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Risk factors related to late metastases in 1,372 melanoma patients disease free more than 10 years

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In many centers, Stage I–II melanoma patients are considered “cured” after 10 years of disease-free survival and follow-up visits are interrupted. However, melanoma may relapse also later. We retrospectively analyzed a cohort of 1,372 Stage I–II melanoma patients who were disease-free 10 years after diagnosis. The aim of this study was to characterize patients who experienced a late recurrence and to compare them to those who remained disease-free to identify possible predictive factors. Multivariate Cox proportional-hazards regression analyses were carried out to evaluate the influence of different factors on the risk of recurrence. Seventy-seven patients out of 1,372 (5.6%) relapsed, 52 in regional sites and 25 in distant ones. The majority of patients (31 out of 52) experienced late recurrence in regional lymph nodes. Brain and lung were the most common site of single distant recurrence (24% each). Patients with multiple distant metastases showed a brain and lung involvement in, respectively, 40 and 48% of cases. A Cox proportional-hazards regression model analysis showed the independent role of age under 40 years, Breslow thickness >2 mm, and Clark Level IV/V in increasing the risk of Late Recurrence. These patients should be followed-up for longer than 10 years. The pattern of recurrence suggests that melanoma cells can be dormant preferentially in lymph nodes, brain and lung. A particular attention should be reserved to these anatomic sites during the follow-up after 10 years of disease-free.

Guidelines to monitor melanoma patients beyond 10–15 years from diagnosis are unstructured. Patients are frequently considered “cured” after such a protracted disease-free time period.[1,2] However, 0.41–6.4% of melanoma patients recur 10 years after the diagnosis.[3–9] These events are denoted as “late recurrences” and they have recently been explained by tumor dormancy.[10] This phenomenon is well described in several malignancies, including melanoma, and it is defined as “a period in cancer progression in which residual disease is present but remains asymptomatic.”[10] A large population of patients and an extensive longitudinal follow-up are required to estimate correctly late recurrences. Small sample size, inadequate follow-up or referral bias can easily hamper the analysis of risk factors. The understanding of this phenomenon could have important implications such as a better definition of follow-up duration. In this study, we retrospectively analyzed Stage I and II melanoma patients who were disease-free 10 years after diagnosis and who continued follow-up visits in our care unit within an academic teaching hospital. To identify possible predictive factors of late recurrence we compared patients who relapse after more than 10 years with those who remained disease-free. The aim of the study was to define patients’ characteristics that should give an indication for a follow-up longer than 10 years.

Materials and Methods

The clinical records of 4,729 melanoma patients who were diagnosed and prospectively followed up at the Dermatologic Clinic of Citt_a della Salute e della Scienza University Hospital of Turin (Italy) from 1975 to 2003 have been reviewed. Patients with noncutaneous or unknown primary melanoma, Stage III and IV AJCC at diagnosis and with a follow-up less than 1 year were excluded, thus leading to a total of 3,580 patients with I to II AJCC stage.[11] Among them, 1,413 patients were disease-free 10 years after diagnosis. In this group, 1,372 showed complete histopathological data and were considered eligible for this study.

Key words: late metastases, melanoma, dormancy, pattern of recurrence Disclosures: The authors declare no conflicts of interest. *S.O.-A. and S.R. contributed equally to this work. Grant sponsor: Lanzavecchia-Lastretti Foundation for “Progetto Melanoma” DOI: 10.1002/ijc.29281 History: Received 17 July 2014; Accepted 1 Oct 2014; Online 21 Oct 2014 Correspondence to: Dr. Simona Osella Abate, Department of Medical Sciences, Section of Dermatology, University of Turin, Turin, Italy, E-mail: simona.osellaabate@unito.it What’s new? After a period of apparent cure lasting 10 or more years, a small percentage of melanoma patients experience late recurrence, in which dormant tumor cells reemerge to cause disease. The factors that precipitate recurrence are unclear, however. In this study, risk of late recurrence in melanoma was found to be elevated among stage I-II patients who were under age 40 at diagnosis and had a Breslow thickness of more than 2 mm or a Clark level IV/V. The regional lymph nodes, brain, and lungs were primary sites of recurrence, suggesting that they are preferential sites of tumor cell dormancy.

