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Research Article

Elastography as a New Screening Tool for Metastatic Lymph Nodes in Melanoma Patients

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Abstract

Objective: In melanoma patients, early detection of lymph node recurrence is essential. Elastography is a non-invasive technique for studying tissue stiffness, already used to assess liver, thyroid and breast lesions, pancreatic and prostate nodules and cervical lymphadenopathy. In a prospective pilot study, we sought to evaluate the value of a combination of elastography and B-mode ultrasonography for detecting lymph node metastases in melanoma patients.

Methods: 49 melanoma patients were screened with lymph node B-mode ultrasound and lymph node elastography. A tissue consistency heat map enabled us to classify lymph nodes into four patterns as a function of the Alam's and Furukawa's criteria

Results: Out of a total of 108 lymph nodes studied, 17 were metastatic. The proportion of metastatic lymph nodes within each of the four classes was as follows: 2% for pattern 1, 7.2% for pattern 2, 64% for pattern 3 and 75% for pattern 4.

Conclusions: Elastography may be a valuable screening test for lymph node recurrence in melanoma patients. It may add diagnostic value in the early detection of sub-centimeter metastatic lymph nodes. The combined use of elastography and B-mode ultrasonography appeared to be especially useful for lymph nodes that were "doubtful" according to the latter technique. It should be borne in mind that we did not directly compare metastatic lymph node tissue with normal lymph node tissue, since the elastographic index is calculated by comparison of a node with its surrounding conjunctive tissue.

Keywords

B-Mode Ultrasound; Elastography; Lymph nodes; Melanoma; Metastasis; Ultrasonography

Introduction

During follow-up in melanoma patients, loco-regional lymph node metastasis or cutaneous in-transit metastasis are observed in about 70% of cases [1-3]. Extensive lymph node involvement is associated with a poor prognosis. The mean 5-year survival rate varies from 53% with one positive node to just 25% with four positive nodes [4]. The early detection of lymph node recurrence is therefore essential for prolonging survival in melanoma patients. The treatment of disseminated metastatic melanoma is still challenging - despite the emergence of promising treatments, such as anti-BRAF [5] and anti-CTLA4 agents [6]. The value of careful, repeated clinical examinations and lymph node B-mode ultrasound (US) monitoring of melanoma patients is now acknowledged. These procedures are now even recommended as part of the initial assessment and monitoring of melanoma patients at American Joint Committee on Cancer (AJCC) stages IIA to IIIC [7]. Although sentinel lymph node biopsy improves the N classification of patients, a positive impact on survival has not yet been demonstrated [8,9]. Ultrasound-guided, fine-needle aspiration cytology only has practical value in the early detection of melanoma metastases when it is positive [10]. Positron emission tomography - X-ray computed tomography (PET-CT) can also be used to detect metastatic lymph nodes. However, the technique's sensitivity for lymph node metastasis detection depends on the tumor size (a diameter of at least 6 mm or a volume of at least 80 mm³), amongst other factors [11].

Elastography is commonly used to monitor hepatic fibrosis but is also applied in oncology to assess breast and thyroid lesions and pancreatic and prostate nodules [12-17]. The technique is based on differences in tissue consistency; malignant tissue becomes harder than healthy tissue. Elastography has been evaluated in cervical lymphadenopathy [18-20] - particularly for the detection of lymph node metastases of head and neck cancers but also for the diagnosis of cervical, mediastinal or abdominal lymphadenopathies studied with endoscopic ultrasonography [21-27]. These studies have shown that elastography may be of value in the diagnosis of malignant lymph nodes. Hinz et al. further showed that this new US tool may be of value in the differential diagnosis of melanocytic skin tumors [28]. And recently, he studies this promising tool for diagnosis of lymph nodes metastases in melanoma patients given the macroscopic hardness and low deformability of melanoma lymph node metastases caused by the infiltration of melanoma cells [29]. So elastography was just been evaluated for lymph node screening in melanoma patients, and we decided to confirm elastography in this indication. In an open prospective pilot study, we examine the superiority of this new diagnostic screening test to just simple B-mode ultrasonography in the follow-up of melanoma patients, and the possible advantages of the combination with PET-CT.

Patients and Methods

Patients

This prospective pilot study was performed over an 11-month period (June 2009 to May 2010, inclusive) in the Department of Dermatology at Amiens University Medical Center. Forty-nine skin melanoma patients were recruited during scheduled follow-up examinations (29 men and 20 women). All the patients gave their written, informed consent to participation. Clinical monitoring, imaging modalities and check-up frequency were based on the 2005 French Consensus Conference recommendations [26].

