Disparities in diagnosis of advanced melanoma: A population-based study

RUNNING TITLE: **Factors associated with advanced melanoma in Ontario**

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Abstract

Background: To investigate whether there is equitable access to timely diagnosis of melanoma in Canada, we undertook a population-based study in Ontario investigating the relationship between advanced melanoma and patient and health system factors.
Methods: We obtained, abstracted, and linked pathology reports for a 65% random sample of all invasive cutaneous melanoma in Ontario from 2007 to 2012 to the Ontario Cancer Registry. Associations between advanced melanoma (thickness >2.0mm) and patient-, health system-, and tumor- factors were described and analyzed using multivariable modified Poisson regression.
Results: In total, 8,043 patients had histologically confirmed melanoma and thickness information. 46.7% were female, median age at diagnosis was 62 years, and 25.7% of patients had advanced melanoma. In multivariate analyses, advanced age (RR:1.53, 95% CI:1.37–1.71), male sex (RR:1.12, 95% CI:1.05–1.20), lowest SES quintile (RR:1.24, 95% CI:1.12–1.38), and health region (RR range:0.92–1.34, p=0.0052 for variable) were significantly associated with advanced melanoma. Presence of ulceration significantly modified many of these associations.
Conclusions: Disparate rates of advanced melanoma according to our variables suggest there may be inequitable access to timely diagnosis of melanoma in Ontario. This highlights a potential opportunity for system improvement to ensure timely and equitable access to melanoma care.

KEYWORDS: epidemiology, cancer, melanoma, advanced stage, health services, equity, access

Introduction

Canadian studies investigating disparities in melanoma thickness at diagnosis have rarely been performed due to the challenges in collecting melanoma stage information at the population level. Studies conducted in other jurisdictions have found disparate rates of advanced melanoma according to race/ethnicity (1–3), socioeconomic status (SES) (4–6), age (7–10), sex (7,10), anatomic site (11,12), histological subtype (13,14), and area of residence (15). As many studies were conducted in a non-universal healthcare setting (i.e. the U.S.), results may not be generalizable to populations where universal healthcare exists.

No published study in Canada has investigated disparities in melanoma thickness in a modern cohort of patients. We set out to evaluate patient- and health system- level factors that are independently associated with advanced melanoma diagnosed in the Canadian province of Ontario. We will also describe the impact of ulceration on identified relationships, hypothesizing that this feature would influence the ease of early detection of melanoma in our cohort.

Methods

Study population

This was a retrospective population-based cohort study, conducted using a 65% random sample of all invasive melanoma cases diagnosed in Ontario between January 1, 2007 and December 31, 2012 in the Ontario Cancer Registry (OCR). Those whose first melanoma diagnosis was purely *in situ* on all specimens were excluded, due to the possibility of greater screening in these individuals, and likely incompleteness of the pure *in situ* data in OCR. Patients determined to be from out of province, and those without a pathology report from Cancer Care Ontario (CCO) were excluded. Details of the earliest melanoma were utilized when multiple primaries were reported. Patients younger than 20 years of age were also excluded.

Data sources

Ontario Cancer Registry and Pathology reports

Data from CCO's population-based Ontario Cancer Registry (OCR) was utilized to identify cases of melanoma. It is known for its very high level of accuracy and completeness levels of 95% overall (16). Data contained in OCR includes patient demographic characteristics and stage information on a subset of patients seen in cancer centers and selected health care sites.

Available pathology reports for all patients were provided from CCO and abstracted according to a standardized algorithm and linked to each patient's OCR record according to their group ID. Reliability testing indicated 97.1% agreement between our abstractors and a clinician experienced in melanoma. M-category data was supplemented by information on stage provided by regional cancer centers.

Classification of independent variables

Patient-level factors

Patient characteristics included age at diagnosis, sex, and SES. Age and sex were ascertained from OCR. SES was assigned using the Ontario Marginalization Index (ON-Marg). The ON-Marg is the Ontario version of the Canadian Marginalization Index, an area-based socioeconomic measure developed to explore differences in marginalization between areas of Ontario (17). ON-Marg has previously been associated with health outcomes (17–19). The material deprivation dimension of the ON-Marg was utilized, incorporating such indicators as education, government subsidies, and income.

Disease-level factors

Disease characteristics include histological subtype, anatomic location of the primary melanoma, and ulceration status. Histological subtype and anatomic location were available in

OCR. Presence of ulceration was available from pathology abstraction. The presence of ulceration was utilized as factor hypothesized to influence the ease of early detection of melanoma, impacting the strength of association between factors of interest and thickness of melanoma. This variable was thus tested for effect modification. When thickness was available but ulceration status was missing, ulceration was assigned as 'absent'.

Health system-level factors

Health region and rurality were investigated. Ontario is subdivided into 14 healthcare regions called Local Health Integration Networks (LHINs), each responsible to fund, coordinate, and provide healthcare services for their region.

Rurality was measured via the Rurality Index of Ontario (RIO). RIO is a measure of relative rurality of Ontario census subdivisions and measures geographic factors related to access to health services using a weighted formula that considers population size and density, travel time to the nearest basic referral centre, and travel time to the nearest advanced referral center (20,21). RIO is based on a 0-100 scale, with higher scores indicative of a greater degree of rurality.

Classification of dependent variable

The primary analyses were conducted with advanced melanoma defined as a Breslow thickness >2.0 mm. Thickness was chosen given its strong independent prognostic value for overall survival, and its relevance to most cases of melanoma diagnosed at the population level; advanced thickness is the most common reason for advanced stage, defined as AJCC stage II-IV. Unlike other stage-related variables (e.g. N- and M-category), thickness is available in pathology reports systematically collected by OCR for the vast majority of patients.

Secondary analyses were conducted defining advanced melanoma as an AJCC 7th edition stage II and above. By definition, all melanomas >2.0 mm are stage II and above. Data abstracted from pathology reports were utilized to derive AJCC stage. When elements of the AJCC stage were missing, minimum stage was assigned.

Statistical analyses

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). Univariate associations were assessed with chi-square statistics. All variables independently associated with advanced melanoma, with $p < 0.20$, were added into a mutually adjusted multivariable modified Poisson model with a robust error variance; variables remained in the model with $p < 0.20$. Effect modification was assessed by including interaction terms with ulceration status and each of the variables, and assessing their significance. Sensitivity analyses were conducted to assess our assumptions regarding missing data. Kaplan-Meier product-limit method was used to characterize survival stratified by the presence of advanced melanoma.

Results

Study population

Our 65% random sample included 9687 patients with a diagnosis of cutaneous melanoma in OCR between 2007 and 2012. Patients were excluded if they did not have melanoma (n=53), were out of province (n=248), had a first melanoma diagnosis captured as purely *in situ* (n=393), were younger than 20 years of age, or if their date of death preceded their date of diagnosis (n=35). There were thus 8958 potential cases of invasive melanoma. Of these, 350 had no pathology report available from OCR. An additional 566 patients were excluded from our primary analysis on thickness due to missing thickness information (e.g. M1 patients with only a metastasis biopsy). The final sample was thus 8042 patients with thickness information.

