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Predicting Survival and Recurrence in Localized Melanoma: A Multivariate Approach

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Several clinical and pathologic factors appear to affect melanoma recurrence and survival. While much attention has been directed at identifying prognostic factors, few researchers have developed predictive models for survival and recurrence. Two major clinical questions are of interest in the management of melanoma: 1) what is the patient's chance of surviving for a given period, e.g., 5 or 10 years, after diagnosis of melanoma; and 2) after a patient has been disease free for a period of time, e.g., 5 years, what is his or her chance of melanoma recurrence or death in the following interval, e.g., 5 years or 10 years. In this paper, a generalized multivariate prognostic model to address both of these clinical questions is presented.

Tables of the estimated probabilities of melanoma recurrence and death for prognostic subgroups are shown to facilitate prediction of an individual patient's outcome. The model was based on a database of 4,568 patients with localized melanoma, one of the largest melanoma databases in the world with detailed clinical and pathologic information, and long-term follow-up. Tumor thickness at diagnosis was the single most important prognostic factor for all outcomes. Tumor ulceration, Clark's level, lesion location, and sex had an impact on overall survival from diagnosis for some of the subgroups defined by tumor thickness. Tumor thickness at diagnosis was strongly indicative of melanoma recurrence and death even after a disease free interval of 2, 5, or 10 years. Lesion location and ulceration were of prognostic importance after disease free intervals up to 5 years, but their impact on melanoma recurrence and death diminished after longer disease free intervals.

Prediction models for melanoma outcome at diagnosis and after a disease free period can provide useful information to clinicians in the management of melanoma patients. Utilization of the model will be valuable in identifying patients at high risk for melanoma recurrence and death.

A large number of clinical and pathologic factors that appear to affect melanoma recurrence and survival rates have been studied extensively over the past 15 years at major melanoma centers around the world. With the aid of powerful statistical techniques, remarkable progress has been made in the identification of dominant factors that characterize the outcome of melanoma [1, 2]. Most of the large melanoma series were analyzed using the multivariate regression analysis methods for survival data so that the relative importance of the prognostic factors considered could be accurately assessed. Balch and colleagues [2] compared the results of prognostic factor analysis from 14 melanoma centers located in 10 countries. Although the overall results varied from center to center, the major significant predictive variables identified from each center were very similar. For example, the majority of the centers that performed a prognostic factors analysis for localized melanoma found tumor thickness, tumor ulceration, and lesion location to be the key prognostic factors.

While a great deal of attention has been focused on identification of prognostic factors, few researchers have developed predictive models for survival and recurrence. Two major clinical applications are of interest in melanoma prognosis: 1) what is the patient's chance of surviving for a given period, e.g., 5 or 10 years, after diagnosis of melanoma; and 2) if the patient is disease-free for a period of time, what is his or her chance of disease recurrence or mortality in successive time intervals. Soong [3, 4] developed a mathematical model and scoring system for predicting outcome in localized melanoma patients. The validity of this model has been tested in several independent data sets, and its high degree of predictability has made it very useful clinically. Clark and colleagues [5] developed a model that predicts survival in localized melanoma based on tumor progression. Both of these papers addressed only the survival outcome following diagnosis. In this paper, a generalized multivariate prognostic model to address both survival following diagnosis and outcome following a disease-free interval will be presented.

Methods

The analyses presented here are based on 2 large melanoma series which have been described previously: one from the University of Alabama at Birmingham (UAB) and one from the Sydney Melanoma Unit (SMU) [1, 6]. These 2 melanoma series were combined since their patient populations were similar in

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composition, patient management, and duration of follow-up. The major prognostic factors identified in these 2 data sets were virtually identical [6]. The model as developed using the combined data base of 4,568 patients for whom each item of clinical and pathologic information was available for the following prognostic factors: 4 clinical factors (age, sex, lesion location, and initial surgical treatment) and 4 pathologic factors (tumor thickness, ulceration, level of invasion, and growth pattern).

