Malignant Melanoma: Risk Appraisal Considerations

Hank George, FALU, CLU, FLMI
Manager of New Business Underwriting
Northwestern Mutual Life

There are more than 17,000 cases of malignant melanoma in the United States each year. The incidence has been rising at an annual rate of 3-7% over the last decade, has doubled in twenty years, and is now twice that of Hodgkin's disease.

Looking beyond these figures, some further observations on the impact of malignant melanoma catch our attention:

1. It has been estimated that surgeons would have to excise 250,000 pigmented nevi to discover one unsuspected melanoma. On the other hand, this "hit rate" is greatly improved by removing nevi arising in patients with the Dysplastic Nevus Syndrome (see below).
2. Ten percent (10%) of all melanomas arise in melanoma-prone families.
3. Given that one has had a melanoma, the risk of developing a second is 900 times greater than the likelihood of that first tumor.
4. The incidence of so-called "low risk" melanoma (i.e., a thin lesion with a favorable prognosis) is rising and may now exceed 50% of all cases.

This paper is limited to cutaneous malignant melanoma and its precursors. These are melanomas derived from neoplastic melanocytes arising in the basilar region of the epidermis. They earn their "cancer" status when they invade the dermis and thereby gain access to routes of metastasis.

This paper will review aspects of the diagnosis, management and prognosis of melanoma, always attempting to relate clinicopathological concepts to the specific problem of assessing insurability.

I. PRECURSORS OF MALIGNANT MELANOMA

A great deal of attention is being focused on two questions. First, are there definite precursors to malignant melanoma? And second, to what extent does heredity play a role in the pathogenesis of melanoma?

There is plentiful evidence that melanomas do arise from various types of pigmented nevi, although the overall incidence of cancerous transformation in most benign pigmented tumors is exceedingly small. Two specific lesions are associated with a notable incidence of later melanoma: the congenital nevus and the dysplastic nevus.

i. Congenital Nevi

We occasionally see applicants with giant nevi. A few of these are huge growths called "bathing trunk" nevi. There is no question about the considerable risk of melanoma arising from such lesions. Since the majority of such later melanomas prove to be fatal, one might be reluctant to accept unoperated giant nevi as an insurable risk.

What about smaller congenital nevi? One percent (1%) of children are born with one or more small congenital nevi. The incidence of malignant change in these lesions is estimated to be at least 1%, perhaps higher.

Since congential nevi of any size may give rise to melanomas, some experts recommend routine removal of congenital nevi greater than one and one half (1.5) centimeters in diameter. Calculating that there are 300 cases of childhood melanoma each year and that 20% arise in congenital nevi, removal of all but the smallest congenital moles would theoretically eliminate 60 melanomas annually, most of which will be fatal.[1]

ii. Dysplastic Nevus Syndrome

The first report of the familial occurrence of melanoma was in 1952. In 1971, Anderson summarized the characteristics of genetically-mediated melanoma and identified factors consistently seen in these cases:[2]

1. Familial melanomas occur at relatively young ages, the average age at diagnosis being 42 years for familial and 49 years for non-familial cases. Familial melanomas before age 30 are not uncommon.
2. Familial patients are prone to multiple melanomas.
3. Patients with familial melanomas have higher survival rates than sporadic cases, but the benefits of indolent tumor behavior are mitigated by the greater risk of additional melanomas in these patients.

Several etiologic factors for familial melanoma have been proposed including autosomal dominant inheritance[3] and a non-genetic sensitizing agent which compromises immunity and predisposes to melanoma formation.[4]

In 1978, Wallace Clark reported on a melanocytic lesion prone to culminate in melanoma.[5] He referred to it as a B-K mole, naming it for two patients who had, between them, seven invasive melanomas. In his original report, Clark told of 25 persons in 6 families who had one or more melanomas. Nine died of metastatic melanoma, leaving no question about the aggressiveness of these neoplasms. Of the 17 patients he examined, 15 had B-K moles. When unaffected family members were examined, 22 of 41 also had B-K moles. And the inspection of these family members also led to the discovery of six unsuspected melanomas. Clark and his co-workers were able to photographically demonstrate the transition from B-K mole to melanoma. Their findings led to the conclusion that patients who have B-K moles are at increased risk for eventually developing one or more melanomas.

Reimer reported on seven melanoma-prone families that same year.[6] B-K moles were present in 18 of the 20 patients and in 24 of 43 first-degree relatives. B-K moles continued to appear in some patients through the seventh decade, a significant factor as we consider insuring applicants with such moles.

