Chapter 7

Diagnostic Approach to Lymph Node Diseases in Ultrasound

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General remarks

The lymphatic system consists of a network of interconnected lymphatic channels that collect lymph fluid and carry it to the next lymphatic tissue. It is estimated that approximately 2 l of lymph fluid is produced within a 24 h period. It is drained from the interstitium by blind-ending lymphatic capillaries. The size of these tiny tubes allows only small molecules and particles (including antigens) to pass through this network. The lymphatic vessels have a valve system that allows the lymph to proceed to the next lymph node and prevents intraluminal fluid from flowing backwards.

The lymph enters a lymph node by several afferent vessels and is filtered and analysed on its way through the lymph node. The cleared lymph is drained by the efferent lymphatic vessels and enters the left and right subclavian vein by the thoracic duct. The efferent lymph vessels may also function as an afferent lymphatic vessel when it enters the next lymph node for clearance. Some lymphatic vessels may bypass the first (sentinel lymph node) or secondary lymph node and enter the next, or one of the next, lymph nodes (Figure 1). The efferent lymph vessels may function again as afferent lymph vessels when they enter the next lymph node.

Figure 1. Lymph nodes with afferent and efferent lymphatic vessels. The black arrow points to a lymph vessel bypassing a lymph node.

Lymph nodes have a capsule of dense connective tissue that covers the outer part of a lymph node, the echo-poor cortex and paracortex. It contains lymphoid follicles. The medulla is found in the central part of a lymph node. The supplying vessels are found in the hilum of the lymph node. In some lymph nodes accessory arteries and veins may enter and leave the organ somewhere outside the hilum and break through the cortex (Figure 17). From the hilum a regular, tree-like branching passes the medulla and paracortex towards the cortex (Figure 2). This is typical for the majority of reactive lymph nodes and can be imaged using sensitive ultrasound equipment (Figure 16).

In a healthy lymph node, the secondary follicles develop when they encounter antigens. B cells are in the centre, the parafollicular zone has T cells, the sinuses have histiocytes and the medulla is full of plasma cells and lymphocytes.
The lymph can contain antigens, which enter the lymph node by the afferent lymphatic vessels, but the majority of lymphocytes enter the lymph node through blood vessels. When in contact with antigens by specialised high endothelial venules (HEV), the palisades of the HEV open to allow lymphocytes to migrate into the interstitium and encounter specific antigens. Lymphocytes that are not involved in this process leave the lymph node by the efferent lymphatic vessels.

Lymphoid tissue is also found in lymphoid follicles (also known as lymphatic nodules) associated with the digestive system such as the tonsils in the gastrointestinal (GI) tract. In contrast to nodes, lymphatic nodules have no capsule. They are also known as mucosa-associated lymphatic tissue (MALT), for example tissue found in the upper GI tract.

**Anatomical remarks and examination technique**

It is estimated that there are approximately 600–700 lymph nodes in humans, including very small ones whose acoustic properties cannot be differentiated from the surrounding tissue.

For the anatomical regions in which transcutaneous ultrasound examination is not possible – such as the mediastinum or perihilar region of the lung – endoscopic ultrasound should be considered, but CT is often the imaging modality of choice. The same is true in patients with unfavourable abdominal scanning conditions. Often the parailiacal region is difficult to image, but a continuous gentle pressure can remove any bowl gas superimposed on the image. A full bladder may act as an acoustic window to image the contralateral parailiacal region in an oblique transducer position.

In the evaluation of peripheral lymph nodes the clinical examination is far less sensitive in the supraclavicular, axillary and infraclavicular regions. For the evaluation of the peripheral lymph node state, the neck, supra- and infraclavicular, axillary and inguinal region should be examined.

Cervical lymph nodes can be classified into eight regions [1]: the submental (region 1), submandibular (region 2), parotid (region 3), upper, middle and lower cervical (regions 4–6), the supraclavicular fossa (region 7) and the posterior triangle (region 8).

Other areas such as the parasternal region in patients with breast cancer or in lymphatic diseases should be included in the examination process. In the case of patients with melanoma, which is distal of the elbow or the knee, the cubital or popliteal fossa should also be examined.

Within the abdomen the regions of interest depend on the underlying disease. In cancer the lymphatic pathways of the diseased organ are used to identify the lymph node involvement, which usually accompanies the supplying vessels. In inflammatory or lymphatic disease the involved abdominal and peripheral lymph nodes have to be examined, and location and size of involved lymph node have to be documented for follow-up examinations. Panoramic view or three-dimensional imaging can help to better demonstrate local lymph node status (Figure 3).

Depending on the depth and local scanning conditions a curved array or linear probe with the highest frequency (ranging from 4–5MHz to 18MHz) should be chosen for imaging peripheral lymph nodes. The transmit frequency also depends on the attenuation of the embedded tissue (such as muscle tissue or scar).

A panoramic view technique or 3D mode may be advantageous in demonstrating a lymph node in a greater topographic perspective (Figure 4).

