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Longitudinal study of prognostic factors for localized cutaneous melanoma in patients who have been disease-free for five years

Background: Most relapses in melanoma patients occur during the first five years after diagnosis. Identifying characteristics associated with recurrence after this period could help delineate guidelines, specifically for follow-up protocols. *Objectives:* The aim of this study was to identify the prognostic factors for relapse and death caused by melanoma in patients who have been disease-free for five years. *Materials & Methods:* We designed a longitudinal retrospective cohort to study Stage I/II cutaneous melanoma patients who have been free of disease for more than five years (late relapse cohort). Prognostic factors for disease-free and melanoma-specific survival were evaluated using the Kaplan-Meier method and Cox regression models. *Results:* A series of 746 patients who had Stage I-II cutaneous melanoma and were free of disease for five years was selected. After a median follow-up of 64 months (124 months since melanoma diagnosis), 51 (6.8%) patients relapsed and 18 (2.4%) died from melanoma. Acral location and presence of ulceration, as well as intermediate growth rate (0.11-0.50 mm/month), were significantly associated with relapse or death due to melanoma. The initial recurrence site was associated with distant metastasis in 48% of the cases. *Conclusion:* In this study, we have identified melanoma characteristics in patients who have been disease-free for five years that may allow us to establish groups at increased risk of relapse or death due to melanoma, which could be helpful for melanoma management.

Key words: melanoma, prognosis, follow-up, survival, growth rate

The incidence of cutaneous melanoma in Europe varies from 8-9 per 100,000 persons-year in Mediterranean countries to 12-25 in northern countries [1, 2].

The main prognostic factors for survival in patients with localized cutaneous melanoma are Breslow thickness and the presence of histological ulceration [3]. Other clinical-pathologic factors, such as age, gender, mitotic index, tumour localization, presence of histological tumour regression and tumour lymphocytic infiltrate, have also been shown to be of prognostic value [4]. Additionally, the prognosis has been related to somatic gene alterations of the tumour, such as *BRAF*, *NRAS* or *TERT* promoter mutations [5-8].

Furthermore, tumours do not grow uniformly in all patients. Fast-growing tumours behave worse than slow-growing tumours. The growth rate (GR) can be estimated based on information provided by the patients or their relatives and the tumour thickness. Despite being based on potentially biased information, GR is an independent predictive factor for sentinel lymph node involvement and a prognostic factor for disease-free and melanoma-specific survival [9-12]. It has been suggested that the timing of appearance of metastatic dissemination depends on melanoma GR, such that the slower a tumour grows, the later the metastasis develops [13].

However, there is significant variability in the follow-up guidelines for melanoma patients concerning imaging tests that are recommended and follow-up intervals [14-17]. Even though the frequency and duration of follow-up examinations depends on the stage, imaging tests are consistently not recommended after the fifth year from the diagnosis of melanoma [14-17]. This is based on the fact that nearly 90% of all metastasis occur during the first five years. Although 7-13% of melanoma patients die due to melanoma between the 5th and 10th year after diagnosis at a localized stage, there is scarce literature on which prognostic factors are associated with a poor prognosis during this period [18, 19]. The development of late metastasis is explained by the concept of tumour latency, in which individual cells or clusters of microscopic cells may remain viable and maintain their malignancy potential, though clinically undetectable over a long period of time [20]. This is why, even after a period of five years free of disease, a patient cannot be considered cured, thus demonstrating the importance of continued follow-up, particularly in groups with increased risk [18].

Since current guidelines do not recommend further complementary testing beyond the fifth year of follow-up and some patients relapse after five years of disease freedom, it

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seems reasonable to attempt to identify prognostic factors that may allow us to establish which patients may benefit from a longer follow-up period.
The aim of this study was to identify prognostic factors for relapse and death for Stage I-II cutaneous melanoma patients who have survived for least five years free of disease, with special emphasis on the GR of melanoma.

Materials and methods

A longitudinal retrospective cohort study was designed based on the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [21]. This study was approved by the Ethical Clinical Research Committee of the Instituto Valenciano de Oncología, Valencia, Spain.
The source of data was the Instituto Valenciano de Oncología (IVO) melanoma database, where all incident cases diagnosed after the year 2000 and follow-up cases treated before 2000 in our hospital are routinely included. This database includes prospectively included clinical, epidemiologic and phenotype characteristics of patients with melanoma. The vital status of the patients is yearly updated through consultation of the National Mortality Registry of Spain.
We selected all patients with localized cutaneous melanoma treated at the IVO's Dermatology Department from January 1, 1995 to December 31, 2010 who did not present with a relapse during the first five years after treatment (late relapse cohort). We excluded patients with a diagnosis of unknown primary melanoma, *in situ* melanomas, multiple melanomas, and extracutaneous melanoma.

