**Title:** Prognostic importance of a second invasive primary melanoma according to tumor stage

**Running head:** Survival of multiple melanomas by tumor stage

**Word counts:** Body of text – 841. **Number of figures:** 0. **Number of tables:** 1

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**Funding/Support:** This project has not received any specific funding. KK is supported by the National Health and Medical Research Council of Australia fellowship.

**Conflicts of Interest:** None reported.

**Abbreviations:** HR = hazard ratio; CI = confidence interval.

**Keywords:** multiple invasive melanoma, stage at diagnosis, survival, time-varying covariate method

It is well known that a considerable proportion of the Caucasian population in many countries are diagnosed with multiple melanomas over time[1]. Despite this, most analyses of melanoma survival, including that of the American Joint Committee on Cancer (AJCC), consider only one tumor for every patient and disregard the potential effect of multiple melanomas on outcomes and this is reflected in the lack of specific management guidelines for patients with multiple melanomas beyond those dictated by the clinicopathological features of each tumour[2-4].

Recently we and others have shown that patients with multiple primary invasive melanomas have an increased risk of melanoma death compared to patients with a single melanoma[5,6]. In contrast, having an in situ melanoma in addition to an invasive melanoma does not alter a patient's prognosis[7]. This prompted us to examine if the reduced survival of patients with multiple invasive melanomas held across all early invasive melanoma stages, namely stages I or II.

Details of our data and methods are provided in the supplementary document. A total of 29,393 eligible patients diagnosed with a first primary invasive melanoma of stage I or II between 1995 and 2008 as recorded in the Queensland Cancer Registry were considered. Among these, 27,510 patients had a single primary stage I (S1) or II (S2) melanoma (94%) and 1,883 (6%) had two stage I or II melanomas diagnosed within ten years of each other (supplemental Tables 1 and 2). These patients were grouped into the following categories: S1S1 and S2S2 if they had two stage I or two stage II tumours respectively. S1S2 if they had a stage I followed by a stage II or S2S1 if tumours occurred in the opposite order. There were approximately 234,500 person-years of follow-up in total, with a median of 9.5 years per patient, varying from 6.5 years for the S2 group to 10.0 years for the S1S1 group. Aside from cases where the two melanomas were diagnosed on the same day (n=142, 8%), the median time between diagnoses was 3.0 years. Significant differences were found between the

groups in terms of age, sex, body site, morphology and ulceration of both the first and second melanoma (supplemental Tables 1 and 2). ~~Most patients (79%) remained alive 10 years after first diagnosis but the range of survival was substantial, from 26% for the dual stage II primary (S2S2) group to 97% for the S1 group (p<0.001). A further~~ By the end of follow-up 6% of patients in the study cohort had died of melanoma and 14% had died of other causes.

*Survival in patients with primary stage I melanomas only*

After making appropriate allowance for time to diagnosis between first and subsequent melanomas by the ~~delayed entry~~ time-varying covariate method, we analyzed melanoma survival in multivariate flexible parametric models ~~as reported previously~~[5]. Unadjusted 10-year melanoma-specific survival was 97% for the S1 group and 92% for the S1S1 group (Table 1 and Supplemental Figure 1). After adjustment for sex, age at diagnosis, body site, histopathological subtype, thickness group and ulceration, patients in the S1S1 group had a 59% increased hazard of melanoma death compared to the S1 group (HR=1.59, p=0.022).

*Survival in patients with at least one primary stage II melanoma*

Ten-year unadjusted melanoma-specific survival was 71% for the S2 group, 64% for the S2S1 group, and 50% for the S1S2 group (Table 1; Supplemental Figure 1). After adjustment there was no significant difference in 10-year melanoma-specific survival for either the S2S1 group (HR = 1.06, p=0.65) or the S1S2 group (HR = 1.32, p=0.10) compared to the S2 group. In contrast, the effect on stage II melanoma patients of being diagnosed with a second stage II primary invasive melanoma (S2S2) within 10 years was to reduce unadjusted survival to 26% (Table 1 and Supplemental Figure 1). After adjustment for other prognostic factors, this equated to ~~more than a~~ an almost two-fold increased hazard of death from melanoma (HR = 1.92, p<0.001) for Group S2S2 compared to Group S2.

