



ORIGINAL ARTICLE

Acral lentiginous melanoma: a single-centre retrospective review of four decades in East-Central Europe

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Abstract

Background Acral lentiginous melanoma (ALM) occurs on the palms, soles and subungual surface and has poor prognosis. It is uncommon in the Caucasian population and has remained unreported in East-Central Europe.

Objectives Our aim was to collect data from East-Central Europe by analysing the demographic and clinicopathologic features of patients with ALM and comparing data with the reports in literature.

Methods We conducted a single-centre, retrospective review between 1976 and 2016 at one of the largest melanoma referral centres in Hungary.

Results We identified 176 patients with ALM (3.83%) from 4593 patients with melanoma (mean age: 66.2 years). The tumours were mainly located on the lower extremities (88.63%). The mean Breslow tumour thickness was 3.861 mm, 37.50% of the tumours were thicker than 4.00 mm, and 71.6% exhibited microscopic ulceration. Nearly one-third of the patients underwent sentinel lymph node (SLN) biopsy, and 60.3% of the biopsies were positive for metastasis. The positive SLN status was associated with significantly thick tumours and reduced survival. Patients with ALM had 5- and 10-year overall survival rates of 60.5% and 41.6%, respectively. The mean delay in diagnosis was 18 months after the discovery of skin tumours. In multivariate analyses, age, tumour thickness and distant metastasis were independent risk factors for poor survival ($P < 0.001$).

Conclusions Our study, which is the first single-centre report in East-Central Europe focusing on ALM, confirms that patient and tumour characteristics and prognostic factors are similar with previous literature data involving Caucasians; however, tumour thickness and survival suggest even worse prognosis.

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Conflicts of interest

None declared.

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Introduction

Acral lentiginous melanoma (ALM) is a unique subtype of melanoma, which arises from the glabrous skin of the palms, soles and nail apparatus.^{1–3} ALM is the least common subtype of cutaneous malignant melanoma (CMM) in Caucasians, accounting for less than 10% of cases, but it is the most common melanoma subtype in dark-skinned and Asian population.^{4–6}

ALM has poor prognosis compared with other histologic subtypes or anatomical locations of melanoma.^{4,7–9} Age, ulceration, tumour thickness and tumour spread at diagnosis are substantial prognostic factors in ALM.^{4,10–13} Given that these factors are

consistent with other CMM subtypes, the relatively poor prognosis in ALM can be attributed to the delay in diagnosis.^{2,12} Misdiagnosis due to various clinical appearances, different dermoscopic features, high rate of amelanosis and low awareness can contribute to the delay in diagnosis.^{2,5,10,14,15}

Clinical subtypes of melanoma have differences in pathogenesis and genetic background; however, ALM as a biologically aggressive subtype remains debatable.^{16–19} Ultraviolet radiation does not play a role in ALM pathogenesis. Compared with the mutations in other CMM subtypes, activating BRAF and NRAS mutations are less frequent in ALM (13–20% and 12–25%,

respectively), whereas KIT mutations are more common (5–36%).^{3,20–23}

Published single institution case series and population-based studies from different countries involving different skin types for ALM are few, and none are available from the East-Central Europe region.^{1,2,4,6,10} Therefore, we chose to study the demographic and clinicopathological features and survival rates of patients diagnosed with ALM at one of the dermatological referral centres in Hungary. We aimed to compare our results with the data from the international literature for Caucasian patients and to understand further this rare and aggressive subtype of cutaneous melanoma.

Patients and methods

This study is a retrospective review of patients diagnosed with ALM at a single institution over a 40-year period (1976–2016). It was conducted at the Department of Dermatology and Allergy in Szeged and was approved by the ethics committee and institutional review board of the University of Szeged in Hungary. We investigated nearly 25 000 histopathology reports and included only those patients for whom the diagnosis of ALM was confirmed by histopathological examination and for whom the melanoma was located on the glabrous skin (non-hair-bearing skin) of the palms, soles or subungual area. Patients presenting melanoma at an acral location but not of an acral lentiginous histological subtype were excluded from this study. Clinical data of patients with ALM were collected from the individual handwritten patient records (1976–1996) and from the electronic database of our institute (1997–2016).