Independent variables

The following characteristics were selected as independent variables:
Clinical characteristics: age at diagnosis, gender and anatomical site (head/neck, extremities, trunk, and hand/foot).
Histological characteristics: Breslow thickness, histological type (grouped as superficial spreading melanoma [SSM], nodular melanoma [NM] and others), tumour-infiltrating lymphocytes (absence, non-brisk, brisk), ulceration, regression, and mitotic index (categorized as <2 mitoses/mm^2 vs. ≥ 2 mitosis/mm^2 because 1 mitosis/mm^2 has been shown to be very similar to 0 mitosis/mm^2 as a predictive and prognostic factor) [22].
Tumoural mutational status: *BRAF*/*NRAS* (wild-type [WT] for both genes or mutation in any of the two genes). The *BRAF*/*NRAS* mutational status was determined by direct sequencing according to previously methods described [23]. *BRAF* mutational status was also determined by COBAS, according to the manufacturer's protocol [24]. We also recorded the type of recurrence (locoregional [satellite/in transit/lymph node] or distant metastasis).
GR of melanoma: according to the definition presented by Grob *et al*., the GR is the measure of the volume increase of a melanoma per unit of time [25]. Because no accepted method exists to measure tumour volume, the Breslow thickness per unit of time is used as a surrogate value. GR is calculated as the ratio between Breslow thickness and time when the lesion is first noticed or when the patient or relatives perceived changes in a pre-existing lesion. We are following the Liu *et al*. method for categorization of this value [9]. Thus, we categorized tumours in three groups: slow growing melanomas [SGM]: ≤ 0.10 mm/month; intermediate growing melanomas [IGM] 0.11-0.50 mm/month; and fast-growing melanomas [FGM]: >0.50 mm/month).

Study outcomes

We analysed disease-free survival (DFS) and melanoma-specific survival (MSS). Because the main outcome variable was survival after five years of disease freedom following definitive melanoma treatment, this period was calculated from the date of melanoma diagnosis to five years later. In cases of relapse or death, we calculated the period up to the date of relapse or death due to melanoma and defined these as DFS and MSS, respectively. Deaths unrelated to melanoma were censored at the time of death. For censored cases (those without relapse or death), the period was calculated up to the date of the last follow-up visit. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. The data were presented as mean and SD for normally distributed continuous variables and as median and interquartile range (IQR) for non-normally distributed continuous variables. Categorical variables were expressed as absolute numbers and percentages. For between-group comparisons, *t*-test and ANOVA were used to compare continuous variables, while the chi-square test and Fisher's exact test were used to compare qualitative variables.
The Kaplan-Meier method was used to estimate survival curves and the log rank test to compare curves between groups. Univariable Cox proportional hazards regression models were used to determine the degree of association between each variable with survival.
GR and all variables associated with survival in the univariable analysis ($p < 0.1$) were included in the multivariable Cox proportional hazards regression model to adjust for confounders. Multivariable analyses were performed using a forward stepwise Cox proportional hazards method. Two models were carried out for each outcome (DFS and MSS). For the first, GR was excluded and Breslow thickness was included as a categorical variable with AJCC cut-off points. The analyses were repeated including GR in which Breslow thickness was used as a continuous variable after log transformation.
For multivariable analysis, we calculated the percentage of missing values for each variable. Based on the assumption that these were missing at random, we created 10 sets of complete data using the multiple imputation technique. To generate the missing values, we used a normal multivariable model featuring all the variables to be subsequently analysed, together with any variables that could help to explain the missing data. In the next step, each of these 10 datasets was analysed using Cox proportional hazards regression to fit the model of interest to the outcome variables (DFS, MSS). In a third step, we combined the results of each set of complete data into a single set of estimates according to Rubin [26].
In all statistical tests, the significance level was established at a p value <0.05. Statistical analysis was performed using the Statistical Package for Social Sciences, version 20.0 (SPSS, IMB, Illinois, USA).

Results

Out of 2,310 cases included in the database, 746 patients met the selection criteria; 315 males (42.2%) and 431 females (57.8%), with a median age of 51 years old (interquartile range: 38-62). *Table 1* summarizes the characteristics of the study population. The characteristics of this population by GR categories are shown in *supplementary material*.

