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Stage IIA Cutaneous Melanoma: Do Regional Ultrasound and CT scan Improve Detection of Relapses? A Multicenter Retrospective Observational Study

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ABSTRACT

Introduction: Stage IIA cutaneous melanoma is typified by a Breslow thickness between 1.1 and 2.0 mm with ulceration or between 2.1 and 4.0 mm without ulceration.The role of radiological investigations in staging and follow-up of this intermediate-risk subgroup of patients is still debated.

Objectives: The aim of this study is to investigate the role of imaging procedures in the follow-up of stage IIA melanoma asymptomatic patients.

Methods: Data were retrieved from two tertiary referral centers in Italy. Among patients with stage IIA melanoma, those who relapsed were investigated concerning type of detection (by patient or by doctor), and modality of detection (clinical examination, ultrasound, CT scan). In addition, false positive data were collected.

Results: In total, 213 patients were retrieved, with 26 patients showing relapse (recurrence rate, 12.2%). The mean follow-up time was 3 years and the mean time to recurrence was 17.8 months. 21/26 (80.7%) recurrences were identified by the doctor and 5/26 (19.2%) by the patient ($P < 0.05$).

Among those identified by the doctor, 16/21 (76,1%) were identified by radiological examinations. Nine out of 15 (60%) lymph node recurrences were detected by ultrasound and 6/7 (85.7%) distant metastases were detected by CT. The false positive rate was 7% ($P < 0.05$).

Conclusions: In our study the great majority of metastases were detected using imaging procedures. Given the new therapeutic options offered by targeted therapy and immunotherapy in relapsing patients, the role of radiological investigations in the follow-up of stage IIA patients should be reconsidered.

Introduction

Stage IIA cutaneous melanoma is characterized by either an ulcerated primary tumor with a Breslow thickness between 1.1 mm and 2 mm (T2b, Figure 1) or a non-ulcerated melanoma with a thickness between 2.1 mm and 4 mm (T3a, Figure 2), without nodal and distant metastases [1]. The 5-year survival rate is 93% for a T2b melanoma and 94% for a T3a melanoma [1]. The 10-year-survival decreases up to 88% for both the substages, as the risk of relapses varies from 9% to 24% [2-5] .

In the literature there is a lack of studies investigating the imaging procedures to be performed in asymptomatic IIA melanoma patients. Therefore, different guidelines propose different management protocols. Comparing the leading international guidelines, concerning staging workup, computed tomography (CT) scan is not recommended by the NCNN guidelines and the Cancer Council Australia (CCA), whereas the AIOM guidelines suggest performing chest and abdomen CT [6-9]. Only the SIDeMaST guidelines suggest performing brain, chest and abdomen CT from stage IIA onwards [10]. Moreover, CT or positron emission tomography (PET)/CT are suggested by SIDeMaST every 12 months as follow-up workup of asymptomatic patients, whereas routine imaging is not recommended in this stage by any of the previously mentioned guidelines.

Regarding ultrasound, AIOM and SIDeMaST recommend nodal basin ultrasound prior to sentinel node biopsy (SNB), NCCN suggests performing it only in case of equivocal physical exam, and CCA indicates nodal ultrasound in case of impossibilities to perform SNB. Regarding follow up imaging in asymptomatic patients, routine nodal basin ultrasound (and abdomen) is suggested with a 6-months interval only by SIDEMAST guidelines.

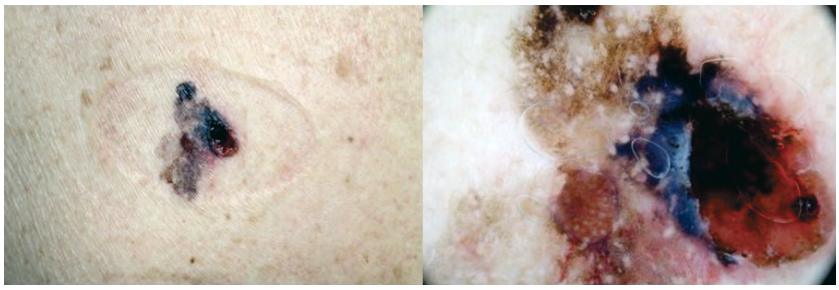

Figure 1. Clinical and dermoscopic images of cutaneous melanoma pT2b, Breslow thickness 1.5 mm with ulceration.