The identification of dominant prognostic factors and the derivation of predictive models were based on the proportional hazards regression model introduced by Cox [7]. The Cox model evaluates the relative impact of the 4 clinical factors and 4 pathologic factors on outcome. The recurrence and mortality rates were estimated from the observed data using the Kaplan-Meier method [8].

Tumor thickness has been well established as the most important prognostic factor for localized melanoma [1, 2]. To evaluate the prognostic value of clinical and other pathologic factors, additional multivariate analyses were performed within each tumor thickness subgroup. To evaluate outcome following a disease free interval, multivariate regression analyses were performed for the following time intervals following diagnosis: 0 to 2 years, 2 to 5 years, 5 to 10 years, and 10 or more years. Of the 4,568 patients in the combined series, 1,128 were followed for <2 years; 631 had recurrences within 2 years; and 2,809 were disease-free at 2 years. The duration of follow-up for 404 patients was >2 years and <5 years. Between 2 to 5 years, 346 patients' disease recurred, leaving 2,059 patients who were disease-free at 5 years. Of these 2,059 patients who were followed for at least 5 years, 993 were followed for <10 years; 130 had recurrences between 5 to 10 years; and 936 were disease-free at 10 years after diagnosis. Of these 936 patients who were followed for at least 10 years, 43 had recurrences after 10 years of initial diagnosis. Within each time interval, analyses for each subgroup defined by tumor thickness were performed.

Table 1. Predicted 5-year and 10-year survival rates from initial diagnosis for patients with localized melanoma.[a,b]

Tumor thickness (mm)	Anatomic site	Ulceration	Clark's level	Sex	5-year survival rate (%)	10-year survival rate (%)[c]
<0.76						
	Extremity	–	II	–	99	97
	Extremity	–	Other	–	97	94
	Axial	–	II	–	96	92
	Axial	–	Other	–	91	84
0.76–1.49						
	Extremity	No	II	–	98	97
	Extremity	No	Other	–	93	89
	Extremity	Yes	II	–	94	91
	Extremity	Yes	Other	–	82	72
	Axial	No	II	–	95	93
	Axial	No	Other	–	85	77
	Axial	Yes	II	–	88	81
	Axial	Yes	Other	–	64	49
1.50–2.49						
	Extremity	No	–	–	86	81
	Extremity	Yes	–	–	76	69
	Axial	No	–	–	76	67
	Axial	Yes	–	–	61	49
2.50–3.99						
	Extremity	No	–	Female	80	72
	Extremity	No	–	Male	73	62
	Extremity	Yes	–	Female	74	64
	Extremity	Yes	–	Male	64	51
	Axial	No	–	Female	73	63
	Axial	No	–	Male	63	51
	Axial	Yes	–	Female	65	52
	Axial	Yes	–	Male	53	39
4.00–7.99						
	–	No	II/III	–	80	73
	–	No	IV/V	–	68	58
	–	Yes	II/III	–	67	57
	–	Yes	IV/V	–	51	38
≥8.00						
	–	–	–	–	43	25

[a] Adapted from [4]

[b] The projected survival rates have been adjusted for the effects of surgical treatment in those subgroups in which it was a significant factor.

[c] The projected 10-year survival rate for an individual patient is considered as this patient's clinical score; for applications see [4].

Results

Soong [4] used the combined data set of 4,568 patients to develop a mathematical model for predicting survival in patients with localized melanoma. This model has been validated and has demonstrated a high degree of predictability. Tumor thickness was a key factor in predicting survival. Other factors which influenced survival within tumor thickness subgroups included anatomic site of lesion, presence or absence of ulceration, Clark's level, sex, and surgical treatment. Table 1, adapted from the paper by Soong [4], summarizes the predicted 5-year and 10-year survival rates from diagnosis after adjustments for the effects of surgical treatment. For example, a patient whose tumor was between 1.50 mm and 2.49 mm thick, ulcerated, and in an axial site had a 61% chance of surviving for 5 years or longer, and a 49% chance of surviving for 10 years or longer.

