Critical meta-analysis of the diagnostic criteria employed for the sonography (US) diagnosis of lymph node metastasis in the melanoma patient

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Purpose

Cutaneous melanoma is a frequent disease, especially in some geographical area, and its incidence has significantly increased worldwide in the last years. Key points for disease staging a prognosis include primary tumor thickness, primary tumor ulceration, primary tumor mitotic rate, number of affected lymph nodes, and nodal metastatic burden.1,2

Approximately 70% of all melanoma metastases involve the regional lymphatic basin, where the first draining lymph node is called the sentinel lymph node and is the basis for treatment planning: if the sentinel lymph node is positive the patient undergoes completion lymphadenectomy while in the sentinel lymph node is negative radical lymphadenectomy will be avoided. Both satellite (< 2 cm) and in-transit (> 2 cm) metastasis may develop along the route of spread from the primary tumor and the lymph node; these tumor deposits are comprised in the "N" parameter (Fig.1 on page 4).1,2 Establishing the lymph node status is fundamental for initial patient staging, therapeutic management, follow-up, and prognosis.2 The "N" status is the best predictor for overall survival, which is significantly greater if only one lymph node is found involved and if the diameter of this node is <15 mm.2,3

Although the effective impact of sonography (US) on patient survival is still debated,3,4 this imaging modality has consistently entered the clinical practice of melanoma, particularly in Europe and Australia.5-8 US is being increasingly employed in the staging of melanoma patients scheduled for the sentinel lymph node biopsy (SLNB) procedure: in this subjects US is carried out in a non-targeted way, exploring all regional lymphatic stations, or in a targeted way, evaluating specifically those lymph node found "hot" at the pre-SLNB lymphoscintigraphy.2,7,9 The complex and expensive SLNB procedure can be avoided in US positive cases, which are directly driven to radical lymphadenectomy.5,6,10 Additionally, US is employed during patient follow-up, having it proven more accurate than physical examination in detecting locoregional relapse3,8 Both during treatment planning and follow-up, US is also relevant to guide percutaneous procedures such as fine-needle aspiration cytology (FNAC) sampling and surgical guidewire placement.5,6,10

The literature on US imaging of melanoma regional spread has some peculiarity. First, the published papers are mainly written by dermatologists and are mostly focused on the clinical impact of US (management, prognosis, etc.), will little attention is given to the proper use of the US technique for itself. The equipment and the exploration methodology are usually described in a concise manner, making it difficult to full understand the imaging technique employed. Most papers rely on the B-mode imaging without any help from Doppler techniques. The diagnostic criteria considered for lymph node metastasis are frequently vague, without clear and univocally-stated definitions. Some papers simply
do not indicate the diagnostic criteria employed\textsuperscript{8-10} while some others\textsuperscript{3,11} generically state to have employed "modified" criteria from those originally developed by Vassallo\textsuperscript{12}. In some papers it is unclear if each single criterion described was considered as a stand-alone indicator of malignancy or if a combination of different criteria was necessary. Moreover, it is uncommon\textsuperscript{13-16} that the accuracy of each single diagnostic criterion is evaluated statistically. Finally, the terminology employed is extremely variable and somehow unusual.

We carried out a systematic review of the original articles dealing with US imaging of lymph node melanoma metastasis. Our main interest was focused on the criteria employed in the literature to diagnose nodal metastasis.
**Fig. 0:** Fig.1 - N staging parameter (from Edge SE et al (eds): AJCC Cancer Staging Manual. New York, Springer, 2009).

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Methods and Materials

The study was approved by the Ethics on Research Committee of our institution. We employed a multimodal search strategy, focused on the online bibliographical database PubMed, personal files, and consultation with experts. On PubMed we checked the last thirty years, ending December 2009. We searched jointly for the terms [melanoma, sonography, lymph node] and for the terms [melanoma, ultrasound, lymph node]. The references of the studies that fulfilled the inclusion criteria were also analyzed to identify original studies that were not identified by the search of the data.

Inclusion criteria were: exclusive relationship to melanoma metastasis (exclusion of papers also including other primary tumors) availability of full text, and use of the English language. Papers dealing with non-cutaneous primary melanomas and with deep lymphadenopaties were excluded as well studies on animals. Abstracts and case reports were also excluded. Review articles and editorials were taken in consideration only if they categorized the criteria for nodal metastasis diagnosis (instead, no original data on US methodology and US accuracy is usually included in this kind of papers).

The PubMed search identified 148 papers for the key words "melanoma - sonography - lymph node" and 190 papers for the key words "melanoma - ultrasound - lymph node". Among the cumulative 201 papers, 147 were found as not being properly related to the topic of US imaging of melanoma lymphadenopaties or as being written in non-English languages. This first selection left 54 papers for further assessment and their full text versions were collect. No paper was excluded because of our inability to get the full text. Data were extracted from these 54 studies, although 23 were subsequently excluded because of having no specific relevance. No overtly duplicated paper was found, although some articles, written by the same groups, surely had a number of shared patients. In the end, complete information could be extracted from a total of 31 final eligible studies. Screening of the references cited in the retrieved articles failed to identify any additional eligible paper.
Fig. 0: Fig.19 - Partial lymph-node metastasis. Hypoechoic, hypervascularized tumor deposit in an inguinal lymph node.