Mean age at diagnosis of patients with FGM (54.7 years) was greater than that with IGM (46.6 years) and SGM (50.7 years) ($p = 0.001$) (*supplementary material*). Similarly, median thickness of FGM was greater (2.5 mm) than that of IGM (1.27 mm) and SGM (0.6 mm). FGM was related to the presence of ulceration, TILs, high mitotic rate, nodular melanomas and anatomical site (head/neck and hand/foot). There was no association with gender, regression or *BRAF*/*NRAS* status (*supplementary material*).

After a median follow-up of 64 months from the beginning of the study (124 months after the melanoma diagnosis), 51 (6.8%) patients relapsed and 18 (2.4%) died due to melanoma.

Univariable analyses showed that increased age, >1 mit/mm^2, greater Breslow thickness, head/neck and acral primary site, histological subtypes other than SSM, *BRAF*/*NRAS* mutation, and IGR were associated with shorter DFS, whereas increased age, greater Breslow thickness, presence of ulceration, histological subtypes other than SSM and NM, and IGR were variables determining shorter MMS (*table 2*). In particular, IGR was associated with a worse five-year DFS (92.3% vs. 97.8% [SGM] vs. 95.2% [FGM]; $p = 0.001$) and MSS (97.8% vs. 99.5% [SGM] vs. 100% [FGM]; $p = 0.01$) (*figure 1*).

Multivariable models, excluding GR, showed that acral site (HR: 5.0; 95% CI: 2.0-12.7; $p = 0.001$) was independently associated with DFS, whereas ulceration (HR: 3.4; 95% CI: 1.2-9.9; $p = 0.027$) and acral site (HR: 4.2; 95% CI: 1.2-14.3; $p = 0.023$) were significantly associated with worse MSS (*table 3*).

The multivariable models including GR showed that, after adjusting for other confounders, the IGM retained its prognostic value for DFS (hazard ratio [HR]: 2.28; 95% CI: 1.05-4.86; $p = 0.037$) and was marginally significant for MSS (HR: 3.3; 95% CI: 0.96-12.5; $p = 0.06$) (*table 3*). Additional independent predictors were age and tumour thickness for DFS and age and ulceration for MSS.

Finally, the type of initial recurrence during follow-up was available in only 21 cases (41%). Ten patients had systemic spreading, six of whom had simultaneous locoregional involvement, while the remaining 11 showed only locoregional recurrence (*figure 2*). Only one locoregional and one systemic recurrence were recorded for FGM.

Table 1. Clinical and pathological characteristics of 746 localized cutaneous melanoma patients who were free of disease for more than five years (late relapse cohort).

Variable	N	%
Age (m.v.= 0)		
≤55 years	369	49,5
>55 years	377	50,5
Gender (m.v.= 0)		
Male	315	42,2
Female	431	57,8
AJCC stage (m.v.= 0)		
IA	292	39,1
IB	296	39,7
IIA	92	12,3
IIB	49	6,6
IIC	17	2,3
Breslow thickness (m.v. =0)		
≤1 mm	456	61.1
>1-2 mm	179	24.0
>2-4 mm	79	10.6
>4 mm	32	4.3
Tumour-infiltrating lymphocytes (m.v.= 325)		
No	278	37,3
"Non-brisk"	124	16,6
"Brisk"	19	2,5
Histological ulceration (m.v.= 23)		
No	633	84,9
Yes	90	12,1
Histological regression (m.v.= 118)		
No	550	73,7
Yes	78	10,5
Mitotic rate (m.v. = 304)		
0-1 mit/mm^2	306	41,0
>1 mit/mm^2	136	18,2
Primary site (m.v. = 0)		
Head/neck	103	13,8
Upper limb	109	14,6
Trunk	299	40,1
Lower limb	192	25,7
Acral	43	5,8
Histological type (m.v.= 0)		
LMM	34	4,6
SSM	559	74,9
NM	90	12,1
ALM	22	2,9
Others/not classified	41	5,5
Growth rate (m.v.= 258)		
≤0.10 mm/month	258	34,6
0.11-0.50 mm/month	169	22,7
>0.50 mm/month	61	8,2
BRAF/NRAS (m.v.= 499)		
WT	143	19,2
Mutation	104	13,9
Relapses (m.v.= 0)		
No	695	93,2
Yes	51	6,8
Death by melanoma (m.v.= 0)		
No	728	97,6
Yes	18	2,4

MM: melanoma; LMM: lentigo maligna melanoma; SSM: superficial spreading melanoma; MN: nodular melanoma; ALM: acro-lentiginous melanoma; WT: "Wild Type"; m.v.: missing values.

