Survival after cutaneous melanoma in kidney transplant recipients: a population-based matched cohort study

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Abbreviations

Adjusted hazard ratio (aHR); Australia and New Zealand Dialysis and Transplant (ANZDATA); American Joint Committee on Cancer (AJCC); Hazard ratio (HR); Interquartile range (IQR); Israel Penn International Transplant Tumour Registry (IPITTR); Surveillance, Epidemiology and End Results database (SEER)

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Abstract

Transplant recipients are at elevated risk of melanoma and may have poorer outcomes than non-transplant recipients. We conducted a national, population-based, matched cohort study of Australian kidney transplant recipients and randomly selected members of the general population matched for age, sex, state, and year of diagnosis with invasive cutaneous melanoma (1982-2003). Melanoma histopathological characteristics were extracted from cancer registry notifications and death data was obtained from the National Death Index (1982-2011). Histopathology was compared using conditional logistic regression and overall survival analysed using Cox proportional hazard models. Compared to melanomas in non-transplant recipients (n=202), melanomas in transplant recipients (n=75) had a higher Clark's level (p=0.007) and higher AJCC pathologic stage (p=0.003), but not Breslow thickness (p=0.11). Post-transplant melanoma conferred higher risk of death (hazards ratio 4.26, 95% CI 2.71-6.72, p <0.001) after adjustment for the matching variables, pathologic stage, histological type, and anatomic site. This was not explained by transplantation alone. Melanomas in transplant recipients are more invasive than in non-recipients. More aggressive tumour behaviour is also supported by a markedly poorer outcome. Treatment algorithms developed for the general population with melanoma may not apply to transplant recipients. A review of patient education and skin cancer screening guidelines is warranted.

Introduction

Melanoma of the skin was the fourth most common cancer and the seventh most common cause of cancer death in Australia in 2012 (1). Increases in survival over the last 20 years in Australia (2) and internationally (3) have been made possible by advances in our understanding of its prognostic determinants (4), and recognition of the need for early detection and tailored treatment. Prognostic tumour characteristics include Breslow thickness, pathologic stage, ulceration, and histology (5). Solid organ transplant recipients are at twice the risk of *de novo* melanoma compared to the general population (6, 7). The factors responsible for the increased risk are unknown, but iatrogenic immune suppression and specifically inhibition of T-cell function is thought to play a role (8, 9).

There is evidence to suggest that transplant recipients with *de novo* melanoma have poorer survival compared to their non-transplant counterparts (8, 10-16). Poor survival rates for transplant recipients with a history of melanoma prior to transplantation give such a finding biologic plausibility (17). However, in most studies the number of post-transplant melanomas has been too small for meaningful comparison with non-transplant populations (8, 10-12). In larger studies, the case ascertainment has not been population-based, the non-transplant melanoma population has been non-contemporaneous, and pathologic stage has been unavailable for all or a large proportion of cases (14-16). Thus there is scarce reliable knowledge with which to inform the clinical management of melanomas in transplant recipients.

We performed a national, population-based cohort study of the prognostic determinants after *de novo* invasive cutaneous melanoma diagnosis in Australian kidney transplant recipients and matched randomly selected members of the general population with melanoma and

transplant recipients without melanoma. We hypothesized a higher risk of death in transplant recipients with melanoma compared to non-transplant recipients after adjustment for tumour clinicopathological characteristics.

Methods

Study populations

This was a matched cohort study in Australia utilising existing records held by population-based cancer registries. We included all Australian residents who had received a kidney transplant between 1st January 1982 and 30th September 2003 and had subsequently been diagnosed with primary cutaneous melanoma (ICD-O-3 872-879). Transplant recipients with *de novo* melanoma diagnoses were identified by record linkage between the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry (n=8152) and the Australian Cancer Database (1982+), a compilation of data from the Australian population-based cancer registries (9). ANZDATA is a population-based registry containing records of all kidney transplant recipients in Australia (1963+). Record linkage was performed using an established probabilistic technique, based on recipient name, date of birth, sex, and state/territory of residence (18).

Non-transplant recipients were people with primary cutaneous melanoma randomly selected from population-based cancer registry records. These individuals were matched to transplant recipients by age (±3 years), sex, state of residence, and year of melanoma diagnosis, up to a ratio of 3:1. A third group of transplant recipients without melanoma were randomly selected from the ANZDATA Registry up to a ratio of 3:1, matched to transplant recipients with melanoma according to age (±3 years), sex, transplant year, state of residence, and conditional on being alive at the time of the matched recipient's diagnosis of melanoma. A

matching ratio of 3:1 was used to maximise statistical power and efficiency. Individuals with a history of malignancy (other than melanoma) were not excluded from any patient group.