Today, B-K moles are usually referred to as dysplastic nevi. Follow-up of melanoma-prone families has demonstrated that patients who develop dysplastic nevi are prone to also get invasive melanomas. This is substantiated not only by Clark's photographic evidence of a nevus-to-melanoma progression but also by the fact that 97% of familial melanomas contain histological residue of dysplastic nevus.[7]

This comparison of the features of common acquired nevi and dysplastic nevi highlights distinctive features of the latter:

	Acquired Nevi	Dysplastic Nevi
Number	15/25	1/100+
Size	<5 mm.	5 – 10 mm/larger
Outline	Regular	Irregular
Color	Uniform	Variegated
Depigmented areas	No	Often
Atypical Melanocytes	No	Yes
Lower extremities	Rare	Common

A survey of reinsurers by this author in 1983 included questions dealing with the Dysplastic Nevus Syndrome. Of ten respondents, only two had a specific practice for underwriting dysplastic nevi. Both took all cases at standard rates.

Is an applicant who has had a dysplastic nevus a standard risk? Should it matter if this was an apparent isolated (sporadic) lesion or if other family members have had dysplastic nevi/melanomas? The answer to these and other questions remain unclear.

A National Institute of Health (NIH) Consensus Conference on Melanoma Precursors convened in October, 1983. As one of the panelists, this author was impressed by the disturbing evidence presented by melanoma experts on the risk of invasive melanoma in Dysplastic Nevus Syndrome. Interested students are referred to the NIH Concensus Statement for the details of that conference and panelists' conclusions.

II. SYMPTOMS SUGGESTING MELANOMA IN A NEVUS

The signs of cancer in a pigmented nevus are important to underwriters because it is not uncommon for examiners to note suspicious nevi, leaving us wondering whether to accept the risk or postpone for a biopsy. The traditional criteria for cancerous change in a mole are inadequate if we expect to discover melanomas at an early and readily curable stage.

If a patient holds off seeking medical advice until an enlarging mole has begun to bleed, ulcerate or feel tender, the likelihood of a low risk melanoma is diminished. Wick studied the relationship of presenting symptoms to the Clark level of the tumor. He found that Level II tumors seldom showed the classic signs of bleeding, ulceration and tenderness. Only 10% of Level II patients noticed bleeding and 4% of Level II tumors were ulcerated.[8]

Deeply invasive, Level V melanomas were frequently associated with bleeding. Tenderness was twice as common at Level V as Level II and ulceration was present in four of ten Level V lesions. As melanoma depth moved from Level II to Level V, elevated tumors were much more common. Elevation is a sign of vertical growth, a phase in the evolution of a melanoma which leads to deep invasion and metastases.

Sober and his coworkers reported similiar findings. Enlargement and color change in pigmented nevi heralded early, minimally-invasive melanomas. Elevation, bleed, ulceration, tenderness and itching were more likely to be present in thick, deeply-invasive melanomas.[9]

Malignant lesions often have combinations of color including shades of tan, brown and black, intermingled with hues of red, white and blue, in contrast to the uniform coloration of benign nevi. Intensely blue-black areas may mark deep penetration by tumor cells.

The shape of a suspicious mole is important. Benign nevi have regular borders; dysplastic nevi and melanomas usually have irregular perimeters with indentation or notching. Such a contour in an enlarging nevus is very suggestive of melanoma.

III. VARIETIES OF MELANOMA

There are four basic types of cutaneous melanoma: superficial-spreading, nodular, lentigo maligna and acral lentiginous. Each is distinct in terms of its natural history and prognosis.

i. Superficial Spreading Melanoma (SSM)

Superficial spreading melanoma is by far the most common form of melanoma in caucasians. It represents 80% of all melanomas.

The growth pattern of superficial spreading melanoma has direct implications for its prognosis. There are two distinct growth phases. The first is the radial phase. In it, cancer cells migrate upward into the epidermis, inward toward the dermis and spread laterally within the junction of the dermis and epidermis. Two of these initiatives are blunted. The cells moving into the epidermis scale off. Those which penetrate the dermis fall prey to host scavenger cells. Thus, the dominant growth pattern in the radial phase is represented by the cells which spread out radially at the junction of the dermis and epidermis.

After the radial phase has persisted for months to several years, a change takes place which involves the direction of tumor growth. It now becomes perpendicular to the earlier radial phase. This is called the vertical phase, which leads directly to invasion of the remaining portions of the dermis and, later, underlying subcutaneous fat. The vertical phase puts the tumor in abundant contact with lymphatics and blood vessels, increasing the likelihood of metastasis. Vertical growth is also more rapid than radial growth, often evolving over several months.

