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Small Nodes, Big Problem. Are They the Reason for Oncological Treatment Failures? LN-RADS - Lymph Nodes Reporting and Data System

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Introduction

Despite technical advances in radiology, there is still a high rate of false-negative results for metastatic Lymph Nodes (LN) in cancer patients. Depending on the modality (US, CT, MR, PET), the type of tumor or the evaluation criteria adopted, authors report values of sensitivity, specificity and accuracy at very different levels, usually between 50% to 80%. Sensitivity values above 80% with decent specificity and relevance parameters are rarely reported. The lack of progress in efficiently detecting LN metastases, despite increasingly better equipment, raises the possibility that outdated evaluation criteria are to blame. Radiological criteria are still primarily based on linear measurements, particularly the Short Axis Diameter (SAD), without a more accurate structural (multi-parametric) assessment.

As a result, contemporary radiological methods underestimate Lymph Node (LN) metastases in approximately 20% to 40% of cases. Thus, there is a clear need for the creation and implementation of a simple tool for better assessment of LNs and communication between radiologists, clinicians and pathologists; particularly describing risk of LNs cancer involvement.

At present, despite many valuable papers focusing on only a single method, region of the body or cancer type, there is no universal system for LN assessment allowing the radiologist to express in a simple, structured way the probability of LN malignancy. LNs can be described based on many radiological features, such as Long Axis Diameter (LAD), Short Axis Diameter (SAD), shape, margins, structure, echogenicity, vascularity, elasticity, density, enhancement pattern, signal intensity in T2 WI, T1 WI, signal intensity in diffusion WI and ADC maps, etc. Radiological evaluations of LNs are not standardized - they are sometimes short and enigmatic *e.g.* “10 mm LNs”, other times very long, sophisticated, and overwhelmed with specialist terminology, rendering them time-consuming and difficult to understand for non-radiologists.

This article proposes an intuitive system for LNs assessment - LN-RADS. This standardizing initiative seeks to improve communication between radiologists, pathologists and other clinicians, promoting more accurate therapeutic decisions. LN-RADS is quick and easy for radiologists to learn and clinicians to understand. For radiologists, LN-RADS is based on knowledge of the patterns of benign and malignant features of LN anatomy and their quick heuristic evaluation. The system is flexible and uses a number of structural features that can be valuable predictors of malignancy, including maximal cortical thickness, Focal Cortical Thickening (FCT), Local Cortical Thickening (LCT) etc. LN-RADS is open, which means that, in parallel with development of radiology, it allows for using new radiological achievements. Importantly, LN-RADS assessment is always done in the wide context of the patient's clinical condition, size, type of primary tumor, and stage of the disease, which allows to increase the accuracy of the diagnosis.

The author's preliminary study shows that LN-RADS detects 22% of metastatic small LNs below …10 mm SAD. The study was presented during the European Congress of Radiology in Vienna and was awarded as The Best Research Presentation Abstract within the topic of Oncologic Imaging.

In the article authors present interesting cases and a review of contemporary radiological tools for LN assessment (Figure 1).

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Discussion

The significance of LNs seems to be undervalued, even though in all neoplastic tumors, careful LN evaluation is crucial for correct staging in the TNM system and for making proper treatment decisions. For instance, the involvement of LNs in head and neck squamous cell carcinoma is the most important prognostic factor [1]. According to Som, the presence of a single ipsilateral or contralateral metastatic LN reduces survival by 50% and bilateral disease by a further 50% [2]. Incorrect assessment of LN involvement with cancer leads to mis-staging and treatment failure. From the point of view of socioeconomic impact, we can distinguish two main aspects of errors in LNs evaluation. Firstly, the social, individual aspect of each patient, a tragedy for the entire family of the person who loses the opportunity for optimal treatment, and secondly, the global economic impact of rising hospitalization costs and medical malpractice compensation. From the perspective of the type of error in the evaluation of LNs, we can equate two types of results - false positives and false negatives. In the case of large benign steatotic LNs, clinical criteria (palpation) as well as traditional measurements in SAD will often yield false positive results. In practice, we can observe high rates of patient referral for LN biopsy for nodes that are only palpable or "seem enlarged" but radiological methods like US, CT or MR scans present no structural features of malignancy. As a result, patients are stigmatized, suffer from a fear of cancer and refuse to believe in a negative diagnosis, demanding additional examinations, which in turn put an even greater strain on health care systems already overloaded with unnecessary procedures. On the other hand, many small metastatic LNs are ignored, only because of their size that is below a certain threshold. As demonstrated in the examples above, the wrong assessment of LNs can result in false positives - large but benign steatotic LN (LN-RADS 2) - or false negatives when the LN is small but has some structural features of FCT, LCT malignancy (LN-RADS 4). A false-negative diagnosis appears to be more dangerous and harmful, both from the perspective of the individual patient and the global social and economic consequences. Ignoring a small metastatic LN leads to an incorrect TNM evaluation, followed by inadequate treatment and ultimately failure. The patient dies, the family suffers, and the system incurs huge economic costs. It seems that one of the reasons for such situations is the lack of a precise and intuitive LN assessment system that goes beyond the classic short-axis measurement paradigm.