Table 1 presents cohort characteristics stratified by ulceration. Description of advanced melanoma according to patient-, system-, and disease- factors are presented in Table 2. Older patients, male patients and those living in the most deprived SES quintile were more likely to have advanced melanoma ($p<0.0001$). Patients with advanced melanoma were also more likely to have nodular melanomas ($p<0.0001$), or present with ulceration ($p<0.0001$). Those with melanomas diagnosed on the head/neck ($p<0.0001$) and unspecified areas ($p<0.0001$) were more likely to be advanced.

Effect modification

Interaction terms for presence of ulceration were statistically significant ($p<0.05$) for age, SES, and histology, and body site approached significance ($p=0.05$). For this reason, we performed analyses stratified by ulceration (Table 2 and Table 3). Similar significance of interactions was observed using the advanced AJCC stage definition (Appendix 1).

Relative risk of advanced melanoma

Results for the univariate and multivariate modified Poisson regression are presented in Table 3. Univariate analyses revealed significant associations between all variables and advanced melanoma ($p<0.05$). When all variables were included in the modified Poisson model, rurality lost significance ($p=0.63$), and was removed from the final model.

After controlling for all variables in the final model, males had a 12% greater risk of being diagnosed with advanced melanoma compared to females (RR: 1.12; 95% CI: 1.05–1.20). Risk of advanced melanoma also increased with age. For example, those between the ages of 76 and 85 had a 27% greater risk compared to those aged 56 to 65 (RR: 1.27; 95% CI: 1.15–1.39). In addition, those living in neighbourhoods in the most deprived SES quintile had a 24% greater risk of advanced melanoma, compared to the least deprived SES quintile (RR: 1.24; 95% CI:

1.12–1.38). There was also variation between the LHINs, with relative risks of individual LHINs ranging from 0.92 to 1.34 (p=0.0052). When stratified by ulceration status, disparities were greatest for non-ulcerated cases, and attenuated for many of the estimated relative risks for ulcerated cases (Table 3), however many remained significant. Similar, albeit attenuated, findings were observed using our AJCC stage-based definition of advanced melanoma when stratified by ulceration (Appendix 1).

Survival analyses

Five-year overall survival was 81% for our entire cohort. Survival with advanced melanoma was 55.9%, compared to 89.7% with non-advanced melanoma (p<0.0001; Figure 1).

Sensitivity analyses

Several sensitivity analyses were conducted to ensure the robustness of the assumptions made for missing data. For cases with thickness data but missing ulceration, there was negligible difference in relative risks in models with unreported ulceration set as 'missing', where unreported ulceration cases were excluded, and where unreported ulceration was set to 'absent'.

It was hypothesized that patients with no pathology report more often had an advanced-stage cancer, and were too ill for further testing. Indeed, those with no pathology reports had lower survival, had a higher proportion of melanoma not otherwise specified (NOS) in OCR, and had 'unspecified' location of the primary melanoma, compared to those who had a pathology report. In a model assuming those without pathology reports had an advanced stage melanoma, there were negligible differences in relative risks compared to the baseline model.

Discussion

In this contemporary Canadian melanoma cohort from Ontario, we discovered substantial differences in risk of advanced melanoma for patients living in more deprived regions of the

province, and for patients living within certain health regions (LHIN). There was also greater risk of advanced melanoma for male sex and for older patients. Findings are important given the large differences in survival observed for advanced melanoma in our cohort. Disparities were greatest when ulceration was absent, which may hold relevance when developing and evaluating system-level prevention strategies. These associations suggest that there may be inequitable access to timely diagnosis of cutaneous melanoma in Ontario, requiring further investigation and action.

There are important strengths to our study. Cases of melanoma came from OCR which is population-based. This provincial database is known for its completeness and accuracy (16,22). This was important as melanoma can be diagnosed and treated in a variety of health care settings. As pathology reports for all cancer diagnoses are archived by OCR, we could undertake primary data collection on pathologic stage information. This improved the generalizability of our findings to the population of Ontario, and allowed us to characterize and measure advanced melanoma burden in Ontario using a population-based sample.

We found disparate rates of advanced melanoma according to sex, age, SES, LHIN, histology, ulceration and anatomic location. Our results suggest that each of these variables is independently associated with advanced melanoma in Ontario. Our stratified analyses suggest that larger disparities exist when ulceration is absent. To explain this finding, we hypothesize that disparities may be more pronounced when melanoma is asymptomatic (e.g. some non-ulcerated melanomas) or there is disparate awareness of certain warning signs between groups (e.g. the ABCDEs of melanoma: Asymmetry, Border, Colour, Diameter and Evolution). Melanoma ABCDE's are perhaps the best known warning signs to the public, and are

particularly relevant to superficial spreading melanoma; thick melanomas are more likely to be nodular, ulcerated, fast growing, and non-pigmented.

Advanced age was associated with advanced melanoma. The reason is probably multifactorial. It may be that when melanoma is more difficult to detect—captured indirectly in our study by lack of ulceration—that older individuals are even less likely to self-detect a melanoma in its early stages or promptly seek medical attention compared to younger individuals. Other health issues and symptoms may be considered more pressing. There may be age-related immunosuppression. It may also be that disparities in awareness of early warning signs of melanoma exist by age, and that this has a stronger influence on the detection of non-ulcerated melanomas.

After adjustment for other factors, males were still at an increased risk of being diagnosed with advanced melanoma, compared to females (RR: 1.12; 95% CI: 1.05–1.20). There may be differences in health seeking behaviour between the sexes, or differences in tumor-related factors other than ulceration. In keeping with known epidemiology, males were more likely to be diagnosed with a trunk melanoma; trunk lesions on males most often occur on the back, impeding self-detection (23).

We found variation in the risk of advanced melanoma according to an area-level measure of SES. Those in the lowest SES quintile (the most deprived) had a 24% increased risk of being diagnosed with advanced melanoma (RR: 1.24; 95% CI: 1.12–1.38). Risk of advanced melanoma was greater among these groups when ulceration was absent. It may be that those living in more deprived neighbourhoods are less likely to appreciate the seriousness of their lesion until it displays more advanced features such as ulceration, or they may be unable to advocate for themselves when they suspect an unusual lesion (24). Moreover, there may be

issues regarding access to care for those of lower SES. For instance, those of lower SES may be unable to afford travel to a specialist, particularly if residing outside of a major urban centre where specialists are concentrated. Notably, dermatologists per 100,000 population is greatest in the Toronto Central, Central and Champlain LHINs, with substantially less supply in all other LHINs (25).

Finally, we observed variations in advanced melanoma diagnoses across health regions in Ontario, even after adjusting for other factors such as SES and age. There may be system-level differences in access to care, and/or quality of care. There is a need for research elucidating details of the diagnostic pathways and access to specialist care for patients in different LHINs. Variation in access to dermatologists and other skin care specialists across the LHINs is one hypothesis.

