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Analysis of Thin Malignant Melanoma Prognostic Factors

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ABSTRACT

The increasing number of thin malignant melanomas (≤1 mm in thickness) asks for better acknowledgement of prognostic factors of the disease; this is the purpose of this research [1, 2]. The plastic surgery unit of the hospital Spedali Civili of Brescia has collected over 450 cases of thin malignant melanoma over a period of 20 years, from 1990 to 2010, in order to obtain as much information as possible about prognostic factors. These data have been analyzed using the Chi-squared test to reveal the influence on prognosis of each one of the 16 prognostic factors that have been chosen for this study; both the development of a metastasis and the death of the patient were considered for outcome study. The univariate analysis describes the presence of the phase of vertical growth as the only prognostic factor statistically significant for both metastasis development and death.

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Introduction

Malignant melanoma is the type of cancer that has shown the most relevant growth in his epidemiology in the last 40 years all over the world. According to different national registries, the total number of cases of malignant melanoma has grown, over the past few decades, of more than 400%; this is possibly due to an increasing exposition to risk factors, such as UV radiations, and to the evolution of diagnosis techniques.

Even though the absolute number of melanomas has grown, the mortality ratio has decreased thanks to several campaigns of primary and secondary prevention; this commitment in social health has shown its results. In fact nowadays, melanomas are diagnosed mostly at early stages and especially when they are less than 1 mm in thickness and they are called thin melanoma. In Europe the average thickness of melanomas has decreased from 1.8 mm in 1976 to 0.5 mm in 2000 with an increasing percentage of thin melanomas from 39% to 65.5% of all melanomas; plus, the 70% of melanoma cases from the SEER are less than 1 mm in thickness [3, 4].

According to the last version of the TNM, from the AJCC of 2010, thin melanomas are classified by prognosis, evaluating the presence of ulceration and the level of invasion [5, 6]. Several studies have been conduced to collect more information about how other histological and clinical features of melanomas influence the overall prognosis. This study is based on the data from the registry of the Plastic Surgery Unit of Spedali Civili of Brescia, that includes more than 1300 patients diagnosed with melanoma; 455 of those were thin melanomas.

Patients and Methods

This research is based on the data available from the registry of Plastic Surgery unit of Spedali Civili of Brescia; among over 1300 cases of melanoma, 455 were thin melanomas and represent the subject of this study. All of the information (or data) was collected between 1990 and 2010 and represent an ensemble of both clinical and histopathological features of each patient. Following the later guidelines, we provide a follow-up period of at least 10 years; clinical examinations are performed every 6 months for the first 5 years and every 6 or 12 months for the following 5 years; for patients with a melanoma that shows signs of ulceration chest X-rays, ultrasound examination of the abdomen and of the lymph node region proximal to the melanoma are required yearly.

Patients age were classified in 5 groups: < 40 years, 40 to 49 years, 50 to 59 years, 60 to 69 years and > 70 years. Bogy sites of primitive tumor were classified in 4 groups: head/neck area, trunk, upper limbs and lower limbs. Maximum diameter of the lesion was classified in one of 4 groups: < 5 mm, 5 to 10 mm, 11 to 20 mm and ≥ 21 mm. Histological features of melanomas were classified in 5 groups: malignant melanoma, lentigo malignant melanoma, acrolentiginous melanoma, nodular melanoma and spitzoid melanoma. Both radial and vertical growth were studied by histopathology and described as absent or present. Number of mitosis per mmq was classified as: no mitosis found, less than 6 mitosis/mmq and more than 6 mitosis/mmq. Tumor thickness was subdivided into 4 groups: ≤ 0.25 mm, 0.26 to 0.50 mm, 0.51 to 0.75 mm and ≥ 76 mm. Ulceration, autoregression or neavus associated to melanomas were described as present or absent.

Statistical Analyses

All the groups in which the variables were subdivided were associated to a numerical parameter and then analyzed. The time between the first melanoma excision and the last date of clinical examination during the follow up period was considered as the follow up time. Both patient's death and metastasis followed by death of the patient development were considered events. To test

the association between every single variable, Chi-square test, Phi coefficient, contingency coefficient and Cramer's V were applied. No multivariate analyses were necessary afterwards.

