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Ultrasound of lymph nodes

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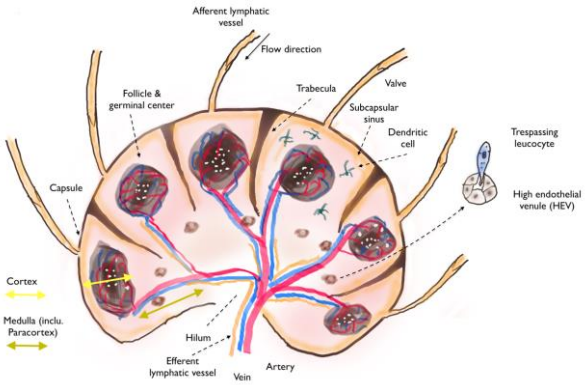
General remarks

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 liters 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 prevents intraluminal fluid from flowing backwards and thus allowing the lymph only to proceed to the next lymph node.

The lymph enters a lymph node by several afferent vessels and is filtered and checked when passing the lymphatic tissue. It passes the subcapsular, peritrabecular space and the medullary sinus [Figure 1]. The cleared lymph is drained by the efferent lymphatic vessels and enters the left and right subclavian vein by the thoracic duct.

Figure 1 **Schematic drawing of a normal lymph node with several afferent lymphatic vessels and usually only one efferent vessel. The lymphatic fluid is filtered and checked for antigens or foreign bodies when passing the cortex and medulla. The lymph node has functional units divided by trabecular septa. Towards the center high endothelial venules (HEV) let leucocytes pass in order to fight intruders being held by dentritic cells. The echo-poor cortex mainly consists of follicles with germinal centers. The hilum consists of echogenic fatty tissue where supplying arteries and veins enter.**



Lymph nodes have a capsule of dense connective tissue that covers the outer part of a lymph node, the echo-poor cortex (B-zone) and more deeply the paracortex (T-zone). From the fibrous capsule trabeculae arise and divide a lymph node in multiple functional areas. The B-zone is located close to the capsule, containing the lymphoid follicles with the germinal center. The paracortex represents mainly the T-Zone, in which the high endothelial venules (HEV) are located. When dendritic cells discover intruders a signal pathway will be activated in order to an open a gap between the endothelial cells of the HEV thus letting lymphocytes enter the T-zone. As the travel time for the lymphocytes between exiting the HEV and reentering the systemic circulation is only a few hours, millions of lymphocytes enter and exit each peripheral LN daily (homing). Fluid from the subcapsular and peritrabecular space will also enter the central part of a lymph node. The supplying vessels are found in the hilum of the lymph node. From the hilum regular, tree-like branching vessels pass the medulla and paracortex towards the cortex [Figure 2]. In some lymph nodes accessory arteries and veins may enter and leave the organ somewhere outside the hilum and break through the cortex [Figure 2]. This architecture is typical for most reactive lymph nodes and can be imaged using ultrasound systems with sensitive colour Doppler equipment.

Figure 2 **Non-Hodgkin lymphoma with echo-poor follicles (yellow arrow), medulla (red stars) and hilum area with vessels (blue arrow, a). Oval shaped lymph node right groin with a tree like arterial vessel architecture (erysipelas right calf, b)**. **Reactive lymph node with an artery trespassing the node (yellow arrow, c)**. **Reactive lymph node with a vein running through the mid portion of the LN (white arrow point to the cortex, d)**.

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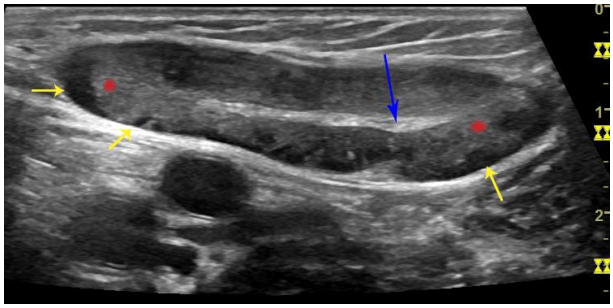

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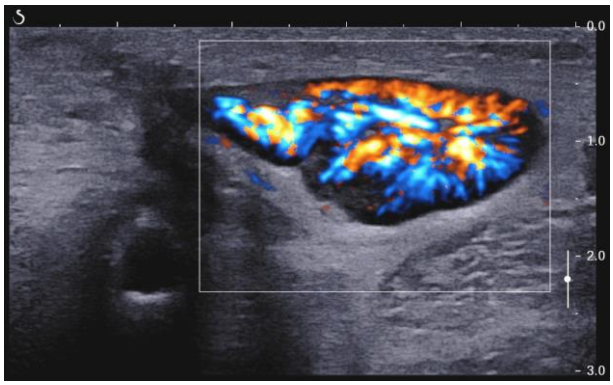

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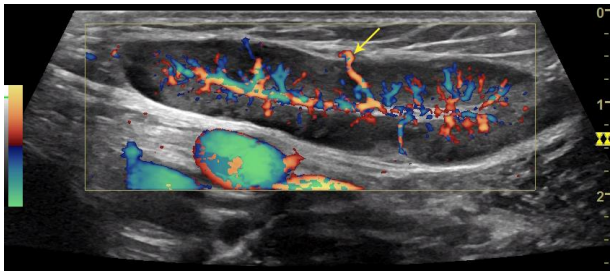

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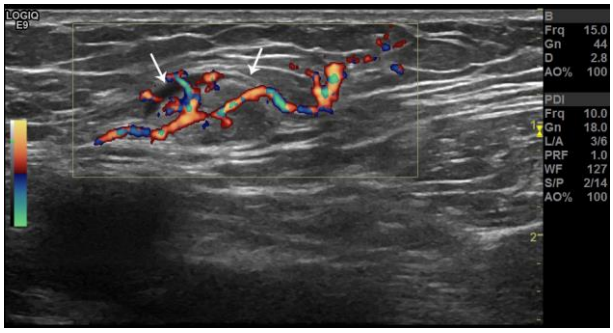
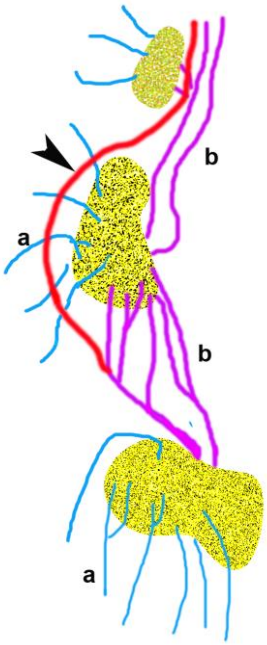


Secondary follicles develop when a lymph node encounters antigens. B cells are found in the center, the parafollicular zone mainly consists of T cells, the sinuses have histiocytes and the medulla is full of plasma cells and lymphocytes.

Beside antigens, which enter the lymph node by the afferent lymphatics, macrophages and dendritic cells enter the lymph node via the lymphatics as well. As soon as the dendritic cells bind an antigen, a signal chain reaction starts aiming at the opening of the palisades of the HEV. Thus, lymphocytes migrate into the interstitial LN tissue and encounter foreign bodies or antigens. Lymphocytes that are not involved in this process leave the lymph node by the

efferent lymphatic vessels. Sometimes an efferent lymph vessel may bypass the next LN, the so-called secondary lymph node [Figure 3].

Figure 3 **Lymph nodes with afferent (a) and efferent (b) lymphatic vessels. The black arrow points to an efferent lymph vessel bypassing a lymph node. The efferent lymph vessels may function again as an afferent lymphatic vessel when entering the next lymph node.**



Lymphoid tissue is also found in lymphoid follicles (also known as lymphatic nodules) associated with the digestive system such as the tonsils and the Peyer`s patches in the lower gastrointestinal (GI) tract. In contrast to lymph nodes, aggregations of lymphatic tissue have no capsule. In the upper GI tract, they are described as mucosa-associated lymphatic tissue (MALT).

Anatomical remarks and examination technique

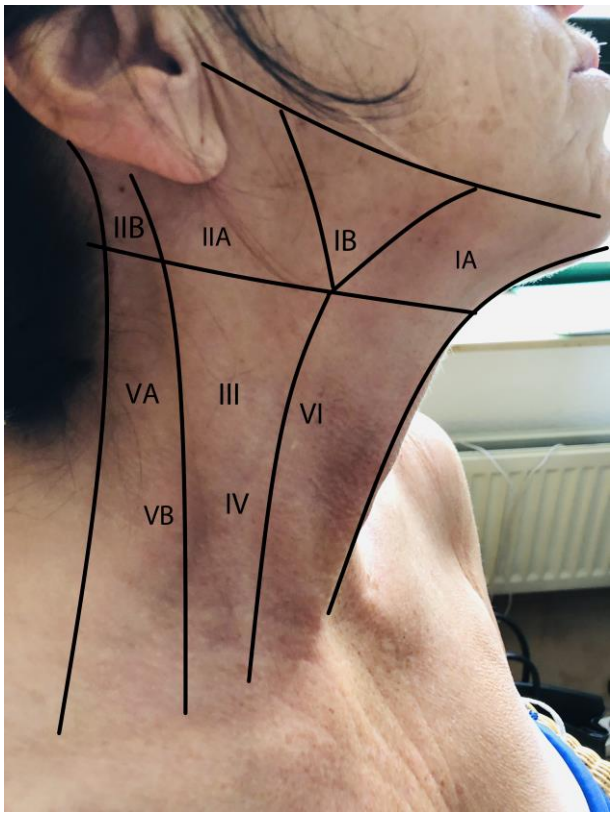
It is estimated that there are approximately 600-700 lymph nodes in humans. The tiny ones whose acoustic properties cannot be differentiated from the surrounding tissue cannot be seen on ultrasound. For the anatomical regions in which transcutaneous ultrasound

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. The standard protocol for evaluation of the peripheral lymph node state must include the neck, supra and infraclavicular, armpit and groin.

Cervical lymph nodes can be classified into eight regions [1]: the submental (region 1), sub-mandibular (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 in these cases be included in the examination process. In patients with melanoma, located distal to the elbow or the knee, the cubital or popliteal fossae should also be checked.

Within the abdominal space 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 must be examined, and location and size of involved lymph node must be documented for follow-up examinations [Figure 4]. Volumetric measurement, panoramic view or three-dimensional imaging may help to better demonstrate local lymph node status especially in follow up studies.

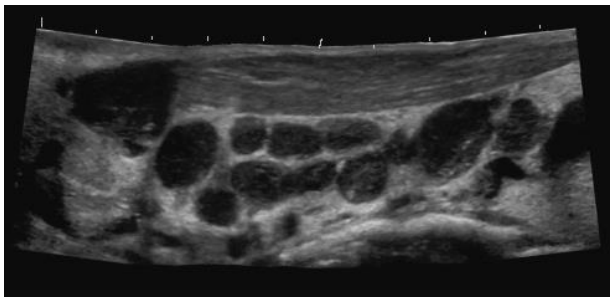
Figure 4 Schematic diagram of neck shows classification of cervical lymph nodes in sonographic examinations.



Depending on the depth and local scanning conditions a linear probe or in deep located areas a curved array with the highest frequency (ranging from 4-5MHz to 18MHz) should be chosen. Transmit frequency and depth define the attenuation of the LN embedded tissue (like posterior to muscle or a scar). A panoramic view technique or 3D mode may be advantageous in demonstrating a lymph node in a greater topographic perspective [Figure 5].

Figure 5 **C-plane images from a 3D tissue block: Multiple lymph nodes in the neck in a Non-Hodgkin Lymphoma patient (a). Parasternal enlarged lymph node between the ribs demonstrated in a c-plane image (b). After lymphadenectomy a local tumour recurrence was best seen adjacent to the scar on a c-Plane image in a melanoma metastasis patient (c).**

a



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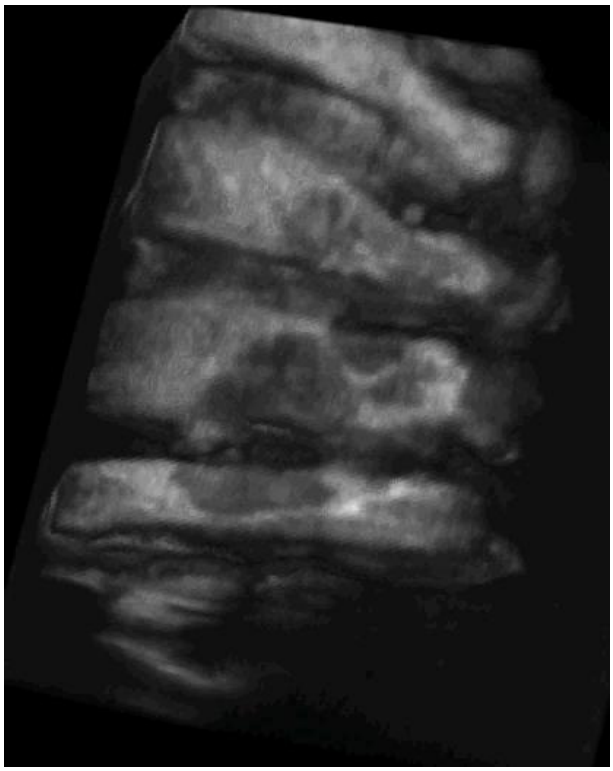

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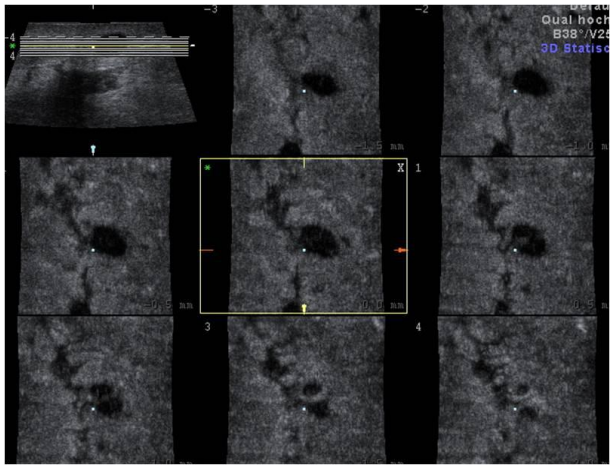
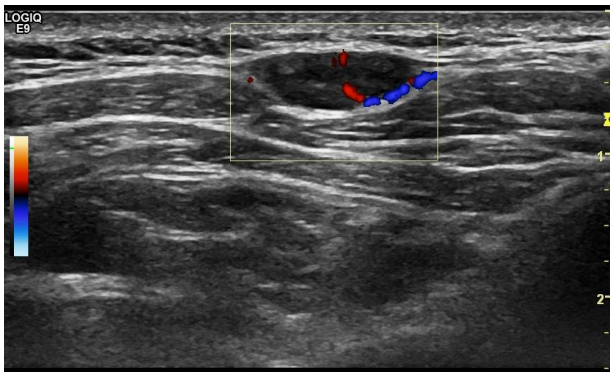


C-level images taken from 3D tissue volumes may help to better demonstrate the topography of diseased lymph nodes. Figure 4 shows location of soft tissue melanoma metastasis in the right groin and parasternal lymph node of Non Hodgkin Lymphoma (NHL). A sensitive colour Doppler technique is needed to image the vascularity of a lymph node, especially its architecture and the presence of arterial and venous flow. Reactive lymph nodes have hilar vascularity or in a chronic state appear to be avascular with a very thin cortex (2). Colour Doppler (bidirectional), power Doppler, B-flow or SMI modes are the preferred flow detection modes. Some ultrasound devices offer B-flow or SMI technique, which have the advantage of avoiding blooming artefacts and can therefore image very small vessels.

Colour Doppler techniques can image larger vessels if the signal strength reflected from the red blood cells is strong enough. In order to image a lymph node`s microvasculature ultrasound contrast agents must be used (see EFSUMB guidelines for extra-hepatic indications). Mechanical pressure by the probe must be avoided when examining superficial lymph node vascularity, as blood flow may be reduced or even blocked [Figure 6].

Figure 6 **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 (a), the right image was recorded with nearly no pressure thus a maximum of intra-nodal vessels could be detected (b). LN metastasis (c), Due to continuous scanning during the arterial phase bubbles in the near field are immediately destroyed (d), after a scan pause the LN shows enhancement also in the near field (e).**

a



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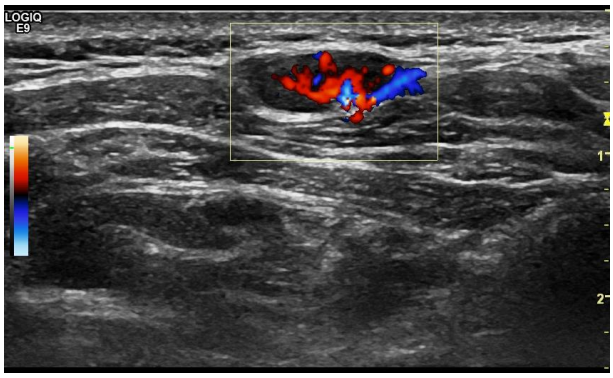

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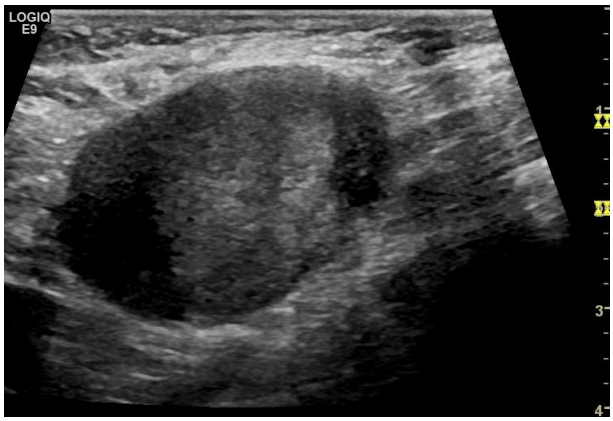

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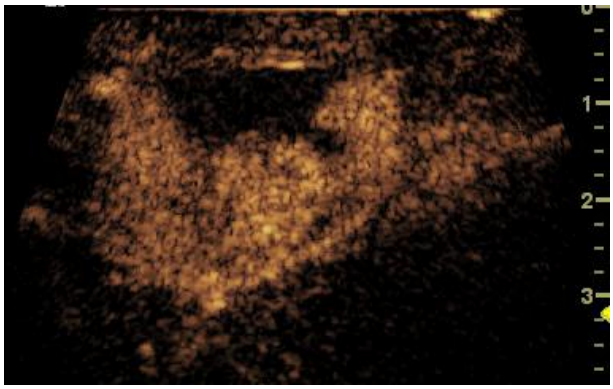

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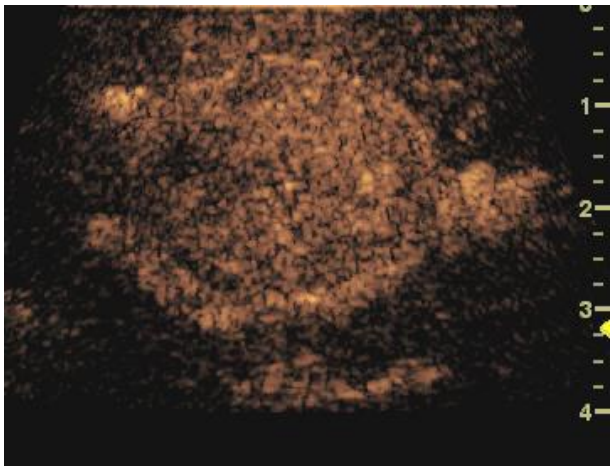

In some clinical settings contrast-enhanced ultrasound (CEUS) may be more valuable than conventional colour Doppler techniques. For high frequency linear probes, a higher dose of contrast agent must be injected (about twice as high as for abdominal studies).