There are several limitations to this study. There is a risk of misclassification of stage and pathologic prognostic factors. To mitigate this risk, thickness and stage data was collected directly from pathology reports using a standardized algorithm. We utilized ecologic measures of SES. Household and individual-level SES variables such as age and income vary substantially within regions. This is a recognized limitation of any study using postal code-based measures, and is acknowledged. We did not investigate pure *in situ* disease as complete population data was unavailable. Finally, there is the possibility of residual confounding. For example, presence of comorbidities has the potential to influence the association between several of our variables and advanced melanoma, however, comorbidity is correlated with age, sex, and SES, which we controlled for in our analysis (26–28).

Conclusions

This was a contemporary study of melanoma in a universal healthcare setting, adding to the limited population-level literature on the diagnosis of advanced melanoma in Canada. We discovered clinically relevant differences in the risk of advanced melanoma according to SES and health region (LHIN). There was also more advanced melanoma diagnosed in males and older individuals that may relate in part to inequitable access to care, even within a universal healthcare setting. As expected, survival was substantially worse for advanced melanoma in our cohort. Disparities were greater when ulceration was absent, and holds relevance when developing and evaluating system-level interventions for early detection. Future research is required to delve into the reasons why these disparities in advanced melanoma diagnosis exist, to help improve early detection, and potentially increase survival.

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TP Hanna and ME Mavor had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Table 1: Cohort patient-, health system-, and disease- factors: overall, and stratified by ulceration status

Characteristic	Overall (Thickness cohort)	Ulceration Absent	Ulceration Present
No. of patients	8042	6581	1461
Patient Factors			
Sex			
Male	53.31%	51.13%	63.11%
Female	46.69%	48.87%	36.89%
Age			
Median age, years (mean)	62 (61.52)	61 (60.28)	69 (67.09)
20 – 45	17.17%	18.72%	10.20%
46 – 55	18.47%	19.54%	13.62%
56 – 65	21.38%	22.00%	18.55%
66 – 75	20.09%	19.69%	21.90%
76 – 85	17.50%	15.85%	24.91%
>85	5.40%	4.19%	10.81%
Material Deprivation			
Least deprived	27.14%	27.84%	24.02%
Quintile 2	23.82%	23.60%	24.85%
Quintile 3	19.47%	19.18%	20.81%
Quintile 4	14.23%	13.83%	16.02%
Most deprived	9.00%	8.37%	11.84%
Missing	6.33%	7.19%	2.46%
Health System Factors			
Local Health Integration Network (LHIN)			
LHIN A	8.33%	8.63%	6.98%
LHIN B	7.67%	8.08%	5.82%
LHIN C	9.34%	9.48%	8.69%
LHIN D	4.94%	4.68%	6.09%
LHIN E	10.63%	11.02%	8.90%
LHIN F	6.64%	6.72%	6.30%
LHIN G	5.83%	5.80%	5.95%
LHIN H	12.19%	12.10%	12.59%
LHIN I	6.45%	6.25%	7.39%
LHIN J	1.29%	*	*
LHIN K	3.31%	3.28%	3.42%
LHIN L	13.29%	12.64%	16.22%
LHIN M	5.66%	5.64%	5.75%
LHIN N	4.43%	*	*
Rurality			
Median rurality (mean)	5.0 (13.49)	5.0 (13.48)	5.0 (13.52)
Rural (≥ 40)	10.15%	10.04%	10.61%
Nonmajor Urban (9.01-39)	26.24%	26.26%	26.15%
Major urban (0-9)	57.36%	56.59%	60.85%
Missing	6.25%	7.11%	2.40%
Disease Factors			
Breslow thickness			
Median thickness (mean)	0.87mm (2.02mm)	0.70mm (1.28mm)	3.86mm (5.34mm)
T1 (≤ 1.0mm)	55.71%	66.75%	5.95%
T2 (1.01 – 2.0mm)	18.57%	19.13%	16.02%
T3 (2.01 – 4.0 mm)	13.08%	9.04%	31.28%
T4 (≥ 4.0mm)	12.65%	5.08%	46.75%
Histological subtype			
Superficial spreading	41.10%	44.96%	23.68%
Lentigo maligna	8.12%	9.31%	2.74%
Acral lentiginous	1.63%	1.12%	3.90%
Nodular	13.18%	7.26%	39.84%
NOS	31.83%	33.70%	23.41%
Other	4.14%	3.63%	6.43%
Body site			
Extremities	46.21%	46.47%	45.04%
Face	12.41%	12.57%	11.70%
Head and Neck	5.70%	5.26%	7.67%
Trunk	32.23%	32.49%	31.07%
Unspecified	3.46%	3.22%	4.52%

Characteristic	Overall (Thickness cohort)	Ulceration Absent	Ulceration Present
Presence of ulceration			
Present	18.17%	-	-
Absent	81.83%	-	-
Lymph node involvement			
Present	9.99%	5.80%	28.82%
Absent	90.01%	94.20%	71.18%
Distant metastases			
Present	1.19%	0.76%	3.15%
Absent	98.81%	99.24%	96.85%
*Censored due to small cell count			

Table 2: Presence of advanced melanoma according to study factors, and table stratified by ulceration status

