Analysis of Sentinel Node Biopsy and Clinicopathologic Features as Prognostic Factors in Patients With Atypical Melanocytic Tumors

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ABSTRACT

Background: Atypical melanocytic tumors (AMTs) include a wide spectrum of melanocytic neoplasms that represent a challenge for clinicians due to the lack of a definitive diagnosis and the related uncertainty about their management. This study analyzed clinicopathologic features and sentinel node status as potential prognostic factors in patients with AMTs. **Patients and Methods:** Clinicopathologic and follow-up data of 238 children, adolescents, and adults with histologically proved AMTs consecutively treated at 12 European centers from 2000 through 2010 were retrieved from prospectively maintained databases. The binary association between all investigated covariates was studied by evaluating the Spearman correlation coefficients, and the association between progression-free survival and all investigated covariates was evaluated using univariable Cox models. The overall survival and progression-free survival curves were established using the Kaplan-Meier method. **Results:** Median follow-up was 126 months (interquartile range, 104–157 months). All patients received an initial diagnostic biopsy followed by wide (1 cm) excision. Sentinel node biopsy was performed in 139 patients (58.4%), 37 (26.6%) of whom had sentinel node positivity. There were 4 local recurrences, 43 regional relapses, and 8 distant metastases as first events. Six patients (2.5%) died of disease progression. Five patients who were sentinel node–negative and 3 patients who were sentinel node–positive developed distant metastases. Ten-year overall and progression-free survival rates were 97% (95% CI, 94.9%–99.2%) and 82.2% (95% CI, 77.3%–87.3%), respectively. Age, mitotic rate/mm^2, mitoses at the base of the lesion, lymphovascular invasion, and 9p21 loss were factors affecting prognosis in the whole series and the sentinel node biopsy subgroup. **Conclusions:** Age >20 years, mitotic rate >4/mm^2, mitoses at the base of the lesion, lymphovascular invasion, and 9p21 loss proved to be worse prognostic factors in patients with ATMs. Sentinel node status was not a clear prognostic predictor.

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Background

Cutaneous melanocytic lesions represent a wide spectrum, ranging from benign to overtly malignant. This composite group includes atypical melanocytic tumors (AMTs), mostly occurring in children, adolescents, and young adults,[1,2] whose biologic behavior and metastatic risk have been controversial and difficult to predict since their initial description by Spitz.[1] In fact, these tumors have some attributes of malignancy, such as cytologic atypia and mitotic activity, that are considered of insufficient severity to justify a diagnosis of frank malignancy. They were later defined as "borderline melanomas"[3,4] or "minimal deviation melanomas"[5–7] because of the interpretative problems they presented to physicians in distinguishing them from benign


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melanocytic nevi. Smith et al[8] and Barnhill et al,[9] in different analyses, described a kind of Spitz nevus showing atypia and the capability of metastasizing, and they classified this neoplasm as Spitz tumor or atypical Spitz tumor. In subsequent studies, Barnhill[10] and Elder and Xu[11] introduced the term "melanocytic tumor of uncertain malignant potential" or "melanocytic proliferation with indeterminate biologic potential," a descriptive diagnosis generally accompanied by a differential diagnosis, to underline the uncertainties in predicting the clinical behavior. Cerroni et al[12] studied a series of melanocytic tumors of uncertain malignant potential and found that the presence of increased mitotic activity, mitoses near the base of the lesion, and an inflammatory reaction were statistically significant parameters unfavorably affecting outcome.

To integrate the conventional morphologic assessment methods for these difficult lesions, some authors proposed sentinel node (SN) status assessment (negative vs positive).[13,14] The MSLT-1 trial demonstrated the utility of sentinel node biopsy (SNB) as a staging tool and found that SN status was the most powerful prognostic factor in patients with melanoma; this trial was the primary reference study supporting the use of SNB in cutaneous melanoma.[15] The rationale behind the use of SNB also in AMT was the assumption that the detection of melanocytic cells in the draining regional lymph node basin generally indicates malignancy.[14]

Although some authors found that SN status did not seem to be useful in predicting outcome in atypical spitzoid tumors, a subset of AMT generally occurring in young patients and associated with a good prognosis, other studies emphasized the possible diagnostic and prognostic role of SN status in AMTs, particularly in older patients and nonspitzoid lesions.[16–18] In different analyses, Gerami et al[19,20] and Shen et al[21] showed that the integration of molecular and histopathologic data improved the risk assessment of spitzoid tumors, and the use of fluorescence in situ hybridization (FISH) has suggested that specific genomic alterations affect the prognosis of atypical spitzoid tumors. Because the few published analyses of AMT are limited by the small series of cases and/or short follow-up,[22,23] further characterization of these lesions could be of relevance. We therefore analyzed a large series of patients with a long follow-up to better define the role of SN status as a prognostic factor and to identify other potential clinicopathologic predictors of survival.

Patients and Methods

Clinicopathologic Features and FISH Analysis

A total of 238 patients eligible for the study analysis were consecutively treated from 2000 through 2010 at the Istituto Nazionale dei Tumori, Milan, University Hospitals of Brescia, Modena, Parma, and Pavia, and General Hospitals of Cremona, Macerata, Siracusa, and Trapani, all in Italy; Istituto Oncologico Svizzera Italiana, Ospedale Regionale Bellinzona e Valli, Bellinzona, Switzerland; University Hospital of Heraklion, Greece; and Queen Mary University, London, United Kingdom. Clinicopathologic data were retrieved from prospectively maintained databases. All cases were reviewed independently by a pool of dermatopathologists (B.V., M.C., M.B., A.P., S.L.P.), with disagreements resolved through discussion. Cases were subcategorized into 2 groups: spitzoid and nonspitzoid. Spitzoid tumors had a morphology resembling a Spitz tumor (large melanocytic cells, spindle cells and/or epithelioid cells, sharp lateral demarcation of the nests of intraepidermal melanocytes, maturity of cells, and rarity of individual melanocytes high above the basal cell layer).[12,24] Nonspitzoid tumors included nevoid lesions (resembling a conventional or dysplastic nevus), pigmented epithelioid melanocytomas, deep penetrating nevi, and atypical blue nevi.[12] Patient age and sex, histologic subtype, tumor thickness, ulceration, mitotic rate (MR)/mm^2, presence of mitotic figures at the base of the lesion (marginal mitoses, within 0.25 mm of the dermal margin of the lesion),[25] lymphovascular invasion (LVI), and tumor-infiltrating lymphocytes were recorded for all cases. Morphologic and FISH analysis provided support for a diagnosis of AMT according to the WHO classification criteria.[26] Two hybridizations were performed: the 4-probe FISH assay targeting 6p25, 6q23, 11q13, and Cep6 was used for the first hybridization, and the 4-probe FISH assay targeting 6p25, 9p21, 11q13, and 8q24 was used for the second.[19,20] The pool of dermatopathologists, having experience in molecular diagnostics and FISH testing, performed the FISH analyses. A patient was considered to have a positive FISH result based on the criteria and cutoff values used by Gerami et al.[19,20,27] All patients received an initial diagnostic biopsy followed by wide (1 cm) excision; SNB was performed in 139 patients (58.4%) after the benefits and potential harms had been discussed with them. A total of 95 patients eligible for SNB declined the procedure, whereas 4 did not undergo it due to the presence of comorbidities. Pathologic assessment of SNs was performed according to the EORTC protocol.[28] Patients with positive SNs were offered completion lymph node dissection (CLND) as additional therapy.

