**Conditional Survival After Surgical Treatment of Melanoma: An Analysis of the
Surveillance, Epidemiology, and End Results Database**

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Natasha M. Rueth, M.D.

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Todd M. Tuttle, M.D., M.S., Advisor

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Natasha M. Rueth, M.D.

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Dedication

This thesis is dedicated to my academic and clinical mentors. I will forever strive to make you proud; thank you for the time and effort you have put into my success.

Abstract

Introduction: Survival curves following surgical treatment of cutaneous melanoma are heavily influenced by early deaths. Therefore, survival estimates may be misleading for long-term cancer survivors. We examined whether conditional survival (CS) is more accurate in predicting long-term melanoma survival.

Methods: We used the Surveillance Epidemiology and End-Results database (1992-2005) to identify patients who underwent surgical treatment for melanoma. We included patients with T2-T4 disease and with known nodal status. Patients were stratified into low-risk (T2-3N0M0) and high-risk (T4N0M0 or T2-4N1-3M0) categories. We defined CS as time-specific estimates conditioned on living to a certain point in follow-up, and calculated 10 year cancer-specific survival curves conditioned on annual survival. We adjusted for potential confounders using a Cox proportional hazards regression model ($\alpha=0.05$).

Results: 8,647 patients met inclusion criteria (low-risk, 5987 [69.2%]; high-risk, 2660 [30.8%]). At diagnosis, low-risk patients had a significantly better 10-year survival rate (low-risk, 79.6%; high-risk, 41.2%; $p<0.001$). On CS analysis, survival differences remained until 8 years after treatment, after which 10-year cancer-specific survival rates were no longer significantly different ($p=0.51$) for low-risk (95.4%) and high-risk (91.7%) groups. Multivariate analysis demonstrated that age, gender, location, and

ulceration (initial predictors of survival) were no longer predictive after 8 years of survival.

Conclusions: For patients who survive 8 years after surgical treatment of melanoma, CS data become discordant with traditionally used estimates. Our findings have important implications for patient counseling, as high-risk melanoma survivors may require no more intensive surveillance than low-risk survivors 8 years after treatment.

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Introduction

For patients with cutaneous melanoma ≥ 1 mm in thickness, adequate local treatment includes wide local excision (WLE) and sentinel lymph node (LN) evaluation.¹⁻

³ Following local treatment, several tumor and patient related characteristics affect prognosis. Tumor ulceration and thickness, anatomic location of primary tumor, patient age and gender, and lymph node metastasis are known to affect cancer survival.⁴ Specifically, lymph node metastases present at the time of original diagnosis are a powerful predictor of patient survival.^{1, 5-7}

These prognostic characteristics define our current understanding of cancer-specific survival (CSS), and provide the basis for patient counseling and long-term decision-making. Because CSS rates are heavily influenced by early cancer deaths, traditional estimates based upon early prognostic factors may not accurately predict long-term outcomes among melanoma survivors.

An alternative approach for understanding long-term cancer-specific outcomes may be through the use of conditional survival (CS). CS calculates the changing risk of cancer death over time and provides estimates of on-going survival given the pre-condition of having already survived to a certain point after initial treatment. Because CS data are not influenced by early cancer deaths, CS analysis may be a more accurate estimate of long-term CSS⁸⁻¹³ and may be a more important factor in determining appropriate surveillance and screening for melanoma survivors.

The objective of this investigation was to analyze large numbers of patients using a national cancer database and determine if, at some point in follow-up, the likelihood of

future survival is no longer impacted by initial tumor stage or by specific patient or tumor prognostic factors that were significant predictors of survival at the time of diagnosis. It was our hypothesis that, after a certain accumulated CSS time, the significant predictive characteristics present at the time of diagnosis would no longer be associated with long-term cancer survival for patients with local and regional melanoma following adequate local treatment.