We aimed to collect and analyse data about the demographics of the patients, clinical and histological characteristics of the primary tumour (location, macroscopic appearance, ulceration, Breslow tumour thickness and Clark level), status of the sentinel lymph node (SLN), stage of the disease (AJCC 8th ed.) and details of the treatment.²⁴ We were interested whether the mean tumour thickness or the mean age of the patients with ALM has changed in the diagnostic delay and in the prognostic factors of ALM in our region over the investigated time period.

The survival probabilities were estimated by Kaplan–Meier analysis. The differences in the survival of the groups were examined by a log-rank test with Bonferroni correction. The mean Breslow tumour thickness between the SLN-positive and -negative groups was investigated by Student's *t*-test. Meanwhile, the trends during the examined time period in terms of age of the patients and Breslow tumour thickness were analysed by Poisson regression and ANOVA models. In addition, $P < 0.05$ was considered statistically significant. The influence of different risk factors on the survival was analysed using univariate and multivariate Cox proportional hazard models. The risk factors for survival were considered to be gender (male vs. female), Clark invasion depth (II/III vs. IV/V), ulceration (absent vs. present), dermal mitotic rate $\geq 1/\text{mm}^2$ (absent vs. present), tumour

site (hand vs. foot), status of SLN (negative vs. positive), nodal status (negative vs. positive) and presence of distant metastases (absent vs. present). Age and Breslow thickness were calculated as continuous variables. Factors with P -values < 0.05 on univariate analysis were included in multivariate analysis, whereas P -value < 0.001 was considered to indicate statistical significance. For the statistical analyses, R software (version 3.2.1) was used.

Results

Between January 1976 and December 2016, 4593 patients were diagnosed with CMM at our centre. Among them, 176 patients had histologically confirmed ALM located on the palms, soles or subungual area.

Patient's demographics and primary tumour characteristics

All patients were Caucasians. The mean age at diagnosis was 66.17 years (29–92, ± 12.97 years). Most of the cases (73.29%) were diagnosed after 60 years old. The average age for males and females was 64.50 (± 11.51) and 67.54 (± 13.93) years, respectively. The male : female ratio was 1 : 1.26, and 55.68% of the tumours occurred in female patients above 60 years old (Table 1).

Of the 88.63% of tumours found on the lower extremities, 72.16% occurred on the soles and heels. Subungual melanoma was diagnosed in 25 cases (14.21%).

The mean Breslow tumour thickness was 3.861 mm (0.000–14.516, ± 2.66 mm); specifically, 75.00% of the tumours were thicker than 2 mm, and 37.50% were thicker than 4 mm. Clark invasion depth levels IV–V were described in 56.25% of the tumours. Microscopic ulceration occurred in 126 cases (71.59%), as observed by histological examination. Macroscopically, 35.79% of the tumours were ulcerated, and 14.20% were bleeding (Fig. 1).

Sentinel lymph node biopsy (SLNB) has been performed routinely at our centre since 1999. In our study group, 32.95% of the patients underwent SLN biopsy, and 60.30% of these biopsies were positive. SLN-negative patients were predominantly females (1 : 4), and these patients had significantly lower mean Breslow tumour thickness and survival rates than SLN-positive patients (2.02 ± 0.36 mm vs. 4.66 ± 0.45 mm; $P < 0.001$). Meanwhile, no differences were observed between the SLN-positive and -negative groups with respect to the mean age of the patients, location of the tumours and amount of time after noticing the tumour before consulting a physician (diagnostic delay).

Survival analysis

The 5- and 10-year overall survival rates of patients with ALM were 60.51% (95% CI, 53.27–68.75) and 41.59% (95% CI, 34.10–50.72), respectively.