Data collection

A trained cancer registry coder or pathologist, blind to the transplant history, extracted information from the melanoma notifications held by the cancer registries. Notifications included histopathology reports, hospital cancer notification forms, and death certificates. The clinicopathological data extracted from the notifications were melanoma anatomic site (head/neck, trunk, upper limb, lower limb), histology (ICD-O-3), Breslow thickness, Clark's level, concurrent nevus (yes, no), ulceration (yes, no), and the remaining American Joint Committee on Cancer (AJCC) staging elements, regional lymph node involvement and distant metastasis. We subsequently assigned AJCC pathologic stage (I, II, III, IV) (19).

Date and cause of death were obtained by probabilistic linkage of the cancer registry records with the National Death Index (NDI; 1982+), a population registry based on death certificate data. Follow-up was from date of melanoma diagnosis until death or 31st December 2011; cause of death was available to 31st December 2010.

The study was approved by human research ethics committees and the requirement for informed consent was waived because the researchers received only de-identified data.

Statistical analysis

The reported clinicopathologic characteristics of melanomas in transplant and non-transplant recipients were compared by examining proportions and using conditional logistic regression models. Survival analysis was conducted on the time from diagnosis to death or censored at

31st December 2011 for all-cause mortality, and to 31st December 2010 for melanoma-specific mortality. Survival probabilities were estimated by the Kaplan-Meier method.

Univariate and multivariate Cox proportional hazards regression models were used to examine differences in all-cause survival with respect to transplant history and clinicopathologic characteristics (20). The multivariate model was obtained by using backward selection, with transplant history, histological subtype and anatomic site specified in the model *a priori* regardless of statistical significance and other variables remaining in the model if $p<0.05$. The proportional hazards assumption was assessed using Schoenfeld residuals and log-log survival plots. Melanoma-specific survival was also analysed using a competing risks model (21). All survival models were adjusted for matching using the Sandwich estimator (22). Effect modification was tested between transplantation and the other variables in the multivariate models and retained if $p<0.10$; this conservative approach was taken because of the relatively small sample size.

As some clinicopathologic data were missing for some melanoma patients, multiple imputation was used. Imputation allowed all patients to be included in the analyses, not just those with complete data. Missing values were imputed for the following variables using chained equations (23, 24), with the percentage missing given in brackets: pathologic stage (12% transplant, 12% non-transplant), anatomic site (9% transplant, 6% non-transplant), Breslow thickness (19% transplant, 8% non-transplant), Clark's level (16% transplant, 10% non-transplant), ulceration (35% transplant, 29% non-transplant), and concurrent nevus (51% transplant, 43% non-transplant). Variables used for imputations were age, sex, year of diagnosis, histology, log of survival time, and vital status at the end of follow-up. To test the effects of our imputation on results, we performed sensitivity analyses limited to those study

participants with complete records for all variables. Analyses were performed using STATA/SE 12.1 (StataCorp, Texas, USA).

Results

Cohort characteristics

Data linkage was originally performed in 2005, and updated in 2011. Of the 82 transplant recipients with cutaneous melanoma identified in the original linkage (9), 75 were included in this study (Figure 1). Five were ineligible, either because they did not re-link when the linkage was refreshed (n=2), review of the histopathology report revealed the neoplasm was not an invasive melanoma (n=2), or the melanoma was of donor origin (n=1). Two recipients were excluded because there were no eligible non-transplant recipients available for matching. Two-hundred and two non-transplant recipients were randomly selected (Table 1). It was not possible to match three non-transplant recipients for each recipient; 57 (76%) transplant recipients had three matching non-recipients, 13 (17%) had two, and five (7%) had only one. Two-hundred and eight transplant recipients without melanoma were also randomly selected.

The majority of transplant recipients with melanoma were male (72%) and diagnosed in the 1990s (53%). The median age at diagnosis was 55 years (interquartile range [IQR] 49-63), and the median time between transplantation and melanoma diagnosis was 4 years (IQR 2-7). The most common specified histology (39%) was superficial spreading melanoma, and 54% were located on the limbs (Table 1). The median reported Breslow thickness was 1.00mm (IQR 0.5-2.4) and most (40%) were Clark's level IV. Concurrent nevi were reported in 30% and ulceration in 24%. At diagnosis, 5% of transplant recipients were reported to have lymph

node metastases and 4% distant metastases; 44% were classified as pathologic stage II or higher.

Compared to melanomas in non-transplant recipients, melanomas in recipients were more likely to have a higher Clark's level (p=0.007) and pathologic stage (p=0.002; Table 1). There was no significant difference in Breslow thickness, melanoma histology, or anatomic site.

