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Acral Lentiginous Melanoma – Misdiagnosis, referral delay and 5 years specific survival according to site

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Abstract. – OBJECTIVES: Acral lentiginous melanoma (ALM) is a defined histopathological entity with peculiar clinical-pathological features and is the most common subtype of malignant melanoma in acral locations. The 5-year survival rate is lower than that for all cutaneous malignant melanoma overall (80.3% versus 91.3%). Controversy exists in the literature as to whether this worse prognosis is attributable to a more aggressive biological nature or to difficult-to-see sites and consequent advanced stage at the time of diagnosis. The main purpose of the study was to explore any prognostic difference according to upper limb or lower limb localizations, based on the hypothesis that upper limb localizations might receive attention sooner than lower limb localizations.

PATIENTS AND METHODS: A cohort longitudinal study was performed through a retrospective review of all patients consecutively referred to our Unit with histological confirmation of ALM. Data were collected from a 10 year period between 1996 and 2006 to allow determination of 5 year survival statistics.

RESULTS: Out of 87 patients included in the study, 32 were men (37%) and 55 were women 63%. The average number of months it took for patients to present was 62 months with a mode of 12 months. Overall 5 year survival was 80% and a multivariate analysis showed that the most reliable prognostic indicators are the Breslow's thickness and the margins of complete excision. When controlling the survival rates for Breslow thickness, the values were similar to the reported rates indicated in the recent literature for cutaneous malignant melanoma.

CONCLUSIONS: The higher aggressiveness of ALM was noticed to be attributable to a later stage and more advanced thickness at diagnosis. No significant difference was found between upper and lower limb localization in terms of prognosis.

Key Words:
Acral lentiginous melanoma, Melanoma, Cutaneous malignant melanoma, Skin cancer.

Introduction

Acral lentiginous melanoma (ALM) refers to a subtype of melanomas arising in the extremities (from greek ακρός: distal) which display a lentiginous histologic pattern. Reed[1] in 1976 defined ALM as a clinical entity with distinct histopathologic features located to palmar and plantar surfaces, subungually, or to glabrous skin of the dorsum of the hand and foot. This description was similar to Hutchinson's melanotic freckle, dating back to 1886[2]. Both the histopathological and localization conditions need to be respected in order to make diagnosis of ALM, as some previous published series confused the simple concept of acral site with the more specific definition of ALM. ALM is rare in caucasian populations (1-7%)[3-8] but has higher incidence in nonwhite individuals, accounting for up to 58% of all cutaneous melanomas in Asia[9] and even more (60-70%) in black populations[10]. Despite its definition as a subtype of melanoma, a long controversy has been apparent in the literature as to whether or not this lesion carries its own prognostic significance with the common assumption that ALM is more aggressive and carries a worse prognosis than other subtypes of melanoma[4,5,11]. Concern arises at the time taken in referral of patients with ALM as the suspicion of a melanotic lesion is often delayed.

This study reviewed all cases of ALM treated at our Institution over a 10 year period to determine the time taken to refer patients for assessment, the stage of disease at presentation and the subsequent 5 year survival rate following treatment. Our hypothesis stated that referral delay accounted for patients presenting with advanced disease rather than inherent tumour aggressiveness.

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Patients and Methods

A cohort longitudinal study was performed through a review of all patients consecutively referred to our Unit with histological confirmation of ALM. Data were collected from a 10 year period between 1996 and 2006 to allow determination of 5 year survival statistics. Information collected included patient demographics, location of lesion, time from initial presentation of patient to their G.P. (general practitioner) to referral to plastic surgery, the standard histology dataset for melanoma, excision margin and 5 year survival rate. All patients were discussed at a local skin cancer MDT (multidisciplinary team) with management based on UK national melanoma guidelines[12,13]. Data protection was respected throughout the investigation as patients were anonymized.

Statistical Analysis

A statistical analysis was performed, aimed at finding the main (statistically significant) predictors to the final outcome up to 5 years. The possible outcome has been classified as: Death, Free survival and Survival with disease. To this end, a multinomial logit model was identified and estimated. The variables assessed in this analysis included: Age; Gender; Time of noticing signs to seeking treatment; Time until definitive treatment; Breslow's thickness; Clark level; Mitotic rate; Ulceration; Final margin of excision in mm; Major axis [cm]. Moreover, the impact of the variable site on the survival was investigated as an univariate factor, as well as the impact of the variable time of noticing signs to seeking treatment and the Breslow thickness.