Let us examine example radiological LNs evaluations and try to decide how to categorize them as "malignant" or "non-malignant":

1. …10 mm axillary node…

2. …50 mm inguinal LNs…

3. …27 mm × 11 mm submandibular LN with hypoechoic cortex, mainly central vascularity in Color Doppler, with vessels along the hilum, low resistance Doppler spectrum, with an elasticity score of 3…

4. … 24 mm × 8 mm iliac LNs with restricted diffusion and low ADC value of approx. 700...

5. …24 mm × 13 mm axillary LNs with strong enhancement and curve type III (washout)

Despite the wealth of measurements, structural and functional information available, it can be problematic for many physicians, especially non-radiologists, to determine the type of LNs described. This challenge is likely to increase in parallel with the development of radiology. According to the well-known RECIST 1.1 criteria, a pathologically enlarged LN is defined as a node greater or equal to 10 mm in the short axis [3]. The Cheson criteria established that LN nodes should be considered abnormal if their long axis is greater than 15 mm, regardless of their short axis [4]; in the last consensus

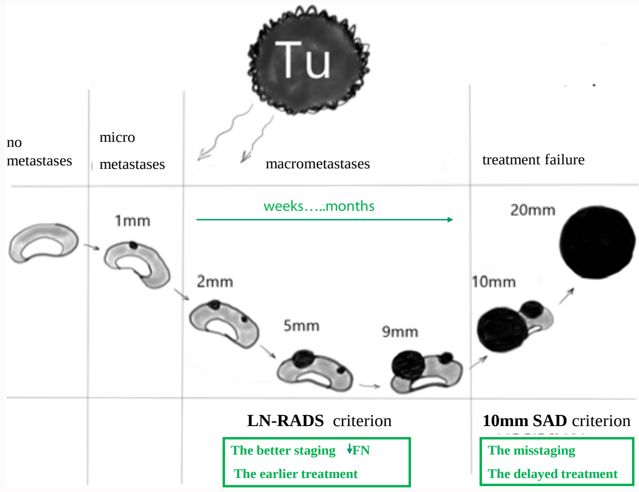

Figure 1: The development of metastases in LN. The structural multi-parametric LN-RADS assessment allows to detect 22% of metastatic small LNs below 10 mm SAD. LN-RADS can reduce false negative diagnoses and provide an earlier and more accurate treatment.

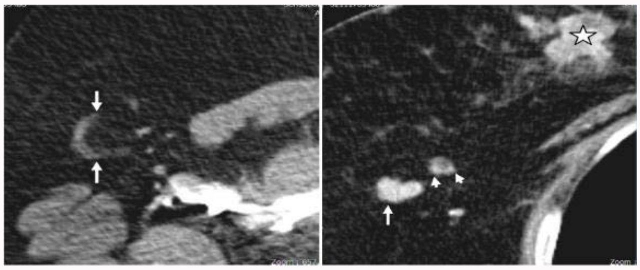

Figure 2: The images above show a breast cancer tumor (star) and three LNs in the right axilla. The largest node (two arrows) is normal-fatty node (LN-RADS 2). Closer to the tumor, there are two smaller LNs suspicious for metastases (LN-RADS 4); the first node (single arrow) has an irregular shape, strong contrast enhancement, without medulla-cortex differentiation; the second, smaller node (two short arrows) is 5 × 4 mm in size, with focal cortical thickening and focal enhancement.