Clinical and imaging follow-up was performed according to guidelines previously described.[12–15] Briefly, physical examinations were performed every 2 to 6 months depending on the Breslow thickness until 10 years after melanoma excision, and once a year after 10 years. Radiological procedures were performed at diagnosis and every 6 to 12 months during followup for 10 years, and if there was a suspect of metastasis or any symptoms afterwards. Sentinel lymph node biopsy (SLNB) was introduced in our Institution in January 1999. SLNB inclusion criteria were previously described. SLN positive patients as stage III melanoma were excluded from the cohort.[16] Patients entered our cohort 10 years after their melanoma diagnosis if they had remained disease-free. We analyzed the incidence of relapses and classified patients in late recurrent (LR) or disease free (DF). Patients were observed until their last physical examination, at which were censored. The event of interest was the first relapse in any site, regional (skin or lymph nodes) or distant. Site of distant metastasis was analyzed to assess if it was associated with late recurrence. Patients’ characteristics were compared using Student t-test or Pearson chi-square test. A multivariable Cox proportionalhazards regression model was used to estimate the association between patient characteristics and late recurrence. The proportionality assumption was assessed by examination of Schoenfeld residuals, giving no reason for violation. Variables selection for the regression model was evaluated considering literature reports and the Akaike information criterion. The variables considered were gender (M/F), ulceration (yes/no), site of primary cancer,

histological type (Nodular Melanoma vs. other), age at diagnosis, Breslow thickness and Clark level. The last three were modeled as continuous variable and dichotomized for the final model (age_40 years old; Breslow thickness>2mm; Clark Level IV/V vs. II/III). Statistical analyses were performed with Stata 12 (StataCorp LP, TX)

Results

Clinical characteristics

We identified 1,372 melanoma patients who were alive without clinical and/or radiological evidence of disease 10 years after diagnosis (Table 1). Seventy-seven (5.6%) progressed after this time point, and 39 subsequently died of melanoma. SLNB was performed in 4 out of 77 LR patients and in 61 out of the remaining 1,295 DF patients. Median follow-up was 5.4 years (range 0.1–30.1) from the entrance in the study. Breslow thickness was significantly higher in the LR than in the DF group (p<0.001); in particular LR patients showed a higher percentage of lesions thicker than 2 mm.

Site of relapse and survival analyses

The first recurrence was regional in 52 and distant in 25 patients (Table 2). Among regional recurrences, 19 patients developed in transit metastases, 31 patients lymph nodes metastases (only one out of the four patients previously resulted negative at SLNB), and two patients in both nodal and in transit metastases. Distant recurrence was characterized by visceral involvement in the majority of cases (21 out of 25); only three patients developed cutaneous metastases and one patient lymph node metastases. Among patients with distant visceral recurrences 13 out of 21 showed initially a single visceral involvement. The two most common single sites were brain (six cases) and lung (six cases). Among patients with multiple visceral involvements the most frequent scenario was the simultaneous development of brain and lung metastases (four out of eight cases). The percentage of brain metastases as single site of relapse (6/25; 24%) was significantly higher in LR patients compared to patients who developed brain metastasis in the first 10 years from diagnosis (18/227; 7%; data not shown; p50.025). The same trend was observed for lung progression, but the statistical significance was not reached (6/25; 24% in LR patients vs. 24/227; 10.6% in patients who progressed in the first 10 years from diagnosis; data not shown). Multivariable analyses supported the independent role of age under 40 years (HR51.65, 95% CI: 1.02–2.65), Breslow thickness>2 mm (HR52.12, 95% CI: 1.15–3.92), and Clark Level IV/V (HR52.09, 95% CI: 1.08–4.02) in increasing the risk of LR. There was no significant evidence that gender (HR51.15, 95% CI: 0.72–1.84), nodular histotype (HR51.14, 95% CI: 0.58–2.24) and ulceration had any effect (HR50.93, 95% CI: 0.40–2.15; Table 3). The model was validated internally. Discrimination was quantified through the concordance index (68%), calculated by bootstrapping 200 samples. The calibration plot shown in Figure 1 was obtained again using 200 bootstrap samples and showed good calibration of the model 10 years after the start of the follow-up.

