Malignant Melanoma: A Study of 217 Cases

Part I: Epidemiology

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"A rare and precious gift is the Art of Detachment by which man may so separate himself from a lifelong environment as to take a panoramic view of the conditions under which he has lived and moved; it frees him . . . to see the realities as they are, the shadows as they appear."

—Sir William Osler

Introduction

OSLER's theme of detachment has been applied to the surgery of cancer by Ransom[18] who stated "the experience of a single large department of surgery with a common malady if critically analyzed and recorded in exact detail should be of interest and possibly of use to others because of the fundamental underlying and only slightly varying pattern of (the) disease." This, then, is the thesis of our study: that our experiences with malignant melanoma over a 22-year-period if critically analyzed will be of use in evaluating the worth of our treatments and will, at any rate, be recorded and available for comparison with the reports of our predecessors and with the reports that will follow.

In 1948, DeWeese[7] reported on 93 cases of malignant melanoma treated at this clinic. The period of our study overlaps that of DeWeese; we have concerned ourselves with the 22-year-period of 1932 through 1953. We have recorded in detail certain characteristics of the patient suffering from malignant melanoma together with the mode of treatment in the light of the one definitive criterion acceptable in a study of cancer—the survival of the patient. When appropriate, the data collected have been analyzed statistically, and conclusions, where tenable, have been drawn. By this means of critical statistical analysis it is hoped that the characteristics of the disease will be elucidated and a rational approach to treatment will evolve free from an individual surgeon's philosophy of conservatism or radicalism.

In this report the designation malignant melanoma is favored over the terms melanoblastoma, melanocarcinoma and melanosarcoma.

History

The first written account of melanotic lesions is attributed to Hippocrates (DeCholnoky) in the fifth century before Christ. It was not until the 19th century, however, that melanomas became a common subject of medical writing. Laennec (Handley) and Dupuytren (Stewart) simultaneously published papers in 1806 describing melanotic growths, and in 1836 Carswell[6] first used the term melanoma to designate these pigmented malignant neoplasms. These works were largely descriptive, and it remained for W. S. Handley[10] to discuss the pathology of the tumor and to suggest methods of treatment. His remarkable paper entitled, The Pathology of Melanotic Growths in Relation to their Operative Treatment, was given as a Hunterian Lecture in 1907. Handley compared the mode of spread of cancer of the breast with that of "Melanotic Sarcomas" based on his dissection of a young female subject with disseminated

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melanoma originating on the heel. In this lecture he described the centrifugal permeation of melanoma cells into lymphatics and the blood stream, and advised a wide excision of the primary lesion together with dissection of the regional lymphatics. Handley suggested amputation for malignant melanomas arising on the digits and correctly interpreted enlargement or ulceration of a pre-existing nevus as a stigma of malignant change.

In 1945, Pack[14] proposed excision and lymph node dissection-in-continuity for primary and metastatic melanoma. This was followed, in 1949, by the report of Stewart, Hay and Varco[20] who recorded their observations of 92 cases. They advocated prophylactic node dissections after a two- to four-week waiting period from the time of excision of the primary so that the sieve-effect of the regional nodes could be utilized.

In 1952, Pack[16] and his co-workers reported on 1,190 cases of malignant melanoma treated from 1917 through 1950. Coincident with the adoption of routine node dissections, the five-year cure rates as reported in this series were increased from 10 per cent for the years 1917–1925 to 27 per cent for the years 1941–1945. Pack's report was followed, in 1953, by the work of Meyer and Gumport[12] who also advocated routine prophylactic node dissection and attained a cure rate of over 50 per cent.

Since 1950 many reports have appeared either championing or disclaiming the value of node dissection combined with wide local excision for malignant melanoma. Booher and Pack,[4] Royster and Baker,[19] Chaudry, Hampel and Gorlin[5] have advocated both therapeutic and prophylactic node dissections. Wilson[24] and Vogler[22] and his co-workers, on the other hand, conclude that node dissection does not add to survival and that wide local excision of the primary lesion is the best possible treatment. Nitter[13] and Dickson[8] have indicated that irradiation combined with node dissection may be of value in the treatment of these lesions. Lund and Ihnen,[11] in 1955, analyzed the data obtained from 93 patients suffering from malignant melanoma. They concluded that therapeutic lymph node dissection was of no use and suggested that prophylactic dissection was of value in only a small number of their patients.

Material

The case records of patients with the diagnosis of extraocular malignant melanoma seen or treated in the University of Michigan Medical Center between the dates January 1, 1932 and December 31, 1953 were reviewed. All instances of the diagnosis without histologic confirmation were set aside and not included in this series. Complete follow up of the cases for at least five years was required. The records of 236 patients met these requirements.