Patients and Methods:

Definition of Conditional Survival

CS is a function of the traditional survival estimates and can be calculated using Kaplan-Meier survival data. Unique to the conditional survival analysis, data are adjusted to reflect the probability of ongoing survival, which is conditioned on already having survived to a certain point in follow-up. For example, to compute the 10-year CS for patients who have already survived 3 years, the 13-year CSS is divided by the 3-year CSS. The specific statistical methods for determining CS have been previously described.^{8, 14}

Data Source

The Surveillance Epidemiology and End Results (SEER) database program of the National Cancer Institute is a well-established, population-based set of cancer registries, encompassing 26% of the United States population as of 2000.¹⁵ It is thus the largest publically available cancer database in the country. Use of the SEER database allows for evaluation of specific patient demographic information; detailed tumor characteristics such as morphology, site, and pathology; first course of cancer treatment; and cancer survival data. SEER has been widely validated and details of use are well described.^{8, 11, 13} As a limitation of the database, SEER does not capture surgical margin status or tumor recurrence data. Additionally, in this study we used the November 2007 submission database (which provides data from 1973 through December 31, 2005); at that time, SEER was not recording the use of adjuvant cancer therapies such as chemotherapy.

Study Cohort

Using the SEER database, we selected patients who underwent WLE of T2-T4 cutaneous melanomas with histological evaluation of regional lymph nodes, and were diagnosed in 1992 or later. Because of their uniformly high survival rates and because melanoma tumors < 1 mm in thickness do not routinely undergo lymph node evaluation, patients with T1 tumors were excluded from our analysis. We included patients with the following International Classification Disease for Oncology, 3rd Edition (ICD-O3) histology codes: 8720, 8721, 8723, 8730, 8740, 8741, 8742, 8743, 8744, 8745, and 8761.

Though SEER registries began collecting LN data in 1988, clinically negative regional lymph nodes weren't routinely assessed until the seminal studies on sentinel lymph node evaluation were published.^{1, 5, 7} Therefore, we limited our data collection to the years 1992 through 2005.

We excluded patients with unknown T-stage or nodal status, non-melanoma skin cancer, systemic metastases, unknown primary melanoma site, or a second primary (non-melanoma) cancer diagnosis. Patients were also excluded if their disease was diagnosed at autopsy or by death certificate only, because they were unlikely to have received appropriate oncologic treatment. Non-white populations were excluded due to their limited numbers and disproportional incidence of advanced disease and poor outcomes.^{4, 11, 16} Due to the negative impact of Hurricane Katrina on data collection, we excluded data collected by the Louisiana cancer registry in 2005. Finally, we excluded patients under the age of 18.

The remaining 8647 patients were then stratified as follows: low-risk (T2-3N0) and high-risk (T4N0 or T2-4N1-3). Low-risk patients were defined as those less likely to have tumor recurrence and better overall and disease-free survival. Our risk-stratified categories were based on the risk categories defined by the Eastern Cooperative Oncology Group Trial.¹⁷

From the SEER database for this defined population of melanoma patients, we then collected information on patient demographics, tumor characteristics (tumor thickness, location of primary tumor, presence of ulceration, and LN status), and CSS from the time of diagnosis for low and high-risk patients.

Outcome Variables

Our primary outcome measures were 10-year CSS and 10-year cancer-specific relative conditional survival among patients stratified by risk category who underwent appropriate local treatment of local or regional melanoma.

Statistical Analyses

Conditional survival was defined as time-specific estimates conditioned on surviving to a certain point in follow-up. We calculated unadjusted 10-year cancer-specific survival rates using the Kaplan-Meier method for low-risk vs. high-risk patients at the time of diagnosis. Patients were censored at the time of death or loss to follow-up. We then calculated 10-year cancer-specific relative conditional survival rates for all melanoma survivors 1 year after surgical treatment, 2 years after treatment, and for every

year of cumulative survival thereafter. Using the log-rank method, we tested for survival rate significance between low and high-risk groups at time zero (defined as the time of diagnosis) and for each year of cumulative CS thereafter, until the curves converged.

We adjusted for potential confounding covariates (age, gender, location of primary tumor, and presence or absence of ulceration) using Cox proportional hazards regression models and analyzed the association between these factors and 10-year CSS.