Statistical Methods

Clinicopathologic characteristics were recorded according to SNB (performed vs not performed) for the whole series of patients, according to SN status (positive vs negative) in the group undergoing SNB, and according to CLND (performed vs not performed) in the SN-positive group.

The primary endpoints of the study were overall survival (OS) and progression-free survival (PFS). The OS and PFS curves were estimated using the Kaplan-Meier method[29] and compared using the log-rank test. Inverse probability of treatment weighting (IPTW)[30] was applied to groups affected by a selection bias. Standardized mean difference (SMD)[31] was used to evaluate the balancing of clinicopathologic characteristics. The association between PFS and all investigated covariates was assessed via univariable Cox models.

We applied the elastic net penalization method in the Cox model to perform covariate selection for PFS between all investigated features in the SNB subgroup.[32] More details on the statistical methods are provided in the supplemental eAppendix 1 (available with this article at JNCCN.org).

Results

Patient and Disease Characteristics

Clinicopathologic characteristics of the 238 patients with a diagnosis of AMT are summarized in Table 1. Patient age ranged from 3 to 53 years; most AMTs (52.5%) were diagnosed in young patients (age ≤20 years). The most frequent primary site was the lower limbs (38.2%). Spitzoid tumors numbered 81 (34%); nonspitzoid tumors numbered 157 (66%) and included nevoid lesions (n=89; 37.4%), pigmented epithelioid melanocytomas (n=19; 8%), deep penetrating nevi (n=43; 18.1%), and atypical blue nevi (n=6; 2.5%). Mitoses at the base of the lesion and LVI were detected in 29% and 23.5% of cases, respectively. In 28.6% of cases, the FISH test showed 9p21 loss.

Clinicopathologic characteristics of the 238 patients according to SNB are summarized in Table 2. The group that underwent SNB and the non-SNB group did not differ with respect to sex, tumor site, tumor thickness, ulceration, MR/mm^2, and tumor-infiltrating lymphocytes. The SNB group differed significantly from the non-SNB group in age (5.8% vs 38.4% aged ≤10 years; 23.0% vs 47.5% aged 11–20 years; and 71.2% vs 14.1% aged >20 years). Histologic subtype differed in the SNB group compared with the non-SNB group: 75.5% of patients who underwent SNB had nonspitzoid tumors and 24.5% had spitzoid lesions; among those in the non-SNB group, 52.5% had nonspitzoid tumors and 47.5% spitzoid lesions. The group that underwent SNB showed significantly higher rates of mitoses at the base of the lesion (33.8% vs 22.2%), LVI (28.1% vs 17.2%), and 9p21 loss (33.8% vs 21.2%) than the non-SNB group.

Of the 139 patients that underwent SNB and the 99 that did not, 55 (39.6%) and 26 (26.3%), respectively, showed FISH abnormalities. SNB revealed metastatic involvement in 37 (26.6%) patients. Clinicopathologic characteristics of the 139 patients according to SN status are summarized in supplemental eTable 1. Patients who were SN-positive significantly differed from those who were SN-negative in median number of mitoses/mm^2 (5 vs 2, respectively; SMD, 1.946), presence of mitoses at the base of the lesion (86.5% vs 14.7%, respectively; SMD, 2.062), and LVI (75.7% vs 10.8%; SMD, 1.733). Patients who were SN-positive showed significantly higher rates of 9p21 loss than those who were SN-negative (45.9% vs 29.4%; SMD, 1.587). Of the 37 patients who were SN-positive, 19 (51.4%) showed FISH abnormalities; 21 (56.7%) of 37 underwent CLND, among whom 1 (4.8%) showed further positive non-SNs. Patients who were SN-positive were not offered further treatment (ie, systemic therapies) other than CLND. After IPTW, SMD reached values <0.1 for all covariates included in the propensity score model.

Survival Analysis

Median follow-up was 126 months (interquartile range, 104–157 months). The 10-year OS and PFS were 97% (95% CI, 94.9%–99.2%) and 82.2% (95% CI, 77.3%–87.3%), respectively (Figure 1). The group that did not undergo SNB showed slightly better 10-year OS and PFS probabilities than the group that did: 100% versus 94.9% (95% CI, 91.3%–98.7%) and 87.8% (95% CI, 81.6%–94.5%) versus 77.9% (95% CI, 71.0%–85.4%), respectively (Figure 2A, C). Weighted comparisons showed that 10-year OS and PFS were 100% versus 96.8% (95% CI, 93.3%–100%) and 88.5% (95% CI, 82.4%–95.1%) versus 84.6% (95% CI, 77.4%–92.4%), respectively; these differences were not statistically significant (Figure 2B, D). Patients who were SN-negative and those who were SN-positive had similar 10-year OS (96.0% [95% CI, 92.3%–99.9%] vs 91.9% [95% CI, 83.5%–100%]; P=.332), whereas patients who were SN-negative showed higher 10-year PFS (84.2% [95% CI, 77.4%–91.6%] vs 63.6% [95% CI, 49.6%–81.7%]; P=.045) (supplemental eFigure 1).

Supplemental eTable 2 summarizes the clinicopathologic characteristics of patients who were SN-positive according to CLND before and after propensity score weighting. Patients undergoing CLND showed observed 10-year OS and PFS probabilities similar to those of patients who did not undergo the procedure: 90.5% (95% CI, 78.8%–100%) versus 93.8% (95% CI, 82.6%–100%) and 61.0 (95% CI, 43.0%–86.3%) versus 67.0% (95% CI, 46.9%–95.8%), respectively (supplemental eFigure 2A, C). After weighting, the 10-year OS and PFS probabilities were 85.8% (95% CI, 65.6%–100%) versus 97.9% (95% CI, 89.0%–100%) and 64.9% (95% CI, 39.6%–100%) versus 61.0% (95% CI, 35.7%–100%), respectively (supplemental eFigure 2B, D).