Among the 236 cases were 52 patients whose disease did not recur after treatment or who had died from other causes without evidence of recurrence of the melanoma. These 52 cases were reviewed by one pathologist, and 19 cases were discarded as not being malignant melanoma. This left the series numbering 217 cases, culled from 22 years of experience, suitable for the statistical appraisal that was planned in this study.

The 217 cases were divided into two groups: 1) the "treatable" and 2) the "hopeless." The treatable patients were those in whom it was judged that the tumor could be removed by operation at the time of first examination. The treatable patients were further subdivided according to whether they had received "adequate" or "inadequate" treatment. Adequate treatment was arbitrarily defined as wide local excision or amputation *with* or *without* regional lymph node dissection. Regional lymph node dissection will be discussed later; it is enough to say at this point that adequate treatment is considered either 1)

TABLE 1. *Malignant Melanoma—University of Michigan Medical Center 1932 through 1953*

Treatable		121
Adequately treated	88	
Inadequately treated	33	
Hopeless		96
Total		217

excisional or 2) excisional coupled with the more extensive lymphadenectomy.

Patients treated by *local* (and *adequate*) *excision* include all cases where either small or large areas of tissue were locally removed around the primary neoplasm. All amputations fall within this category of treatment when regional lymph node dissection was *not* a part of the operation. Surgical specimens containing the primary lesion and the specimens of local re-excisions were noted to have varied in their dimensions—in some cases to have included an extremity—but their essential similarity is that *none* had included the regional nodal basin. Perhaps this disparity in size of surgical specimens appears too haphazard to allow a simplified classification. It is our opinion that the common feature of *not* embracing the regional lymp nodes defines this large group from the standpoint of treatment as excisional.

"Inadequate treatment" includes all cases where treatment was refused, where quackery was employed (such as unguents, caustics, cancer pastes, etc.), where there was no pathologic control by microscopic section, where biopsy only was performed, and where—without further treatment—there was extension of the lesion microscopically to the edge of the specimen.

"Hopelessness" was established as the condition of the patient when first seen at the University Hospital with malignant melanoma wherein there was evidence of visceral or generalized metastatic disease or the local extent of the tumor was such that operation for total removal was judged to be technically impossible.

Regional metastatic disease in lymph nodes and locally recurrent malignant melanoma were *not* used as criteria for hopelessness when there were no stigmata of incurable disease.

Tabulations and Statistical Appraisal

Our material was drawn from a selected population: the patients who came to the University of Michigan Medical Center. What seems to be true from our own experience may or may not be true were a broader clinical population sampled and submitted to the statistician's method. Nevertheless, we believe our method of inquiry to be valid, and from our study has come some insight into the epidemiology of malignant melanoma.

TABLE 2. *Age and Incidence: Distribution by Age—Treatable Patients (121)*

Age.....	<30	30–39	40–49	50–59	60–69	>70	Total
Men							
Observed	8	7	15	16	17	7	70
Expected*	34.93	10.36	8.96	7.70	5.18	2.87	
$X_5^2 = 67.81$		P<0.01					
Women							
Observed	10	10	9	7	12	3	51
Expected*	25.6	7.85	6.38	5.20	3.57	2.35	
$X_5^2 = 30.92$		P<0.01					
Chi-square to 5 degrees of freedom (P = 0.05) = 11.07							

* From 1950 Distribution of Population State of Michigan.

TABLE 3. *Age and Incidence: Distribution by Age Between Treatable and Hopeless Cases (217)*

Age.....	<30	30–39	40–49	50–59	60–69	>70
Men						
Hopeless— observed	7	14	8	16	13	3
expected	6.98	9.78	10.71	14.9	13.97	4.66
Treatable—observed	8	7	15	16	17	7
expected	8.02	11.22	12.29	17.10	16.03	5.34
Totals	15	21	23	32	30	10
$X_5^2 = 6.09$ P = 0.3						
Women						
Hopeless— observed	3	11	7	7	5	2
expected	5.29	8.55	6.51	5.70	6.92	2.04
Treatable—observed	10	10	9	7	12	3
expected	7.71	12.45	9.49	8.30	10.08	2.96
Totals	13	21	16	14	17	5
$X_5^2 = 4.32$ P = 0.47						

Incidence

Age and Incidence. Table 2 shows the distribution among age groups of the 121 patients entering the University of Michigan Medical Center with treatable malignant melanoma together with the population of the State of Michigan in 1950. The incidence of malignant melanoma is not the same for all age groups, and this is verified by a Chi-square test (Table 2). The peak incidence of malignant melanoma as determined by the heaviest contributor to Chi-square is in the seventh decade of life for both men and women. This same test shows the incidence of the disease to be relatively infrequent in both sexes under 30 years of age. Testing was done to determine if the hopeless cases represented different age groups from the treatable cases. A Chi-square analysis indicated that there is no significant difference in age between the two groups of patients (Table 3).

