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The Integrated Role of Ultrasonography in the Diagnosis of Soft Tissue Metastases from Melanoma: Preliminary Report of a Single-center Experience and Literature Review

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Abstract. *Currently melanoma has the fastest growing incidence of all cancers in men and the second in women (after lung cancer) in Western countries. Since prognosis of skin melanoma is excellent in early stages but dramatically worsens in advanced stages, an early diagnosis is fundamental in granting patients a favorable outcome. Sentinel node (SN) biopsy represents the gold standard for accurately staging melanoma, but other tests are commonly endorsed both in the initial staging work-up and in the follow-up, such as ultrasonography, computed tomography (CT)-scan and positron emission tomography (PET)-CT. PET-CT, among others, has high sensitivity and specificity for the study of distant metastases, the assessment of soft tissues and lymph node involvement, and for the guidance of surgical biopsies. Ultrasonography (US) is a non-invasive procedure whose use has recently expanded in our service, both preoperatively, intraoperatively and postoperatively, thanks to its wide availability, low costs and easy and fast reproducibility; ultrasonography even surpassed the reliability of PET-CT or CT-scan in the seven cases presented herein. US is operator-dependent, and this is probably the major limitation of the procedure, together with lack of prospective studies validating its strength, but our preliminary study demonstrates that ultrasound can assume an important role in melanoma, both for staging and the follow-up of patients, especially with lymph nodal or subcutaneous involvement.*

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Malignant melanoma represents an emerging social problem in Western countries, since its incidence has risen faster than any other malignancy in Caucasian populations over the last 30 years (1); in fact, melanoma has the fastest growing incidence of all cancers in men and is second in incidence in women, after lung cancer (2). The average age at diagnosis is 59 years and the disease has second place after leukemia for loss of potential years of life (3). In 2009, the American Cancer Society estimated 68,720 new cases of melanoma in the United States, with 8,650 disease-related deaths (4). Similar data are also provided for Europe, with slightly higher incidence in Northern countries (5). The estimates for Italy indicate 143 new cases/year every 1,000,000 men and 136/year every 1,000,000 women, with approximately 1,500 deaths per year (6).

The general outcome of patients with melanoma is excellent in stage I but dramatically worsens in advanced stages (Table I), thus stressing the importance for early diagnosis and correct staging. For the latter, the sentinel node (SN) biopsy is currently recognised worldwide as a paramount procedure (7), assuming that traditional imaging techniques do not reveal the distant spreading of tumor.

Ultrasonography (US) and computed tomography (CT) scans, sometimes even positron emission tomography (PET) CT and magnetic resonance imaging (MRI), are commonly used as the first step (8, 9) in primary staging of newly-diagnosed melanoma, as well during follow-up. Ultrasonography in particular, has recently gained wide consideration in the identification of suspicious lymph nodes, both preoperatively and in patient follow-up (10, 11), even if the role of the SN biopsy remains essential for the staging of the disease.

Our study aimed to evaluate the complementary role of US in perioperatively identifying secondary localizations of melanoma in the soft tissues and lymph nodes, as we have occasionally recently seen US findings to be even more precise than conventional imaging. Here we present the first seven clinical cases, amid a prospective study design.

Table I. *Stage related survival (American Joint Committee on Cancer) (15).*

Stage	5-year survival rate
IA	95%
IB	91%
IIA	77-79%
IIB	63-67%
IIC	45%
IIIA (T1-4aN1aM0)	70%
IIIA (T1-4aN2aM0)	63%
IIIB (T1-4bN1aM0) and (T1-4bN2aM0)	50-53%
IIIB (T1-4a, N1b, M0) and (T1-4aN2bM0)	46-59%
IIIC	24-29%
IV (M1a)	19%
IV (M1b)	7%
IV (M1c)	10%

Patients and Methods

We reviewed the data of our last 500 patients who underwent SN biopsy for melanoma; patients were treated at the Perugia General Hospital - University of Perugia, from 2007 to May 2013. During the same period a similar number of patients underwent a lymph node biopsy for suspected lymphoma or leukemia at the same center, whose diagnosis of lymphadenopathy and the identification of lymph node stations was made in 100% of cases with US.

During the follow-up, according to different stages, patients underwent US of lymphatic basins; whenever suspected metastatic lesions were noted, CTscan or PET-CT were used to obtain a total-body picture of the spreading disease and candidates for surgery were all subjected to preoperative US in order to confirm the diagnosis and to mark the surgical site.

