Factors Related to Thickness of Melanoma

Multifactorial Analysis of Variables Correlated with Thickness of Superficial Spreading Malignant Melanoma in Man

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Computer analyses to identify correlations between thickness of primary superficial spreading malignant melanoma and eighteen variables previously reported to be related to prognosis were performed on a series of malignant melanomas.

The variables that showed statistically significant (≤0.05) direct relationships to thickness were level (Clark), elevation of lesion, age of patient, least and greatest diameters of lesion, history of bleeding, ulceration, clinical and histologic stage, anatomic location, pedunculation, and satellitosis. The variables that did not correlate with thickness were clinical diagnosis of regional lymphadenopathy, in-transit metastasis, duration of lesion, sex, history of a previous malignant melanoma, and history of a pre-existing lesion at the site of the development of melanoma.

Multiple regression analysis of the factors that showed statistically significant correlation with thickness of the primary lesion revealed a subset of six dominant variables that were most predictive of thickness, namely, level, elevation, largest diameter of lesion, ulceration, histologic stage, and age of the patient.

INTRODUCTION

In 1970 Breslow[1] reported that the survival rate of cutaneous malignant melanoma is related to the thickness of the primary lesion. Lesions less than 0.76 mm thick were associated with high survival rate, whereas progressively thicker lesions had increasingly lower cure rates.[2,3] Subsequently, Breslow's concept was confirmed by others.[4-12] Recently, multifactorial analyses have shown that the thickness of a primary melanoma is the dominant prognostic variable in predicting the clinical course of malignant melanomas and survival rates of affected patients.[4,9,13,24,25]

The purpose of the present study was to examine a series of 18 variables in an attempt to identify those that correlate with thickness of primary cutaneous malignant melanoma of the superficial spreading type. In addition, a multifactorial analysis was done on those variables that were found to correlate with thickness to determine their order of dominance.

METHODS

Information concerning anamnestic, clinical, and histologic features of a prospective series of 820 patients with all types of malignant melanomas seen between November 1972 and October 1979 by the Melanoma Cooperative Group at New York University Medical Center has been recorded on special forms designed for computer analysis.

The thickness of each primary malignant melanoma was measured in millimeters by the use of a calibrated ocular micrometer in a light microscope. The thickness

of each lesion was measured as the distance between the uppermost portion of the stratum granulosum and the deepest identifiable neoplastic cells in the dermis or subcutis.[2]

All data were entered in a Control Data Corporation 6600 computer at the Courant Mathematics and Computing Laboratory at New York University. The initial analyses performed on 18 variables concerning the patients and their lesions were reviewed separately in order to determine their possible relationship to thickness of the primary cutaneous malignant melanomas of the superficial spreading type.[14] The Statistical Package for the Social Sciences, version 8.0, was used for the mathematical calculations.[15] Chi square analysis or, where appropriate, linear regression analysis was performed to determine the significance of the relationship of each of these variables to thickness. The p value was calculated for each analysis; a value of $p \leq 0.05$ was considered to be statistically significant.

Multiple regression analysis using the Statistical Package for the Social Sciences was subsequently performed upon those variables that were found to have significant correlations with thickness. For this analysis there were 348 superficial spreading melanomas for which data were available for all 12 variables. By this method the dominant factors predictive of thickness were determinable. Each variable was analyzed in sequence for its additive predictive value after the preceding factors had been accounted for. Thus, the model selected a subset of variables that was most predictive of the thickness of the melanoma and excluded those variables that were related directly to the other predictive variables themselves rather than to thickness.

RESULTS

Table 1 summarizes the variables studied in relation to the thickness of malignant melanoma. Of the 18 variables tested, 12 showed, in descending order, statistically significant correlations with thickness, namely, Clark level,[16] elevation of the lesion (in millimeters), age of the patient (in years), least diameter of lesions (in millimeters), history of bleeding, history of ulceration, stage (based on histologic examination of definitive surgical specimens), largest diameter of lesion (in millimeters), location (head and neck, trunk, upper limb, lower limb), pedunculation, stage at entry into study (clinical and/or histologic), and satellitosis. Factors that did not significantly correlate with thickness were regional lymphadenopathy (based on clinical judgment), in-transit metastases, duration of the lesion (by history), sex, history of a previous malignant melanoma, and history of a preceding lesion at the primary site.

Table 1
Variables Studied for Their Relationship to Thickness of Superficial Spreading Malignant Melanoma*

Variable	Number of Lesions	p	Significance
Clark level	355	0.00001	Significant
Elevation	293	0.00001	Significant
Age	353	0.00002	Significant
Least diameter	341	0.00003	Significant
History of bleeding	346	0.00001	Significant
Ulceration (clinical)	342	0.0001	Significant
Stage (histologic)	357	0.0001	Significant
Largest diameter	341	0.00045	Significant
Location	352	0.0012	Significant
Pedunculation	347	0.0022	Significant
Stage (at entry into study)	352	0.0079	Significant
Satellite metastasis	372	0.0123	Significant
Regional nodes clinically involved	348	0.0900	Not significant
In-transit metastasis	352	0.1787	Not significant
Duration of lesion (by history)	321	0.5819	Not significant
Sex	353	0.5989	Not significant
History of previous malignant melanoma	350	0.9278	Not significant
History of preceding lesion	350	0.9857	Not significant

* Dependent factor = thickness.