Description of Sample

The sample consisted of 45.17% of male patients with a mean age at the time of diagnosis of 52.82 years. Among the patients, the 29.87% developed a melanoma in the head/neck area, the 36.36% developed a melanoma in the trunk area (chest, back and abdomen region), the 11.04% had a melanoma located at the upper limbs and the 29.73% had a primary lesion at the lower limbs. Analyzing the maximal diameter of the primary lesion, the 13.32% of the patients had a melanoma less than 5 mm in diameter, the 40.44% had a melanoma with a diameter of 5 to 10 mm, the 36.32% had a lesion of 11 to 20 mm and the 9.93% had a lesion of more than 21 mm in diameter. After the histological examination the 76.39% of the melanomas was described as malignant melanoma, the 18.52% was described as lentigo malignant melanoma, the 3.59% of the melanomas was acrolentiginous, the 0.44% were nodular type melanoma and the 0.89% were spitzoid type melanoma.

The radial growth was described in the 99.30% of the melanomas while the vertical growth was present in the 60.97% of the melanoma. No mitosis was found in the 46.53% of the cases. In the 52.44% of the melanomas there were less than 6 mitosis per mmq and there were more than 6 mitosis per mmq in the 1.03% of the cases. The presence of TIL was described in the 60.05% of the cases. According to the definition of thin melanoma, all the primary lesions were less than 1 mm in thickness; we therefore divided the lesions thickness into four subgroups. The 14.46% of the lesions had a thickness from 0.00 to 0.25 mm, in the 38.20% of the cases they were between 0.26 and 0.50 mm thick, in the 22.92% the lesions were from 0.51 to 0.75 mm thick and the thickness was from 0.76 to 1.00 mm in the 24.72% of the cases. Ulceration was found in 10 out of 455 cases; signs of autoregression were described in 124 out of 455 cases (30.24%). The primitive lesion was associated to a melanocytic naevus in the 37.35% of the cases and signs of vascular invasion were found in 9 lesions.

In our study the mortality rate was 1.32% and incidence of metastasis was 8.31%. After a univariate statistical analysis we found that the only parameter that can actually have an influence on survival rate was the presence of vertical growth. Among the patients that presented a metastasis, 9 had a syncrone metastasis, 4 had a metastasis within a year from the beginning of follow up period, 18 had a metastasis within 2 to 5 years from the primitive lesion, 4 had a metastasis within 6 to 10 years after follow up beginning and 2 presented a metastasis after 10 years from the first lesion excision.

Metastasis then occurred on an average 2.34 years from the beginning of follow up period. The whole six cases of deaths occurred within 10 years from the diagnosis of the first melanoma; in particular one case occurred within a 1 year from the diagnosis, one within 2 to 3 years, three cases occurred within 4 to 5 years and one death occurred 10 years from the beginning of the follow up period. (Table 1)

Table 1: Distribution of variables in the sample; cases of metastases and deaths. SSM, superficial spreading melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma; ALM, acral lentiginous melanoma. Met=metastasis

Prognostic factor	Sample size	N° metastasis	N° deaths
sex			
Male	201 (45.17)	21	22
Female	244 (54.83%)	16	17
Age			
<40	102 (23.8%)	5	5
40-49	64. (14.48%)	10	10
50-59	80 (18.10%)	9	9
60-69	106 (23.98)	6	6
≥ 70	90 (20.36%)	7	9
Localization			
Head/neck	106 (23.87%)	14	15
Trunk	157 (35.36%)	8	9
Superior limbs	49 (11.04%)	6	6
inferior limbs	132 (29.73%)	9	9
Max diameter			
≤ 5 mm	55 (13.32%)	2	2
5-10 mm	167 (40.44%)	13	14
11-20 mm	150 (36.32%)	14	14
≥ 21 mm	41 (9.93%)	4	5
Histologic subtype			
SSM	330 (76.39%)	27	28
LMM	80 (18.52%)	9	10
ALM	16 (3.70%)	1	1
NM	2 (0.46%)	0	0

SM	4 (0.93%)	0	0
Radial growth			
Yes	424 (99.30%)	36	38
No	3 (0.70%)	0	0
Vertical growth			
Yes	239 (60.97%)	28	29
No	153 (39.03%)	6	7
Mitosis/mmq			
0/m mq	181 (46.53%)	14	16
< 6/ mmq	204 (52.44%)	18	18
> 6/mmq	4 (1.03%)	1	1
TIL			
Slight/moderate	174 (43.18%)	19	20
Marked	68 (16.87%)	5	5
Absent	161 (39.95%)	9	10
Breslow			
0.00-0.25 mm	63 (14.16%)	4	5
0.26-0.50 mm	170 (38.20%)	11	12
0.51-0.75 mm	102 (22.92%)	9	9
0.76-1.00 mm	110 (24.72%)	13	13
Clark			
I	20 (4.63%)	3	3
II	263 (60.88%)	18	20
III	127 (29.40%)	12	12
IV	22 (5.09%)	2	2
Ulceration			
Yes	10 (2.44%)	2	2
No	399 (97.56%)	30	32
Regression			
Yes	124 (30.24%)	12	13
No	286 (69.76%)	20	21
Naevus			
Yes	152 (37.35%)	12	13
No	255 (62.65%)	20	21
Vascolar invasion			
Yes	9 (2.20%)	0	0
No	401 (97.80%)	32	34