**Figure 2. Lymph node architecture**

**Figure 3 Schematic diagram of neck shows classification of cervical lymph nodes in sonographic examinations (scheme taken from [1])**

**Figure 4a. Multiple echo-poor lymph nodes in chronic lymphatic leukaemia of the neck imaged in an extended field of view technique (panoramic image). b. A C-plane image from a 3D tissue block shows five superficial neighbouring metastases with local oedema and dilated afferent lymphatic vessels in the right groin.**
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C-level images taken from 3D tissue volumes may also help to better demonstrate the topographic situation of diseased lymph nodes. Figure 4c shows location of parasternal lymph nodes of a melanoma.

*Figure 4c. Enlarged lymph nodes between the ribs can be demonstrated by evaluation a tissue volume taken from the parasternal region (arrows).*

A sensitive colour Doppler technique is needed to image the vascularity of a lymph node, especially its architecture and the presence of arterial and venous flow. Normal and reactive lymph nodes tend to have a hilar vascularity or appear to be avascular when the cortex is very thin (known as fatty involution). Use of colour Doppler (bidirectional), power Doppler or B-flow mode as the preferred flow detection modes will depend on the system applied. Some ultrasound devices offer B-flow or colour B-flow technique (Figure 26, 27, 35 and 48), which has the advantage of avoiding blooming artefacts and can therefore image very small vessels [2].

Colour Doppler techniques can only image larger vessels, but not lymph node microvasculature. For this purpose ultrasound contrast agents have to be used (see EFSUMB guidelines for extrahepatic indications, to be published 2011 [32])

High pressure by the probe should be avoided when examining superficial lymph node vascularity as blood flow may be minimised or even stopped (Figure 5).

*Figure 5. Enlarged lymph node (non-Hodgkin’s lymphoma) of the left groin. In case of slightly increased local pressure caused by the transducer, colour Doppler may show only a few central vessels (left), the right image was recorded with nearly no pressure thus a maximum of intra-nodal vessels could be detected.*

In some clinical settings contrast-enhanced ultrasound (CEUS) may be more valuable than conventional colour Doppler techniques. When using high frequency probes the dose of contrast agent has to be higher (about twice as high in comparison to abdominal probes).

Elastography is another relatively new technique for characterising lymph nodes. So far it cannot be recommended as a reliable imaging technique because there are no large studies on elastography that include a wide range of tumour entities. Furthermore, different technical solutions have been developed to image and quantify tissue elasticity. Elastography is based on the principle that malignant tissue is stiffer than non-malignant tissue. In a study by Lyshchik lymph nodes were characterised by their relative brightness, margin regularity and margin definition. In addition, strains of lymph node and surrounding neck muscles were measured on elastograms, and the muscle-to-lymph node strain ratio (that is, the strain index) was calculated. It was concluded that elastography with a 98% specificity and 85% sensitivity, was superior, even to the best greyscale criterion in lymph node metastases of thyroid or hypopharyngeal cancer (a short-to-long-axis diameter ratio - Solbiati index - greater than 0.5), which had 81% specificity, 75% sensitivity and 79% overall accuracy [3]. But in many locations a “reference” muscle at the same depth as the lymph node for a comparison study is not always available. Another limitation is the variance of intranodal pressures in metastatic lymph nodes that modify the elasticity of a node (Figure 6 b,c).

*Figure 6 a-e. Elastography study of peripheral lymph nodes. Colour code: The reference tissue is coded in green. Softer tissue is displayed in shades of red, harder tissue in shades of blue. Note that the scale for hard tissue is compressed. Soft tissue scale ranges from 1 to 0, hard tissue from 1 to 6. A ratio between two tissue types can be calculated (image on upper row right). Above: Elastography of a reactive lymph node. In comparison to muscle tissue malignant lymph nodes are much harder. Middle: A hyper-vascularised lymph node metastasis with a soft tumour tissue (same case as in Fig. 42). The soft character of the transit metastasis can be probably be explained by its rich vasculature and a missing capsule. Below: Hard lymph node metastasis.*
Role of ultrasound in diagnosing lymph node diseases

Lymph node enlargement is a common feature of various benign and malignant disorders. It is well recognised that ultrasound is superior to palpation in detecting and characterising subcutaneous lymph nodes. In the evaluation of peripheral lymph node status ultrasound is, therefore, the first choice imaging modality in patients with inflammatory or malignant diseases.

Enlarged lymph nodes can be an immune response to bacteria, virus or fungus infection. Among the malignant diseases infiltration of neoplastic cells by lymphatic or blood circulation and localised neoplastic proliferation of lymphocytes or macrophages (e.g., leukaemia or lymphoma) will cause an enlargement of lymph nodes.

Reactive lymph nodes are detected by their typical B-mode appearance. The echo-poor cortex can be easily depicted within the surrounding echogenic fatty tissue and will enlarge depending on acuteness and severity of inflammation. When using high frequency curved or linear transducers, echo-poor to cystic follicles within the cortex can sometimes be seen (Figure 7b).

A typical reactive lymph node has an oval shape with a cortex of even thickness and a hilum where the supplying vessels entering can be seen in all early cases. In bigger lymph nodes the vessels can be identified even on greyscale images. Colour Doppler ultrasound demonstrates direction and pulsatility of blood flow. The vessels branch in a tree-like way from the hilum to the cortex.

When the contrast resolution is good, high frequency probes can easily detect echo-poor lymph node down to 3mm in size, supplying vessels should be seen in lymph nodes of about 4-5 mm in size. In the abdomen scanning conditions may be challenging and limit the detection of small lymph nodes. In addition, moving bowel gas can limit the ability of ultrasound to demonstrate small lymph nodes vasculature.