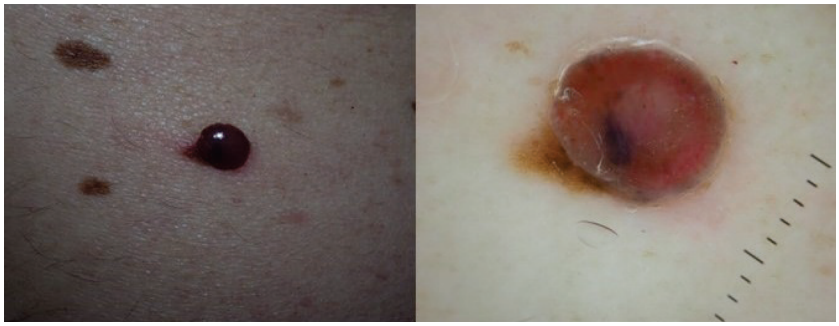

Figure 2. Clinical and dermoscopic images of cutaneous melanoma pT3a, Breslow thickness 2.7 mm without ulceration

The reason of these discrepancies relies on the different National Health Care reimbursement systems and on the lack of studies about the real cost benefit ratio of these procedures. As stage IIA is often grouped with IB or with IIB and IIC, data of this small cohort are often not statistically significant, when retrievable [11-13]. Stages IIB/IIC are characterized by a five-year melanoma specific survival rate very similar to stage III and clinical trials are ongoing to evaluate the efficacy of adjuvant therapy in this category of patients [1,14] . While IIB/C represent a high-risk cohort, IIA remains an intermediate risk substage, where patients are only candidate to follow up.

Objectives

The aim of this study is to investigate the role of imaging procedures in the follow-up of stage IIA melanoma asymptomatic patients.

Methods

This study was designed as a multicenter retrospective observational study. All data about consecutive patients who excised a melanoma staged as IIA were retrieved from the databases of two academic referral centers. Patients were followed-up three times a year. Every four months they practiced clinical and dermoscopic total body examination, exhibiting nodes ultrasound twice a year and CT scan once a year. Patients missed to follow up were not recalled.

Age at diagnosis, sex, and follow-up (FUP) period were recorded. Among these cohort of patients, those who relapsed during FUP, were further investigated by reporting the modality of detection (by patients or by doctors through clinical examination, ultrasound or CT scan).

Moreover, false positive (FP) imaging results and other diseases detected during FUP were also recorded. Any event that changed the normal patient follow-up, eg adding new radiological tests or anticipating the next visit, was indicated as a FP case.

Statistical analyses were performed with Software R. Descriptive statistics of the cohort are provided with confidence intervals. Chi-squared test for categorical variables and the T-test for continuous variables were used. Statistical significance was set at $P < 0.05$.

Results

We identified 213 patients with stage IIA melanoma, with a male/female ratio of 1. The overall median age was 58 years. Median Breslow thickness of the primary tumor was 2.3 mm and 61% of the lesions were not ulcerated. Concerning lesions location, 70% of melanomas were equally distributed between trunk and extremities, followed by the head/neck (12.67%). The differences between the two groups of recurred versus non recurred patients are described in Table 1. Median overall FUP period was 2.84 years (range 1.0-11.1 years) The recurrence rate was 12.2% and the median time of recurrence was 13.8 months (range 2.4 months-5.5 years).