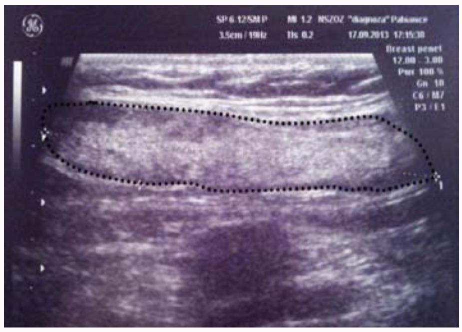

Figure 3: The image above presents a typical enlarged but benign steatotic LN with extended fatty hilum and a thin, regular, atrophic cortex (according to the proposed new classification LN-RADS 2). It is worth noting that a lymph node with significantly narrowed cortices may be difficult to detect when surrounded by adipose tissue of similar echogenicity. The border in this example is marked by dots.

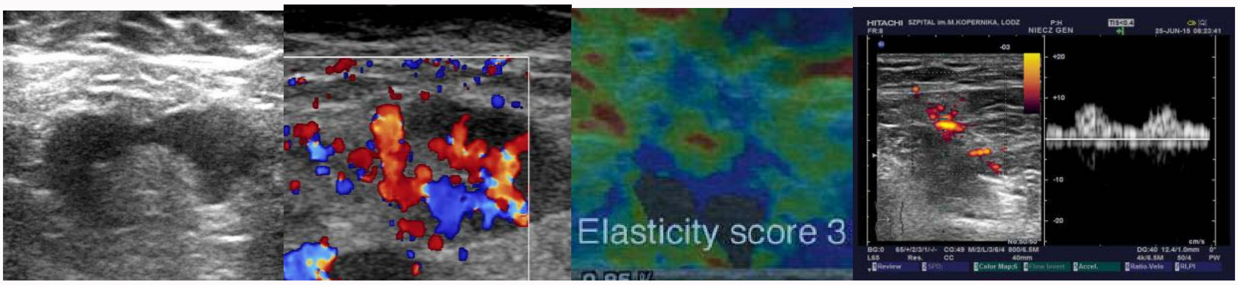

Figure 4: The four images above represent B-mode, Color Doppler, Spectral Doppler and elastography. An enlarged LN is depicted, with a hypoechoic, normal-width cortex and a well-defined, hyperechoic hilum.

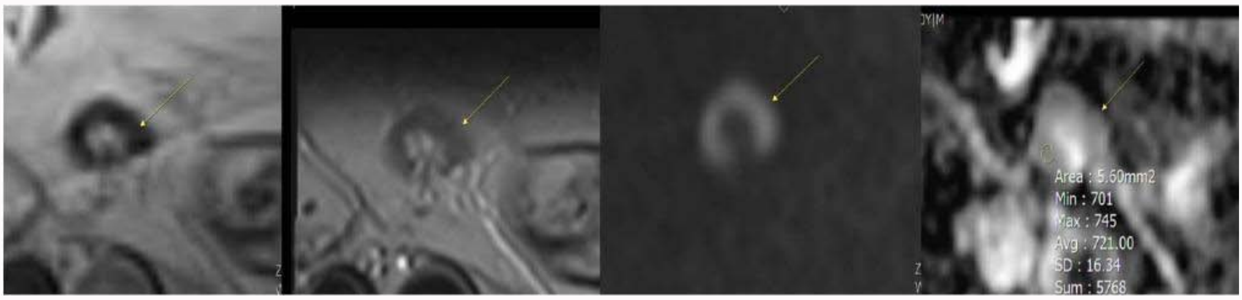

Figure 5: Iliac LNs in T1WI, T2WI, DWI and ADC. Images present normal anatomy of LNs but evident restriction of diffusion - high signal in DWI with a low ADC value.