Data were analyzed using SAS version 9.1 (SAS Institute, Cary, NC). For all statistical testing, we used a two-sided significance level of 0.05.

The University of Minnesota Institutional Review Board: Human Subjects Committee determined that this study was exempt from review under Code of Federal Regulations 45 part 46.101(b).

Results:

A total of 8,647 patients met the inclusion criteria during the specified time (Table 1).

Table 1: Step-wise Ascertainment of Final Cohort

	Number in group	Cumulation of cohort
START:		
Invasive melanoma cases diagnosed 1992-2005	124,294	124,294
Exclude unknown tumor thickness and T1 tumors	100,633	23,661
Exclude >1 primary cancer diagnosis	6,903	16,758
Exclude unknown lymph node status (none evaluated or not reported)	7,556	9,202
Exclude unknown primary site	26	9,176
Exclude metastatic disease	186	8,990
Exclude Louisiana 2005	1	8,989
Exclude reporting source	1	8,988
Exclude non-Caucasian and unknown race	229	8,759
Exclude unknown ulceration status	31	8,728
Exclude age < 18 at diagnosis	81	8,647
FINAL:		8,647

Using the definition outlined previously, 5987 patients (69.2%) were placed into the low-risk category (T2-T3, N0), and 2660 patients (30.8%) into the high-risk category (T4N0 or T2-4N1-3). Patient and tumor characteristics presented by risk category at time of diagnosis are presented in Table 2. Nearly half of patients were between the ages of 40 and 60 years old in the combined cohort (n=3731, 43.1%). This remained true when separated by risk group; low-risk patients were not younger than high-risk patients, with the majority of patients in each group falling between the ages of 40-60 (43.7% and 42.0% respectively). Male gender was predominant.

Tumor characteristics varied somewhat across groups; extremity was the most common primary tumor site overall (n=4181, 48.4%), followed by trunk (n=2936, 33.9%) and head and neck (n=1530, 17.7%). When categorized by risk, 50.1% of low-risk patients and 44.5% of high-risk patients had extremity tumors; high-risk patients had slightly more primary trunk tumors (37.8%) than low-risk patients (32.2%). In all patients, ulceration was uncommon (n=1482, 17.1%) although it was more prevalent in the high-risk group (n=677, 25.5%).

Table 2: Patient and Tumor Characteristics

Demographic and primary tumor information for combined cohort, low-risk group, and high-risk group.

		Low-Risk Group T2-3N0		High-Risk Group T4N0 or T2-4 N1-3		Combined	
		n (Total 5987)	%	n (Total 2660)	%	n (Total 8647)	%
Age by category							
	< 30	379	6.3	188	7.1	567	6.6
	30-39	693	11.6	319	12.0	1012	11.7
	40-49	1266	21.2	580	21.8	1846	21.3
	50-59	1349	22.5	536	20.2	1885	21.8
	60-69	1094	18.3	472	17.7	1566	18.1
	70-79	887	14.8	355	13.3	1242	14.4
	80+	319	5.3	210	7.9	529	6.1
Gender							
	Male	3454	57.7	1700	63.9	5154	59.6
	Female	2533	42.3	960	36.1	3493	40.4
Primary Tumor Location							
	Head/Neck	1058	17.7	472	17.7	1530	17.7
	Extremities	2998	50.1	1183	44.5	4181	48.4
	Trunk	1931	32.2	1005	37.8	2936	33.9
Ulceration							
	Present	805	13.4	677	25.5	1482	17.1
	Absent	5182	86.6	1983	74.5	7165	82.9
Risk Category							
	Low: T2-3N0					5987	69.2
	High: T4N0 or T2-4N1-3					2660	30.8

At diagnosis (Time 0), low-risk patients had a significantly better unadjusted 10-year CSS rates (low-risk, 79.6%; high-risk, 41.2%; $p < 0.001$). Analysis of 10-year CSS rates conditioned on annual cumulative survival remained significantly different between low and high-risk groups after 1, 2, 3, 4, 5, 6, and 7 years of CS; after 5 years of CSS, low-risk patients ($n = 2247$) still have a higher likelihood of 10-year survival (91.3%) when compared to high-risk ($n = 651$, 84.1%, $p < 0.001$). This difference held until 8 years after local treatment; at that point, CS rates were no longer significantly different between low ($n = 1472$) and high-risk ($n = 373$) groups (low-risk, 95.4%; high-risk, 91.7%; $p = 0.51$) (Figures 1a, 1b, and 1c).