Figure 1 illustrates the factors for predicting survival from diagnosis to year 2 and after a disease free interval of 2 years, 5 years, and 10 years. Tumor thickness was the most significant prognostic factor for each of the time intervals. During the first 2 years following diagnosis, tumor thickness (<0.76 mm, 0.76–1.49 mm, 1.50–2.49 mm, 2.50–3.99 mm, 4.00–7.99 mm, ≥8.00 mm), ulceration, and lesion location were highly predictive of outcome. Table 2 summarizes the estimated probabilities of melanoma recurrence and death in the first 2 years after diagnosis for each tumor thickness subgroup. Within each tumor thickness subgroup, ulceration was a significant prognostic factor. Lesion location had an impact on 2-year disease-free survival in all tumor thickness subgroups with the exceptions of the <0.76 mm thickness group and the >=8.00 mm thickness group. For example, patients with extremity lesions which were between 1.50 mm and 2.49 mm thick and were not ulcerated had a 2-year melanoma recurrence rate of 15% and a mortality rate of 4%. In contrast, patients with ulcerated lesions 8.00 mm or thicker had a 2-year recurrence rate of 69% and a mortality rate of 43%.

Two years following diagnosis, 2,809 patients were alive and disease-free. The same 3 factors (tumor thickness, ulceration, and lesion location) which were of prognostic significance

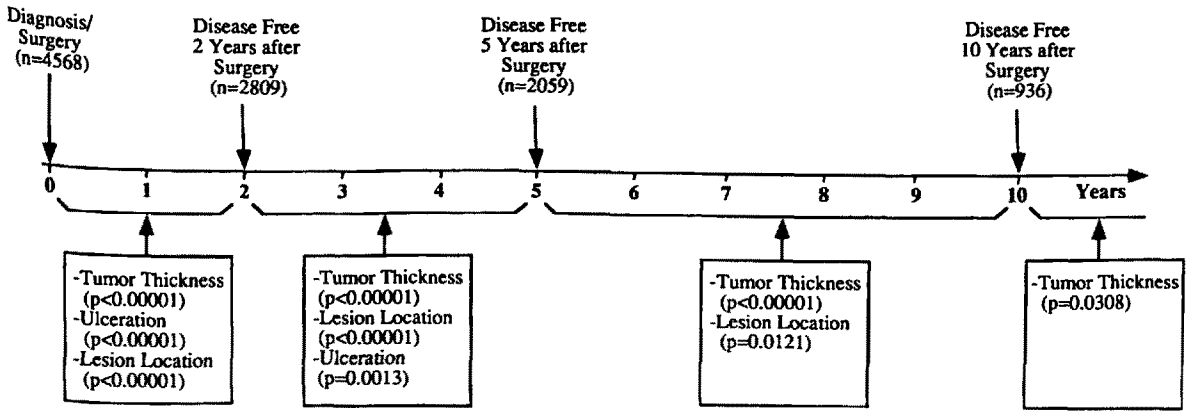

Fig. 1. Localized melanoma: Factors predicting melanoma recurrence and death within each time interval assuming that patients are free of disease at the beginning of each time interval. Only those factors evaluated at the time of initial diagnosis/surgery were considered. The significant prognostic factors listed were adjusted for the effects of surgical treatment. Reprinted with permission [4].

Table 2. Estimated probabilities of melanoma recurrence and death within 2 years after initial diagnosis of localized melanoma.[a]