Sex and Incidence. The effect of sex selection in the incidence of melanoma appeared to be operative in our total series, there being 131 men and 86 women. Analysis shows that such a disparity due to chance alone would occur less than one time in 100 (Table 4). This is based on the weighted average of men and women in the State of Michigan. The same ana-

TABLE 4. *Sex and Incidence: Distribution by Sex*

Entire series	(217)
Men—observed	131
expected*	111.0
Women—observed	86
expected*	106.0
$X_1^2 = 11.77$ P<0.01	
Treatable cases	(121)
Men—observed	70
expected*	61.86
Women—observed	51
expected*	59.14
$X_1^2 = 1.9306$ P = 0.15	
Hopeless cases	(96)
Men—observed	61
expected*	49.08
Women—observed	35
expected*	46.92
$X_1^2 = 5.44$ P = 0.02	

* Expected obtained from 1940 and 1950 State of Michigan population (weighted average 1943). Factors: Men—0.511; Women—0.488.

TABLE 5. *Site and Incidence: Distribution of Malignant Melanoma by Region—Treatable Cases (121)*

Men		
Region	Observed	Expected
Head & Neck	23	4.02
Upper Extremity	8	12.06
Lower Extremity	20	25.46
Torso	16	25.46
Unknown	(3)	—
Totals	67(3)	67.00

$X_3^2 = 95.66$ $P < 0.01$

Women		
Region	Observed	Expected
Head & Neck	13	2.88
Upper Extremity	6	8.64
Lower Extremity	19	18.24
Torso	10	18.24
Unknown	(3)	—
Totals	48(3)	48.00

$X_3^2 = 40.12$ $P < 0.01$

lytical technic was re-applied to the hopeless and treatable groups separately, and the differences of incidence are shown in Table 4. There is statistically significant sex selection in the hopeless group but not in the treatable group, even though the number of men in each group is greater than the number of women. Because statistical significance is based on the size of the sample, it would appear that the effect of sex selection is operative in the incidence of malignant melanoma when the entire series is analyzed. This conclusion is held to be valid from our total series.

Site and Incidence. To see if the distribution of primary sites of malignant melanoma as shown in Table 5 is due to chance alone without a true predilection for site, a Chi-square test was applied. A regional breakdown of surface area of the adult body was made, and the surface areas were expressed in the conventional form of percentages of the whole. Were it true that no pedilection for site exists, then a distribution of primary malignant melanomas over the regional skin surfaces of the body would be the same, and any given percentage of cutaneous area would contribute the same percentage of primary foci of malignant melanoma. This, however, is not what we observed; the Chi-square test very strongly suggests that this cancer has a predilection for arising on the surfaces of the head and neck and that our observed distribution is not due to chance alone. Conversely, the same test indicates that the torso is significantly spared as a site of primary malignant melanoma. This observation is the same for both sexes and for the hopeless as well as the treatable groups (Table 6).

Survival

Age and Survival. We consider here for the first time survival rates. Note that the term *survival* is used and not *cure;* our total knowledge of this cancer is not enough to predict its vagaries, and we must reserve the concept of complete cure.[3] There are some troublesome aspects in making survival analyses which should be discussed. How much, if not all, of our total series of 217 cases should be used in this survival analysis? It is this question that has had to be answered for each analysis to which we subjected our data. An easy group to dismiss from this particular analysis was

TABLE 6. *Site and Incidence: Distribution of Malignant Melanoma by Region—Hopeless Cases (96)*

Men and Women		
Region	Observed	Expected
Head & Neck	31	5.04
Upper Extremity	13	15.12
Lower Extremity	24	31.92
Torso & Genitals	16	31.92
Unknown	(12)	—
Totals	84(12)	84.00

$X_3^2 = 143.917$ $P < 0.01$

the inadequately treated group of patients. To combine survival statistics of this group with the adequately treated group would be to blur the real and better survival rates that may be achieved by adequate treatment. The remaining group of patients in the study, those in the hopeless category, did not survive five years, and, therefore, does not contribute to survival. We have already shown statistically that in age and incidence, sex and incidence, and site and incidence, both the hopeless and treatable patients are representative of the same disease. Therefore, in survival analyses, the group of 88 adequately treated patients comprises the most meaningful sample.