Discussion

The risk of melanoma recurrence is highest in the first 2 to 4 years from diagnosis.[11] In many Countries patients who are disease-free 10 years after diagnosis are considered “cured” and discharged from follow-up. However, patients can recur also after such a prolonged time period[3–9] and they would profit from an early detection of progression.[11,17] Up to date, the characteristics of the patients who should be monitored beyond 10 years are not defined. Late recurrences in melanoma have been investigated in different studies, but small sample sizes, inadequate follow-up and referral bias have often affected the assessment of risk factors.[3–9] In this study, we analyzed a cohort of Stage I and II melanoma patients who were disease-free 10 years after diagnosis. All the patients were followed-up beyond this time point and they were later divided in two groups: patients who developed a recurrence (LR) and patients who were still disease-free. Surveillance methods and treatments changed over time and this could represent a possible limitation of our study, introducing heterogeneity in our population. However, the extensive longitudinal follow-up was required to be able to compare LR with a control group with DF survival longer than 10 years. Previous studies found that LR are characterized by thinner lesions and absence of ulceration, when they are compared to patients who experienced an early relapse.[8,9] However, the correlation of thicker lesions and ulceration with early progression is not unexpected since these are the major negative prognostic factors in primary melanoma. We were more interested in comparing LR to patients with the same stage of disease at diagnosis who did not progress over time, to understand which should be the patients not to discharge from the follow-up. Hansel et al. tried to answer to the same question analyzing 1,881 Stage I and II melanoma patients followed-up for more than 10 years.[7] Their study did not identify any significant risk factor for late metastases, probably because of the inadequate statistical power (19/1,881 LR patients). In our case series 77 out of 1,371 patients developed a late recurrence, and this allowed us to identify younger age (_40 years old), Breslow thickness> than 2 mm, and Clark Level IV/V as independent negative prognostic indicators for late recurrence. Our results suggest that both tumour and host characteristics could play a role in the late metastases occurrence. Older patients might be less likely to develop late recurrences because of competing mortality risk.[9] Crowley et al.[3] previously suggested that some aggressive melanomas after a first dissemination could reprogram or be reprogrammed into temporary quiescence forms. Our finding of a correlation between higher Clark levels and Breslow thickness seems to support this complex and probably multifactorial process for some aggressive melanomas. Recently late recurrence has been explained by neoplastic cell dormancy: metastatic cells could implant in different organs and remain dormant for years thanks to intrinsic controlling mechanism or systemic host control. This phenomenon could explain the appearance of liver metastases many years after the excision of ocular melanomas[3] and the development of melanoma metastases after organ transplantation when the patients are treated with immunosuppressive drugs.[18] Moreover, circulating tumor cells could be identified in peripheral blood of melanoma patients by PCR based amplification of melanocyte specific tyrosinase genes.[19,20] The pattern of recurrence observed in our patients provides further support to the dormancy theory. The majority of our patients developed the first recurrence in regional lymph nodes (31 out of 55 regional site LR patients) suggesting that this is a site where occult

tumor cells can persist dormant. Shen et al. already showed that elective lymph node dissection (ELND) performed together with the wide local excision of the primary tumor decreases the risk of late nodal recurrence. They further suggested that ELND should be reserved for patients with a positive sentinel node biopsy (SLNB), as this procedure should be able to catch occult tumor cells implanted in the nodes.[6] In our Department SLNB was introduced in 1998,[16] so only few LR patients were submitted to this procedure and could benefit of a lymph nodes clearance. Based on this evidence we could expect a future decrease of late regional lymph nodes metastases due to the impact of SLNB. Also the pattern of distant metastases found in our study supports the dormancy theory: 25% of late metastases appeared in the brain, an organ which melanoma has a high tropism for. Brain involvement is described in up to 45–50% of advanced melanoma patients. Metastases in the brain were detected in 75% of postmortem examinations in Stage IV melanoma patients.[21] They represent a common finding also in patients without neurological symptoms.[22,23] Comparing our results with historical data from our Clinic[24] we observed that LR have a higher percentage of first single progression in the brain compared to patients who relapsed in the first 10 years of follow-up (6/25; 24% vs. 18/227; 7%, p50.025). This percentage further increased (10/25, 40%) when we considered the simultaneous presence of brain and other sites metastases in the LR group. This finding supports the idea that a small agglomerate of cells may survive for many years in the brain, untouched by the immune system. It is also possible that cancer cells will metastasize to organs from a similar embryological origin and behavior. Similarly, the other most represented metastatic distant site was the lung even if statistical significance was not reached comparing our results with historical data from our Clinic. Recently, Eyles et al. showed model that tumor latency in the lung results from reduced proliferation of melanoma tumor cells in a mouse melanoma.[25] Although the formal construction of a predictive model was beyond the aim of this study, we used data of a clinical cohort from a single hospital to assess the role of important predictors of late recurrences that should be considered for inclusion in future models to be validated on external data. In summary, our findings suggest that Stage I–II patients younger than 40 years at diagnosis, with a Breslow thickness greater than 2 mm or a Clark Level IV/V should be not discharged from follow-up also after 10 years of disease-free for the risk of disease recurrence, even taking in consideration the limitation of a monocentric case series. The pattern of recurrence seems to support the recent dormancy theory: it suggests that during patients' follow-up a particular attention should be reserved to possible brain and lung metastases in addition to more expected lymph node regional site. It could open an interesting field in melanoma biology that should be investigated and validated in larger case series.