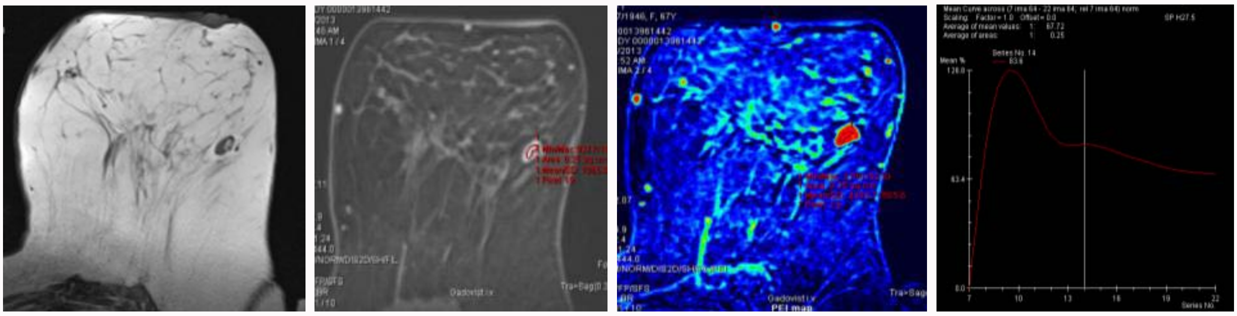

Figure 6: It is widely accepted that dynamic contrast enhancement curve of type III, referred to as “washout”, is a typical feature of breast cancer; it is also a frequent pattern of enhancement observed in normal and reactive LNs. When localized intramammary, it may be confused for a malignant lesion [4].

from 2014, apart from FDG-PET, there are no changes in guidelines concerning LN assessment [5]. Although the RECIST 1.1 criteria were not created to differentiate between benign and malignant nodes, the 10 mm short axis value has become very prevalent in radiological evaluation. Independent of the Recist 1.1 criteria, many scientific studies point to 10mm as the optimal cutoff point in LN evaluation.

Commentary on Case 1: “…10 mm axillary node…”

This is a typical example of a quick and minimalistic radiological approach. Only one diameter is provided, without specifying the axis - long or short diameter. Not only does this description provide insufficient measurement information, but LN size is an important though not crucial factor in malignancy classification. For example, in a prostate cancer study, only 30% of metastatic LNs were detected; of those detected, 83% had a long axis of only 5 mm and 50% were barely 3 mm [6]. In this case, using a 10 mm short-axis criterion, we miss over 80% of metastatic LNs, despite possible features of malignancy in smaller nodes.

Figure 2 presents a breast cancer tumor (star) and three LNs in the right axilla. The largest (two arrows) is a normal-fatty node (LN-RADS 2). Closer to the tumor, there are two smaller LNs suspicious for metastases (LN-RADS 4); the first (one arrow) has an irregular shape, strong contrast enhancement, without medulla-cortex differentiation; the second, 5 mm × 4 mm in size with Focal Cortical Thickening (FCT) and focal enhancement (two short arrows), which are radiological features of macrometastases.

It has been repeatedly shown that LN size is not a reliable parameter for the evaluation of metastatic involvement [7-9]. We should therefore analyze additional structural features such as shape (rounded or irregular), focal cortical thickening, and the absence of normal fatty hilum [10,11]. Choi et al. [12] revealed that cortical thickness greater than 3 mm was the most accurate indicator, with a 4.14 times increased risk of the presence of an axillary LN metastasis compared to cortical thickness less than 3 mm. The absence of a hilum demonstrated the highest specificity for axillary LN metastasis (94.6%).

Skeptics will correctly point out that even the best radiological tools cannot visualize micrometastases. Do we really need to visualize micrometastases? Probably not, as outcomes may depend on the quantity of cancer cells present in LNs. If a "critical mass" is reached, the prognosis significantly worsens. This phenomenon was observed by Huvos et al. [13], who compared the prognosis of a patient with breast cancer in the context of axillary nodes levels involvement and its type - macro- *vs.* micrometastases. Macrometastases, defined as having a diameter of 2 mm or more, present a 100 to 100,000-fold greater volume than micrometastases, which measure less than 2 mm. Results demonstrated that patients with 1st level micrometastases had a very similar prognosis to patients with no metastases and quite a different prognosis to the group with macrometastases at the same 1st level. According to this observation, micrometastases have a small influence on the outcome, whereas macrometastases appear to be a key point in treatment improvement. Contemporary radiological tools have enough resolution to observe foci of macrometastasis between 2 mm to 10 mm, which are ignored by the present RECIST 10mm diameter approach.