Tumor thickness (mm)	Ulceration	Lesion location	n	Estimated probability of melanoma recurrence within 2 years (%)	Estimated probability of melanoma death within 2 years (%)
<0.76					
	No	–	1397	2 ± 0.4	0
	Yes	–	59	12 ± 5	2 ± 2
0.76–1.49					
	No	Extremity	644	6 ± 1	1 ± 0.3
	No	Axial	511	13 ± 2	3 ± 0.9
	Yes	Extremity	62	27 ± 5	7 ± 3
	Yes	Axial	56	15 ± 6	9 ± 4
1.50–2.49					
	No	Extremity	299	15 ± 2	4 ± 1
	No	Axial	282	23 ± 3	7 ± 2
	Yes	Extremity	161	23 ± 4	11 ± 3
	Yes	Axial	129	33 ± 4	15 ± 3
2.50–3.99					
	No	Extremity	149	23 ± 4	4 ± 2
	No	Axial	152	32 ± 4	14 ± 3
	Yes	Extremity	119	33 ± 5	13 ± 3
	Yes	Axial	116	43 ± 5	25 ± 4
4.00–7.99					
	No	Extremity	61	24 ± 6	4 ± 2
	No	Axial	87	32 ± 6	15 ± 4
	Yes	Extremity	96	47 ± 5	18 ± 4
	Yes	Axial	111	52 ± 5	29 ± 5
≥8.00					
	No	–	25	52 ± 11	22 ± 9
	Yes	–	52	69 ± 7	43 ± 8

[a]Estimated probability ± standard error.

during the first 2 years after diagnosis remained predictive of outcome from years 2 to 5. The estimated probabilities of melanoma recurrence and death from year 2 to year 5 following a disease free interval of 2 years are shown in Table 3 for each tumor thickness subgroup. Ulceration was not a significant factor for patients whose tumor was <0.76 mm thick. Patients with extremity lesions between 0.76 mm and 1.49 mm thick which were not ulcerated and who were disease free at 2 years had a melanoma recurrence rate of 7% and mortality rate of 3%

Table 3. Estimated probabilities of melanoma recurrence and death within the next 3 years if a patient is free of disease 2 years after initial diagnosis of localized melanoma.[a]

Tumor thickness (mm)	Ulceration	Lesion location	n	Estimated probability of melanoma recurrence within the next 3 years (%)	Estimated probability of melanoma death within the next 3 years (%)
<0.76					
	–	Extremity	517	2 ± 0.7	1 ± 0.5
	–	Axial	405	8 ± 1	4 ± 1
0.76–1.49					
	No	Extremity	467	7 ± 1	3 ± 0.8
	No	Axial	329	11 ± 2	7 ± 2
	Yes	Extremity	38	25 ± 8	16 ± 7
	Yes	Axial	35	33 ± 9	28 ± 9
≥1.5					
	No	Extremity	344	21 ± 2	7 ± 1
	No	Axial	309	25 ± 3	17 ± 2
	Yes	Extremity	202	21 ± 3	11 ± 2
	Yes	Axial	163	32 ± 4	21 ± 4

[a]Estimated probability ± standard error.

within the next 3 years. Patients with ulcerated lesions on the extremities which were ≥1.5 mm thick at diagnosis and who were disease free at 2 years experienced a recurrence rate of 21% and a mortality rate of 11% between year 2 and year 5 after diagnosis.

Five years following diagnosis and surgery, 2,059 patients were known to be alive and had not experienced a recurrence of their melanoma. Tumor thickness at diagnosis and lesion location continued to play a key role in predicting disease-free survival and melanoma recurrence following a 5-year disease free interval. Table 4 summarizes the probabilities of melanoma recurrence and death from year 5 to year 10 after a 5-year disease free interval. Among patients whose lesions at diagnosis were ≥1.5 mm thick, lesion location was not a significant prognostic factor in predicting 5-year disease free survival following a 5-year disease free interval. In this group, the probability of recurrence is 14% and the probability of death is 9% from year 5 to year 10. Patients with axial lesions which

Table 4. Estimated probabilities of melanoma recurrence and death within the next 5 years if a patient is free of disease 5 years after initial diagnosis of localized melanoma.[a]

Tumor thickness (mm)	Lesion location	n	Estimated probability of melanoma recurrence within the next 5 years (%)	Estimated probability of melanoma death within the next 5 years (%)
<1.5				
	Extremity	846	4 ± 0.8	2 ± 0.5
	Axial	582	7 ± 1	5 ± 1
≥5				
	–	631	14 ± 2	9 ± 1

[a]Estimated probability ± standard error.