Supplemental Table 3 shows the results when all stage I and II melanomas were included in the same model. This additional analysis demonstrates that all patients with at least one

primary stage II melanoma had a higher risk of mortality than those in the S1S1 group. There was also little difference when the data were reanalysed using the delayed entry method, an approach that we have used previously (Supplemental Table 4)[5].

In conclusion, the present study demonstrates that stage I patients diagnosed with a second stage I melanoma, and stage II patients with a second stage II melanoma, despite the small number of patients in the latter category, have a significantly worse outcome compared to those diagnosed with a single primary stage I or stage II melanoma, respectively. Current guidelines for the clinical management of melanoma do not reflect the peculiar survival of these important melanoma patients. We therefore propose that health providers take a careful and accurate history of earlier melanomas and consider the occurrence of a second primary invasive melanoma of equivalent stage within 10 years of the first diagnosis, as an additional criterion of poorer prognosis. In particular, we propose that patients with two stage II melanomas, who fare especially poorly, would benefit from closer monitoring such as recommended for stage III patients, as well as inclusion in adjuvant therapy trials.

**Author Contributions:** Youlden had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: All authors. *Analysis and interpretation of data*: All authors. *Drafting of the manuscript*: Khosrotehrani and Youlden. *Critical revision of the manuscript for important intellectual content*: Baade, Aitken and Green. *Statistical analysis*: Youlden. *Obtained funding*: Not applicable. *Administrative, technical, or material support*: Not applicable. *Study supervision*: Khosrotehrani.

**Acknowledgements:** The authors wish to thank the staff of the Queensland Cancer Registry who provided the data extract used in this study.

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**Table 1: Ten year unadjusted cause-specific survival estimates and adjusted cumulative excess mortality hazard ratios by analysis group, Queensland, 1995-2013[1]**

| Analysis group | n | Unadjusted 10-year cause-specific survival estimate[2] (95% CI) | Adjusted cumulative 10-year excess mortality hazard ratio[3] (95% CI) | *p* |
|---|---|---|---|---|
| **Study cohort - stage I primary melanomas only** | | | | |
| S1 | 23,693 | 96.7 (96.5-97.0) | 1.00 | |
| S1S1 | 1,355 | 91.7 (89.4-93.6) | 1.59 (1.07-2.36) | 0.022 |
| Overall effect: p = 0.022 | | | | |
| **Study cohort - at least one stage II primary melanoma** | | | | |
| S2 | 3,817 | 70.8 (69.1-72.4) | 1.00 | |
| S1S2 | 223 | 50.1 (38.7-60.4) | 1.32 (0.95-1.83) | 0.100 |
| S2S1 | 214 | 63.7 (54.6-71.4) | 1.06 (0.82-1.37) | 0.658 |
| S2S2 | 91 | 26.4 (15.5-38.6) | 1.92 (1.36-2.71) | <0.001 |
| Overall effect: p = 0.004 | | | | |

Notes: 1. First primary invasive melanomas were diagnosed between 1995 and 2008, with follow-up to 31 Dec 2013 for diagnosis of subsequent primary invasive melanoma (maximum of 10 years of follow-up from the date of diagnosis of the first primary invasive melanoma). 2. Survival time was calculated from the date of diagnosis of the first primary invasive melanoma using the time-varying covariate method if a subsequent melanoma was diagnosed. 3. Adjusted for entry time, sex and the following variables relating to the first primary invasive melanoma: age at diagnosis, body site, morphology, tumor thickness group, and ulceration.

**Supplemental text and data**

**Title:** Prognostic importance of a second invasive primary melanoma according to tumor stage

## Patients and Methods

*Data source*

De-identified data were obtained under approval from Queensland Health. This study was exempt from requiring approval by an ethics committee as only de-identified data were used. Unit records for cases of invasive cutaneous melanoma (ICD-O-3 code C44 and morphology M872-M879) diagnosed between 1995 and 2013 were extracted from the Queensland Cancer Registry (QCR), a population-based collection of all notified cancer diagnoses (excluding keratinocyte skin cancers) among residents of the state of Queensland, Australia. Data were available for all Queensland residents who were diagnosed with a first primary invasive melanoma between 1995 and 2008, with follow-up until 31 December 2013.