There were 4 local recurrences, 43 regional recurrences, and 8 distant metastases as first events. Six patients died as a result of disease progression. Of the

Table 1. Clinicopathologic Characteristics

Characteristic	n (%)
Total	238 (100)
Age	
≤10 y	46 (19.3)
11–20 y	79 (33.2)
>20 y	113 (47.5)
Sex	
Female	122 (51.3)
Male	116 (48.7)
Tumor site	
Head and neck	78 (32.8)
Upper limbs	43 (18.1)
Trunk	26 (10.9)
Lower limbs	91 (38.2)
Histologic subtype	
Spitzoid	81 (34.0)
Nonspitzoid[a]	157 (66.0)
Tumor thickness, mm	
Median (IQRE)	2.34 (2.20–2.49)
Ulceration	
Absent	225 (94.5)
Present	13 (5.5)
Mitosis, per mm^2	
Median (IQRE)	2 (1–4)
Mitosis at the base of the lesion	
Absent	169 (71.0)
Present	69 (29.0)
Lymphovascular invasion	
Absent	182 (76.5)
Present	56 (23.5)
Tumor-infiltrating lymphocytes	
Absent	83 (34.9)
Brisk	79 (33.2)
Nonbrisk	76 (31.9)
FISH test 6p25	
Negative	209 (87.8)
Positive	29 (12.2)
FISH test 6q23/Cep 6	
Negative	231 (97.1)
Positive	7 (2.9)
FISH test 6p25/Cep 6	
Negative	233 (97.9)
Positive	5 (2.1)
FISH test 11q13	
Negative	211 (88.7)
Positive	27 (11.3)
FISH test 9p21	
Negative	170 (71.4)
Positive	68 (28.6)
FISH test 8q24	
Negative	234 (98.3)
Positive	4 (1.7)
Sentinel node biopsy	
Negative	102 (42.9)
Positive	37 (15.5)
Not performed	99 (41.6)

Abbreviation: FISH, fluorescence in situ hybridization; IQRE, interquartile range extremes.
[a]Nevoid, deep penetrating nevus, or atypical blue nevus.

patients who developed regional recurrences, 34 (79.1%) had not undergone SNB, 6 (13.9%) underwent SNB and were SN-positive, and 3 (7%) underwent SNB and were SN-negative. Of the 51 patients who developed regional and distant metastases, 40 (78.4%) showed FISH abnormalities. Five patients who were SN-negative and 3 who were SN-positive, all belonging to the nonspitzoid group, developed distant metastases beyond the regional nodal basin; of these patients, 4 developed distant metastases after regional recurrence and 4 had distant spread in the absence of previous regional node metastases. The 8 patients who developed distant disease—6 of whom died of their disease—had an age range from 28 to 42 years; the histologic diagnosis was nevoid lesion in 6 cases, deep penetrating nevus in 1 case, and atypical blue nevus in 1 case. Three patients developed another malignancy, and 1 died of causes unrelated to AMT.

In univariable analysis of the whole series, age ≤10 versus >20 years and age 11–20 versus >20 years; MR ≥4/mm^2; mitoses at the base of the lesion; LVI; and 9p21 loss (all $P<.001$) were strongly associated with a worse PFS, whereas SN status ($P=.024$) was mildly associated. All of the strongly associated variables were observed in the group in which SNB was performed (Table 3). The hazard ratio of PFS increased from 0 to 4 for MR and then reached a plateau, whereas for age, it increased up to 30 years and then decreased. Among the 55 patients with recurrences, 37 (67.3%) had MR ≥4, 35 (63.6%) had mitoses at the base of the lesion, 33 (60%) had LVI, and 34 (61.8%) showed 9p21 loss. Of the 183 patients without recurrences 21 (11.5%) had MR ≥4, 19 (10.4%) had mitoses at the base of the lesion, 24 (13.1%) had LVI, and 26

Table 2. Clinicopathologic Characteristics According to SNB, Before and After Propensity Score Weighting

	Unweighted Statistics			Weighted Statistics		
	SNB Not Performed n (%)	SNB Performed n (%)	SMD	SNB Not Performed n (%)	SNB Performed n (%)	SMD
Total	99 (41.6)	139 (58.4)		96.4 (50.8)	96.1 (49.2)	
Age			0.160			0.005
≤10 y	38 (38.4)	8 (5.8)		37.2 (38.6)	37.5 (39.0)	
11–20 y	47 (47.5)	32 (23.0)		46.1 (47.8)	48.4 (50.4)	
>20 y	14 (14.1)	99 (71.2)		13.1 (13.6)	10.2 (10.6)	
Sex			0.026			0.016
Female	51 (51.5)	71 (51.1)		50.3 (52.2)	50.9 (53)	
Male	48 (48.5)	68 (48.9)		46.1 (47.8)	45.2 (47)	
Tumor site			0.230			0.067
Head and neck	34 (34.3)	44 (31.7)		32.7 (33.9)	33.8 (35.2)	
Upper limbs	17 (17.2)	26 (18.7)		16.5 (17.1)	17.1 (17.8)	
Trunk	10 (10.1)	16 (11.5)		10.0 (10.4)	7.2 (7.5)	
Lower limbs	38 (38.4)	53 (38.1)		37.2 (38.6)	38.0 (39.5)	
Histologic subtype			0.049			0.078
Spitzoid	47 (47.5)	34 (24.5)		46.3 (48.0)	44.8 (46.6)	
Nonspitzoid[a]	52 (52.5)	105 (75.5)		50.1 (52.0)	51.3 (53.4)	
Tumor thickness, mm			0.056			0.007
Median (IQRE)	2.32 (2.21–2.50)	2.35 (2.22–2.49)		2.32 (2.20–2.50)	2.35 (2.25–2.48)	
Ulceration			0.031			0.021
Absent	94 (94.9)	131 (94.2)		91.4 (94.8)	91.6 (95.3)	
Present	5 (5.1)	8 (5.8)		5 (5.2)	4.5 (4.7)	
Mitosis, per mm^2			0.218			0.002
Median (IQRE)	2 (1–2)	2 (1–5)		2 (1–2)	2 (1–2)	
Mitosis at the base of the lesion			0.260			0.001
Absent	77 (77.8)	92 (66.2)		75.4 (78.2)	75.2 (78.3)	
Present	22 (22.2)	47 (33.8)		21 (21.8)	20.9 (21.7)	
Lymphovascular invasion			0.262			0.001
Absent	82 (82.8)	100 (71.9)		79.4 (82.4)	79.1 (82.3)	
Present	17 (17.2)	39 (28.1)		17 (17.6)	17.0 (17.7)	
Tumor-infiltrating lymphocytes			0.155			0.141
Absent	38 (38.4)	45 (32.4)		37.3 (38.7)	32.1 (33.4)	
Brisk	29 (29.3)	50 (36.0)		27.4 (28.5)	33.2 (34.5)	
Nonbrisk	32 (32.3)	44 (31.7)		31.6 (32.8)	30.8 (32.1)	
FISH test 6p25			0.110			0.072
Negative	89 (89.9)	120 (86.3)		86.6 (89.9)	88.4 (92.0)	
Positive	10 (10.1)	19 (13.7)		9.8 (10.1)	7.7 (8.0)	
FISH test 6q23/Cep 6			0.096			0.105
Negative	96 (97.0)	135 (97.1)		93.4 (96.9)	93.4 (97.2)	
Positive	3 (3.0)	4 (2.9)		3.0 (3.1)	2.7 (2.8)	
FISH test 6p25/Cep 6			0.136			0.136
Negative	97 (98.0)	136 (97.8)		94.4 (97.9)	92.2 (95.9)	
Positive	2 (2.0)	3 (2.2)		2.0 (2.1)	3.9 (4.1)	