Elastography is another relatively new technique for characterising lymph nodes. It is based on the idea that malignant tumours are stiffer than non-malignant tissue. The stiffness of lymph nodes can be estimated by comparing lymph node's elasticity to the surrounding neck muscles (muscle-to-lymph node strain ratio; that is, the strain index). So far the value of strain elastography is under discussion, as this technique only refers to relative differences between reference and tumour tissue, and there are differences between US devices as well regarding the differentiation of benign and metastatic cervical lymph nodes (LNs) in patients suspected of having thyroid or hypopharyngeal cancer, using sonoelastography. Lyshchik reported a 98% specificity and 85% sensitivity, and 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 [7]. 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 variation in intranodal pressures in metastatic lymph nodes that modify the elasticity of a node [Figure 7].

Figure 7 Strain 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. Two images show a superficial transit metastasis of a melanoma in the left groin with a tumour appearing soft on strain elastography. The soft character of the transit metastasis can be explained by the imaging technique, which displays only the relative elasticity when compared to the surrounding tissue (a). Below left demonstrates a hard lymph node (metastasis) (b). Below right: Fatty involuted LN with a thin cortex (arrow) the echo-poor part within the centre (red star). Strain elastography characterizes this part as soft (fat).

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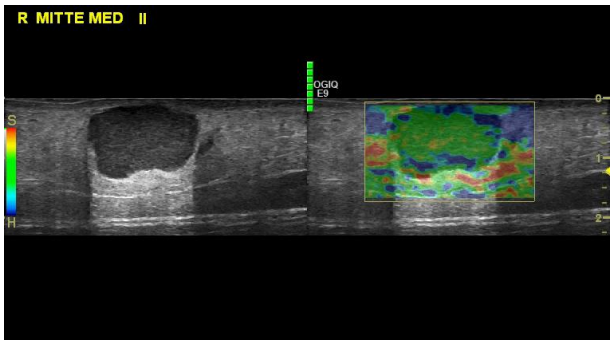

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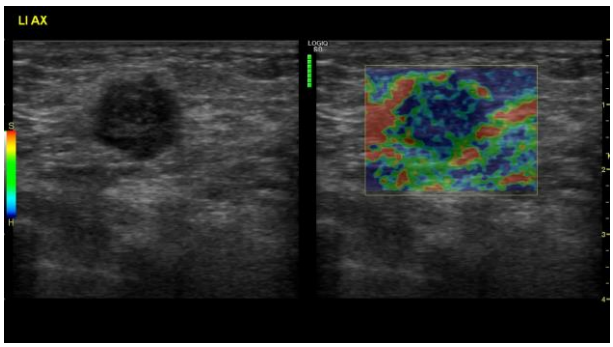

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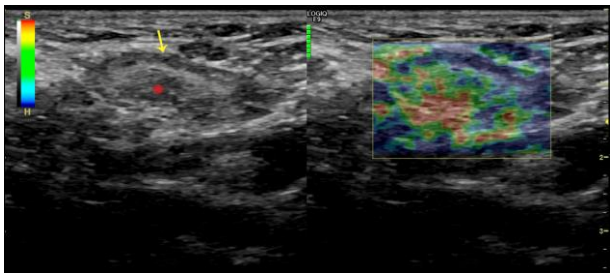


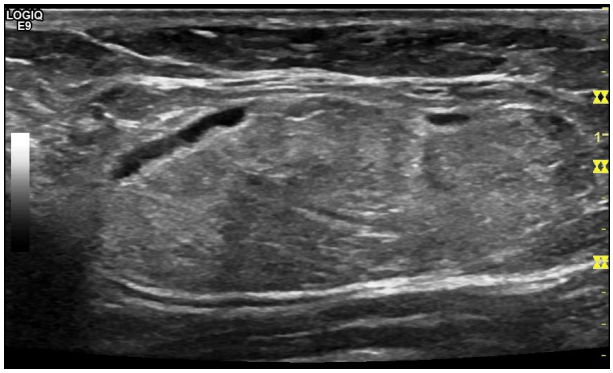
Role of ultrasound in diagnosing lymph node diseases

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 the first-choice imaging modality in patients with inflammatory or malignant disease.

Enlarged lymph nodes can be an immune response to bacteria, virus, fungus infection or other immune stimulating agents [Figure 8].

Figure 8 **A 64-year-old male with tenderness of the left armpit 3 days after a flu vaccination. An enlarged chronic reactive lymph node with a fatty centre and a 1mm thick cortex shows a short length cortical thickening (a) and local hypervascularity (b) as a reactive lymphatic response.**

a



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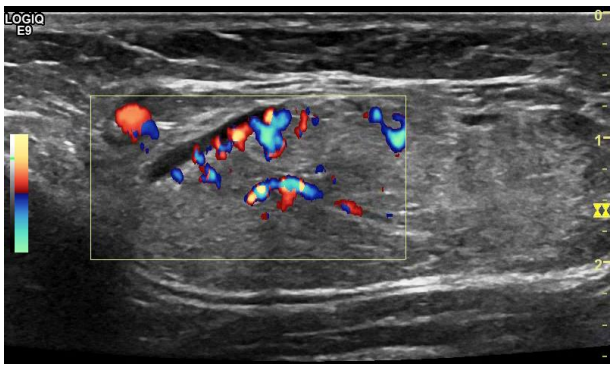

Among the malignant diseases, infiltration of neoplastic cells by lymphatic or blood circulation and localised neoplastic proliferation of lymphocytes or macrophages (e.g., leukaemia or lymphoma) will cause an enlargement of lymph nodes.

Inflammatory/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 2].

A typical reactive lymph node has an oval shape with a cortex of even thickness and an echogenic hilum where the supplying vessels enter. In bigger lymph nodes the vessels can be identified even on grey scale images. Colour Doppler ultrasound demonstrates direction and character of blood flow (artery, vein). The vessels branch in a tree-like way from the hilum to the cortex.

With good contrast resolution, high frequency probes can easily detect lymph nodes down to 2-3mm in size. In the abdomen scanning conditions may be challenging and may limit the detection of small lymph nodes. In addition, moving bowel gas may prevent the demonstration of small lymph nodes vasculature.

Chronic LN will show a thin cortex and mostly an echogenic centre. Fatty involution of the medulla and hilum will not always present as echogenic but may be more echo-poor as the surrounding fatty tissue adjacent to the LN [Figure 9]. In some cases, echo-poor areas within the LN may be misinterpreted as tumour infiltration [Figure 10].

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

Figure 9 Non-active chronic LN with a small cortex and fatty central involution. Echogenic centre (a). Sandwich like echogenic and more echo-poor centre (b). Cloud like echo-poor centre (c).

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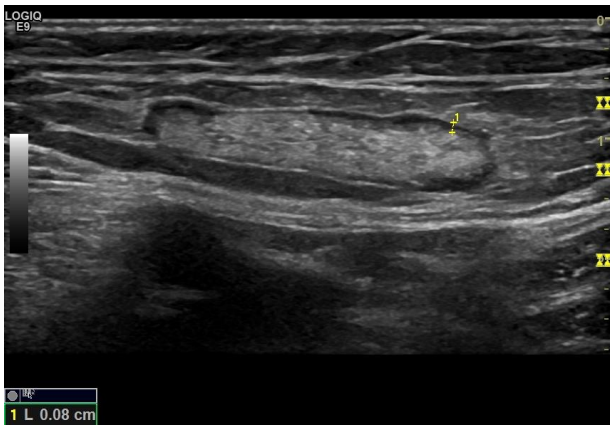

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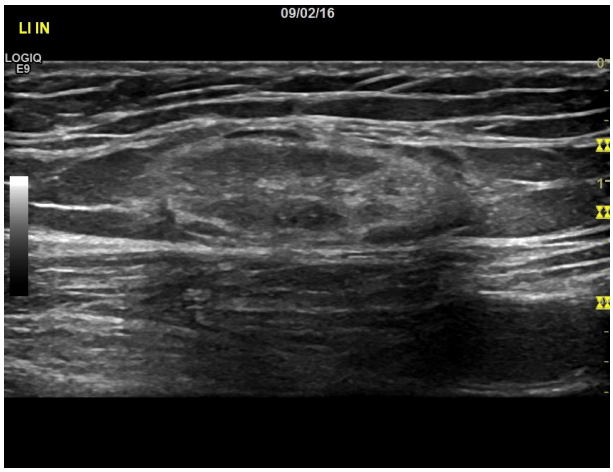

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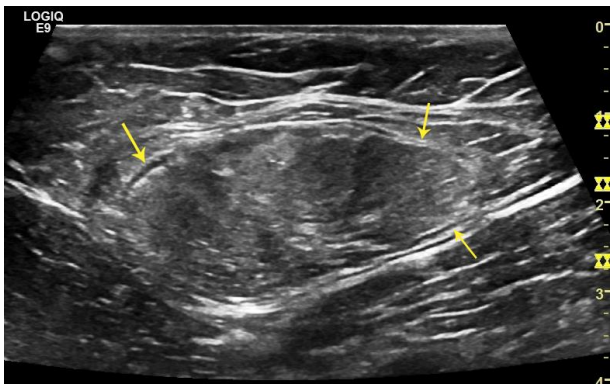

Figure 10 Eccentric echo-poor area in an axillary LN with no vascularity on CFI (a). FNB (b) proved atypical echo-poor fatty tissue.

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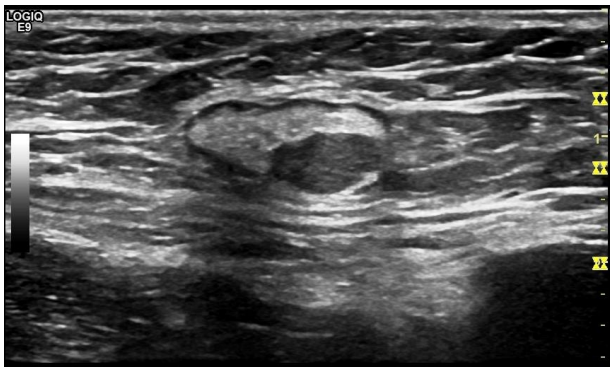

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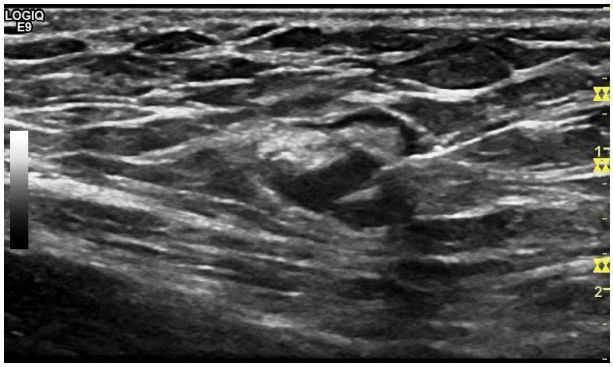


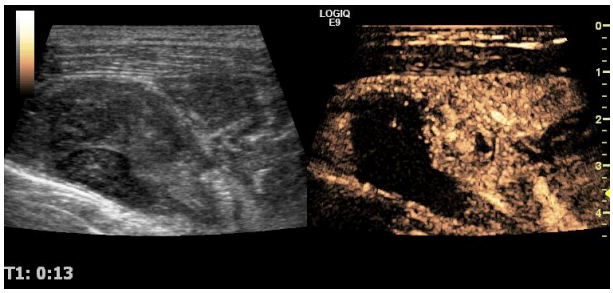
As fine needle biopsies do not always provide diagnostic clues and its findings are not always reliable, a single or multiple core biopsies with a needle size for at least 18G is recommended [Figure 10].

Ultrasound for imaging lymph nodes can be summarized as follows:

- detecting lymph nodes especially in the axillary and infraclavicular region.
- Characterization of lymph nodes
- B-Mode US is able to detect tiny LN, but mostly not the sentinel lymph node. US contrast agents especially targeted bubbles may in future substitute lymphoscintigraphy [4].
- Localisation of all metastatic lymph nodes.
- It is clinically important to evaluate whether the lymph node capsule is intact. Perinodal oedema in a malignant LN is a surrogate marker for a destruction of the capsule, due to leakage of interstitial fluid and tumour cells into the perinodal fatty tissue.
- Ultrasound is the method of choice for needle guidance to puncture suspicious peripheral lymph nodes.

US guidance aids the puncture of LNs with suspicious cortical thickening. The sensitivity and specificity of FNA or if possible core biopsies in characterising thickened LN are reported to be around 90% [5-7] with core biopsy recommended for bigger LNs. In a few cases CEUS can help to guide the needle to viable tissue by avoiding non-viable, necrotic tumour tissue, especially in fast growing bulky tumours [Figure 11].

Figure 11 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 (Sezary disease).

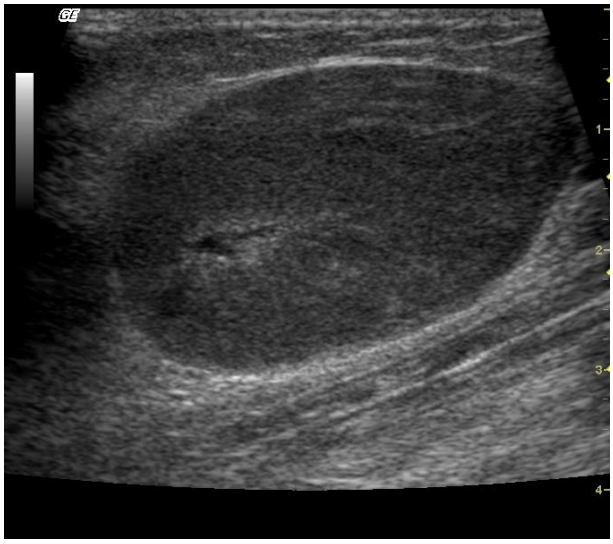


In monitoring tumour therapy, ultrasound can evaluate the change in number, size and vascularity of involved lymph nodes. A reduction of intralesional vascularity and perfusion (colour Doppler, B-Flow, SMI or CEUS) may be a first, and early sign of response to chemotherapy [Figure 37]. It must be noted that early during immune therapy the LN may as a result of lymphocyte invasion even grow before they shrink.

Sinus hyperplasia indicates hemophagocytic syndrome and sinus histiocytosis with splenomegaly. Tuberculosis LNs may show central necrosis while diffuse granulomas from diseases such as cat-scratch disease or sarcoidosis are non-destructive. A focal necrosis can be seen in malignant lymph nodes as well 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 a thin hilum or none at all. They may have a rich and regular vasculature [Figure 12]. The diagnosis must be confirmed by core biopsy or lymphadenectomy.

Figure 12 Sarcoidosis in a lymph node of the left groin (B-mode, a) and colour Doppler imaging (b).

a



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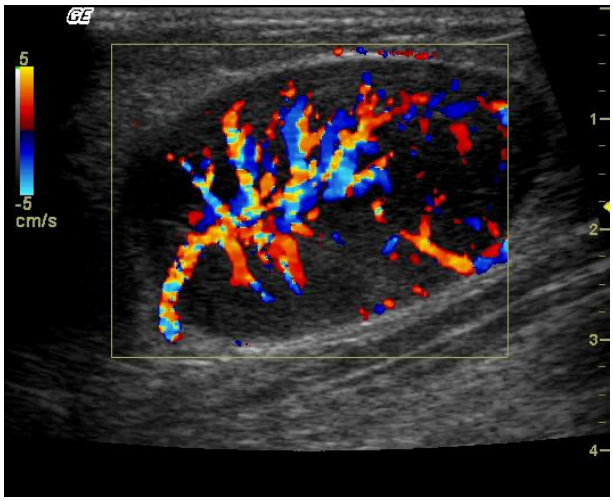


Imaging of reactive vs. neoplastic lymph nodes

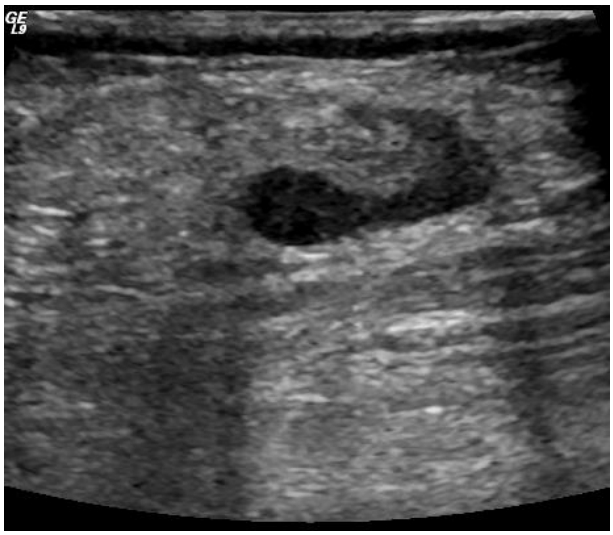
Reactive lymphadenopathy is a non-neoplastic enlargement in response to antigenic stimuli. Clinically reactive lymph nodes are tender and mobile. Depending on the cellular response three histological types can be differentiated: a follicular hyperplasia is most common (differential diagnoses are rheumatoid 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 hemophagocytes and sinus histiocytosis is also seen.