Ultrasound-guided puncture is an important way to reach a diagnostic conclusion, but in many cases (especially for diagnosis and correct typing of malignant lymphoma) the complete removal of lymph node is needed to get a reliable histological diagnosis for the basis of treatment.

Figure 7a and b. Reactive lymph node with an echo-poor round shaped area at the lower pole of 3mm, a ultrasound-guided fine needle biopsy of this tiny lesion (right image, arrow points to the needle tip) proved its inflammatory character.

As fine needle biopsies do not always provide diagnostic clues and its findings are not always reliable, a core biopsy with a needle size for at least 18G is recommended (Figure 7 and 8).

Ultrasound for imaging lymph nodes has several goals:

- Palpating lymph nodes: for characterising lymph nodes B-mode is the basic examination mode, colour Doppler ultrasound, B-Flow and to some degree CEUS can image a lymph nodes vessels including microvascularity. Ultrasound-guided puncture for final diagnosis.

- Detection of suspicious lymph nodes: especially sentinel lymph nodes in malignant diseases. For this purpose B-mode ultrasound is the basic mode, in the future, and with targeted bubbles, CEUS may be able to substitute lymphoscintigraphy [3].

- Localisation of all metastatic lymph nodes.

- For differentiation of soft tissue, transit and lymph node metastases B-mode and in a few cases additional 3D imaging can be beneficial.

- It is clinically important to evaluate if the lymph node capsule has been invaded by a tumour or destroyed and so B-mode ultrasound is used in the first instance, in some cases CEUS, colour Doppler and pulsed wave Doppler may give additional information

- Ultrasound is used for needle guidance for lymph node puncture (Figure 8 and 9)

Ultrasound is used for guidance of needles in fine or core biopsies (Figure 8). It also helps to puncture areas from the lymph node such as thickened cortex or areas suspicious for malignant infiltration. The sensitivity and specificity of FNA biopsy in determining the aetiology of lymphadenopathy are both more than 90% [4–6].
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Figure 8. Core biopsy taken from a small lymph node metastasis (18G), right: Histological specimen

Figure 9. Ultrasound guided puncture (16G core biopsy) of a thickened cortex (B-non-Hodgkin’s lymphoma)

In a few special cases CEUS can help in location choice for biopsy by avoiding the puncture of non-viable tumour tissue, especially in bulky tumours (Figure 10).

Figure 10. CEUS may help to decide which part of a lymph node is best suited for puncture. Obviously non-viable or severe ischaemic tissue should not be chosen for biopsy (Sézary disease).

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In monitoring tumour therapy ultrasound can contribute by estimating the change in number and size of involved lymph nodes. A reduction of intralymphosascular vascularity (colour Doppler, B-Flow or CEUS) may be the first, and early, sign of response to chemotherapy, and when using ultrasound contrast agents it is possible to reliably evaluate if a lymph node still contains viable tissue (see Figure 29).

Sinus hyperplasia indicates haemophagocytic syndrome and sinus histiocytosis with splenomegaly.

Granulomatous lymphadenitis may also have a central necrosis while diffuse granulomas are non-destructive – such as cat-scratch disease or sarcoidosis. A focal necrosis can be seen in malignant lymph nodes, but is rare in destructive lymphadenitis.

Infiltrated peripheral lymph nodes in sarcoidosis are found in approximately 30% of cases. They are echo-poor and have no or a thin hilum. They may have a rich and regular vasculature (Figure 11). The diagnosis has to be confirmed by core biopsy or lymphadenectomy.

Figure 11. Sarcoidosis in a lymph node of the left groin.

Imaging of reactive lymph nodes

Reactive lymphadenopathy is a non-neoplastic enlargement in response to antigenic stimuli. Clinically reactive lymph nodes are tender and mobile. Depending on the cellular response three histological types can be differentiated: a follicular hyperplasia is most common (differential diagnoses are rheumatoid arthritis, Sjogren’s syndrome or toxoplasmosis); a paracortical hyperplasia with a preferred stimulation of T cells can histologically be diagnosed (such as infectious mononucleosis or other viral infections); and rarely sinus hyperplasia is seen in haemophagocytosis and sinus histiocytosis is also seen.

It is important to note that infectious material can cause a focal cortical thickening. In these patients a local infectious focus can, in most cases, be detected clinically or on ultrasound. It is characterised by a regular segmental vascularisation (Figure 12). As focal cortical thickening is also highly suspicious of tumour invasion, a biopsy is recommended.
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Figure 12. Inflammatory focal swelling of a lymph node in the left groin (due to a Bartolini abscess). Note to regular vascularization of the swollen cortex.

In case of a lymphatic spread the tumour cells enter a lymph node through the afferent lymphatic vessels and start to grow where they enter the cortex (Figure 13). Thus, a nodular thickening of the cortex is highly suspicious for metastatic spread or involvement in Hodgkin’s or non-Hodgkin’s disease (Figure 36).

Figure 13. 6mm metastatic nodule of a melanoma in a lymph node of the left groin (left). Cytologic image (middle) and histologic specimen (right)

Patients undergoing interferon treatment may also develop echo-poor, round-shaped lymph nodes (Figure 23).