The age at which a patient is treated for malignant melanoma appears to affect his chances for survival, and analysis was made of the adequately treated patients. Testing was done in two ways: the first method compared the five-year survival curve of patients with malignant melanoma in various decades of life with the five-year survival curve for the population of the United States (Fig. 1); the second method employed a Chi-square analysis. Figure 1 shows the slope of the curve of five-year survival for the general population to be different from the five-year survival curve of patients with malignant melanoma. Patients with malignant melanoma have a steadily decreasing rate of survival with advancing age, and, although this is also true of the general population, the divergence of the two slopes indicates that malignant melanoma exerts an effect upon survival which is less favorable with each advancing decade of life. The curve is without irregularity except for the point plotting the five-year survival point of patients in the seventh decade. Here the rate is seen to rise, but this deviation from the slope has been analyzed and found to be statistically insignificant. The slope of the curves and their divergence from a similar curve for the entire population graphically illustrate both the lethal effect of the tumor

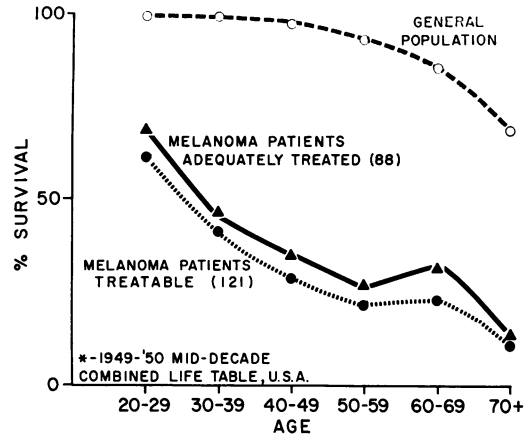

FIG. 1. Curve of proportions: Five-year survival at each decade of life.

and the operative effect of age upon survival. Chi-square also shows that there is quite probably an effect of age on five-year survival from malignant melanoma. The value of Chi-square while not quite at the level to give 95 per cent statistical confidence, showed between a 93 and 94 per cent statistical confidence that approaches the desired level (Table 7, 8).

Sex and Survival. The 88 cases which were adequately treated were analyzed to determine the effect of sex upon survival. Figure 2 is the curve of survival for patients exposed to adequate treatment. It is apparent that for both sexes the curves are similar. If each curve represented the *true* mean surviving at any given time between 0 and ten years, we could say that women have a somewhat better prognosis than men after three years of survival. However, there is overlapping of the confidence intervals which makes this observation statistically invalid. By *confidence intervals* the statistician means a range or spread of values within which may be expected to lie the true mean for an entire set of values. The larger the sample, the *narrower* will be the range of values which will embrace the true mean; the higher the degree of confidence desired to enclose the true mean, the *wider* will be the range. *Confi-*

TABLE 7. *Age and Survival: Five Year Survival by Age—Adequately Treated Patients (88)*

Age..	<30	30–39	40–49	50–59	60–69	>70	Total
Died							
Observed	5	7	11	11	13	7	54
Expected	9.82	8.0	10.4	9.25	11.6	4.92	53.9
Survived							
Observed	11	6	6	4	6	1	34
Expected	6.18	5	6.6	5.75	7.4	3.08	34.1
Totals	16	13	17	15	19	8	88

$X_5^2 = 10.125$ P = 0.068

dence is expressed as a percentage, and the degree of confidence desired is such that 95 times in 100 the range will not be due to chance alone. Briefly stated then, 95 per cent of the time a sample such as ours will have a mean survival rate for five years between 26.4 per cent and 57.8 per cent for women and between 22.6 per cent and 49.3 per cent for men. We, therefore, cannot generalize from our own five-year survival rates of 42.1 per cent and 36.0 per cent for women and men respectively because there is overlapping of the confidence intervals.

Age-adjusted survival means that we have taken into account causes of death other than the disease in question. By way of explanation, the five-year survival rate (expressed as a percentage) of a very aged sample population afflicted with malignant melanoma and treated adequately might be very small because of the inter-current and unrelated causes of death to be expected in older people; the "true" survival rate of malignant melanoma then becomes obscured unless a correction is made for other causes of death. That our data may be more meaningful we shall correct our percentages to refer to *age-adjustment* when pertinent. Age-adjusted survival rates based upon 1949–1951 mortality experience in the State of Michigan were used in this study.