(continued on next page)

Table 2. Clinicopathologic Characteristics According to SNB, Before and After Propensity Score Weighting (cont.)

	Unweighted Statistics			Weighted Statistics		
	SNB Not Performed n (%)	SNB Performed n (%)	SMD	SNB Not Performed n (%)	SNB Performed n (%)	SMD
FISH test 11q13			0.680			0.030
Negative	89 (89.9)	122 (87.8)		86.6 (89.9)	85.5 (88.9)	
Positive	10 (10.1)	17 (12.2)		9.8 (10.1)	10.6 (11.1)	
FISH test 9p21			0.285			0.001
Negative	78 (78.8)	92 (66.2)		75.4 (78.2)	75.2 (78.3)	
Positive	21 (21.2)	47 (33.8)		21 (21.8)	20.9 (21.7)	
FISH test 8q24			0.092			0.114
Negative	97 (98.0)	137 (98.6)		94.4 (97.9)	92.7 (96.5)	
Positive	2 (2.0)	2 (1.4)		2.0 (2.1)	3.4 (3.5)	
SNB			—			—
Negative	0 (0.0)	102 (73.4)		0 (0)	77.6 (80.7)	
Positive	0 (0.0)	37 (26.6)		0 (0)	18.5 (19.3)	
Not performed	99 (100)	0 (0.0)		96.4 (100)	0 (0)	

Abbreviations: AMT, atypical melanocytic tumor; FISH, fluorescence in situ hybridization; IQRE, interquartile range extremes; SMD, standardized mean difference; SNB, sentinel node biopsy.
[a]Nevoid, deep penetrating nevus, or atypical blue nevus.

(14.2%) showed 9p21 loss. After IPTW, SMD reached values <0.1 for all covariates included in the PS model (data not shown).

Predictive Covariate Selection

The elastic net penalized Cox model selection procedure led to the selection of higher MR, mitoses at the base of the lesion, LVI, and 9p21 loss as the most relevant covariates for PFS prediction. The sparsity of the events and the high correlation issue in our series prevented us from developing a reliable predictive model based on the selected variables.

Discussion

We found a positive SN rate of 26.6%, in line with data reported in other studies in which a higher proportion of positive SNs was observed in patients with AMTs compared with those with conventional melanomas.[15,33] However, our study did not clearly show that SN status was a predictor of OS. Although most of the variables associated with a worse prognosis (MR/mm^2 ≥4, mitoses at the base of the lesion, LVI, and 9p21 loss) were prevalent in patients who were SN-positive and could be considered to identify individuals eligible for SNB, in our analyses, SN status did not seem to provide the same important prognostic information for AMT as observed in cutaneous melanoma.[15] Because our findings are not strong enough to mandate SNB for AMT currently, ultrasound imaging could be an alternative approach during follow-up.[34] However, the number of positive SNs in our series was small, and further analyses of larger series of patients are needed to better evaluate the prognostic role of SN status.

Previous studies in small series with a shorter follow-up focusing on the role of SN status yielded controversial results. Busam et al[35] reported that children and teenagers with spitzoid AMTs and positive SNs had a less aggressive clinical course than patients with SN-positive melanoma. Ghazi et al,[16] in a study of patients with AMTs with a median age of 24 years, showed that lymph node assessment did not predict the outcome of spitzoid AMTs. Gamblin et al[36] and Murali et al,[37] in different analyses, reached the opposite conclusion, arguing that SNB could offer a means for assessing the metastatic potential of spitzoid AMTs and represented an adjunct tool in patient management.

In our series, the 6 deaths as a result of disease progression confirmed that AMT should be considered a provisional diagnosis pending molecular and genetic analyses, expert review, and outcome; all our data were used to predict the likelihood of melanoma in these patients. Our analysis showed that MR ≥4 and the presence of mitoses at the base of the lesion correlated with a worse prognosis. These factors seemed to be indicators of a more aggressive clinical behavior and to be associated with a higher probability of distant metastatic spread beyond the regional nodal basin. Mitosis should be taken into consideration as a prognostic factor in AMTs, and its relevance should be carefully evaluated in clinical decision-making.

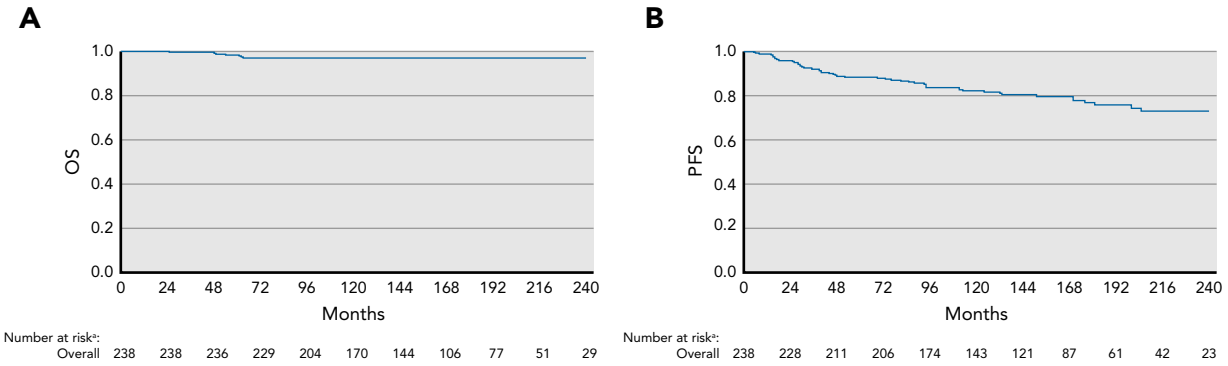

Figure 1. Atypical melanocytic tumors. Kaplan-Meier curves for (A) OS and (B) PFS in the whole series.
Abbreviations: OS, overall survival; PFS, progression-free survival.
[a]Number of patients at risk for an event.