Over time reactive lymph nodes age and fatty involution changes the lymph node appearance. A tiny cortex will surround an echogenic centre, so these lymph nodes are more difficult to detect (Figure 14 b,c).

Figure 14 a-e. Above: a: Oval shaped reactive lymph node, Solbiati index of 4.8, b: Round shaped reactive lymph node, Solbiati index about 1.0. c: fatty involution of an inguinal lymph node with a 0.6mm thin cortex, Solbiati index >2. Below two images: reactive lymph node in the hepatic hilum, Solbiati index 1.2, central vessels.

In contrast to other imaging modalities, ultrasound can image internal anatomical structures to build up an image of the normal architecture of a lymph node, that is, a thin, slightly echo-poor cortex, which increases in size in inflammatory status.

Figure 15. a, 55-year-old patient with neurodermitis and locally enlarged lymph nodes in the groin with a thickened echo-poor cortex. b, lymph node in the neck of the same patient. Note the enlarged echo-poor follicles (arrows).

Sometimes enlarged follicles within the cortex can be seen (Figure 16). This can be caused by inflammation, but in indolent non-Hodgkin’s lymphoma tiny numerous echo-poor spots within the thickened cortex can be detected (Figure 47). Owing to the underlying disease (acute lymphadenitis or lymphomas) the echogenic centre of the lymph node can become less echogenic.
The spatial resolution and dynamic range means that the recognition of a normal architecture in abdominal lymph node is difficult to image. In slim patients a high frequency probe can help (Figure 14 c,d).

In colour Doppler imaging the vascular supply of a lymph node can be detected from the hilum branching towards the cortex. Red and blue coded adjacent vessels indicate arterial supply and venous drainage (Figure 16). Usually colour Doppler ultrasound will overestimate the size of the tiny vessels and, in this situation, B-Flow will perform better. Some lymph nodes receive their vascular supply, not only from the hilum but some vessels also break through the cortex (Figure 17). In case of an acute lymphadenitis an intranodular oedema may reduce blood flow, occasionally an abscess will cause a complete destruction of the lymph node.

**Figure 16.** Reactive lymph node in B-mode (left, 15MHz TX) with supplying vessels sprouting tree-like from the hilum towards the echo-poor cortex (Right: Bidirectional colour Doppler image).

**Figure 17.** Accessory artery supplying the lymph node entering the cortex via the upper pole (B-mode; non-Hodgkin’s lymphoma)

CEUS helps to evaluate the vascularity and vessel architecture of abdominal lymph nodes (Figure 18).

Ahuja [9] described tuberculous nodes with varied vascular pattern, simulating both benign and malignant conditions (Figure 19). Displaced vascularity and apparent avascularity are common in tuberculous nodes, which are related to the high incidence of cystic necrosis in tuberculous lymph nodes.

**Figure 18 a-c.** Lymph node in the hilum of the liver in a patient with chronic hepatitis (a; B-mode image, b; Late phase of CEUS shows the washed out lymph node. After a second bolus injection of 0.6mL SonoVue a central artery is enhanced with tiny vessels branching towards the capsule (c).

**Figure 19.** Tuberculosis in a lymph node of the neck. CFI shows different vessel densities of the node

The branchial cleft cysts of the neck may be misinterpreted as an enlarged suspicious lymph node. They are avascular, have a cystic or echo-poor appearance and sometimes have moving tiny echoes that can be seen when pressure is exerted on the cyst (Figure 20). They may change in size and echogenicity. A puncture can verify this diagnosis.
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Figure 20. A cystic (left) and more echogenic branchial cleft cyst (right), the latter showing moving echoes when putting pressure on the tumour. Patients report on a slowly growing, palpable submandibular tumour mostly without local symptoms. As the fluid is rather thick, a bigger needle is needed for successful puncture.

Another differential diagnosis of a single mass in the neck that is found between the ICA and ECA is a glomus tumour, which is echo-poor, has a rich vasculature and has the typical location shown in (Figure 21).

*Figure 21. Glomus tumour. Colour Doppler shows a rich vasculature.*

Other differential diagnoses of palpable masses in the inguinal region include inguinal hernias, undescended testicles, post-operative seromas and haematomas

Differentiating benign from malignant lymph nodes

For characterising lymph nodes it is necessary to image their vessels. To understand the differences between benign and malignant lymph nodes it is important to examine how tumour vessels are organised and in which way they differ from normal vessels. In general malignant tumours have a higher vessel density, which can make-up up to 10% of the tumour volume. The vessel density may be inhomogeneous within a tumour or malignant lymph node. Tumour vessels often have arteriovenous shunts. Tumour vessels are imperfect, their size may change and arteries may be split (Figure 22). Therefore, resistive index measurement of a single intranodal artery will not be representative of the peripheral resistance in a lymph node.

Tumour vessels have no muscle layer. Their wall is characterised by different sized pores. Within one tumour, a pore size range of 200nm to 1.2μ has been described [7]. Owing to these pores and their widths, fluid will leak into the interstitium, thus increasing the intra-tumoural pressure leading to an ischaemia, which can then stimulate a neo-angiogenesis. As long as the organ has an intact capsule the pressure will rise. Tumours of the brain, pleura and peritoneum have no capsule, which is why the intratumoural pressure does not rise and the fluid is collected as a pleural effusion or ascites, an increase of free-fluid in the brain causes typical symptoms such as headache, convulsion and other neurological symptoms.

