• Context.—Acral lentiginous melanoma is a rare and aggressive type of cutaneous melanoma that arises on the acral skin and the nail unit. The prognostic significance of subungual anatomic site in acral lentiginous melanoma is not established.

Objective.—To assess the impact of subungual anatomic site on overall survival and disease-specific survival in acral lentiginous melanoma.

Design.—Retrospective cohort analysis. Clinicopathologic characteristics of 627 primary acral lentiginous melanomas (45 [7%] subungual and 582 [93%] non-subungual) were summarized, and the impact of these characteristics on overall survival and disease-specific survival was determined using univariate and multivariable analyses.

Results.—No significant differences in clinicopathologic features were identified between the subungual and nonsubungual acral lentiginous melanomas. The 1-, 5-, and 10-year overall survival rates were 81%, 40%, and 28%, respectively, for subungual acral lentiginous melano- noma and 94%, 59%, and 38%, respectively, for non-subungual acral lentiginous melanoma (P = .04); risk of death was significantly higher for subungual tumors (hazard ratio [95% confidence interval] = 1.59 [1.02–2.50]; P = .04). The 1-, 5-, and 10-year disease-specific survival rates were 94%, 56%, and 48%, respectively, for subungual acral lentiginous melanoma versus 96%, 69%, and 55%, respectively, for nonsubungual acral lentiginous melanoma (P = .18). By multivariable analysis, independent poor prognostic factors included older age and ulceration for overall survival and greater Breslow thickness and sentinel lymph node positivity for overall survival and disease-specific survival. Subungual anatomic site was not an independent prognostic factor for overall or disease-specific survival.

Conclusions.—Subungual anatomic site is not an independent prognostic factor for acral lentiginous melanoma.

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Acral lentiginous melanoma (ALM) is a rare type of cutaneous melanoma that arises on the acral skin, including the palms, soles (Figure 1, A), and digits (Figure 1, B), as well as on the nail unit (Figure 1, C), where it is clinically classified as subungual melanoma.1 The latter is a clinical term used to define a particular clinical subtype of melanoma arising on the nail unit irrespective of its histologic type.

ALM is defined by its histologic growth pattern of confluent single-cell “lentiginous” array of the neoplastic melanocytes at the dermoeipidermal junction irrespective of its specific anatomic site (Figure 2, A and B).

ALM accounts for fewer than 5% of cases of cutaneous melanoma in white patients but is the most common type of cutaneous melanoma in non-white patients2,3 and associated with greater Breslow thickness, higher rates of ulceration and sentinel lymph node metastasis, advanced clinical stage at presentation, and worse prognosis than other types of cutaneous melanoma.4

In addition to the powerful pathologic factors such as Breslow thickness and ulceration, several clinical factors, such as patient’s age, sex, ethnicity, and the anatomic location of the primary tumor, may play an important prognostic role in cutaneous melanoma and may provide
helpful prognostic information for individual risk stratification.

Previous studies revealed that melanoma arising from certain anatomic sites such as melanomas of the BANS area, namely, the back, arms, neck, and scalp are associated with a 4.6% to 15% lower 5-year overall survival (OS) rate than cutaneous melanomas of other anatomic sites,5,6 and the hazard ratio for melanoma-specific death is 1.8 for cutaneous melanoma of the back compared with cutaneous melanoma of other sites.7 However, in ALM, the prognostic significance of subungual anatomic site is not well explored. Therefore, in an attempt to determine the prognostic impact of subungual anatomic site on OS and disease-specific survival (DSS) in ALM, we performed a comprehensive analysis of the clinicopathologic factors and their impact on OS and DSS in a large series of subungual and non-subungual ALMs.

METHODS

Patients

After obtaining institutional review board approval, we searched the pathology archives of our institution covering the period from January 1999 through April 2014 integrated in the electronic interface system. We searched (1) all records with ("acral" and "melanoma") but without "metastatic" in the diagnosis field; (2) all records with ("acral" and "lentiginous" and "melanoma") but without "metastatic" in the diagnosis field; and (3) all records with ("ungual" and "nail" and "lentiginous" and "melanoma") but without "metastatic"
in the diagnosis field. This yielded 3 sets of search results. We removed any duplicate cases and cases of cutaneous ALM of the digit with secondary involvement of the nail unit.