Our data are in line with various previous reports in which these variables were heavily weighted for their diagnostic and prognostic significance. Cerroni et al[12] identified only 3 parameters that were statistically different between 2 groups of AMTs with favorable and unfavorable behavior based on clinical follow-up: high MR, mitoses near the base of the lesion, and an inflammatory infiltrate. In a more recent study, Gerami et al[38] assessed interobserver agreement in diagnosis by 13 expert dermatopathologists for 75 atypical spitzoid tumors and confirmed that frequent mitoses and deep mitoses were histomorphologic features that correlated with disease progression. In our analysis, no statistically significant association was found between an inflammatory infiltrate and patient outcome.

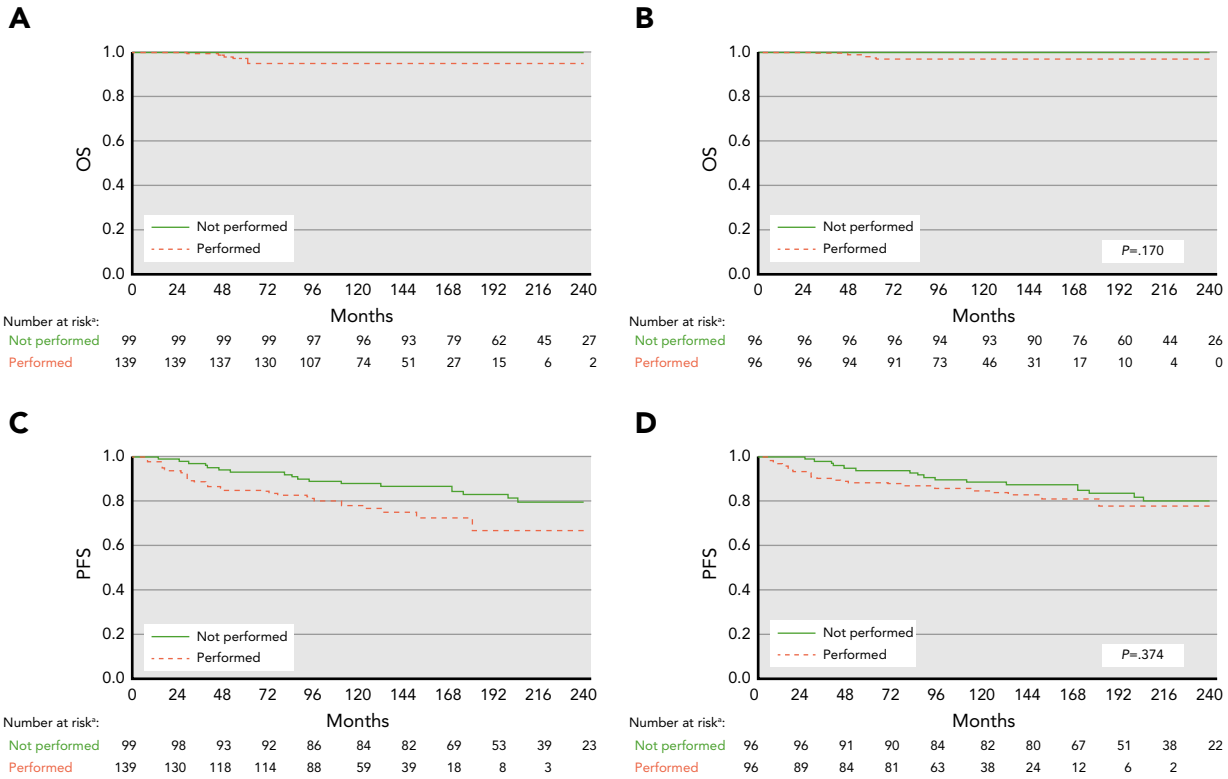

Figure 2. Unweighted and weighted Kaplan-Meier curves for (A, B) OS and (C, D) PFS according to sentinel node biopsy (performed or not performed).
Abbreviations: OS, overall survival; PFS, progression-free survival; SNB, sentinel node biopsy.
[a]Weighted number of patients at risk for an event (rounded to the integer in the weighted analysis).

Table 3. Results of Univariable Cox Model Analysis for Progression-Free Survival

	Whole Series		SNB Performed	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age[a]				
34 vs 26 y	5.28 (2.01–14.02)	<.001	5.18 (2.46–9.83)	<.001
≤10 vs 11–20 y	1.83 (1.04–3.10)	.060	1.83 (0.94–3.62)	.101
≤10 vs >20 y	3.43 (1.72–6.46)	<.001	3.86 (2.49–8.46)	<.001
11–20 vs >20 y	3.26 (1.54–6.17)	<.001	3.75 (2.37–8.28)	<.001
Sex		.189		.081
Male vs female	1.47 (0.85–2.54)		1.88 (0.94–3.77)	
Tumor site		.142		.146
Head and neck vs lower limbs	0.81 (0.27–2.28)		0.86 (0.31–2.36)	
Trunk vs lower limbs	2.28 (0.96–5.71)		2.39 (0.99–5.75)	
Upper limbs vs lower limbs	1.43 (0.51–3.77)		1.45 (0.55–3.83)	
Histologic subtype		.139		.128
Spitzoid vs nonspitzoid[b]	0.82 (0.36–2.28)		0.48 (0.23–0.89)	
Tumor thickness[a]		.106		.101
2.49 vs 2.20 mm	0.72 (0.51–1.02)		0.36 (0.14–0.93)	
Ulceration[b]		.067		.189
Present vs absent	0.16 (0.00–1.09)		0.24 (0.00–1.66)	
Mitoses[a] per mm^2		<.001		<.001
4 vs 1	4.73 (2.18–8.50)		3.96 (2.05–7.60)	
Mitoses at base of lesion		<.001		<.001
Present vs absent	4.49 (2.04–7.86)		4.65 (2.34–8.08)	
Tumor-infiltrating lymphocytes		.927		.677
Brisk vs absent	1.09 (0.56–2.13)		1.14 (0.52–2.51)	
Not brisk vs absent	1.14 (0.58–2.24)		0.77 (0.31–1.92)	
Lymphovascular invasion		<.001		<.001
Present vs absent	3.60 (1.96–6.87)		4.05 (2.19–8.06)	
FISH test 6p25		.182		.179
Positive vs negative	1.90 (0.97–3.94)		1.74 (0.78–3.87)	
FISH test 6q23/Cep6		.490		.917
Positive vs negative	1.64 (0.40–6.74)		0.90 (0.12–6.57)	
FISH test 6p25/Cep6[c]		.533		.283
Positive vs negative	0.46 (0.00–3.20)		0.51 (0.00–3.61)	
FISH test 11q13		.176		.184
Positive vs negative	1.81 (0.76–4.05)		1.91 (0.88–4.22)	
FISH test 9p21		<.001		<.001
Positive vs negative	4.53 (2.16–7.84)		4.67 (2.38–8.16)	
FISH test 8q24[c]		.618		.719
Positive vs negative	0.53 (0.00–3.68)		0.62 (0.00–4.41)	
SNB[d]		.024		—
Performed vs not performed	2.01 (1.10–3.67)		—	
Sentinel node status		—		.189
Positive vs negative	—		2.01 (1.00–4.02)	