In malignant lymph nodes a great number of changes in detectable vascularisation can be seen. Similar changes can also be seen in reactive lymph nodes when inflammation causes local oedema and destroys lymphatic tissue. When intranodular pressure rises, RI also rises. At the same time small venous vessels are compressed and can no longer be detected on colour Doppler techniques. Only peripheral, larger draining veins can be seen in the lymph nodes. At this stage an intratumoural ischaemia can start to develop. With a further rise in pressure the smaller, and at a later stage the bigger, intratumoural arteries can be missed. Ahuja has already shown that peripheral vascularity is not found in normal or reactive nodes, and the presence of peripheral vascularity, regardless of sole peripheral or mixed vascularity is highly suspicious of malignancy [1,10–12]. This also explains why chemotherapy may not reach the areas of high intratumoural (or ischaemic) pressure [13–16].

Visualising preserved vessel architecture is important in characterising lymph nodes in patients with melanoma who are undergoing interferon treatment, because their lymph nodes may become echo-poor and round in shape, but in contrast to malignant lymph nodes still have a regular vessel architecture (Figure 23).
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**Figure 23** a-c: 6mm reactive lymph node under Interferon therapy with a central vascular tree and b: an 8mm lymph node metastasis with vessels in the periphery of the lymph node (melanoma). c: a 2cm oval shaped lymph node metastasis from a prostate cancer showing nearly only peripheral vessels.

As soon as the capsule is infiltrated or destroyed by the tumour the fluid in the interstitium can leave the lymph node and cause oedema of the surrounding mostly fatty tissue (Figure 24). The RI will then decrease again and colour Doppler demonstrates a lower intranodular vasculature again (Figure 25). So the same primary tumour can have lymph node metastases that show different vascular patterns because the number of shunts and bigger tumour vessels may differ. In the first instance it can be assumed that differences in the intranodular pressure are responsible for different intratumoural vasculature.

**Figure 24.** C-plane images of the destroyed capsule caused by a lymph node metastasis (melanoma).

Leaking of fluid into the surrounding fatty tissue results in a constant flow of tumour cells into the neighbouring soft tissue. If a surgical intervention is planned this finding has to be taken into account because the amount of resected tissue will need to be bigger.

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**Figure 25.** Lymph node metastasis of a small cell lung cancer. Tumour invasion and destruction of the capsule causing an oedema in the neighbouring fatty tissue (left) relatively high vasculature (middle, power Doppler technique) with a relatively low RI number of 0.64 (right).

It is well known that metastatic nodes have a higher RI and PI than reactive nodes [1, 10, 17-19]. Controversy regarding the RI and PI measurements in benign versus malignant nodes can probably be solved by the influence of the intranodular pressure on the resistance values that may change even within one malignant lymph node. Colour Doppler or B-flow imaging can depict the changes of vascularity during systole and diastole, especially in metastatic lymph nodes (Figure 26). B-flow can also characterise the intranodal tumour vessels (Figure 22, 26, 27).

**Figure 26.** Vasculature of a lymph node metastasis (melanoma) imaged in CFI (left) and B-flow during systole (middle) and a reduced flow during diastole (right). B-Flow shows a different vessel density and sudden changes in diameter.
A rise in intratumoural pressure is not observed in cancerous lymph nodes. In inflammatory lymph nodes a destruction of tissue can minimise the detection of intranodular vessels as a result of oedema, but in most cases the RI numbers are low in reactive lymph nodes.

Highly differentiated tumours can also be characterised by their rich intratumoural vasculature. They often mirror the vascularity of the primary tumour. Hyper-vascularised lymph nodes can therefore be found in patients with thyroid, ovarian, breast or renal cell cancer, as well as other forms in which the primary tumour is hyper-vascularised (Figure 28).

**Figure 28 a and b. Papillary carcinoma of the thyroid. The tiny calcifications within the tumour (a) can be seen in the local lymph node metastasis as well (b).**

The lymph nodes vasculature is an indicator for response to chemotherapy or radiotherapy. In case of radiotherapy the surrounding tissue will develop a hyperaemia over several weeks (Figure 29).
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Advantages of colour Doppler ultrasound over CEUS include the demonstration of flow direction and calculation of the RI number of single vessels. In Figure 34 the elevated RI number of the tumour-supplying artery is compared with the lower RI number of the non-involved section of lymph node.

Figure 34. 35 year old male with a metastatic urothel carcinoma lymph node metastasis left neck. Note the differences of the RI number of the tumour and normal lymph node supplying arteries (RI 1.0 and 0.57 respectively).

Tumour cells may invade a lymph node from more than one afferent lymphatic vessel. In this case focal, echo-poor, round cortical tumours can be seen when using a high frequency probe. Depending on the site and growth of these metastases the lymph node can have a more oval or more round shape (Figure 35).