Overall survival

The total follow-up time was 5349 person-years (range 0.1-28 years). During this period 57 (76%) transplant recipients with melanoma, 61 (30%) non-transplant recipients with melanoma, and 117 (56%) transplant recipients died. The median time between melanoma diagnosis and death was 6.6 years for recipients and 27.4 years for non-recipients. Overall survival was significantly lower for transplant recipients with melanoma compared to non-recipients with melanoma (hazard ratio [HR] 5.26, 95% CI 3.26-8.49; p<0.001, Figure 2). Overall survival was also significantly lower when transplant recipients with melanoma were compared to transplant recipients without melanoma (HR = 2.33; 95% CI = 1.62 to 3.34; p<0.001). Figure 3 shows survival by pathologic stage at time of melanoma diagnosis: survival was lower for recipients compared to non-recipients at each stage (interaction p=0.58).

Transplantation, pathologic stage, histology, Breslow thickness, Clark's level, and ulceration were significantly associated with risk of death in univariate analyses (Figure 4). In the final multivariate model, transplantation (p<0.001), and pathologic stage (p=<0.001) were associated with risk of death (Figure 3). An increased risk of death was observed for

transplant recipients compared to non-recipients (aHR 4.26, 95% CI 2.71-6.72), and for stage II (aHR 2.56, 95% CI 1.54-3.24) and stage III/IV melanomas (aHR 6.44, 95% CI 3.22-12.9) compared to stage I. There was no evidence of effect modification between transplantation and stage (p=0.12), histology (p=0.77), or anatomic site (p=0.87). The analysis without imputation gave similar results (not shown).

Melanoma-specific survival

Melanoma was the reported cause in 22 of the 55 deaths in transplant recipients with melanoma, and 26 of the 61 deaths in non-transplant recipients with melanoma. The melanoma-specific mortality hazard for transplant recipients was 2.59 (95% CI 1.39-4.84), reducing to 1.74 (95% CI 0.79-3.79) after adjustment for pathologic stage, histology and anatomic site. Although the adjusted hazard was not statistically significant in this small sample, there was some evidence of effect modification by pathologic stage (p=0.09). Transplantation increased risk of melanoma-specific death for stage I melanoma (aHR 3.55, 95% CI 1.09-11.54), but not stage II (aHR 1.30, 95% CI 0.49-3.45) or stage III/IV (aHR 1.21, 95% CI 0.27-5.41) melanoma. Sensitivity analysis limited to non-imputed data did not change these findings (data not shown).

Discussion

We found a 4-fold increased risk of death for kidney transplant recipients with melanoma compared to non-transplant recipients with melanoma, after controlling for demographic and tumour clinicopathologic characteristics. This relative risk is not explained by pre-existing comorbidities or the increased risk of death associated with transplantation in the absence of melanoma. The excess deaths among transplant recipients were predominantly in early stage melanoma, a finding confirmed for melanoma-specific survival. At diagnosis, melanomas in

transplant recipients were of higher Clark's level and of more advanced stage compared to those in non-transplant recipients. Taken together, the poorer outcome and the greater local and distal invasion at diagnosis indicate that melanomas in transplant recipients behave more aggressively than melanomas in the general population. The survival profile suggests that melanoma management algorithms developed for the general population do not hold for transplant recipients, and may need to be more aggressive. The more advanced stage at diagnosis warrants the development of enhanced patient education strategies and revised guidelines for skin checks by patients and health professionals.

In agreement with prior case series, most melanomas in transplant recipients were superficial spreading melanoma and less than 1mm in thickness (8, 13, 14, 16). The predominant location on the limbs is discordant with prior studies that observed a predominance on the trunk (8, 14). Our finding of more advanced stage melanoma in transplant recipients also agrees with a comparison of melanomas from the Israel Penn International Transplant Tumour Registry (IPITTR) and general population melanomas in the US Surveillance, Epidemiology and End Results database (SEER) (15).

A strength is our study design, which avoided the potential bias of all prior prognostic work. A multicentre European study of 53 solid organ transplant recipients (1976-2007) with melanoma and matched United States AJCC cutaneous melanomas (1990-1999) found no difference in melanoma-specific survival for T1/T2 stage melanomas and significantly lower survival for T3/T4 stage melanomas (14). In contrast, a study comparing IPITTR melanomas (1980-2007; n=45) and SEER melanomas (1988-2004) found no significant difference in melanoma-specific survival when stratified by AJCC stage (15). However, that study did report a significant 2-fold increased risk of melanoma-specific mortality for recipients after

adjustment for age, gender, race, melanoma treatment (surgery, radiation therapy), and stage (15). The analyses did not control for year of diagnosis and the treatment data was not collected the same way for transplant and non-transplant recipients. A study combining IPITTR and United States transplant melanomas (1967-2007; n=175) found lower melanoma-specific mortality compared to that expected based on SEER melanoma mortality rates (1973-2006), but only for Clark's level III or IV tumours (16). As all previous studies compared melanomas ascertained using different reporting mechanisms, in different geographical areas, in different treatment eras, and measured outcomes using different records, they are likely to have residual confounding. Also, no data was provided on survival relative to transplant recipients without melanoma. Our study addressed these design flaws, and so is likely to be the least biased estimate of comparative melanoma behaviour.