Unique patient numbers were used to identify second primary invasive melanomas that occurred within 10 years of the index melanoma. If two melanomas were diagnosed on the same day, the order was determined according to the sequence in which they were registered. Data items for each patient included demographic and tumor characteristics, date of diagnosis and date and cause of death (where applicable). Variables relating to stage at diagnosis, namely tumor thickness, ulceration, nodal spread and distant metastasis were manually extracted from pathology reports. Information on mitosis was not available. Ulceration was assumed to be absent when there was no report of ulceration in pathology descriptions. Stage was categorized according to the AJCC melanoma staging rules [8].

The study cohort consisted of patients aged 15-89 years who were diagnosed with a single stage I or II melanoma or two primary stage I and/or II melanomas within ten years of each other. In situ melanomas were not considered as they are known not to influence survival [9]. Patients were excluded if they had multiple melanomas that included stage III or IV tumors, second primary melanomas diagnosed more than ten years after the first diagnosis, or three or more primary invasive melanomas within ten years (regardless of melanoma stage). Cases were also excluded if stage could not be ascertained, if the date of diagnosis was the same as the date of death or where the basis of diagnosis was either autopsy or death certificate only.

*Analysis*

The study cohort was stratified into the following groups, depending on the number and stage at diagnosis of invasive melanomas for each patient during their 10-year follow-up:

- S1 = single Stage I primary melanoma
- S2 = single Stage II primary melanoma
- S1S1 = Stage I primary melanoma followed by Stage I primary melanoma
- S1S2 = Stage I primary melanoma followed by Stage II primary melanoma
- S2S1 = Stage II primary melanoma followed by Stage I primary melanoma
- S2S2 = Stage II primary melanoma followed by Stage II primary melanoma

Characteristics of the first and second primary invasive melanomas were compared across these groups using chi-squared tests. Differences in thickness were not assessed since thickness is included in the staging definition.

Melanoma-specific survival time was assessed from the date of diagnosis of the first primary invasive melanoma until either the date of death, the end of the study period (31 December

2013) or a maximum of ten years, whichever occurred first. Survival was censored at the date of death for patients who died from causes other than melanoma, or at 31 December 2013 for those who remained alive but who had less than 10 years of follow-up.

We used the ~~delayed entry~~ time-varying covariate method ~~[10]~~ to avoid bias in estimating survival for individuals with multiple primary melanomas. Under this approach, survival time is partitioned according to when a subsequent melanoma is diagnosed i.e. the survival time prior to the second diagnosis is attributed to the first melanoma. We have previously used the delayed entry method to calculate survival for multiple melanomas, and so for comparison the data was also reanalysed using delayed entry. ~~Details of this method have been reported previously [9]. If h1 and h2 are the respective mortality associated with the first and second melanoma (dependent on the effect of covariates and time since diagnosis), then the delayed entry method is appropriate when testing the null hypothesis (h1+h2)=h1 versus the alternative (h1+h2)>h1. That is, delayed entry should be used when the question of interest is whether the combined effect of two melanomas on survival is greater than the effect of being diagnosed with a single melanoma. In contrast, a time-varying study design, which has been used by others to examine survival for multiple melanomas [6], is better suited when testing whether the mortality associated with the first and second melanoma is equivalent i.e. h1=h2 versus some alternative hypothesis such as h1<h2.~~

Crude survival estimates ~~(based on delayed entry)~~ were obtained from the Kaplan-Meier method. A multivariate flexible parametric survival model [11] was then utilized to adjust for known prognostic factors. Restricted cubic splines are used to model the log baseline cumulative hazard in flexible parametric survival models. The Bayes information criterion

statistic was used to select the scale (normal) and number of degrees of freedom (four) for the model which provided the best fit to our data.

The multivariate models were adjusted for sex, age group at diagnosis, body site and melanoma histopathological subtype. Thickness group and ulceration (of the melanoma deemed to be at highest risk of recurrence for patients with multiple melanomas) were also included in the model. Given that delayed entry was only relevant for patients with two invasive melanomas, independence between the entry and failure events could not be assumed, and entry time was incorporated as a covariate to avoid introducing late entry bias [12]. Two multivariate models were run – the first containing patients with one or two primary stage I melanomas only (groups S1 and S1S1), and the second containing patients with at least one primary stage II melanoma (groups S2, S1S2, S2S1 and S2S2). In both models, patients with a single primary melanoma were the reference group (that is, S1 and S2, respectively).