Figure 35. Left: Three lymph node metastases within one lymph node causing a round shaped lymph node, the normal cortex can still be identified as a small echo-poor rim (arrow). Middle and right image: Infiltration of three metastases in one lymph node has caused an echo-poor oval shape of the lymph node. B-Flow demonstrates differences in vessel density between metastatic nodules and lymph node tissue in between. The vessels between the metastases show a high flow indicating the high blood supply of the tumour, which probably consists mainly of tiny vessels, not imaged by conventional flow detection methods.

The same can be true in lymphoma patients. In CFI the focal cortical thickening can be vascularised depending if the vessels are very small or the flow volume is too low (Figure 36).
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Figure 36. Focal lymph node thickening in 26 year old male with non-Hodgkin disease. Note that in colour Doppler the echo-poor infiltration seems to be non vascularized

In lymphomas neovascularisation and microvessel density are important tumour characteristics. Beside colour Doppler techniques and B-flow, CEUS is capable of demonstrating lymph node microvasculature and is regarded as the most sensitive ultrasound imaging technique to identify vasculature and viability of a lymph node. Contrast is required for the imaging of peripheral lymph nodes, and with a high frequency probe higher doses should be used (double compared with probes for abdominal imaging). The kinetics are also different (shorter duration of enhancement) and the bubbles are more prone to rupture if the probe is kept on one spot for a long time (Figure 37).

Figure 37. Axillary lymph node metastasis. Middle: constant scanning in one spot caused a bubble destruction in the near field, a sweep performed after 1 min (right) showed no near field “pseudo-necrosis”.

A metastatic lymph node can also be characterised by different enhancement levels (or microvessel density) (Figure 9, 38, 41 and 42).

Figure 38. Paracaval lymph node metastasis of a prostate cancer. Note the difference in regional enhancement levels.

There may be a discrepancy between CEUS and colour Doppler imaging of vessel distribution, the latter is fairly sensitive for imaging vessels with a relatively high volume flow, and CEUS can be used to detect tumour microvasculature (Figure 39 and 40).

Figure 39. Lymph node metastasis of the neck (from lung cancer). Note that the CFI image shows an inhomogeneous vessel distribution of the larger vessels, while in CEUS a homogeneous microvascular enhancement is seen which is quickly washed out. The enhancement did not show a centrifugal progression, but started homogeneously nearly at the same time (CEUS images 18s, 22s and 31s after bolus injection).

Figure 40 a-c. Lymph node metastasis with a thin normal remaining cortex (a, arrow). CFI shows a hyper-vascularization, PW Doppler indicates a high peripheral resistance (RI: 0.82, b). CEUS demonstrates an inhomogeneous vessel density (21s post bolus injection, c).
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Transit metastases, sentinel lymph node

By definition a transit metastasis is a metastatic deposit occurring in the lymphatic pathway between the primary tumour and its draining lymph nodes. Because they are located subcutaneously, metastases from melanoma are in most cases easy to palpate and can be detected by the patient themselves (Figure 43 and 44). Intracutaneous metastases from melanoma can be visually detected and do not require imaging.

Figure 43. Small, palpable subcutaneous transit metastasis from a melanoma (15MHz; probe). CFI demonstrates a high vascularisation (transit metastases have no capsule)

Conventional ultrasound is in most cases not able to detect the sentinel lymph node, and therefore other imaging modalities such as lymphoscintigraphy are the methods of choice, especially in breast cancer and melanoma. In the same way as lymphoscintigraphy, ultrasound contrast agents can be used to detect sentinel lymph node. For this purpose, the agent is injected subcutaneously in each quadrant of the location of the tumour. After massage in the area, the agent will be taken up by the lymphatic channels and will reach the sentinel and possibly the secondary lymph node (Figure 45).

Recently published papers have shown that ultrasound contrast agents are reliably taken up by the sentinel lymph node, but so far this technique is still not regarded as suitable for routine use [25, 26].

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Figure 41. Focal lymph node metastasis (melanoma). The normal cortex (arrow) as well as the cortical metastasis are enhanced, but the latter one is less enhanced in its central portion (probably due to high intra-nodular pressure). Note the slow wash out over time (middle: 17s, right: 58s).

Criteria for malignancy in CEUS are centripetal enhancement [21], inhomogeneous enhancement, perfusion defects [22, 23] and the substitution of normal vessels by a network of mostly tiny tumour vessels (Figure 40, 41, 42).

Figure 42. Centripetal enhancement of a lymph node metastasis in the neck (Merkel cell carcinoma)

The gold standard in patients with breast cancer is conventional ultrasound with or without needle biopsy. Unlike cutaneous melanoma, ultrasound in breast cancer carries a false-negative rate of up to 30% of nodes, which have normal morphology but are metastatic. With a primary tumour size ranging between 0.3cm and 12cm (mean, 3cm) the sensitivity of ultrasound-guided FNA for predicting positive results at axillary or sentinel lymph nodes was 71–75% and increased with size. Specificity was 100% [24]. In addition, CEUS can be helpful in characterising suspicious lymph nodes. Ouyang [21] described metastatic lymph nodes as having a centripetal progress (66.7%), a heterogeneous pattern (55.6%), or no or little perfusion (25.9%), whereas non-metastatic lymph nodes have been characterised by a centrifugal enhancement (56.0%) and a homogeneous pattern (80.0%). The difference between hypervascular and hypovascular regions was higher in metastatic lymph nodes than in non-metastatic ones (p<0.001). Furthermore, CEUS may be of help in predicting the aggressiveness of breast cancer by evaluating the degree of the maximum and minimum enhancement level [21].
Lymphatic diseases

Lymphomas account for 10–15% of childhood cancers. A peak in incidence also occurs in the mid to late 20s and then after 50 years of age. Four histological subtypes of Hodgkin’s disease (HD) have been described: lymphocytic predominance, mixed cellularity, lymphoctic depletion and nodular sclerosis. Nodular sclerosis is the most common subtype and affects approximately 60% of children with Hodgkin’s disease, whereas the lymphocytic depletion subtype is very rare [27].