Characteristic	Overall % Advanced (> 2.0 mm)	Ulceration Absent % Advanced (> 2.0 mm)	Ulceration Present % Advanced (> 2.0 mm)	p-value†
No. of patients	2069	929	1140	
Patient Factors				
Sex				Overall: p<0.0001
Male	29.55%	15.81%	79.72%	Abs: p<0.0001
Female	21.36%	12.34%	75.14%	Pres: p=0.0414
Age				Overall: p<0.0001
Median age, years (mean)	69 (67.16)	67 (65.88)	71 (68.20)	
20 – 45	14.99%	8.20%	71.14%	Abs: p<0.0001
46 – 55	19.39%	10.96%	73.87%	Pres: p<0.0001
56 – 65	22.40%	13.05%	72.32%	
66 – 75	26.98%	14.89%	75.94%	
76 – 85	37.10%	20.90%	83.52%	
>85	53.23%	31.52%	91.14%	
Material Deprivation				Overall: p<0.0001
Least deprived	22.86%	12.83%	75.21%	Abs: p<0.0001
Quintile 2	25.31%	12.88%	78.51%	Pres: p=0.3783
Quintile 3	28.29%	16.24%	78.29%	
Quintile 4	29.98%	17.80%	77.35%	
Most deprived	35.08%	19.78%	83.82%	
Missing	8.84%	3.81%	75.00%	
Health System Factors				
Local Health Integration Network (LHIN)				Overall: p=0.0009
LHIN A	21.34%	11.27%	77.45%	Abs: p=0.0101 Pres: p=0.6349
LHIN B	22.69%	13.53%	80.00%	
LHIN C	23.44%	13.46%	72.44%	
LHIN D	23.93%	9.09%	75.28%	
LHIN E	24.33%	14.21%	80.77%	
LHIN F	24.72%	13.80%	77.17%	
LHIN G	25.37%	15.18%	70.11%	
LHIN H	25.51%	12.81%	80.43%	
LHIN I	26.78%	13.63%	76.85%	
LHIN J	26.92%	*	*	
LHIN K	27.07%	15.74%	76.00%	
LHIN L	29.19%	15.14%	78.48%	
LHIN M	31.21%	19.41%	83.33%	
LHIN N	31.74%	*	*	
Rurality				Overall: p<0.0001
Median rurality (mean)	5.0 (13.41)	5.0 (13.26)	5.0 (13.53)	
Rural (≥ 40)	27.82%	16.04%	78.06%	
Nonmajor Urban (9.01-39)	25.73%	14.47%	76.70%	Rurality abs: p<0.0001 Rurality pres: p=0.8977
Major urban (0-9)	27.16%	14.88%	78.63%	
Missing	9.15%	4.06%	77.14%	
Disease Factors				
Histological subtype				Overall: p<0.0001
Superficial spreading	13.62%	7.98%	61.85%	Abs: p<0.0001
Lentigo maligna	9.34%	6.53%	52.50%	Pres: p<0.0001
Acral lentiginous	51.15%	22.97%	87.72%	
Nodular	77.92%	62.97%	90.21%	
NOS	18.87%	10.55%	72.81%	
Other	54.65%	42.26%	86.17%	
Body site				Overall: p<0.0001
Extremities	24.62%	13.21%	77.66%	Abs: p<0.0001
Face	25.45%	15.36%	74.27%	Pres: p=0.3221
Head and Neck	38.86%	23.99%	84.82%	
Trunk	24.23%	12.82%	80.30%	
Unspecified	33.81%	19.34%	77.97%	

Characteristic	Overall % Advanced (> 2.0 mm)	Ulceration Absent % Advanced (> 2.0 mm)	Ulceration Present % Advanced (> 2.0 mm)	p-value†
Presence of ulceration				Overall: p<0.0001
Present	78.03%	-	-	-
Absent	14.12%	-	-	-
Lymph node involvement				Overall: p<0.0001
Present	73.35%	54.45%	90.50%	Abs: p<0.0001
Absent	20.44%	11.63%	72.98%	Pres: p<0.0001
Distant metastases				Overall: p<0.0001
Present	61.46%	38.00%	86.96%	Abs: p<0.0001
Absent	25.30%	13.93%	77.74%	Pres: p=0.1373

*censored due to small cell counts
Note: % Advanced = 100% - % non-advanced
†p-values based on chi-square test.

Table 3: Relative risk of advanced melanoma from Modified Poisson regression; results stratified by ulceration status are included (Continued on next page)

	Unstratified Unadjusted Model		Unstratified Adjusted Model*		Stratified Adjusted Model				
					Ulceration absent**		Ulceration present**		
Variable	**RR (N=8042)**	**95% CI**	**RR: No interactions (N=8042)**	**95% CI**	**RR (N=6581)**	**95% CI**	**RR (N=1461)**	**95% CI**	**Significance of interaction**
Patient Factors									
Sex	**p<0.0001**		**p=0.0006**		**p=0.0296**		**p=0.0119**		**p=0.4114**
Male	1.38	(1.28 – 1.49)	1.12	(1.05 – 1.20)	1.14	(1.01 – 1.27)	1.08	(1.02 – 1.14)	
Female	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		
Age	**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**
20 – 45	0.67	(0.57 – 0.78)	0.83	(0.73 – 0.94)	0.75	(0.61 – 0.93)	1.01	(0.90 – 1.14)	
46 – 55	0.87	(0.76 – 0.99)	0.97	(0.87 – 1.09)	0.92	(0.77 – 1.12)	1.04	(0.94 – 1.16)	
56 – 65	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		
66 – 75	1.20	(1.07 – 1.36)	1.13	(1.03 – 1.25)	1.13	(0.95 – 1.34)	1.08	(0.98 – 1.18)	
76 – 85	1.66	(1.48 – 1.85)	1.27	(1.16 – 1.40)	1.40	(1.19 – 1.64)	1.15	(1.05 – 1.25)	
>85	2.38	(2.10 – 2.69)	1.53	(1.37 – 1.72)	2.04	(1.68 – 2.49)	1.26	(1.16 – 1.37)	
Deprivation	**p<0.0001**		**p<0.0001**		**p<0.0001**		**p=0.3471**		**p<0.0001**
Least deprived	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		
Quintile 2	1.11	(0.99 – 1.23)	1.05	(0.96 – 1.15)	0.99	(0.84 – 1.16)	1.05	(0.97 – 1.13)	
Quintile 3	1.24	(1.11 – 1.38)	1.12	(1.02 – 1.23)	1.24	(1.05 – 1.46)	1.03	(0.95 – 1.12)	
Quintile 4	1.31	(1.17 – 1.48)	1.14	(1.03 – 1.26)	1.19	(1.00 – 1.41)	1.01	(0.93 – 1.10)	
Most deprived	1.53	(1.35 – 1.74)	1.24	(1.12 – 1.38)	1.31	(1.08 – 1.58)	1.10	(1.01 – 1.20)	
Missing	0.39	(0.29 – 0.52)	0.56	(0.44 – 0.71)	0.40	(0.26 – 0.63)	1.01	(0.83 – 1.22)	
Health System Factors									
LHIN	**p=0.0014**		**p=0.0053**		**p=0.1053**		**p=0.2405**		**p=0.6475**
LHIN A	0.73	(0.62 – 0.87)	1.04	(0.90 – 1.19)	0.88	(0.69 – 1.14)	1.06	(0.94 – 1.19)	
LHIN B	0.78	(0.65 – 0.92)	1.08	(0.94 – 1.25)	1.04	(0.82 – 1.33)	1.06	(0.94 – 1.19)	
LHIN C	0.80	(0.68 – 0.94)	1.09	(0.95 – 1.24)	0.99	(0.79 – 1.25)	0.99	(0.88 – 1.12)	
LHIN D	0.82	(0.67 – 1.00)	1.00	(0.86 – 1.18)	0.76	(0.53 – 1.09)	1.06	(0.93 – 1.21)	
LHIN E	0.83	(0.72 – 0.97)	1.10	(0.97 – 1.24)	0.99	(0.79 – 1.24)	1.08	(0.98 – 1.20)	
LHIN F	0.85	(0.71 – 1.01)	1.09	(0.94 – 1.26)	0.98	(0.76 – 1.27)	1.06	(0.94 – 1.20)	
LHIN G	0.87	(0.73 – 1.04)	0.92	(0.79 – 1.07)	0.83	(0.65 – 1.06)	0.90	(0.78 – 1.03)	
LHIN H	0.87	(0.76 – 1.01)	1.05	(0.93 – 1.18)	0.95	(0.76 – 1.18)	1.06	(0.96 – 1.17)	
LHIN I	0.92	(0.77 – 1.09)	1.04	(0.91 – 1.19)	0.97	(0.75 – 1.27)	1.04	(0.93 – 1.16)	
LHIN J	0.92	(0.66 – 1.28)	1.20	(0.91 – 1.58)	1.15	(0.70 – 1.90)	1.07	(0.86 – 1.33)	
LHIN K	0.93	(0.75 – 1.15)	1.15	(0.96 – 1.38)	1.02	(0.77 – 1.36)	1.04	(0.88 – 1.23)	
LHIN L	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		
LHIN M	1.07	(0.91 – 1.26)	1.34	(1.16 – 1.54)	1.33	(1.04 – 1.70)	1.15	(1.03 – 1.29)	
LHIN N	1.09	(0.91 – 1.30)	1.27	(1.09 – 1.47)	1.25	(0.95 – 1.64)	1.13	(1.01 – 1.26)	
Rurality	**p<0.0001**								
Major urban	1.00 (ref)								
Non-major urban	0.95	(0.87 – 1.03)							
Rural	1.02	(0.91 – 1.16)							
Missing	0.34	(0.25 – 0.45)							