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Results

The data retrieved from the studies we selected on the topic of US scanning for lymph node melanoma metastasis are listed in table 1 on page 9. The diagnostic criteria described in these papers are shown in table 2 on page ___.

On the basis of this critical review we summarize below some consideration on the assessment of lymph nodes in the melanoma patient.

First of all, the operator should be adequately aware of the US appearance of normal, reactivity-enlarged, involutively-enlarged (fatty metamorphosis), inflammatory (acute and chronic lymphadenitis), and neoplastic lymph nodes (Fig.2 on page 9, Fig.3 on page 10, Fig.4 on page 11, Fig.5 on page 12). He/she should also be aware that the appearance of normal lymph nodes may differ between the various lymphatic stations (neck, axilla, and inguinal region).

To assess the abnormal lymph nodes, combination of B-mode and color-Doppler pattern should be considered (Fig.6 on page 13, Fig.7 on page ___). Lymph node assessment is based on analyzing the size, shape, border, and internal echotexture. We do not rely on the lymph node size by itself (Fig.8 on page __). Some older papers consider a longitudinal diameter >2 cm\(^2\) or >3 cm\(^2\) as a suspicion criterion. We do not, but we believe that a lymph node with a non-specific appearance becomes more suspicious when it also shows a large size. Small-sized lymph nodes may sometime appear as round or may show a loss of the hilum hyperechogenicity or a cortical thickening but they will still be regarded as benign if these changes are not so marked. Instead, the same changes would be considered suspicious in a large size lymph node.

We take in consideration the shape of the lymph node, being suspicious when oval or even more when round and being not suspicious if markedly elongated (Fig.9 on page __, Fig.10 on page ___). Some author consider as suspect a longitudinal/transverse (L/T) diameter <2\(^2\) while some other author, as well as us, an L/T ratio <1.5.\(^{12,14,19}\) We believe that a 1.5 threshold increases the rather low specificity of the size criterion. Anyway, differently from other authors,\(^{30}\) we do not consider this single criterion as sufficient for diagnosing malignancy and we always try to match it with other features.

We give much relevance to the cortical changes, which can indicate an early stage of lymph node metastatization, eventually preceding the typical finding of a round and diffusely hypoechogenic lymph node. We consider as indeterminate those lymph nodes exhibiting a diffuse but symmetric (circumferential) thickening of the cortex, as the only abnormality (Fig.11 on page __). We regard instead as highly suspicious those lymph nodes showing an asymmetric (unilateral) cortical thickening (Fig.12 on page __, Fig.13 on page __, Fig.14 on page __). We finally consider as overtly metastatic...
the lymph nodes with a focal, eventually nodular, thickening of the cortex. This "nodule within the node" may vary in size from millimetric to a large deposit involving most of the lymph node (Fig.15 on page , Fig.16 on page , Fig.17 on page , Fig.18 on page , Fig.19 on page ).

We also consider the changes within the central hyperechoic "hilum". The hilum region can be displaced, can be reduced in size, can become overtly inhomogeneous, or can totally disappear (Fig.20 on page , Fig.21 on page ). A small hilum can be a non specific finding but in our experience a hilar displacement by an asymmetric or focal cortical thickening or a partial or total substitution of the hilum with hypoechoic tissue indicate metastasis.

The borders of a metastatic lymph node are commonly described as being sharp, eventually irregular in most cases while reactive lymphadenopathy are said to show both sharp or blurred margins. In our opinion the evaluation of the nodal border is too subjective, and we currently do not rely on the appearance of the borders to distinguish between reactive and metastatic lymph nodes.