Table 1 Demographic and tumour characteristics of patients with acral lentiginous melanoma (ALM) in the Hungarian study

Sex (n)	
Male, n (%)	78 (44.32)
Female, n (%)	98 (55.68)
Male : female ratio	1 : 1.26
Age at diagnosis (year)	
Range	29–92
Median	67.43
Mean (±SD)	66.17 (±12.97)
Mean age male (±SD)	64.50 (±11.51)
Mean age female (±SD)	67.54 (±13.93)
Location of the primary tumour	
Upper extremity, n (%)	20 (11.37)
Palms	9 (5.12)
Nails	9 (5.12)
Other	2 (1.13)
Lower extremity, n (%)	156 (88.63)
Soles	86 (48.86)
Heels	41 (23.30)
Nails	16 (9.09)
Other	13 (7.38)
Breslow tumour thickness (mm)	
Range	0.000–14.516
Median	3.344
Mean (±SD)	3.861 (±2.66)
Breslow tumour thickness, n (%)	
≤1.00 mm	18 (10.23)
1.01–2.00 mm	26 (14.77)
2.01–4.00 mm	66 (37.50)
>4.00 mm	66 (37.50)
Clark level, n (%)	
I	2 (1.14)
II	16 (9.09)
III	59 (33.52)
IV	68 (38.64)
V	31 (17.61)
Microscopic ulceration, n (%)	
Present	126 (71.59)
Not present	47 (26.70)
No data	3 (1.71)
Delay in diagnosis, n (%)	
<1 year	67 (48.55)
1–3 years	55 (39.86)
3–5 years	9 (6.52)
>5 years	7 (5.07)

n, number of the patients; SD, standard deviation.

Patients with ALM at tumour stage I had a significantly ($P < 0.001$) better disease-specific survival rate than those at tumour stages II, III and IV (Fig. 2). No significant differences were noted in the disease-specific survival rates between patients with stage II and III tumours, but both of these patient groups



Figure 1 Acral lentiginous melanoma (ALM) on the thumb (71-year-old male, pT1a), great toe (44-year-old male, pT1a), palm (85-year-old female, pT3b) and sole (81-year-old female, pT3b).

had significantly ($P < 0.001$) better disease-specific survival rates than those with stage IV tumour.

Analysis according to Breslow tumour thickness revealed that the 5-year disease-specific survival rate of patients with T1 tumours was 92.31% (95% CI, 78.90–100.00), whereas that of patients with T4 tumours was 28.56% (95% CI, 19.03–42.87). In addition, patients with T4 tumours had significantly ($P < 0.001$) worse disease-specific survival rates than those with T1–T3 tumours (Fig. 2).

The 5-year disease-specific survival rate in the SLN-negative group (84.21%; 95% CI, 69.31–100.00) was significantly better ($P < 0.001$) than that in the SLN-positive group (54.61%; 95% CI, 39.95–74.65; Fig. 2).

The results of the Cox univariate and multivariate analyses for disease-specific survival are shown in Table 2. In univariate analysis, age ($P < 0.001$), gender ($P = 0.03$), Breslow tumour thickness ($P < 0.001$), Clark level ($P < 0.001$), ulceration ($P < 0.001$), positive SLN ($P = 0.004$), positive nodal status ($P = 0.008$) and presence of distant metastasis ($P < 0.001$) were statistically significant ($P < 0.05$) and were, therefore, associated with worse survival. On the other hand, dermal mitoses and anatomical sites were not associated with worse survival. In subsequent multivariate analysis, patients' age [hazard ratio (HR) 1.058, 95% confidence interval (CI) 1.035–1.083], Breslow tumour thickness (HR 1.187, 95% CI 1.099–1.282) and presence of distant metastasis (HR 3.002, 95% CI 1.850–4.871) remained statistically significant ($P < 0.001$) and became independent risk factors for survival.

Delay in the diagnosis of ALM

Of the 176 patients with ALM, 138 had data describing the delay in the diagnosis. The delay between the time the patient noticed the tumour, and the time of diagnosis was extremely variable and ranged from 1 month to 10 years (mean time: 18 months). Approximately half (51.45%) of the patients waited more than 1 year after noticing the skin lesion before seeking medical help.