The likely explanation for the poorer survival in transplant recipients is inhibition of the immune response to melanoma cells by immunosuppression, resulting in enhanced tumour growth and spread or "biologic aggressiveness" (8). The possibility of constraints to routine non-surgical melanoma therapy in transplant recipients because of their immunosuppressive therapy and a greater prevalence of co-morbid conditions cannot be excluded as contributory factors. However, as Miao *et al* (2009) noted (15), the greater Clark's level and advanced melanoma stage at diagnosis in recipients appears to support a direct effect of immunosuppression on melanoma progression, particularly in a population under close medical surveillance, including regular skin screening. Further, our finding is similar to the reported 8.9-fold increased risk of death for immune suppressed compared to non-immune suppressed patients with Merkel cell carcinoma (25). In addition, kidney transplant recipients with colorectal cancer or breast cancer have a significantly lower 5-year relative survival compared to non-transplant recipients (26). Thus, a consistent picture is emerging of poorer

outcomes for patients diagnosed with cancer in the context of immune suppression, and warrants a review of oncological practice for this patient subgroup.

Given the likelihood of more biologically aggressive melanomas in the context of immunosuppression, our findings support improved transplant patient education strategies aimed at minimising personal sun exposure and enhancing compliance with regular self skin examinations. Our data also warrant a review of the current guideline for professional skin cancer screening of transplant recipients (27). Annual skin examinations by qualified health professionals appear to be a minimum requirement. High-risk patients, specifically those with a family history of melanoma, or a personal history of non-melanocytic skin cancer or dysplastic naevi, should undergo more regular examinations with a low threshold for biopsy of suspicious lesions. Such a guideline may allow earlier diagnosis and opportunity for altering the poor outcomes that our study has revealed.

In terms of clinical management after melanoma diagnosis, there is a lack of evidence regarding the benefits of reducing or discontinuing immunosuppression in kidney transplant recipients (15). Similarly, there is no evidence to support a change in immunosuppressive agent after melanoma is diagnosed. While our findings suggest that Stage I melanomas in kidney transplant recipients have a poorer prognosis, there is no evidence that more aggressive treatment will achieve improved outcomes. Sentinel lymph node biopsy may be instructive for melanomas ≥0.75mm in thickness or ≥IV Clark level (28). While recipients may experience increased morbidity and mortality with such a strategy (15), the excess risk of death we observed is compelling evidence that these knowledge gaps must be addressed.

The strengths of this study include the population-based design, the use of contemporaneous controls, identical and blinded data collection methods for transplant and non-transplant melanomas, and the long follow-up time. Our clinicopathologic data was limited to the information reported on the cancer registry notifications. As a result of missing data, we examined prognostic factors with and without imputation. Our findings were unaltered by imputation, but greater precision was obtained by the inclusion of all patients, including those with metastastic melanoma at diagnosis where the primary site was not examined histopathologically. Due to the extent of missing data, we were unable to comprehensively examine the role of pre-existing nevi or ulceration. While pre-existing nevi do not predict melanoma prognosis (29), the prognostic association with ulceration is strong (5). The extent of any bias caused by potentially inadequate control for ulceration, and the lack of adjustment for melanoma treatment, is not expected to account for the observed 4-fold risk differential that we observed. Importantly, immunosuppression will neither delay nor prevent the surgical excision of melanoma (30). Being a population-based study, the findings are generalizable to Australian kidney transplant recipients with melanoma. Given the similarity of the melanoma clinicopathological characteristics with prior published studies of transplantation recipients, the findings may also be representative of this population in other settings.

A limitation is the study sample size and the observed number of deaths. In particular, the melanoma-specific survival had lower power to show an association with transplantation, as melanoma-specific deaths are a subset of all deaths and also because cause of death was not known for 2011. There is also the potential for misclassification of the registered cause of death for people with multiple co-morbidities, such as transplant recipients (31). Compared to cause of death data generated from chart reviews, data from death certificates are less reliable. The attributed cause of death in transplant recipients with cancer can be complex,

and because a standardized approach for the transplant and non-transplant recipients in our cohort is not possible, cause-specific risk estimates may be biased. Nevertheless, these findings showed evidence that early stage melanomas in transplant recipients behave more aggressively than those in the general population.