Table 5. Estimated probabilities of melanoma recurrence and death within the next 5 or 10 years if a patient is free of disease 10 years after initial diagnosis of localized melanoma.[a]

Tumor thickness (mm)	n	Estimated probability of melanoma recurrence within the next 5 years (%)	Estimated probability of melanoma death within the next 5 years (%)	Estimated probability of melanoma recurrence within the next 10 years (%)	Estimated probability of melanoma death within the next 10 years (%)
<1.5	672	4 ± 1	1 ± 1	8 ± 2	3 ± 1
≥1.5	264	6 ± 1	4 ± 1	13 ± 3	7 ± 2

[a]Estimated probability ± standard error.

were <1.5 mm thick and who were disease free at 5 years experienced a 7% recurrence rate and 5% mortality rate over the next 5 years.

A total of 936 patients were disease-free 10 years following diagnosis and surgery, 264 (28%) of whose lesions were originally ≥1.5 mm thick. After a disease-free interval of 10 years, the only factor which was predictive of melanoma recurrence or mortality was tumor thickness at diagnosis. Table 5 shows the estimated probabilities of melanoma recurrence and death from year 10 to year 15 and year 20 for each tumor thickness subgroup after a 10-year disease free interval. From year 10 to year 15, patients with lesions ≥1.5 mm had a recurrence rate of 6% and a mortality rate of 4% and those with lesions <1.5 mm thick had a recurrence rate of 4% and a mortality rate of 1%.

Discussion

The multivariate prognostic model presented in this paper for localized melanoma was based on one of the largest melanoma databases in the world with detailed clinical and pathologic features of melanoma and long-term follow-up. Using this model, clinical and pathologic features of melanoma which influenced overall survival from diagnosis, and those which had an impact on melanoma recurrence and death in the first 2 years following diagnosis, and after disease-free intervals of 2, 5, and 10 years were identified.

Tumor thickness at diagnosis was the single most important prognostic variable for all outcomes. As a result, other potential prognostic factors were evaluated after adjusting for tumor thickness. Tumor ulceration, Clark's level, lesion location, and sex were correlated with overall survival for some of the tumor thickness subgroups. Prediction of overall survival based on these prognostic factors has already proved useful in a clinical setting for patient evaluation and treatment planning.

Estimation of the probabilities for melanoma recurrence and survival following a disease-free interval represents an innovative approach to assessing the clinical course of disease after diagnosis. The importance of tumor thickness at diagnosis in predicting outcomes did not diminish with the length of the disease-free interval. Tumor thickness, ulceration, and lesion location were significant prognostic factors in predicting melanoma recurrence and death in the first 2 years following diagnosis, and from year 2 to year 5 following a 2 year disease-free period. After a disease-free interval of 5 years, ulceration of the lesion was no longer a prognostic indicator of outcome from year 5 to year 10. Following a disease-free interval of 10 years, only tumor thickness at diagnosis was predictive of melanoma recurrence and death from year 10 to year 15 or year 20.

Prediction of melanoma outcome following a disease-free interval is critical in the management of melanoma patients in the years following diagnosis and treatment. In general, the greatest risk of disease recurrence and mortality occurs in the first 5 years following diagnosis. Although patients who are disease-free for 5 years cannot be considered as "cured", their risk of recurrence and death related to their melanoma is relatively low.

This paper has addressed the role of clinical and pathologic factors in predicting survival and recurrence in melanoma patients. Further studies are needed to determine the role of immunologic, genetic, nutritional, and socioeconomic factors in influencing the clinical course of melanoma.

Résumé

Plusieurs facteurs cliniques et anatomopathologiques semblent déterminer la récidive et la survie des mélanomes. De nombreux auteurs se sont intéressés à l'identidification des facteurs de pronostic, mais peu d'équipes ont essayé d'élaborer un modèle permettant de prédire survie et récidive. Deux problèmes restent à résoudre dans le traitement des mélanomes: 1) quelles sont les chances de survie après le diagnostic de mélanome pour un patient donné, pendant une période donnée, par exemple 5 à 10 ans et 2) quels sont les risques de récidive ou de décès dans les 5 à 10 ans qui suivent une période donnée (par exemple 5 ans) où un patient semblait en rémission. Dans cet article, nous avons créé un modèle d'évaluation pronostique multifactorielle pour tenter de répondre à ces 2 questions.

