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ORIGINAL ARTICLES

Longitudinal Study of Different Metastatic Patterns in the Progression of Cutaneous Melanoma

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Abstract. *Introduction.* Compared with other tumors, melanoma has displayed one of the largest increases in incidence in recent years, and it is known to have a high metastatic potential. In cases of metastasis, approximately two-thirds of patients have lymph-node metastases and one-third develop systemic metastases. However, few studies have been reported that analyzed different metastatic patterns according to the natural history of melanoma. The main aim of this study was to analyze the different metastatic pathways and patterns and to assess the time course of development of metastases from cutaneous melanoma.
Material and methods. A retrospective study was performed in 575 patients with onset of primary melanoma between 1990 and 2004. During follow-up, 67 patients developed metastases. Different pathways for metastasis were established and evaluated. We identified 4 metastatic pathways according to the metastatic pattern during progression of the melanoma. The time course of metastases was also evaluated. Finally, we analyzed melanomas with local recurrence in terms of whether or not systemic progression occurred.
Results. Melanoma metastases first occurred in local lymph nodes in 55.2% of the patients. Initial metastasis was systemic in 14.9% of the patients. The anatomical location and tumor thickness influenced which metastatic pathway was followed. Distant metastases occurred after a mean of 25 months regardless of the pathway followed.
Conclusions. The development of distant metastases displays a constant time course and the time to onset is independent of the metastatic pathway. This observation may explain why sentinel lymph node biopsy has a limited impact on overall survival of melanoma patients.

Key words: melanoma, metastatic pathways, natural history, prognostic factors, time course. melanoma

ESTUDIO TEMPORAL DE LOS DIFERENTES PATRONES METASTÁSICOS EN LA PROGRESIÓN DEL MELANOMA CUTÁNEO

Resumen. *Introducción.* El melanoma es uno de los tumores que más ha aumentado en las últimas décadas y posee un elevado potencial de diseminación. Cuando metastatiza, hasta en dos tercios de las ocasiones lo hace a los ganglios linfáticos regionales y aproximadamente en un tercio de los casos a nivel sistémico. Existen, sin embargo, pocos estudios en la literatura que hayan analizado los diferentes patrones metastásicos en el contexto de la historia natural del melanoma. El objetivo principal del presente estudio es analizar las diferentes vías y patrones metastásicos y el tiempo de evolución en el desarrollo de metástasis en el melanoma cutáneo.
Material y métodos. Se realizó un estudio retrospectivo en una serie de 575 pacientes con melanoma primario como primera presentación entre los años 1990 y 2004. En el seguimiento, 67 pacientes desarrollaron metástasis. Se establecieron y evaluaron diferentes vías de diseminación. También se establecieron cuatro rutas de diseminación dependiendo del patrón de diseminación en la progresión del melanoma. Se evaluó el cur-

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so temporal de las metástasis. Por último, se analizaron aquellos melanomas con recurrencia locorregional comparando los melanomas con y sin progresión sistémica.
Resultados. Las metástasis linfáticas regionales constituyen la primera vía de diseminación de los melanomas (55,2 %). Las metástasis sistémicas aparecieron como primera vía metastásica en el 14,9 % de los casos. La localización anatómica y el grosor tumoral influyen en las diferentes vías metastásicas. Las metástasis a distancia aparecieron con una media de 25 meses, independientemente de la ruta de diseminación.
Conclusiones. La aparición de metástasis a distancia es un evento con un curso temporal constante. Surgen al mismo tiempo independientemente de la ruta metastásica del melanoma. Esto podría explicar el beneficio limitado de la biopsia del ganglio centinela sobre la supervivencia global de los pacientes con melanoma.