Infectious material arriving via one or a few afferent lymphatic vessels may 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 hypervascularisation. [Figure 13]. As focal cortical thickening is also highly suspicious of tumour invasion, a biopsy will in most cases be recommended [Figures 10, 15, 17]. Viral infection will enlarge the whole LN, but the vessel architecture will not be destroyed. Necrotic LN due to inflammation is -except in tuberculosis- a rare complication and is mostly seen in immune incompetent patients. Ahuja [9] described tuberculous lymph nodes with varied vascular pattern, simulating both benign and malignant conditions, as a central necrosis and perfusion in the periphery will be found in both tumour types.

Figure 13 Inflammatory focal thickening of a lymph node in the left groin, due to a Bartolini abscess (a, b). Note the regular vascularization of the regional thickened cortex (c). Round shaped LN right groin with tree-like branching arteries, biopsy proved mononucleosis in a 22 years old female patient.

a



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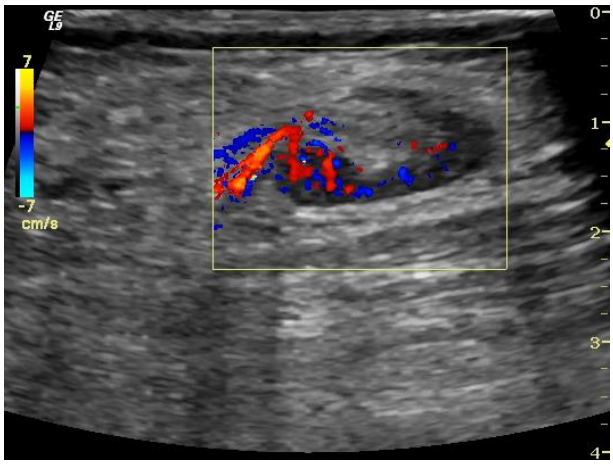


c

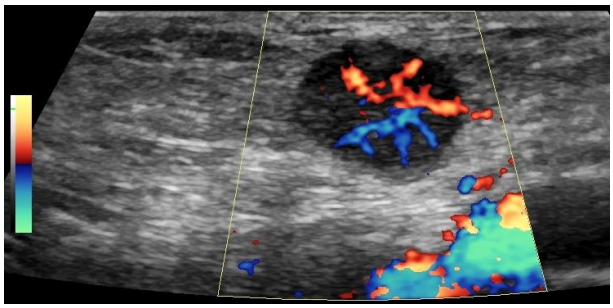
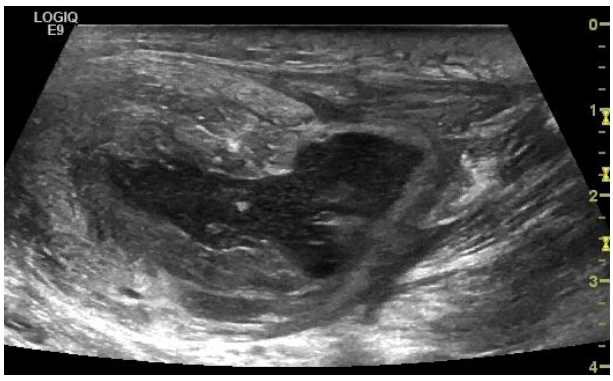


Figure 14 Lymph node abscess in an immune incompetent patient. B-mode image with central fluid and some scatters (a). CEUS proves a hyperperfusion of the cortex and a non-viable center (b). Fine needle aspiration showed pus; the aspirated volume was refilled by contrast agent (c). No fistula after contrast injection could be imaged.

a



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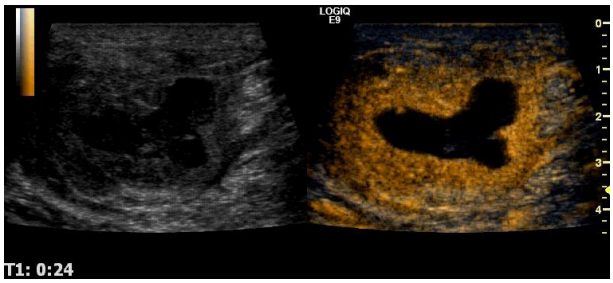
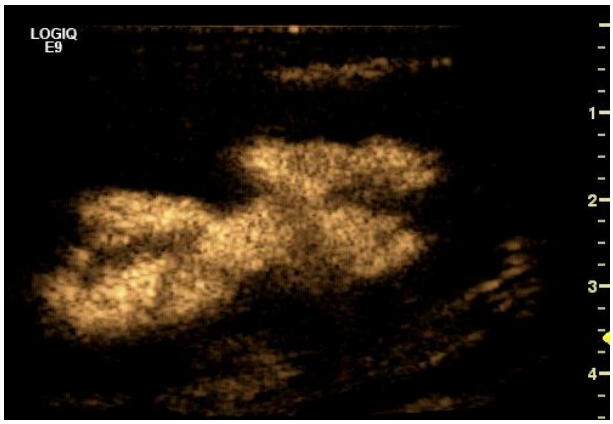


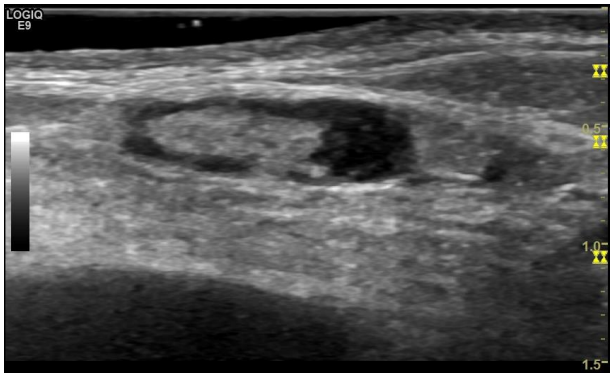
c



Reactive lymph nodes may be also be caused by local infection or immune therapy (like Interferon) which may induce a hypervascularity in colour Doppler or CEUS [Figure 15]

Figure 15 Reactive lymph node with an echo-poor round shaped area of 3mm at the lower pole (left groin) (a). Colour and PW Doppler shows a high vascularity with tiny intranodal arteries and veins (RI: 0.60), which is uncommon in metastatic infiltration (b). An ultrasound-guided fine needle aspirate proved its inflammatory character (c).

a



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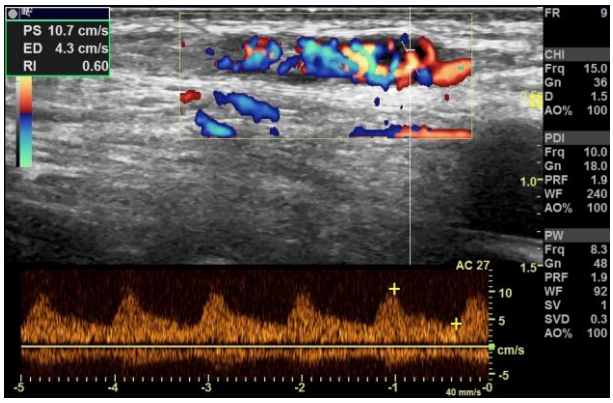


c

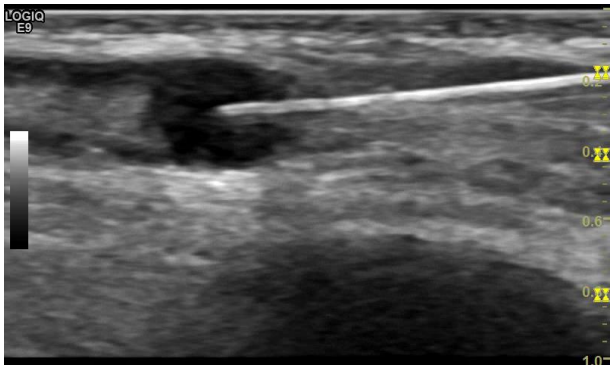
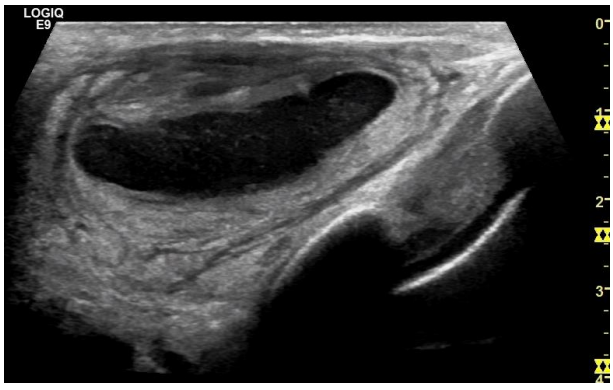


Figure 16 **A 82 year old female with a palpable indolent mass in the armpit. B-Mode showed an unclear delineated lymph node with an echofree centre (a). On B-Flow the centre showed a regular vascularity (b), histology (core biopsy) proved a T-cell lymphoma**

a



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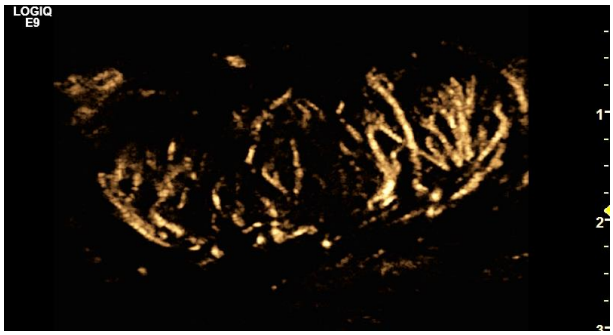
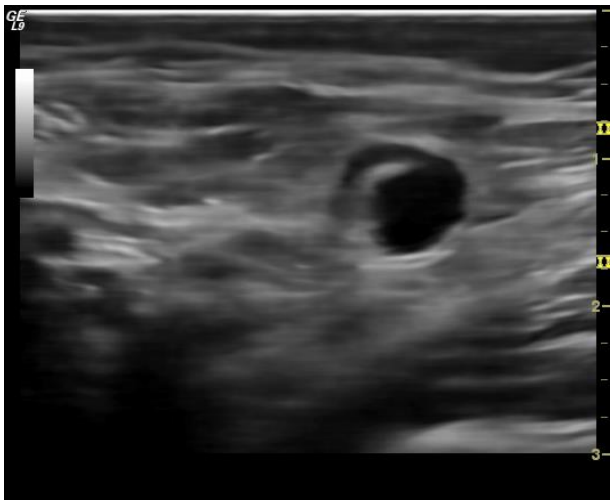


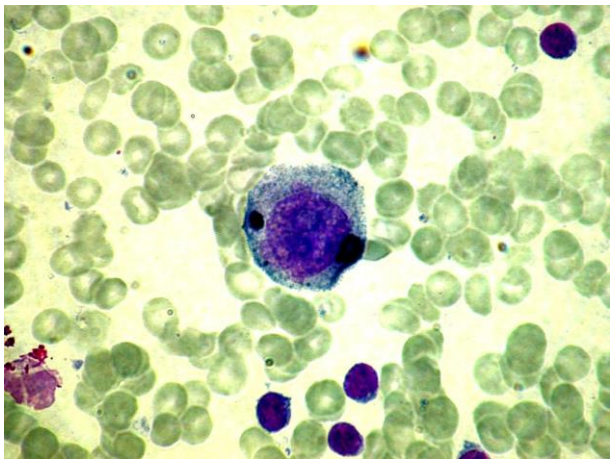
Regional cortical thickening, especially when round shaped, may be caused by a lymphatic or hematogenous spread of tumour cells via afferent lymphatic or blood vessels and start to grow where they first enter the cortex [Figure 17]. A nodular thickening of the cortex is highly suspicious for metastatic spread or involvement in Hodgkin's, Non-Hodgkin's disease or lymphatic spread of cancerous tumours [Figure 18, 19].

Figure 17 A 6mm metastatic nodule of a melanoma in a lymph node of the left groin (a). Cytologic image (b) and histologic specimen (c).

a



b



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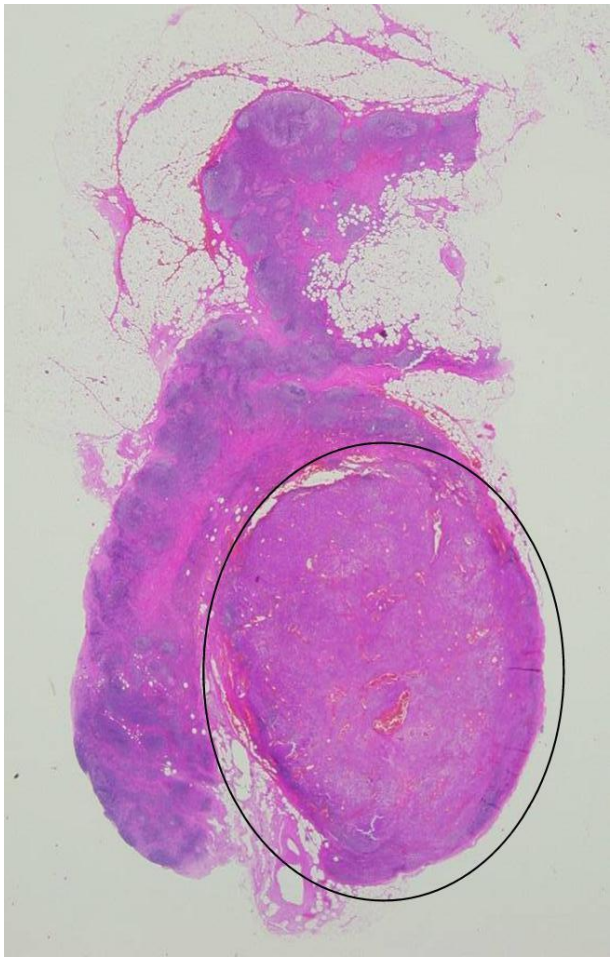
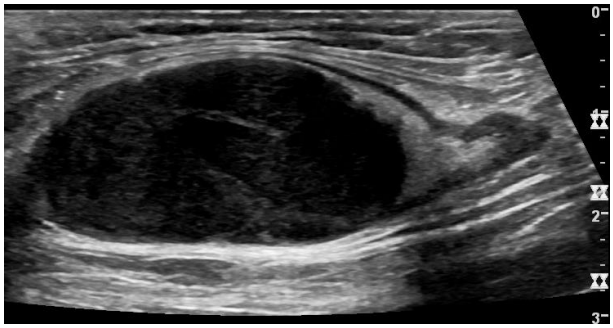


Figure 18 **Echo-poor thickening of the upper pole of a LN in the groin (a). Core biopsy (14G) proved a Hodgkin disease. Supplying vessels arise from the capsule (b, Colour Doppler). LN metastasis from a liposarcoma in right groin (c, d). The**

lower part seems not to be infiltrated (c). On CFI radiating arteries arising from the capsule, but in the lower part vessels seem to have a regular architecture.

a



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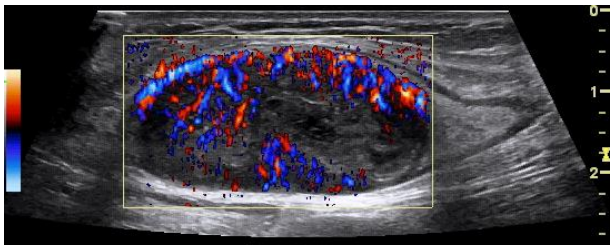
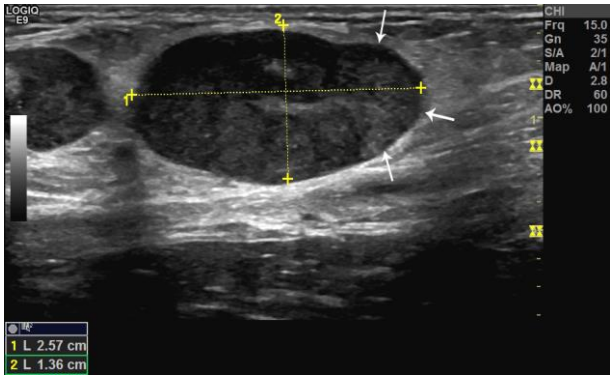


c



d

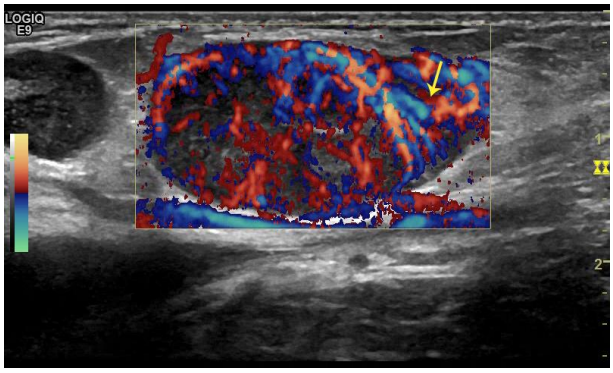
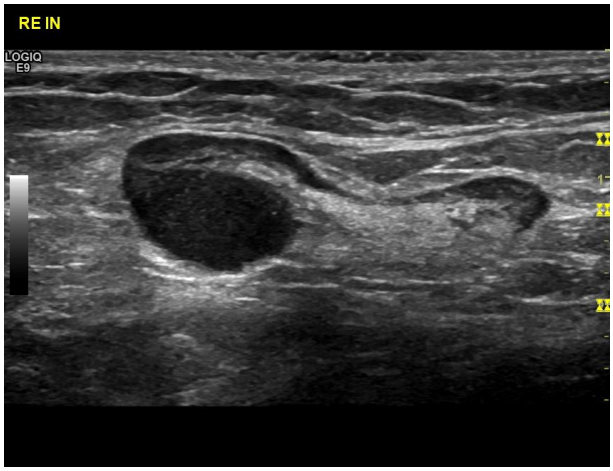


Figure 19 Echo-poor tumour of the upper pole in an inguinal LN (a). Colour Doppler demonstrates regular branching of arteries (b). Histology proved a regional NHL infiltration.

a



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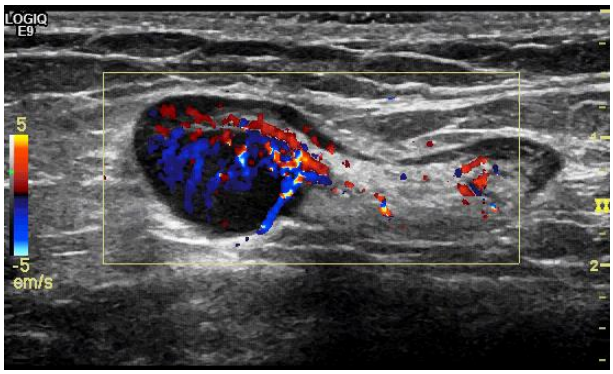
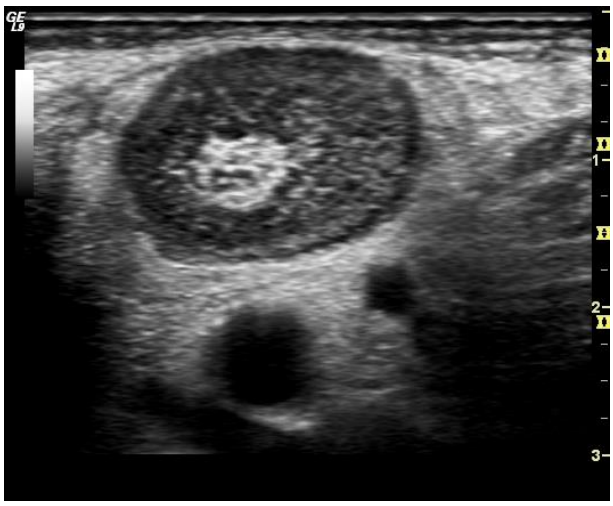


Patients undergoing interferon treatment may also develop echo-poor, round-shaped lymph nodes [Figures 2]. Over time reactive lymph nodes age and fatty involution changes the lymph node appearance [Figures 8]. Sometimes enlarged follicles within the cortex can be seen. It may be caused by inflammation [Figures 2]. In indolent non-Hodgkin's lymphoma tiny numerous echo-poor spots within the thickened cortex can be detected as well [Figures 20, 42]. Owing to the underlying disease (acute lymphadenitis or lymphomas) the echogenic centre of the lymph node gets more echo-poor [Figures 12, 13] the echogenic centre shrinks.