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Methods

A clinical examination at the hospital included a review of the entire skin surface area and palpation of the melanoma excision site and the lymph nodes. Additional morphologic examinations included a lymph node US scan and (depending on the Breslow stage and the presence of local or distant recurrence), a chest X-ray, a US examination of the abdomen and pelvis, or a CT scan of the head, thorax, abdomen, pelvis. The US lymph node examination was followed immediately by elastography. Patients were divided into three groups on the basis of their clinical and US findings: (i) patients with one or more clinically suspicious lymph nodes, (ii) patients with no clinically suspicious lymph nodes but one or more suspicious lymph nodes on US and (iii) patients included prior to any clinical or US examinations systematic. The study population's characteristics are summarized in Table 1. Data on the melanoma's regression and mitotic index were not been collected because the final version of 2009 AJCC melanoma staging and classification system was published in December 2009.

Lymph nodes were considered to be clinically suspicious if any of the following criteria were met: a largest dimension greater than one cm, a hard consistency and adherence to underlying structures. Clinically suspicious lymph nodes were then analyzed in a coupled ultrasound-elastography procedure. To minimize recall bias, the B-mode and elastographic images were reevaluated by one of the authors in a blind manner.

If suspicious lymph nodes were detected by US and/or clinically, a US-guided, fine-needle aspiration cytology procedure or a PET-CT scan was performed (depending on which technique could be performed first). If the cytology or PET-CT results were positive, lymph node dissection and histopathologic analysis was performed. If the cytology or PET-CT results were negative, standard follow-up monitoring was continued.

To assess the value of elastography as a new diagnostic tool, we considered that the patient's lymph node status was healthy if (i) the histological analysis or the PET-CT scan was negative and (ii) there was no recurrence (i.e. stable lymph node size and consistency) within the following 6 months. The patient's lymph node status was considered to be metastatic if (i) metastatic melanoma cells were detected by the histopathologic analysis or (ii) elevated standardized uptake value in PET-CT.

B-mode ultrasound and elastography

All US examinations were performed with a EUB-7500 HighVision system (Hitachi Europe, Maidenhead, United Kingdom) equipped with three transducers operating at between 3.5 and 14 MHz (B-mode, 25 pictures per second, color Doppler, power mode, real-time tissue elastography EZU TE3). For each lymph node, B-mode images were obtained first. The metastatic invasion criteria most frequently reported in the literature were then noted [15,27,28]: a circular aspect, a Sobialti index (the longitudinal diameter/transverse diameter ratio) below 1.5, loss of hilum, hypo-echogenicity and the presence of peripheral perfusion. Lymph nodes were measured, described and classified in real time as either "very suspicious" (meeting at least four US malignancy criteria), "doubtful" (meeting one to three criteria) or "benign" (not meeting any criteria).

Real-time, freehand elastography was performed during the same examination. A stable image was obtained after repeated compression and decompression with light pressure. B-mode US and elastographic images appeared simultaneously on separate screens. Elastography measures the correlation between successive US images. It can monitor tissue deformation and determine the tissue's Young's modulus. In fact, elastography can be likened to "computer-assisted palpation". After being coded on a gray scale, travel tissue (or, reciprocally, tissue hardness) can be expressed as a heat map (also referred to as an elastogram) in which red corresponds to soft lesions and blue corresponds to hard lesions. The lymph nodes elastographic index was determined by comparison with the surrounding conjunctive tissue.

The color-coded elastogram was inspected visually in terms of the percentage of dark blue areas. This procedure was inspired by Alam's and Furukawa's reports on cervical lymph nodes [18,19]. After storage on a hard drive and printing, all images were analyzed by two authors. The inter-and intra-individual variabilities were assessed.

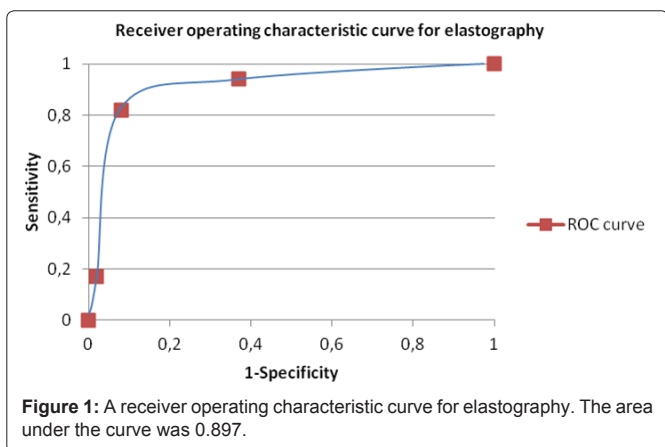### Histopathologic evaluation of excised lymph nodes