For the majority of patients, the results of CT and/or PET-CT concurred with US findings, which were then confirmed by histological findings; recently, however we noticed in at least seven patients (Table II) that US allowed a more precise distinction of lymph node structures involved compared to the imaging scan.

Case 1. A 53-year-old male underwent excision of a dorsal nodular melanoma and then axillary completion lymph node dissection (CLND) in 2012 following the finding of a positive SN. During the follow up, PET-CT highlighted two small active nodules, located nearby the *trapezium* and the *latissimus dorsi* muscles. Preoperative US indicated an iso-hypoechoic lesion in the *trapezium* without pathological significance, and a hypoechoic lesion, with blurred margins and without cleavage plane, in the *latissimus dorsi* suspected for metastasis of melanoma. A second US was necessary intraoperatively to find the mass in the *trapezium*, while the dorsal lesion was easily found. The pathological assessment on the nuchal specimen did not identify any tumoral lesion, while the dorsal mass was found to be a fibro-muscular metastasis of melanoma. A repeat PET-CT was negative for any further tumor.

Case 2. A 31-year-old female had undergone removal of a subcutaneous popliteal metastasis of melanoma of unknown origin. The PET-CT in March 2013 indicated suspicion of a massive femoral nodal metastasis together with hyperactivity in the popliteal area. After a fine-needle biopsy, wich confirmed the nodal involvement, we scheduled the patient for a femoral lymphadenectomy and popliteal fossa exploration. The latter was preceeded by US that showed three distinct subcutaneous nodules. In the operative session, we accomplished both the lymphadenectomy and the removal of the popliteal nodules, with pathological assessment of one out of 14 metastatic femoral nodes and three nodular metastases of melanoma in the popliteal fossa.

Case 3. A 69-year-old male, underwent excision in 2011 of dorsal nodular non-ulcerated melanoma, Breslow thickness 5.1 mm, 1 mitosis/mm. The SN biopsy was positive in three nodes, and the subsequent CLND retrieved five positive nodes out of 19. During the follow-up, in April 2013, PET-CT revealed two suspected subclavian relapses; the patient underwent preoperative US that identified five subclavian structures compatible with the PET-CT findings. The lesions were excised through anterior subclavian access, and histological examination documented three out of five metastatic lymph nodes.

Case 4. A 32-year-old female was operated on at another center for a primary melanoma of the upper arm with negative SN; she was referred to our service since the PET-CT showed two hyperactive lesions at the level of the right shoulder (Figure 1), without any clinical findings. We carefully studied the patient with US, identifying two suprafascial lesions, compatible with lymph nodes, in the area indicated by PET-CT. Since no lesion was palpable, we performed intraoperative US (Figure 2) which was essential in enabling retrieval of the nodules which were found to be non-neoplastic lymph nodes on pathological assessment. A further PET-CT failed to identify any other lesions.

Case 5. In 2008, a 70-year-old male underwent the excision of dorsal animal type nodular melanoma and axillary CLND following a positive SN biopsy, with removal of 19 negative non-SN. Subsequent follow-up was negative until February 2013, when a clinical examination found a supraclavicular lymphadenopathy. The US examination revealed that the mass was actually a conglomerate of three nodes, and an excisional biopsy allowed pathological assessment of metastases of melanoma in two out of three lymph nodes, ultimately indicating the patient for neck dissection.

Case 6. In September 2012, a 69-year-old male underwent removal of nodular ulcerated melanoma of the right arm (Breslow thickness 6 mm); a fine-needle biopsy directed toward an enlarged axillary node (Figure 3) was negative, hence the patient underwent a SN biopsy (diseased node) followed by axillary CLND, with removal of 15 negative non-SN. During the follow-up, in May 2013, a CT scan highlighted a nodule in the operated axilla; the radiologist also performed an US, finding that the nodule was only a thickening of the CLND scar, while multiple subcutaneous nodules were detected near the scar on the right arm, with mixed structure and rich vascularization. A biopsy was then conducted, demonstrating subcutaneous metastases of melanoma; the patient underwent electro-chemotherapy of the part.