Palabras clave: **melanoma, vías metastásicas, historia natural, factores pronóstico, tiempo de evolución.**

Introduction

Compared with other tumors, cutaneous melanoma has displayed one of the largest increases in incidence and mortality in recent years in Europe.[1] However, recent studies have begun to reflect a decrease in mortality from the 1990s onwards in some countries of the European Union,[2] Spain included.[3] In fact, Spain has one of the lowest mortality rates in Europe.[4]

Cutaneous melanoma is known to be highly malignant. Regional lymph nodes are involved in approximately half the cases in which metastases occur.[5] This observation favored the development of a technique known as sentinel lymph node biopsy, which is widely used today although its usefulness in the management of cutaneous melanoma is still the subject of debate.[6,7] Little information is available about the true impact of this technique on survival of patients with cutaneous melanoma, and we must await the findings of ongoing clinical trials.[8] Of the remaining types of recurrence in cutaneous melanoma, direct distant metastases account for around 20% and satellite metastases, defined as those at less than 2 cm from the primary tumor, or in-transit metastases, defined as those in the area anterior to the lymphatic drainage node but more than 2 cm from the primary tumor, for the remaining 30%.

Little is currently known of what factors might influence which type of recurrence occurs. Few studies have investigated the natural history of cutaneous melanoma or paid attention to the time to development of metastases at different sites and whether this, along with prior development of satellite/in-transit metastases and/or regional lymph node metastases, which are often observed in the course of cutaneous melanoma, somehow influences the appearance of distant metastases. Knowledge of such aspects would be very useful for drawing up diagnostic, therapeutic, and follow-up protocols.

The primary objective of this study was to analyze the different metastatic pathways for the spread of cutaneous melanoma (divided into satellite/in-transit metastases, regional lymph node metastases, and distant metastases), with particular emphasis on the time to development of metastases and their progression according to different metastatic patterns in patients with melanoma treated in the dermatology services of the participating hospitals. Other objectives were to analyze how frequently these metastases developed and compare a series of clinical and histopathological characteristics of the primary tumor in patients who developed satellite/in-transit metastases or regional lymph node metastases as the first metastasis according to whether or not they developed distant metastases during follow-up.

Materials and Methods

Between 1990 and 2004, 480 patients with melanoma were treated by the dermatology service of the Hospital Universitario Virgen de la Victoria in Malaga, Spain. Of the cases initially diagnosed with localized disease, 56 developed some kind of metastasis during the disease course. Likewise, the dermatology service of the Hospital Costa del Sol in Marbella, Spain, saw 95 patients with cutaneous melanoma between 2001 and 2004; 11 of these patients diagnosed initially with localized disease developed metastases during the subsequent disease course. Thus, in total, 67 of the 575 patients treated for melanoma were analyzed.

The follow-up protocol for these patients was similar in both hospitals. Visits were scheduled every 3 months during the first 2 years after diagnosis and then every 6 months until 5 years had elapsed. From then on, annual visits were scheduled. According to the follow-up protocol, at each visit a full physical examination of the skin, lymph node stations, and abdomen was undertaken and laboratory tests, including lactate dehydrogenase, were done. Chest radiography and abdominal ultrasound were done at diagnosis, then every 6 months for the first 2 years, and then annually until 5 years had elapsed. Imaging studies, such as computed tomography or magnetic resonance imaging, were only performed if

metastases were suspected from the findings of the scheduled follow-up visits.

First, the different metastatic pathways in the progression of cutaneous melanoma were analyzed. A metastatic pathway was taken to be the first pathway of spread in disease progression. Three groups were defined: satellite/in-transit metastases, regional lymph node metastases, and distant metastases. The incidence of each type of metastasis was determined according to site and thickness of the primary tumor.

Furthermore, the involvement of 1, 2, or 3 pathways of metastatic spread in melanomas with systemic progression gives rise to different patterns of spread, which are known as metastatic patterns. Four main patterns of progressive metastatic spread are considered, as described in a previous study[9]: pattern 1, development of satellite/in-transit metastases followed by the appearance of regional lymph node metastases and distant metastases; pattern 2, development of satellite/in-transit metastases followed by distant metastases; pattern 3, development of lymph node metastases followed by distant metastases; and pattern 4, development of distant metastases as a first recurrence of the tumor.