Number at risk (n):

Low Risk	2309	1542	1161	830	622	486
High Risk	667	452	347	293	232	197

Number at risk (n):

Low Risk	670	438	300
High Risk	183	115	72

Figure 1: Kaplan-Meier 10-year cancer-specific survival curves at time zero (Figure 1a), after 5 years of cancer-specific survival (Figure 1b) and after 8 years of cancer-specific survival (Figure 1c).

Heterogeneity testing demonstrated a significant interaction between LN status and presence of ulceration; however, this interaction was not clinically relevant. When stratified by ulceration status, the survival data for low and high-risk tumors still converge and lose significance after 8 years of cancer-specific survival.

Table 3 lists hazard ratio (HR) and 95% confidence intervals (CIs) for tumor and patient characteristics stratified by survival time. Multivariate analysis demonstrated that high-risk tumors, ulcerated tumors, trunk tumors, head and neck tumors, male gender, and age > 60 at the time of diagnosis adversely affected 10-year CSS. These factors began to lose significance after 5 years of CSS; at this time, only high-risk tumors (HR 2.2, 95% CI 1.6-3.0) and head and neck primary tumors sites (HR 1.6, 95% CI 1.1-2.5) were significant. Notably, ulceration (an important prognostic factor at the time of diagnosis), lost significance after 5 years of survival. After 8 years of cumulative CSS, all of the early risk factors were no longer significant predictors of future cancer-specific outcome.

Table 3: Multivariate Regression Analysis of 10-year Cancer-Specific Mortality.

For all patients at time of diagnosis, at 5 years of conditional survival, and at 8 years of conditional survival.

Risk Factor	TIME OF DIAGNOSIS		5-YEAR CONDITIONAL SURVIVAL		8-YEAR CONDITIONAL SURVIVAL	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Tumor						
Low risk tumor	1.0		1.0		1.0	
High risk tumor	4.6 *	4.1-5.1	2.2 *	1.6-3.0	1.4	0.5-4.2
Ulceration Status						
Absent	1.0		1.0		1.0	
Present	1.8 *	1.6-2.0	1.4	0.9-2.2	0.5	0.06-3.6
Primary Tumor Site						
Extremity	1.0		1.0		1.0	
Head and neck	1.6 *	1.3-1.8	1.6 *	1.1-2.5	1.0	0.3-3.2
Trunk	1.3 *	1.2-1.5	1.3	0.9-1.9	1.9	0.6-6.4
Gender						
Female	1.0		1.0		1.0	
Male	1.2 *	1.1-1.3	1.2	0.8 - 1.6	0.8	0.3-2.1
Age at Diagnosis						
≤ 60	1.0		1.0		1.0	
>60	1.5 *	1.4-1.7	1.3	0.96-1.9	0.8	0.2-2.7

***p<0.05**
CI = Confidence Interval

Discussion

The utility of CS as a means of stratifying risk and survival after a certain cancer-free period is becoming increasingly established.^{8, 9, 11, 12, 18} A potentially useful tool for clinical practitioners, CS assesses the changing risk of dying from cancer over a period of time and may serve to guide the implementation of appropriate surveillance strategies for long-term cancer survivors. Such information has the potential to significantly impact patient counseling and decision-making. In the current study evaluating over 8700 patients, we demonstrated that melanoma conditional survival data may be a more appropriate tool for understanding on-going survival for patients who survive the initial period following WLE and sentinel lymph node biopsy (SLNB).