Results

Clinical Features

For thin melanomas some studies have shown that male gender, older age and trunk and head/neck area as body sites of the lesion are linked to a worst prognosis; male sex is most of all associated to a decreased survival rate and a higher probability to develop metastasis. However in our study none of the clinical features appear to negatively influence patients prognosis [7-9].

Histologic Subtype

Thin melanomas are mostly superficial spreading lesions or lentigo maligna melanoma type. Nowadays it is known that melanoma's histologic subtype goes not represent an independent prognostic factor; it is believed, on the other hand, that different outcomes of the neoplastic process are due to the differences in the mean thickness of the lesions, depending on their histological features. It is also important to remember that different histologic subtype should be considered as different morphological and histopathological variety of the same kind of lesion [10]. Therefore, histologic features are important for a mere description of the lesion rather than for prognostic value. In this study we did not find any statistical correlation between histologic subtypes and the events "metastasis" and "death".

Growth Pattern

Clark supposed that cutaneous melanoma has a particular kind of evolution; it first presents a "in situ" growth, then a microinvasive phase after which one or more neoplastic dermal nodes can provide metastasis development [11]. It is then possible to describe a first growing phase named radial growth for "in situ" and microinvasive stages and a second phase named vertical growth for those lesions that already show one or more dermal nodes. In the same scientific

article Clark and coll. assumed that the different growing phases had a main prognostic importance.

In fact while melanomas with evidence of vertical growth have the capacity to get metastatic process started, those with only radial growth phase have almost no risk of developing secondarism. Although in some cases, the presence of regression can lead to underrating the measurement of lesion thickness. EORTC Melanoma Group has recently scaled down the influence growth pattern has on thin melanoma prognosis [12]. Our data analysis shows statistical evidence of the correlation between the presence of vertical growth phase and both metastasis development and death of patients. 34 patients that developed metastasis during the follow up period had a lesion with evidence of vertical growth phase; in case of metastasis development, X2 value was 7.1536 with p=0.0075; in case of patients death X2 value was 6.3903 with p=0.0115.

Mitotic Rate

The definition of mitotic rate, evaluated as the number of mitosis per mmq, in melanoma prognosis is still a disputed topic. In a study of more than 800 patients with thin melanoma and a follow up period of at least ten years, mitotic rate was found to be an important prognostic factor. In fact it was described that those patients with a lesion with no mitotic activity had an overall risk of relapse of 1.8% in ten years; on the other hand those patients whom lesions had only one mitotic figure had a risk of relapse of 19.9% in ten years. Number of mitosis is in fact indicative of growing speed and can be related to a higher probability for the tumor to get the capacity of staring the metastatic process. Other studies although have confuted this association after some experiment about the expression of Mib-1 protein in tumoral cells [13-15]. Similarly our study has not shown any statistically important correlation between the number of mitosis/mmq and the metastasis development or patients death.

Inflammatory Infiltrate and TIL (Tumor Infiltrating Lymphocytes)
The ability of the host to evoke an immune response against the tumor can represent a crucial phenomenon for long term survival rate. It was supposed that T lymphocytes and macrophages, leg by some tumor specific antigens, have a protective role due to the production of factors that inhibit the activity of neoplastic cells. Tumor growth can also be limited by the activity of lymphocytes CD8+ [16].

Today, the absence of proper parameters to define and evaluate qualitative and quantitative characteristics of inflammatory infiltrate is a serious issue; consequently, the meaning of TIL in the evaluation of thin melanoma prognosis is controversial. Most studies agree on the favorable influence that TIL has on melanoma prognosis. It is nevertheless true that only a small number of thin melanomas show a vertical growth phase and in melanomas with evidence of only radial growth, TIL has no prognostic significance [17-19]. In this study no association between presence of TIL and better prognosis was revealed.