Relapses were categorized according to the site (local/in-transit, nodal, and systemic). The most frequently observed relapses were nodal (N = 15, 57,6%, 95% confidence interval [CI] 37%-76%), followed by distant (N = 7, 26.9%, 95%CI) and local (N = 4, 15.3% 95%CI) (Table 2). Lungs were the most frequent site of systemic relapse, being involved in 70% of the cases, followed by the brain (30%).

The method of detection was firstly divided into two categories, namely, patient-detected (19.3% of cases) and physician-detected (80.7%), with a $P < 0.05$). Patients were able

Table 1. General findings and differences between the two groups of recurred versus non recurred patients.

	No Reccurred patients	Recurred patients
	N 187 (%)	N 26 (%)
Sex		
M	91 (48.7)	15 (57.7)
F	96 (51.3)	11 (42.3)
Location		
Head and Neck	25 (13.4)	2 (7.7)
Trunk	83 (44.4)	14 (53.8)
Extremities	75 (40.1)	10 (38.5)
Unknown	4 (2.1)	0
Ulceration		
Yes	72 (38.5)	9 (34.6)
No	115 (61.4)	17 (65.3)
Breslow[a], mm	2.3	2.5
Age[a], years	58	65

[a]= average

Table 2. Relapses and method of identifications

Type of recurrence	Patient detected N (%)	Doctor detected N (%)	P	Total N
Local	2 (50%)	2 (50%)	ns	4
Regional	2 (13.4%)	13 (86.6%)*	ns	15
Distant	1 (14.3%)	6 (85.7)♦	ns	7
Total	5 (19.3%)	21 (80.7)	<0.05	26

Ns = not statistically significant.

to identify 2 out of 4 of the local recurrences and 13.3% of the nodal metastases (2/15 cases) due to visible and/or palpable lesions. One distant metastasis was found by the patient due to its localization in the muscle.

Physicians were able to detect 2 out of 4 of local/in-transit metastases and 3 out of 5 nodal metastases thanks to clinical examination. Surveillance imaging of asymptomatic patients led to the identification of a total of 61.5% relapses, with 7/16 identified by CT scan and 10/16 by ultrasound (Table 2). Considering only nodal metastases, 69.2% were diagnosed by ultrasound (9/13 cases), 23% (3/13 cases) by clinical examination, and 7.7% by CT (1/13 cases).

The FP rate during the follow up was 7% ($P < 0.05$). These were due to one patient with lung micronodules detected by CT scan and subsequently diagnosed as an inflammatory process by further follow-ups. Another patient was found positive to suspected secondary lesions of the liver but a subsequent magnetic resonancerevealed the presence of multiple cysts and an angioma. Some patients referred nodal pain and a nodal ultrasound was performed revealing negative results. A patient developed a palpable nodule on the primary scar, which was excised and diagnosed as pilomatrichoma. Melanoma surveillance imaging led to the detection of one kidney cancer, one lung cancer and one brain meningioma.

Conclusions

In our study 12.2% of stage IIA melanoma patients relapsed after a mean follow-up period of 3.7 years. This is in line with previous studies, in which the reported percentage varies between 9%[2] and 24% [2,5]. The median age of patients who had a recurrence (64 years) was older than those who did not recur (58 years; $P < 0.05$). Almost 60% of the patients who recurred were male and the location of the primary tumor was the trunk in more than 50% of cases. These findings are according to literature, where axial melanomas of middle aged men are more prone to recur than other categories [15,16]. Time to recurrence was 18 months, which is slightly inferior than that previously reported (median, 22-25 months) [15,16].