Commentary on Case 2: …50 mm inguinal LNs…

A diameter of 50 mm may seem worrisome, however, the printout from the ultrasound procedure reveals typical benign wide fatty hilum, with a regular, atrophic and very thin cortex. Despite the considerable long axis size, further investigation in this case is unnecessary. It is a common phenomenon for nodal adipose tissue to grow outward from the hilum toward the cortical zone, producing distention of the capsule and causing atrophy of the lymphoid tissue, occasionally attaining considerable volume that is interpreted as neoplasm [14].

According to the size criteria, many similar fatty LNs nodes are considered enlarged and therefore incorrectly regarded as pathologic (metastatic). This example demonstrates the resulting misdiagnosis and improper treatment caused by examining LNs nodes solely through the lens of their size. There is a need for additional information describing the general probability of the involvement of metastases. We accept that fatty LNs nodes are a normal finding in the axillary and groin regions, especially in elderly patients. This is an example of the LN-RADS 2 category (Figure 3).

Commentary on Case 3: ...27 mm × 11 mm submandibular LN with hypoechoic cortex, central vascularity in Color Doppler, with vessels along the hilum, and low resistance spectrum, with an elasticity score of 3…

Case 3 - an example of a "confusing report" for many clinicians and radiologists. Despite the wealth of information, the following question remains: "What should I do with this patient?"

The majority of authors agree that the most important information depicted are B-mode features such as a well-preserved hyperechoic hilum and oval shape, with a longest to transverse diameter ratio (L/T) over 2, and a regular, hypoechoic cortex, which are typical of benign, normal, or reactive LNs. On the other hand, metastatic LNs nodes are more rounded or irregular-shaped, without a hilar echo, occasionally with blurred borders due to capsular infiltration [15-18].

Power Doppler and Color Doppler may be helpful, but their value is controversial and color-flow criteria have fewer predictive advantages. Ariji et al. [19] reported that the hilar blood flow was demonstrated only in reactive LNs and did not appear in the metastatic nodes. In contrast, Tschammler et al. [20] noted that hilar blood flow in reactive and metastatic LNs appeared at equivalent rates. Both authors suggested that a parenchymal blood flow pattern or presence of subcapsular vessels indicate metastatic LNs. Toru, in the study of HNSCC, demonstrated that hilar blood flow appeared exclusively in reactive LNs. The difference in outcomes may be caused by technical issues, the type of neoplasm, and the size of LNs. Hilar flow is heavily dependent on node size and may therefore be difficult to observe in smaller nodes, where transducer sensitivity is limited. In summary, flow pattern assessment using Power or Color Doppler should be performed in a wider context, taking into consideration other factors, such as body region and type of pathology (e.g., cancer, lymphoma, tuberculosis).

Elastography is relatively novel ultrasound feature that demonstrates color maps of the elasticity of examined structures. According to many researchers, metastatic LNs have lower elasticity in comparison to normal or reactive LNs. The sensitivity, specificity, and accuracy of elastography was 83%, 100% and 89%, respectively [21]. With a cutoff between elasticity scores of 2 and 3, elastography demonstrated 80.7% sensitivity, 66.7% specificity and 73.4% accuracy. With a cutoff between B-mode sonographic scores of 1 and 2, B-mode sonography demonstrated 74.2% sensitivity and 78.8% specificity. Combined B-mode and elastographic sonography revealed higher sensitivity (87.1%) than B-mode sonography alone. With a strain ratio cutoff point of 2.3, sensitivity was 82.8%, and specificity was 56.3% [22].

The method is highly subjective, examiner-dependent, and difficult to standardize, especially between different departments or hospitals equipped with various apparatuses and software. While the use of elastography may not be easily applicable on a wider scale, it may be beneficial in certain scenarios. In Figure 4, the submandibular LNs does not contain any stiff regions - a feature of benignity, suggesting reactive LNs.