Discussion

In this study of 746 melanoma patients free of disease for at least five years, we show that the most important prognostic factors for survival after five years were age at melanoma diagnosis, Breslow thickness and GR for DFS, age, ulceration and possibly GR for MSS.

Table 2. Univariable analysis of prognostic factors for disease-free survival and melanoma-specific survival in 746 patients with localized cutaneous melanoma without recurrence for more than five years (late relapse cohort).

	Disease-free survival		**Melanoma-specific survival**	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Variable				
Age	1.03 (1.01-1.05)	0.001	1.04 (1.01-1.08)	0.007
Gender				
Male	Ref.		Ref.	
Female	0.62 (0.35-1.07)	0.08	0.59 (0.23-1.49)	0.26
Log Breslow (mm)	6.01 (2.99-12.7)	<0.001	4.69 (1.32-16.7)	0.017
Breslow thickness				
≤1 mm	Ref.		Ref.	
>1-2 mm	2.6 (1.3-5.2)	0.005	3.1 (1.1-9-3)	0.040
>2-4 mm	3.7 (1.7-7.9)	0.001	4.4 (1.4-14.5)	0.014
>4 mm	6.2 (2.5-15.8)	<0.001	N.C.	N.C
TILs				
Absence	1.5 (0.19-10.71)	0.65	0.45 (0.05-3.65)	0.46
Non-brisk	1.96 (0.25-15.2)	0.7	0.57 (0.05-5.5)	0.62
Brisk	Ref.		Ref.	
Ulceration				
Absence	Ref.		Ref.	
Presence	1.83 (0.92-3.97)	0.08	4.47 (1.62-12.61)	0.004
Regression				
Absence	Ref.			
Presence	0.62 (0.19-2.01)	0.42	0.84 (0.1-6.64)	0.87
Mitotic index (mitoses/mm^2)				
≤1	Ref.		Ref.	
>1	2.22 (1.11-4.45)	0.02	1.07 (0.48-2.4)	0.85
Primary site				
Head/Neck	Ref.		Ref.	
Extremities	0.32 (0.14-0.7)	0.004	0.38 (0.08-1.71)	0.2
Trunk	0.39 (0.18-0.83)	0.015	0.66 (0.17-2.57)	0.55
Hand/Foot	2 (0.86-4.33)	0.1	3.16 (0.7-14.1)	0.13
Histological subtypes				
SSM	Ref.		Ref.	
NM	4.02 (2.05-7.85)	<0.001	2.18 (0.58-8.24)	0.24
Others	4.82 (2.5-9.3)	<0.001	6.46 (2.33-17.83)	<0.001
BRAF/NRAS				
WT	Ref.		Ref.	
Mutation	2.1 (1.01-4.36)	0.04	0.69 (0.15-3.2)	0.17
Growth rate (mm/month)				
≤0.10	Ref.		Ref.	
0.11-0.50	4.8 (1.91-12.01)	0.001	9.91 (1.12-80.65)	0.03
>0.50	1.46 (0.29-7.24)	0.64	-	-

CI: Confidence interval. Ref.: Reference. TILs: Tumour infiltrating lymphocytes. SSM: Superficial spreading melanoma. NM: Nodular melanoma. WT: Wild type. N.C.: not calculable.

Information about the characteristics that can predict relapse or death from melanoma beyond the usual five-year period of recommended follow-up in all guidelines is useful as current diagnostic and therapeutic strategies for these patients may be modified accordingly. In the literature, there are several studies focusing on what has been called "late relapses". However, after a review of the literature, the approach to consider cases as "late relapses" was not uniform, and the definition of late relapse varies according to several studies. In some articles, late relapse is considered after 15 years, while in others it is considered after 10. Moreover, the methodology of studies has been

aimed at describing the characteristics that were present at late metastases or by comparing between late and early recurrences, and few studies have identified the prognostic factors [18, 27-29]. This has impeded studies to establish which prognostic factors might have an influence on whether a relapse is late or early.