Imposed upon the curves for both men and women at the five- and ten-year intervals are symbols (△, ▲) which represent the age-adjusted five- and ten-year survival rates. It may be pointed out that such a refinement, raising as it does the values on the established curve by a few percentage

TABLE 8. *Age and Survival: Five Year Survival by Age—Treatable Patients (121)*

Age..	<30	30–39	40–49	50–59	60–69	>70	Totals
Died							
Observed	7	10	17	18	23	8	83
Expected	12.3	11.6	16.4	15.7	20.5	6.15	82.65
Survived							
Observed	11	7	7	4	7	1	38
Expected	5.7	5.4	7.6	7.3	9.5	2.85	38.35
Totals	18	17	24	23	30	9	121

$X_5^2 = 17.870$ P<0.01

points is inappropriate when the confidence intervals are broad. However, these age-adjusted percentages are what we have found from our case experience at the University of Michigan Medical Center.

Site and Survival. The location of the primary site of malignant melanoma of the adequately treated patients is shown in Table 9. The survival of these patients was analyzed to see if there was any correlation between the location of the primary site and the five-year survival. We find that there was no statistically significant correlation. For men and for women the age-adjusted per cent survival is shown by location in Table 9. A casual observation of the survival of males with malignant melanoma of the lower extremity shows a survival rate close to two and one-half times that of males with malignant melanoma of the head and neck. This favored rate is chimerical and vanishes when statistical analysis is applied. The analysis shows a probability of 0.48, and such a value indicates that the rate is probably due to chance alone.

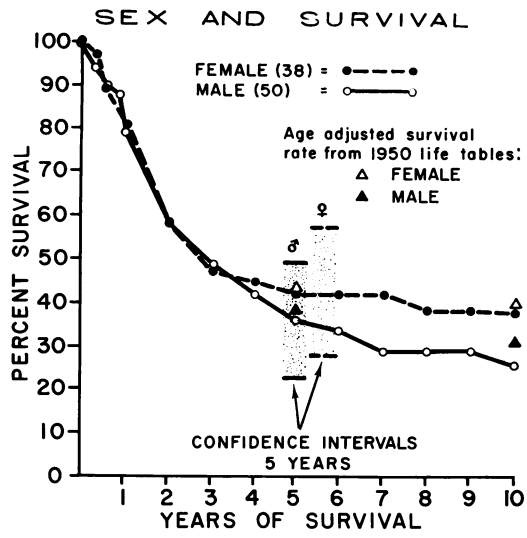

FIG. 2. Five-year survival rate: Melanoma Patients exposed to definitive treatment (88) at University of Michigan Medical Center, 1932–1953.

Lesion Size and Survival. While reviewing the cases for this study, it was disappointing to note how often an accurate measurement of the size of the primary lesion was not recorded. Too frequently

TABLE 9. *Site and Survival: Adjusted Percentage Survival by Site-Adequately Treated Patients (88)*

Men

Site	No.	5-Year Survival	% Survival	Σ Age	___ Age	Adjusted %
Head & Neck	15	3	20.0	886	59.07	22.87
Upper Extremity	8	3	37.5	434	54.25	40.91
Lower Extremity	14	7	50.0	658	47.00	52.30
Torso	12	5	41.6	542	45.17	43.24
Unknown	1	0	—	—	—	—

$X_3^2 = 2.7784$ P = 0.48

Women

Site	No.	5-Year Survival	% Survival	Σ Age	___ Age	Adjusted %
Head & Neck	10	5	50.0	506	50.6	51.94
Upper Extremity	5	2	40.0	201	40.2	40.61
Lower Extremity	13	5	38.4	589	45.3	39.36
Torso	9	4	44.4	358	39.7	45.12
Unknown	1	0	—	—	—	—

$X_3^2 = 0.0395$ P = 0.9

TABLE 10. *Lesion Size and Survival: Distribution of Survivors by Lesion Size (67 Adequately Treated Patients)*

Lesion size	<2 cm.	2–4 cm.	>4 cm.	Total
Survived				
Observed	19	6	2	27
Expected	18.2	5.23	3.63	27.06
Died				
Observed	26	7	7	40
Expected	26.8	7.77	5.37	39.94
Totals	45	13	9	67

$X_2^2 = 1.44$ $P = 0.46$

the dimensions of the melanoma were compared to a dime, a bean, or a millet. We made, wherever possible, a note of the size in centimeters—actually substituting the metric diameter of the coin, etc., where measurement was not noted but a comparison made. The resulting compilation was then condensed into three groups. Table 10 shows this condensation. Tabulation was made only within the group of adequately treated patients. Of the 88 cases there were 21 patients whose lesion size was unknown. The remaining 67 cases were divided into groups were the melanoma was: 1) smaller than 2.0 cm.; 2) between 2.0 and 4.0 cm.; or 3) greater than 4.0 cm. in diameter. The crude percentage of five-year survivals suggests that the primary tumors greater than 4.0 cm. in size were twice as deadly as the ones less than 2.0 cm. in size. Chi-square analysis shows this supposed difference in survival rate to be statistically insignificant.

