Melanoma incidence, stage, and survival after solid organ transplant: A population-based cohort study in Ontario, Canada

Christina K. Park, MD, MSc,[a] Erin J. Dahlke, MD,[b] Kinwah Fung, MSc,[c] Jessica Kitchen, MSc,[d] Peter C. Austin, PhD,[c] Paula A. Rochon, MD, MPH,[c,d,e] and An-Wen Chan, MD, DPhil[b,c,d,e]
Toronto, Ontario, Canada

Background: Risk of melanoma is increased with potentially worse outcomes after solid organ transplant.

Objective: To estimate the incidence, stage, and survival in transplant recipients with melanoma.

Methods: Population-based, retrospective, observational study using linked administrative databases. Adults receiving their first solid organ transplant from 1991 through 2012 were followed to December 2013.

Results: We identified 51 transplant recipients with melanoma, 11 369 recipients without melanoma, and 255 matched patients with melanoma from the nontransplant population. Transplant recipients were at increased risk of melanoma (standardized incidence ratio, 2.29; 95% confidence interval [CI], 2.07-2.49) and more likely to be diagnosed at stages II through IV (adjusted odds ratio, 4.29; 95% CI, 2.04-9.00) compared with the nontransplant population. Melanoma-specific mortality was increased in transplant recipients compared with the nontransplant population (adjusted hazard ratio, 1.93; 95% CI, 1.03-3.63). Among transplant recipients, all-cause mortality was increased after melanoma compared with those without melanoma (stage T1/T2: adjusted hazard ratio, 2.18; 95% CI, 1.13-4.21; T3/T4: adjusted hazard ratio, 4.07; 95% CI, 2.36-7.04; III/IV: adjusted hazard ratio, 7.92; 95% CI, 3.76-16.70).

Limitations: The databases did not contain data on immunosuppressive drugs; ascertainment of melanoma metastasis relied on pathology reports.

Conclusion: Melanoma after solid organ transplant is more often diagnosed at a later stage and leads to increased mortality, even for early-stage tumors. (J Am Acad Dermatol 2020;83:754-61.)

Key words: epidemiology; immunosuppression; melanoma; population-based cohort; statistics; transplant.

Melanoma is an immunogenic and potentially fatal form of skin cancer that has been increasing in incidence in North America.[1,2] Melanoma is more common after solid organ transplant because of chronic immunosuppression.[3,4] A systematic review of population-based

From the Faculty of Medicine, University of Toronto[a]; Division of Dermatology, Women's College Hospital[b]; ICES[c]; Women's College Research Institute, Women's College Hospital[d]; and Department of Medicine, University of Toronto, Ontario.[e]

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Correspondence to: An-Wen Chan, MD, DPhil, Women's College Hospital, 76 Grenville St, Toronto, Ontario M5S 1B2, Canada. E-mail: anwen.chan@utoronto.ca.

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cohort studies found that transplant recipients had a more than 2-fold increased melanoma incidence compared with the general, nontransplant population.[5] Melanoma stage and outcomes may also be worse in the context of chronic immunosuppression.[6-9]

In this population-based cohort study, we estimated the relative incidence, stage, and mortality associated with posttransplant melanoma compared with melanoma in the nontransplant population. We also compared the all-cause mortality between transplant recipients with and without melanoma. We hypothesized that there would be a higher incidence, later stage at diagnosis, and increased mortality associated with posttransplant melanoma.

CAPSULE SUMMARY

- Melanoma in solid organ transplant recipients is more likely to be diagnosed at an advanced stage and has higher mortality compared with melanoma in the nontransplant population.
- Intensified skin cancer screening and patient education may be warranted to promote early detection and prevention.

PATIENTS AND METHODS

We conducted a retrospective, observational, inception cohort study using population-based administrative health databases that were linked using unique encoded identifiers at ICES in Toronto, Canada. Approval of the study was granted by the Women's College Hospital Research Ethics Board, which allowed a consent waiver as we used deidentified administrative databases held securely at ICES.