Reactive LNs are due to inflammatory processes, making clinical history a very important factor in their evaluation and final diagnosis. This is particularly important in the submandibular region (field II), where reactive node enlargement is very common. In terms of body distribution, the head and neck region contains approximately 55% of adenopathy. Statistics reveal that lymphadenopathy is a frequent disorder - 0.6% annual incidence in the general population [23]. Fijten analyzed a population of 2,556 patients who presented with unexplained lymphadenopathy to their GPs. Of those patients, 256 (10%) were referred to a subspecialist and 82 (3.2%) required a biopsy, but only 29 (1.1%) had a malignancy [24]. Age is a crucial factor - patients over the age of 40 years with unexplained lymphadenopathy have approximately a 4% risk of cancer versus a 0.4% risk in patients younger than 40 years [23]. Despite high value of age-related and other statistic factors, every patient should be treated individually and independently. This data illustrates just how effective radiological criteria can be versus the classical clinical criterion "palpable vs. nonpalpable" with statistical factors, especially in the neck region, where LNs are easily accessible for precise high frequency ultrasound.

In a clear clinical inflammatory process with a typical appearance of reactive LNs, category LN-RADS 3 should be assigned. If there are any morphological deviations or a presence of an oncological background, category LN-RADS 4 should be considered.

Commentary on Case 4: …24 mm × 8 mm iliac LNs with restricted diffusion and low ADC value of approx. 700...

Diffusion-Weighted Imaging (DWI) is a functional technique that depicts the level of movement of water molecules, known as Brownian motion. The magnitude Brownian motion in such tissue

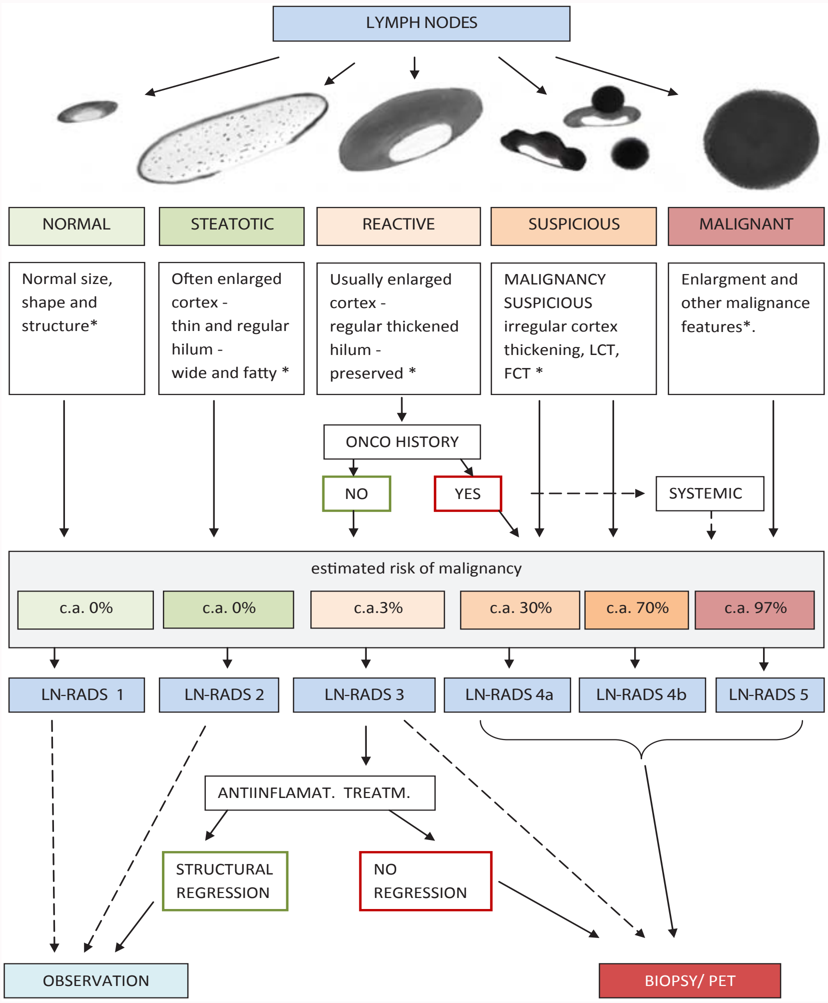

Figure 7: The algorithm of LN-RADS.