Discussion

Incidence. An essential homogeneity of our cases of malignant melanoma has been achieved by histopathologic control and by epidemiologic comparisons of the hopeless and treatable groups. Age, sex and site relative to incidence have been analyzed.

Extraocular malignant melanoma is not a rarity, but neither is it a common affliction. At the University of Michigan Medical Center over the 22 years covered by this report an average of about ten cases per year was seen. We found malignant melanoma to be a disease of older people, rarely seen in persons under 30 years of age and most commonly found in patients in their sixties. This has been observed by others: Wilson [24] noted a peak incidence in the seventh decade and White,[23] Allen and Spitz [1] and Stewart [20] agree generally that the incidence increases with advancing age until the normally expected life-span is achieved. Between 60 per cent and 70 per cent of the reported cases of malignant melanoma are over 40 years of age.[1, 9, 11, 23]

Our youngest patient was one year of age and was our only case in the first decade of life. The infrequency of malignant melanoma in the first three decades of life would have been obscured in this series had not the microscopic sections of the patients been reviewed. Eleven of the 19 cases rejected from this series were patients in the first three decades of life who are alive and well at this time. Among these rejections were instances of the juvenile melanoma described by Allen and Spitz.[1, 2] The juvenile melanoma is not confined to the prepubertal age groups but may persist as a benign lesion into the fourth decade of life.[1, 2]

Several series reviewed by White [23] show an equal susceptibility of men and women

to malignant melanoma. Our data indicate that in both the treatable and hopeless categories there were more men than women and this difference has statistical validity. In this regard our report is at variance with that of White and his sources.

The predilection for malignant melanoma to arise on the skin surfaces of the head and neck was noted. The data of Allen and Spitz,[1] Wilson,[24] Stewart[20] and Hall[9] afford the same conclusions. Vogler[22] and his group disqualified themselves from making this observation because of a preponderance of head and neck cases in their clinic. These studies and ours show that the torso is significantly spared as a site of the tumor. The regional occurrence of moles has been subjected to Chi-square analysis which shows the head and neck to be a significantly more frequent site of moles than other areas[17] (Table 11). This correlates with the oft-observed fact that a high percentage of malignant melanomas arise from pre-existing nevi.

TABLE 11. *Distribution of Moles by Regional Skin Surface (after Pack, G. T.:Surgery, 46:449, 1959)*

Region	% Surface (E)	Incidence Moles (O)
Head & Neck	6	13.2
Upper Extremity	18	30.2
Lower Extremity	38	17.42
Torso & Genitals	38	39.4

$X_3^2 = 28.12 \quad P < 0.01$

In the entire series there were only two instances of subungual primaries. These were both treatable lesions, received adequate treatment, and did not survive. A third patient was reported to have had a subungual malignant melanoma of the thumb, and amputation of the digit was performed elsewhere. Further study showed the suspected tumor not to be a malignant melanoma, and this case is, therefore, not included in our series. We have refrained from subdividing the extremities into hands, feet or digits because our number of cases is not large enough to warrant this. Employing statistical methods as we have, an effort to keep numbers of usable size has been made.

Except for two patients who were negroes, our entire series is comprised of white persons.

In a review of a large series, unusual cases will often be found. Such a case is that of V.P. (UMH 637505), a 63-year-old white man who in March 1950 underwent local excision at another hospital of a malignant melanoma arising from a brown mole on the left thigh. A biopsy of an inguinal mass in December 1950 revealed metastatic malignant melanoma. Referral was made to the University of Michigan Medical Center, and in October 1951, the patient received I^{131}-tagged tumor antibody obtained from rabbits—a therapeutic project which underwent extensive trial here at that time. By December 1951 pulmonary metastases had developed. In February 1954, additional tumor was subtotally excised from the groin and reported as malignant melanoma. Meantime, the patient had enjoyed a profound remission with clearing of the pulmonary metastases. Following the subtotal excision of this last appearance of the tumor, a complete remission ensued. At the time of the patient's death in February 1958, from coronary artery thrombosis, necropsy revealed no evidence of neoplasm. The treatment which the patient received has been uniformly unsuccessful in a significant number of other cases. It is the opinion of the authors that this case represents a true spontaneous remission.