Using the Canadian Organ Replacement Register, which records data on all transplants in Canada, we identified adult Ontario residents who received their first kidney, liver, heart, or lung transplant from 1991 through 2012, had no pretransplant melanoma recorded in the Ontario Cancer Registry,[10] and survived beyond 3 months after the transplant. The 3-month survival criterion was intended to exclude patients who died of acute complications of their transplant surgery. The last date of follow-up was December 31, 2013.

Using the validated Ontario Cancer Registry,[10] we identified the first primary cutaneous invasive melanoma diagnosed after transplant through December 31, 2013. From each pathology report, we recorded the melanoma site, histologic subtype, Breslow thickness, and specimen collection date. We excluded tumor ulceration and mitotic rate from the staging criteria because they were inconsistently reported in pathology reports, particularly during the earlier study years before their inclusion in staging criteria in 2002.[11] Data were entered directly into an electronic form in duplicate by 2 data extractors (EJD and JK). Discrepancies were resolved by discussion and, if still unresolved, reviewed by a third adjudicator (AWC). Stage was classified as I through IV according the seventh edition of the American Joint Committee on Cancer tumor parameters T1 through T4 and pathology reports from lymph node and visceral biopsy specimens collected within 3 months of the melanoma diagnosis date.[12] Five patients with melanoma from the nontransplant population in Ontario were matched for age, sex, and diagnosis year to each posttransplant patient with melanoma. Melanoma-specific mortality was extracted from the Ontario Registrar General Vital Statistics database, which records all deaths and contributing causes listed in death certificates in Ontario.

We extracted demographic data (age, sex, rurality, and quintile of median neighborhood income based on residential postal code) and vital status from the Registered Persons Database, which is maintained by the Ontario Ministry of Health and Long-Term Care. We determined race based on information available from other linked databases in the following hierarchical order: the Canadian Organ Replacement Register; Organ Transplant Tracking Record at University Health Network; Canadian Cystic Fibrosis Patient Data Registry; Ontario Renal Reporting System for predialysis and dialysis patients; a validated surname algorithm applied to the Registered Persons Database[13]; and Immigration, Refugees and Citizenship Canada. We recorded transplant-related variables (organ type, multiorgan transplant, subsequent transplants, transplant year) from the Canadian Organ Replacement Register.

Statistical analyses

Among transplant recipients, we calculated the crude melanoma incidence rate as the number of incident melanoma cases during follow-up divided by the total posttransplant follow-up time. To quantify the incidence of melanoma in transplant recipients relative to the nontransplant population, we divided the observed by the expected number of posttransplant melanomas, yielding the standardized incidence ratio.[14] The expected number was calculated with indirect standardization methods by multiplying the age-, sex-, and diagnosis year–specific incidence rates in the entire Ontario

Abbreviation used:

CI: confidence interval

population and the corresponding person-years of follow-up in the transplant cohort. For the general population rates, the population size (denominator) was obtained from census data collected every 5 years in Canada, with linear interpolation between census years.[15]

Among melanomas diagnosed in transplant recipients compared with the nontransplant population, we estimated the association between transplant and advanced melanoma stage using odds ratios and 95% Wald confidence intervals (CIs) obtained from multivariable, conditional logistic regression. The model included urban residence and income quintile (4-5 vs 1-3) for adjustment because these factors were previously found to be associated with melanoma incidence.[16] We defined *advanced melanoma* as being either metastatic (stage III/IV) or localized with a Breslow thickness greater than 2 mm (American Joint Committee on Cancer tumor stage T3/T4).

To evaluate melanoma-specific mortality in transplant recipients compared with the nontransplant population, we used multivariable cause-specific hazards regression that accounted for the competing risk of death due to causes other than melanoma. The index date was the date of melanoma diagnosis. To adjust for potential confounding, the model included melanoma stage, urban residence, and income quintile as covariates.