While most of the papers published on this topic only rely on the B-mode findings, we use color- and power-Doppler imaging for any abnormal lymph node or subcutaneous lesion encountered. Benign lymph nodes show a monopolar vascularization, with vessels entering the lymph node hilum and distributing regularly toward the periphery (without reaching the nodal cortex). In malignant lymph nodes this "color hilum" is lost or displaced while multiple vessels penetrate the nodal capsule and enter the lymph node distributing anarchically (Fig.22 on page , Fig.23 on page , Fig.24 on page ). We find Doppler US being particularly helpful in some indeterminateness circumstance, improving operator’s confidence in suspecting malignancy.
<table>
<thead>
<tr>
<th>First author/paper and publication year/reference</th>
<th>Center</th>
<th>Study design</th>
<th>Number of patients and clinical scenario</th>
<th>Enrollment period</th>
<th>Transducers</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vossel et al. 2009 [9]</td>
<td>Berlin, Germany</td>
<td>Retrospective review</td>
<td>14, consecutive patient cohort study during stage I follow-up</td>
<td>2001-2006</td>
<td>7.5 MHz, linear</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Weller et al. 2008 [2]</td>
<td>Lyon, France</td>
<td>Prospective study</td>
<td>148, with internal mammary lymph nodes during stage I follow-up</td>
<td>2001-2007</td>
<td>7.5 MHz, linear</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Hammar et al. 2006 [1]</td>
<td>Stockholm, Sweden</td>
<td>Retrospective review</td>
<td>271, with internal mammary lymph nodes during stage I follow-up</td>
<td>2001-2006</td>
<td>7.5 MHz, linear</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Becker et al. 2005 [5]</td>
<td>New York, USA</td>
<td>Prospective study</td>
<td>149, with internal mammary lymph nodes during stage I follow-up</td>
<td>2001-2006</td>
<td>7.5 MHz, linear</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Schauer et al. 2004 [6]</td>
<td>Munich, Germany</td>
<td>Prospective study</td>
<td>211, with internal mammary lymph nodes during stage I follow-up</td>
<td>2001-2006</td>
<td>7.5 MHz, linear</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Hedges et al. 2003 [4]</td>
<td>Munich, Germany</td>
<td>Prospective study</td>
<td>148, with internal mammary lymph nodes during stage I follow-up</td>
<td>2001-2006</td>
<td>7.5 MHz, linear</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Hedges et al. 2002 [3]</td>
<td>Munich, Germany</td>
<td>Prospective study</td>
<td>148, with internal mammary lymph nodes during stage I follow-up</td>
<td>2001-2006</td>
<td>7.5 MHz, linear</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Hedges et al. 2001 [2]</td>
<td>Munich, Germany</td>
<td>Prospective study</td>
<td>148, with internal mammary lymph nodes during stage I follow-up</td>
<td>2001-2006</td>
<td>7.5 MHz, linear</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Hedges et al. 2000 [1]</td>
<td>Munich, Germany</td>
<td>Prospective study</td>
<td>148, with internal mammary lymph nodes during stage I follow-up</td>
<td>2001-2006</td>
<td>7.5 MHz, linear</td>
<td>80%</td>
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<tr>
<td>Hedges et al. 1999 [9]</td>
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<td>2001-2006</td>
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<td>80%</td>
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</tbody>
</table>

**Fig. 0**

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**Fig. 0:** Fig.2 - Drawing of normal (A), fatty (C and D), and reactive (B) lymph nodes.

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Fig. 0: Fig.3 - Fatty lymph node of the inguinal region. Note very thin, residual cortex peripherally.

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**Fig. 0:** Fig. 4 - Very large, fatty lymph node of the inguinal region.

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Fig. 0: Fig.5 - Reactive lymph node of the inguinal region. Diffuse and homogeneous cortical thickening with hilar vascularization.

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**Fig. 0:** Fig.6 - Drawing of the morphological and structural changes in metastatic lymph nodes.

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Conclusion

The diagnostic criteria employed in the literature to diagnose lymph node malignancy with US are frequently vague and contradictory. Few series estimate the accuracy of each sign and no series analyzes the intraobserver and interobserver variability of the US performance (which is notoriously an operator dependent modality) and of the US criteria. Many authors highlight how the reported results for the US lymph node assessment vary greatly in the literature: they try to explain somehow these inconsistencies but the differences in the diagnostic criteria employed are rarely considered. We believe that large, prospective series with state-of-art US equipments, specifically-trained operators, and most of all with strictly-stated and histologically-validated criteria are still needed.
### Table 2

Diagnostic criteria employed in the published studies on the topic of US scanning of lymph nodes in melanoma patients. Both lymph nodes and regional lymph nodes were evaluated. 

<table>
<thead>
<tr>
<th>First author/Article and publication year</th>
<th>Shape</th>
<th>Size</th>
<th>Echotexture, color</th>
<th>Echogenic structures</th>
<th>Margin</th>
<th>Border</th>
<th>Color Doppler findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pena et al. 2002 [11]</td>
<td>Circular or oval</td>
<td>-</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
</tr>
<tr>
<td>Boccia et al. 2003 [12]</td>
<td>Round or oval</td>
<td>-</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
</tr>
<tr>
<td>Acosta et al. 2004 [13]</td>
<td>Oval or irregular</td>
<td>-</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
</tr>
<tr>
<td>San et al. 2005 [14]</td>
<td>Lenticular, oval</td>
<td>-</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
</tr>
<tr>
<td>Andrade et al. 2006 [15]</td>
<td>Irregular</td>
<td>-</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
</tr>
<tr>
<td>Veli et al. 2007 [16]</td>
<td>Elliptical or oval</td>
<td>-</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
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<tr>
<td>Lee et al. 2008 [17]</td>
<td>Irregular</td>
<td>-</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
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<tr>
<td>Chen et al. 2009 [18]</td>
<td>Multilobated, oval</td>
<td>-</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
<td>Poor echotexture</td>
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<tr>
<td><strong>Legend</strong></td>
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<tr>
<td>Elliptical</td>
<td></td>
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<tr>
<td>Circular</td>
<td></td>
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<tr>
<td>Oval</td>
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<tr>
<td>Lenticular</td>
<td></td>
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<tr>
<td>Irregular</td>
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<td></td>
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<tr>
<td>Multilobated</td>
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</tbody>
</table>

**Fig. 0**

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