environments is expressed as the Apparent Diffusion Coefficient (ADC). Diffusion-weighted imaging is an important component of contemporary MRI imaging in oncology. It has demonstrated that many types of cancerous tissues exhibit a dense cellular structure caused by a restriction of Brownian motion, resulting in an increased signal on DWI images and presenting a low value on ADC maps (Figure 5). Moreover, the value of ADC may be a measurement of malignancy - ADC values were observed to be negatively correlated with the postsurgical Gleason grade in patients with prostate cancer; ADC values also significantly predict tumor aggressiveness [25-31]. DWI may help in monitoring the response to chemo or radiotherapy [32]. While DWI may be useful in LN assessment, differentiation between benign and metastatic status is challenging, as even normal nodes can reduce diffusion due to primary high cellularity. Despite such difficulties stemming from the natural high cellular density of LNs and a high range of ADC value standard deviation between patients, certain authors have focused on these issues. Yasui [33] noted that LN ADC to tumor ADC ratio (LN:T) is a more reliable approach that improves accuracy in metastatic LN detection with a sensitivity of 76.6% and specificity of 80.2%. Apart from attempts to differentiate normal and metastatic LNs on ADC maps, there is another advantage of using DWI. Due to their natural high tissue density, even small nodes are very well recognizable in DWI, especially on high b-value images, providing an opportunity for their quick identification, for further morphological evaluation in other sequences [34]. Another important reason for exploring DWI potential is the "wait-and-see policy" for clinically complete responders after chemoradiation for rectal cancer, where there is a real need for early detection of recurrence in LNs [35]. In summary, DWI is a valuable method in node assessment, but due to its inherent complexity, the radiologist's report may be difficult to interpret for non-radiologists. In such cases, summarizing the results using the LN-RADS classification could help clarify the radiological report.

Commentary on Case 5: …24 mm × 13 mm axillary LN with strong enhancement and curve type III (washout)

It is well established that dynamic contrast enhancement curve type III, otherwise known as the "washout curve", is a typical feature of breast cancer and can raise suspicion of malignancy [36]. In reality, washout is a frequent pattern of enhancement of normal or reactive LNs, particularly axillary and intramammary nodes (in the latter case mimicking a malignant breast lesion). Understanding that washout can appear physiologically in certain nodal regions and clinical scenarios helps to avoid unnecessary invasive procedures. Many intramammary LNs are visible during an ultrasound consultation, demonstrating the typical echo structure of normal or reactive LNs. This case illustrates the pitfall of applying radiological rules of primary tumor for the evaluation of LNs (Figure 6).

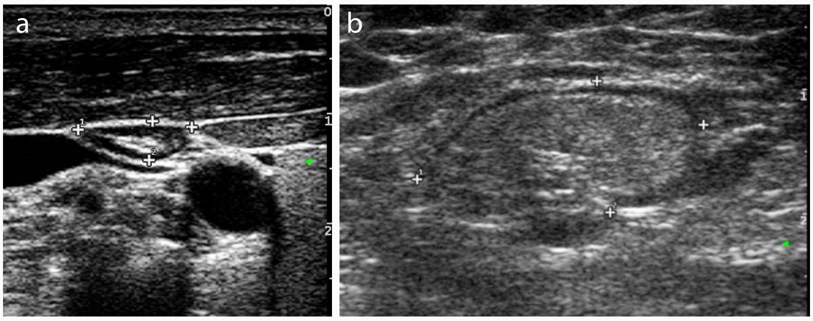

Figure 8a: LN-RADS 1 normal LN 10 × 3.5 mm History: Local cervical pain (HP negative).
Figure 8b: LN-RADS 2 - steatotic LN 23 × 11 mm. History: Palpable LN enlargement (HP negative).

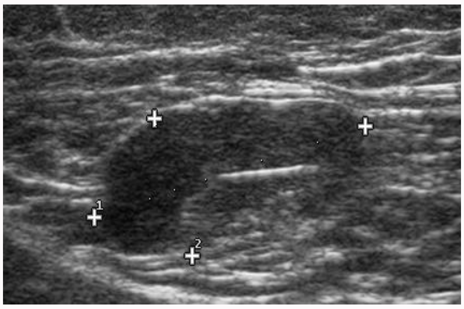

Figure 9: LN-RADS 3 - reactive LN 29 × 16 mm; acute laryngitis- (HP negative).

Summary

As seen in the examples explored in this article, the wealth of radiological methods and abundance of features describing the wide range of LN morphology creates a challenging communication barrier between radiologists and other specialists (*e.g.*, oncologists, surgeons, pathologists). Difficulties in interpreting detailed radiological reports contribute to misdiagnoses and incorrect treatment strategies.