After applying these criteria, we identified 627 patients with primary acral melanoma histologically classified as ALM. These included 45 patients (7%) with subungual ALM and 582 patients (93%) with ALM arising from nonsubungual acral sites. These 627 patients with ALM were included in our study. All the available patient’s histologic and clinicopathologic characteristics and management details were carefully annotated from the medical records and pathology reports. There were some missing data and its status was reported as unknown wherever detected.

Collection of Clinical and Histologic Features

For each patient, the following data were collected: date of initial diagnosis; patient’s age at initial diagnosis, sex, and race/ethnicity; anatomic site of the primary melanoma; lymph node status; last follow-up date; date of diagnosis and site(s) of regional and distant metastasis; and date and cause of death, when applicable.

Hematoxylin and eosin (H&E)-stained slides or whole-slide scanned images of ALMs were re-evaluated by at least 1 and up to all 7 of the participating dermatopathologists. The following histopathologic parameters were recorded: histologic type, Clark level, Breslow thickness, number of mitotic figures per square millimeter, presence or absence of ulceration, regression, vertical growth phase, predominate cytology, lymphovascular invasion, perineural invasion, tumor-infiltrating lymphocytes, microsatellitosis, associated nevus, status of resection margin, status and number of regional lymph node metastasis, and status of distant metastasis.

The status of regional lymph node metastasis was determined using our institutional protocol of sentinel lymph node (SLN) examination for cutaneous melanoma. The protocol requires initial evaluation of H&E-stained sections. If no obvious metastatic melanoma is identified, 3 sections are cut at approximately 200 μm into the block and placed on slides. One slide is stained with H&E, 1 is stained with pannmelanocytic cocktail (HMB45, tyrosinase, and MART1), and 1 is left unstained to allow for any additional immunohistochemical study that might be needed.

Statistical Methods

The clinical and pathologic characteristics were summarized by anatomic location of ALM, subungual or nonsubungual. Data were summarized as frequencies and percentages in the case of categoric variables and as medians and ranges in the case of continuous variables. Data were compared between groups using Fisher exact test or its generalization for categorical variables and the Wilcoxon rank-sum test for continuous variables.

OS and DSS were measured from the date of initial diagnosis to the date of last known follow-up. Administratively censored cases included patients alive at last follow-up for OS and patients who died from causes other than melanoma for DSS. The Kaplan–Meier method was used to estimate OS and DSS, and the log-rank test was used to assess differences between groups.

Univariate Cox proportional hazards regression models were used to assess the association between survival and clinicopathologic factors, and a multivariable Cox proportional hazards regression model was determined using backward elimination with an exit criterion of P ≥ .05.

All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC). All statistical tests used a significance level of 5%. No adjustments for multiple testing were made.

The adjustment of statistical analyses for missing data is included in the supplemental digital content at https://meridian.allenpress.com/aplm in the August 2021 table of contents.

RESULTS

Patients’ Clinical and Histopathologic Characteristics

The clinical and histopathologic characteristics of patients with subungual and nonsubungual ALM are summarized in Table 1. The 2 groups did not differ with respect to any of the characteristics examined, although the difference in age approached significance; patients with nonsubungual ALM had older median age at diagnosis (62.0 versus 56.8 years).

Characteristics Associated With OS

The 1-, 5-, and 10-year OS rates were 81%, 40%, and 28%, respectively, for subungual ALM and 94%, 59%, and 38%, respectively, for nonsubungual ALM (P = .04) (Table 2; Figure 3, A). No significant differences in the OS were identified when the subungual and nonsubungual ALM stratified by the upper and lower extremity location.

In univariate analysis, patients with subungual ALM had a higher risk of death than patients with nonsubungual ALM (hazard ratio [95% CI] =1.59 [1.02, 2.50]; P = .04). In univariate analysis, for the entire cohort of ALM, factors significantly associated with worse OS included male sex, older age (≥62 years), higher Clark level (IV–V), greater Breslow thickness (>1 mm), ulceration, lymphovascular invasion, mitosis, vertical growth phase, spindled cytology, lack of associated nevus, regional nodal metastasis, and higher number of positive nodal metastases. After adjustment for the significant clinicopathologic factors, Breslow thickness, patient’s age, presence of ulceration, and SLN positivity were identified as independent prognostic factors associated with worse OS (Table 2).