Superficial spreading melanomas in their radial growth phase are discovered at Level II. Once the lesion has progressed to Level III or deeper, vertical growth has begun. This helps to explain why prognosis is favorable in Level II but becomes progressively worse at Levels III, IV and V.

ii. Nodular Melanoma (NM)

The second most common variety of melanoma is nodular melanoma. It accounts for 15% of melanomas and differs from SSM in several ways. Most important, there is no radial growth phase. Instead, nodular melanoma begins with invasion of the dermis. Most NM's will have invaded the reticular dermis or underlying fat by the time they are discovered.

Nodular melanomas are prone to arise on the back, head and neck. As fate would have it, they occur twice as often in men as in women.

Occasionally, nodular melanomas lack pigment and are dubbed "amelanotic." If all one is told about a melanoma is that it is amelanotic, one can be relatively sure it was nodular.

The prognosis in nodular melanoma is less favorable than in superficial spreading. Since this is largely a function of deep invasion and high proportion of advanced tumors, distinct underwriting criteria for nodular melanoma are not necessary. The key is to rate melanoma risks according to the thickness and/or depth of invasion of the tumor (see below).

iii. Lentigo Maligna Melanoma (LMM)

The definition of lentigo maligna melanoma must begin with a point of clarification: Lentigo maligna is <u>not</u> the same as lentigo maligna melanoma. The former is precancerous; the latter <u>is</u> cancer.

Lentigo malinas used to be called "Hutchinson's Freckles." Another way of describing these tumors is to think of them as the "solar keratoses of melanocytes." Clinically, they appear as brown or tan macular lesions resembling grown freckles. There is usually a history of slow enlargement over a decade or longer.

Lentigo malignas may remain non-invasive or undergo malignant transformation. Cancerous change begins with a radial growth phase in the papillary dermis, roughly equivalent to a Level II superficial spreading tumor. Once the lesion becomes invasive, its name changes to lentigo maligna melanoma. Now, we are dealing with a potentially lethal cancer.

The radial phase in LMM may persist for years but will eventually be followed by vertical growth capable of deeply invading the dermis. Most lentigo maligna melanomas are diagnosed early, however, and this accounts for their favorable overall prognosis.

Lentigo maligna melanomas are not a major risk selection problem because the median age at diagnosis is 70. The main point is to be clear about the distinction between the <u>innocent</u> lentigo maligna and the <u>invasive</u> lentigo maligna melanoma.

iv. Acral Lentiginous Melanoma (ALM)

Acral lentiginous melanoma is the newest melanoma variety to be agreed to by pathologists. Virtually all arise from the palms and soles or under the fingernail beds, so one tends to think of them as being distinct for these sites. This is not true. Superficial spreading and nodular melanomas can also arise on the soles and palms. The term "acral

lentiginous" is a histological distinction, not an anatomic reference point.

ALM begins with a radial phase, similar to SSM. This gives way to rapid, sometimes explosive vertical growth with deep invasion and early matastases. For this reason, overall prognosis is as bad as nodular melanoma. Also, late detection jeopardizes survival in ALM. Early lesions in their radial phase may look like brown or black stains rather than tumors, so patients do not seek care promptly.

In one series, 71% of ALM's arose on the soles. The second leading site was the fingernail bed. Plantar (sole) tumors had the best survival but prognosis depended more on level, thickness and whether or not there were metastases, than on the fact that the lesion happened to arise at one site or another.[10] When considering thickness as a prognostic guide, remember that the soles and palms are thick. This can directly influence tumor thickness measurements. A one millimeter ALM on the sole or palm is a thin lesion, equivalent to 0.75 mm elsewhere.[11]

IV. MELANOMA PROGNOSIS: GENERAL FACTORS

These are the main variables which have been identified as influencing prognosis is malignant melanoma:

1. Stage.
2. Level of invasion.
3. Measured thickness.
4. Location.
5. Sex.
6. Age.
7. Mitotic rate.
8. Degree of inflammatory response.
9. Ulceration.
10. Vascular invasion.
11. Cell type.
12. Regression within the tumor.
13. Whether or not surgery was limited to excision or included lymph node dissection (lymphadenectomy).

We will review the most important of these factors in detail, citing evidence to put each in perspective. All of this is intended to help sort melanoma patients as risks by trying to identify measurable factors which have a bearing on whether the policy is apt to be settled as an early claim or eventually pay a retirement income.