	Unstratified Unadjusted Model		Unstratified Adjusted Model*		Stratified Adjusted Model				
					Ulceration absent**		Ulceration present**		
Variable	**RR (N=8042)**	**95% CI**	**No interactions (N=8042)**	**95% CI**	**RR (N=6581)**	**95% CI**	**RR (N=1461)**	**95% CI**	**Significance of interaction**
Disease Factors									
Histology	**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**
Superficial	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		
Acral	3.76	(3.11 – 4.53)	2.15	(1.83 – 2.52)	2.52	(1.62 – 3.92)	1.40	(1.23 – 1.59)	
Lentigo maligna	0.69	(0.53 – 0.88)	0.67	(0.52 – 0.85)	0.63	(0.45 – 0.87)	0.86	(0.63 – 1.18)	
Nodular	5.72	(5.22 – 6.27)	2.84	(2.57 – 3.15)	6.60	(5.71 – 7.64)	1.45	(1.33 – 1.59)	
NOS	1.39	(1.23 – 1.56)	1.29	(1.16 – 1.44)	1.33	(1.12 – 1.58)	1.16	(1.04 – 1.29)	
Other	4.01	(3.52 – 4.57)	2.79	(2.45 – 3.18)	4.82	(3.97 – 5.87)	1.36	(1.21 – 1.52)	
Body site	**p<0.0001**		**p=0.0024**		**p=0.0076**		**p=0.1477**		**p=0.0493**
Extremities	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		
Head and Neck	1.58	(1.39 – 1.79)	1.17	(1.05 – 1.30)	1.36	(1.13 – 1.63)	1.05	(0.96 – 1.14)	
Face	1.03	(0.92 – 1.17)	0.97	(0.87 – 1.08)	1.05	(0.88 – 1.26)	0.92	(0.83 – 1.01)	
Trunk	0.98	(0.90 – 1.07)	0.97	(0.90 – 1.05)	0.96	(0.84 – 1.10)	1.00	(0.93 – 1.06)	
Unspecified	1.37	(1.15 – 1.63)	1.22	(1.05 – 1.42)	1.29	(1.01 – 1.66)	1.08	(0.95 – 1.23)	
Ulceration	**p<0.0001**		**p<0.0001**						
Present	5.53	(5.18 – 5.90)	3.22	(2.97 – 3.49)	-	-	-	-	
Absent	1.00 (ref)		1.00 (ref)		-	-	-	-	
			*controlled for sex, age, deprivation, LHIN, histology, site, and ulceration		**controlled for sex, age, deprivation, LHIN, histology, and site		**controlled for sex, age, deprivation, LHIN, histology, and site		
p-values based on chi-square test									

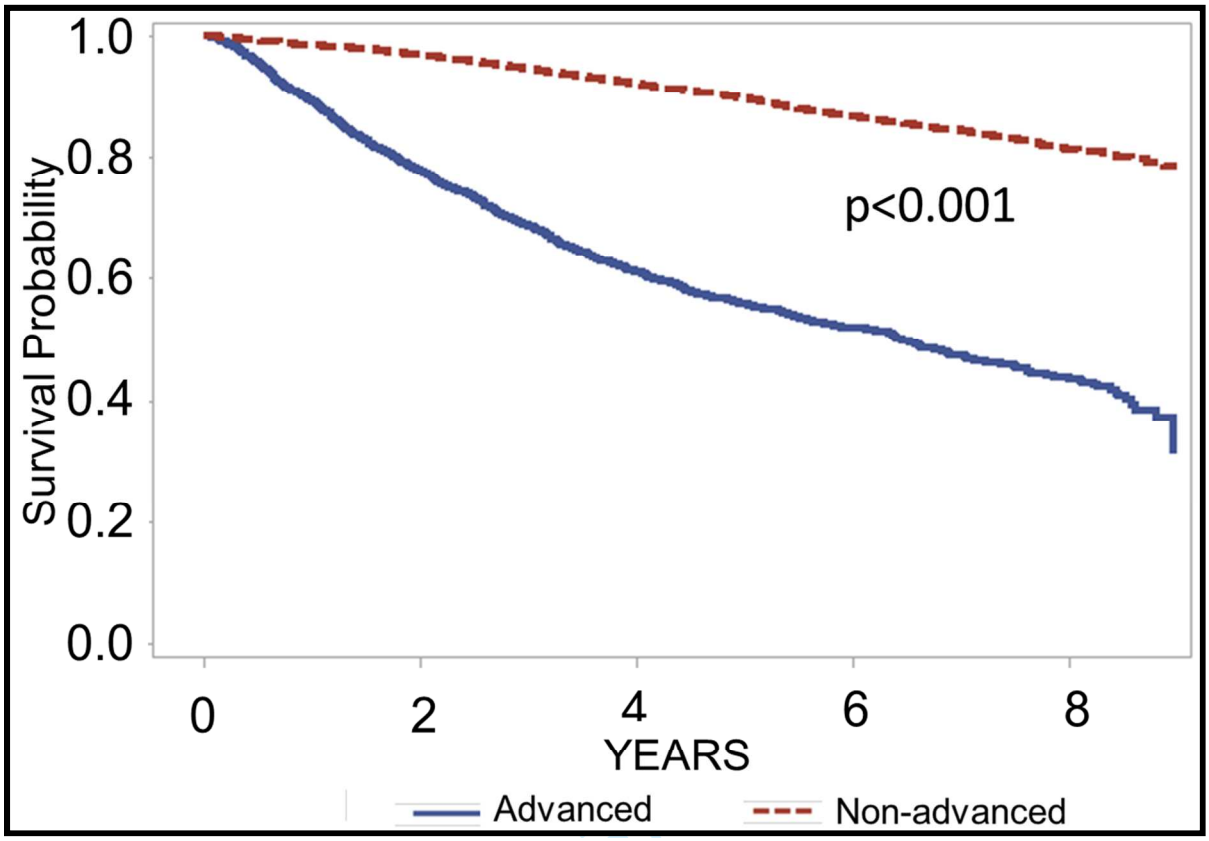

Figure 1: Overall survival stratified by presence of advanced melanoma (>2.0 mm thick). Five-year survival is 90% for non-advanced patients and 56% for advanced.