The risk of pregnancy effecting malignant change in pigmented nevi has been advanced as a special hazard for women in the development of malignant melanoma.[15] In our study we noted only two cases out of a total of 86 females in which pregnancy was recorded as a factor in the history. Forty-five of the 86 women were between 15 and 45 years of age, the years of childbearing. In one instance, the pa-

tient was seven months pregnant when first treated for malignant melanoma by wide local excision. The second instance was a woman in the child-bearing age who related that changes in a pigmented nevus which later proved to be a malignant melanoma took place during two previous pregnancies. Both these patients succumbed. Malignant melanoma in the child-bearing decades does not have the mortality that is noted in more advanced years of life. Our data are insufficient for a statistical study, and it remains to be shown that malignant melanoma is developed three times as frequently in pregnant women as in nonpregnant women as stated by Pack.[17] In no other cases of the women in our series of the child-bearing age, was pregnancy cited as a feature of the history. We also wonder if the pregnancy-malignant melanoma relationship is spurious as suggested by White.[23]

It was hoped that useful data would come from an inquiry into the history of the primary lesion, but a welter of confusion resulted. Generally, the primary lesion was a pigmented nevus in which changes occurred. The location, duration, configuration, pigmentation and mensuration of a mole too frequently depended all or in part on the patient's memory. Whereas we do not mean that true values of these observations are not important, we found that they did not constitute reliable information, and we can make no further comment about them from our study. To be forewarned as to what constitutes dangerous or suspicious change in the common mole is probably as good a weapon as the patient or physician can have in avoiding the fatal outcome of uncontrolled malignant melanoma.

Survival. A multitude of factors influence the relationship of the patient-host to an invading cancer. Such factors as the age or sex of the host are obviously tangible; others, such as the immune response of the host and the virulence of the tumor are intangible and usually defy measurement. Nevertheless, the resultant of these various biologic forces can be expressed simply and completely as survival. In turn, such varied influences as sex, age and site of the lesion can be considered in light of the survival.

In discussing survival we have limited ourselves to that group of 88 patients who were *adequately treated.* As was previously indicated, this was done so that the factor to be considered will evolve from a homogenous group of patients. In this portion of the presentation no attempt is made to differentiate between the various forms of *adequate treatment.*

We have demonstrated that individuals below the age of 30 have a low incidence of malignant melanoma while those individuals in the seventh decade of life are more prone to the disease than is the general population. Since it appears that some biologic factors associated with aging influence the occurrence of the disease, it is reasonable to inquire as to a possible age-effect in survival from malignant melanoma. Lund and Ihnen[11] found that there is no statistical correlation between age and survival. Other recent reports concerning melanoma have not considered this aspect of survival.

To test the effect of age upon survival, we considered separately the treatables and those patients who were adequately treated. In this consideration the inadequately treated patients were included in our evaluation so as to eliminate any possible bias that might arise from giving effective treatment to all but aged individuals. The first analysis was accomplished by Chi-square testing of a null hypothesis. The null hypothesis was that the age of the patient at the time of treatment did not affect survival. In both the treatable and adequately treated groups, Chi-square was significant and thus invalidated the null hypothesis to $P = 0.01$ for treatable and $P = 0.068$ for adequately treated pa-

tients. From Table 7 we see that patients under 30 and over 70 years were the heaviest contributors to the Chi-square.

Our second method of testing was by a curve of proportions. Again both treatable and adequately treated patients were analyzed separately.

From our data we are persuaded that there is an effect of age upon the chances for survival of a patient treated for malignant melanoma. The younger patients possess a relatively good prognosis while aged individuals have a uniformly poor prognosis despite adequate treatment or its lack. From this data it is reasonable to advance the proposition that the more energetic or so-called radical treatment of malignant melanoma be restricted to the younger patients whose chances for survival are better.

We have determined that there is a statistically significant sex effect operative in the occurrence of a malignant melanoma. Men predominate in our total series and in the subdivisions of treatable and hopeless cases. Our next concern is the effect of sex upon the survival of those patients who were adequately treated. The reports of White,[23] Allen and Spitz,[1] Pack[16] and Vogler[22] indicate that a greater percentage of women than men are either *cured* or survive for five years following treatment. White validates his observation statistically; Vogler and his co-workers show a curve of proportions that indicates the survival of women to be out of proportion to the survival of men and to the population in general. Lund and Ihnen[11] have tested for statistical validity and conclude that there is not a statistically significant sex effect operative in the survival of treatable patients.