Melanoma is a highly immunogenic tumour, and new insights into melanoma behaviour, including clinicopathologic characteristics at diagnosis and survival in the immunosuppressed, may benefit not only the immunosuppressed but also the general population with melanoma. We found clear evidence of a strong excess risk of death after melanoma in transplant recipients that is not due to their advanced tumour stage at diagnosis, nor explained by their higher background risk of death. Our findings justify the need for evidence-based guidelines for the oncologic management of these patients and bring into question the current recommended frequency of skin cancer screening in this high-risk population subgroup.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

Figure legends

Figure 1: Study flow chart

Figure 1 footnote:

*Matched to kidney transplant recipients with melanoma by age (±3 years), sex, state of residence, and year of melanoma diagnosis or first transplant

Figure 2: Overall survival of kidney transplant recipients, transplant recipients with invasive *de novo* cutaneous melanoma, and non-transplant recipients with invasive cutaneous melanoma

Figure 3: Overall survival of kidney transplant recipients and non-transplant recipients with invasive *de novo* cutaneous melanoma, by AJCC pathologic stage; (A) Stage I, (B) Stage II, and (C) Stage III/IV

Figure 4: Univariate (A) and multivariate (B) risk factors for death in Australian kidney transplant recipients and non-transplant recipients with invasive *de novo* cutaneous melanoma matched for age, sex, state of residence, and year of diagnosis (1982-2003)

Figure 4 footnote:

*Other histology: malignant melanoma regressing (ICD-O-3: 8723), amelanotic melanoma (8730), malignant melanoma in junctional nevus (8740), malignant acral lentiginous melanoma (8744), malignant desmoplastic melanoma (8745), malignant melanoma in giant pigmented nevus (8761), mixed epithelioid and spindle cell melanoma (8770), epithelioid cell melanoma (8771), spindle cell melanoma not otherwise specified (8772)

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Table 1: Clinicopathologic characteristics of invasive cutaneous melanomas in Australian kidney transplant recipients and non-transplant recipients matched for age, sex, state of residence, and year of diagnosis (1982-2003)

Clinicopathologic characteristic	Kidney transplant (n=75)	Non-transplant (n=202)	p-value[4]
	n (%)	n (%)	
AJCC pathologic stage[1]			
I	37 (56)	138 (77)	0.002
II	23 (35)	32 (18)	
III	3 (5)	6 (3)	
IV	3 (5)	3 (2)	
Unknown	*9*	*23*	
Histological subtype			
Superficial spreading	29 (39)	89 (44)	0.08
Nodular	6 (8)	21 (10)	
Lentigo maligna	2 (3)	20 (10)	
Other[2]	9 (12)	13 (6)	
Not otherwise specified	29 (39)	59 (29)	
Anatomic site			
Head and neck	18 (26)	32 (17)	0.06
Trunk	13 (19)	73 (38)	
Upper limb	21 (31)	44 (23)	
Lower limb	16 (24)	41 (22)	
Unknown - not specified	*4*	*8*	
Unknown - primary site unknown[3]	*3*	*4*	
Breslow thickness (mm)			
≤1.0	31 (51)	125 (67)	0.11
>1.0 to 2.0	13 (21)	31 (17)	
>2.0 to 4.0	9 (15)	23 (12)	
>4	8 (13)	7 (4)	
Unknown - not specified	*11*	*12*	
Unknown- primary site unknown[3]	*3*	*4*	
Clark's level			
II	19 (30)	75 (41)	0.007
III	12 (19)	52 (29)	
IV	25 (40)	52 (29)	
V	7 (11)	3 (2)	
Unknown - not specified	*9*	*16*	
Unknown - primary site unknown[3]	*3*	*4*	
Ulceration			
Present	12 (24)	24 (17)	0.30
Absent	37 (76)	119 (83)	
Unknown - not specified	*23*	*55*	
Unknown - primary site unknown[3]	*3*	*4*	
Concurrent nevus			
Present	26 (70)	67 (58)	0.08
Absent	11 (30)	48 (42)	

Unknown - not specified	*35*	*83*
Unknown - primary site unknown[3]	*3*	*4*

[1]American Joint Committee on Cancer classification for cutaneous melanoma pathologic stage

[2]Other histology: malignant melanoma regressing (ICD-O-3: 87233), amelanotic melanoma (87303), malignant melanoma in junctional nevus (87403), malignant acral lentiginous melanoma (87443), malignant desmoplastic melanoma (87453), malignant melanoma in giant pigmented nevus (87613), mixed epithelioid and spindle cell melanoma (87703), epithelioid cell melanoma (87713), spindle cell melanoma not otherwise specified (87723)

[3]The primary anatomic site of the melanoma was unknown because the melanoma diagnosis was made on the basis of metastatic disease, and measurements relating to the primary melanoma were never taken.

