducted a study using near-infrared (NIR) fluorescence imaging to monitor response to therapy in a subject suffering head and neck Lymphedema following surgery and radiation treatment. NIR fluorescence imaging provided a mapping of functional lymph vessels for direction of efficient manual lymphatic drainage (MLD) therapy in the head and neck.

Currently it is unclear how effective this approach will be in early detection of malignancy. Additionally, there is very little information on various parameters such as the effects of vessel depth and scattering on the ability to resolve differences in vessel diameter or the effects of protein binding on ICG fluorescence. Quantifying these and other effects will allow proper component selection and will provide more detail in regards to the applications of the technique as a non-invasive tool for quantifying lymphatic function.

Optical coherence tomography (OCT): Optical coherence tomography (OCT) is an emerging in vivo imaging modality which is capable of providing real-time microscopic images of up to 2 mm beneath the tissue surface. In addition, OCT has shown the potential for imaging morphological features related to cancer metastasis and intraoperatively identifying metastatic nodes. Identifying OCT image-based microscopic structural changes that enable lymph node assessment and classification as normal, reactive, or metastatic would aid the clinical staging of the disease, with the potential for assessment and staging to occur in real-time, during surgical procedures.

Three-dimensional OCT imaging of lymph nodes at varying stages of metastatic involvement show image based optical scattering features that strongly correlate

with histological findings. These results suggest that 3-D OCT has potential for future in situ analysis of lymph nodes for staging cancer metastases intraoperatively. OCT studies were performed in a well-characterized preclinical animal model for lymph node metastases. The use of this animal model enabled the investigation of optical scattering and OCT image changes at various time-points and stages during metastatic involvement in a way that would not have be possible in human patients.[31]

Further work is required to investigate the biological variability between lymph nodes at any given time point. Ongoing studies are exploring the potential of high resolution OCT for detecting early micrometastasis of sizes <100 µm within the intact lymph nodes, which has clinical significance. Study results obtained to date are very promising, and support OCT as a potentially cost-effective technique that could allow lymph node assessment in situ without having to physically resect and histologically process the tissue, as well as reduce potential morbid complications like lymphedema.[31,32]

CONCLUSION:

Enlarged lymph nodes are commonly encountered during clinical examination. Clinicians and radiologists often are in dilemma with the nonspecific features of some nodes, which are most commonly reactive secondary to infection but can also be related to more aggressive processes, including malignancy. Appropriate clinical evaluation is paramount in the assessment of enlarged lymph nodes. Imaging plays an important role, particularly when lymph nodes lack benign features or fail to resolve with treatment. Currently available advanced imaging has the potential to characterize nodal features including size, distribution, internal architecture, vascularity, and enhancement. It is upto the clinician's discretion to make the right choice of the available modality on the basis of clinical diagnostic status of the lymph nodes. Radiologists on the other end also must be well aware of the nodal pathologies and the resultant variations in their presentation.

Judicious selection of the imaging technique will enhance the diagnostic acumen of the clinicians and improve the disease management.

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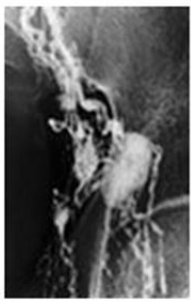
FIGURES:



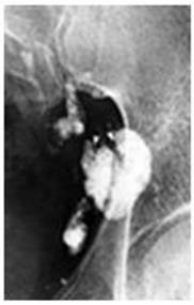


Fig 1: Normal appearance of lymph nodes. (a) Lymphogram obtained during the filling phase shows a homogeneous appearance of the lymph nodes. (b) Lymphogram obtained during the nodal phase shows a smooth peripheral indentation (arrowheads), which corresponds to the hilar area.

courtesy: Guermazi A et al. Radiographics.2003. vol 23.Issue 6.

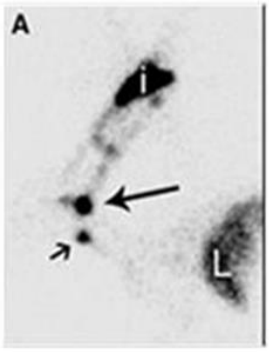


Fig 2: (A)Static planar lymphoscintigraphy image (10 min after injection of 99mTc-nanocolloidal albumin). Parotid lymph node (large arrow) and caudal mandibular lymph node (small arrow) are clearly visible. i = injection site; L= Liver

Courtesy: Heuveling DA et al. J Nucl Med. 2011. Vol.52 no.16

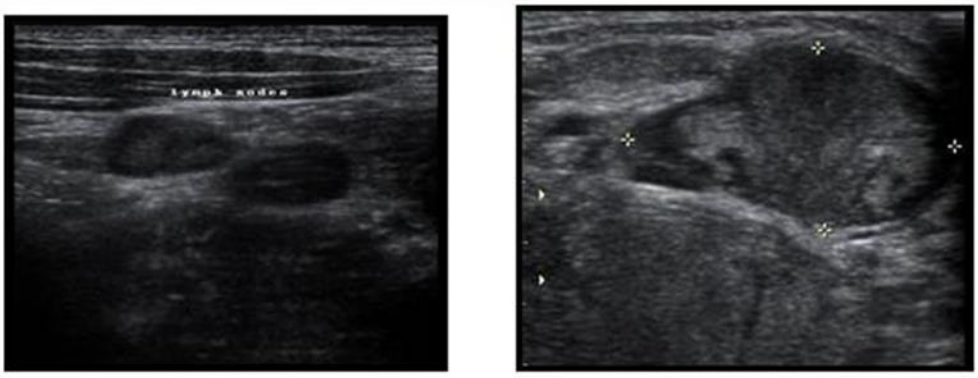


Fig 3: A) Ultrasonograph of benign lymph node showing homogenous hypoechoiec pattern. B) Ultrasonograph of malignant lymph node showing heterogenous pattern

courtesy: Dr. Namitha J. "Differentiation between benign and metastatic cervical lymph nodes using ultrasound"

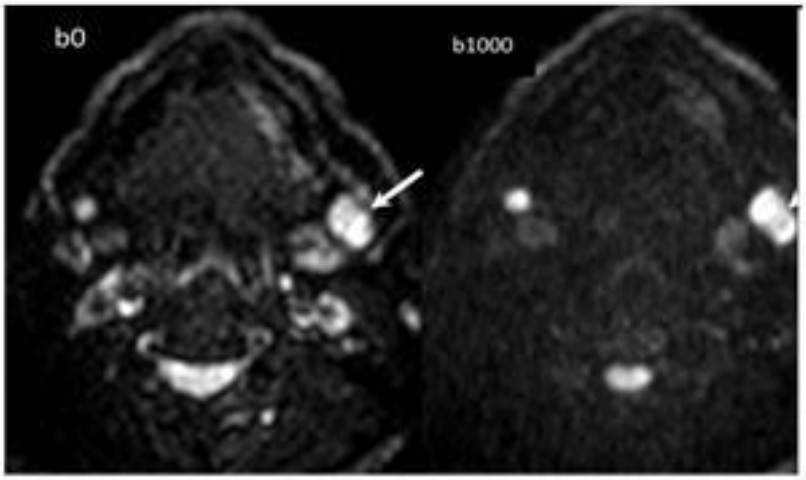


Fig 4: diffusion weighted MRI showing left sided retromolar malignant mass of insidious onset with increased signals and low ADC

courtesy: Noha Abd ElShafy ElSaid et al. The Egyptian Journal of Radiology and Nuclear Medicine (2014) 45, 1115–1125