Multiple Regression Analysis. A stepwise multiple regression analysis was performed on the 12 variables (Table 1) that were found to correlate with thickness in order to determine which had the most influential relationships to lesion thickness. Six of the twelve factors proved to be independently predictive of thickness, namely, Clark level, elevation, greatest diameter of the lesion, ulceration, stage (histologic), and age of patient. The resulting model using these six variables was able to explain the distribution of thicknesses of these lesions to a degree of 59%.

DISCUSSION

A significant direct correlation was found between the thickness of superficial spreading malignant melanoma and histologic level (Clark). It is to be expected that, as a lesion progresses to deeper levels anatomically, its thickness increases. That a significant direct correlation was found between the elevation above the surrounding normal skin of the primary melanoma and thickness was also expected, because elevation is a clinical expression of outward expansion of the neoplasm. Thus, a deeper level of penetration into the dermis/subcutis is a correlate of endophytic growth, greater elevation of the lesion is a correlate of exophytic growth, and both are directly related to the thickness of the tumor. Similarly, it is to be expected that sessile and pedunculated lesions are thicker than those which are not.

Our findings indicate that the older the patient, the greater is the thickness of the melanoma. Again, the relationship is significant statistically. A discussion of this finding has appeared in another report.[17] The precise reasons for this correlation are not clear, although several likely explanations are increase in thickness with time; breakdown of immunologic response with aging; and delay in diagnosis in the aged.

Both the greatest and the least diameter of the malignant melanoma correlated with thickness of lesion. This is, of course, a reflection of the growth of these tumors in three dimensions.

Bleeding and ulceration are indications of the disruption of blood vessels and of the integrity of the epidermis overlying a malignant melanoma. Apparently, these phenomena occur more readily in thicker lesions. Whether this is due to greater epidermal penetration by pagetoid cells of superficial spreading malignant melanoma or to greater friability as it enlarges, or both events, remains to be clarified. On multivariate analyses performed by Balch et al.,[4] Eldh,[9] and Day et al.,[24] ulceration was found to be one of few dominant prognostic variables. In a detailed study of the prognostic significance of ulceration on survival rates, Balch[18] reported a survival rate of 80% for non-ulcerated and 55% for ulcerated Stage I malignant melanomas (p = 0.001). For Stage II malignant melanomas the respective rates were 53% and 12% (p = 0.009).

Anatomic location is correlated with thickness. In our series, we found superficial spreading malignant melanomas on the lower limbs to be significantly thicker than those on the head and neck, upper limbs, or trunk.[19]

As anticipated, thickness was also found to be directly correlated with the clinical and histologic stage of a malignant melanoma. That is, patients in Stage I (primary melanomas only without detectable regional adenopathy) had, in general, thinner lesions than those in Stage II (regional lymph-node metastases).

As a group, malignant melanomas of the superficial spreading type that were associated with satellitosis were significantly thicker than those that did not have this clinical manifestation. Satellitosis is a sign of advancing disease and, therefore, its association with thicker lesions is to be expected.

Although there was a trend in the direction of a direct correlation of in-transit metastases and tumor thickness, the association was not found to be statistically significant (p = 0.18). This lack of statistically significant correlation may be due to the relative rarity of the clinical phenomenon of in-transit metastases at the time our patients were first examined by us. There were only four such patients in our series.

One would expect there would be a correlation between the thickness and the stated duration of the malignant melanoma. This was not found in our data (p = 0.58). In all probability the apparent lack of correlation is principally due to the inability on the part of patients to recall with accuracy the date of onset of their lesions. It is likely that the durations of the lesions related by many patients are unreliable. Not infrequently, by reviewing photographs taken years before patients recalled having lesions, pre-existence of a pigmented lesion at the site of the eventual development of a malignant melanoma was identified.[20]

The sex of patients in our study did not correlate with thickness of the primary superficial spreading malignant melanoma. We thought that men would have thicker lesions because they are known to have, in general, poorer prognoses than women. Shaw et al.,[6] however, reporting from Australia, found that the average thickness of lesions in women was significantly less than in men. Furthermore, in both men and women, these authors reported a direct correlation between five-year survival rate and thickness of the melanomas in their series of cases, but women had a higher survival rate than men at each thickness level. We are at a loss to explain our inability to verify the findings of Shaw and her colleagues. Perhaps the malignant melanomas seen in Australia in a predomi-

nantly Anglo-Saxon population living in a semitropical environment that has intense sunshine behave in a biologically different way from those in the New York City area.