In brief, lymph nodes were fixed for 24 hours in buffered formalin. After fixation, the nodes were cut in half (through the hilum, along the longest axis) and embedded in paraffin. Five serial step sections of 4-6 μm each was cut from each face of the lymph node and were stained with hematoxylin-eosin. The sections were immunohistochemically stained for S100 protein and human melanoma black 45 antigens.

Statistics

To assess the diagnostic performance of US elastography (when used alone for identifying involved lymph nodes and in combination with B-mode US for "doubtful" lymph nodes), we calculated the corresponding sensitivity, specificity and positive and negative predictive values. The diagnostic parameters' precision was expressed as a 95% confidence interval. We used receiver operating characteristic (ROC) curve analysis to select the cut-off between healthy and metastatic lymph nodes (percentage deep blue). The area under the ROC curve was calculated (Figure 1).

Table 1: Patient presentations and melanoma characteristics.

Population characteristics	N = 49 (29 men, gender ratio: 1.45) Mean age = 62.4 years (range: 31 to 93) Time interval between melanoma excision and elastography = 3.5 years (range: 0.3 to 16 years)	
Melanoma characteristics	Site	Legs : 16 out of 52 Trunk : 16 out of 52 Head and neck : 10 out of 52 Extremities : 6 out of 52 Upper limbs : 4 out of 52
	Histology	Superficial spreading melanoma : 32 out of 52 Nodular : 10 out of 52 Acrolentiginous : 5 out of 52 Not classifiable : 5 out of 52
	Mean Breslow thickness Breslow thickness under 1 mm Breslow thickness between 1 and 2 mm Breslow thickness between 2 and 4 mm Breslow thickness over 4 mm	2.2 mm (0.28 to 10mm) 31% 25% 31% 13%
	Mean Clark level	III
	Ulcerated	10
	Mean AJCC stage	II

Figure 1: A receiver operating characteristic curve for elastography. The area under the curve was 0.897.

Results

Forty-nine patients underwent US examination and elastography. Nine patients had with one or more clinically suspicious lymph nodes, 12 patients had no clinically suspicious lymph nodes but one or more suspicious lymph nodes on US and 28 patients were included at random and prior to any clinical or US examinations. Three patients had two melanomas. The characteristics of the patients and their melanomas are presented in Table 1.

A total of 111 lymph nodes were studied (i.e. an average of 2.2 nodes per patient) and 20 measured over a centimeter in size. There were 78 inguinal nodes, 20 axillar nodes and 13 cervical nodes. In all 17 lymph nodes were confirmed to be metastatic and 94 were found to be normal according to PET-CT and histologic criteria.

A total of 21 lymph nodes (of which 11 were metastatic) were analyzed in patients in the "clinically suspicious" group. The corresponding value for the "suspicious on US" group was 35 (of 5 were metastatic). Lastly, 55 lymph nodes were evaluated in the "systematic inclusion" group and only one was metastatic. The lymph nodes' characteristics and correlations between the various parameters are presented in Table 2.

In the B-mode US examination, 41% of the round-shaped lymph nodes were found to be metastatic. The corresponding metastasis rates were 38% for nodes with a Sobialti index < 1.5, 94% for hypo-echogenic nodes, 100% for nodes lacking a hilum and 64% for nodes with peripheral perfusion.

We attempted to evaluate all 111 nodes with elastography but there were three failures (due to technical problems). The elastography patterns for the remaining 108 nodes are presented in Table 3 and also in Table 4 as a function of the US malignancy criteria: there were 9 lymph nodes that met four US malignancy criteria ("highly suspicious"), 33 lymph nodes that met one to three US malignancy criteria ("doubtful") and 66 that did not meet any US malignancy criteria ("benign"). The proportion of metastatic lymph nodes within each of the four classes was as follows: 2% for pattern 1, 7.2% for pattern 2, 64% for pattern 3 and 75% for pattern 4. The mean elasticity indices for metastatic and non-metastatic nodes were 3.8 and 1.31, respectively.

The second author's evaluation showed 16 disagreements (15%): reexamination of five nodes prompted a node status change from "benign" to "malignant" because of a transition from pattern 2 to 3.