[4]P value comparing transplant and non-transplant recipients, calculated on non-missing data only (before imputation), using conditional logistic regression to adjust for matching

Figure 1

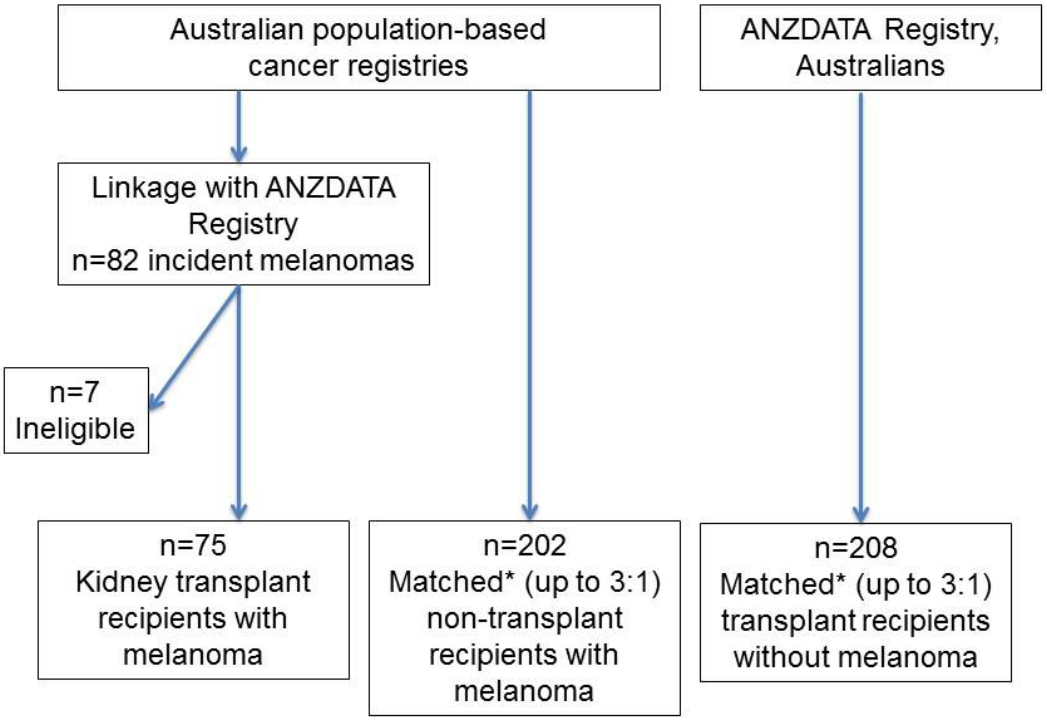
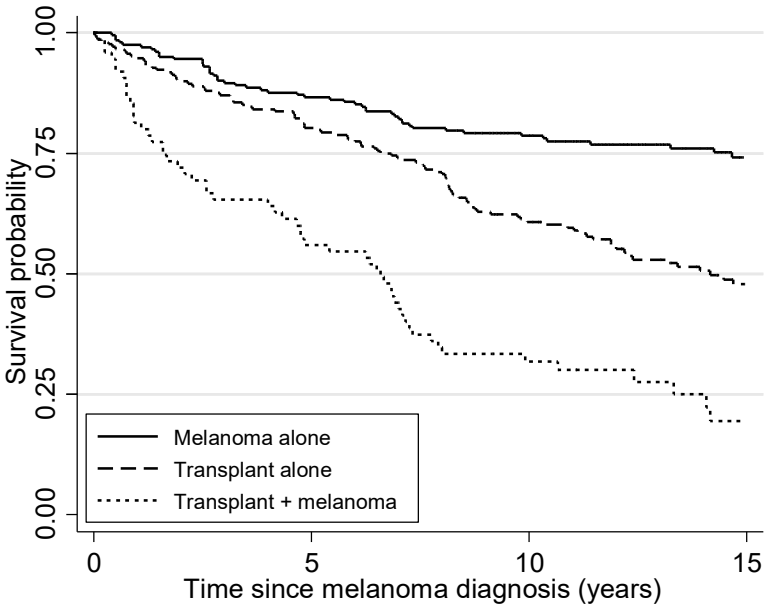