There have been many detailed prognostic assessments of melanoma. One of the best was by Charles M. Balch and his associates, published in Annals of Surgery in December, 1978[12]. The Balch study presents a comprehensive analysis of prognostic variables. Of thirteen factors identified, five were found to independently impact survival:

1. Measured thickness.
2. Pathological stage.
3. Ulceration.
4. Whether surgery was limited to wide excision or included a node dissection.
5. Location (that is, upper extremities vs. lower extremities vs. trunk vs. head and neck).

Balch's report (and nearly all others) conclude that measured thickness is the most important single factor in melanoma prognosis.

i. Level of Invasion and Measured Thickness

Wallace Clark is the father of a microstaging system which separates melanomas according to their levels of penetration into the dermis and subcutis. The following five levels are described:

Clark Level	Depth of invasion
I	Confined to epidermis (in-situ)
II	Into papillary dermis
III	Filling papillary dermis
IV	Into reticular dermis
V	Into subcutaneous fat

A Level I lesion is NOT a true invasive melanoma. It is confined to the epidermis and has no routes of metastasis. Level I is melanoma in-situ. It is now called "atypical melanocytic hyperplasia" rather than Level I melanoma. It represents no extra mortality risk when, as an isolated lesion, it has been fully excised and carefully studied by a pathologist.

The medical literature abounds with reports of survival based on level of invasion. This paper uses figures from two studies which show that Level II has a favorable outlook and also that prognosis progressively worsens at deeper levels:[13, 14]

5 Year Survival

Level	Sober (1979)	Van Der Esch (1981)
II	93%	91.4%
III	74	76.4
IV	63	67.3
IV	39	58.6

ii. Measured Thickness

Measured thickness is the most reliable prognostic criterion in malignant melanoma. The actual thickness is calculated by the pathologist using an ocular micrometer.

Although criteria for thickness were defined by Breslow a decade ago, it is only recently that we have consistently seen measured thickness reported on pathology reports. For this reason, it is not surprising that four of the ten reinsurers who

responded to this author's 1983 survey indicated they had no selection criteria based on thickness.

Breslow described five categories of thickness. These are his breakdowns, along with the survival data cited in his report:[15]

Thickness (Millimeters)	5 Year Survival
<0.76 MM	100%
0.76 - 1.50	74
1.51 - 2.25	79
2.26 - 3.00	44
>3.00 MM	22

Breslow found that his cases involving thin melanomas (i.e., lesions less than three-quarters of a millimeter in thickness) were cured. Conversely, thick tumors were associated with metastases and death.

Balch reported thickness-mediated survival figures in 1978. As in Breslow's study, tumors less than 0.76 millimeters were associated with disease-free survival:[16]

Thickness	5 Year (N.E.D.*) Survival
<0.76 MM	100%
0.76 - 1.49	66
1.50 - 2.25	69
2.26 - 3.00	37
>3.0 MM	23

*N.E.D. = No Evidence of Disease

More recently, researchers have redefined "thin" lesions to include melanomas up to 0.85 mm. Day and his associates, reporting in the New England Journal had virtually 100% 8-year survival where melanomas were less than 0.85 mm.[17]

Among lesions in the 0.85 mm to 1.69 mm category, most metastases arise from melanomas located in the BANS anatomic distribution. BANS stands for upper back, posterolateral arm, posterior and lateral neck and posterior scalp.

Which is the better risk selection criterion: level of invasion or measured thickness? Consider the following reports:

Balch reports on the various levels of invasion present in each of four thickness categories, with these results:

	Level of Invasions				
Thickness	II	III	IV	V	
0.76 or less	65%	28%	7%	0%	= 100%
0.76 - 1.49	16	51	33	0	= 100
1.50 - 4.00	3	39	46	12	= 100
4.00 or more	0	11	45	43	= 100

Seven percent (7%) of "thin" melanomas had invaded the reticular dermis and were reported as Level IV. Undoubtedly, these arose at sites where the dermis is thin and the demaraction between the papillary dermis and the reticular dermis is poorly defined.

Conversely, 3% in the 1.50 to 4.00 mm category were at Level II. Should one take them at the same rating one would charge a thin Level II? The distribution of levels at any thickness is broad. It is not safe, therefore, to assume we are doing adequate rating if we do it solely according to level of invasion.[18]

Balch reported thickness survival data broken down by level. These are his figures for levels III and IV:

Level	Thickness	5-Year Survival
III	<0.76 MM	100%
	0.76 - 1.49	71
	1.50 - 3.99	65
IV	0.76 - 1.49	76%
	1.50 - 3.99	67
	>3.99 MM	25

There are marked differences in survival in Levels III and IV based on thickness.[19]

One final note on measured thickness. It has been shown that frozen sections overstate thickness, as compared to permanent sections. On average, lesions appear to be from 0.1 to 0.4 mm thicker on frozen sections.[20] If one is assessing a borderline melanoma close to falling into a more or less favorable category, consider an adjustment for thickness if only a frozen section pathology report is available.

iii. Sex, Site and Survival

Virtually every prognostic study on malignant melanoma has shown higher survival for women as compared to men. Although there are probably several reasons for this advantage, the main factor appears directly related to the location of the tumor. Women have more extremity melanomas, whereas men are apt to develop these cancers on the trunk.