Results

Between 1996 and 2006, 87 patients were diagnosed with histologically-proven acral lentiginous malignant melanoma. Out of these 87 individuals, 32 were men (37%) and 55 were women (63%). Mean age at diagnosis was 67 (range 26-91). Distribution into classes of age is shown in Table I.

In terms of ethnicity, 100% of cases were white. Five patients (5%) had previous melanoma. Time of noticing signs to seeking treatment varied between a minimum of 1 month and a maximum of 30 years, with a statistical mode of 1-3 years before seeking treatment, corresponding to the 26%

Table I. Distribution of patients into age intervals.

n=86	Number of cases	Percentage
10-19	0	0.00%
20-29	2	2.33%
30-39	1	1.16%
40-49	6	6.98%
50-59	13	15.12%
60-69	18	20.93%
70-79	21	24.42%
80-89	19	22.09%
90-99	6	6.98%

(Figure 1). Reasons for delayed referral (defined as greater than 7 months) were varied. These included misdiagnosis of the lesion as a mole (14%), an ulcer, an abscess or another type of infection (16%), a wart (8.3%), a nail bed dystrophy (6%), and lastly as the result of a trauma (28%). In 22% of cases lesions were picked up on incidental examination (Figure 2). Time until definitive treatment (complete excision, without wider excision) was on average 1 month since diagnosis. The most common diameter of the lesion, in terms of major axis, was 1 to 1.4 cm, with a minimum of 0.5 cm and a maximum of 6.7 cm, as shown in Table IV and Figure 3. The most frequently affected sites were by far the feet and ankles (84%), followed by hands (16%).

Within feet, the most common sites were the hallux (19% of the total study group) and the heel (12%). In the hand the thumb was the most common site (6%). Breslow's thickness varied between a minimum value of 0.7 mm and a maximum of 56 mm with a mean value of 7.9 mm. When distributed into 1 mm intervals, the most frequent Breslow's thickness group was between 1.01 and 2.00 mm (Figure 4).

Clark level was 4 in the majority of cases (74%), followed by 1 (24%), corresponding to intraepidermal lesions (in situ) and 2 (2%). Histological features of regression were present only in one case (2%), while frank vascular invasion was noticed in 2 cases (3%). In 3 cases (5%) there were foci of vascular invasion and in the vast majority of cases it was absent (92%). The mitotic rate was most commonly 1 mitosis per high power field (35%). Ulceration was present in 39% of cases, with variable extents of ulceration.

The final margin of complete excision (including the wider excision) varied between a minimum of 1 mm and 64 mm, with the most common values being in the ranges 10-19 mm (39%),