Characteristics Associated With DSS

The 1-, 5- and 10-year DSS rates were 94%, 56%, and 48%, respectively for subungual ALM and 96%, 69%, and 55%, respectively, for nonsubungual ALM (P = .18) (Table 3; Figure 3, B). The anatomic site of ALM (subungual versus nonsubungual) was not significantly associated with DSS. No significant differences in the DSS were identified when the subungual and nonsubungual ALM were stratified by the upper and lower extremity location.

By univariate analysis, except for patients’ age, all clinical and histopathologic factors that were significantly associated with poor OS were also significantly associated with poor DSS (Table 3). After adjustment for the significant clinicopathologic factors, Breslow thickness and SLN positivity were identified as independent prognostic factors associated with poor DSS (Table 3).

DISCUSSION

In this current study, patients with subungual ALM had lower 1-, 5-, and 10- year OS rates and a significantly higher risk of death than patients with nonsubungual ALM, but no significant difference in DSS rates was detected between the subungual and nonsubungual groups. Furthermore, stratifying the subungual and nonsubungual ALMs by the upper and lower extremity revealed no significant difference in the OS and DSS.

Our findings that Breslow thickness and SLN positivity were independent prognostic factors for both OS and DSS and that ulceration was an independent prognostic factor for OS agree with the previously reported findings regarding the prognostic impact of Breslow thickness,4,8–14 ulceration,13 and SLN metastasis8,9 in ALM.

Age is considered one of the least consistent clinical prognostic factors in melanoma. In our current study, we found that age was an independent poor prognostic factor for OS. In ALM, several previous single-institution studies have failed to detect age as a prognostic factor.10,11,13–20
Table 1. Characteristics of Patients With ALM by Subungual Versus Nonsubungual Location

| Characteristic                          | Subungual (n = 45) | Nonsubungual (n = 581) | P Value |
|-----------------------------------------|--------------------|------------------------|---------|
| **Sex, n (%)**                          |                    |                        |         |
| Male                                    | 24 (53)            | 299 (51)               | .88     |
| Female                                  | 21 (47)            | 282 (49)               |         |
| **Age, yr**                             |                    |                        | .06     |
| Median (range)                          | 56.8 (30.6–86.1)   | 62.0 (9.8–99.4)        |         |
| **Race/ethnicity, n (%)**               |                    |                        | .87     |
| White                                   | 33 (75)            | 407 (72)               |         |
| Hispanic                                | 6 (14)             | 95 (17)                |         |
| Other                                   | 5 (11)             | 62 (11)                |         |
| Unknown                                 | 1                  | 17                     |         |
| **Extremity**                           |                    |                        | <.001   |
| Upper                                   | 21 (47)            | 76 (13)                |         |
| Lower                                   | 24 (53)            | 505 (87)               |         |
| **Clark level, n (%)**                  |                    |                        | .49     |
| I                                       | 0                  | 11 (2)                 |         |
| II                                      | 5 (11)             | 57 (10)                |         |
| III                                     | 1 (2)              | 57 (10)                |         |
| IV                                      | 31 (70)            | 362 (62)               |         |
| V                                       | 7 (16)             | 93 (16)                |         |
| Unknown                                 | 1                  | 1                      |         |
| **Breslow thickness**                   |                    |                        | .75     |
| Thin (≤1 mm), n (%)                     | 9 (20)             | 120 (21)               |         |
| Intermediate (≥1–4 mm), n (%)           | 22 (49)            | 299 (53)               |         |
| Thick (≥4 mm), n (%)                    | 14 (31)            | 148 (26)               |         |
| Unknown                                 | 0                  | 14                     |         |
| Median (range), mm                      | 2.2 (0.3–15.0)     | 2.3 (0.2–21.0)         | .81     |
| **Mitosis, /mm²**                       |                    |                        | >.99    |
| <1, n (%)                               | 7 (20)             | 113 (22)               |         |
| ≥1, n (%)                               | 28 (80)            | 403 (78)               |         |
| Unknown                                 | 10                 | 65                     |         |
| Median (range)                          | 5.0 (0–25.0)       | 3.0 (0–53.0)           | .13     |
| **Ulceration, n (%)**                   |                    |                        | .64     |
| Absent                                  | 24 (53)            | 329 (58)               |         |
| Present                                 | 21 (47)            | 240 (42)               |         |
| Unknown                                 | 0                  | 12                     |         |
| **Lymphovascular invasion, n (%)**      |                    |                        | .41     |
| Absent                                  | 39 (89)            | 476 (83)               |         |
| Present                                 | 5 (11)             | 97 (17)                |         |
| Unknown                                 | 1                  | 8                      |         |
| **Perineural invasion, n (%)**          |                    |                        | >.99    |
| Absent                                  | 35 (78)            | 446 (78)               |         |
| Present                                 | 10 (22)            | 127 (22)               |         |
| Unknown                                 | 0                  | 8                      |         |
| **Regression, n (%)**                   |                    |                        | .81     |
| Absent                                  | 31 (84)            | 412 (85)               |         |
| Present                                 | 6 (16)             | 73 (15)                |         |
| Unknown                                 | 8                  | 96                     |         |
| **Tumor-infiltrating lymphocytes, n (%)**|                    |                        | >.99    |
| Nonbrisk/minimal                        | 37 (100)           | 512 (98)               |         |
| Brisk                                   | 0                  | 8 (2)                  |         |
| Unknown                                 | 8                  | 61                     |         |
However, Teramoto et al., a population-based study of the German central malignant melanoma registry, reported that patient’s age was an independent prognostic factor for lower DSS. The discrepant findings regarding the prognostic impact of patient’s age in ALM might be attributed to differences in sample size and the nature of the cohorts retrieved from population-based databases versus single institutions.