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Appendix 1

Table A1: Advanced stage (AJCC definition) cohort patient-, health system-, and disease- factors

Characteristic	Overall (Stage cohort)	Ulceration absent	Ulceration present
No. of patients	8477	6599	1466
Patient Factors			
Sex			
Male	53.93%	51.17%	63.17%
Female	46.07%	48.83%	36.83%
Age			
Median age, years (mean)	62 (61.61)	61 (60.30)	69 (67.12)
20 – 45	16.96%	18.68%	10.16%
46 – 55	18.41%	19.49%	13.57%
56 – 65	21.40%	22.05%	18.49%
66 – 75	20.22%	19.70%	21.96%
76 – 85	17.52%	15.88%	24.97%
>85	5.49%	4.20%	10.85%
Material Deprivation			
Least deprived	27.32%	27.81%	24.15%
Quintile 2	23.69%	23.58%	24.76%
Quintile 3	19.66%	19.17%	20.80%
Quintile 4	14.26%	13.84%	15.96%
Most deprived	9.02%	8.44%	11.87%
Missing	6.04%	7.17%	2.46%
Health System Factors			
Local Health Integration Network (LHIN)			
LHIN A	8.27%	8.64%	6.96%
LHIN B	7.99%	8.09%	5.87%
LHIN C	9.27%	9.49%	8.66%
LHIN D	4.92%	4.68%	6.07%
LHIN E	10.44%	11.00%	8.87%
LHIN F	6.65%	6.70%	6.34%
LHIN G	5.73%	5.80%	5.93%
LHIN H	12.30%	12.08%	12.55%
LHIN I	6.46%	6.24%	7.44%
LHIN J	1.32%	1.36%	1.09%
LHIN K	3.31%	3.27%	3.41%
LHIN L	13.21%	12.62%	16.17%
LHIN M	5.66%	5.64%	5.73%
LHIN N	4.45%	4.38%	4.91%
Rurality			
Median Rurality	5.0 (13.50)	5.0 (13.50)	5.0 (13.61)
Rural (≥ 40)	10.19%	10.08%	10.71%
Nonmajor Urban (9.01-39)	26.26%	26.29%	26.13%
Major urban (0-9)	57.57%	56.54%	60.78%
Missing	5.98%	7.09%	2.39%
Disease Factors			
AJCC stage			
I	16.04%	20.61%	0%
IA	21.01%	26.97%	*
IB	28.21%	34.99%	5.59%
IIA	7.97%	7.32%	13.17%
IIB	6.69%	3.42%	23.26%
IIC	4.65%	*	26.74%
III	1.83%	*	0%
IIIA	3.66%	3.50%	5.39%
IIIB	3.72%	1.35%	15.42%
IIIC	2.25%	0.79%	7.09%
IV	3.98%	0.91%	3.27%
Histological subtype			
Superficial spreading	39.04%	44.84%	23.60%
Lentigo maligna	7.76%	9.30%	2.73%
Acral lentiginous	1.55%	1.12%	3.89%
Nodular	12.61%	7.26%	39.90%
NOS	34.73%	33.81%	23.47%
Other	4.32%	3.67%	6.41%

Characteristic	Overall (Stage cohort)	Ulceration absent	Ulceration present
Body site			
Extremities	44.77%	46.43%	45.02%
Face	11.94%	12.55%	11.73%
Head and Neck	5.78%	5.26%	7.64%
Trunk	31.58%	32.43%	31.11%
Unspecified	5.93%	3.33%	4.50%
Presence of ulceration			
Present	17.29%	-	-
Absent	77.85%	-	-
Missing	4.86%	-	-
Lymph node involvement			
Present	11.43%	5.91%	28.79%
Absent	88.57%	94.09%	71.21%
Distant metastases			
Present	3.98%	0.91%	3.27%
Absent	96.02%	99.09%	96.73%
Note: 412 (4.86%) patients had unreported ulceration and were not included in stratified analyses *Censored due to small cell counts			

Table A2: Presence of advanced melanoma according to study factors, and stratified by ulceration status – stage-based definition

Characteristic	Overall % Advanced (>stage I)	Ulceration Absent % Advanced (> Stage I)	Ulceration Present % Advanced (> Stage I)	p-value†
No. of patients	8477	6599	1466	
Patient Factors				
Sex				Overall: p<0.0001
Male	39.59%	19.51%	95.25%	Abs: p<0.0001
Female	29.07%	15.24%	92.78%	Pres: p=0.0483
Age				Overall: p<0.0001
Median age, years (mean)	67 (65.60)	65 (64.23)	69 (67.43)	
20 – 45	23.99%	12.08%	93.96%	
46 – 55	28.51%	14.70%	90.45%	
56 – 65	32.08%	16.77%	92.25%	Abs: p<0.0001 Pres: p=0.0050
66 – 75	36.70%	18.00%	94.10%	
76 – 85	44.92%	23.19%	96.45%	
>85	59.57%	32.85%	98.74%	
Material Deprivation				Overall: p<0.0001
Least deprived	32.82%	16.35%	94.07%	
Quintile 2	33.57%	15.87%	93.11%	
Quintile 3	37.97%	19.76%	93.77%	Abs: p<0.0001
Quintile 4	39.70%	21.03%	96.58%	Pres: p=0.2166
Most deprived	44.84%	25.31%	95.55%	
Missing	10.74%	4.23%	88.89%	
Health System Factors				
Local Health Integration Network (LHIN)				Overall: p=0.0001
LHIN A	29.10%	13.86%	94.12%	
LHIN B	35.30%	18.91%	94.19%	
LHIN C	31.93%	15.65%	94.49%	
LHIN D	33.09%	12.62%	89.89%	
LHIN E	30.51%	16.53%	93.08%	
LHIN F	34.75%	17.65%	95.70%	Abs: p=0.0086
LHIN G	34.98%	19.06%	93.10%	Pres: p=0.7379
LHIN H	34.42%	15.81%	92.93%	
LHIN I	36.50%	16.75%	95.41%	
LHIN J	34.82%	18.89%	100.00%	
LHIN K	35.59%	18.06%	92.00%	
LHIN L	39.55%	19.81%	96.20%	
LHIN M	38.96%	22.31%	95.24%	
LHIN N	39.52%	21.80%	97.22%	
Rurality				Overall: p<0.0001
Median rurality (mean)	5.0 (13.31)	5.0 (13.16)	5.0 (13.50)	
Rural (≥ 40)	36.11%	18.65%	92.99%	
Nonmajor Urban (9.01-39)	35.09%	18.27%	92.95%	Rurality abs: p<0.0001 Rurality pres: p=0.1132
Major urban (0-9)	36.84%	18.49%	95.40%	
Missing	10.65%	4.06%	88.57%	
Disease Factors				
Histological subtype				Overall: p<0.0001
Superficial spreading	18.98%	10.81%	87.86%	Abs: p<0.0001
Lentigo maligna	13.22%	8.14%	82.50%	Pres: p<0.0001
Acral lentiginous	58.78%	27.03%	100.00%	
Nodular	84.85%	67.22%	99.15%	
NOS	34.04%	14.25%	91.57%	
Other	66.67%	49.59%	100.00%	
Body site				Overall: p<0.0001
Extremities	31.12%	16.32%	92.42%	
Face	31.32%	17.51%	93.02%	
Head and Neck	46.94%	26.51%	95.54%	Abs: p<0.0001 Pres: p=0.0152
Trunk	32.69%	16.50%	96.71%	
Unspecified	67.99%	27.27%	98.48%	