Figure 20 B-mode images of lymph nodes follicle B-cell lymphomas (a). Note the cortical echo-poor tiny spot like lesions can also be seen in the abdomen (liver hilum) and subhepatic area (b, c).

a



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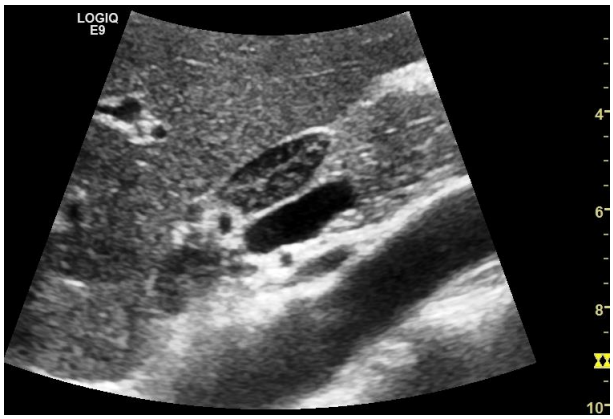

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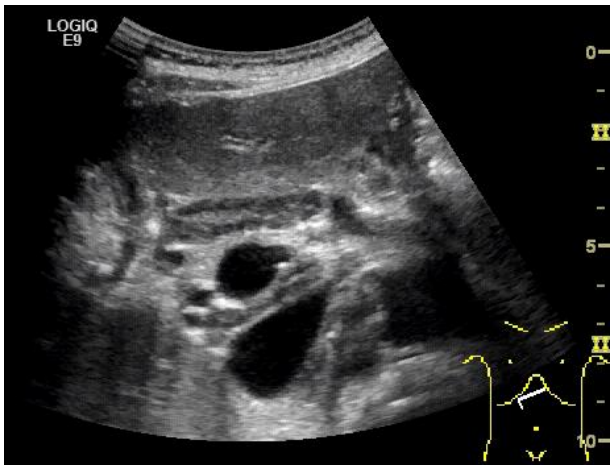
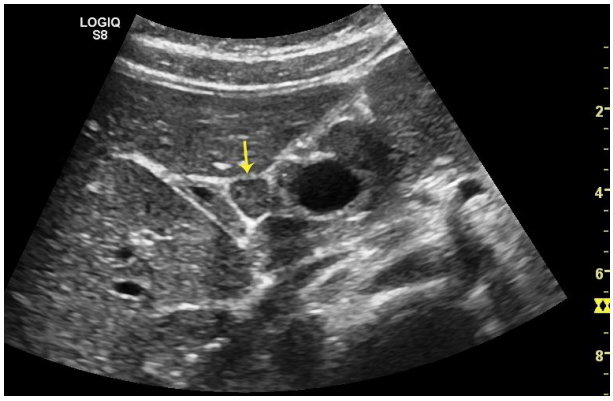


Due to a lower spatial resolution and sound attenuation it will make it much more difficult to image the normal architecture in abdominal lymph nodes [Figures 20]. In colour Doppler imaging the vascular supply of a reactive lymph node can be followed from the hilum towards the cortex. Red and blue coded adjacent vessels indicate arterial supply and venous drainage [Figures 2, 6, 12, 13, 15, 29]. Usually colour Doppler ultrasound will overestimate the size of the tiny vessels and, in this situation, B-Flow or SMI will have a higher spatial resolution. The supplying vessels may not only enter from the hilum but sometimes they also migrate through the cortex [Figure 2].

The vessel architecture of abdominal LNs can be imaged as well, if the contrast setting provides a high spatial and time resolution. A regular branching of vessels plus a centrifugal direction of enhancement indicates a benign reactive LN [Figure 2], whereas a peripheral enhancement with low or absent central enhancement is highly suspicious for malignancy, independent of the flow detection technique applied [Figures 22, 23, 28, 29, 31, 33, 34]

Figure 21 Lymph node in the hilum of the liver in a patient cholecystitis (arrow in a, b) and chronic hepatitis (c, d). CFI shows a central supplying artery (b), while CEUS demonstrates a central artery branching towards the periphery (c). During late phase the LN has been washed out from contrast material (d).

a



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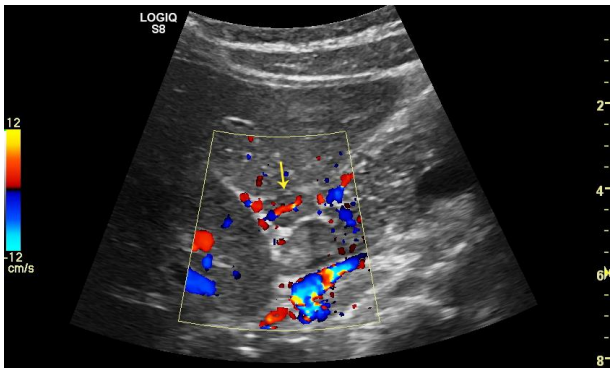
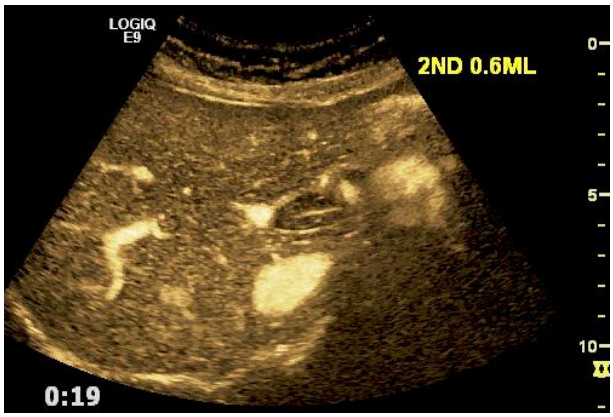


c



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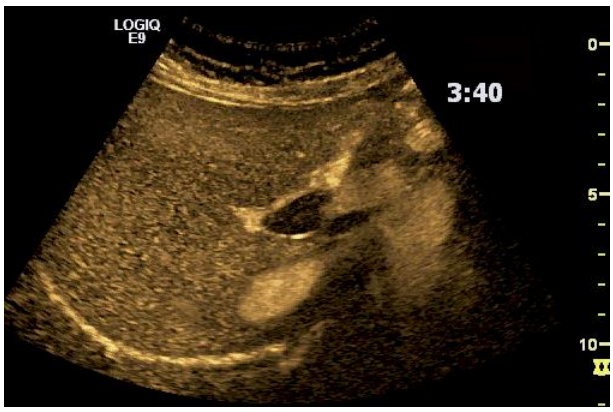
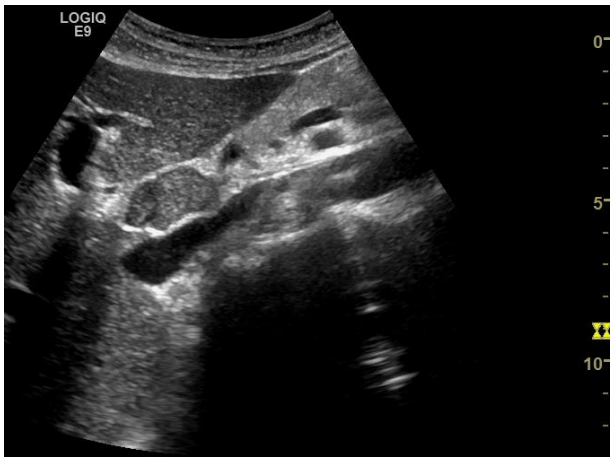


Figure 22 **Two LN metastases of the liver hilum on B-Mode (a) and during the arterial phase after bolus injection of 1.6mL Sonovue (b). Note the rim enhancement that lasted only for about 10s, before washing out (45y old patient with a hepatic metastasis in Stage IVa of breast cancer).**

a



b

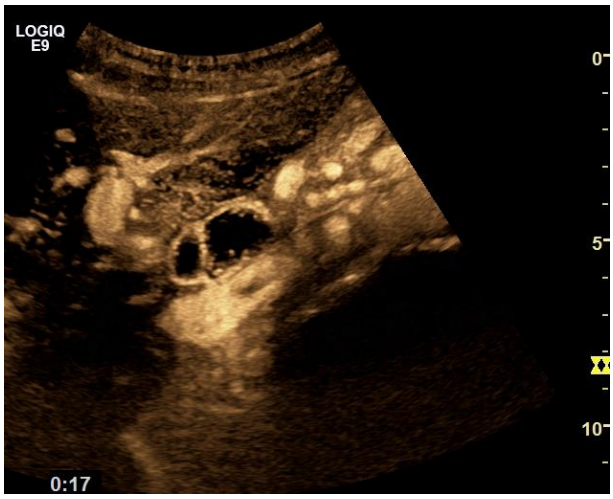
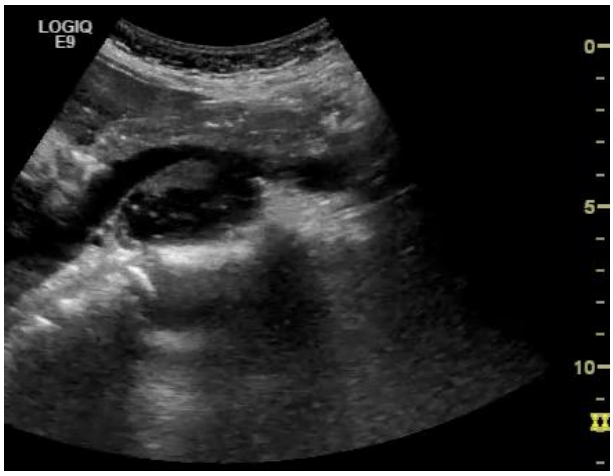


Figure 23 Pericaval lymph node metastasis from an urothelial tumour (a). CEUS proved a hypoperfused LN indicating a high interstitial intranodal pressure (32s post contrast injection, b).

a



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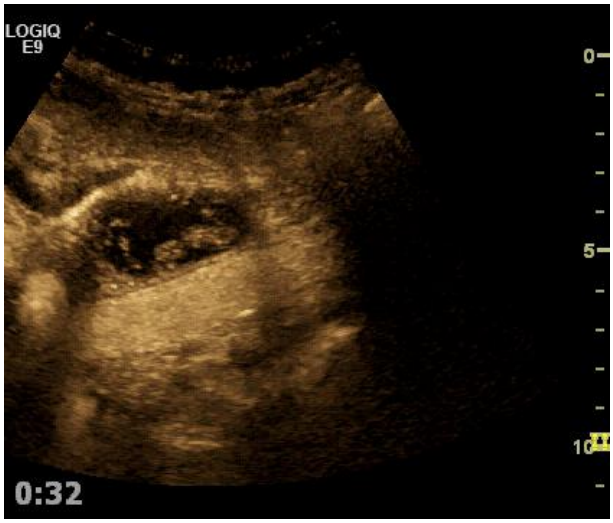


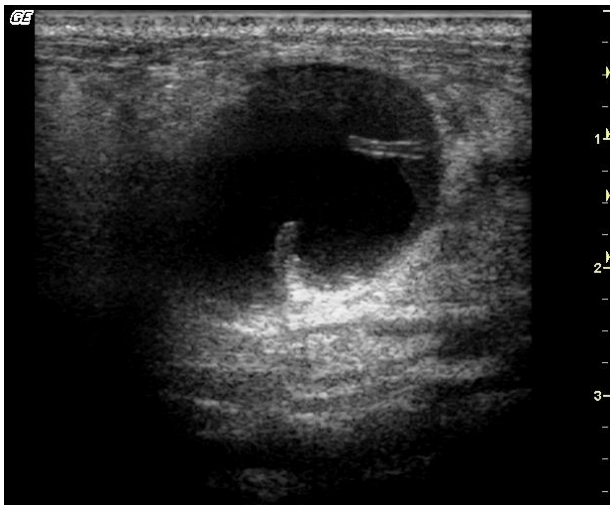
Differential diagnoses

The branchial cleft cysts of the neck may be misinterpreted as an enlarged lymph node. They are avascular, have a cystic or echo-poor appearance and sometimes have tiny echoes that move with the direction of sound beam or when pressure is exerted on the cyst [Figure 24]. They may change in size and echogenicity.

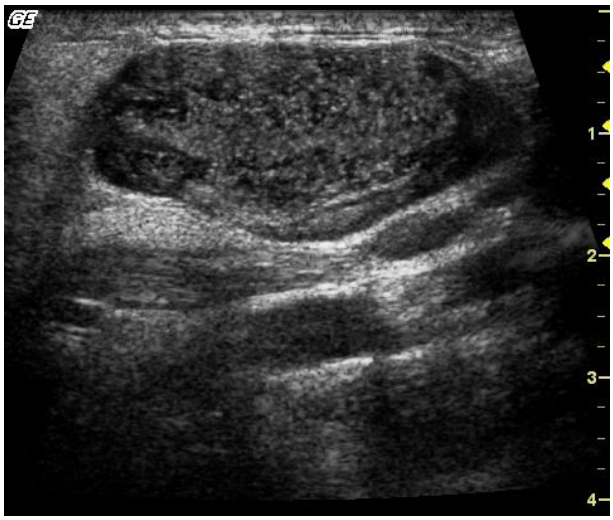
Figure 24 A cystic (a) and more echogenic branchial cleft cyst (b), the latter showing downwards moving echoes when scanning. As the fluid is rather thick, a bigger

needle is needed for successful puncture, but surgery may remain the preferred option.

a



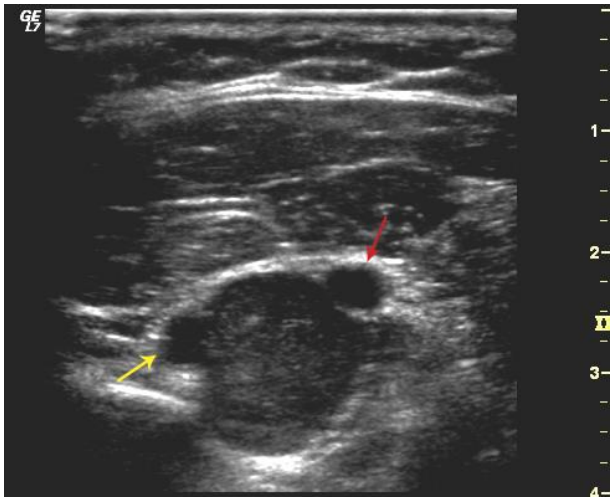
b



Another differential diagnosis of a single mass in the neck that is found between the Internal Carotid Artery and External Carotid Artery is a glomus tumour, which is echo-poor, has a rich vasculature and has the typical location shown in [Figure 25], neuroma [Figure 27] or lateral neck cysts [Figure 24].

Figure 25 Glomus tumour at the carotid bifurcation (a). Colour Doppler shows a rich vasculature (b).

a



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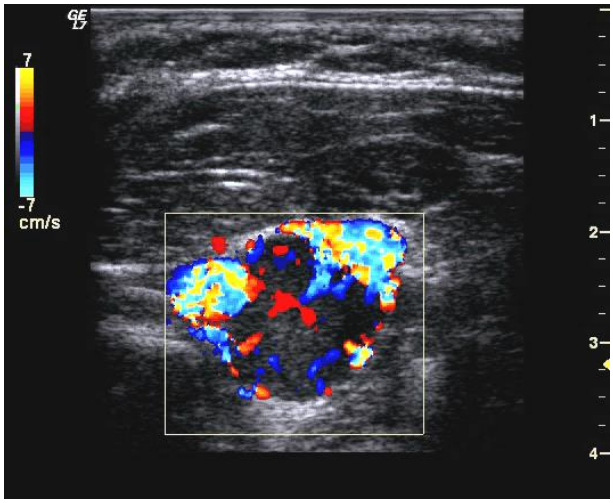


The differential diagnoses for a palpable mass in the inguinal region include inguinal hernia, undescended testicle [Figure 26], post-operative seroma and haematoma.