The presence or absence of a history of a previous malignant melanoma did not correlate with thickness of melanoma. One would think that a second primary melanoma would be recognized early, and when thinner, by a patient who had a previous malignant melanoma or by his physician in follow-up. In this study, however, the small size of samples (two cases) could explain failure to find a significant relationship.

Whether or not a superficial spreading malignant melanoma arose in a previously existing lesion (by clinical history) was not found to be relevant to thickness of the neoplasm. Again, much more study is required to see if the biologic behavior of malignant melanomas of the same thickness arising in nevocytic nevi differs from those that begin de novo.

When the 12 variables that were found to correlate with thickness of superficial spreading melanoma were subjected to multiple regression analysis, only six proved to be significantly predictive, namely, level, elevation, diameter, ulceration, histologic stage, and age of the patient (Table 2). In Table 3 we summarize previously published data in which multifactorial analyses were performed. As can be seen, although there is considerable overlap in the variables found to be of predictive value, some variables appear only intermittently in these studies. These differences in results may be explained in part by the choice of the dependent variable used in each of these studies (e.g., five-year survival; five-year disease-free survival; thickness). Perhaps it is time for the different groups studying malignant melanomas to standardize their data bases so that intergroup comparisons may be possible in order to determine if the seemingly disparate findings are real and, if so, the reasons for the differences. In this way important regional variations in the biologic behavior of malignant melanomas may be discernible in geographically separated areas.

Table 2
Subset of Variables Most Predictive of Thickness Based on Multifactorial Analysis ($N = 348$)*

Factor	p
Level	<0.0001
Elevation of lesion	<0.001
Largest diameter of lesion	<0.0001
Ulceration	0.011
Histologic stage	0.047
Age of patient	0.053

* $p < 0.001$; adjusted $R^2 = 0.5897$.

Table 3
Present and Previously Published Multivariate Analyses of Factors Predicting Thickness or Outcome of Malignant Melanomas

Authors	Dependent Variable	Factors Analyzed	Factors Significantly Predictive
Balch et al.[4]	Five-year survival rates for clinical and histologic Stages I and II	Histologic stage Ulceration Surgical treatment Thickness Location Age Sex Level Pigmentation Lymphocytic infiltration Growth pattern Regression	Histologic stage Ulceration Surgical treatment Thickness Location
Larsen and Grude[21]	Five-year survival rate for clinical Stage I	Level Age Location Mitotic count Sex Vascular invasion Pigmentation Lymphocytic infiltration Ulceration Cell type Cellular atypia Solar elastosis	A. *For all types of melanomas* Level Age Sex Location (trunk) Pigmentation Lymphocytic infiltrate Ulceration B. *For superficial spreading melanomas only* Level Mitotic count Location (trunk) Location (foot) C. *For nodular melanomas only* Level Age Vascular invasion Location (trunk)
Cohen et al.[22]	Ten-year survival rates for clinical and histologic Stages I and II	Number of lymph nodes histologically involved Lymph node palpability Primary site Level (Clark) Thickness (Breslow) Sex	Number of lymph nodes histologically involved Lymph node palpability Primary site

Table 3 (*Continued*)

Authors	Dependent Variable	Factors Analyzed	Factors Significantly Predictive
Balch et al.[23]	Five-year survival rate for histologic Stage II	Number of metastatic nodes Ulceration Location Age Sex Remission duration Thickness Growth pattern Level Lymphocytic infiltrate Pigmentation	Number of metastatic nodes Ulceration
Day et al.[24]	Five-year disease-free survival rate for clinical Stage I (hand—posterior arm vs. forearm—anterior arm)	Thickness Histologic ulceration Sex Age Location Surgical treatment Histologic type Level Lymphatic invasion Histologic regression Mitoses/mm² Pathologic stage	Thickness Histologic ulceration
Day et al.[25]	Five-year disease-free survival for patients with nodal metastases (high-risk vs. low-risk groups)	Thickness Percentage of positive nodes Lymphocytic response Sex Age Location of primary tumor Adjuvant therapy Histologic type Level Lymphatic invasion Histologic regression Ulceration Mitoses/mm² Node metastases size (mm²) Node percentage	Thickness Percentage of positive nodes Lymphocytic response

Table 3 (*Continued*)

Authors	Dependent Variable	Factors Analyzed	Factors Significantly Predictive
Cascinelli et al.[26]	Five-year survival (Stage I)	Thickness Sex Diameter Elevation Level Type	Thickness Sex
Present study	Thickness (Breslow) for clinical and histologic Stages I and II superficial spreading malignant melanoma	Level Elevation Largest diameter Ulceration Stage (histologic) Age Least diameter Bleeding Location Pedunculation Stage (at entry) Satellitosis	Level Elevation Largest diameter Ulceration Stage (histologic) Age

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