The strength of LN-RADS lies in its simplicity. Moreover, this system is universal and can be used for different radiological modalities - US, CT, MRI or PET and it can be based on various radiological data - size, structure, power Doppler, spectral Doppler, CEUS, elastography, DCE, DWI, ADC, etc.

According to LN-RADS scoring, LN-RADS 1 includes normal LNs - oval, no changes in architecture, size and vascularization; LN-RADS 2 encompasses fatty, post-inflammatory LNs - may be enlarged, with fatty hilum and a regular, thin cortex, without other changes; LN-RADS 3 describes reactive, probably benign LNs due to an active inflammatory process - usually moderately enlarged, with a regular cortex, possibly hyper vascularized, with central regular vessels; LN-RADS 4 indicates LNs suspicious for malignancy with an irregular cortex and focal thickening, especially abnormal vascularization architecture, while the size may be normal; LN-RADS 5 identifies LNs with a high probability of malignancy - enlarged, more round than oval, without normal differentiation between the hilum and the cortex, especially with abnormal vascularization architecture or blurred borders.

LN-RADS seems to be reliable tool for LN assessment. However, we can foresee an increase in false positive diagnoses. On the other hand, according to the literature, the underestimation of metastatic LNs is quite high - approx. 20% to 40%. LN-RADS serves as a complementary tool, addressing the issue of the underestimation of metastatic LNs. With regard to a 20% to 40% risk of occult LNs metastases, our preliminary study detecting 22% of metastatic small LNs can reduce false negative diagnoses and provide a more accurate assessment of nodal involvement. The LN-RADS system shows promise but requires further study.

LN-RADS Classification Structure Reporting for Lymph Nodes

LN-RADS 1 normal LN - oval, no changes in architecture, size and vascularization

LN-RADS 2 fatty, post-inflammatory LN - may be enlarged, with fatty hilum and regular thin cortex

LN-RADS 3 reactive probably benign due to active inflammation - usually moderately enlarged, with regular cortex, occasionally hyper vascularized, with central regular vessels

LN-RADS 4 suspicion of malignancy (LN-RADS 4a low suspicion; LN-RADS 4b high suspicion of malignancy) irregular cortex with

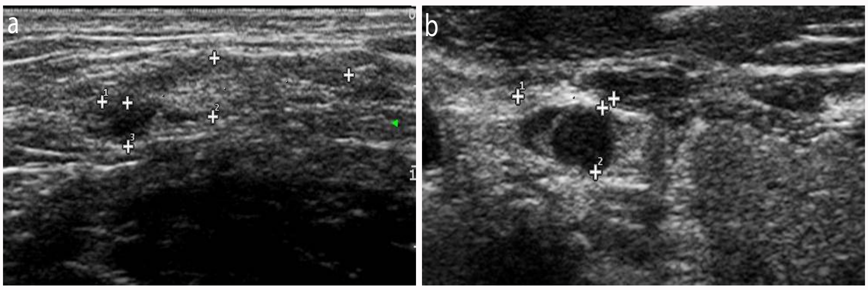

Figure 10a: LN-RADS 4a - low suspicious; 20 × 2.6 mm with focal thickening of cortex. History of Melanoma malignum. (HP Melanoma malignum).
Figure 10b: LN-RADS 4b LN 8.5 × 4 mm with 4 mm FCT. History: Cervical lymphadenopathy. HP: Non-small cell cancer.

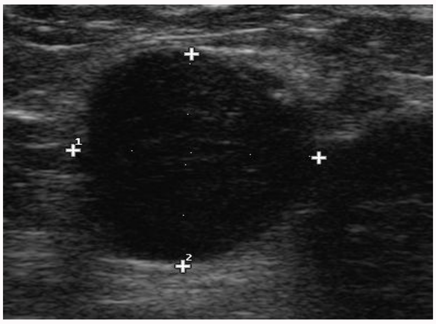

Figure 11: LN-RADS 5 LN 21 × 21 mm History: Merkel Cell Carcinoma. HP: Small cell cancer.

focal thickening, especially abnormal architecture of vascularization, size maybe normal

LN-RADS 5 very high probability of malignancy - usually enlarged, more-round than oval, without normal differentiation hilum and cortex, often with abnormal chaotic vascularization architecture or blurred borders etc. (Figure 7-11).

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