Figure 26 Small undescended testicle right groin on B-mode image (a). CDI showing a few corkscrew like peripheral arteries (b).

a

b

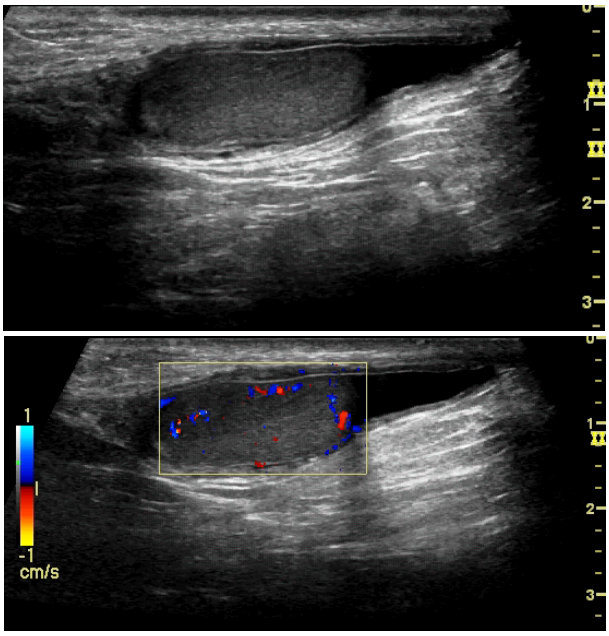
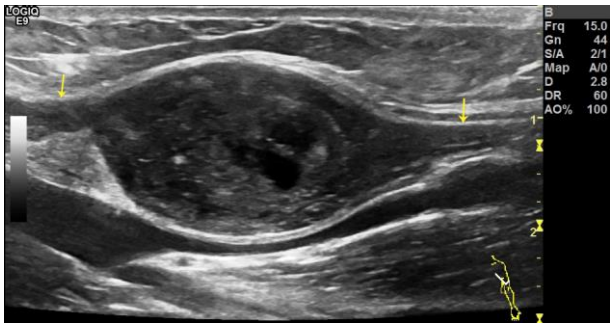


Figure 27 shows the image of a neuroma that developed in the course of a nerve associated with local tenderness.

Figure 27 Neuroma of left upper arm in a 72 years old female in the course of the thickened nerve yellow arrow, a). Colour Doppler detects the supplying corkscrew artery (b).

a



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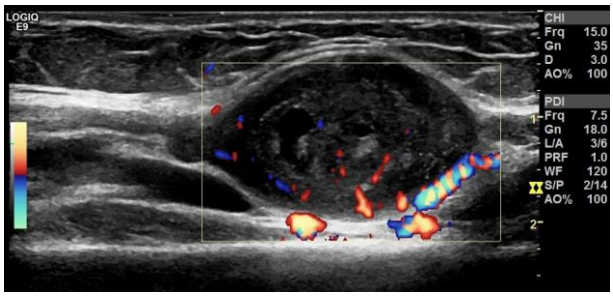
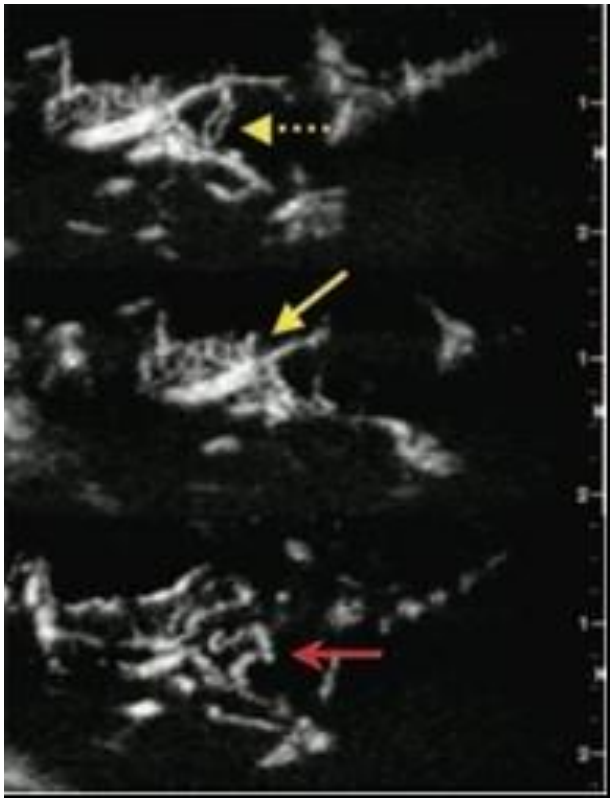


How ultrasound helps in characterizing lymph nodes: Which are the valuable criteria for differentiating?

In order to better characterize lymph nodes, it is mandatory to look not only at B-mode criteria but image their intranodal vessels as well: Reactive and Non Hodgkin Lymphoma (LHN) LN have a preserved vessel architecture: Artery and vein have a tree like branching from the hilum towards to capsule. In metastatic LN a chaotic vessel architecture will be found, often central vessels are absent, sometimes supplying vessels arise from branching capsule arteries [Figure 28, 29, 33, 34]. Using US contrast agents, the direction of enhancement (centripetal from the periphery to the centre in malignant LN or centrifugal in reactive or NHL LN), may help to better characterize LN. In general, malignant tumours have a higher vessel density, which may account for up to 10% of the tumour volume. In contrast to colour Doppler, CEUS is capable of imaging the vessel density, especially when using a time intensity analysis software. The vessel density may be heterogenous in malignant lymph node. Tumour vessels often have arteriovenous shunts: Pulse wave Doppler spectrum show a slow rise time and a low Resistive Index (RI) number of the supplying artery split [Figure 31, 32]. Tumour vessels are imperfect, their size may change, arteries may have a torturous course and AV shunts are quite common. Therefore, resistive index measurement of a single intranodal artery will not be representative of the peripheral resistance in the whole lymphatic arterial system [Figure 31]. Different RI numbers of more than 2 intranodal arteries characterize a LN metastasis better than a RI number from a single artery. Intranodal AV shunts are more reliable distinguishing malignant from reactive LN [Figure 32].

Figure 28 Evaluation of the tumour vasculature of a subclavicular lymph node metastasis from a renal cell carcinoma using B-Flow technique. B-Flow demonstrates split arteries (dotted arrow), different density of vessel network (yellow arrow), sudden change in vessel diameter, winding arteries with irregular branching (red arrow).

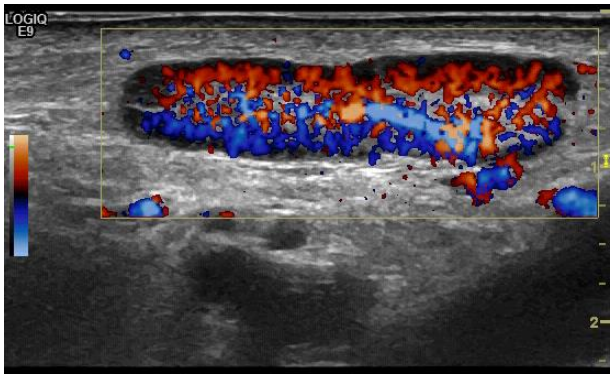


Tumour vessels have no muscle layer and poorly functioning or even no pericytes. Their wall is characterised by varying pores sizes. Within one tumour, pore sizes range from 200 nm to 1.2 µm. [13]. Owing to these pores and their widths, fluid will leak into the interstitium, thus increasing the intra-tumoural pressure, leading to ischaemia, thus stimulating neo-angiogenesis. If a LN has an intact capsule, the intranodal pressure will rise. When intranodular pressure rises, arterial RI will also rise, small veins will be compressed and are no longer detected on colour Doppler. Only peripheral, larger draining veins will be seen in the lymph nodes [Figure 29]. At this stage intratumoural ischaemia will develop. With a further rise in pressure intratumoural arteries can be missed, first when using Colour Doppler, and with higher sensitivity on contrast studies [Figure 34]. Ahuja reported that peripheral vascularity is not found in normal or reactive nodes, and the presence of

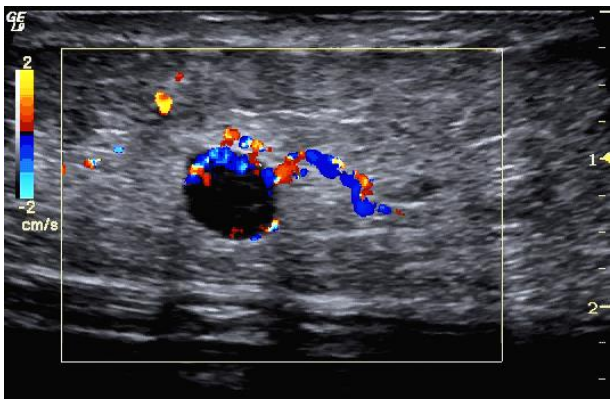
peripheral vascularity, regardless of sole peripheral or mixed vascularity is highly suspicious of malignancy [1, 11-13], This also explains why chemotherapy will not reach the central part of a LN metastasis [14-17]. As soon as there is a high demand on blood supply, arteries may branch from a capsule artery in the lymph node [Figure 29]. It is highly suspicious for malignancy (carcinoma or NHL) but it can sometimes also be imaged in patients under immune therapy.

Figure 29 Palpable LN in the right groin with a thickened echo-poor cortex and hypervascularity in a patient with neurodermitis (a). A 8 mm lymph node metastasis with vessels in the periphery of the lymph node (melanoma, b). A 20 mm oval shaped lymph node metastasis from a melanoma with supplying vessels arising from a capsule artery (c).

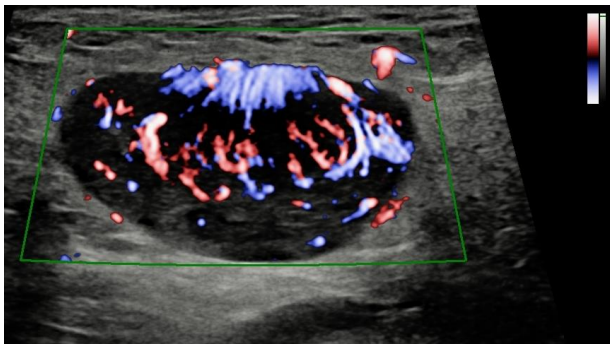
a



b



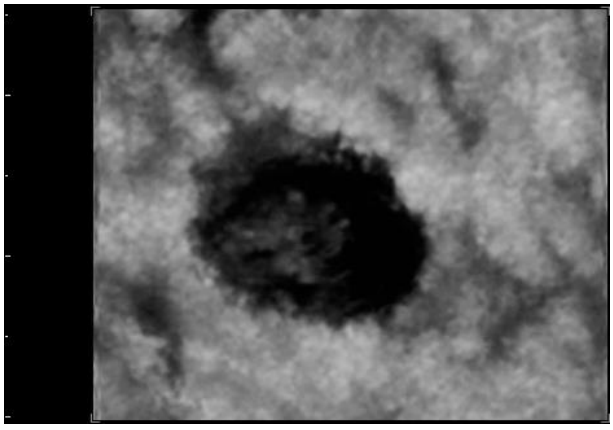
c



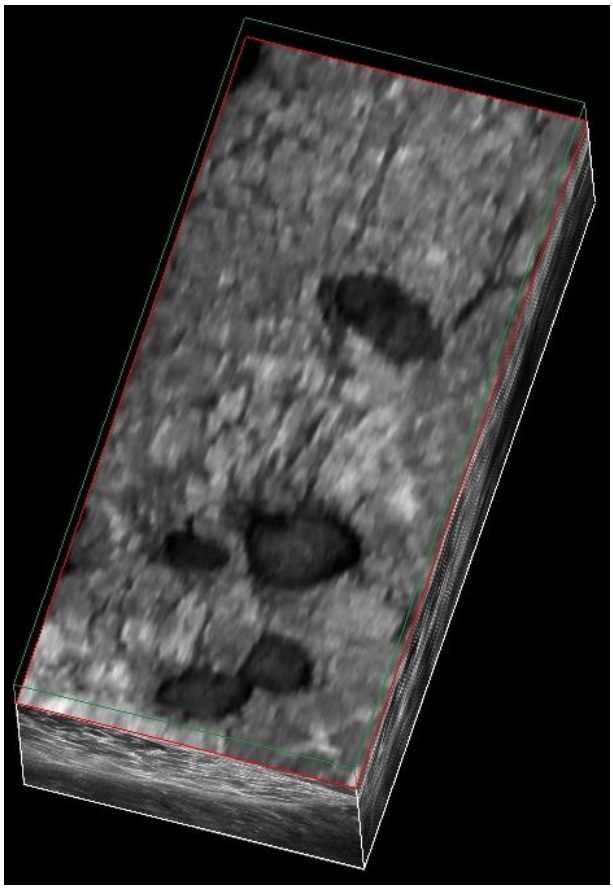
As soon as the capsule is infiltrated or destroyed by the tumour, the interstitial fluid leaks out of the LN causing an oedema of the surrounding fatty tissue [Figure 30]. The RI will then decrease again, and colour Doppler detects intranodular vasculature again.

Figure 30 C-plane images of a superficial lymph node with a destroyed capsule. (a), Due to a high interstitial pressure fluid is leaking out of LN metastases (b).

a



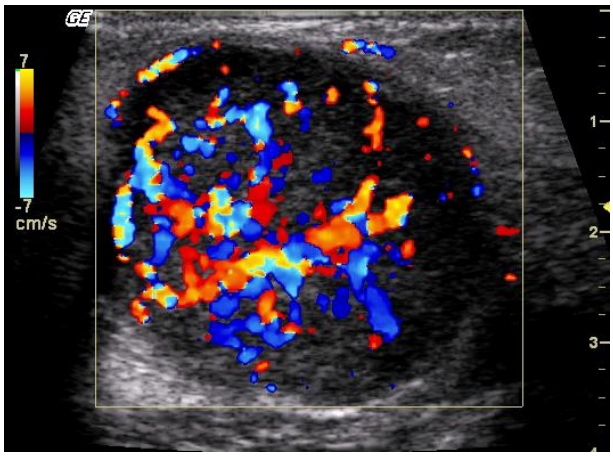
b



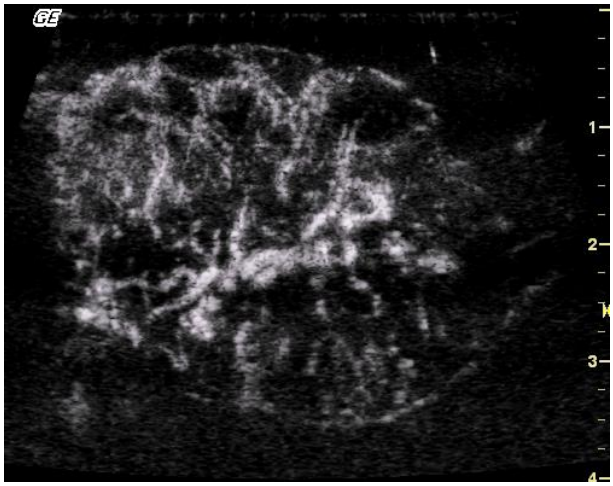
If a surgical intervention is planned, this finding must be considered as the volume of resected tissue has to be bigger. It is well known that metastatic nodes have a higher RI and PI compared to reactive nodes [1, 12, 18-20]. Colour Doppler or B-Flow imaging can already depict the change of vascularity during systole and diastole. B-flow can also characterise the intra-nodal tumour vessels [Figure 31].

Figure 31 Vasculature of a lymph node metastasis imaged in CFI (a) and B-flow during systole (b) and a reduced flow during diastole (c). B-Flow shows a different vessel density and sudden changes in diameter. On PW Doppler RI number change from 0.58 to 0.80 (d, e), the low RI number probably caused by AV shunts.

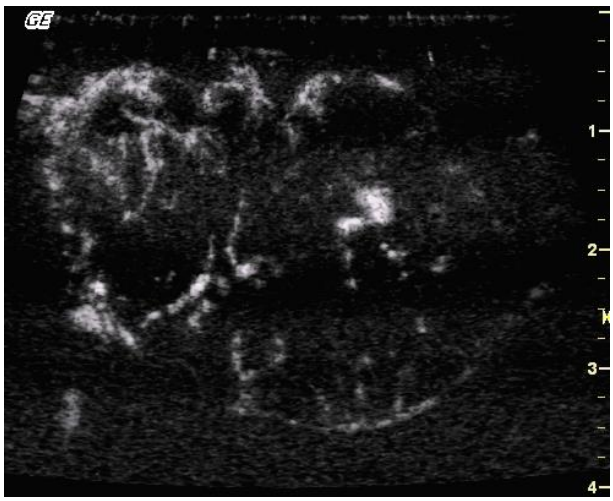
a



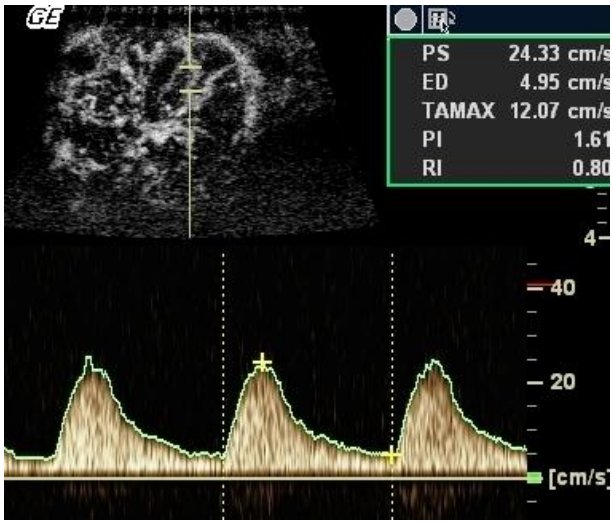
b



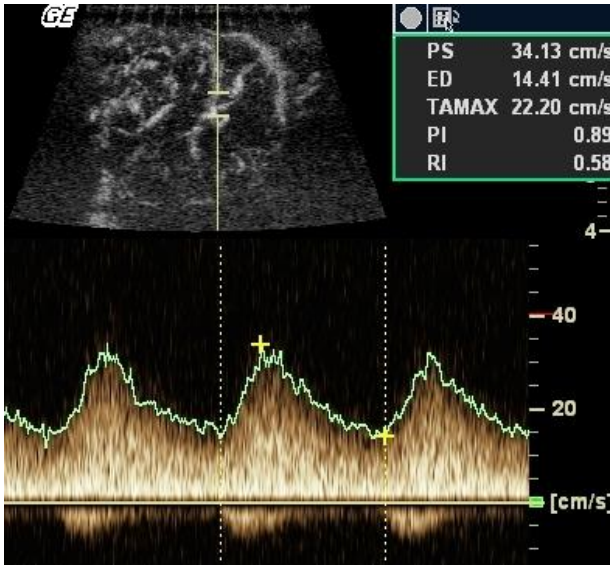
c



d



e



In highly differentiated tumours a rich intra tumoural vasculature can be found. They often mirror the vascularity of the primary tumour. Hyper vascularised lymph nodes are found in patients with thyroid, ovarian, breast, sarcoma, neuroendocrine or renal cell cancer, as well as other highly vascular tumours. Unlike cutaneous melanoma, ultrasound in breast cancer carries a false-negative rate of up to 30% of nodes, which may have normal architecture but have tumour infiltration. With a primary tumour size ranging between 0.3 cm and 12cm (mean, 3 cm) 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

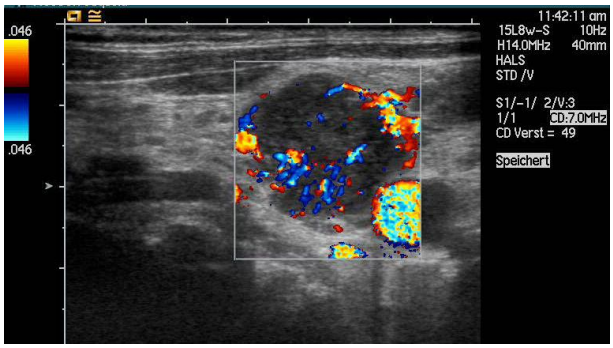
pattern (55.6%), or little to no perfusion (25.9%), whereas non-metastatic lymph nodes have been characterised by a centrifugal enhancement (56.0%) and a homogeneous pattern (80.0%). The difference between hyper- and hypovascular regions was higher in metastatic lymph nodes than in non-metastatic ones ($p < 0,0001$). 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].