Finally, among the patients whose first metastasis was satellite/in-transit metastasis or regional lymph node metastasis, a series of clinical and histopathological characteristics were compared according to whether systemic progression occurred or not.

The variables used in this comparative analysis included the anatomic site of the primary tumor classified in 4 categories: head or neck, trunk, arms, and legs. The age and sex of the patients were also assessed. For the clinicopathological classification, the traditional forms of cutaneous melanoma were considered: lentigo maligna melanoma, superficial-spreading melanoma, nodular melanoma, and acral lentiginous melanoma. The tumor thickness was divided into 4 groups according to the TNM classification of the American Joint Committee on Cancer[10]: ≤1 mm, 1.01-2 mm, 2.01-4 mm, and >4 mm. The level of invasion was classified according to the system described by Clark et al.[11] The presence or not of ulceration and the number of mitoses per 10 high-magnification fields (400×) were taken into account. Finally, the time course of development of the first metastasis was classified as follows: <12 months, 12-24 months, and >24 months.

The statistical analysis was carried out using the SPSS statistical package, version 12.0 for Windows. The differences between the distributions were assessed using the χ^2 test or the Fisher exact test as appropriate. Quantitative variables were compared with the *t* test. The probability of metastasis in the group comparison was done by the Kaplan-Meier method. Statistical significance was established at $P<.05$.

Results

The mean follow-up time for the 67 patients who were treated for localized melanoma and who went on to suffer some kind of recurrence was 64 months. Table 1 shows the characteristics of the patients analyzed. There were more men than women (58% vs 42%). The mean age was 55.7 years. The most common clinicopathological form was superficial-spreading melanoma (41.8%) followed by nodular melanoma (34.3%). The least common forms were acral lentiginous melanoma (10.4%) and lentigo maligna melanoma (9%). The most common anatomical site was the legs (40.3%) followed by the head or neck (22.4%), trunk (22.4%), and arms (14.9%).

A Breslow thickness greater than 4 mm was reported in 40.2% of the cases of cutaneous melanoma. The Breslow thickness was between 2.01 and 4 mm in 28.3% of the cases, between 1.01 and 2 mm in 23.8%, and less than 1 mm in

Table 1. Characteristics of the Patient Population With Metastatic Melanoma (n=67)

Characteristic		*No.*	*%*
Sex	Men	39	58
	Women	28	42
Age, y	Mean	55.7	
	Range	24-89	
Primary tumor site	Head or neck	15	22.4
	Trunk	15	22.4
	Arms	10	14.9
	Legs	27	40.3
Clinicopathological classification	LMM	6	9
	SSM	28	41.8
	NM	23	34.3
	ALM	7	10.4
	Others	3	4.5
Breslow thickness, mm; mean		4.61	
	< 1	5	7.4
	1.01-2.00	16	23.8
	2.01-4.00	19	28.3
	> 4.01	27	40.2
Ulceration	Present	35	52.2
	Absent	24	35.8
	Not available	8	11.9

Abbreviations: SSM, superficial-spreading melanoma; ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma

Table 2. Distribution of the First Metastatic Pathway By Site and Thickness of the Primary Tumora

Site	*ST Pathway*	*L Pathway*	*M Pathway*
Head or neck	6 (40%)	6 (40%)	3 (20%)
Trunk	2 (13.3%)	10 (66.7%)	3 (20%)
Arms	3 (30%)	5 (50%)	2 (20%)
Legs	9 (33.3%)	16 (59.3%)	2 (7.4%)
Total	20 (29.9%)	37 (55.2%)	10 (14.9%)
Maximum tumor thickness (Breslow index)	*ST Pathway*	*L Pathway*	*M Pathway*
<1 mm	2 (50%)	2 (50%)	0 (0%)
1.01-2 mm	8 (47%)	8 (47%)	1 (5.9%)
2.01-4 mm	4 (21.1%)	12 (63.2%)	3 (15.8%)
>4 mm	6 (22.2%)	15 (55.6%)	6 (22.2%)
Total	20 (29.9%)	37 (55.2%)	10 (14.9%)

[a]Data are shown as number of patients (%)
Abbreviations: L, regional lymph node metastasis; M, distant metastasis; ST, satellite/in-transit metastasis.