When relating survival to sex and tumor location, Weidner found superior survival among women was present only during the first four years after treatment. Thereafter, survival rates in remaining patients ran nearly parallel on the basis of sex. Weidner concluded that prognostic differences between sexes with comparably deep tumors depended on tumor site. He found no evidence for sex-specific factors in the behavior of melanoma. His report showed the following eight-year survival rates by location:[21]

Site	8-Year Survival
Upper Extremity	60.7%
Lower Extremity	62.7
Trunk	40.3
Head and Neck	52.8

Because women have more extremity lesions, they do much better in terms of survival. However, at any one site, Weidner found no significant sex-related differences in survival.

Balch's statistical analysis showed similar results. Upper extremity lesions were statistically superior in terms of survival to lesions of the head, neck or trunk. Because Balch found 70% of melanomas in men arose on the trunk and 79% of melanomas in women arose on extremities, women would be expected to have a distinct prognostic advantage.[22]

A third investigator looked at this apparent female superiority in survival and found that when one compares men to women at a specific location, women still came out ahead. In a paper published in 1980, Shaw and co-workers reported the following figures regarding extremity lesions:[22]

EXTREMITY MELANOMA

	Men	Women
% Lesions at extremity site	31.5%	65.7%
Overall 5-yr. Survival	71.6	85.0
% < 1.50 MM	45.6	61.6
5-yr. Survival ≤ 1.50 mm	85.7	96.8
5-yr. Survival > 1.50 mm	61.3	70.5

Five-year survival in extremity lesions was better in women as was the proportion of thin lesions.

Shaw also reported the following:

1. Sixty-eight percent (68%) of female melanomas arose prior to age 50, comparing to 57% in men.
2. Under age 50, women have many more thin lesions (42.8%) than men (32.9%).
3. Premenopausal women have a distinct survival advantage over men. This appears to be lost after menopause, raising the question about some barrier to metastasis in premenopausal females.
4. Women also did better than men with melanomas that had metastasized to lymph nodes.

Other reports by anatomical site support the conclusions of Weidner and Balch. Most of the female advantage seems to be due to the fact that women have more melanomas at favorable sites. It also appears women are diagnosed earlier and have more thin lesions. From an underwriting point of view, it may be appropriate to give favorable consideration to female applicants under age 50 who have had thin and/or extremity melanomas.

One additional factor regarding location and prognosis relates to lesions in the BANS distribution. As noted above, BANS refers to upper back, posterolateral arm, posterior and lateral neck and posterior scalp. The following figures, reported by Day and his associates in 1982, show the probability of death from Stage I melanoma in the first 7½ years after diagnosis. Thickness is a key factor but most of the deaths in tumors less than 1.70 mm occurred in melanomas arising at BANS sites. These statistics reflect life-table analyses of 598 patients.[24]

Probability of Death
7½ Years after Diagnosis

Thickness	Non-BANS Extremities*	Non-BANS Head-Neck	Non-BANS Trunk	BANS Areas
0.85 MM	0	0	0	2
0.85 - 1.69	0	0	3	22
1.70 - 3.64	14	36	23	42
3.64 MM	17	35	78	67

*Excludes hands and feet

iv. Additional Prognosis Factors

Four additional factors might be considered in assessing melanoma prognosis: (1) the degree of mitotic activity, (2) whether or not ulceration is present, (3) the specific melanoma cell type and, in lesions of intermediate thickness, (4) whether or not a lymph node dissection was performed. None is as important as thickness or level of invasion, but when forced to make "yes/no" decisions on recent melanoma cases, we may take a measure of comfort if some or all of these additional factors are favorable.

v. Mitotic Activity

In 1978, Schmoeckel and Braun-Falco attempted to devise a melanoma prognostic index. They looked at the relationship of mitotic activity (number of cell divisions seen by the pathologist) to the incidence of metastatic disease. They found that when mitotic activity was increased, so was the likelihood of metastases. Their index linked mitoses to thickness. By their definition, the index is the product of thickness times mitotic rate. Once this exceeds 12, the probability of metastasis is quite high.[25] A World Health Organization melanoma study also found a correlation between mitoses and survival. According to its figures, when significant mitotic activity was not present, five-year survival was 81%. This dropped to 44% with large numbers of mitoses.[26] Similarly, a study of acral lentiginous melanoma revealed the degree of mitotic activity to be a key factor in predicting survival.[27]