A third model was also included, which contained all six groups (S1, S1S1, S2, S1S2, S2S1 and S2S2) with S1 used as the reference category. Although the effect for each of the other variables included in the multivariate model was highly significant ($p<0.001$), testing of the amount of variance explained by each factor (using the str2d command in Stata) revealed that analysis group (i.e. stage and multiplicity) accounted for 33% of R2 compared to 11% due to morphology, 6% due to age group at diagnosis, 3% due to sex and 2% due to anatomic site.

Results from the multivariate flexible parametric survival models were expressed in terms of excess mortality hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs).

All analyses were conducted using Stata/SE version 14.1 for Windows. The 'stpm2' command [11] was used to fit the flexible parametric survival models.

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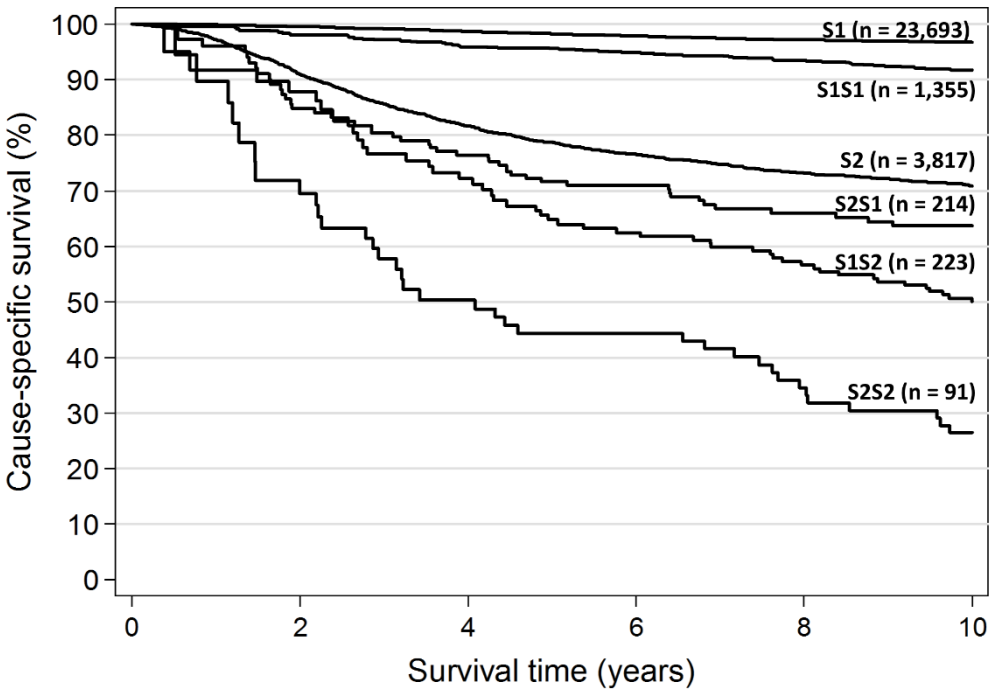


**Supplemental Figure 1: Unadjusted cause-specific survival by analysis group, Queensland, 1995-2013.**

Note: Melanomas with unknown ulceration were assumed to be not ulcerated. S1 = single stage I primary melanoma; S2 = single stage II primary melanoma; S1S1 = stage I primary melanoma followed by stage I primary melanoma; S1S2 = stage I primary melanoma followed by a stage II primary melanoma; S2S1 = stage II primary melanoma followed by a stage I melanoma; S2S2 = stage II first primary melanoma followed by stage II second primary melanoma.

## Supplemental Table 1: Cohort and tumor characteristics of stage I and II first primary invasive melanomas[1,2] by analysis group, Queensland, 1995-2013[3]