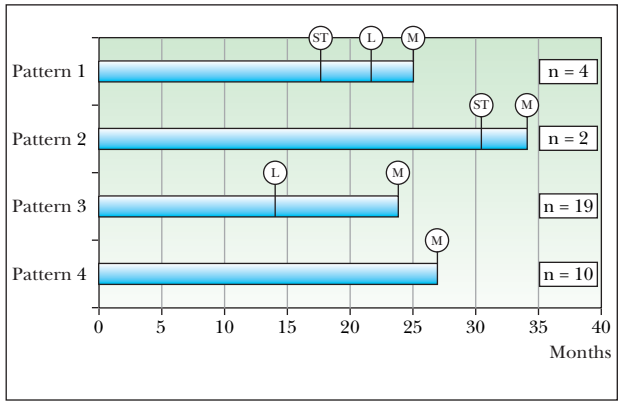

Figure 1. Graphical representation of the time course of the different metastatic patterns of progression from diagnosis of primary melanoma. L indicates regional lymph node metastasis; M, distant metastasis; ST, satellite/in-transit metastasis.

7.4%. Ulceration was reported in more than half the cases (52.2%).

The study of the first metastatic pathway in relation to the primary tumor site showed that more than half the primary recurrences were lymphatic (55.2%) (Table 2); in fact, this metastatic pathway was the most frequent for all primary tumor sites, and particularly for cutaneous melanomas on the trunk (66.7%). When the primary sites were on the legs and arms, the distribution was similar, with an incidence of satellite/in-transit metastases of approximately 30%. The lowest percentage of direct distant metastases was reported for cutaneous melanomas on the legs (7.4%). Of the patients with melanoma on the head or neck, 40% had satellite/in-transit metastases and 40% had regional lymph node metastases.

When the first metastatic pathway was analyzed in terms of tumor thickness (Table 2), it was found that the rate of satellite/in-transit metastases and regional lymph node metastases was approximately 50% in both cases for melanomas less than 2 mm thick. In the case of satellite/in-transit metastases, this rate decreased markedly for thicker tumors (21.1% for thicknesses of 2.01-4 mm and 22.2% for thicknesses >4 mm). However, the greater frequency of regional lymph node metastases is noteworthy for tumors with a thickness between 2.01 and 4 mm (63.2%). Finally, the percentage of distant metastases as the first metastatic pathway increased with increasing tumor thickness, reaching 22.2% of tumors with a Breslow thickness greater than 4 mm.

The analysis of the metastatic patterns is depicted graphically in Figure 1. The most common pattern for progression of cutaneous melanoma was pattern 3 (lymph node metastases followed by distant metastases), with 19 patients, followed by pattern 4 (distant metastases as the first recurrence of the tumor), with 14 patients. The least common was pattern 2 (satellite/in-transit metastases followed by distant metastases) with just 2 patients. The timing of appearance of satellite/in-transit metastases varied greatly according to the metastatic pattern. Thus, the mean time to development was 17 months for pattern 1 and 31 months for pattern 2. The mean time to development of regional lymph node metastases was 14 months for pattern 3, and 22 months for pattern 1.

It is of note that pattern 4 showed a mean time to development of distant metastases of 26 months, which is close to the mean time to development of distant metastases in pathways 1 (25 months) and 3 (24 months). Pattern 2 showed a mean time to development of distant metastases of 34 months.