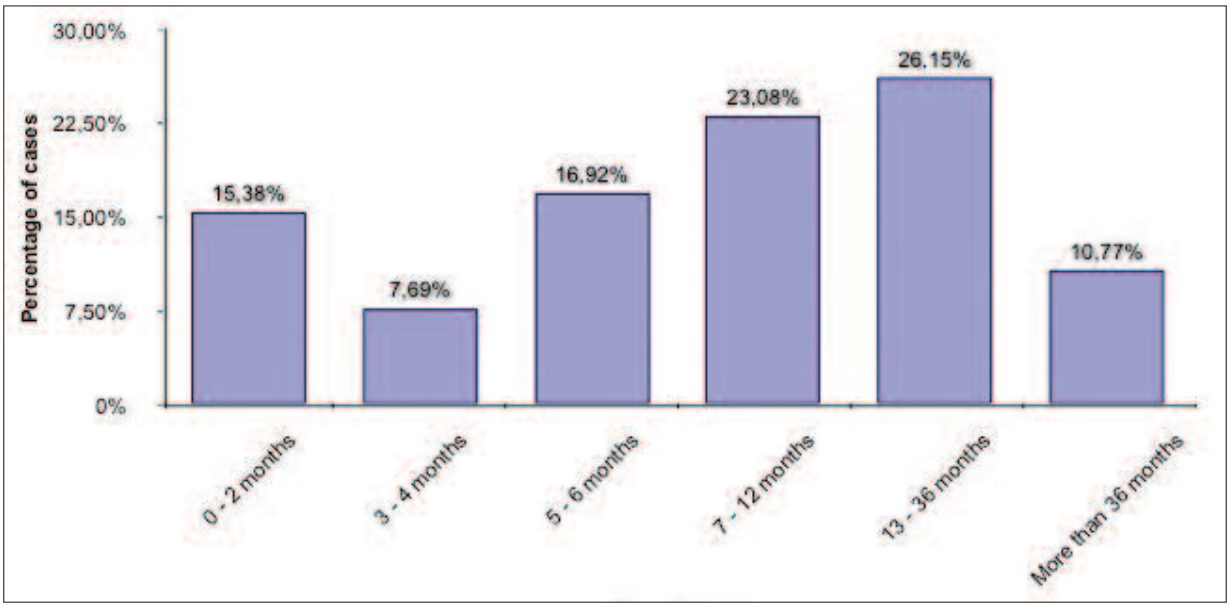

Figure 1. Time of noticing signs of the suspicious mole to seeking specialist's surgical attention.

20-29 mm (23%) and 1-9 mm (19%). The excision was incomplete in the first instance, either intentionally (punch biopsy) or unintendedly, in 10% of cases. In 8% of these cases the patient did not attend for the wider excision due to poor compliance with medical treatment, although 2% of cases subsequently underwent completion of excision.

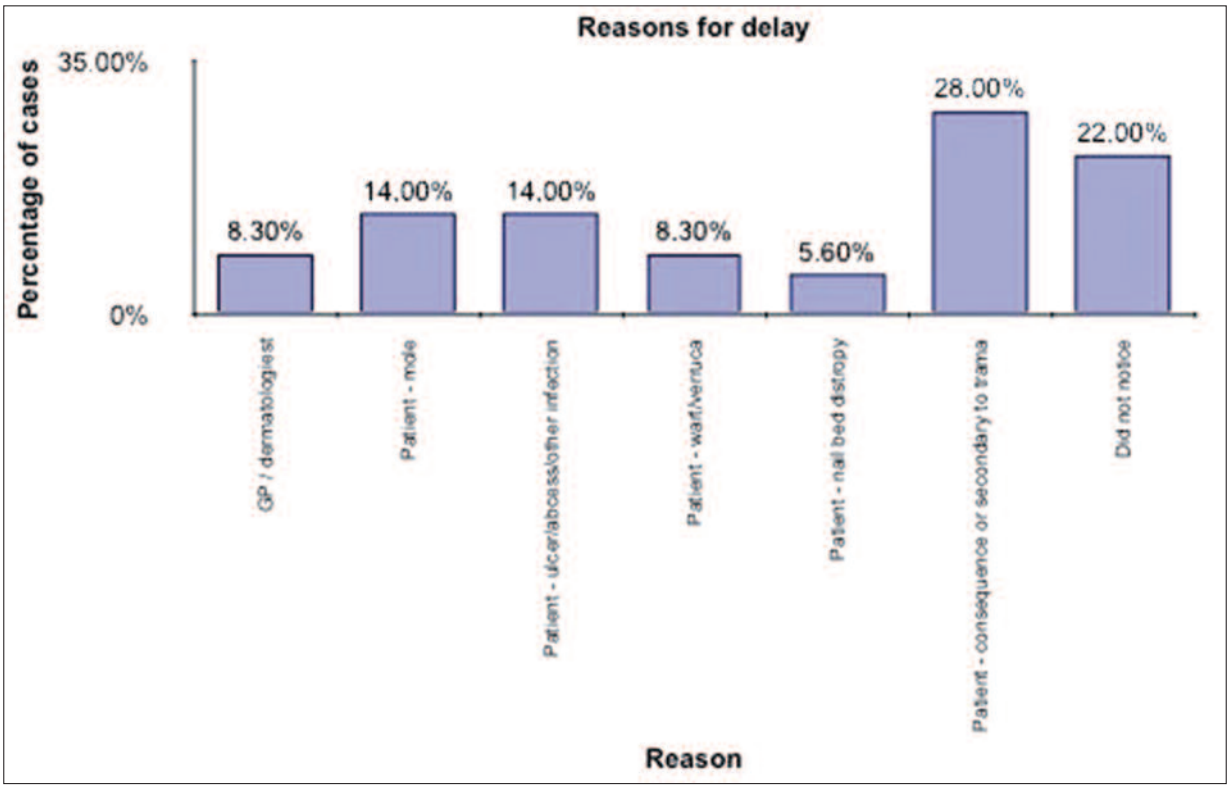

Figure 2. Reasons for delay in taking a suspicious mole on extremities to surgical specialist's attention.