Case 7. An 83-year-old-male, underwent removal in November 2012 of dorsal nodular ulcerated melanoma (Breslow thickness 3.4 mm); a CT scan revealed enlarged lymph nodes in both axillae, and a fine-needle biopsy and allowed the pathological confirmation of bilateral

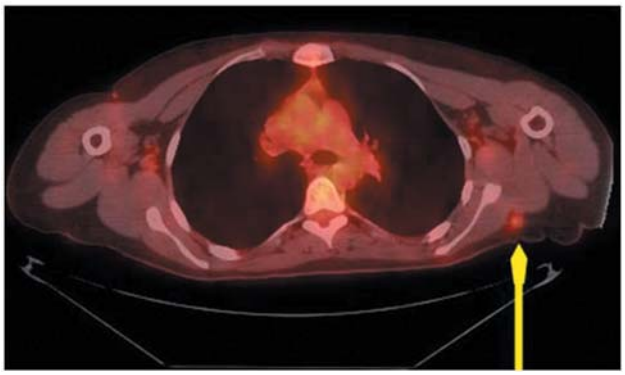

Figure 1. *PET-CT showing two hyperactive lesions at the level of the right shoulder.*

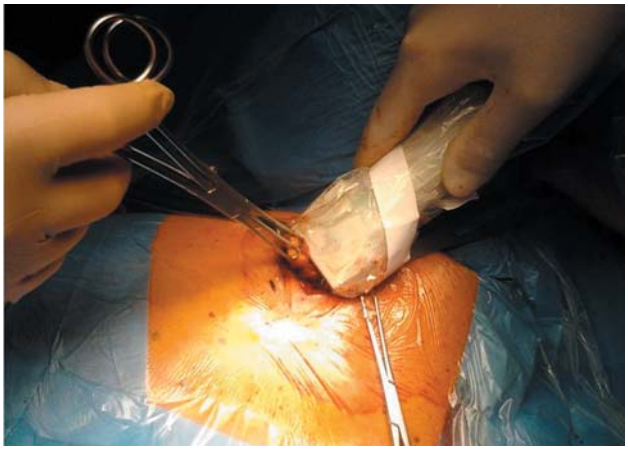

Figure 2. *Intraoperative US was essential to retrieve non-palpable nodules.*

axillary metastasis of melanoma. The patient was subjected to bilateral axillary lymphectomy, with removal of two lymph node macrometastases of melanoma out of 27 nodes in the right axilla and 1 lymph node macrometastasis of melanoma out of 14 nodes in the left axilla. Six months later, the follow up CT scan revealed multiple subcutaneous nodules in the right axilla, suspected as being metastases of melanoma. US was then conducted, revealing the lymph-nodal nature of the nodules, as confirmed later by the pathological study of the removed specimens (13 diseased lymph nodes).

Results

Our preliminary study shows an acknowledgeable impact of US in patient management, summarized in Table III.

In case 1, US was essential in identifying the correct location of nodes to be biopsied, since neither clinical examination nor PET-CT was able to precisely direct the surgeon's scalpel. This was also true for cases 2-4.

In case 1 and 4, indeed US guided the biopsy to non-palpable lymph nodes that PET-CT had highlighted as diseased but that were actually not involved by the tumor.

US was also crucial in identifying non-lymphatic structures to be biopsied, as for the popliteal nodules in case 2.

In cases 3, 5 and 7, US not only localized the nodule site (case 3) but also clarified the lymph-nodal nature of the masses and the exact number of structures to be removed, improving on the results of PET-CT (case 3 and 5) or CT scan (case 7).

In case 6, US was able to discriminate the presence of subcutaneous relapse that a CT scan had missed.

Figure 3. *A fine needle biopsy toward an enlarged axillary node.*

Discussion

Melanoma is one of the most lethal malignancies and represents a severe social problem, considering that its incidence rate has exponentially grown for several decades. The involvement of regional lymph nodes is one of the most important prognostic factors (12), moving patients from stage I or II to III, hence the need for proper nodal staging to identify patients at danger. The gold standard to diagnose nodal metastases is SN biopsy, nowadays a standardized practice, and adequate for finding micrometastases in patients without clinical or radiological evidence of disease who then go on to CLND, avoiding the cost and morbidity of a major intervention for those with negative SN (13, 14).