Several studies have recorded the prevalence rate of ALM anatomic site; however, its prognostic significance on disease survival is not well explored. Häfliger et al. reported the prevalence and distribution of 168 of 172 (97.7%) ALMs according to their specific anatomic location, but they did not estimate the prognostic significance of ALM anatomic location. Although Boriani et al. found significant difference in prognostic impact between ALM of the upper and lower limb, the prognostic significance of the subungual anatomic site was not investigated. In our current study, we found no prognostic impact of subungual anatomic site on OS or DSS in ALM.

Our findings on univariate analysis that several other characteristics impacted OS and DSS are in agreement with findings from previous ALM studies regarding male sex, higher Clark level (IV–V), presence of ulceration, lymphovascular invasion, mitosis, and higher number of positive regional lymph node metastasis. In addition, we also found vertical growth phase and the spindled cytology as dependent factors associated with lower OS and DSS.

### Table 1. Continued

| Characteristic                  | Subungual (n = 45) | Nonsubungual (n = 581) | P Value |
|---------------------------------|-------------------|------------------------|---------|
| Vertical growth phase, n (%)    |                   |                        |         |
| Absent                          | 7 (18)            | 67 (12)                | .33     |
| Present                         | 33 (83)           | 475 (88)               |         |
| Unknown                         | 5                 | 39                     |         |
| Microsatellitosis, n (%)        |                   |                        |         |
| Absent                          | 41 (91)           | 542 (95)               | .31     |
| Present                         | 4 (9)             | 31 (5)                 |         |
| Unknown                         | 0                 | 8                      |         |
| Predominant cytology, n (%)     |                   |                        |         |
| Epithelioid                     | 18 (45)           | 308 (57)               | .29     |
| Spindle                         | 11 (28)           | 116 (22)               |         |
| Nevoid                          | 11 (28)           | 114 (21)               |         |
| Unknown                         | 5                 | 43                     |         |
| Associated nevus, n (%)         |                   |                        |         |
| Absent                          | 45 (100)          | 535 (93)               | .10     |
| Present                         | 0                 | 38 (7)                 |         |
| Unknown                         | 0                 | 8                      |         |
| SLNs, n (%)                     |                   |                        | >.99    |
| Negative                        | 13 (48)           | 199 (50)               |         |
| Positive                        | 14 (52)           | 203 (51)               |         |
| Unknown                         | 18                | 179                    |         |
| Number of positive SLNs         |                   |                        | .26     |
| N                               | 14                | 203                    |         |
| Median (range)                  | 1 (1–3)           | 1 (1–6)                |         |
| Non-SLNs, n (%)                 |                   |                        | .54     |
| Negative                        | 13 (50)           | 116 (43)               |         |
| Positive                        | 13 (50)           | 156 (57)               |         |
| Unknown                         | 19                | 309                    |         |
| Number of positive non-SLNs     |                   |                        | .37     |
| N                               | 13                | 152                    |         |
| Median (range)                  | 4 (1–21)          | 3 (1–34)               |         |
| Local recurrence, n (%)         |                   |                        | .21     |
| No                              | 39 (95)           | 475 (88)               |         |
| Yes                             | 2 (5)             | 66 (12)                |         |
| Unknown                         | 4                 | 40                     |         |
| Distant metastases, n (%)       |                   |                        | .26     |
| No                              | 25 (56)           | 374 (64)               |         |
| Yes                             | 20 (44)           | 207 (36)               |         |