The intra-individual variability was calculated to be 10%.

The elastography procedure's diagnostic performance is described in Table 5. It had a sensitivity of 82[75-89] % and a specificity of 92[87-97] %. Elastographic analysis of nodes considered to be "doubtful" in B-mode US yielded a sensitivity of 87[75-98] % and a specificity of 84[71-96] %. The ROC curve for elastographic differentiation between healthy and metastatic lymph nodes is shown in Figure 1. The cut-off for healthy versus metastatic was situated between patterns 2 and 3; patterns 1 and 2 were considered to indicate healthy lymph nodes and patterns 3 and 4 (i.e. more than 60% of dark blue) were considered to indicate metastatic lymph nodes. The area under the ROC curve was 0.897.

Table 2: B-mode ultrasonography: lymph node characteristics.

Patients included on the basis of clinical criteria	21 lymph nodes
Balloon shape	9
Sobialti index < 1.5	10
Absence of hilum	9
Hypo-echogenicity	10
Peripheral perfusion	7
Patients included on the basis of ultrasound criteria	**35 lymph nodes**
Balloon shape	9
Sobialti index < 1.5	10
Absence of hilum	2
Hypo-echogenicity	5
Peripheral perfusion	7
Patients included systematically	**55 lymph nodes**
Balloon shape	6
Sobialti index < 1.5	6
Absence of hilum	0
Hypo-echogenicity	2
Peripheral perfusion	3

Table 3: Elastography patterns for the three groups of patients.

Patients included on the basis of clinical criteria	21 lymph nodes
Pattern 1	7
Pattern 2	5
Pattern 3	6
Pattern 4	2
Patients included on the basis of ultrasound criteria	**35 lymph nodes**
Pattern 1	20
Pattern 2	6
Pattern 3	8
Pattern 4	1
Patients included systematically	**55 lymph nodes**
Pattern 1	32
Pattern 2	17
Pattern 3	3
Pattern 4	1

Table 4: Elastography patterns for three groups of lymph nodes.

		Elastography patterns	Final status of node	
			positive	negative
Ultrasonographic status	Highly suspicious n=9	1 and 2	2	0
		3 and 4	7	0
	Doubtful n=33	1 and 2	1	21
		3 and 4	7	4
	Benign n=66	1 and 2	0	63
		3 and 4	0	3

Table 5: Diagnostic performance measures for elastography.

Performance measure	Elastography	Elastography for "doubtful" nodes in B-mode ultrasonography
Sensitivity (%, [95% CI])	82 [75-89]	87 [75-98]
Specificity (%)	92 [87-97]	84 [71-96]
Positive predictive value (%)	66 [57-74]	63 [46-79]
Negative predictive value (%)	96 [92-99]	95 [20-102]

Discussion

This first prospective study has documented the performance of US elastography in the differential diagnosis of healthy and metastatic lymph nodes in melanoma patients. We found that elastography was an effective tool for screening for lymph node involvement and appears to be a good diagnostic test for detecting lymph node recurrence in melanoma patients. The combined use of US elastography and B-mode US appears to be of value for examining lymph nodes that are "doubtful" on US, diagnosing metastatic lymph nodes and reducing the frequency of unnecessary invasive examinations and lymphadenectomy.

In terms of morphologic criteria on US, Voit et al. recently showed that peripheral perfusion, loss of central echoes and a balloon-like shape are the most important factors for lymph node involvement and survival (with an overall sensitivity of 82%) [30]. These criteria were respectively present in 65% (11 out of 17), 65% (11 out of 17) and 59% (10 out of 17) of our cases. These low values can be explained by the high number of sub-centimeter lymph nodes observed in the present study. In fact, most studies considered only lymph nodes greater than one centimeter in size. However, overall hypo-echogenicity was present in 94% (16 out of 17) of our cases. This factor has been reported to be a discriminant criterion for determining healthy or metastatic lymph node status [15].

Elastography is a non-invasive method and is quick to perform. In the present series, the technique had a good diagnostic value in the early detection of sub-centimeter lymph node metastases. The high specificity (92%) observed here shows that elastography may reduce the frequency of unnecessary invasive procedures that would otherwise be used to distinguish between healthy and metastatic nodes. In the literature, the sensitivity of elastography ranges between 85 and 91 % [18-24]. The sensitivity observed here (82%) is similar to that found by Alam et al. for cervical lymph nodes (83%), whereas our area under the curve is higher (0.897 and 0.873, respectively). The elastographic technique was more sensitive (87%) when only considering "doubtful" B-mode US lymph nodes. This shows that elastography improves the performance of US when confirming the presence of a benign lymphadenopathy or a suspected malignancy. Similarly, Alam et al.'s work on cervical lymph nodes showed that combined evaluation increased the diagnostic power when compared with each individual technique. As a result, the researchers recommended the use of both methods in clinical practice.