P values were calculated using the Wald test.
Abbreviations: FISH, fluorescence in situ hybridization; HR, hazard ratio; SNB, sentinel node biopsy.
[a]Modeled as restricted cubic spline. Reference values are third and first quartiles.
[b]Nevoid, deep penetrating nevus, or atypical blue nevus.
[c]Estimated with Firth's penalized model.
[d]Inverse probability treatment weighted comparison.

Our study also provides evidence that LVI was associated with shorter survival. We found that the tumor-associated lymphatic network constituted a potential criterion in the selection of high-risk patients who should be candidates for careful follow-up. Another investigation into the prognostic role of LVI in AMT conducted by Abraham et al[39] in a small number of lesions related this parameter to a poorer prognosis.

Furthermore, our findings showed that the groups of younger patients (aged <10 years and 11–20 years) with AMT had a longer survival. Spatz et al[40] analyzed various parameters, including age, to define a grading system for risk stratification of atypical Spitz tumors. They found that diagnosis at age >10 years carried a likelihood ratio >1.50, so this variable was used for the grading system. The low rate of local recurrences (1.7%) in our series confirmed that wide surgical excision with 1-cm margins was adequate to control local recurrence. Ludgate et al,[41] in another study of 67 patients with atypical Spitz tumors, observed 1 local recurrence and recommended 1-cm excision margins to prevent local recurrences.

Finally, in our analysis, AMTs were classified into specific risk categories based on the cytogenetic changes determined by FISH. In the survival analysis, we found that 9p21 loss was associated with a higher risk of distant spread. Gerami et al[20] evaluated 2 small subgroups of high-risk melanocytic neoplasms in children—including spitzoid melanomas, atypical Spitz tumors with chromosomal copy number changes, and conventional melanomas—and found that the presence of a homozygous deletion of 9p21 and a positive SNB in atypical Spitz tumors was associated with a higher risk of systemic metastasis and death. Another analysis by Gerami et al[19] showed that also the presence of 6p25 and/or 11q13 gain was significantly associated with tumor progression beyond the SN when compared with FISH-negative tumors. In our series, 6p25 and 11q13 gains were not associated with a higher risk of distant spread. Additional techniques to assess molecular genetic alterations, such as comparative genomic hybridization, next-generation sequencing, microRNA and mRNA analysis, and mass spectrometric imaging, will help improve the differential diagnosis and clinical management of AMTs in the near future.[42]

Conclusions

Our findings showed that age >20 years, MR ≥4, mitoses at the base of the lesion, LVI, and FISH evidence of 9p21 loss were all independent predictors of more aggressive tumor behavior. SN status did not prove to be a clear prognostic factor. Our retrospective analysis may contribute to establishing a practical framework for managing patients with AMTs in which clinical decisions are supported by identifying at-risk patients who may benefit from more frequent and longer-term follow-up.

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Analysis of Sentinel Node Biopsy and Clinicopathologic Features as Prognostic Factors in Patients With Atypical Melanocytic Tumors