To evaluate all-cause mortality in transplant recipients with melanoma compared with those without melanoma, we used multivariable Cox proportional hazards regression. The index date was the date of transplant. Because melanoma could develop at any point after transplant, the diagnosis of melanoma was treated as a time-varying covariate to prevent immortal time bias. Thus, the at-risk time preceding the date of melanoma diagnosis was attributed to the unexposed group, whereas any time after the diagnosis was attributed to the exposed group. The model included age, sex, race, urban residence, income quintile, transplant year, and graft organ type (kidney/liver vs lung/heart) as covariates for adjustment. Associations were measured with hazard ratios and 95% CIs.

RESULTS

A total of 19 910 patients received a solid organ transplant in Ontario between 1991 and 2012. Exclusions were made based on the following criteria: not the first transplant (n = 1888), residence outside of Ontario (n = 4429), age younger than 18 years (n = 1128), bowel transplant (n = 13), pretransplant melanoma (n = 29), death within 90 days after transplant (n = 564), and kidney graft failure within 90 days (n = 439). The final transplant cohort consisted of 11 420 patients whose characteristics are shown in Table I. Overall, the most commonly transplanted organ was kidney (61.5%), followed by liver (23.6%), lung (7.8%), and heart (7.1%). Transplant recipients were observed for a total of 93 475 person-years.

Melanoma was diagnosed in 51 (0.45%) transplant recipients, representing an incidence rate of 0.55 (95% CI, 0.41-0.72) per 1000 person-years. The 51 patients with posttransplant melanoma were matched to 255 nontransplant patients with melanoma (Table I). In both groups, the median age at diagnosis was 61 years (interquartile range, 51-68), and the majority (88.2%) were male with an urban residence (posttransplant, 86.3%; nontransplant, 86.7%) (Table I). Posttransplant melanomas were more frequently located on the head and neck than melanomas in the nontransplant population (31.4% vs 20.0-21.6%) (Table II). For both groups, the most frequent histologic subtype was superficial spreading (posttransplant, 35.3%; nontransplant, 40.0%).

The standardized incidence ratio was 2.29 (95% CI, 2.07-2.49) for melanoma in transplant recipients compared with the entire general population of Ontario. Among patients with melanoma diagnosis, transplant recipients were more likely to receive the diagnosis at an advanced stage than matched patients with melanoma from the nontransplant population (adjusted odds ratio, 4.29; 95% CI, 2.04-9.00), with more than half (52.9%, 27/51) of the posttransplant melanomas being stage T3/T4/III/IV compared with 28.6% (73/255) of nontransplant melanomas (Table II).

Melanoma-specific mortality was also higher in transplant recipients than in the nontransplant population, independent of stage (adjusted hazard ratio 1.93; 95% CI, 1.03-3.63) (Table III). More than a quarter (27.5%, 14/51) of patients with posttransplant melanoma died of melanoma, compared with 12.5% (32/255) in the nontransplant group (Table I).

Among 11 420 transplant recipients, 37% (19/51) of those with melanoma and 71% (8037/11 369) of those without melanoma were alive at the end of follow-up (Table I). Similar proportions of transplant recipients with and without melanoma died of causes other than melanoma (35% vs 29%, $P = .35$). A diagnosis of melanoma was associated with an

Table I. Characteristics of transplant recipients with posttransplant melanoma, matched patients with melanoma from the nontransplant population, and transplant recipients without melanoma