Abbreviations: ALM, acral lentiginous melanoma; SLN, sentinel lymph node.
Table 2. Relationships Between Clinicopathologic Characteristics and OS in Patients With ALM by Univariate and Multivariable Analysis

| Characteristic                               | Number of Patients | OS Rate 1 yr | OS Rate 5 yr | OS Rate 10 yr | P Value | HR (95% CI) | P Value |
|----------------------------------------------|--------------------|--------------|--------------|---------------|---------|-------------|---------|
| OS by univariate analysis                    |                    |              |              |               |         |             |         |
| All patients                                 | 583                | 93           | 57           | 38            |         |             |         |
| ALM subgroup                                 |                    |              |              |               |         |             |         |
| Nonsubungual ALM                             | 542                | 94           | 58           | 38            | .04     | 1.59 (1.02–2.50) | .04     |
| Subungual ALM                                | 41                 | 81           | 40           | 28            | .04     |             |         |
| Upper extremity                              |                    |              |              |               |         |             |         |
| Nonsubungual ALM                             | 67                 | 87           | 47           | 44            |         |             |         |
| Subungual ALM                                | 21                 | 78           | 33           | 16            | .16     | 1.62 (0.82–3.21) | .16     |
| Lower extremity                              |                    |              |              |               |         |             |         |
| Nonsubungual ALM                             | 475                | 94           | 60           | 38            |         |             |         |
| Subungual ALM                                | 20                 | 83           | 43           | 43            | .62     | 1.19 (0.59–2.43) | .62     |
| Sex                                          |                    |              |              |               |         |             |         |
| Male                                         | 306                | 90           | 54           | 28            | .006    | 0.69 (0.52–0.90) | .007    |
| Female                                       | 277                | 96           | 60           | 48            |         |             |         |
| Age                                          |                    |              |              |               |         |             |         |
| Continuous                                   | 583                | -            | -            |               | 1.02    | (1.01–1.03) | <.001   |
| <62 yr                                       | 293                | 95           | 61           | 47            |         |             |         |
| ≥62 yr                                       | 290                | 90           | 53           | 26            | .002    | 1.54 (1.17–2.02) | .002    |
| Race/ethnicity                               |                    |              |              |               |         |             |         |
| White                                        | 421                | 92           | 57           | 40            |         |             |         |
| Hispanic                                     | 95                 | 95           | 59           | 32            | 1.00    | (0.68–1.45) | .98     |
| Other                                        | 65                 | 91           | 57           | 25            | .70     | 1.19 (0.79–1.81) | .41     |
| Clark level                                  |                    |              |              |               |         |             |         |
| I–III                                        | 118                | 97           | 75           | 60            | <.001   | 2.46 (1.64–3.70) | <.001   |
| IV–V                                         | 463                | 91           | 52           | 31            | <.001   | 2.46 (1.64–3.70) | <.001   |
| Breslow thickness                            |                    |              |              |               |         |             |         |
| Continuous                                   | 570                | -            | -            |               | 1.15    | (1.11–1.20) | <.001   |
| Thin (≤1 mm)                                 | 114                | 96           | 81           | 67            |         |             |         |
| Intermediate (>1–4 mm)                       | 303                | 96           | 59           | 38            | 2.64    | (1.62–4.30) | <.001   |
| Thick (>4 mm)                                | 153                | 83           | 36           | 14            | <.001   | 5.62 (3.40–9.29) | <.001   |
| Ulceration                                   |                    |              |              |               |         |             |         |
| Absent                                       | 326                | 95           | 64           | 49            |         |             |         |
| Present                                      | 246                | 90           | 48           | 20            | <.001   | 1.90 (1.45–2.48) | <.001   |
| Regression                                   |                    |              |              |               |         |             |         |
| Absent                                       | 411                | 94           | 60           | 41            | .16     | 0.70 (0.42–1.16) | .16     |
| Present                                      | 75                 | 95           | 74           | 51            | .16     | 0.70 (0.42–1.16) | .16     |
| Lymphovascular invasion                      |                    |              |              |               |         |             |         |
| Absent                                       | 475                | 93           | 61           | 40            | <.001   | 1.96 (1.41–2.72) | <.001   |
| Present                                      | 99                 | 89           | 39           | 23            | <.001   | 1.96 (1.41–2.72) | <.001   |
| Perineural invasion                          |                    |              |              |               |         |             |         |
| Absent                                       | 449                | 93           | 59           | 39            |         |             |         |
| Present                                      | 126                | 91           | 50           | 31            | .06     | 1.36 (0.98–1.87) | .06     |
| Mitosis                                      |                    |              |              |               |         |             |         |
| <1/mm²                                       | 108                | 98           | 83           | 50            |         |             |         |
| ≥1/mm²                                       | 408                | 91           | 49           | 32            | <.001   | 3.06 (1.95–4.82) | <.001   |
| Microsatellitosis                            |                    |              |              |               |         |             |         |
| Absent                                       | 540                | 93           | 58           | 38            |         |             |         |
| Present                                      | 35                 | 83           | 53           | 43            | .42     | 1.27 (0.71–2.27) | .42     |
| Vertical growth phase                        |                    |              |              |               |         |             |         |
| Absent                                       | 66                 | 96           | 80           | 53            |         |             |         |
| Present                                      | 480                | 92           | 55           | 36            | .002    | 2.35 (1.36–4.05) | .002    |
| Tumor-infiltrating lymphocytes               |                    |              |              |               |         |             |         |
| Nonbrisk/minimal                             | 515                | 92           | 58           | 39            |         |             |         |
| Brisk                                        | 7                  | 100          | 57           | 57            | .70     |             |         |
Table 2. Continued