There is, however, another side to the mitotic activity

question. The majority of studies have failed to establish a statistically significant relationship between mitoses and survival. One should not consider high mitotic rates in melanomas as ominous as in soft tissue sarcomas, but it could be a factor influencing a decision on a borderline risk.

vi. Ulceration

Evidence of ulceration on microscopic analysis has been reported as a risk adverse factor by nearly every investigator. In the WHO study, five-year survival in the absence of ulceration was 79.8%. It dropped to 52.8% when ulceration was present.[28] In Balch's study, the results were similar. With ulceration, there was 52% five-year survival; without, survival rose to 77%.[29]

The best reason to relegate ulceration to auxiliary prognostic status is that it tends to correlate with thickness. Ulceration is more common in lesions thicker than three millimeters than it is in thinner melanomas. Still, in one report 12.5% of melanomas measured at less than 0.76 mm did show ulceration.[30] On balance, if ulceration is reported by the pathologist, it probably makes the case worse overall.

vii. Cell Type

There are two basic types of cells in melanoma: spindle and epithelioid. In some lesions, the pattern is mixed and both are present. Investigators have found it is better to have spindle cells than epithelioid cells. They exhibit less biological aggressiveness and so, melanomas made up of spindle cells are associated with more favorable prognoses.[31]

Looking at it from the other side, a predominantly epithelioid pattern is less desirable. A regression analysis of 205 cases showed the epithelioid cell type to be one of six important adverse risk factors.[32] Overall, cell pattern is a much more important consideration in the prognosis of choroidal melanomas than it is in their cutaneous cousins. It is another of those factors one might consider in underwriting a borderline case.

viii. Elective Lymph Node Dissection

The last of these supplemental risk factors happens to be a somewhat debated topic. This is the value of elective lymph node dissection in patients with clinically negative nodes. There seems to be a consensus against lymphadenectomy in thin, minimally invasive lesions. Conversely, if the primary is thick and deeply invasive, node dissection might not make any difference in the outcome. This leaves open the question of the value of surgical attack on nodes in tumors of intermediate thickness and moderately favorable prognosis.

One study showed that elective dissection confers its main advantage on patients with lesions 1.5 mm to 4.0 mm thick. Balch, Murad and co-workers compared intermediate melanomas treated by wide excision only to those which also had lymph node removal. The comparsion is based on the incidence of distant metastasis after five and eight years. The results are dramatic:[33]

Incidence of Metastasis

	Wide Excision & L. N. Dissection	Wide Excision Only
5 Years	15%	78%
8 Years	16%	86%

Ariel's analysis of Stage I melanomas of the lower extremity also shows an advantage to elective node dissection. At 10 years, survival was 49% where dissection was done but only 32% where treatment was limited to wide excision only.[34] Other authors have reported similar results on lesions of intermediate thickness and then, there have been studies which have failed to give any advantage to lymph node dissection. One may be inclined to put aside lymph node removal as a prognostic consideration because overall results have been equivocal. In consideration of the Balch/Murad findings, however, it seems realistic to stir them into our pot. We might be more comfortable accepting borderline thickness melanomas in the early years if negative node dissection can be confirmed.

V. IS METASTATIC MELANOMA EVER INSURABLE?

Melanomas with systemic metastases have dismal prognoses. But long-term, disease-free survival is not rare in cases where metastases involve only a few regional lymph nodes.

A point of clarification on staging terminology is in order. When node metastases are present in melanoma, the disease is said to be in Stage III in most staging systems. Stage II is reserved for local recurrence and/or peripheral cutaneous tumor nodules (sometimes called satellites) proximal to the primary tumor.

Day and his workers identify low risk cases with node metastases by the following criteria:

1. Measured thickness of the primary tumor less than 3.50 mm.
2. Moderate to marked inflammatory response.
3. Less than 6 mitoses per cubic mm.
4. Less than 4 nodes with metastases.

They found that when all four criteria were present, 80% of patients survived five years.[35]

From an underwriting perspective, accepting up to three positive nodes may be too generous. Balch

studied 185 cases with node metastasis and found two factors affecting prognosis: the number of involved nodes and the presence/absence of ulceration.