The direction of enhancement during wash in phase (centrifugal, centripetal) and the uniform distribution of tumour enhancement are important criteria in characterizing LN pathology on CEUS [21]. Heterogenous enhancement, perfusion defects or a non-perfused centre are highly suspicious for malignant transformation [22, 23] [Figures 33-34]. Important exceptions are abscesses or caseating tuberculosis. As LN are solely supplied by arteries, the detection of the direction of contrast enhancement it an important criterion. Therefore a contrast setting with the highest time resolution is mandatory, especially in smaller LN (>20 fps). Washing out is not a reliable criterion for malignancy. In tumours with a low intranodal pressure or a destroyed capsule the duration of enhancement will last longer.

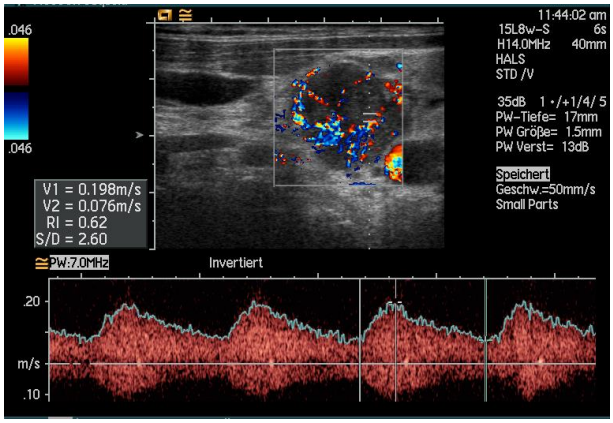
Often a discrepancy between colour Doppler and CEUS will be seen in terms of imaging vessel or microvessel distribution [Figure 32]. Colour Doppler is suitable for detection of larger vessels with a relatively high-volume flow, while areas with a low intravascular volume flow and tiny vessels will show no Doppler signals. CEUS on the other hand will enhance the microvasculature independent of flow velocity and vessel size. Figure 33 demonstrate a minimal heterogenous contrast enhancement of the LN with tiny hypoenhanced areas.

Figure 32 Lymph node metastasis of the neck (from lung cancer). Note that the CFL image shows an heterogenous vessel distribution with vessel spared areas (a), on PW Doppler a slow systolic upstroke rise (b) while CEUS shows a homogeneous enhancement during the arterial phase with tiny less enhanced spots (c, d), and washing out at the end of the arterial phase (e). The enhancement did not show a centrifugal progression but started nearly at the same time, but a bit heterogenous (CEUS images 18s, 22s and 31s after bolus injection of 2.4 mL SonoVue).

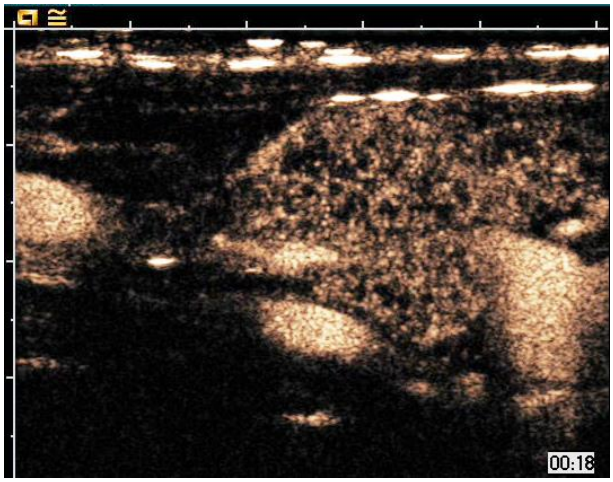
a


.046
.046
11:42:11 am
15L8w-S 10Hz
H14.0MHz 40mm
HALS
STD /V
S1/-1/ 2/V:3
1/1 CD:7.0MHz
CD Verst = 49
Speichert

b


.046
.046
11:44:02 am
15L8w-S 6s
H14.0MHz 40mm
HALS
STD /V
35dB 1 •/+1/4/ 5
PW-Tiefe= 17mm
PW Größe= 1.5mm
PW Verst= 13dB
Speichert
Geschw.=50mm/s
Small Parts
V1 = 0.198m/s
V2 = 0.076m/s
RI = 0.62
S/D = 2.60
PW:7.0MHz
Invertiert
.20
m/s
.10

c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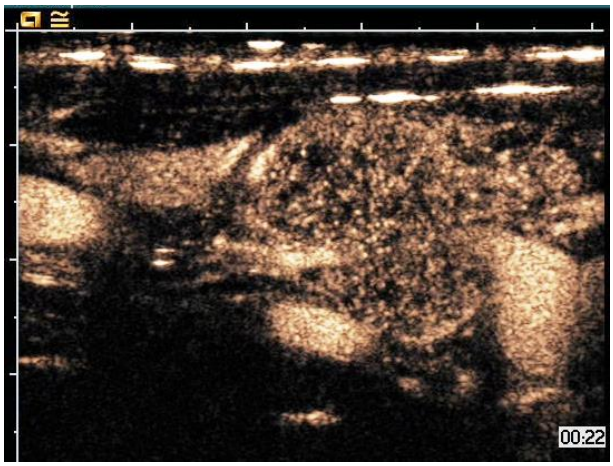
d



e

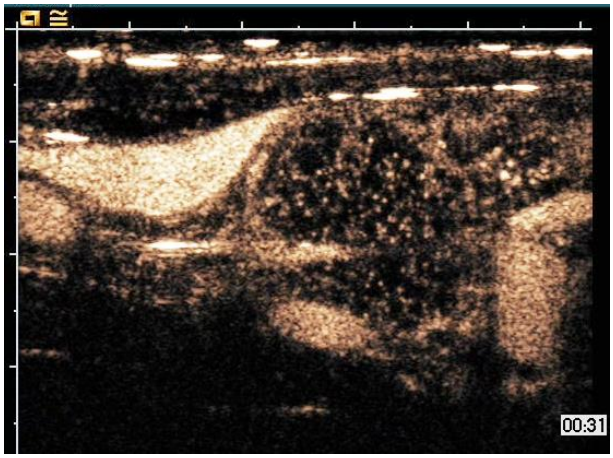
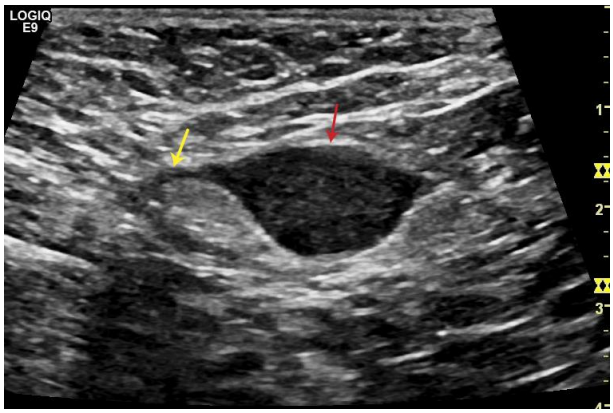
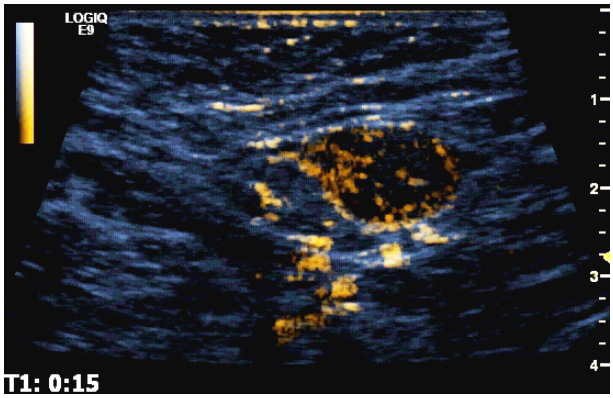


Figure 33 Regional lymph node metastasis (melanoma, red arrow, a). The normal cortex (yellow arrow) as well as the cortical metastasis are enhanced (b). Probably due to high intra-nodular pressure on CEUS the centripetal enhancement starts in the periphery (b, c, hybrid contrast mode). Note the slow wash out over time (d at 58 s).

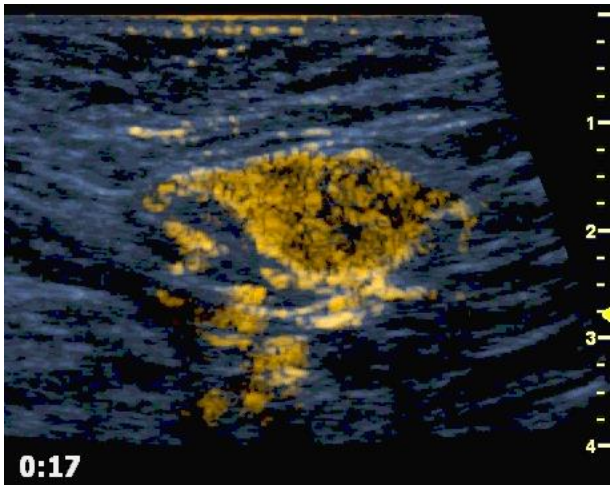
a



b



c



d

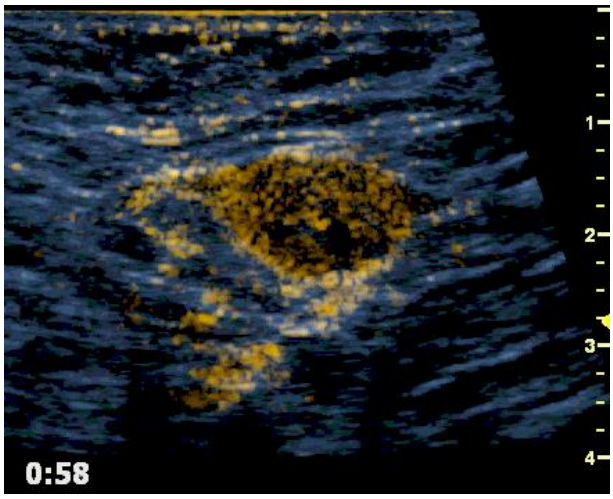
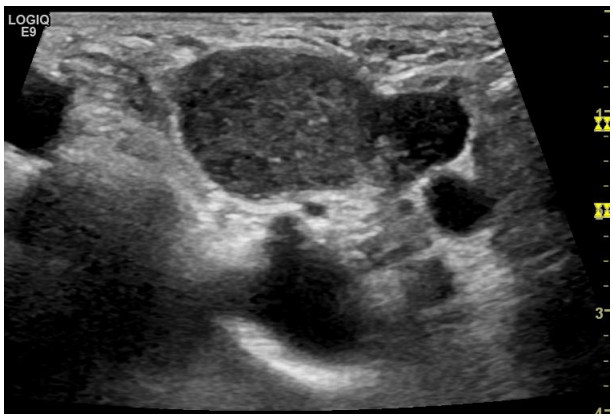
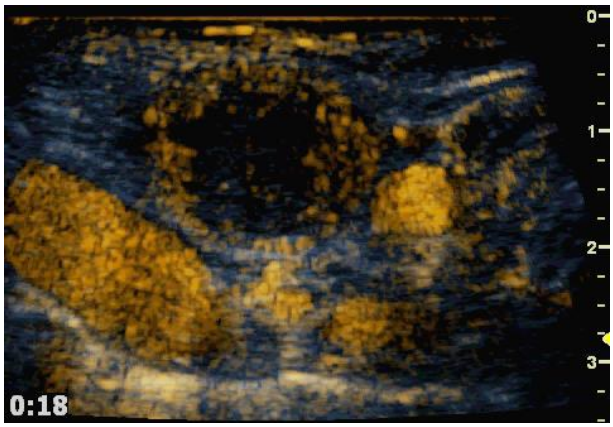


Figure 34 Centripetal enhancement of a lymph node metastasis with a central ischemia in the neck (Merkel cell carcinoma). B-mode image (a), 18s post contrast injection (1.6mL Sonovue) (b), 21s p.i. (c) and 29s p.i.(d) and slow washing out in the late phase.

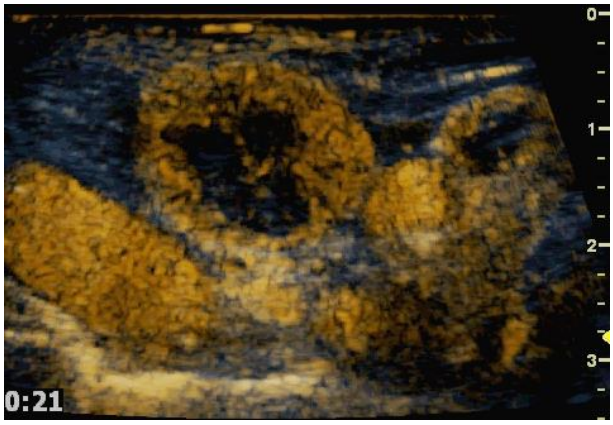
a



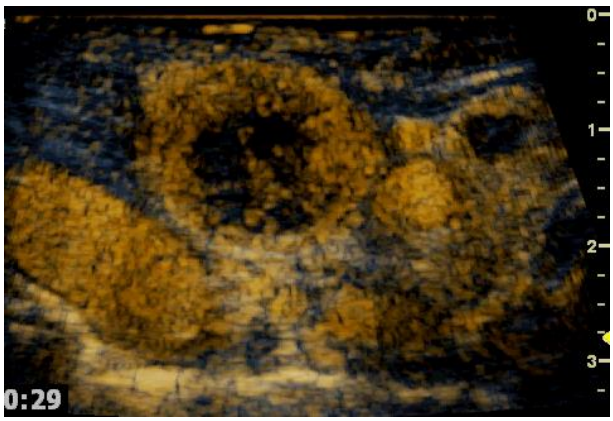
b



c



d



Follow up examinations

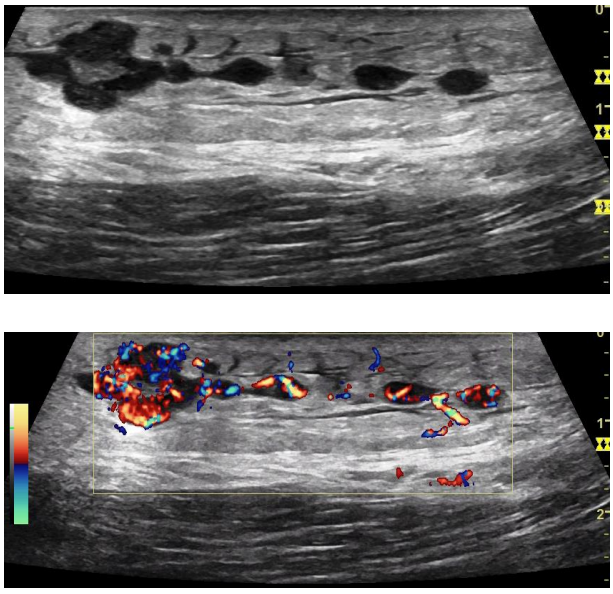
Transit metastasis, sentinel lymph node, local recurrence

A transit metastasis is, by definition, 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 sometimes be detected by the patient themselves [Figure 35]. Intracutaneous metastases from melanoma can be detected visually and do not require imaging.

Figure 35 Multiple hypervascularized transit metastases right thigh with local oedema from a melanoma of the lower leg (a, b).

a

b

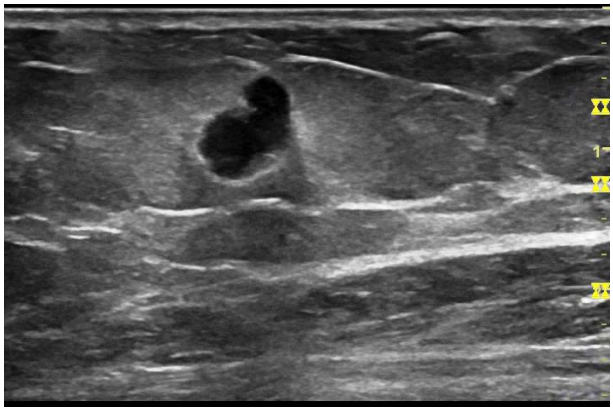


Conventional ultrasound is in most cases not able to detect the sentinel lymph node, and therefore other imaging modalities such as lymphoscintigraphy are the methods of choice, especially in breast cancer and melanoma. In the same way as lymphoscintigraphy, ultrasound contrast agents can be used to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

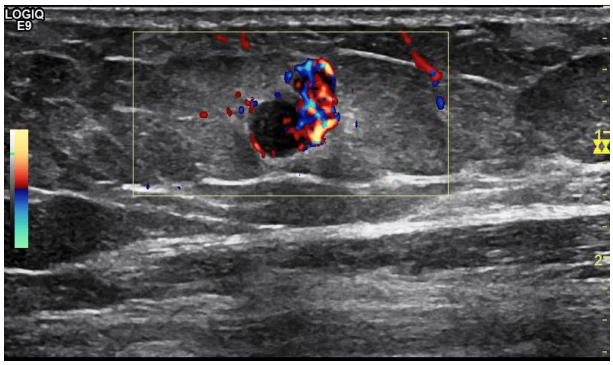
Especially in the follow up of patients with cutaneous malignancy, breast cancer or other superficial tumours, the scar must be carefully examined with high frequency probes [Figure 33]. Mechanical pressure by palpation or instruments used during surgery may promote a tumour cell dislocation and cause local recurrence [Figure 6, 30].