| Characteristic                        | Number of Patients | 1 yr | 5 yr | 10 yr | P Value | HR (95% CI) | P Value |
|--------------------------------------|--------------------|------|------|-------|---------|-------------|---------|
| Predominant cytology                 |                    |      |      |       |         |             |         |
| Epithelioid                          | 306                | 93   | 64   | 45    |         |             |         |
| Spindled                             | 121                | 86   | 46   | 20    |         |             |         |
| Nevoid                               | 115                | 95   | 54   | 39    | <.001   | 1.11 (0.77–1.61) | .57    |
| Associated nevus                     |                    |      |      |       |         |             |         |
| Absent                               | 541                | 92   | 56   | 34    |         |             |         |
| Present                              | 32                 | 94   | 73   | 73    | .01     | 0.43 (0.22–0.84) | .01    |
| SLNs                                 |                    |      |      |       |         |             |         |
| Negative                             | 207                | 99   | 82   | 58    |         |             |         |
| Positive                             | 213                | 94   | 42   | 25    | <.001   | 3.46 (2.40–4.97) | <.001 |
| Number of positive SLNs              |                    |      |      |       |         |             |         |
| Continuous                           | 213                | -    |      |       |         |             |         |
| Non-SLNs                             |                    |      |      |       |         |             |         |
| Negative                             | 126                | 97   | 65   | 45    |         |             |         |
| Positive                             | 168                | 87   | 31   | 14    | <.001   | 2.45 (1.69–3.56) | <.001 |
| Number of positive non-SLNs          |                    |      |      |       |         |             |         |
| Continuous                           | 164                | -    |      |       |         |             |         |