Changes over four decades in the number of diagnosed cases, Breslow thickness of the tumours and age of the patients

During the 40 years of analysis, no significant change was noted either in the mean Breslow tumour thickness ($P = 0.964$) of the

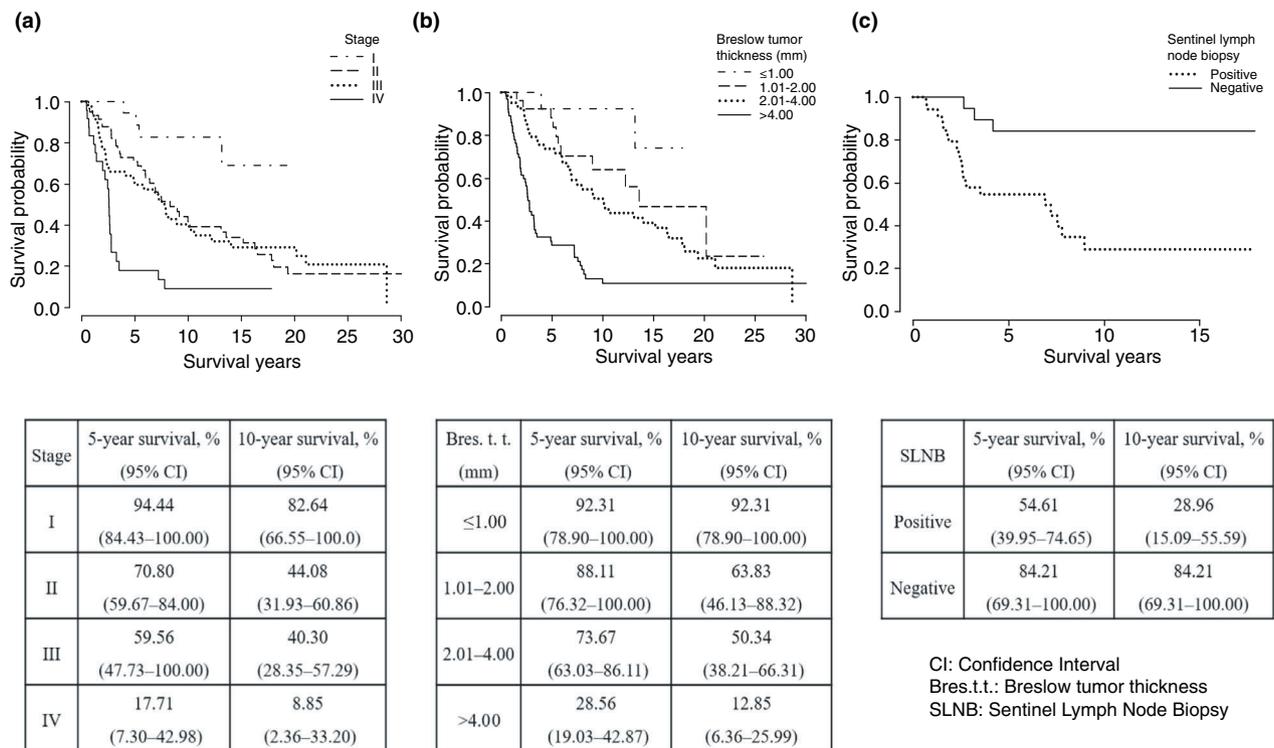


Figure 2 Kaplan–Meier disease-specific survival curves and rates stratified by TNM stage (a), Breslow primary tumour thickness (b) and SLN status (c) in our patients with acral lentiginous melanoma (ALM).

Table 2 Results of Cox proportional hazard models of covariates

	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.046 (1.027–1.065)	<0.001	1.058 (1.035–1.083)	<0.001
Female gender	0.652 (0.443–0.960)	0.030	0.506 (0.326–0.784)	0.002
Breslow thickness (mm)	1.253 (1.173–1.339)	<0.001	1.187 (1.099–1.282)	<0.001
Clark level IV/V (vs. II/III)	2.842 (1.871–4.316)	<0.001	1.768 (1.071–2.918)	0.026
Presence of ulceration	3.625 (1.934–6.795)	<0.001	2.591 (1.302–5.154)	0.006
Presence of dermal mitoses $\geq 1/\text{mm}^2$	1.149 (0.601–2.195)	0.674		
Anatomical site: foot (vs. hand)	1.471 (0.714–3.032)	0.296		
SLNB† positivity	6.087 (1.799–20.600)	0.004		
Positive nodal status	1.714 (1.154–2.156)	0.008	2.585 (1.088–6.139)	0.031
Presence of distant metastasis	2.834 (1.840–4.364)	<0.001	3.002 (1.850–4.871)	<0.001

†Analysis of 58 patients.