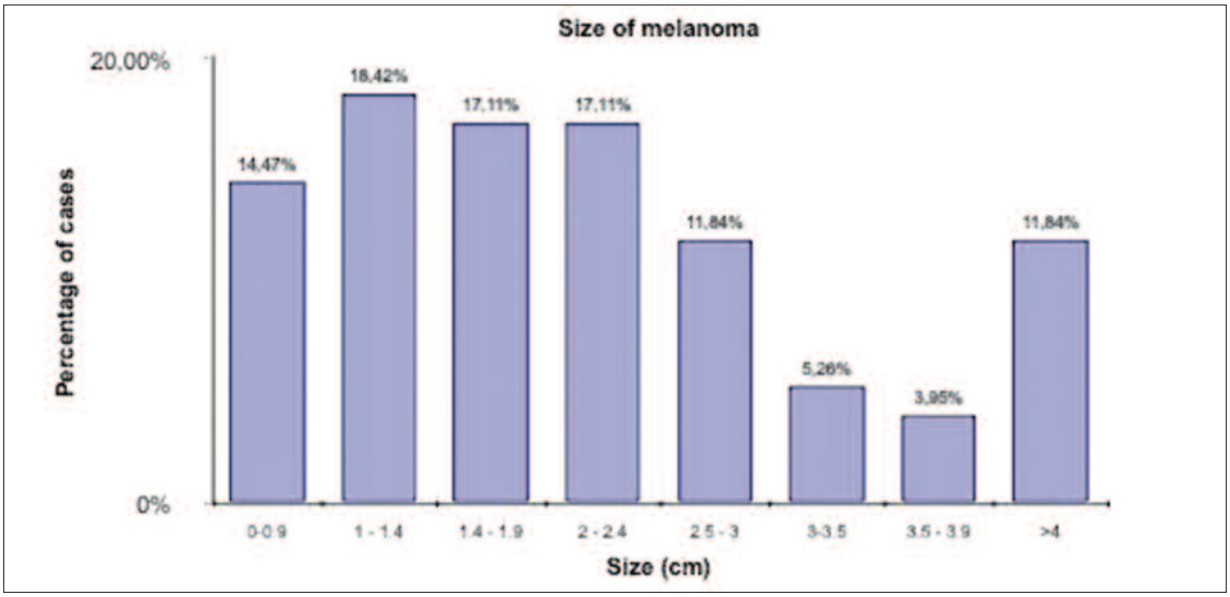

Figure 3. Size (major diameter) of acral lentiginous melanomas.

Five-year survival rate was 80%, and in 14% of cases metastases were found at 5 years' follow up. Table II shows specific 5 year survival rates according to Breslow's thickness and figure 5 displays the Kaplan-Meier survival curves for hand localizations, feet localization and for all patients.

The prognostic effect of the site of the melanoma was explored, considering location to the upper limb versus lower limb. The population associated with the upper limb showed the following frequencies: 42% (Death), 33% (Free survival) and 25% (Survival with disease).

For the feet, the observed frequencies are: 31% (Death), 60% (Free survival) and 9% (Survival with disease). This empirical data suggest that there may exist some prognostic effect of the variable site.