Table II. *Patients' characteristics.*

Patient	Age, years	Gender	Primary melanoma	Sentinel lymph node	Nodal dissection	Diagnosis of metastasis after first diagnosis by
Case 1	53	M	NM, BT 4.2, NU, dorsal	Axillary - positive	yes – axilla (24/24 negative)	PET
Case 2	31	F	Unknown	Groin nodes FNB positive	yes – groin (1 massive metastasis)	PET
Case 3	69	M	SSM, BT 5.1, M 1, NU, dorsal	3 Positive axillary limph nodes	yes – axillary (5/19 lymph node positive)	PET
Case 4	32	F	Unknown	Axillary - negative	no	PET
Case 5	70	M	NM, BT 3.1, NU, dorsal	Axillary - positive	yes – axilla (19/19 negative)	Clinical + US
Case 6	69	M	NM, BT 6, U, M 6 , arm	Axillary - positive	yes – axilla (15/15 negative)	CT – US – FNB
Case 7	83	M	NM, BT 3.4, U, dorsal	Axillary, bilateral - positive (FNB)	yes – right axilla (2/27 positive), left axilla (1/14 positive)	CT

NM, Nodular melanoma; SSM, superficial spreading melanoma; BT, Breslow thickness, mm; U, ulcerated; NU, non-ulcerated; M, mitosis; U, ultrasonography; FNB, fine-needle biopsy; CT, computed tomography.

Table III. *Difference between (PET-CT), ultrasonography (US) and pathological findings.*

	PET-CT	CT	US	Pathology
Case 1	2 Subcutaneous nodules	Unavailable	2 Subcutaneous nodules	1 Diseased, 1 non-diseased
Case 2	2 Subcutaneous nodules	Unavailable	3 Subcutaneous nodules	3 Diseased
Case 3	1 Subclavian mass	Unavailable	5 Subclavian LN	3 Diseased LN, 2 non-diseased LN
Case 4	2 Subcutaneous nodules	Unavailable	2 Subcutaneous LN	2 non-diseased LN
Case 5	Negative	Unavailable	3 Subclavian LN	2 Diseased LN, 1 non-diseased LN
Case 6	unavailable	Negative	Multiple subcutaneous nodules	Multiple subcutaneous metastases
Case 7	unavailable	Multiple subcutaneous nodules in right axilla	Multiple pathologic lymp nodes	13 Diseased LN

LN, Lymph nodes.

Both patients with negative SN and those who underwent CLND will then undergo a long (often life-long) clinical and instrumental follow-up, where integrated imaging techniques are used. The primary purpose of these investigations is to improve the general outcome by interventions aimed at changing the natural history of the disease; a secondary purpose is to early identify patients with occult stage III and IV disease. As for other malignancies, in melanoma, clinical stage also strictly correlates to prognosis that is excellent in early stages (according to TNM staging system) (15) but dramatically worsens in advanced stages (16).

In patients with stage III disease, with regional metastases, the most important prognostic factor is the number of involved lymph nodes: the greater the number of involved lymph nodes, the worse the prognosis. Macroscopic or clinical involvement of the nodes is also related to a poor prognosis (15). In stage IV disease, with distant metastases, a poor prognosis can become even worse with the increase of metastatic sites, especially when internal parenchyma is involved (17).

Every patient with a diagnosis of invasive melanoma is at risk of developing locoregional lymph node metastases, and this risk increases with the thickness of the primary melanoma according to Breslow classification (18). Nodal metastases are infrequent when melanomas are thin (0.75 mm), are present in 5% of tumors with thickness ranging from 0.75 to 1.0 mm, range from 8% to 30% in melanomas of intermediate thickness (1-4 mm) and rise to 36% when melanoma thickness exceeds 4 mm; in the latter group nodal metastases are often clinically evident (18-20). For this

Table IV. *Advantages and disadvantages of ultrasonography.*

Advantages	Disadvantages
Wide availability	Operator-dependent
Low cost	Absence of prospectic studies
Easy and fast reproducibility	
Non-invasive	
Preoperative use	
Intraoperative use	
Follow-up	
Greater sensitivity than PET-CT in stage I and II	

PET-CT: Positron emission tomography.

purpose, it is essential to perform a thorough evaluation of all the superficial lymph nodes in each patient with a first diagnosis of melanoma: metastatic lymph nodes rapidly enlarge, are not painful and can adhere to the surrounding planes with an increased consistency.

The current international guidelines are not univocal on how to perform the follow-up of patients with melanoma (21), and data are especially discordant regarding the usefulness of investigations in stage I or II disease. Even in the third stage, no randomized study have demonstrated the effectiveness of any technique at increasing survival (22, 23), with US, CT and PET-CT as the most used procedures.