Thickness

It was demonstrated that there is a direct relation between thickness and prognosis. Also in T1 category the thicker the lesion is, the worse the prognosis [5, 20]. On the contrary our study did not identify any statistical relation between mortality and metastasis rate with different thickness levels.

Clark Levels

The true significant of Clark staging for thin melanomas is still a matter of controversy. In certain body sites the exact Clark level is a parameter difficult to define. In fact the distinction between different levels is uncertain for thin melanomas in relation to thick ones. The same holds true for the distinction between the 2nd and 3rd level; the boundary between papillary dermis and reticular dermis is not consistent and often subjective. This led authors to suggest eliminating Clark levels from TNM classification [21-24]. Other studies had instead highlighted the main importance of Clark levels in prognostic evaluation for their importance in long term survival rate [5, 25]. In this study we did not find any statistical correlation between Clark's levels and prognosis.

Ulceration

Ulceration can be found in only 6% of melanomas and is considered, by its importance, the second prognostic factor for melanoma, after tumor thickness [5]; two different studies from Filho and Azzola attempt to confirm this [26, 16]. This can be explained by the biological malignancy of the tumor with ulceration that seems to be related to a quicker tumoral growth. Statistical analysis of our data did not find any correlation between ulceration and events "metastasis" and "death".

Regression

Even for the prognostic influence of tumor regression, there are no concordant results in literature; this is possibly due to the lack of uniformity in definition and criteria that allow to identify the regression itself. As for ulceration phenomena, it is believed that regression can lead to an underrated value of tumor thickness [27, 28]. Also for regression we did not find any statistical relation with prognosis.

Tumor Associated Naevus

Thin melanomas are associated to a melanocytic naevus in the 25-30% of the cases. So far, however it was not possible to find any statistical relation between the presence of a neavus and the presence of a skin melanoma. A new dermoscopic sign was recently found to be predictive of a melanoma spreading: the dermoscopic island. Further studies are needed to prove this evidence. In our study no correlations between the presence of a naevus and different outcomes were found.

Vascularity

Authors did not come to an agreement on the meaning of vascularity on thin melanoma prognosis. Some studies have shown that vascular density, measured as mean number of vessels within the lesion, was predictive of melanoma outcome [29]; other authors have otherwise demonstrated that neovascularization has no influence on thin melanoma prognosis [30]. This mismatch is probably due to the eterogenity of samples studied and to the technical difficulty to quantify angiogenetic processes. In this study no links between vascularity and outcomes of the melanoma were found.

Table 2: X^2 and p=0.05 for each prognostic factor; SSM, superfcial spreading melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma; ALM, acral lentiginous melanoma. Met=metastasis

Prognostic Factor	X^2 met	p=0.05 met	X2 death	p=0.05 death
Sex	2.1881	0.1391	2.1812	0.1397
Male				
Female				
Age	7.9121	0.0949	7.6886	0.1037
< 40				
40-49				
50-59				
60-69				
≥ 70				
Localization	6.8295	0.0775	7.0045	0.0718
Head/neck				
Trunk				
Superior limbs				
Inferior limbs				
Max diameter	1.9697	0.5787	2.5360	0.4688
≤ 5mm				
5-10 mm				
11-20 mm				
≥ 21 mm				
Histologic subtype	0.7568	0.3843	2.0386	0.7287
SSM				
LMM				
ALM				
NM				
SM				
Radial growth	0.2782	0.5979	0.2951	0.5870
Yes				
No				
Vertical growth	7.1536	0.0075	6.3903	0.0115
Yes				
No				
Mitosis/mmq	1.5666	0.4569	1.2641	0.5315
0/mmq				
< 6/mmq				
> 6/mmq				
TIL	3.2353	0.1984	3.1260	0.2095
Slight/moderate				
Marked				
Absent				
Breslow	2.8834	0.4100	1.9558	0.5816
0.00-0.25 mm				
0.26-0.50 mm				
0.51-0.75 mm				
0.76-1.00 mm				
Clark	2.1754	0.5368	1.5018	0.6819
I				
II				

III				
IV				
Ulceration	2.1073	0.1466	1.8369	0.1753
Yes				
No				
Regression	0.8662	0.3520	1.1223	0.2894
Yes				
No				
Naevus	0.0004	0.9851	0.0125	0.9109
Yes				
No				
Vascolar Invasion	0.7790	0.3774	0.8321	0.3617
Yes				
No				

Disclosure

There are no conflicts of interest to declare.

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