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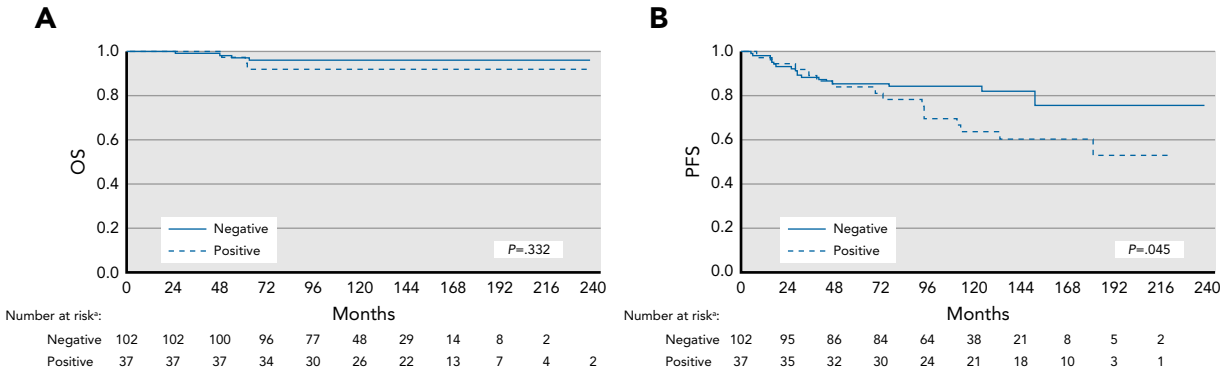
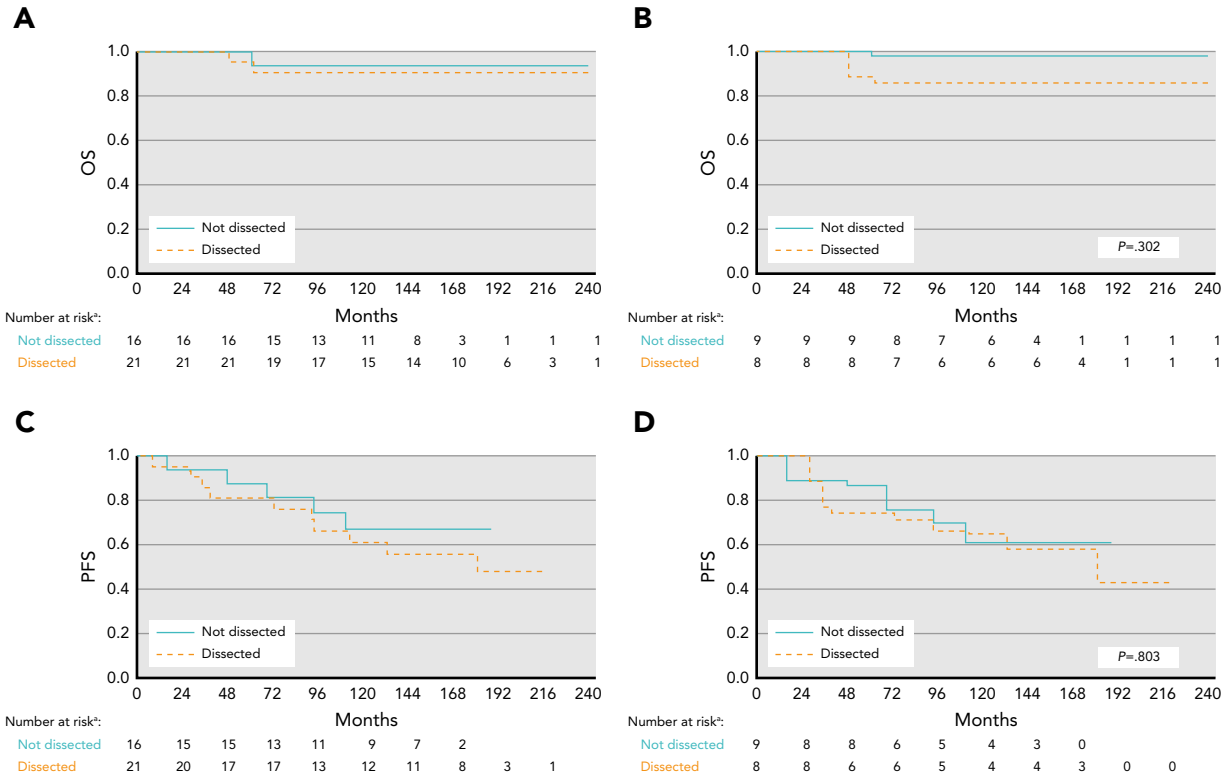


eFigure 1. Kaplan-Meier curves for (A) OS and (B) PFS according to sentinel node biopsy result (positive or negative).
[a]Number of patients at risk of an event.
Abbreviations: OS, overall survival; PFS, progression-free survival.



eFigure 2. Unweighted and weighted Kaplan-Meier curves for (A, B) OS, and (C, D) PFS according to complete dissection (performed or not performed).
[a]Weighted number of patients at risk of an event (rounded to the integer in the weighted analysis).
Abbreviations: OS, overall survival; PFS, progression-free survival.

eTable 1. Clinicopathologic Characteristics of Patients With AMT According to SN Status

	SN-Negative n (%)	SN-Positive n (%)	SMD
Total	102 (73.4)	37 (26.6)	
Age			0.137
≤10 y	6 (5.9)	2 (5.4)	
11–20 y	23 (22.5)	9 (24.3)	
>20 y	73 (71.6)	26 (70.3)	
Sex			0.425
Female	54 (52.9)	17 (45.9)	
Male	48 (47.1)	20 (54.1)	
Tumor site			0.328
Head and neck	34 (33.3)	10 (27.0)	
Upper limbs	19 (18.6)	7 (18.9)	
Trunk	12 (11.8)	4 (10.8)	
Lower limbs	37 (36.3)	16 (43.2)	
Histologic subtype			0.190
Spitzoid	24 (23.5)	10 (27.0)	
Nonspitzoid[a]	78 (76.5)	27 (73.0)	
Tumor thickness, mm			0.471
Median (IQRE)	2.36 (2.25–2.51)	2.34 (2.15–2.40)	
Ulceration			0.413
Absent	95 (93.1)	36 (97.3)	
Present	7 (6.9)	1 (2.7)	
Mitoses per mm^2			1.946
Median (IQRE)	2 (1–2)	5 (4–6)	
Mitosis at the base of the lesion			2.062
Absent	87 (85.3)	5 (13.5)	
Present	15 (14.7)	32 (86.5)	
Lymphovascular invasion			1.733
Absent	91 (89.2)	9 (24.3)	
Present	11 (10.8)	28 (75.7)	
Tumor-infiltrating lymphocytes			0.017
Absent	33 (32.3)	12 (32.4)	
Brisk	37 (36.3)	13 (35.1)	
Non brisk	32 (31.4)	12 (32.4)	
FISH test 6p25			0.002
Negative	88 (86.3)	32 (86.5)	
Positive	14 (13.7)	5 (13.5)	
FISH test 6q23/Cep 6			0.023
Negative	99 (97.1)	36 (97.3)	
Positive	3 (2.9)	1 (2.7)	
FISH test 6p25/Cep 6			
Negative	100 (98.0)	36 (97.3)	0.046
Positive	2 (2.0)	1 (2.7)	
FISH test 11q13			0.157
Negative	90 (88.2)	32 (86.5)	
Positive	12 (11.8)	5 (13.5)	
FISH test 9p21			1.587
Negative	72 (70.6)	20 (54.1)	
Positive	30 (29.4)	17 (45.9)	
FISH test 8q24			0.113
Negative	101 (99.0)	36 (97.3)	
Positive	1 (1.0)	1 (2.7)	

[a]Nevoid, deep penetrating nevus, or atypical blue nevus.
Abbreviations: AMT, atypical melanocytic tumor; FISH, fluorescence in situ hybridization; IQRE, interquartile range extremes; SMD, standardized mean difference; SN, sentinel node.

eTable 2. Clinicopathologic Characteristics of Patients With Positive SN According to CLND, Before and After Propensity Score Weighting