| | Analysis group | | | | | | |
|---|---|---|---|---|---|---|---|
| **Cohort and tumor characteristics (first primary invasive melanoma)** | **S1** | **S1S1** | **S1S2** | **S2** | **S2S1** | **S2S2** | ***p*[4]** |
| Eligible patients (n) | 23,693 | 1,355 | 223 | 3,817 | 214 | 91 | |
| Median follow-up in years (IQR) | 9.9 (6.7-10.0) | 10.0 (7.3-10.0) | 8.8 (5.7-10.0) | 6.5 (3.0-10.0) | 7.5 (4.8-10.0) | 6.7 (3.2-9.7) | <0.001 |
| Median age at diagnosis in years (IQR) | 55 (42-68) | 61 (49-71) | 68 (59-76) | 69 (55-78) | 69 (57-77) | 74 (64-80) | <0.001 |
| | | | | | | | |
| | Col % | Col % | Col % | Col % | Col % | Col % | |
| Sex | | | | | | | <0.001 |
| Males | 55.2 | 66.8 | 78.9 | 63.4 | 80.8 | 69.2 | |
| Females | 44.8 | 33.2 | 21.1 | 36.6 | 19.2 | 30.8 | |
| Body site | | | | | | | <0.001 |
| Head and neck | 14.4 | 14.5 | 21.1 | 23.9 | 15.9 | 24.2 | |
| Trunk | 37.7 | 39.9 | 35.4 | 27.8 | 40.2 | 27.5 | |
| Upper limbs and shoulders | 24.8 | 24.7 | 29.6 | 25.5 | 18.2 | 25.3 | |
| Lower limbs | 22.2 | 20.0 | 13.9 | 22.4 | 24.8 | 23.1 | |
| Not specified | 0.9 | 1.0 | 0.0 | 0.4 | **[5] | 0.0 | |
| Subtype | | | | | | | <0.001 |
| Superficial spreading melanoma | 63.0 | 62.3 | 54.3 | 24.8 | 28.5 | 20.9 | |
| Lentigo maligna melanoma | 6.4 | 6.7 | 14.8 | 2.5 | 2.3 | 5.5 | |
| Nodular melanoma | 3.7 | 3.2 | 2.7 | 36.5 | 35.5 | 38.5 | |
| Other specified melanoma | 4.6 | 4.3 | 4.9 | 16.7 | 17.8 | 11.0 | |
| Not otherwise specified | 22.4 | 23.5 | 23.3 | 19.5 | 15.9 | 24.2 | |
| Thickness | | | | | | | n.a.[6] |
| <= 1.00mm | 86.7 | 86.6 | 79.4 | 0.0 | 0.0 | 0.0 | |
| 1.01mm-2.00mm | 13.3 | 13.4 | 20.6 | 16.2 | 14.5 | 15.4 | |
| 2.01mm-4.00mm | 0.0 | 0.0 | 0.0 | 55.5 | 59.4 | 55.0 | |
| >4.00mm | 0.0 | 0.0 | 0.0 | 28.3 | 26.2 | 29.7 | |
| Ulceration | | | | | | | <0.001 |
| No[7] | 98.1 | 97.6 | 96.9 | 47.8 | 54.7 | 37.4 | |
| Yes | 1.9 | 2.4 | 3.1 | 52.2 | 45.3 | 62.6 | |
| Vital status at 10 years after diagnosis | | | | | | | <0.001 |
| Alive | 84.5 | 83.5 | 57.0 | 49.5 | 57.9 | 38.5 | |
| Melanoma-specific death | 2.9 | 4.3 | 21.1 | 24.9 | 21.5 | 38.5 | |
| Non-melanoma death | 12.6 | 12.2 | 22.0 | 25.6 | 20.6 | 23.1 | |

Abbreviation: IQR = interquartile range.

Notes: 1. Characteristics shown are for first primary melanoma only. 2. T2 thickness melanomas with unknown ulceration were assumed to be not ulcerated and were therefore stage I. 3. First primary invasive melanomas were diagnosed between 1995 and 2008, with follow-up to 31 Dec 2013 for diagnosis of subsequent primary invasive melanoma (maximum of 10 years of follow-up from the date of diagnosis of the first primary invasive melanoma). 4. P-values based on chi-squared tests for categorical variables and nonparametric k-sample tests for medians. 5. ** = data withheld due to cell count < 5. 6. n.a. = not applicable (due to structural zeros). 7. The category of "no" for ulceration includes cases for whom the ulceration status was not stated in the medical record.