In adult patients non-Hodgkin’s lymphomas have an incidence of up to 20 per 100,000 and the incidence has increased over the past decade. Indolent non-Hodgkin’s lymphomas are clinically differentiated from aggressive ones because the latter have a poorer prognosis. As lymphomas can involve almost any organ in the body, the number of possible differential diagnoses is substantial and will not be discussed in this chapter.

Histological analysis remains the primary mode of final specific diagnosis for a patient with suspected lymphoma. Some authors prefer the first diagnostic step to be a core biopsy, which has a sensitivity of 89% and a specificity of 97% [28].

Lymphomas can be present in all lymph node in the abdomen and periphery. In the vast majority of cases, the lymph nodes are echo-poor or even cystic, they can be arrange in chains and in most cases the swollen lymph node is not painful (Figure 3). Some lymph nodes lose their architecture, in others the cortex and hilum can still be differentiated from each other. In B-mode ultrasound only minor changes of the cortex may be seen. In other cases, lymph node with a multiple cystic appearance around the aorta can mimic an abdominal aortic aneurysm or Ormond’s disease (Figure 56).

A lymphomatous lymph node may look like a reactive one and only its high vasculature, in the absence of an infectious focus, is evidence of lymphatic disease (Figure 47). Focal infiltration can cause echo-poor hypervascularised cortical thickening (Figure 36 and 46).

Therefore, no greyscale or colour Doppler ultrasound criterion exists that can reliably differentiate between reactive lymph node enlargement and non-Hodgkin’s lymphoma involvement. In the same way as other malignancies, lymphomas are characterised by a high microvessel density (MVD), especially aggressive lymphomas. Similar to cancerous tumours a high MVD is associated with a poor prognosis [28–31]. But CEUS cannot always detect a high microvessel density because an elevated interstitial pressure can prevent its detection. As yet, there are no studies on whether CEUS can contribute to the differentiation of different subtypes of non-Hodgkin’s lymphoma.

CFI lymphomas can show a rich vasculature with clearly visible arteries and veins. The normal architecture is preserved, especially in non-Hodgkin’s lymphoma with low malignancy (Figure 47 and 48).

Figure 47. Non-Hodgkin disease with tiny echo-poor spots and preserved vessel architecture.

B-flow ultrasound has the potential to display very small vessels at their actual size without a blooming effect. Applying a 3D technique, the intact native vasculature of the whole lymph node can be imaged (Figure 47).
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Figure 48. Regular vessel architecture of an indolent non-Hodgkin’s lymphoma lymph node of the groin (3-D B-Flow technique).

Elevated intranodular pressure causes a decrease in the ability of tiny vessels to be detected, but the central major vessels are normally detectable (Figure 49 and 50).

Figure 49. B-non-Hodgkin’s lymphoma, two out of many lymph nodes. The native vasculature is preserved in both lymph nodes: The left lymph node still shows a normal and an infiltrated regular vascularised cortex (only arteries), while the right, echo-poor one has a normal central artery (no adjacent vein) and a hyper-vascularised rim. This finding indicates an increased intra-nodular pressure.

In contrast to cancerous nodules, native vessels are neither destroyed nor substituted by neo-vascularisation. Colour Doppler and CEUS may show a distorted vascular branching and vessel amputation (Figure 50).

Figure 50. Echo-poor lymph node of the right groin surrounded by a thin oedema (a). Vessel architecture is preserved (b, different scan plane). Colour flow and CEUS show different degrees of intra-nodular oedema causing a vessel amputation and a central decrease in the level of enhancement. Note that the lymph node enhancement differs from lymph node to lymph node, which does not depend on the lymph node size. The oedema around the lymph node on B-mode can predict an elevated intra-tumoural pressure.

Although most lymph nodes transformed by non-Hodgkin’s lymphoma have a typical greyscale appearance, some show perinodular infiltration, as seen in inflammatory oedema of soft tissue. In these cases CEUS can demonstrate a high vessel density as seen in Figure 51. The involvement of lymphatic channels within the perinodular tissue can be better demonstrated using contrast-enhanced ultrasound compared with other imaging modalities (Figure 51).

Figure 51. One of multiple lymph nodes in the groin (small cell non-Hodgkin’s lymphoma). B-mode shows a perinodular oedema combined with a high level enhancement on CEUS imaging also of the perinodular space (11 s after 2ml contrast bolus injection). Thus the tumour appears to be much bigger compared to B-mode image. After 18 s (right image) clear wash out.