OS by multivariable analysis

| Characteristic                        | Number of Patients | 1 yr | 5 yr | 10 yr | P Value | HR (95% CI) | P Value |
|--------------------------------------|--------------------|------|------|-------|---------|-------------|---------|
| Age                                  | 322                |      |      |       |         |             |         |
| Ulceration                           |                    |      |      |       |         |             |         |
| Absent                               | 191                |      |      |       |         |             |         |
| Present                              | 131                |      |      |       |         |             |         |
| Breslow thickness ≥1 mm              | 60                 |      |      |       |         |             |         |
| >1–4 mm                              | 199                |      |      |       |         |             |         |
| >4 mm                                | 63                 |      |      |       |         |             |         |
| SLNs                                 |                    |      |      |       |         |             |         |
| Negative                             | 165                |      |      |       |         |             |         |
| Positive                             | 157                |      |      |       |         |             |         |

Abbreviations: ALM, acral lentiginous melanoma; CI, confidence interval; HR, hazard ratio; OS, overall survival; SLN, sentinel lymph node.

Figure 3. Kaplan-Meier estimates of (A) overall survival and (B) disease-specific survival for patients with acral lentiginous melanoma (ALM) arising from subungual and nonsubungual locations.
| Characteristic                        | Number of Patients | DSS Rate | 1 yr | 5 yr | 10 yr | P Value | HR (95% CI) | P Value |
|--------------------------------------|-------------------|----------|------|------|-------|---------|-------------|---------|
| **DSS by univariate analysis**       |                   |          |      |      |       |         |             |         |
| All patients                         | 583               |          | 96   | 68   | 55    | -       | -           |         |
| ALM subgroup                         |                   |          |      |      |       |         |             |         |
| Nonsubungual ALM                    | 542               |          | 96   | 69   | 55    | -       | -           |         |
| Subungual ALM                       | 41                |          | 94   | 56   | 48    | .18     | 1.47 (0.83–2.61) | .18     |
| **Upper extremity**                 |                   |          |      |      |       |         |             |         |
| Nonsubungual ALM                    | 67                |          | 94   | 58   | 58    | -       | -           |         |
| Subungual ALM                       | 21                |          | 94   | 47   | 35    | .34     | 1.51 (0.64–3.58) | .35     |
| **Lower extremity**                 |                   |          |      |      |       |         |             |         |
| Nonsubungual ALM                    | 475               |          | 96   | 70   | 55    | -       | -           |         |
| Subungual ALM                       | 20                |          | 94   | 65   | 65    | .80     | 1.12 (0.46–2.76) | .80     |
| **Sex**                             |                   |          |      |      |       |         |             |         |
| Male                                | 306               |          | 94   | 65   | 46    | -       | -           |         |
| Female                              | 277               |          | 97   | 71   | 63    | .03     | 0.69 (0.49–0.96) | .03     |
| **Age**                             |                   |          |      |      |       |         |             |         |
| Continuous                          | 583               |          | -    | -    | -     |         |             |         |
| <62 yr                              | 293               |          | 96   | 67   | 54    | -       | -           |         |
| ≥62 yr                              | 290               |          | 95   | 69   | 58    | >.99    | 1.00 (0.72–1.40) | >.99    |
| **Race/ethnicity**                  |                   |          |      |      |       |         |             |         |
| White                               | 421               |          | 96   | 68   | 55    | -       | -           |         |
| Hispanic                            | 95                |          | 98   | 72   | 49    | 0.99 (0.63–1.57) | .97     |
| Other                               | 65                |          | 93   | 64   | 64    | .92     | 1.11 (0.66–1.88) | .70     |
| **Clark level**                     |                   |          |      |      |       |         |             |         |
| I–III                               | 118               |          | 99   | 85   | 79    | <.001   | 3.37 (1.90–5.97) | <.001   |
| IV–V                                | 463               |          | 95   | 63   | 47    | <.001   | 9.06 (4.50–18.25) | <.001   |
| **Breslow thickness**               |                   |          |      |      |       |         |             |         |
| Continuous                          | 570               |          | -    | -    | -     |         |             |         |
| Thin (≤1 mm)                        | 114               |          | 99   | 90   | 82    | -       | -           |         |