To date, a survival study of patients with metastases from five years after diagnosis has been described in only two reports. First, Osella-Abate *et al*., contrary to our study, identified age under 40 years as a factor associated with increased risk of late recurrence [19]. They also identified a Breslow thickness greater than 2 mm and Clark level IV/V as characteristics associated with an increased risk of late relapse in patients with Stage I or II cutaneous melanoma. Second, Faries *et al*., also included Stage III and identified age under 50 years, a thinner Breslow thickness relative to early relapse, and a negative sentinel node biopsy as factors associated with an increased risk of late relapse [30].

In our study, almost half of patients showed initial recurrence following haematogenous spread. Most studies of late metastasis, but not all, observed that distant metastases (55-65.5%) were more frequent than locoregional metastases (34.5-40%) [31]. Locoregional disease as a late relapse seems to be more frequent when localized to the lower extremities and, to a lesser degree, the trunk [18]. Moreover, lymphatic dissemination is proposed to be more strongly associated with hematogenous dissemination than cell dormancy. This can explain why locoregional relapse occurs predominantly in early relapses, while haematogenous metastases can be much more variable [27, 30].

In addition, Faries *et al*. [30] found that patients with a positive sentinel node at diagnosis tended to have an earlier relapse, and the absence of locoregional relapse in patients with late recurrence suggests that tumours that spread through the lymph nodes are unlikely to become latent. This suggests that, unlike early relapse, late relapse occurs predominantly through the haematogenous route.

In our study, the inclusion of GR and its prognostic value for both DFS and MSS seem to support the hypothesis of Tejera-Vaquerizo [13], that GR determines the time of relapse; the fastest growing melanomas relapse early and the slowest later. Thus, patients with intermediate-growth melanomas are at greater risk of relapse or death due to melanoma than those with fast and slow growth during the period from the fifth to the tenth year of follow-up. Furthermore, the reduced number of relapses from fast-growing and slow-growing tumours seems to suggest that, on the one hand, tumours with fast GR relapse during the first five years after diagnosis, while slow-growing tumours are likely to recur later. Confirmation of the latter requires a longer follow-up period relative to that for our cohort.

The limitations of the study to bear in mind include the fact that some cases were old and much data were missing. Moreover, this may have influenced the lack of prognostic value for mitotic index, as well as GR, which demonstrated a moderate positive correlation with mitotic index [32]. In addition, we were unable to replicate previous studies beyond 10 years, without relapse, based on the follow-up period. In contrast, an adequate follow-up period of five years was provided for the study objective, and the data were uniformly collected. In addition, vital status was confirmed by consulting the National Mortality Registry of Spain.