Figure 36 Upper arm transit metastasis from a melanoma right forearm. B-mode image (a). Colour Doppler (b). Note that the posterior part is much less vascularized. 17s p.i. the soft tissue metastasis looks a bit bigger on CEUS and only a little part of the posterior tumour is less enhanced (c). At 32s p.i. the wash out has started from the centre so only a rim enhancement can be detected at this time (d).

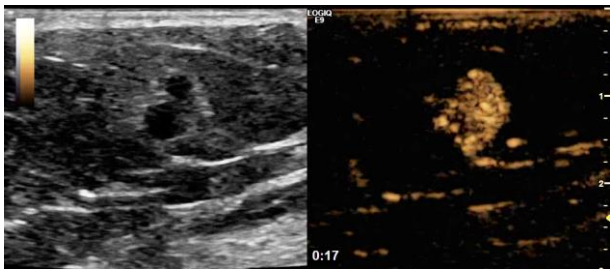
a



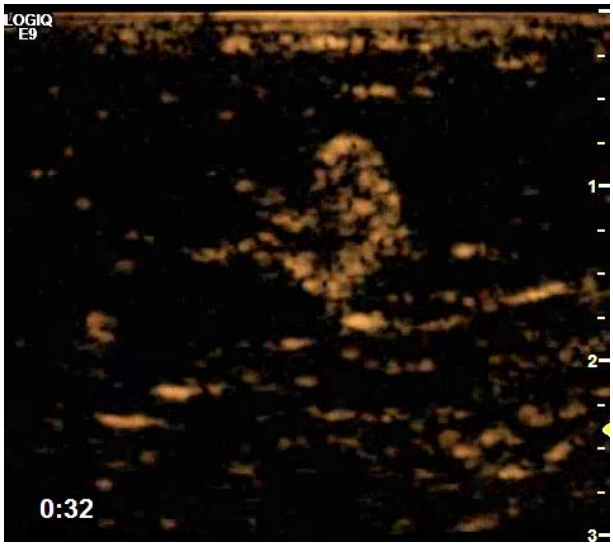
b



c



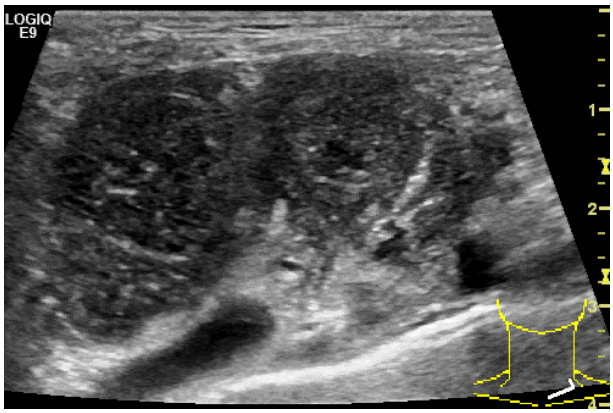
d



Lymph node vasculature is an indicator for response to chemo-, immune- or radiotherapy. In case of radiotherapy the surrounding tissue will develop a hyperaemia as well – like the skin [Figure 37].

Figure 37 41-year-old male with cutaneous T-cell lymphoma (Sezary disease) and lymph node involvement (two lymph nodes in the left axilla) before (a: B-mode, b: CEUS) and after radiation therapy (c). CEUS demonstrates hyper-perfusion of the LN before radiation therapy (b) but only hyper-perfusion of the surrounding fatty tissue after therapy (c).

a



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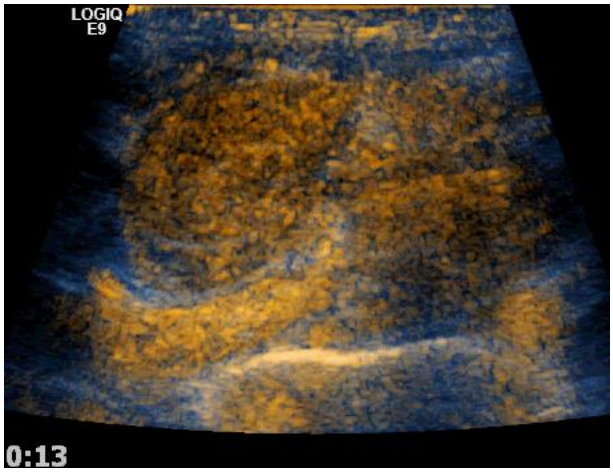
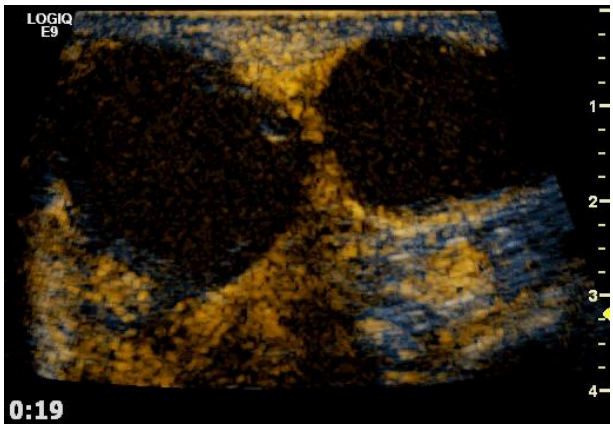


c

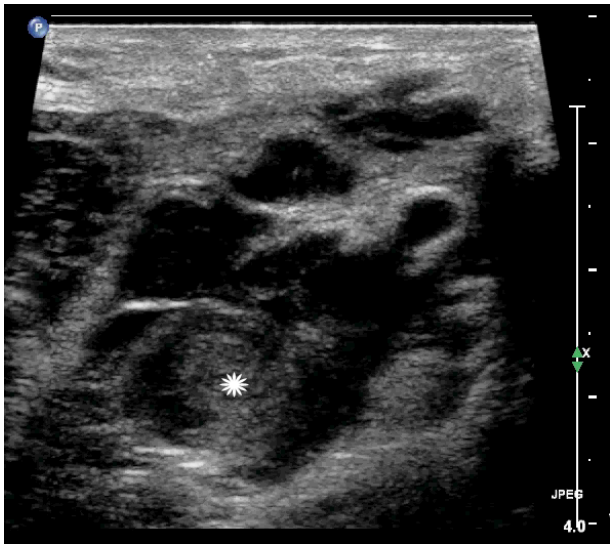


In a follow up examination of an axillary lymph node (Hodgkin disease) after chemotherapy CEUS can demonstrate presence or absence of intra-nodal blood flow. As tumour growth requires neovascularisation, CEUS can help to detect not only focal nodular tumour recurrence but also diffuse soft tissue infiltration, as it may occur after lymphadenectomy.

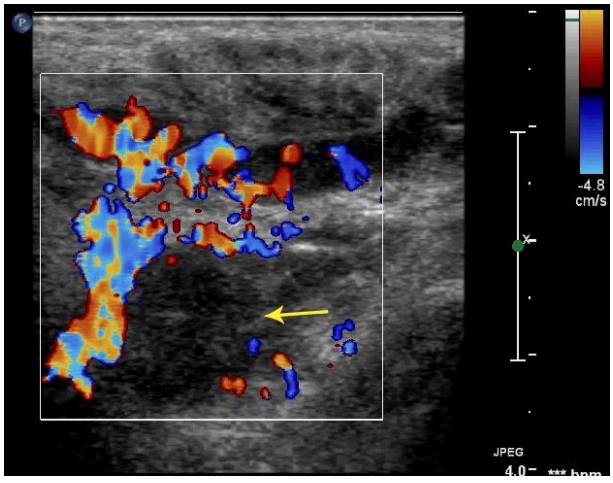
In the case of a diffuse tumour infiltration CEUS may help to navigate the needle into the area of hyperenhancement [Figures 38, 39]. The differential diagnosis of tumour infiltration is local inflammation.

Figure 38 Tumour infiltration left armpit 6 weeks after axillary lymphadenectomy because of a LN metastasis of a melanoma. a. Suspected tumour on B-Mode image (white star) (a), and Colour Doppler (yellow arrow) (b). On CEUS this area did not show any enhancement (c), instead the strongly enhanced area was core biopsied and proved diffuse tumour infiltration.

a



b



c

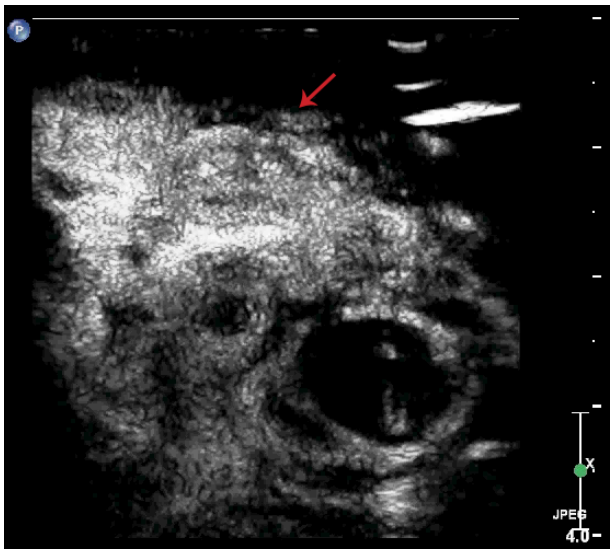
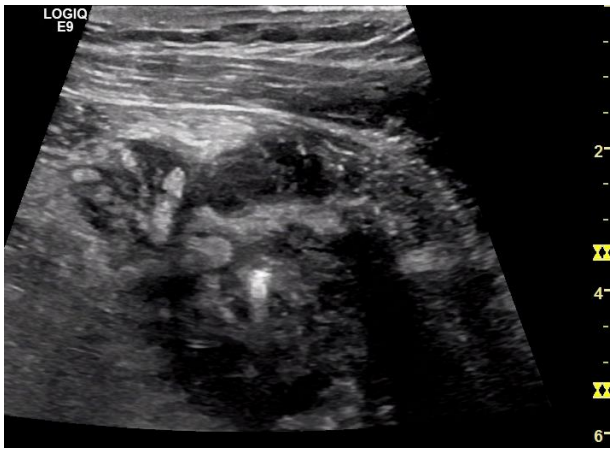
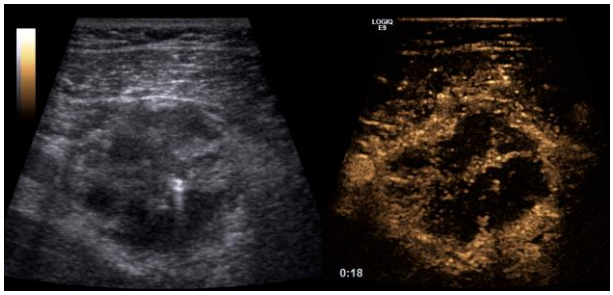


Figure 39 3 weeks after lymphadenectomy of an infraclavicular located LN metastasis (melanoma) a diffuse local tumor recurrence (a) was suspected on CEUS (b) and confirmed by core biopsy (c). Note the clip in the center of the operation area.

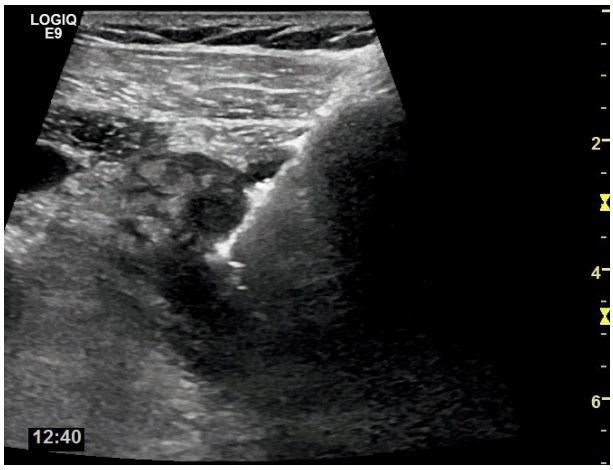
a



b



c

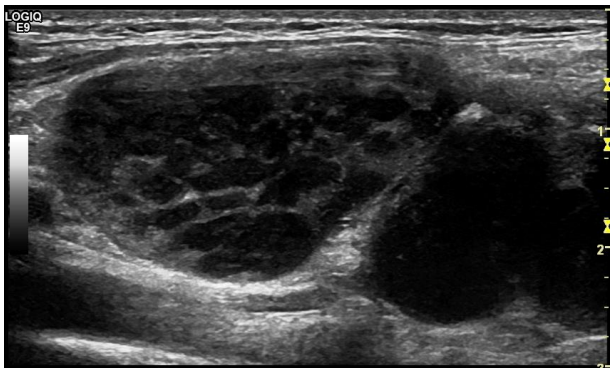


Lymph node appearance in Hodgkin and Non-Hodgkin diseases

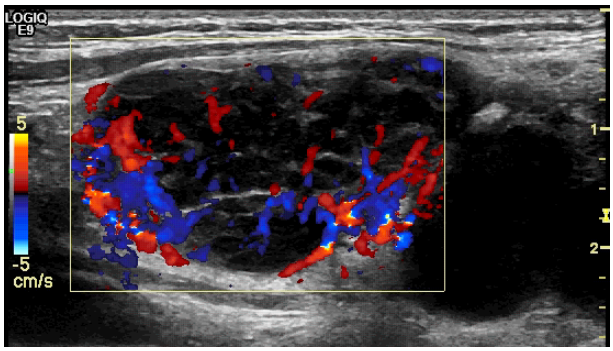
Lymphomas account for 10-15% of childhood cancers. A peak in incidence also occurs in the mid to late 20s and then after 50 years of age. Four histological subtypes of Hodgkin's disease (HD) have been described: lymphocytic predominance, mixed cellularity, lymphocytic depletion and nodular sclerosis. Nodular sclerosis is the most common subtype and affects approximately 60% of children with Hodgkin's disease [Figure 40-45], whereas the lymphocytic depletion subtype is very rare [27]. There is no typical B-Mode image, vascular architecture [Figure 40] or contrast behaviour [Figure 41] that alone would allow a differentiation from metastases. But a regular, tree like branching of intranodal vessels are suggestive for NHL [Figures 42-44], but core biopsy or surgery is still needed.

Figure 40 Hodgkin disease in a 23y old female. Lymph nodes in the neck with multiple echo-poor areas (a). On colour Doppler a typical vascular pattern is missed (nodular sclerosis) (b).

a



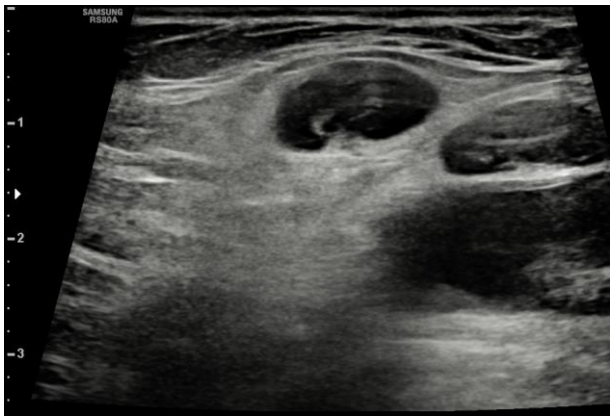
b



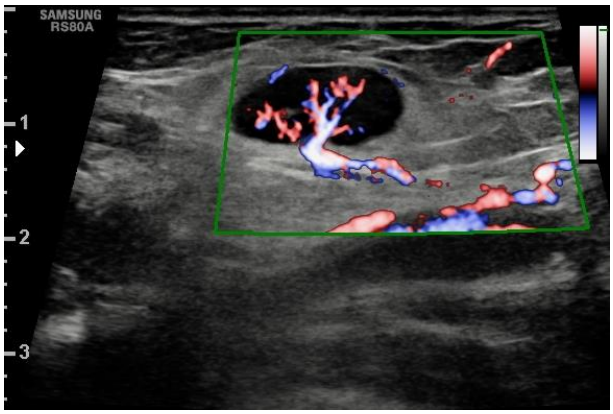
In adult patients non-Hodgkin's lymphomas have an incidence of up to 20 per 100,000 and the incidence has increased over the past decade.

Figure 41 Nodular sclerosing type of Hodgkin disease in B-mode and CFI (a-d). Lymphocyte depleted type of HD, atypical B-Mode image of a LN left neck, looking bigger on CEUS compared to B-mode image with a homogeneous enhancement on CEUS (18s p.i., e,f), mixed-cellularity subtype.