In the comparative study of cases with initial recurrence as satellite/in-transit metastases or regional lymph node metastases with and without subsequent systemic dissemination, regional lymph node metastases in the group of patients who went on to suffer distant metastases became manifest before regional lymph node metastases in the group of patients who did not suffer subsequent distant metastases (Figure 2), although this difference was not statistically significant (P=.14). On stratification by time course, lymph node metastases with systemic progression occurred more often within 12 months compared to recurrence in regional lymph nodes without subsequent systemic involvement (63.2% vs 16.7%). This difference was statistically significant (P=.014) (Table 3). The variables

sex, age, primary tumor site, clinicopathological classification, Breslow thickness, Clark level, and number of mitoses were balanced between the 2 groups. Ulceration was more common in the group who developed distant metastases (58.8% vs 29.4%), a difference that was almost significant (*P*=.08). Furthermore, in the group of patients with cutaneous melanoma who developed satellite/in-transit metastases followed by distant metastases, the time to development of satellite/in-transit metastases was somewhat shorter than in patients without subsequent systemic involvement (Figure 3), although the difference was not statistically significant (*P*=.52). Comparison of the variables in these 2 groups did not reveal any noteworthy differences.

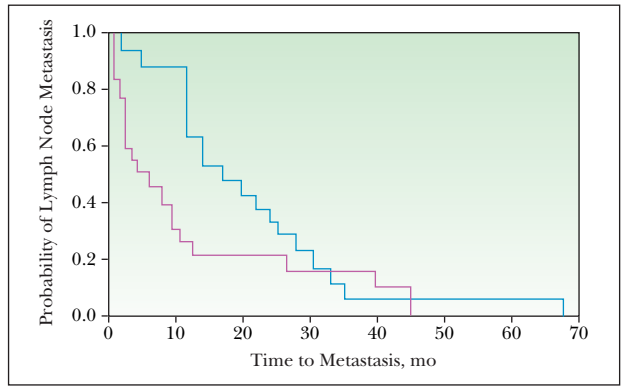

Figure 2. Time to development of regional lymph node metastasis for melanomas with progression to systemic disease (red) and without subsequent progression (blue) (*P*=.14).

Table 3. Clinicopathological Correlation Between Melanomas With Local Recurrence With and Without Systemic Progression[a]

Characteristics		*Lymph Node Metastasis Without Progression*	*Lymph Node Metastasis With Progression*	*P*	*Satellite/ In-transit Metastasis Without Progression*	*Satellite/In-transit Metastasis With Progression*	*P*
Sex	Men	7 (38.9%)	8 (12.4%)	*P*=.84	3 (42.9%)	4 (57.1%)	*P*=.37
	Women	11 (61.1%)	11 (57.9%)		10 (66.7%)	5 (33.3%)	
Age, y	Mean	53.2	52,8	*P*=.91	61	59.3	*P*=.75
Site	Head or neck	2 (11.1%)	4 (21.1%)		4 (30.8%)	3 (33.3%)	
	Trunk	5 (27.8%)	5 (26.3%)		0 (0%)	2 (22.2%)	
	Arms	4 (22.2%)	1 (5.3%)		2 (15.4%)	1 (11.1%)	
	Legs	7 (38.9%)	9 (47.4%)		7 (53.8%)	3 (33.3%)	
Clinicopathological classification	LMM	0 (0%)	2 (10.5%)		2 (16.7%)	3 (33.3%)	
	SSM	9 (50%)	10 (52.6%)		4 (33.3%)	4 (44.4%)	
	NM	7 (38.9%)	5 (26.3%)		4 (33.3%)	2 (22.2%)	
	ALM	2 (11.1%)	2 (10.5%)		2 (16.7%)	0 (0%)	
Breslow thickness, mm	Mean	4.27	4.83	*P*=.69	2.73	3.66	*P*=0.82
	< 2 mm	6 (33.3%)	4 (22.2%)	*P*=.45	5 (50%)	5 (50%)	*P*=.95
	> 2 mm	12 (66.7%)	14 (77.8%)		5 (50%)	4 (44.4%)	
Clark level	≤ III	5 (27.8%)	6 (33.3%)	*P*=.71	3 (27.3%)	2 (22.2%)	*P*=.79
	> III	13 (72.2%)	12 (66.6%)		8 (72.7%)	7 (77.8%)	
Ulceration	Present	10 (58.8%)	5 (29.4%)	*P*=.08	4 (44.4%)	6 (66.7%)	*P*=.63
	Absent	7 (41.2%)	12 (70.6%)		5 (55.6%)	3 (33.3%)	
No. of mitoses	< 10	10 (71.4%)	8 (53.3%)	*P*=.45	4 (80%)	3 (50%)	*P*=.54
	≥ 10	4 (28.6%)	7 (46.7%)		1 (20%)	3 (50%)	
Time to development of first metastasis, months	< 12	3 (16.7%)	12 (63.2%)	*P*=.014	5 (38.5%)	4 (44.4%)	*P*=.94
	12-24	8 (44.4%)	3 (15.8%)		2 (15.4%)	1 (11.1%)	
	≥ 24	7 (38.9%)	4 (21.1%)		6 (46.2%)	4 (44.4%)	