Traditional American Joint Committee on Cancer survival rates, which are commonly used for clinical decision making and risk counseling, are heavily influenced by early death; as such, traditional survival data may not be the most accurate predictor for long-term melanoma survivors.¹⁹ As an example of this, Cormier and colleagues performed a review of patients with melanoma of all stages. Using the extensive national data available from SEER, they found that patients with stage II disease had a 10-year disease specific survival (DSS) of 61.5%; this decreased to 44.1% for patients with stage III disease, and 16.1% for patients with distant (stage IV disease). After 5 years of survival, however, the likelihood of surviving another 5 years increased to 86% for patients with stage II disease, 87% for those with stage III disease, and 84% for those with stage IV disease.¹⁴

As a logical extension of this data, we hypothesized that a direct comparison of CS survival curves would demonstrate that after a certain period of accumulated survival, stage at the time of diagnosis would no longer be a significant predictor of on-going survival. We sought to define the time in follow-up when survival curves would converge, regardless of original cancer stage. We further hypothesized that the specific patient and tumor variables that predicted survival at the time of diagnosis would not be predictive after a period of time for patients who had appropriate oncologic treatment of their disease.

In our analysis, we defined appropriate oncologic treatment based on the recommended guidelines published by the National Comprehensive Cancer Network (NCCN). This consists of WLE with 1 cm margins for thin melanoma (< 1 mm in thickness) and 2 cm margins for tumors ≥ 1 mm.² In a 2003 meta-analysis representing over 2000 patients, Haigh and colleagues found that surgical excision margins beyond 2 cm conferred no significant survival benefit regardless of the depth of the original tumor.²⁰ Because the SEER database does not collect information on margin status for patients who undergo excision, we were limited in the current analysis to including patients based on a documented surgical intervention, without knowledge of the margins obtained.

As an additional therapy for tumors ≥ 1 mm, SLNB is recommended for patients who present with clinically negative nodes.^{1, 5, 7} In the Multicenter Selective Lymphadenectomy Trial (MSLT) Morton and colleagues reported a significant 5-year survival benefit for patients undergoing SLNB (72.3%) versus those managed with

delayed completion node dissection if metastatic disease became clinically detectable (52.4%).²¹

Additionally, as our understanding of the prognostic factors associated with melanomas <1mm in thickness has evolved, NCCN guidelines now recommend consideration of SLNB if “adverse features” (ulceration, positive deep margin, lymphovascular invasion, or mitotic rate > 1 per mm²) are present; however, the survival benefit of SLNB to this population of patients remains unclear.² In the current study, 43,441 patients were identified with T1 tumors; of those, 16.8% underwent LN evaluation and 13% of those were positive, resulting in an overall upstaging of less than 2%. Because patients with T1 tumors have an overall 10-year CSS of 90%, and because LN evaluation is a discretionary part of their management, we excluded them from our analysis; regardless of factors present at diagnosis, patients with thin tumors who undergo WLE are likely to survive. As such, the benefit from a CS analysis in this population is limited. This exclusion is supported by the CS analysis published in 2010 by Xing and colleagues, who found that the 5-year CS estimates were constant over time for patients with stage I disease.¹⁴

Despite the fact that the technical details of intraoperative lymphatic mapping were published in the early 1990s²²⁻²⁴ and have been recommended as an appropriate step in oncologic care since 1992, we found it interesting in the current study that more than 7,500 patients (45%) were excluded because SLNB was not performed or reported. This was much higher than the single-institution rate of non-compliance published by Erickson-Foster and colleagues in 2008, who estimated that nearly 20% of patients are

undertreated based on current NCCN guidelines.³ This discrepancy can likely be explained by our use of a large, national database rather than a single-institution review; it is likely that unmeasured and unavailable factors—such as surgical oncology surgical specialty training, hospital volume, and/or patient selection—may be impacting our data and contributing to the higher non-compliance rate. As such, our findings are likely to be more reflective of what can be expected from current national practice patterns. The national underutilization of SLNB seen in our study highlights the need for ongoing education initiatives and more aggressive quality of care measures to assure appropriate oncologic therapy for melanoma patients nationwide.