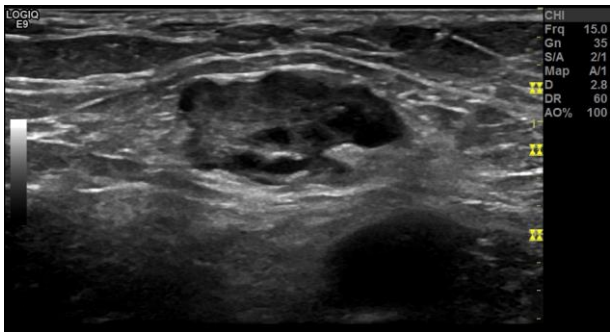
a



b


SAMSUNG
RS80A
1
2
3

c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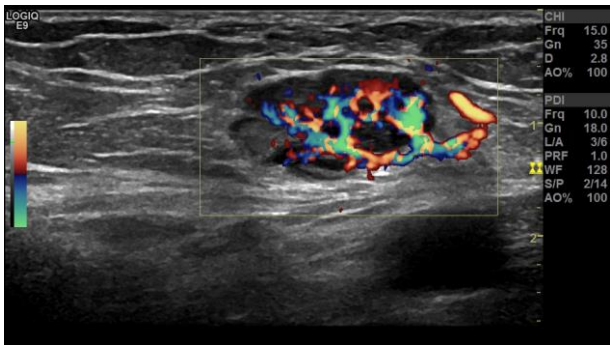
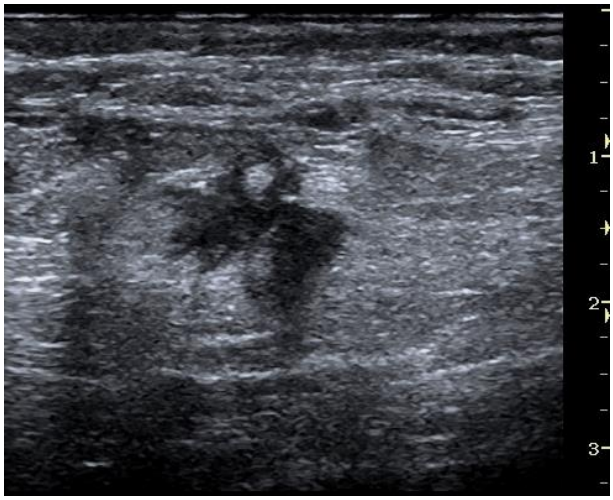
E9
CHI
Frq 15.0
Gn 35
S/A 2/1
Map A/1
D 2.8
DR 60
AO% 100

d


LOGIQ
E9
CHI
Frq 15.0
Gn 35
D 2.8
AO% 100
PDI
Frq 10.0
Gn 18.0
L/A 3/6
PRF 1.0
WF 128
S/P 2/14
AO% 100

e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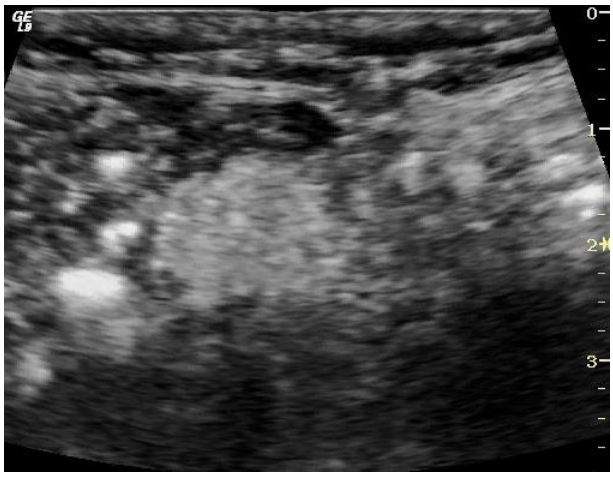
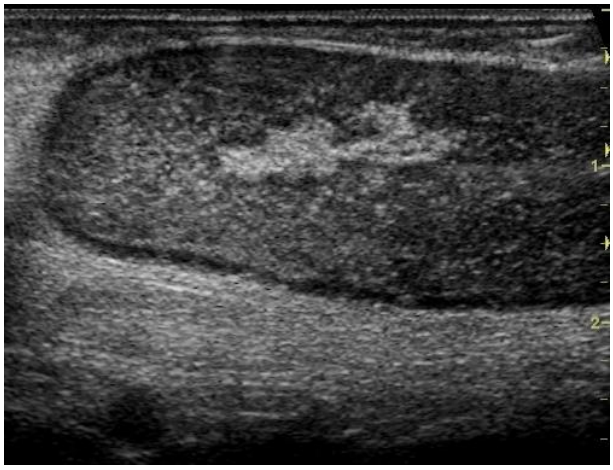


Indolent Non-Hodgkin's lymphomas are clinically differentiated from aggressive ones because the latter have a poorer prognosis. As lymphomas can involve almost any organ in the body, the number of possible differential diagnoses is substantial and will not be discussed to this chapter. Histological analysis 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 most cases, the lymph nodes are echo-poor or even cystic, they can be arranged in chains and in most cases the swollen lymph node is not painful [Figures 5, 45]. Some lymph nodes lose their architecture and have a nearly cystic appearance; in others the echo-poor cortex medulla and echogenic hilum can still be differentiated. In B-mode ultrasound only minor changes of the cortex may be seen. In a few tiny echo-poor spots can be imaged. Lymph nodes with a cystic appearance around the aorta can mimic an abdominal aortic aneurysm or Ormond's disease [Figure 46]. A lymphomatous lymph node may look like a reactive one and only its high vasculature, in the absence of an infectious focus points to a lymphoma. Focal infiltration will cause an echo-poor hypervascularised cortical thickening. It may be more challenging to discriminate reactive LN from lymphoma, especially when examining only one enlarged LN. On the other hand, in a centimetre LN, a sensitive Colour Doppler may detect intranodel vascularity.

Figure 42 Non-Hodgkin disease with tiny echo-poor spots (a) and preserved vessel architecture on Colour Doppler (b) and B-Flow (taken from a 3-D loop) (c).

a



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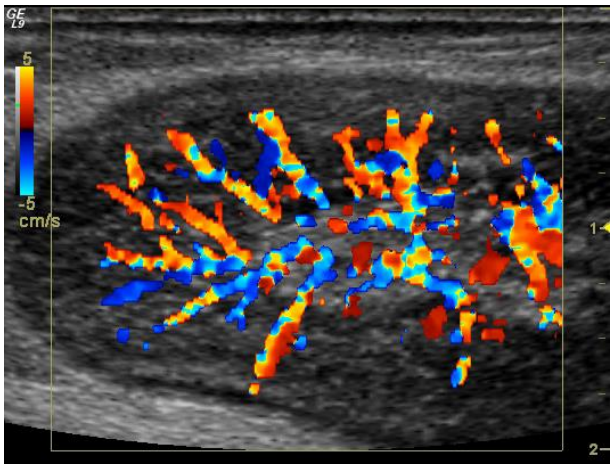

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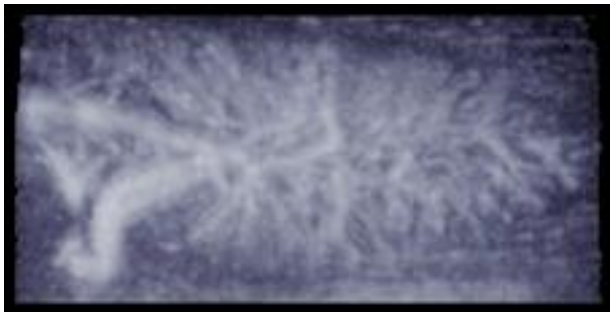
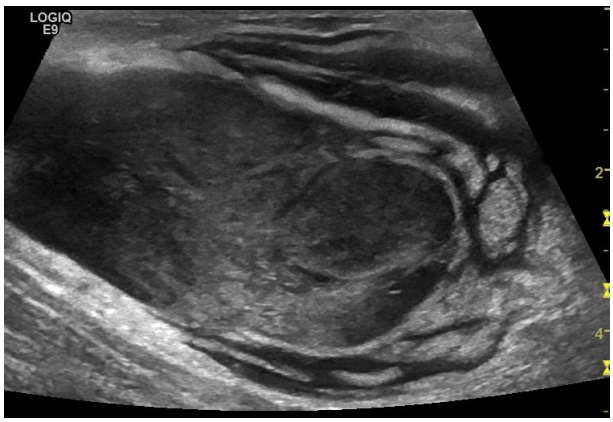


In lymphomas neovascularisation and a high microvessel density are important tumour characteristics. Beside colour Doppler techniques and B-flow, CEUS can demonstrate lymph

node microvasculature and is regarded as the most sensitive ultrasound imaging technique to identify vasculature and viability of a lymph node [Figure 43]. Contrast is required for the imaging of peripheral lymph nodes, and with a high frequency probe higher doses should be used (double dose when compared to 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 43 71y old male 2 years after complete remission on an NHL, now palpable mass left groin. B-mode image depicts the LN surrounded by interstitial fluid (a). CEUS proves a rich vasculature with a regular vessel architecture (b).

a



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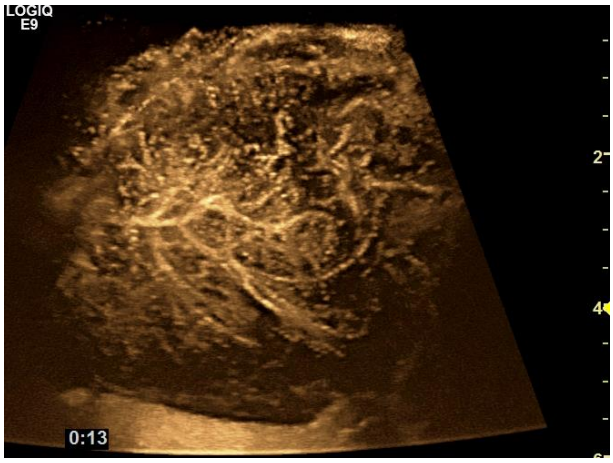
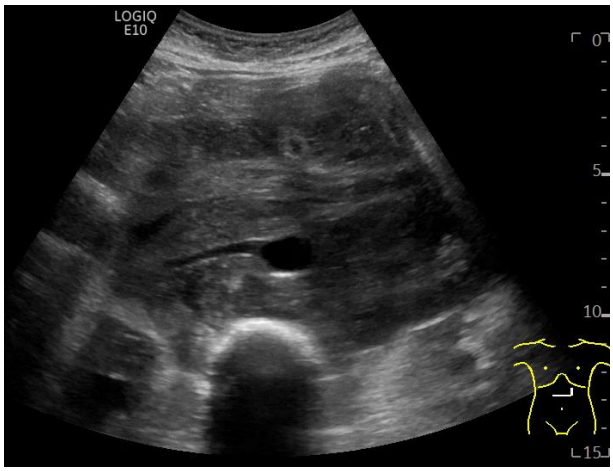


Figure 44 **Aggressive diffuse large B-cell lymphoma at the time of diagnosis. A large tumour from subdiaphragmal region down to the pelvis surrounding all big conduit arteries branching from the aorta. Cross section image with the right renal artery branching (a), coronal longitudinal scan pane (b), CEUS study demonstrates that the tumour is respecting the abdominal vessels.**

a



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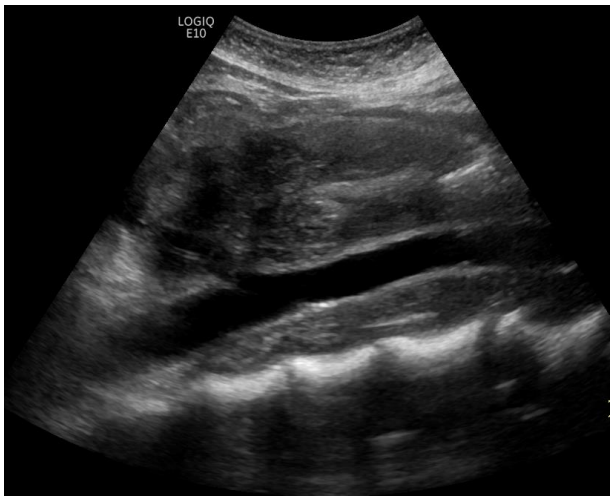

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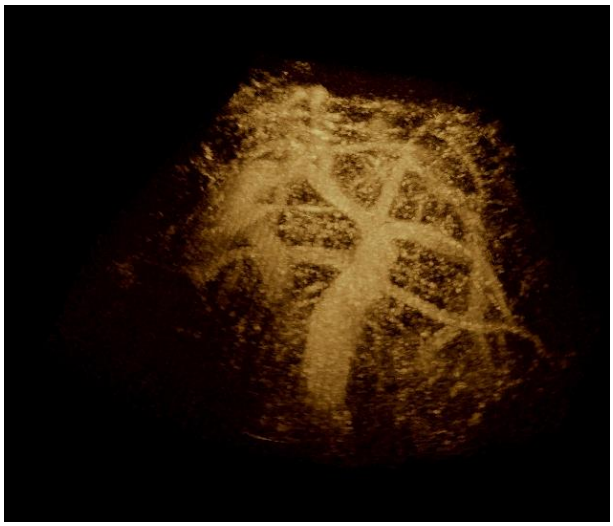
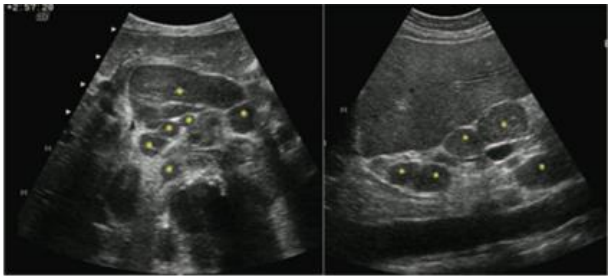


If the LN distribution and clinical settings are ignored, it is not possible to differentiate an inflammatory/ reactive from a lymphatic disease. B- Mode may be very suggestive, if tiny echo-poor cortical spots can be recognized [Figures 20, 42], which is not often the case. Like other malignancies, lymphomas are characterised by a high microvessel density (MVD), especially aggressive lymphomas. Like cancerous tumours a high MVD is associated with a poor prognosis [8, 28-30]. A high concentration of tiny lymphatic tumour cells may compress mainly peripheral vessels, while the central vessels are preserved.

Colour Doppler and CEUS may show a slightly distorted vascular branching and vessel amputation.

In NHL, lymph nodes in the abdominal space can be detected in both the intra- and retroperitoneal space and have the same characteristics as the peripheral lymph nodes except that they usually must be examined with a lower frequency [Figures 45, 46].

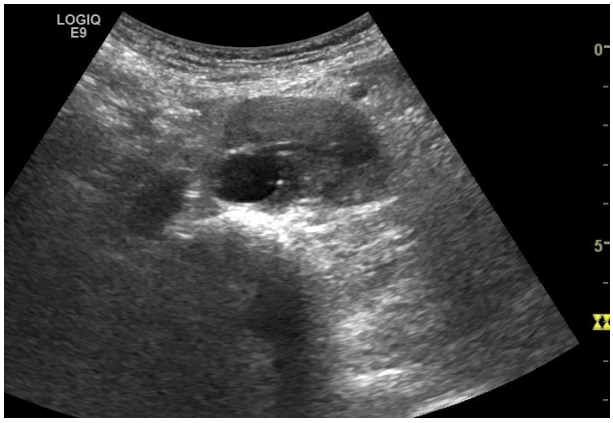
Figure 45 Non-Hodgkin 's lymphoma (CLL) transformed lymph nodes (stars) are seen intra und retroperitoneal and are often lined up along the vessels (right: paracaval lymph nodes).



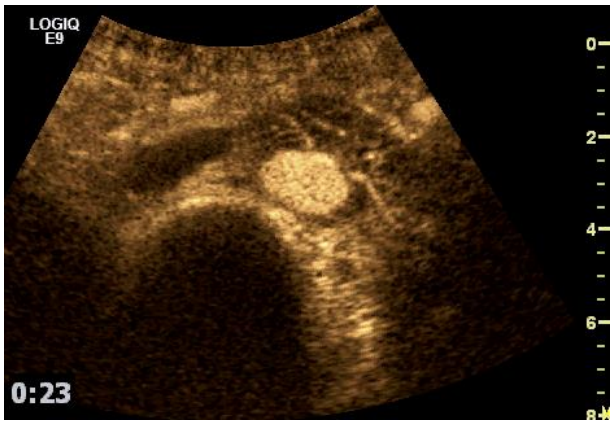
Among the differential diagnoses of lymphomas are abdominal aneurysms, Ormond's disease hematoma and seroma, which should not be misinterpreted as lymph nodes and vice versa [Figure 46].

Figure 46 Cross section image of the caudal aorta. An echo-poor mass around the aorta and partly the vena cava was suggestive for an Ormond disease (a). CEUS showed no hyperperfusion, biopsy proved the diagnosis (b).

a



b



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 characterize lymph nodes. High-resolution ultrasound performed with transmit frequencies above 12 MHz is able to detect very small lymph nodes and minimal echo-poor intranodal spots. In addition, ultrasound guided cytological aspiration can provide the final diagnosis in most cases. New imaging techniques such as CEUS may in selected cases be of benefit in the management of tumour patients, especially during follow up. Nevertheless, there are limitations in differentiating benign (reactive) from malignant lymph nodes. It is virtually impossible to differentiate between tuberculosis and metastases, or lymph nodes in Non-Hodgkin's disease from reactive lymph nodes such as in mononucleosis, neurodermitis, HIV, sarcoidosis or drug related lymph node enlargement. A lymphoma is suggested when multiple echo-poor intranodal spots are detected, liver and spleen may be enlarged and show infiltrates. In contrast a few or multiple metastatic lymph nodes may be detected along the lymphatic and venous drainage of the tumour-bearing organ. Because of their descent from the mid-abdomen, lymph node metastasis from malignant testicular or ovarian cancers are located to close to the aorta, vena cava or close to the diaphragm. Some criteria can help [Table 1], but for the final diagnosis a biopsy or in selected cases a surgical lymphadenectomy should be performed. For a complete staging, CT or MRI and/or PET-CT must be performed.

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 (LN: Lymph node. RI: Resistive Index. MET: Metastasis. Non-Hodgkin's lymphoma: NHL. HD: Hodgkin Disease. E: Enhancement).

	B-mode	**Colour Doppler Imaging**	RI	**B-Flow/ SMI**	CEUS	**Elastography**
Probably reactive lymph node	Homogeneous, thin cortex, preserved architecture. Note, NHL may look the same	Regular tree-like vessel architecture. Intranodal & arteries, much less In chronic state	Mostly a low RI	Tree-like branching arteries and veins from the hilum to the periphery, straight course Note, non-Hodgkin's lymphoma may show the same vascular pattern	Homogeneous enhancement Note, non-Hodgkin's lymphoma can behave in this way	Softer compared to muscle or similar to perinodal fat
Suspicious lymph node	Globally or focal thickened cortex. (to differentiate NHL or other malignancies, more information needed)	Few arteries, no veins	Indifferent, not helpful	More peripheral than central vessels, course of Intranodal vessel may help	Rapid global and homogeneous enhancement	Slightly harder than reference tissue
Probably malignant lymph node	Focal or global echo-poor cortical thickening. Destroyed B-mode architecture. edema possible	Few central vessels, vasculature mostly detected in the periphery. Branching arteries from capsule	High and low RI numbers within the the same lymph node, high diastolic flow, slow rise time	Depends on tumour type and intactness of capsule. Mixed vascularity heterogenous vessel density, split arteries, torturous course of vessels	Centripetal enhancement and wash out, ischemic center	Markedly harder than reference tissue
Probably a lymphoma	Focal or global echopoor - cystic cortical thickening. Echo-poor spot like areas.	Preserved native vasculature in NHL, mixed vasculature in HD	Indifferent, not helpful	Regular vessel branching	Homogeneous centrifugal E., rapid filling if also supplied by capsular arteries	mostly harder than then reference tissue tissue

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