[a]Data are shown as number of patients (%) unless otherwise indicated.
Abbreviations: SSM, superficial-spreading melanoma; ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma

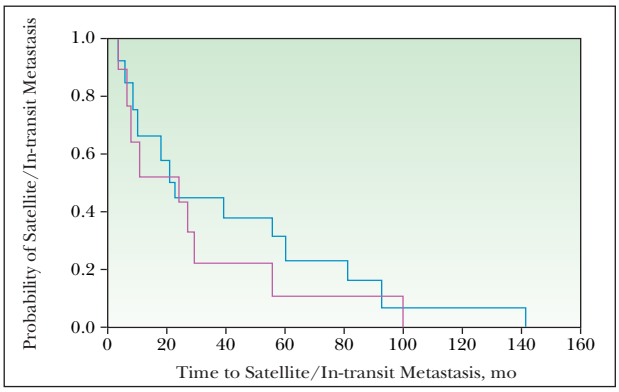

Figure 3. Time to development of satellite/in-transit metastasis for melanomas with progression to systemic disease (red) and without subsequent progression (blue) (*P*=.52).

Discussion

In our study, 67 out of 575 patients with early-stage melanoma went on to develop metastases during follow-up. The regional lymph nodes were the most frequent site for the first metastasis (55.2%); satellite/in-transit metastases were the next most common type of metastasis (29.9%); and distant metastases were least common (14.9%). The few studies available to date reflect similar rates of recurrence at these sites.[9,12]

Regional lymph node metastases were the most frequent type of recurrence when the primary tumor was located on the trunk (66.7%), whereas satellite/in-transit metastases were more frequent when the primary site was on the head or neck (40%). Distant metastases were equally frequent for all primary sites (20%), except for the case of the legs—this site was associated with a lower frequency (7.4%). These findings suggest that melanomas on the trunk, arms, and head or neck have a worse prognosis than those on the legs. Some authors have suggested that this better prognosis for the legs is due to the higher barrier to metastatic cells presented by the longer lymphatic vessels and greater number of lymph nodes before reaching systemic circulation.[13]

The greatest frequency of satellite/in-transit metastases as the first metastatic pathway was found for primary melanomas less than 2 mm thick, whereas the rate of distant metastases as the first pathway was proportional to the tumor thickness. Regional lymph node metastases occurred most often as the first metastatic pathway in melanomas with a thickness between 2.01 and 4 mm. Although it is well established that greater thickness is associated with greater distant metastatic potential, there are currently no markers that can account for the variation in the different metastatic pathways according to tumor thickness. It is not clear why satellite/in-transit metastases and regional lymph node metastases do not show the same variation in frequency according to tumor thickness.

Analysis of the time course of the different metastatic patterns shows that the time to diagnosis of distant metastasis remains constant at around 25 months regardless of the first metastatic pathway; this period is similar to that reported by other authors.[9,12] This finding takes on particular importance in the context of the different hypotheses or models for spread of melanoma. At present, there are 3 main models that attempt to explain how melanoma spreads. The first is known as the "stepwise spread" model, in which the melanoma spreads first by a lymphatic pathway towards the regional lymph nodes, from where systemic dissemination is initiated with a certain time lag. Proponents of this model include Balch et al,[14] Leong,[15] and Morton and Cochran.[7] Morton and Cochran[7] refer to this model as the "incubator hypotheses." Although they recognize that some melanomas may undergo direct hematogenous spread, they are of the opinion that such cases represent the minority. This model is also favored by proponents of routine sentinel lymph node biopsy, a technique which, according to some, may help prevent some cases of distant metastasis and so represent an advantage over delayed lymph node dissection.