Results of Cox proportional hazard models of covariates (significant *P*-value marked with bold).

tumours or in the mean age of the patients at the time of diagnosis ($P = 0.157$; Fig. 3). We diagnosed nearly the same number of ALM cases in each decade. When analysing all patients with CMM, we noticed a significant ($P < 0.001$) decrease in the proportion of patients with ALM over the past 40 years, possibly because of the dramatic increase of the superficial spreading melanoma (SSM) subtype (Fig. 4).

Treatment of ALM patients

All 176 ALM patients in our study underwent wide local excision of the primary tumour with different safety margins during the study period of 40 years (Table S1). Regional lymph node dissection (RLND) was performed with an elective intent until 1998 in 24 patients (28.5%). From 1999, after the introduction of SLN biopsy at our department, 58 patients with ALM

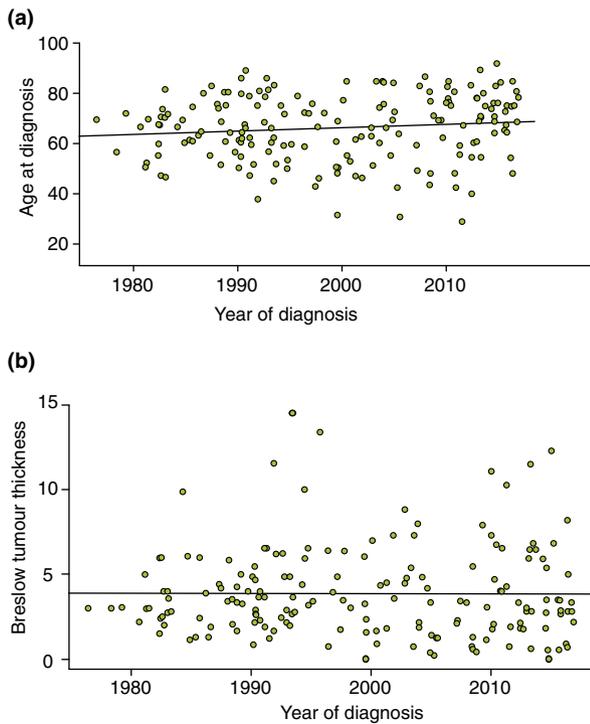


Figure 3 Distribution of the mean age at diagnosis (a) and Breslow primary tumour thickness (b) in our acral lentiginous melanoma (ALM) cases during the past 40 years.

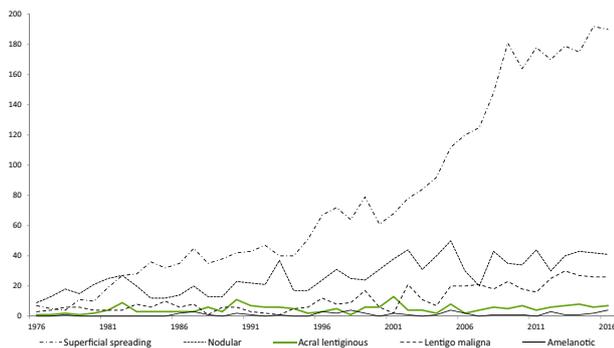


Figure 4 Distribution of cutaneous melanoma by subtypes (4593 patients) during the past 40 years.