	Unweighted Statistics			Weighted Statistics		
	No CLND n (%)	CLND n (%)	SMD	No CLND n (%)	CLND n (%)	SMD
Total	16 (43.2)	21 (56.8)		9.0 (50.8)	8.7 (49.2)	
Age			1.413			1.637
≤10 y	1 (6.3)	1 (4.8)		1.7 (19.0)	0 (0.3)	
11–20 y	7 (43.7)	2 (9.5)		2.2 (24.6)	0.6 (6.8)	
>20 y	8 (50.0)	18 (85.7)		5.1 (56.5)	8.1 (92.9)	
Sex			0.048			0.057
Female	7 (43.7)	10 (47.6)		4.3 (47.6)	4.4 (50.5)	
Male	9 (56.3)	11 (52.4)		4.7 (52.4)	4.3 (49.5)	
Tumor site			0.966			0.874
Head and neck	5 (31.2)	5 (23.8)		1.1 (12.1)	1.2 (13.9)	
Upper limbs	3 (18.8)	4 (19.0)		0.7 (7.6)	2.7 (32)	
Trunk	0 (0)	4 (19.0)		3 (32.7)	1.8 (20.2)	
Lower limbs	8 (50.0)	8 (38.1)		4.3 (47.6)	3 (34)	
Histologic subtype			0.872			0.177
Spitzoid	2 (12.5)	8 (38.1)		1.3 (14.6)	1.5 (17.4)	
Nonspitzoid[a]	14 (87.5)	13 (61.9)		7.7 (85.4)	7.2 (82.6)	
Tumor thickness, mm			0.047			0.035
Median (IQRE)	2.39 (2.20–2.40)	2.3 (2.12–2.36)		2.31 (2.08–2.40)	2.35 (2.17–2.38)	
Ulceration			<0.001			<0.001
Absent	16 (100)	20 (95.2)		9 (100)	8.2 (96.8)	
Present	0 (0)	1 (4.8)		0 (0)	0.5 (3.2)	
Mitoses per mm^2			1.036			0.009
Median (IQRE)	6 (5–7)	5 (4–5)		5 (4.36–6.00)	5 (4.24–6.00)	
Mitosis at the base of the lesion			0.791			0.107
Absent	0 (0)	5 (23.8)		0 (0)	0 (0.6)	
Present	16 (100)	16 (76.2)		9 (100)	8.7 (99.4)	
Lymphovascular invasion			0.512			0.050
Absent	2 (12.5)	7 (33.3)		1.3 (14.8)	1.1 (13.1)	
Present	14 (87.5)	14 (66.7)		7.7 (85.2)	7.6 (86.9)	
Tumor-infiltrating lymphocytes			0.675			0.739
Absent	5 (31.2)	7 (33.3)		2.4 (26.4)	4.1 (46.6)	
Brisk	4 (25.0)	9 (42.9)		5.2 (58.2)	3.8 (44.7)	
Non brisk	7 (43.8)	5 (23.8)		1.4 (15.4)	0.8 (8.7)	
FISH test 6p25			0.183			0.410
Negative	14 (87.5)	18 (85.7)		5 (55.4)	5.3 (60.8)	
Positive	2 (12.5)	3 (14.3)		4 (44.6)	3.4 (39.2)	
FISH test 6q23/Cep 6			<0.001			<0.001
Negative	16 (100)	20 (95.2)		9 (100)	8.2 (96.8)	
Positive	0 (0)	1 (4.8)		0 (0)	0.5 (3.2)	
FISH test 6p25/Cep 6			<0.001			<0.001
Negative	16 (100)	20 (95.2)		9 (100)	8.2 (96.8)	
Positive	0 (0)	1 (4.8)		0 (0)	0.5 (3.2)	

(continued on next page)

eTable 2. Clinicopathologic Characteristics of Patients With Positive SN According to CLND, Before and After Propensity Score Weighting (cont.)

	Unweighted Statistics			Weighted Statistics		
	No CLND n (%)	CLND n (%)	SMD	No CLND n (%)	CLND n (%)	SMD
FISH test 11q13			0.183			0.410
Negative	14 (87.5)	18 (85.7)		5 (55.4)	5.3 (60.8)	
Positive	2 (12.5)	3 (14.3)		4 (44.6)	3.4 (39.2)	
FISH test 9p21			1.091			0.307
Negative	8 (50.0)	12 (57.1)		5.3 (58.4)	5.5 (62.4)	
Positive	8 (50.0)	9 (42.9)		3.7 (41.6)	3.2 (37.6)	
FISH test 8q24			<0.001			<0.001
Negative	16 (100)	20 (95.2)		9 (100)	8.2 (96.8)	
Positive	0 (0)	1 (4.8)		0 (0)	0.5 (3.2)	

[a]Nevoid, deep penetrating nevus, or atypical blue nevus.
Abbreviations: CLND, completion lymph node dissection; FISH, fluorescence in sit hybridization; IQRE, interquartile range extremes; SMD, standardized mean difference; SN, sentinel node.

eAppendix 1. Statistical Methods

Survival Outcome Definitions

Overall survival (OS) was defined as the time from diagnosis to death from any cause; time was censored at the latest follow-up for patients still alive. Progression-free survival (PFS) was defined as the time between tumor diagnosis and the first event (regional nodal and/or in-transit metastases, distant metastases) or death, whichever occurred first; time was censored at the date of last follow-up for alive and event-free patients. Median follow-up was calculated with the reverse Kaplan-Meier method using OS data.[1]

Inverse Probability Treatment Weighting and Balance Assessment

When a direct comparison was feasible (ie, when the compared groups did not consist of selected patients as in the SNB-positive vs SNB-negative comparison), the curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Inverse probability treatment weighting (IPTW)[2] based on the propensity score (PS) method was used to balance the comparison between groups. The covariates included in the logistic model for PS estimation were tumor thickness, mitotic rate/mm^2, ulceration, lymphovascular invasion (LVI), mitosis at the base of the lesion, spitzoid histology, and 9p21 loss and 11q13 gain as determined by fluorescence in situ hybridization (FISH). The standardized mean difference (SMD)[3] was used to evaluate the unbalanced and balanced clinicopathologic characteristics of patients with atypical melanocytic tumors (AMT). SMDs $\geq$0.3 were considered indicative of a relevant between-group imbalance.

Association Analyses

We studied the binary association between all investigated covariates by evaluating the Spearman correlation coefficients, and the association between PFS and all investigated covariates by means of univariable Cox models. Subgroup analyses were performed in patients who underwent sentinel node biopsy. We applied Firth's penalized method to obtain hazard ratio estimates in sparse samples.[4] Mitotic rate, age, and tumor thickness were modeled as continuous variables using a 3-knot restricted cubic spline to obtain a flexible fit.[5] The small number of events precluded statistical modeling on OS.

Variable Selection Method

The elastic net penalization method is a combination of the ridge and lasso penalties, sharing with the latter the ability to set some coefficient estimates to zero but distributing the weight to more features, so that the elastic net tends to select more features.

We considered a statistical test significant when the corresponding P value was $<$.05. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc) and R software 2018 (R Foundation for Statistical Computing).

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