A model of simultaneous spread has been proposed by authors such as Pharis and Zitelli[16] and Medalie and Ackerman,[6] who are opposed to sentinel lymph node biopsy. Morton and Cochran[7] described this model as the "marker hypothesis," in which the primary tumor would metastasize simultaneously by lymphatic and hematogenous pathways, and lymph node involvement would therefore be a marker of systemic disease. It is well known that visceral metastases finally appear in around 70% of patients with stage III disease.[10] This model is clearly viable in such patients. However, it does not fit with the fact that regional lymph node dissection is curative in the remaining 30% of cases.

Finally, we have the model of differential spread. This is an alternative model based on the "seed and soil" hypothesis first described by Paget in 1889. In this hypothesis, several independent dissemination pathways are considered.[17,18] Thus, some melanomas will not have the biological potential to metastasize, others will only be able to metastasize to regional lymph nodes or to metastasize to both regional lymph nodes and other organs or tissues. Finally, some melanomas will only be able to metastasize at the systemic level. Each melanoma would probably fit into one of these 4 groups from relatively early phases in the disease course, with minimal capacity to jump from one group to another as the disease progresses.

This model can explain some premises about the natural history of melanoma that cannot be explained by the other models. Firstly, given that some melanomas would

metastasize exclusively to lymph nodes, it can explain why therapeutic lymph node dissection can achieve complete and lasting remission in around 30% of patients with stage III disease. It would also explain why neither preventative lymph node dissection nor lymph node dissection according to the findings of sentinel lymph node biopsy improves overall survival. That is, some patients develop lymph node and distant metastases at the same time and no type of lymph node dissection would be curative in such cases. Finally, it would explain why a negative finding in the sentinel lymph node biopsy does not provide an absolute guarantee of survival because some melanomas undergo exclusively distant metastasis.

Our findings on the time course of metastasis in the different patterns provide greater support for both the simultaneous spread model and the differential spread model. Thus, like the study of Meier et al,[9] our study suggests that prior recurrence, whether in the form of satellite/in-transit metastases or regional lymph node metastases, does not affect the time to development of distant metastases. Our findings also suggest that the metastatic potential may be predetermined in each melanoma from the early stages of tumor progression, as is the case in other solid tumors.[19] In fact, preliminary studies have undertaken a molecular classification of the primary melanoma according to the gene expression profile; such a classification could predict in which tissue metastasis is likely to occur.[20]

Finally, as discussed earlier, in the differential spread model there are melanomas that can only metastasize to regional lymph nodes. If we apply this model to our findings, such melanomas would be differentiated from those that, in addition to metastasizing to regional lymph nodes, also progress to systemic involvement. We note that these regional lymph node metastases appeared in the first year of follow-up in a greater proportion of cases in the group with systemic progression (63.2% vs 16.7%; *P*=.014). In such cases, ulceration of the primary tumor was also more common (70.6% vs 41.2%; *P*=.08).

In conclusion, the first pathway of spread was the regional lymph nodes in more than half the melanoma patients with disease progression. However, our findings suggest that the appearance of distant metastases is independent of both the prior occurrence of regional lymph node metastases and satellite/in-transit metastases. These findings would explain why a technique currently as widespread as sentinel lymph node biopsy, although useful for staging and regional control of the disease,[21] has shown no clear benefit in overall survival in these patients.[22] Further studies are necessary to clarify the true benefit of sentinel lymph node biopsy in patients with cutaneous melanoma.

Conflicts of Interest

The authors declare no conflicts of interest.

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