When only one node contained metastases, 58% of patients were alive at five years and 40% at ten years. With 2-4 nodes invaded, five-year survival dropped to 27% and ten-year survivors numbered just 15%. Looking at the results closely, survival curves tend to level off after ten years, suggesting that ten-year survival may be tantamount to cure. Balch found that stage III (nodal metastasis) patients with ulceration present had a 15% five-year survival. Without ulceration, 30% survived sixty months.[36]

A UCLA study identified three factors predicting long survival in melanoma metastatic to nodes: the number of involved nodes, the thickness of the primary and ulceration. Overall survival was 55% at two years, 37% at five years, and 33% at ten years and there was little drop in survival between the fifth and tenth years. The study also showed 45% five-year survival with fewer than three nodes involved. This dropped to 21% with more than four nodes.

Thickness of the primary tumor was a major prognostic factor in the UCLA report. When it was less than one millimeter thick, five-year survival was 62%. Between one and three millimeters, survival dropped to 46%. In the range of three to four millimeters, survival was just 31% after five years. There were no five-year survivors in primaries thicker than four millimeters.

Ulceration was an unfavorable finding (34% five-year survival) when compared to non-ulcerated cases (47% alive at five years). In addition, the UCLA study failed to demonstrate any value for age, sex, level of invasion, number of mitotic figures or the presence of satellite lesions in terms of influencing survival in melanoma with nodal metastases.[37]

In summarizing these and other studies, it appears that malignant melanoma which has spread to regional lymph nodes may be insurable in a few cases. Sorting out risk factors to identify the best cases suggests the following benchmarks for insurability:

1. Metastases in one or two nodes only.
2. Primary tumor less than 3 millimeters thick.
3. Non-ulcerated primary tumor.
4. Evidence of marked inflammatory response, suggesting a strong host immune response.

It is also advisable to require that the primary melanoma be in clinically Stage I prior to the discovery of an unsuspected nodal metastasis. These are the cases where the node dissection is truly elective. When nodes are suspicious because they are enlarged and firm, the likelihood of a substantial tumor burden is greatly increased.

The huge drop-off in survival rates over the first five years after surgery argues for a five-year postponement, measured from completion of treatment, in all Stage III cases. Thereafter, a "healthy" flat extra may be required for another half decade even in the carefully selected cases.

A related question on the matter of insuring metastatic melanoma has to do with cases where the diagnosis was made solely from a lymph node biopsy because no primary tumor was evident. Memorial Sloan-Kettering Hospital has had 166 such cases in 25 years. Seventy-five had only node metastases; the remainder had systemic disease as well. Survival results for "node-only" patients differ markedly depending on whether or not a prompt lymphadenectomy was performed. If node surgery was undertaken within three months, 65% were alive at five years and 56.7% remained well at ten years. In contrast, where intervention was delayed more than three months, only 18.3% of the patients survived five years. All those who did make it five years, however, remained disease-free for the next half decade as well.[38]

VI. HOW LATE DOES MELANOMA RECUR?

Certain malignant neoplasms are prone to very late recurrence, sometimes two decades after treatment has rendered the patient free of apparent disease. Infiltrating ductal breast cancer and adenoid cystic carcinoma belong in this group. Intraocular melanomas arising in the choriod fall into this category as well. What about cutaneous malignant melanoma?

A study by Epstein and Bragg followed 193 cases of Stage I melanoma for 25 years. They found the probability of fatal relapse after ten years to be quite small. After 15 years, there were no relapses. All things considered, it is probably reasonable to stop rating even marginally insurable cases by the tenth year after diagnosis and treatment.[39]

VII. THE "PROBLEM" OF THE THIN REGRESSING MELANOMA

In 1978, Gromat, Epstein and Blois published a review of 121 cases, contrasting melanomas with foci of so-called regression to others without regression. All of the melanomas were thin lesions with overall favorable prognoses due to minimal invasion.

Regression is defined as areas within a melanoma which appears as pale or white. Histologically, they consist only of connective tissue, lymphocytes and other non-tumor cells. Cancer cells have been eliminated, presumably as a result of host immune/phagocytic responses.

There were 23 thin melanomas in the Gromat Study which showed regression. Five metastasized. In contrast, only two of 98 thin lesions without regressed areas developed metastases. Because of this difference, a question was raised about the risk to patients with thin melanomas who have definite areas of regression.[40]

Subsequent studies have failed to substantiate these findings. Thau studied 41 thin lesions, all exhibiting regression. Only one metastasized. And he followed his cases nearly twice as long (43 months) as Gromat (23 months).[41] Balch reported regression in 17 of 170 lesions. Like Thau, he did not find regression to be significant in predicting metastasis.[42]

Research has shown that regression is a common late event in the radial growth phase of superficial spreading melanoma. Given this, it is logical that if any thin lesions give off metastases, it will probably be those discovered just as they are beginning to invade deeply (i.e., at the very onset of vertical growth).