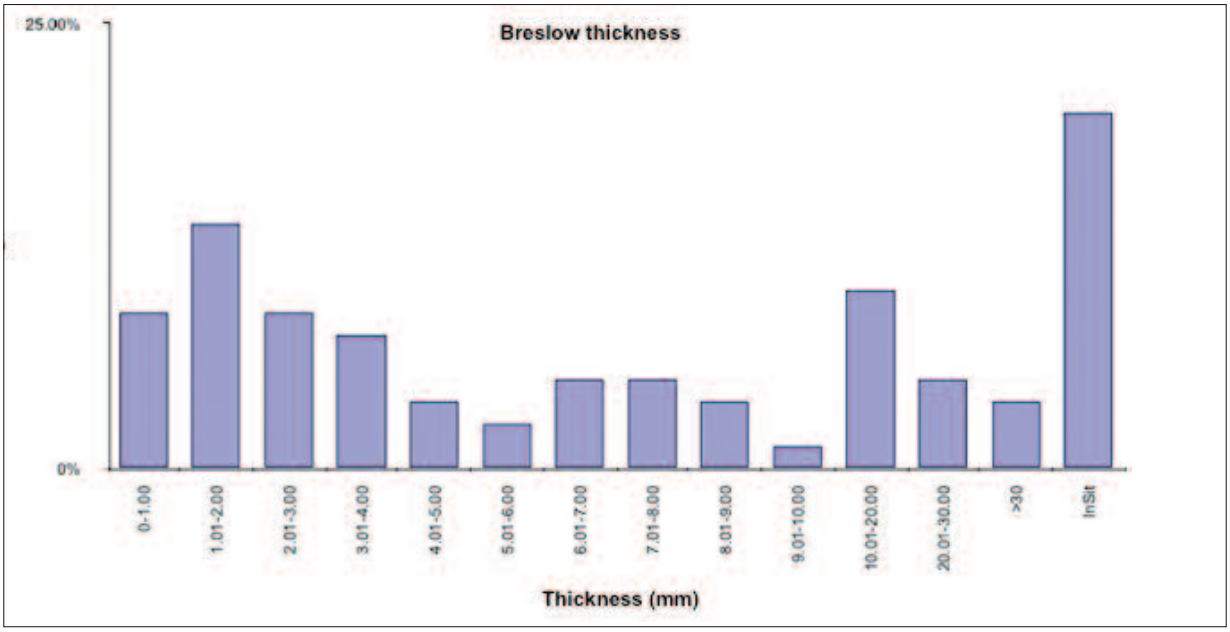

Figure 4. Breslow's thickness expressed as 1 mm classes.

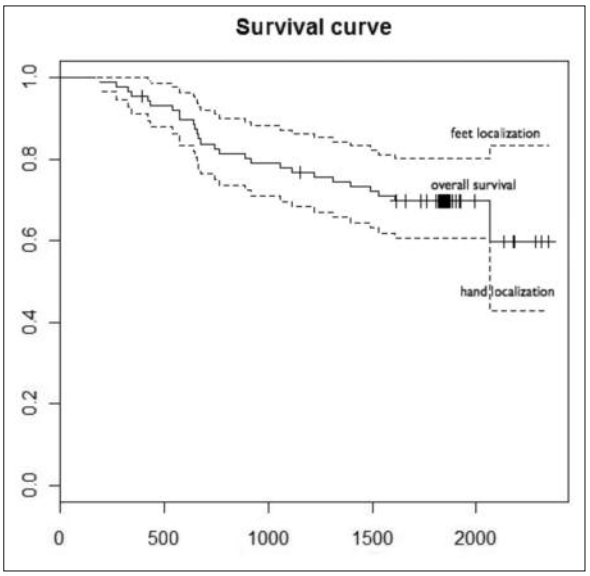

Figure 5. Survival curves according to Kaplan-Meier method. Feet localizations (*superior curve*), hands localizations (*inferior curve*) and overall (*central curve*).

More formally, we identified a multinomial logit model on the whole database, with all the possible predictors previously mentioned including Breslow's thickness, margin tumour site.

In addition, the variable tumour site was explored as a univariate factor to check the hypothesis that localization to upper limbs carries worse prognosis than localization to lower limbs. The *p*-value associated with this test was found to be 0.06797. This value (slightly greater than 0.05) does not allow to conclude there is significance at $\alpha = 0.05$ but shows significance at $\alpha = 0.1$, for instance. This denotes that a certain influence of the site of the melanoma actually exists, although its impact is not strong. Another univariate analysis correlated the Breslow's index with the variable time of noticing signs to seeking treatment, in the hypothesis that the longer the wait the deeper the Breslow's thickness. Unexpectedly, the *p*-value relative to this correlation was negative ($p = -0.2932563$), indicating that the time elapsed from the appearance to the medical consultation correlated negatively with the Breslow's thickness, although this was not statistically significant.

Table II. Specific survival rates according to Breslow thickness.