Lymph node elastography has not been standardized. Furukawa suggested the visual qualitative assessment of elastography patterns according to the percentage of blue color (as used in the present work). Alam et al. subsequently proposed a morphologic analysis of elastograms [18,19]. Lyshchik et al.'s study of cervical lymph nodes applied a qualitative analysis based on a gray scale. The method had

already been used in the quantitative diagnosis of thyroid nodules, in which the data to an external computer that calculates an index of pressure [20]. The test's sensitivity and specificity values were 85% and 98%, respectively.

When elastography is combined with Ultrasonography, various researchers have applied the procedure used for pancreatic nodules. This is based on an assessment of lymph node tissue homogeneity [21-24]. Saftoiu et al. combined a qualitative elastogram analysis with a quantitative, dynamic analysis running on an external computer. A software routine was used to measure the color percentage for an entire sequence of images, rather than for a single, "static" picture. This quantitative technique was more sensitive (95.8%) than the visual method alone (91.7%) [22].

Elastography be of value when a potentially metastatic lymph node is too small for diagnosis with PET-CT or if a needle biopsy is not available. In the present study, three of the 17 metastatic lymph nodes were sub-centimeter and did not meet more than two US criteria for malignancy. However, these nodes were classified as pattern 3 or 4 in the elastographic analysis and malignancy was confirmed in a pathologic analysis. In view of the low number of positive US criteria in these patients, a "wait-and-see" approach had been adopted. However, a PET-CT scan performed four months later revealed a significant increase in node size and confirmed the malignant status suggested by elastography.

Furthermore, elastography might improve US-guided, fine-needle cytology by visualizing lymph nodes areas invaded by melanoma. Aoyagi et al. have shown that elastography is an effective way of detecting metastatic, focal lymph node invasion in squamous cell carcinoma (corresponding to an asymmetric, hard cortical area) [31]. With this type of highly localized metastatic invasion, one could envisage "elasto-guided" fine-needle cytology.

Our study results indicate the presence of a correlation between a high elasticity index and metastatic lymphadenopathy, since the mean index of elasticity was 3.8 for metastatic lymph nodes and 1.31 for non-metastatic lymph nodes. The index of elasticity is rather high for a metastatic lymph node, whereas a low index does not necessarily mean that the lymph node is healthy. In the absence of literature data on this topic, we are unable to compare and contrast our findings.

This study had some limitations. The tissue around the lymph nodes has an influence on the elastographic analysis because the suspect node is compared with the conjunctive tissue and not with another node. This technique has been validated in studies of the cervical lymph nodes [18,19]. However, it is conceivable that a conjunctive tissue disease may interfere with the elastographic analysis. It is difficult to diagnose recurrent lymph node involvement if one or more lymph nodes have already been dissected, post-excision fibrosis is likely to interfere with the lymph node analysis; when combined with B-mode US, elastography might be able to provide useful information in this context.

Other difficulties were related to the lymph nodes' proximity to large blood vessels: the elastogram is distorted by the loss of pressure homogeneity induced by the vessels. Nearby vessels also interfere with the choice of the reference window for healthy tissue and thus complicate evaluation of the elasticity index.

Our small sample size prevented us from analyzing the data as a function of the node site.

We cannot be sure that the lymph node imaged elastographically corresponds exactly to that dissected by the pathologist.

Lastly, evaluation of the percentage of blue is subjective – especially in the mixed blue-green areas. Use of dedicated image processing software to measure the percentage of hard tissue would probably reduce this source of measurement bias. Furthermore, analysis of a static image induces selection bias. The software mentioned by Saftoiu (enabling dynamic analysis of the elastogram) would be very useful [19].

Conclusion

Non-invasive, real-time elastography can improve the performance of B-mode ultrasonography for the diagnosis of metastatic lymph nodes (especially those over one centimeter in size) in melanoma. Elastography appears to be a useful adjunct to PET-CT and fine-needle aspiration. Indeed, "elasto-guided" aspiration may be especially valuable for partially invaded or partially necrotic lymph nodes. The promising results obtained here must be confirmed in a controlled study, with refinement of the measurement technique.

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