It does not appear necessary to consider regression an important factor in underwriting the risk in melanoma cases, except perhaps when we are dealing with the lesion in the upper limits of the "thin" category (e.g., one millimeter thick). In such cases, one might consider a lesion with regression best slotted in the next (higher) rating category.

VIII. WHAT'S NEW IN MELANOMA TREATMENT?

As far as the vast majority of melanoma cases are concerned, there have been no advances in therapy which have directly led to major improvements in cure rates or long-term survival. Nonetheless, observations about immunotherapy, radiotherapy and isolation perfusion chemotherapy are relevant to our risk appraisal problem.

i. Immunotherapy

Immunotherapy is not new. In fact, it has been around for more than a decade and has been used in various oncological settings. It may be given prophylactically as a surgical adjuvant in high risk cases or be administered after a local recurrence (Stage II). More recently, it has been combined with the drug DTIC as chemoimmunotherapy. The main immune-stimulating agent used in melanoma is BCG (bacillus Calmette-Guerin), administered primarily by intradermal injection. It has produced some desirable results, most notably shrinkage of local tumors. Overall, however, BCG therapy has had little effect on survival.

One recent success with adjuvant immunotherapy may help to make more high risk patients into insurance candidates. One hundred patients with primaries thicker than one millimeter were given transfer factor post-operatively. Transfer factor is an extract of white blood cells capable of evoking delayed hypersensitivity. It has been successful as an immune potentiating agent specific for cell-mediated immunity. Of 100 melanoma patients given transfer factor therapy, 90% survived disease-free for five years. Forty-six other patients who had surgery only did not fare as well, having a relapse-free survival rate of 63% at five years.[43]

ii. Radiotherapy

Therapeutic irradiation has long been considered a waste of time in treating melanoma. Today, radiation therapy is being used to aggressively treat some high risk patients. It is used as a surgical adjuvant, following wide excision. Melanomas of the head and neck appear to be particularly responsive to such therapy.

A report from Princess Margaret Hospital in Toronto puts this in perspective. Johanson and his colleagues administered radiotherapy to nodular melanoma patients. Although long-term survival data is inconclusive, complete remissions were realized in some patients with recurrent or residual disease following surgery.[44]

iii. Hyperthermic Isolation Perfusion

The overall results of chemotherapy in melanoma have been very poor. From an underwriting point view, a melanoma patient treated with chemotherapy is unlikely to be acceptable for insurance. There is, however, one possible exception.

Hyperthermic isolation perfusion is a technique for delivering large quantities of anti-tumor drug into direct battle with cancer cells. The therapist infuses heated phenylalanine mustard (L-PAM, Melphalan) into an extremity harboring melanoma. The extremity has been isolated from systemic circulation with a tourniquet, permitting an otherwise lethal dose of this alkylating agent to overwhelm local tumor cells.

Isolation perfusion is used on advanced limb melanomas and on patients with Stage II disease having recurrent nodules or satellite tumors. The latter may be candidates for insurance if they remain disease-free following this therapy and careful follow-up for five years or longer.

IX. TUMOR MARKERS FOR MELANOMA

Assaying tumor markers is rapidly becoming an integral part in the early diagnosis and/or post-treatment surveillance of various cancers. The contributions of CEA, chorionic gonadotrophin (hCG) and alpha fetoprotein (AFP) to the management of colon and testicular cancers are well known.

Two markers have been identified in melanoma. One is lactic dehydrogenase (LDH), an old friend from SMA profiles. The other, gamma-glutamyl transpeptidase, is best known as a screening test for early liver dysfunction and alcoholism.

A report on LDH as a melanoma marker revealed that it gave a clue to recurrence in patients with nodal metastases. LDH began to rise in 12.5% of patients before symptoms or findings materialized. Nearly all patients with rising LDH had liver metastases.[45]

Gamma-glutamyl transpeptidase (GGT) levels were markedly higher in patients with disseminated melanoma than in those who had no identifiable metastases. In patients with widespread disease, the GGT level was 46.5 compared to 10.97 units in patients with a resected primary and no detectable metastatic disease.[46]

It might be appropriate, in view of these findings, to consider a blood profile reporting LDH and/or GGT when working up a jumbo case involving high risk Stage I melanoma or any melanoma with node metastases. There are numerous other causes for elevation of both enzymes, but it may nonetheless be prudent to postpone issuing if either LDH or GGT is significantly above normal in such cases.

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