## Supplemental Table 2: Cohort and tumor characteristics of stage I and II second primary invasive melanomas[1,2] by analysis group, Queensland, 1995-2013[3]

| | Analysis group | | | | |
|---|---|---|---|---|---|
| **Cohort and tumor characteristics (second primary invasive melanoma)** | **S1S1** | **S1S2** | **S2S1** | **S2S2** | ***p*[4]** |
| Eligible patients (n) | 1,355 | 223 | 214 | 91 | |
| Median time to diagnosis after first primary melanoma (years) | 3.0 | 4.4 | 1.7 | 2.4 | <0.001 |
| Median age at diagnosis (years) | 64 | 72 | 71 | 77 | <0.001 |
| | | | | | |
| | Col % | Col % | Col % | Col % | |
| Body site | | | | | <0.001 |
| Head and neck | 15.9 | 29.2 | 15.4 | 33.0 | |
| Trunk | 40.2 | 26.0 | 41.1 | 22.0 | |
| Upper limbs and shoulders | 25.3 | 24.7 | 25.2 | 16.5 | |
| Lower limbs | 18.1 | 20.2 | 17.8 | 27.5 | |
| Not specified | 0.4 | 0.0 | **[5] | **[5] | |
| Morphology | | | | | <0.001 |
| Superficial spreading melanoma | 61.7 | 20.6 | 55.6 | 16.5 | |
| Lentigo maligna melanoma | 9.2 | 3.6 | 7.0 | **[5] | |
| Nodular melanoma | 2.5 | 31.4 | 3.7 | 37.4 | |
| Other specified melanoma | 4.1 | 21.1 | 9.8 | 22.0 | |
| Not otherwise specified | 22.6 | 23.3 | 23.8 | 20.9 | |
| Thickness | | | | | n.a.[6] |
| <= 1.00mm | 88.3 | 0.0 | 86.5 | 0.0 | |
| 1.01mm-2.00mm | 11.7 | 19.3 | 13.6 | 14.3 | |
| 2.01mm-4.00mm | 0.0 | 52.5 | 0.0 | 45.1 | |
| >4.00mm | 0.0 | 28.3 | 0.0 | 40.7 | |
| Ulceration[7] | | | | | <0.001 |
| No | 98.4 | 46.6 | 98.6 | 54.9 | |
| Yes | 1.6 | 53.4 | **[5] | 45.1 | |

Notes: 1. Characteristics shown are for second primary melanoma only. 2. The numbers shown are for analysis 1, where all of the T2 thickness melanomas with unknown ulceration were assumed to be not ulcerated and were therefore stage I. 3. First primary invasive melanomas were diagnosed between 1995 and 2008, with follow-up to 31 Dec 2013 for diagnosis of subsequent primary invasive melanoma (maximum of 10 years of follow-up from the date of diagnosis of the first primary invasive melanoma). 4. P-values based on chi-squared tests for categorical variables and nonparametric k-sample tests for medians. 5. ** = data withheld due to cell count < 5. 6. n.a. = not applicable (due to structural zeros). 7. The category of "no" for ulceration includes cases for whom the ulceration status was not stated in the medical record.

## Supplemental Table 3: Ten year unadjusted cause-specific survival estimates and adjusted cumulative excess mortality hazard ratios, Queensland, 1995-2013[1]