Characteristic	Overall % Advanced (> stage I)	Ulceration Absent % Advanced (> Stage I)	Ulceration Present % Advanced (> Stage I)	p-value†
Presence of ulceration				Overall: p<0.0001
Present	94.34%	-	94.34	-
Absent	17.43%	17.43	-	-
Missing	100%	-	-	
Lymph node involvement				Overall: p<0.0001
Present	100.00%	100.00%	100.00%	Abs: p<0.0001
Absent	26.32%	12.24%	92.05%	Pres: p<0.0001
Distant metastases				Overall: p<0.0001
Present	100.00%	100.00%	100.00%	Abs: p<0.0001
Absent	32.04%	16.67%	94.15%	Pres: p=0.0844
412 (4.86%) patients had unreported ulceration and were not included in stratified analyses †p-value based on chi-square test Note: % Advanced = 100% - % non-advanced				

Table A3: Relative risk of advanced melanoma from Modified Poisson regression; table stratified by ulceration – stage-based definition

	Unstratified Unadjusted Model		Unstratified Adjusted Model*		Stratified Adjusted Model				
					Ulceration absent**		Ulceration present**		
Variable	**RR (N=8477)**	**95% CI**	**RR: No interactions (N=8477)**	**95% CI**	**RR (N=6599)**	**95% CI**	**RR (N=1466)**	**95% CI**	**Significance of interaction**
Patient Factors									
Sex	**p<0.0001**		**p=0.0018**		**p=0.0065**		**p=0.26**		**p=0.01**
Male	1.36	(1.28 – 1.45)	1.08	(1.03 – 1.13)	1.15	(1.04 – 1.28)	1.02	(0.99 – 1.05)	
Female	1.00 (ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		
Age	**p<0.0001**		**p<0.0001**		**p<0.0001**		**p=0.002**		**p<0.0001**
20 – 45	0.75	(0.67 – 0.84)	0.90	(0.83 – 0.98)	0.85	(0.71 – 1.01)	1.02	(0.97 – 1.07)	
46 – 55	0.89	(0.80 – 0.99)	0.97	(0.89 – 1.04)	0.96	(0.81 – 1.13)	0.99	(0.93 – 1.04)	
56 – 65	1.00 (ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		
66 – 75	1.14	(1.04 – 1.25)	1.06	(0.99 – 1.14)	1.06	(0.91 – 1.23)	1.03	(0.99 – 1.08)	
76 – 85	1.40	(1.28 – 1.53)	1.11	(1.04 – 1.19)	1.23	(1.06 – 1.42)	1.04	(1.00 – 1.08)	
>85	1.86	(1.68 – 2.05)	1.23	(1.13 – 1.34)	1.72	(1.43 – 2.06)	1.07	(1.03 – 1.11)	
Deprivation	**p<0.0001**		**p<0.0001**		**p<0.0001**		**p=0.3204**		**p<0.0001**
Least deprived	1.00 (ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		
Quintile 2	1.02	(0.94 – 1.11)	1.00	(0.94 – 1.07)	0.97	(0.84 – 1.11)	1.00	(0.96 – 1.03)	
Quintile 3	1.16	(1.06 – 1.26)	1.07	(1.01 – 1.15)	1.20	(1.04 – 1.38)	1.00	(0.96 – 1.04)	
Quintile 4	1.21	(1.11 – 1.32)	1.11	(1.03 – 1.19)	1.15	(0.99 – 1.35)	1.03	(0.99 – 1.06)	
Most deprived	1.37	(1.24 – 1.51)	1.17	(1.08 – 1.27)	1.36	(1.15 – 1.61)	1.02	(0.98 – 1.06)	
Missing	0.33	(0.25 – 0.42)	0.50	(0.41 – 0.61)	0.33	(0.22 – 0.51)	0.95	(0.84 – 1.07)	
Health System Factors									
LHIN	**p=0.0001**		**p=0.13**		**p=0.14**		**p=0.52**		**p<0.0001**
LHIN A	0.74	(0.64 – 0.84)	0.97	(0.87 – 1.07)	0.83	(0.67 – 1.04)	0.99	(0.94 – 1.04)	
LHIN B	0.89	(0.79 – 1.01)	1.06	(0.96 – 1.17)	1.10	(0.89 – 1.35)	0.99	(0.94 – 1.05)	
LHIN C	0.81	(0.71 – 0.92)	1.02	(0.93 – 1.13)	0.89	(0.72 – 1.10)	1.00	(0.96 – 1.05)	
LHIN D	0.84	(0.72 – 0.98)	0.95	(0.85 – 1.06)	0.80	(0.59 – 1.08)	0.96	(0.90 – 1.04)	
LHIN E	0.77	(0.68 – 0.87)	0.98	(0.89 – 1.07)	0.88	(0.72 – 1.07)	0.98	(0.93 – 1.03)	
LHIN F	0.88	(0.77 – 1.00)	1.03	(0.93 – 1.14)	0.95	(0.76 – 1.19)	1.01	(0.96 – 1.06)	
LHIN G	0.88	(0.77 – 1.02)	0.97	(0.87 – 1.08)	0.83	(0.67 – 1.04)	0.97	(0.92 – 1.03)	
LHIN H	0.87	(0.78 – 0.97)	0.98	(0.90 – 1.07)	0.90	(0.74 – 1.09)	0.98	(0.93 – 1.03)	
LHIN I	0.92	(0.81 – 1.05)	0.98	(0.89 – 1.08)	0.91	(0.72 – 1.15)	1.01	(0.96 – 1.06)	
LHIN J	0.88	(0.68 – 1.15)	1.05	(0.85 – 1.28)	0.94	(0.60 – 1.48)	1.05	(1.01 – 1.09)	
LHIN K	0.90	(0.76 – 1.07)	1.04	(0.91 – 1.19)	0.91	(0.70 – 1.18)	0.98	(0.90 – 1.07)	
LHIN L	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		
LHIN M	0.99	(0.86 – 1.13)	1.15	(1.03 – 1.28)	1.15	(0.92 – 1.43)	1.01	(0.96 – 1.07)	
LHIN N	1.00	(0.86 – 1.15)	1.11	(0.99 – 1.25)	1.13	(0.89 – 1.43)	1.02	(0.98 – 1.07)	
Rurality	**p<0.0001**								
Major urban	1.00 (ref)								
Non-major urban	0.95	(0.89 – 1.02)							
Rural	0.98	(0.89 – 1.08)							
Missing	0.29	(0.22 – 0.37)							