Australian population-based cancer registries
ANZDATA Registry, Australians
Linkage with ANZDATA Registry n=82 incident melanomas
n=7 Ineligible
n=75 Kidney transplant recipients with melanoma
n=202 Matched* (up to 3:1) non-transplant recipients with melanoma
n=208 Matched* (up to 3:1) transplant recipients without melanoma

Figure 2



Number alive				
Melanoma alone	202	175	141	74
Transplant alone	208	167	114	49
Transplant + melanoma	75	42	20	6

Figure 3

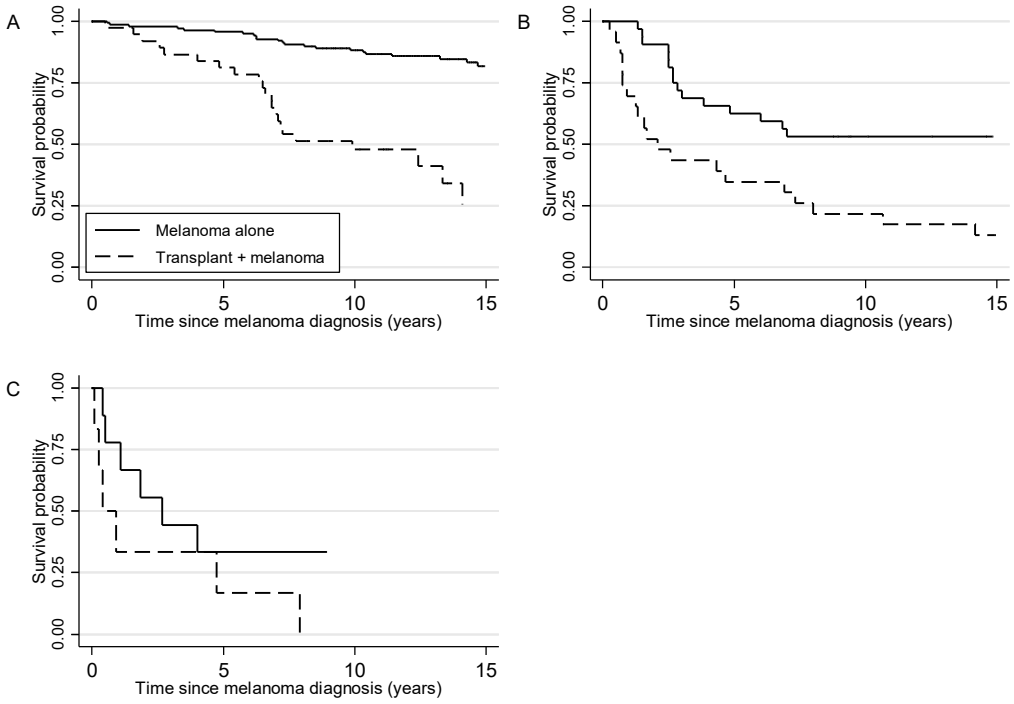
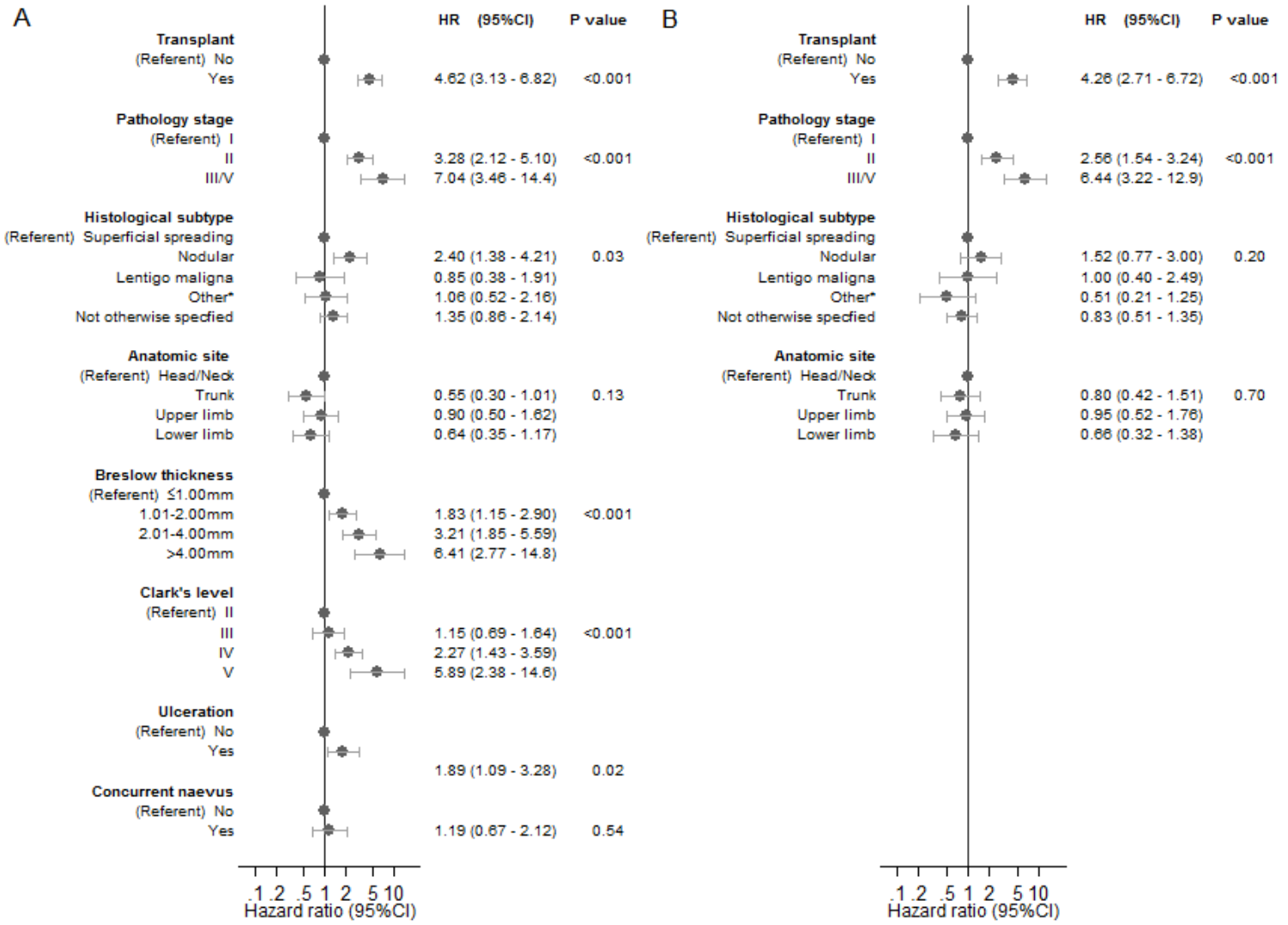