underwent SLNB, followed by complete RLND in 26 patients (28.2%). In patients with clinically detectable lymph node metastases, RLND was performed in 20 patients (23.8%) until 1998 and in seven patients (7.6%) from 1999. Regarding adjuvant systemic treatment, dacarbazine was mainly used until 1998 (19.0%), whereas interferon-alpha (22.8%) was used from 1999. For irresectable and/or metastatic disease, the systemic treatment

of choice was chemotherapy until 2015 (until 1998: 11.9%; from 1999: 20.6%). Since 2015, novel treatment options, such as target and immunooncological therapies, became available and were used in a total of 14 patients (imatinib: 2; dabrafenib and trametinib: 1; ipilimumab: 4; nivolumab: 4; pembrolizumab: 3). Radiotherapy was used in 16.5% of our patients, either in an adjuvant or a metastatic (cutaneous: 7; lymph node: 2; brain: 11) setting. From 2007, electrochemotherapy was performed in 2.2% of our patients for loco-regional cutaneous metastases of melanoma. Based on the changes in the treatment strategies and available drugs, we identified three important time periods (1976–1998, 1999–2014 and 2015–2016) during the investigated 40 years. The sample size allowed us to compare the first two periods. No statistically significant differences were observed between the two groups with respect to demographic data (age, male : female ratio and Breslow tumour thickness); however, clinically detectable lymph node metastases (20 vs. 5 patients) were numerically higher in the first group (1976–1998) than in the second group (1999–2014). Using the Kaplan–Meier analysis, 5- and 10-year overall survival rates were 74.33 (95% CI, 66.10–83.59) and 63.72 (54.36–74.70), respectively, with a significantly better ($P < 0.001$) survival in the patients treated between 1999 and 2014 (Fig. S1).

Discussion

Acral lentiginous melanoma in Caucasians is a rare subtype of CMM, accounting for less than 10% of all CMM cases.^{2,7} ALM is often detected in advanced age and clinical stage and is associated with poor survival. During the past 40 years, 3.83% of the 4593 patients with CMM presenting at our department were diagnosed with ALM. Our results confirmed that ALM mainly affects elderly people, considering that most of the tumours occurred at 70 years of age.^{2,4,7,8} Similar to the study of Teramoto *et al.*,¹² the mean age of the patients with ALM in the present study was 66 years. Data in the literature concerning sex predominance for ALM are conflicting.¹⁰ The study of Phan *et al.*¹⁰ reported a female predominance in patients with ALM, and female sex was an independent prognostic factor for survival. Other studies did not find significant sex differences in the occurrence of ALM. In our study, the male : female ratio was 1 : 1.26.^{2,7,8}

The mean Breslow tumour thickness of ALM tumours in our study was nearly 4 mm, and 75% of the primary tumours were thicker than 2 mm and were microscopically ulcerated. In more than half of the tumours, the invasion depth was at Clark level IV or V. In previous studies, the number of ALM lesions arising on the foot was 5–16 times higher than that on the hand.¹⁰ In our study, melanoma on the lower extremities was exhibited in nearly 90% of the patients, occurring mainly on the soles (48.86%) and heels (23.30%). Subungual melanoma is seemingly more common on the fingernails than on the toenails.¹⁰ In our study, 14.20% of the melanomas were subungual, appearing

mostly on the lower extremities. The mean age of patients with ALM at the time of diagnosis and the location of the tumours in our study were similar to the results published by other authors.^{6,10,14} However, the mean Breslow tumour thickness was significantly ($P < 0.001$) higher in our study than most in other literature data for Caucasian patients.^{2,10,12,25}

Patients with ALM have poor survival and unfavourable prognosis. In the study of Bradford *et al.*,⁴ the 5- and 10-year overall survival rates of patients with CMM are 91.3% and 87.5%, respectively, whereas those of patients with ALM have significantly worse survival rates. Comparing our results with other studies involving Caucasians, we concluded that both the 5- and 10-year overall survival rates (70–80% and 56–67%, respectively) of our patients with ALM are lower.^{4,8,10}

After investigating the relationship between survival and the TNM stage of the disease, we found that progression from one stage to the next stage corresponded with significantly low chances of survival, and this difference is the highest between stages I and III and between stages I and IV. Therefore, survival rate is highly influenced by the lymph node metastasis (stage III) and presence of distant metastases (stage IV). With regard to tumour thickness, the most significant difference in the survival rate is found between the tumours thinner than 2 mm (T1–T2) and the tumours thicker than 4 mm (T4). Tumours thicker than 4 mm correspond to a significantly lower survival rate in every case than thinner tumours.