Adherence to the current recommendation for SLNB is of particular interest for our baseline understanding of melanoma survival; based on patient and tumor characteristics present at the time of diagnosis, LN status is the greatest predictor of cancer survival^{5, 7, 25, 26} and is an important part of initial cancer staging. Because we excluded patients without appropriate LN evaluation from our study, we are unable to assess the impact, if any, that non-adherence to current recommendations may have on long-term melanoma survival. Our analysis, however, demonstrated that among patients who did have LN evaluation and who survived the first 8 years after treatment, original LN status was no longer a significant predictor of on-going survival. These findings may have important implications for the counseling of long-term melanoma survivors, in that the presence of LN metastases was no longer associated with cancer mortality after 8 years of survival.

Clearly, after a certain period of cancer-free survival, patient prognosis is actually better than what would have been predicted at the time of diagnosis. Several studies have demonstrated that the risk of cancer-specific death changes over time. Gamel and colleagues published a series of over 5800 melanoma patients in 2002, demonstrating that after 15 years of cancer-specific survival, the probability of on-going survival was equal among all risk groups.⁴ Similarly, Slingluff and colleagues reported that after 10 years of survival, the risk of melanoma death in early stage disease was nearly eliminated.³¹ Our data support these data in a novel and direct comparison of CSS among low and high-risk melanoma categories, with the finding that high-risk melanoma is no longer a significant prognostic indicator after 8 years of CSS. In our direct comparison of melanoma conditional survival rates, we demonstrated that traditional survival curves are too heavily impacted by early death, causing an initial steep drop. When this initial steep drop stabilizes, CS rates provide more accurate estimates of long-term survival, and are based on the premise that as survival time increases, the likelihood of further survival increases.^{10-12, 18}

Similarly, we demonstrated that beyond original tumor stage, the prognostic significance several other patient and tumor factors diminish as survival time accumulates. In our study, neither patient gender, age, anatomic location, nor ulceration status of the primary tumor were predictive of CSS after 8 years of cumulative survival, despite the finding that these factors were significant predictors of survival prior to that time.^{4, 27-30} This observation suggests that cumulative survival time is the greatest

predictor of future survival for long-term melanoma survivors after adequate melanoma treatment.

We acknowledge the limitations of our analysis. For uniformity, we focused on those patients with documented LN staging, excluding over 7,500 patients without nodal status documented. Thus, our cohort is limited to those patients who received care consistent with established treatment guidelines. Regional variations in adherence to guidelines may interfere with any population-based survival analysis, including ours. Similarly, SEER does not record the use of adjuvant systemic therapies, such as interferon-alpha, nor does it capture specific surgical or disease details such as margin status or cancer recurrence. Thus, we are unable to analyze the impact, if any, that the use of adjuvant therapies, surgical margin status, or tumor recurrence may have on CS.

Despite the potential limitations, our analysis has several strengths. SEER is population-based and includes patients from diverse locations and practices in the United States, making our findings broadly reflective of standard practice. By using population-based, national data rather than single-institution, specialized cancer center data, our analysis has likely captured a more accurate estimate of what can be expected for modern practice patterns at the national level. Moreover, our population-based study includes large numbers of patients with long-term follow-up. Importantly, we have performed the first direct survival analysis of this type, comparing the long-term CSS among patients with different disease stages and different baseline survival risk categories. Our findings provide support for similar studies in other surgically-resected tumors and have important implications for current practice patterns.

Conclusion

This is the first analysis that directly compares survival rates between low-risk and high-risk patients, and demonstrates that after 8 years of melanoma survival, CS data become discordant with traditionally used estimates. As an alternative to traditional estimates, CS data provide a more accurate understanding of patients' changing risk of cancer death over time, resulting in meaningful implications for patient surveillance and follow up. The results of this study suggest that after a certain point in follow-up, prognostic factors present at the time of diagnosis are no longer significant predictors of on-going survival; as such, patients who initially present with high-risk tumors may require no more aggressive surveillance than their low-risk counterparts after 8 years of survival. Alternatively, ongoing surveillance may potentially be standardized, focusing on clinical skin and lymph node evaluation for all melanoma survivors. The elimination of routine and potentially unnecessary imaging studies has important implications for resource utilization, a timely finding given the current medical economy.

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