A
B
C
Survival probability
0.00
0.25
0.50
0.75
1.00
0
5
10
15
Time since melanoma diagnosis (years)
Melanoma alone
Transplant + melanoma

Figure 4


A
HR (95%CI)
P value
Transplant
(Referent) No
Yes
4.62 (3.13 - 6.82)
<0.001
Pathology stage
(Referent) I
II
3.28 (2.12 - 5.10)
<0.001
III/V
7.04 (3.46 - 14.4)
Histological subtype
(Referent) Superficial spreading
Nodular
2.40 (1.38 - 4.21)
0.03
Lentigo maligna
0.85 (0.38 - 1.91)
Other*
1.06 (0.52 - 2.16)
Not otherwise specfied
1.35 (0.86 - 2.14)
Anatomic site
(Referent) Head/Neck
Trunk
0.55 (0.30 - 1.01)
0.13
Upper limb
0.90 (0.50 - 1.62)
Lower limb
0.64 (0.35 - 1.17)
Breslow thickness
(Referent) ≤1.00mm
1.01-2.00mm
1.83 (1.15 - 2.90)
<0.001
2.01-4.00mm
3.21 (1.85 - 5.59)
>4.00mm
6.41 (2.77 - 14.8)
Clark's level
(Referent) II
III
1.15 (0.69 - 1.64)
<0.001
IV
2.27 (1.43 - 3.59)
V
5.89 (2.38 - 14.6)
Ulceration
(Referent) No
Yes
1.89 (1.09 - 3.28)
0.02
Concurrent naevus
(Referent) No
Yes
1.19 (0.67 - 2.12)
0.54
.1 .2 .5 1 2 5 10
Hazard ratio (95%CI)
B
HR (95%CI)
P value
Transplant
(Referent) No
Yes
4.26 (2.71 - 6.72)
<0.001
Pathology stage
(Referent) I
II
2.56 (1.54 - 3.24)
<0.001
III/V
6.44 (3.22 - 12.9)
Histological subtype
(Referent) Superficial spreading
Nodular
1.52 (0.77 - 3.00)
0.20
Lentigo maligna
1.00 (0.40 - 2.49)
Other*
0.51 (0.21 - 1.25)
Not otherwise specfied
0.83 (0.51 - 1.35)
Anatomic site
(Referent) Head/Neck
Trunk
0.80 (0.42 - 1.51)
0.70
Upper limb
0.95 (0.52 - 1.76)
Lower limb
0.66 (0.32 - 1.38)
.1 .2 .5 1 2 5 10
Hazard ratio (95%CI)