Our study showed that most of relapses are physician-detected (80.7%), and among these, 76.1% were detected by imaging techniques. This is in contrast to previous studies that reported the majority of relapse as patient-detected [17-20]. Francken et al in 2007 found that 67% of the recurrences were detected by the patient on the total of 211 recurring patients [17]. Moreover, they did not find a significant survival difference between patient-detected and doctor-detected relapses or between asymptomatic and symptomatic relapses. Thus, the authors concluded that self-examination may be sufficient and did not encourage the use of surveillance imaging. The similar survival rates of patient- and doctor-detected relapses might have been influenced by the fact that in those years target therapies and immunotherapy were still not available, thus an earlier detection of metastases was not leading to an improved survival.

In the last decade, the therapeutical management of melanoma has improved radically. Sustained recurrence-free survival benefit in patients with resected stage IIIB-C or IV melanoma treated with immunotherapy and target therapy have been demonstrated [21,22]. Since it has already been demonstrated that an early relapse detection is associated with improved overall survival due to the new therapies, more efforts are needed in this direction [2,23,24].

Furthermore, in the study by Francken et al imaging tests were not performed routinely as these were requested according to 'physician criteria' or the patient symptomatology [17]. This may probably have led to biases and to the erroneous conclusion that image-based protocols are not superior to clinical-based FUP.

Similar results were achieved by Moore et al, who found 10 relapses detected by imaging in a total of 66 relapses (15%) in the group of stage IIA melanoma patients [18]. Patients whose recurrence was self-detected by physical examination had a significantly improved survival compared to those detected by symptoms or by imaging. Suffice to say that this could be referring only to loco-regional recurrences that might eventually be self-detected by the patient; whereas distant metastases can be detected only by the occurrence of systemic symptoms or a positive radiologic test. In a more recent study, Lee et al retrospectively reviewed 738 patients with pathologic stage II melanoma [3]. Of 400 patients with stage IIA melanoma, 24% relapsed. Among these, patient-detected accounted for 66% relapses, whereas 22% was detected by physician examination and 12% by imaging.

In our study, 61.5% of relapses were detected by surveillance imaging ($P < 0.05$). This is a much higher rate than those reported in the literature (12% to 20%) [3,5]. The higher incidence of imaging-detected recurrence in our cohort is probably related to the routine imaging monitoring practiced in Italy. In all, 60% of nodal metastasis were diagnosed by ultrasound that has already reported as a more sensitive and specific technique for lymph node assessment than palpation or other imaging techniques [25,26].

Although Ribero et al reported no difference in survival between clinical-based and ultrasound-based FUP in stage IB and IIA melanoma, this result might be mainly related to stage IB melanoma that accounted for the great majority of cases in their study (70% of patients) [11].

Our study has several limitations. First, the sample size of relapsed patients, responsible for a low precision of the estimates. Several patients were missed, since they decided to

continue in other hospitals. Second, the relatively short mean follow-up of our patients (3.7 years). However, it is known that the highest probability of identifying recurrences occurs in the first two years from the diagnosis [15]. Third, the retrospective study design, which can affect the robustness of the evaluation of factors influencing the outcomes.

Regarding the problem of FP, our study revealed 7% of FP ($P < 0,05$). Most of FP studies are on stage III. However, our finding is according to literature. Variable FP rates of 7%-9% are reported and the authors conclude that the possibility to offering new therapies far outweighs the false-positive problem [20,27].

Another problem related to melanoma surveillance is the psychologic burden of the periodic screening tests. Some patients refer that frequent follow-ups cause anxiety, fear, and a repeated reminder of the possibility of cancer recurrence and mortality. Other patients think that regular clinic visits evoke a sense of safety and reassurance [28]. The physicians have to promote tailored supportive care program in the form of educational techniques, behavioral or skill training, social support, and psychotherapy.

Prospective studies are needed, particularly comparing, in stage IIA patients, those followed with clinical examination and radiographic surveillance and those without, in order clarify whether imaging exams allow an earlier diagnosis and a better survival.

Since it is known that early detection of relapses could improve the prognosis and systemic therapies are increasing the survival of relapsed patients, the role of imaging procedures in the follow up of asymptomatic stage IIA patients should be reevaluated.

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