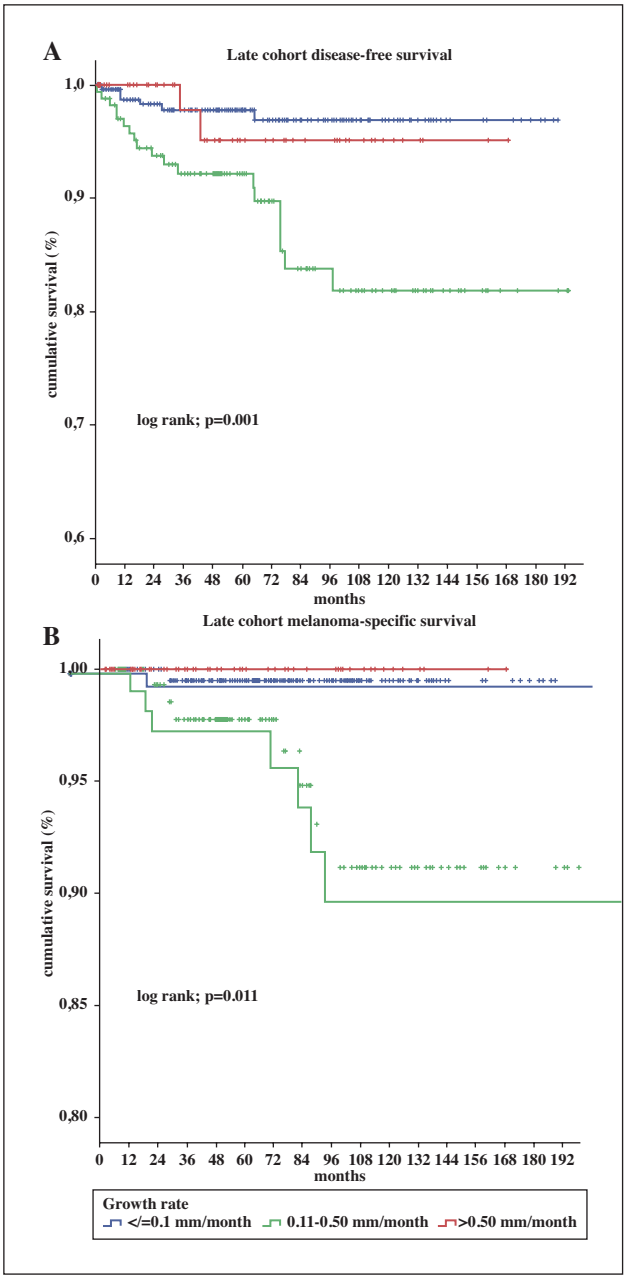

Figure 1. Kaplan-Meier estimated survival curves for disease-free (**A**) and melanoma-specific (**B**) survival after five years of follow-up from the time of diagnosis, according to tumour growth rate (late relapse cohort).

In conclusion, we have identified that up to 6.8% and 2.4% of patients who are free of disease for five years relapse or die from melanoma, respectively. Patients with acral localization and the presence of ulceration could benefit from a longer follow-up with the aim of earlier diagnosis of possible relapse. In addition, the value or IGR for DFS and MSS highlights the importance of melanoma kinetics and suggests that the slower the GR, the later the progression. Should our results be confirmed in other cohorts, it may be reasonable to modify follow-up periods in patients who are at increased risk.

Table 3. Multivariable analysis of prognostic factors for disease-free survival and melanoma-specific survival in patients with localized cutaneous melanoma without recurrence for more than five years (late relapse cohort).

Models excluding GR*		
Disease-free survival		
Variable	Hazard ratio (95% CI)	P-value
Localization		
Trunk/extremities	Ref.	Ref.
Head/neck	1.9 (0.6-5.8)	0.281
Acral	5.0 (2.0-12.7)	0.001
Melanoma-specific survival		
Ulceration	3.4 (1.2-9.9)	0.027
Localization		
Trunk/extremities	Ref.	Ref.
Head/neck	1.3 (0.3-5.7)	0.779
Acral	4.2 (1.2-14.3)	0.023
Models including GR*		
Disease-free survival		
Age	1.02 (1-1.04)	0.02
Log Breslow thickness	2.84 (0.98-8.32)	0.052
Growth rate (mm/month)		
≤0.10/ > 0.50	Ref.	
0.11-0.50	2.28 (1.05-4.86)	0.037
Melanoma-specific survival		
Age	1.04 (1.01-1.08)	0.026
Ulceration	3.24 (1.1-9.5)	0.032
Growth rate (mm/month)		
≤0.10/ > 0.50	Ref.	
0.11-0.50	3.3 (0.96-12.5)	0.06

*CI: Confidence interval. Log: logarithm. *Breslow thickness was included as a continuous variable after logarithmic transformation in the analyses including GR, but was analysed as categorical variable using AJCC cut-offs in the models where GR was excluded.*

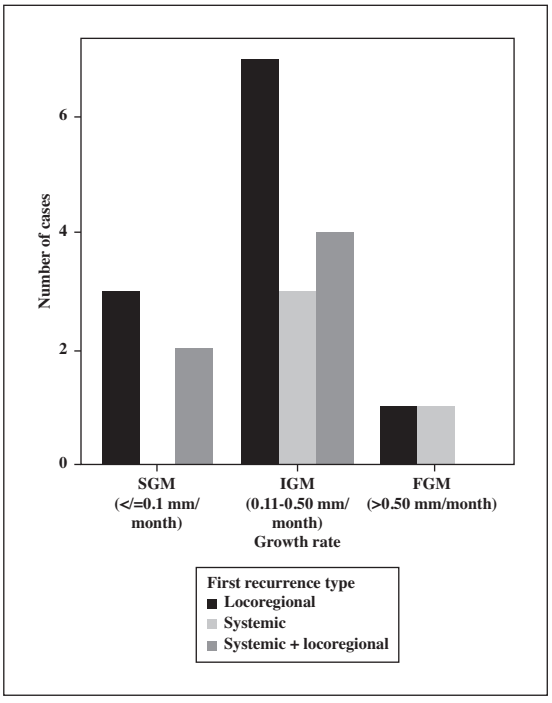

Figure 2. Bar diagram showing the frequency of systemic and locoregional type of first recurrence.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1684/ejd.2021.4022. Table S1. Clinical and pathological characteristics of 746 localized cutaneous melanoma patients who were free of disease for more than five years (late relapse cohort) with respect to growth rate.

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