At first glance it would appear that in our series a sex effect is operative in survival and that women have a better chance of survival than do men. True, in our series a greater proportion of women survive both five and ten years than did men. However, when this concept is tested statistically it is shown to be invalid.

The literature is replete with reports indicating a favored survival from those malignant melanomas that arise on certain areas of the body. If this were the case, then the surgeon would have a valuable prognostic aid and would be inclined to direct his most aggressive therapies to lesions arising in the favored sites. Unfortunately, what one author labels as a favored site, another will brand as near hopeless.

Lund and Ihnen[11] and Hall and his coworkers[9] indicate preferential survival for lesions arising on the head and upper extremities. Meyer and Gumport[12] make similar observations. Vogler[22] reports preferential survivals from lesions arising on the head and neck while Allen[1, 2] found lesions of the head to have a more dire prognosis. Wilson[24] indicates that the most favorable prognosis is associated with lesions of the torso while Vogler has described these lesions as having a dismal future. The majority of these reports deal with a sample population of a magnitude comparable to each other and to our series. The disparity of conclusions from similar samples immediately raises the question of validity and invites a statistical appraisal of the results.

Those lesions in our series arising on the genitals or mucosal surfaces were either hopeless when first seen or did not receive adequate treatment. The two patients whose primary was unkown survived less than five years. The sites of origin of lesions for both men and women were considered separately so that any possible sex effect upon survival would be eliminated and so age-adjustment could be used. The percentage survival by sites of origin for women shows no outstanding disparity between regions. For men, however, there appears to be a preferential survival from lesions arising in the lower extremities, while lesions of the head and neck appear to be associated with a low survival. The

series as a whole without division by sex indicates no site effect operational in survival; using this large number of patients, all regions have a five year survival rate approximating 40 per cent. We must conclude from our observations that there is no site-effect operative in the survival of adequately treated patients. We are persuaded that preferential survivals reported in other series may well be the reflection of chance alone.

From our data we can make no dogmatic statement regarding melanoma arising from a mucosal surface or whose site of origin is unknown. These lesions can rightly be viewed with pessimism as we had no survivors in our series. However, an accurate analysis of these lesions must await a larger series.

A similar situation exists in the literature for the effect of lesion size upon survival as it does for the effect of site upon survival. Here again the reports of various authors are in disagreement. Lund and Ihnen [11] postulate that lesion size is a reflection of the chronicity and virulence of the tumor and, therefore, influences the prognosis. They found that lesions less than 2.0 cm. in diameter were associated with the highest survival. The reports of Tompkins [21] and of Allen and Spitz [1, 2] agree in essence with this observation. Vogler [22] on the other hand, reported his lowest survivals with lesions less than 2.0 cm. in diameter.

Several of these authors [1, 2, 22] have considered certain characteristics of the tumor such as ulceration, bleeding, dermal invasion, etc. together with lesion size. We have not attempted these considerations. Nevertheless, we are in general agreement with Allen and Spitz [1, 2] and Vogler [22] who indicate that the degree of dermal invasion as seen through the microscope is a reflection of the virulence of the tumor and, perhaps, its chronological age. We must inject a note of caution here, however, to point out that without invasion demonstrated microscopically we are loathe to make the diagnosis of malignant melanoma.

From our data we can conclude that although smaller lesions are associated with survival rates almost twice that of larger lesions, the observation is not statistically significant and the seemingly higher survival rates for small lesions may be due to chance.

Conclusions

On the basis of our data we make the following conclusions:

1. Malignant melanoma occurs primarily in older patients with a peak incidence during the seventh decade of life. The tumor appears infrequently in individuals below the age of 30.

2. Males are afflicted by malignant melanoma more commonly than females. In our series men predominated in a ratio of 1.5 : 1.

3. The head and neck have a predilection for the development of malignant melanoma as opposed to other areas of the body. The torso is significantly spared as a site of the primary disease.

4. There is an age effect operative in survival of patients suffering from malignant melanoma. Treatable patients below the age of forty approach a survival rate of 50 per cent for five years; individuals above the age of 70 have an 11 per cent chance to survive five years.

5. There is no preferential survival from malignant melanoma for either sex.

6. There is no statistically significant differential in survival based on the size of the primary lesion.

7. Primary malignant melanomas arising in various cutaneous areas are associated with similar survivals. There is no preferential survival according to site of the primary tumor.

8. A case representing spontaneous remission from malignant melanoma is reported.

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