	Unstratified Unadjusted Model		Unstratified Adjusted Model*		Stratified Adjusted Model				
					Ulceration absent**		Ulceration present**		
Variable	**RR (N=8477)**	**95% CI**	**RR: No interactions (N=8477)**	**95% CI**	**RR (N=6599)**	**95% CI**	**RR (N=1466)**	**95% CI**	**Significance of interaction**
Disease Factors									
Histology	**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**
Superficial	1.00 (ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		
Acral	3.10	(2.64 – 3.63)	1.76	(1.55 – 1.99)	2.28	(1.54 – 3.37)	1.16	(1.11 – 1.22)	
Lentigo maligna	0.70	(0.57 – 0.86)	0.71	(0.59 – 0.86)	0.63	(0.47 – 0.85)	0.95	(0.82 – 1.10)	
Nodular	4.47	(4.15 – 4.82)	2.14	(1.98 – 2.32)	5.43	(4.79 – 6.15)	1.13	(1.08 – 1.17)	
NOS	1.79	(1.64 – 1.96)	1.26	(1.17 – 1.37)	1.34	(1.16 – 1.55)	1.04	(0.99 – 1.10)	
Other	3.51	(3.18 – 3.89)	2.14	(1.93 – 2.37)	4.30	(3.64 – 5.09)	1.13	(1.08 – 1.17)	
Body site	**p<0.0001**		**p=0.0002**		**p=0.0017**		**p=0.0016**		**p=0.0007**
Extremities	1.00 (ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		
Head and Neck	1.51	(1.36 – 1.68)	1.12	(1.03 – 1.22)	1.27	(1.08 – 1.50)	1.02	(0.98 – 1.07)	
Face	1.01	(0.91 – 1.12)	1.00	(0.92 – 1.08)	1.01	(0.86 – 1.19)	1.00	(0.95 – 1.04)	
Trunk	1.05	(0.98 – 1.13)	1.02	(0.96 – 1.08)	0.99	(0.88 – 1.11)	1.05	(1.02 – 1.08)	
Unspecified	2.18	(2.02 – 2.36)	1.18	(1.10 – 1.28)	1.49	(1.21 – 1.85)	1.08	(1.04 – 1.13)	
Ulceration	**p<0.0001**		**p<0.0001**						
Present	5.41	(5.13 – 5.71)	3.71	(3.47 – 3.96)					
Absent	1.00 (Ref)		1.00 (Ref)						
Missing	5.74	(5.44 – 6.05)	4.45	(4.11 – 4.81)					
			*controlled for sex, age, deprivation, LHIN, histology, site, and ulceration		*controlled for sex, age, deprivation, LHIN, histology, and site		*controlled for sex, age, deprivation, LHIN, histology, and site		

*412 (4.86%) patients had unreported ulceration and were not included in stratified analyses
p-values based on chi-square test

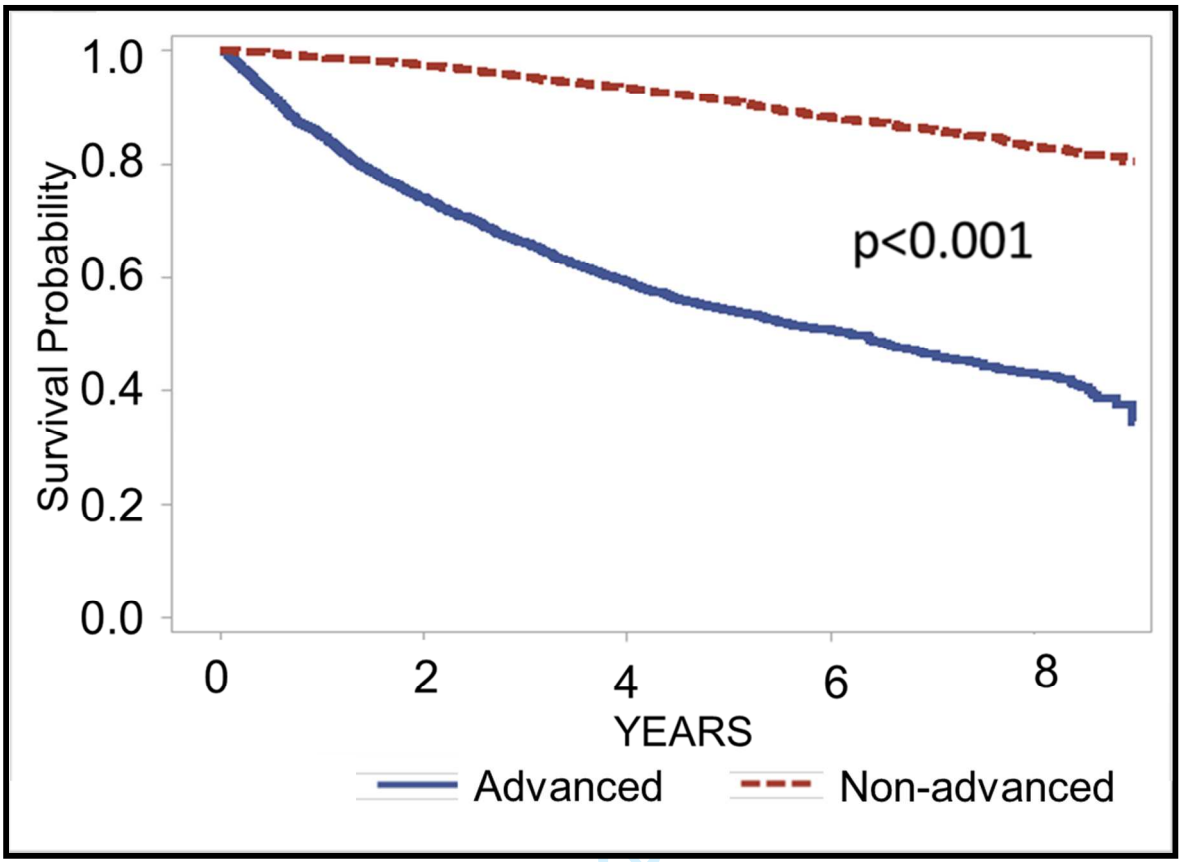

Figure A1: Overall survival stratified by presence of advanced melanoma (>stage I). Five-year survival is 91% for non-advanced patients and 54% for advanced. Curves compared using log-rank test.