	5 year survival (%)
Overall	80%
Thickness 0-1.00 mm	92%
Thickness 1.01-2.00 mm	80%
Thickness 2.01-4.00 mm	71%
Thickness > 4 mm	52%

The multivariate statistical analysis to identify the most significant predictors was performed through the statistical software R (www.r-project.org/). Several multinomial logit models were taken into account, considering combinations of the possible predictors, which were added to the model in a nested way. These models were compared pairwise through a likelihood ratio test. Using this approach, we found that the most reliable prognostic indicator is Breslow's thickness and margin of complete excision. This is in agreement with current literature.

Discussion

Acral lentiginous melanoma distinguishes itself from the other subtypes for many features, both histological and clinical-prognostic. A long controversy has been occurring since its description, with regard to the cause of the worse prognosis compared to the other subtypes. According to some studies, the ALM is considered a subtype of melanoma with an intrinsic higher aggressiveness[14-18]. However, in many of these studies the material utilized included all melanomas localized to extremities, rather than actual histologically proven lentiginous acral melanomas. This means that the site was explored, rather than the ALM subtype, and indeed the localization to feet and hands has proven to be a prognostic negative factor compared to more proximal localization. The ALM subtype itself, when corrected for thickness values, does not show in our study a significantly more negative prognosis.

When controlling the survival rates for Breslow's thickness, the values were similar to the reported rates indicated in the recent literature[19] for cutaneous malignant melanoma (Table III).

Therefore, the alleged higher aggressiveness of ALM is really attributable to a later stage and more advanced thickness at diagnosis, which is also verified for other melanoma subtypes with acral localizations.

These findings are in line with many other reports that also pointed out the problem of relatively later diagnosis for ALMs and other acral melanomas[4,5,11,19-24]. The initial thought that a possible higher mitotic rate could be the cytolog-

Table III. 5 year survival rates, overall and controlled for Breslow's thickness. Comparison between authors' series (ALM) and recent reported data for cutaneous malignant melanoma.

5 year survival (%)	Present series of ALM	Bradford et al[19] series of CMM
Overall	80%	91%
Thickness 0-1.00 mm	92%	97%
Thickness 1.01-2.00 mm	80%	88%
Thickness 2.01-4.00 mm	71%	72%
Thickness > 4 mm	52%	58%

ical feature explaining the higher intrinsic aggressiveness[14], was later disproved by Mc Govern[25] who showed how mitotic rate rises with increasing Breslow's thickness of the melanoma and, therefore, loses its significance when lesions of similar thickness are compared.

Bastian et al[18] with their research on gene amplifications, described, after correcting for thickness 15 cases of ALM and 15 cases of SSMM, distinct genetic features in ALM, which consist of more frequent gene amplifications occurring early in tumorigenesis and malignant cells present beyond the histologically detectable boundaries. In this context new research is necessary, in order to better correlate biology and genetics of the ALM with clinicoprognostic evaluations. The observation that ALM is a lesion affecting hidden areas of the body only partially explains the relatively delayed diagnosis, as palmar areas are definitely well visible body parts, but still the clinicoprognostic teatures of ALM do not change significantly between hands and feet, as demonstrated in this and other studies[26].

However, the standardized guidelines for treatment in terms of margins for wider excision seem to achieve a good control of these "extra-boundary cells", as described by Bastian, according to our outcome data and the multivariate analysis, which defines the margin as a strong predictor of outcome, and based on other published series[4,5,11,19-24].

The multivariate analysis performed in this study, which stressed the value of thickness and final excision margin as most powerful prognostic predictors, is a clear indicator that Breslow's thickness should still be considered the most significant prognostic factor also for ALM, which appears to be a more lethal tumour.

The current guidelines for the treatment of melanoma are valid also for this melanoma subtype. ALM should be managed exclusively under the care of specialized centres where plastic surgical expertise is present, because of the challenges faced in reconstructing the highly specialized areas it effects i.e. palmar and plantar skin, fingers and nailbeds.

Conclusions

ALM is a form of melanoma which tends to be diagnosed at later stages due to both medical diagnostic mistakes and patients' poor attention to lesions arising on extremities. The current indications for treatment of melanoma have shown in this study to be equally effective on ALM as in the overall population of melanoma patients.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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