Des tables montrant les probabilités de récidive et de décès par mélanome, calculées à partir de sous groupes différents, peuvent aider à déterminer le pronostic. Ce modèle repose sur une banque de données de 4568 patients atteints de mélanome non disséminé. Il s'agit d'une des plus grandes banques de données au monde contenant des informations cliniques, anatomopathologiques et sur l'évolution à long terme. L'épaisseur de la tumeur au moment du diagnostic était le facteur pronostic le

plus important pour déterminer l'évolution. Le caractère ulcéré, le stade de Clark, la localisation de la lésion et le sexe avaient tous une importance pronostique, influant sur la survie globale liée à l'épaisseur de la tumeur. L'importance de l'épaisseur de la tumeur au moment du diagnostic était un facteur de récidive et mortalité même après un intervalle long de 2, 5 ou 10 ans. Le site de la tumeur et son caractère ulcéré étaient également des facteurs associés à un risque de récidive tumorale ou de décès après une rémission de 5 ans. L'influence de ces facteurs diminuait en cas de rémission plus prolongée.

Les modèles permettant d'évaluer l'évolution du mélanome malin au moment du diagnostic et apreès un intervalle de rémission sont utiles au cours du traitement du mélanome. Ils doivent permettre d'identifier les patients à risque de récidive et de décès.

Resumen

Diversos factores clínicos y patológicos parecen afectar las tasas de recurrencia y mortalidad del melanoma. En tanto que se ha dispensado bastante atención en cuanto a identificar factores de pronóstico, pocos investigadores han desarrollado modelos de predicción de sobrevida y de recurrencia. Dos interrogantes principales son de interés en cuanto al manejo del melanoma: 1) cual es la probabilidad del paciente de sobrevivir un determinado período, por ejemplo 5 o 10 años, después del diagnóstico de melanoma; y 2) después de que el paciente se ha mantenido libre de enfermedad por un período de tiempo, por ejemplo 5 años, cual es su probabilidad de recurrencia del melanoma o de muerte en el siguiente período de tiempo, por ejemplo 5 o 10 años. En este artículo se presenta un modelo generalizado y multivariable de pronóstico para enfrentar estos interrogantes clínicos.

Se presentan tablas para estimar las probabilidades de recurrencia y de muerte en divesos subgrupos de pronóstico que facilitan la predicción del destino final de un individuo. El modelo se fundamentó en una base de datos de 4568 pacientes con melanomas localizado, una de las más grandes bases de datos de melanoma existentes en el mundo, con detallada información clínica y patológica y con seguimiento a largo plazo. El espesor del tumor en el momento del diagnóstico apareció como el factor individual de pronóstico de mayor importancia. La ulceración del tumor, el nivel de Clark, la ubicación de la lesión y el sexo exhibieron importancia en cuanto a la sobrevida para algunos de los subgrupos definidos según el espesor del tumor. El espesor del tumor en el momento del diagnóstico fue un factor fuertemente indicativo de recurrencia y de muerte, aún después de un intervalo libre de enfermedad de 2, 5 o 10 años. La ubicación de la lesión y la ulceración aparecieron como de importancia en cuanto el pronóstico después de intervalos libres de enfermedad hasta de 5 años, pero tal importancia disminuyó después de intervalos libres de enfermedad de mayor duración.

Los modelos de predicción del resultado final en el melanoma aplicados en el momento del diagnóstico y después de un período libre de enfermedad pueden proveer información útil para el manejo clínico de pacientes con melanomas. La utilización del modelo es de valor en la identificación de pacientes con mayor riesgo de recurrencia y muerte por melanoma.

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