Colour Doppler examination is mandatory in the evaluation of a lymph node’s character. Even lymph nodes that appear to be fatty involution may have malignant cells, especially following treatment (Figure 52).
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Figure 52. In a 66 year old patient with large cell B-non-Hodgkin’s lymphoma all formally large and typical non-Hodgkin’s lymphoma lymph node became much smaller, but despite its normalized architecture showed a highly vascularised lymph node. FNAB proved the malignant character of this lymph node.

Abdominal lymphoma can be seen in the intra- and retroperitoneal space, and have the same characteristics as the peripheral lymph nodes except that they usually have to be examined with a lower frequency (Figure 53).

Figure 53. Non-Hodgkin’s lymphoma transformed lymph nodes (stars) are seen intra und retroperitoneal, and are often lined up along the vessels (right: para-caval lymph nodes).

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Figure 54 a and b. B-non-Hodgkin’s lymphoma para-aortic lymph node (a) with preserved architecture and a central hilar vasculature (b)

Among the differential diagnoses of lymphomas are abdominal aneurysms, Ormond’s disease haematoma and seroma, which should not be misinterpreted as lymph nodes and vice versa (Figure 55 and 56).

Figure 55 a and b. A. Partly thrombosed false aneurysm of the aorta just before its bifurcation.
B. Densely packed lymph nodes adjacent to the aorta (non-Hodgkin’s lymphoma), post-surgical para-caval haematoma

Figure 56. 75 years old patient with a histological proven Ormond’s disease. CEUS does not show a typical lymph node vasculature; beside the small aortic branches (inferior mesenteric artery) a tiny microvascular network is seen, representing a low “inflammatory” activity. CEUS still frame captured during the arterial phase, the inferior vena cava is not yet enhanced.
General criteria for characterization of lymph node diseases

With its high spatial resolution and ability to evaluate lymph nodes vasculature, ultrasound is an ideal tool to characterise lymph nodes. In particular high-resolution ultrasound performed with transmit frequencies above 12MHz is capable to detect very small lymph nodes and minimal intranodal lesions. In addition, ultrasound-guided puncture can identify the final diagnosis in most cases. New imaging techniques such as CEUS and elastography will, in selected cases, be of benefit for the management of tumour patients. Nevertheless, there are limitations in differentiating benign (reactive) from malignant lymph nodes. It is virtually impossible to differentiate between tuberculosis and metastases, or non-Hodgkin’s lymphoma lymph nodes from reactive lymph nodes such as in mononucleosis, HIV, sarcoidosis or drug-related lymph node enlargement. A lymphoma is likely when multiple echo-poor lymph nodes are detected around the course of a major vessel and the spleen is also enlarged or infiltrated. A few or multipe metastatic lymph nodes will be found along the lymphatic drainage of the tumor baring organ. As a consequence of their decent from the mid-abdomen, lymph node metastasis from malignant testicular or ovarian cancers are located to close to the aorta or vena cava. Some criteria can help (Table 1), but the final diagnosis can normally be made only by histology.

Table 1. Scheme of criteria on lymph node characterization using different US modes. Note that there are no reliable criteria that allow a differentiation between a reactive lymph node and lymphoma.(RI: Resistive Index; E: Enhancement)

<table>
<thead>
<tr>
<th>B-mode</th>
<th>Colour Doppler</th>
<th>RI</th>
<th>B-Flow</th>
<th>CEUS</th>
<th>Elastography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probably a reactive lymph node</td>
<td>Homogeneous, thin cortex, preserved architecture. Note, non-Hodgkin’s lymphoma can appear the same</td>
<td>Regular tree-like vessel architecture. Vessels adjacent to arteries</td>
<td>Probably a low RI</td>
<td>Tree-like branching arterries and veins from central hilar vessels. Note, non-Hodgkin’s lymphoma can also behave in this way</td>
<td>Homogeneous enhancement from the LN centre. Note, non-Hodgkin’s lymphoma can behave in this way</td>
</tr>
<tr>
<td>Suspicious of a lymph node</td>
<td>Globally or focal thickened cortex (possibly a non-Hodgkin’s lymphoma or metastasis) Multiple, enlarged echo-poor it is probably a cystic lymph node</td>
<td>Few native vessels</td>
<td>Indifferent</td>
<td>More peripheral than central vessels</td>
<td>Rapid global and homogeneous enhancement</td>
</tr>
<tr>
<td>Probably a malignant lymph node</td>
<td>Focal or global echo-poor cortical thickening. Destructed architecture. Perinodal oedema destroyed</td>
<td>Few or no central vessels, lymph node vasculature is mostly detected in the periphery</td>
<td>High RI or different RI numbers within the same lymph node</td>
<td>Depends on tumour type and capsule. Mixed vascularity inhomogeneous vessel density, split arteries, tortuous course of vessels</td>
<td>Centripetal E., different intranodal enhancement levels, inhomogeneous wash-out</td>
</tr>
<tr>
<td>Probably a lymphoma</td>
<td>Focal or global echo-poor cortical thickening. Perinodal oedema</td>
<td>Preserved native vasculature in non-Hodgkin’s lymphoma, mixed vasculature in Hodgkin’s</td>
<td>Mostly elevated</td>
<td>Regular branching of vessels</td>
<td>Homogeneous E., peripheral hypo-or non-enhancement</td>
</tr>
</tbody>
</table>

References

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