| | n | Unadjusted 10-year cause-specific survival estimate[2] (95% CI) | Adjusted cumulative 10-year excess mortality hazard ratio[3] (95% CI) | *p* |
|---|---|---|---|---|
| **Analysis group** | | | | |
| S1 | 23,693 | 96.7 (96.5-97.0) | 1.00 | |
| S1S1 | 1,355 | 91.7 (89.4-93.6) | 1.74 (1.19-2.56) | 0.005 |
| S2 | 3,817 | 70.8 (69.1-72.4) | 7.78 (6.68-9.06) | <0.001 |
| S1S2 | 223 | 50.1 (38.7-60.4) | 14.21 (9.66-20.90) | <0.001 |
| S2S1 | 214 | 63.7 (54.6-71.4) | 8.55 (6.00-12.19) | <0.001 |
| S2S2 | 91 | 26.4 (15.5-38.6) | 22.03 (14.51-33.46) | <0.001 |
| Overall effect: p < 0.001 | | | | |
| **Sex** | | | | |
| Males | 16,817 | 91.2 (90.7-91.7) | 1.49 (1.31-1.69) | <0.001 |
| Females | 12,576 | 95.1 (94.6-95.5) | 1.00 | |
| Overall effect: p < 0.001 | | | | |
| **Age at first diagnosis** | | | | |
| 15-29 years old | 2,056 | 96.8 (95.9-97.5) | 1.00 | |
| 30-49 years old | 8,057 | 95.6 (95.1-96.1) | 1.19 (0.89-1.59) | 0.243 |
| 50-69 years old | 11,627 | 93.3 (92.8-93.8) | 1.50 (1.13-1.98) | 0.005 |
| 70-84 years old | 6,809 | 87.5 (86.5-88.4) | 2.10 (158-2.79) | <0.001 |
| Overall effect: p < 0.001 | | | | |
| **Body site** | | | | |
| Head and neck | 4,623 | 88.4 (87.3-89.4) | 2.00 (1.67-2.40) | <0.001 |
| Trunk | 10,725 | 92.7 (92.1-93.2) | 1.62 (1.38-1.90) | <0.001 |
| Upper limbs/shoulders | 7,312 | 94.6 (94.0-95.1) | 1.00 | |
| Lower limbs | 6,494 | 94.1 (93.4-94.6) | 1.21 (1.01-1.46) | 0.043 |
| Not specified | 239 | 98.3 (95.4-99.4) | 0.46 (0.15-1.41) | 0.176 |
| Overall effect: p < 0.001 | | | | |
| **Morphology** | | | | |
| Superficial spreading melanoma | 16,911 | 95.4 (95.1-95.8) | 1.00 | |
| Lentigo maligna melanoma | 1,742 | 94.4 (92.8-95.6) | 0.71 (0.52-0.99) | 0.044 |
| Nodular melanoma | 2,420 | 76.0 (74.0-77.8) | 2.12 (1.79-2.51) | <0.001 |
| Other specified melanoma | 1,845 | 87.8 (86.0-89.4) | 1.15 (0.92-1.44) | 0.223 |
| Not otherwise specified | 6,475 | 93.3 (92.6-93.9) | 1.19 (1.03-1.39) | 0.022 |
| Overall effect: p < 0.001 | | | | |

Notes: 1. First primary invasive melanomas were diagnosed between 1995 and 2008, with follow-up to 31 Dec 2013 for diagnosis of subsequent primary invasive melanoma (maximum of 10 years of follow-up from the date of diagnosis of the first primary invasive melanoma). 2. Survival time was calculated from the date of diagnosis of the first primary invasive melanoma using the time-varying covariate method if a subsequent melanoma was diagnosed. 3. Adjusted for entry time, sex and the following variables relating to the first primary invasive melanoma: age at diagnosis, body site, morphology, tumor thickness group, and ulceration.

**Supplemental Table 4: Ten year unadjusted cause-specific survival estimates and adjusted cumulative excess mortality hazard ratios by analysis group, Queensland, 1995-2013[1]**

| Analysis group | n | Unadjusted 10-year cause-specific survival estimate[2] (95% CI) | Adjusted cumulative 10-year excess mortality hazard ratio[3] (95% CI) | *p* |
|---|---|---|---|---|
| **Study cohort - stage I primary melanomas only** | | | | |
| S1 | 23,693 | 96.6 (96.4-96.9) | 1.00 | |
| S1S1 | 1,355 | 91.7 (89.3-93.6) | 1.47 (1.02-2.13) | 0.047 |
| Overall effect: p = 0.047 | | | | |
| **Study cohort - at least one stage II primary melanoma** | | | | |
| S2 | 3,817 | 70.0 (68.3-71.6) | 1.00 | |
| S1S2 | 223 | 49.8 (38.4-60.2) | 1.40 (0.88-2.24) | 0.160 |
| S2S1 | 214 | 63.5 (54.5-71.3) | 1.03 (0.71-1.49) | 0.866 |
| S2S2 | 91 | 26.3 (15.4-38.5) | 2.42 (1.53-3.81) | <0.001 |
| Overall effect: p < 0.001 | | | | |

Notes: 1. First primary invasive melanomas were diagnosed between 1995 and 2008, with follow-up to 31 Dec 2013 for diagnosis of subsequent primary invasive melanoma (maximum of 10 years of follow-up from the date of diagnosis of the first primary invasive melanoma). 2. Survival time was calculated from the date of diagnosis of the first primary invasive melanoma with delayed entry if a subsequent melanoma was diagnosed. 3. Adjusted for entry time, sex and the following variables relating to the first primary invasive melanoma: age at diagnosis, body site, morphology, tumor thickness group, and ulceration.