| Intermediate (>1–4 mm)              | 303               |          | 98   | 72   | 59    | 3.27 (1.63–6.57) | <.001   |
| Thick (>4 mm)                       | 153               |          | 88   | 41   | 23    | <.001   | 9.06 (4.50–18.25) | <.001   |
| **Ulceration**                      |                   |          |      |      |       |         |             |         |
| Absent                              | 326               |          | 98   | 74   | 65    | -       | -           |         |
| Present                             | 246               |          | 93   | 59   | 38    | <.001   | 2.08 (1.49–2.91) | <.001   |
| **Regression**                      |                   |          |      |      |       |         |             |         |
| Absent                              | 411               |          | 97   | 72   | 57    | -       | -           |         |
| Present                             | 75                |          | 98   | 85   | 81    | .07     | 0.52 (0.25–1.07) | .08     |
| **Lymphovascular invasion**         |                   |          |      |      |       |         |             |         |
| Absent                              | 475               |          | 97   | 73   | 59    | -       | -           |         |
| Present                             | 99                |          | 91   | 45   | 32    | <.001   | 2.43 (1.66–3.55) | <.001   |
| **Perineural invasion**             |                   |          |      |      |       |         |             |         |
| Absent                              | 449               |          | 96   | 70   | 56    | -       | -           |         |
| Present                             | 126               |          | 93   | 59   | 48    | .09     | 1.40 (0.95–2.09) | .09     |
| **Mitosis**                         |                   |          |      |      |       |         |             |         |
| <1/mm²                              | 108               |          | 98   | 89   | 75    | -       | -           |         |
| ≥1/mm²                              | 408               |          | 94   | 61   | 48    | <.001   | 3.53 (1.95–6.41) | <.001   |
| **Microsatellitosis**               |                   |          |      |      |       |         |             |         |
| Absent                              | 540               |          | 96   | 69   | 55    | -       | -           |         |
| Present                             | 35                |          | 89   | 57   | 46    | .13     | 1.64 (0.86–3.12) | .13     |
| **Vertical growth phase**           |                   |          |      |      |       |         |             |         |
| Absent                              | 66                |          | 98   | 91   | 76    | -       | -           |         |
| Present                             | 480               |          | 95   | 66   | 52    | .001    | 3.60 (1.59–8.18) | .002    |
| **Tumor-infiltrating lymphocytes**  |                   |          |      |      |       |         |             |         |
| Nonbrisk/minimal                    | 515               |          | 95   | 69   | 56    | -       | -           |         |
| Brisk                               | 7                 |          | 100  | 67   | 67    | .56     | -           | -       |
Our study had some limitations. Owing to the rarity of ALM, the sample size of subungual ALM is relatively lower than that of the control group of ALM from other acral locations. Similarly, the subungual ALM groups is smaller than the sample size in previously reported series of subungual melanoma. However, most of the reported studies of subungual melanoma included other histologic types of melanoma of the nail unit, such as superficial spreading melanoma and nodular melanoma. Because our institution is a tertiary cancer center, the potential for referral bias should also be considered in interpretation of our findings. Finally, factors such as patient’s socioeconomic status and access to healthcare, which could have influenced the results of our study, were not evaluated.

While it is reassuring that subungual anatomic site is not a poor prognostic factor in ALM, it remains concerning that the diagnosis of subungual ALM is often delayed in comparison to the diagnosis of cutaneous melanoma of other sites. Patients’ awareness of clinical presentation and dermatologists’ recognition of longitudinal melanonychia as a key finding should improve early diagnosis. However, a subset of subungual melanoma, particularly, amelanotic subungual melanoma poses a diagnostic challenge as it may mimic a variety of benign processes, such as nail infection or infestation.

Although the subungual ALM showed lower OS rates suggesting a relatively more aggressive type of ALM, the OS rates were mainly attributed to advanced Breslow thickness, higher rates of ulceration and SLN metastasis, and possibly advanced age rather than the subungual anatomic site. In addition, the OS may not precisely reflect the biologic behavior and disease outcome as it is more likely to be confounded by the other factors such as patient’s general health and comorbidities when compared with the DSS. In conclusion, our findings indicate that subungual site is not an independent prognostic factor for OS or DSS in ALM. However, owing to the study limitation including the relatively small sample size of subungual ALM, larger prospective studies are necessary to validate our current findings.

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