In recent years PET-CT has gained enthusiastic acceptance, but the most recent studies have downgraded its role in patients with melanoma (24). PET-CT cannot play a main role in patients with stage I and II disease (25-28), since it is absolutely incapable of capturing micrometastases (29-31) due to its low sensitivity compared to the SN biopsy. PET-CT instead is useful in advanced stages, for the identification of distant metastases (24) due to its high sensitivity and high predictive value for stage III palpable nodes and stage IV distant metastases (32-34). An article by Bastiaannet *et al*. in 2012 demonstrated a sensitivity of 86.1% and a specificity of 93.1% for PET-CT in patients with stage III or IV melanoma, thus stressing out the importance of the procedure during the follow-up (33).

The role of US in the diagnosis of lymphadenopathy in patients with melanoma has recently been re-evaluated, both during the initial work-up and in the follow-up, where US should be considered a routine examination. Several studies have shown the superior sensitivity and specificity of US compared to clinical examination, but recent articles have also demonstrated a superiority of US compared to PET-CT in the study of lymphatic basins (8, 35, 36, 38); the main problem with US is that it is an operator-dependent technique, and further examinations are required to validate its real usefulness (35-37,39). In all the cases that we present here, we could appreciate a relevant impact of US on the surgical planning, improving the imaging technique results, impacting on the procedure both on the elucidation of the nature of the mass and of its actual topography and number. In five cases, the comparison was between US and PET-CT, in two between US and CT. Of course, US has a major relevance during the follow-up of high-risk patients, where the early identification of nodal involvement can direct the patient through to an early surgery, relevantly impacting on the patient's outcome.

If we had to compare US to clinical examination, which retains its usefulness during the follow-up mainly in exploring supraclavicular and axillary nodes (35), US claims a superior reliability thanks to sensitivity of 89.2% and specificity of 99.7% (35, 36). In particular, Brountzos *et al*. found US to have a sensitivity of 100% in the identification of axillary lymphadenopathy, and 93.3% in the groin (36). In two of the cases presented were (cases 1 and 4), we successfully trusted in intra-operative US as being the only tool to find non-palpable masses to remove, and in almost every case we treated, the US assessment of tissues to be collected overcame the palpatory findings in precision and accuracy.

In 2010 Sijan *et al*. tried to outline the sonographic features of pathological lymph nodes in patients with melanoma, so as to conduct directly in these patients nodal dissection avoiding SN biopsy, without, however, concrete results; as a matter of fact, they confirmed that lymph node enlargement is not sufficient to define a neoplastic involvement so as to enrol the patient for nodal dissection (38). Our group, with an experience of over 1,000 SN biopsies, has never based the nodal dissection indication on data different from the pathological assessment of metastatic disease, as demonstrated by cases 2 and 6, where a clear discordance between fine-needle biopsy and imaging demanded a surgical biopsy to confirm the nodal involvement. In the literature some data are reported on the fine-needle biopsy and US in superficial nodal districts (40), but sensitivity and positive predictive value were extremely unsatisfactory for disclosing micro metastases. Conversely the integration of US and fine-needle biopsy may be useful in cases of macrometastases, directing patients to immediate lymphadenectomy (41), as shown in case 7; nodal metastases of size greater than 4.5 mm can be easily identified by US (42).

Our experience and the literature are concordant in assuming that SN biopsy is currently a fundamental tool in patients with stage I and II melanoma, superior to US or US-guided biopsy; however US examination has proven to be superior to the most renowned PET-CT to study lymphatic basins, also considering the costs and benefit balance (43).

In a 2011 meta-analysis by Xing *et al*., US was the main test to diagnose large lymph node metastases of melanoma in patients with clinical stage I and II disease, while PET-CT retained its value in patients with stage III or higher disease, for the detection of distant metastases (44) .

In our experience, albeit limited, and in agreement with the literature, US has greater sensitivity than PET-CT for the diagnosis of lymph nodal and subcutaneous metastases in patients with advanced stage or symptomatic melanoma. US even has other advantages, since it is of low cost and repeatable, widely available and easily allows the operative site to be marked before the intervention and to be checked intraoperatively, if necessary (Table IV).

Conclusion

From our preliminary study and a thorough review of the most recent international literature, we conclude that US examination is essential in the study of patients affected by skin melanoma, both in initial staging and in follow-up, notably in patients presenting with early-stage disease. US in particular demonstrates a high diagnostic sensitivity and

specificity, compared to PET-CT and CT, in the identification of possibly involved lymph nodes and in the characterization of their site, number and topography.

Conflicts of Interest

The Authors state that none of them involved in the manuscript preparation has any conflicts of interest regarding the manuscript itself, neither financial nor moral conflicts. Furthermore, none of the Authors received support in the form of grants, equipment, or pharmaceutical items.

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