SLN biopsy has been performed routinely at our centre since 1999, and 32.95% of the patients in our study underwent SLN biopsy. SLN-positive cases occurred at a significantly ($P < 0.001$) higher proportion than the results from Pavri *et al.*²⁶

Delay in ALM diagnosis is well documented and is reportedly greater than 7 months on average.^{10,15} Factors contributing to the delay might include the age and/or the cognitive state of the patients, hidden location, unusual clinical presentation, low public awareness, and misdiagnosis and mistreatment by health-care professionals, especially when pigmentation is absent. Rex *et al.* and Teramoto *et al.* attributed the poor survival in patients with ALM to the diagnostic delay rather than to a difference in

biological behaviour of this melanoma subtype.^{2,12} In our study, more than half of the patients waited more than 1 year, and nearly 12% waited more than 3 years before seeking medical help. In a study by Phan *et al.*,¹⁰ the delay between the time the patient first noticed the lesion and the time they were diagnosed ranged from 2 months to 30 years; in our study, this delay ranged from 1 month to 10 years.

Besides the parameters of malignant disease and patients' characteristics, treatment is definitely the most important factor that may influence the survival of melanoma sufferers. In patients with malignant melanoma, treatment strategies changed quite extensively during the investigated 40 years of our study. Based on the Kaplan–Meier analysis, survival improved with the introduction of new treatment strategies; however, due to the various and constantly changing treatment options, major conclusions cannot be achieved from this analysis.

We compared our data with the literature for Caucasian patients with ALM from Europe (Table 3). In all the chosen studies, ALM occurred after 60 years old, with a female and lower-extremity predominance. The mean Breslow tumour thickness was greater than 2 mm in every study, but the thickness (nearly 4 mm) observed in our country was second only to that in the United Kingdom.^{2,12,15}

Our study confirmed that patient and tumour characteristics and prognostic factors are similar with those found in previous literature data involving Caucasians; however, tumour thickness and survival suggest even worse prognosis.^{7,8,10,25}

More than 2000 new patients with melanoma are diagnosed in Hungary annually, and one dies every day due to this malignant disease [National Cancer Registry, <http://www.ksh.hu>]. Based on our observations at our dermato-oncology centre, the number of patients diagnosed with melanoma increased dramatically in the past few decades. This increase, especially with respect to SSM and LMM, can be explained at least partially with the increasing popularity of tanning and the lack of appropriate photoprotection.

When analysing the tendencies of the past four decades, with respect to the incidence of the disease, we diagnosed the same number of ALM cases each decade, and we did not find major

Table 3 Comparison of our data with other studies involving Caucasians^{2,10,12,15}

	France (2006) 1996–2004	Spain (2009) 1987–2007	UK (2014) 1996–2006	Germany (2017) 1983–2015	Hungary (2019) 1976–2016
N	126	89	87	2243	176
Non-Caucasian patients (n)	Asian (1)	Asian (2)	–	–	–
Mean age (years)	63.0	61.6	67.0	63.1	66.2
Male : female ratio	1 : 1.86	1 : 1.69	1 : 1.71	1 : 1.48	1 : 1.26
Mean Breslow tumour thickness (mm)	2.51	2.8	7.9	3.08	3.86
Location	87.3%, lower extremities 37%, nails	79.8%, lower extremities 24.7%, nails	84%, lower extremities No data	82.1%, feet 35.6%, nails	88.6%, lower extremities 14.2%, nails

changes in the Breslow tumour thickness or in the mean age of the patients at diagnosis. As UV-induced pathogenesis has increased during this same period, this constant rate of diagnosis is unlikely to be associated with UV exposure.

Our study, which is the first single-centre report in East-Central Europe focusing on ALM, found that despite the improvement in early diagnosis of melanoma and improved public awareness in general, ALM in our region remains a subtype of melanoma that is diagnosed with high Breslow tumour thickness and advanced stage.²⁷ Therefore, we would like to emphasize the importance of early diagnosis of ALM by increasing disease awareness through education and prevention programmes.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Treatment of ALM patients according to the three time periods.

Figure S1. Survival probability of patients treated between 1976 and 1998 vs. those between 1999 and 2014.