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Table 1. Clinical characteristics of patients included in the study ($n = 1,372$)

		LR ($n = 77$)	DF ($n = 1295$)	p
Age (median and range) years		48 (23–79)	50 (12–84)	NS
Age <40 years		49/77	979/1,295	0.019
Gender	Male	31	515	NS
	Female	46	780	
Breslow	Mean ± SD	2.26 ± 1.78	1.34 ± 1.33	<0.001
Breslow AJCC	≤1	22	760	<0.001
	1<Br≤2	23	300	
	2<Br≤4	26	184	
	>4	6	51	
Clark	2	9	412	<0.001
	3	47	751	
	4	20	123	
	5	1	9	
Ulceration	Yes	7	60	0.078
	No	70	1,235	
Primary sites	Head/ Neck	6	139	NS
	Trunk	40	673	
	Upper extremities	0	14	
	Lower extremities	31	469	
Histotype[1]	SSM	53	1,037	<0.001
	NM	13	92	
	LMM	1	92	
	ALM	4	43	
	Other	6	31	

SSM = superficial spreading melanoma, NM = nodular melanoma, LMM = lentigo maligna melanoma, ALM = acral lentiginous melanoma; NS = not significant; SD = standard deviation

Table 2. Pattern of late recurrences

Site of metastases			No. of patients	
Regional metastases		In transit	19	
Lymph nodes			31	
Skin + lymph nodes			2	
Distant metastases	Soft tissue	skin	3	
		Lymph nodes	1	
	Visceral	One site	13	Six brain
				Six lung
				One liver
		Multiple sites	8	Two lung, brain
				Two liver, spleen, bone
				One lung, brain, kidney
				One lung, brain, liver
				One lung, bone
				One lung, liver, bone, lymph node, skin

Table 3. Hazard ratios (HR) of late recurrence ($n = 1,372$)

	HR	95% CI	$p>\|z\|$
Gender (male *vs.* female)	1.15	0.72 1.84	0.561
Age ≤40 years old *vs.* >40	1.65	1.02 2.65	0.040
Breslow thickness > 2 mm *vs.* ≤ 2 mm	2.12	1.15 3.92	0.016
Clark Level IV/V *vs.* II/III	2.09	1.08 4.02	0.028
Ulceration (present *vs.* absent)	0.93	0.40 2.15	0.870
Nodular melanoma (*yes vs.* no)	1.14	0.58 2.24	0.707

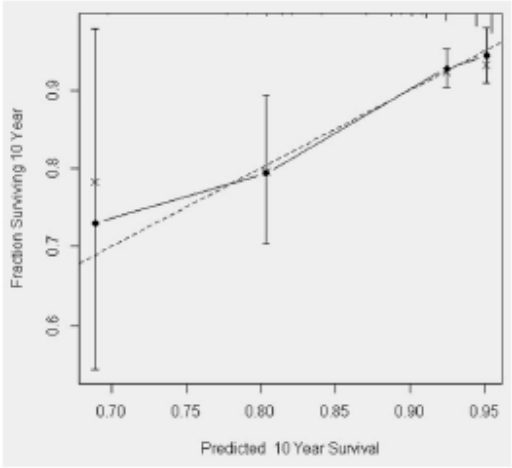

Figure 1. Calibration plot based on 200 bootstrap samples showing observed and predicted 10 years disease-free survival. Full circles: observed; solid line: ideal; X: optimism corrected.