Variable	Posttransplant melanoma (n = 51)	Matched patients with melanoma from the nontransplant population (n = 255)	Transplant recipients without melanoma (n = 11 369)
Male sex, n (%)	45 (88.2)	225 (88.2)	7315 (64.3)
Median (IQR) age at melanoma diagnosis, y	61 (51-68)	61 (51-68)	N/A
Race, n (%)			
White	37 (72.5)	*	6776 (59.6)
Nonwhite	1-5 (2.0-9.8)†	*	2050 (18.0)
Unknown	9-13 (17.6-25.5)†	*	2543 (22.4)
Urban residence, n (%)	44 (86.3)	221 (86.7)	9981 (87.8)
High income quintile (4th or 5th), n (%)	29 (56.9)	135 (52.9)	4387 (38.6)
Median (IQR) age at transplant, y	55 (45-62)	N/A	51 (40-59)
Transplant organ, n (%)			
Kidney	34 (66.7)	N/A	6984 (61.4)
Lung	1-5 (2.0-9.8)†	N/A	893 (7.9)
Liver	12 (23.5)	N/A	2682 (23.6)
Heart	1-5 (2.0-9.8)†	N/A	810 (7.1)
Calendar year of transplant, n (%)			
1991-1996	18 (35.3)	N/A	2286 (20.1)
1997-2004	21 (41.2)	N/A	3695 (32.5)
2005-2012	12 (23.5)	N/A	5388 (47.4)
Vital status at end of follow-up, n (%)			
Alive	19 (37.3)	191 (74.9)	8037 (70.7)
Death due to melanoma	14 (27.5)	32 (12.5)	0 (0)
Death due to other causes	18 (35.3)	32 (12.5)	3332 (29.3)
Median (IQR) follow-up time after transplant, y	9 (6-14)	N/A	7 (3-12)
Median (IQR) follow-up time after melanoma, y	3 (1-5)	5 (3-9)	N/A

IQR, Interquartile range; *N/A*, not applicable.
*Not available.
†Range of values presented to protect privacy due to small cell size.

increased rate of all-cause mortality (adjusted hazard ratio, 3.48; 95% CI, 2.45-4.94). The relative difference in hazard rates progressively increased with higher melanoma stage (adjusted hazard ratio, 2.18; 95% CI, 1.13-4.21 for T1/T2; adjusted hazard ratio, 4.07; 95% CI, 2.36-7.04 for T3/T4; and adjusted hazard ratio, 7.92; 95% CI, 3.76-16.70 for stage III/IV) (Table IV).

DISCUSSION

In this population-based cohort study, we found that solid organ transplant recipients had a significantly greater risk of developing melanoma overall and had melanoma diagnosed at a later stage than age- and sex-matched individuals from the nontransplant population. Posttransplant melanoma was also associated with lower melanoma-specific survival compared with melanoma in the nontransplant population. Transplant recipients who developed melanoma had an increased overall mortality compared with transplant recipients without melanoma, even for early stage tumors.

Our finding of an increased melanoma incidence in transplant recipients is consistent with a 2014 systematic review of population-based cohort studies, which found a pooled standardized incidence ratio of 2.4 (95% CI, 2.0-2.9).[5,9,17-19] There are several proposed mechanisms for the increased risk of cancers in transplant recipients. Increased immunosuppression and subsequent decreased immunosurveillance have been reported to promote posttransplant skin cancer.[9,20] The direct carcinogenic effects of systemic immunosuppressive therapies can also increase skin cancer risk. For example, azathioprine in particular has been shown to promote ultraviolet light-induced DNA damage.[21] Although rare, another cancer mechanism is through transplant donor transmission of melanoma.[22-25]

Table II. Characteristics of melanomas diagnosed after transplant and in the matched nontransplant population

Tumor characteristics	Patients with melanoma, n (%)	
	Posttransplant (n = 51)	Matched nontransplant population (n = 255)
Site of primary tumor		
Trunk	18 (35.3)	104 (40.8)
Upper and lower extremities	12-16 (23.5-31.4)*	95 (37.3)
Head and neck	16 (31.4)	51-55 (20.0-21.6)*
Unknown primary	1-5 (2.0-9.8)*	1-5 (0.3-2.0)*
Subtype		
Superficial spreading	18 (35.3)	102 (40.0)
Nodular	7 (13.7)	50 (19.6)
Other†	8 (15.7)	34 (13.3)
Not reported	18 (35.3)	69 (27.1)
American Joint Committee on Cancer Stage		
Localized T1/T2 (tumor stage)	18 (35.3)	171 (67.1)
Localized T3/T4 (tumor stage)	17 (33.3)	47 (18.4)
III	5-9 (9.8-17.6)*	21-25 (8.2-9.8)*
IV	1-5 (2.0-9.8)*	1-5 (0.3-2.0)*
Unclear	6 (11.8)	11 (4.3)
Breslow thickness, mm‡		
≤1.0	12 (34.3)	122 (56.0)
1.01-2.0	6 (17.1)	49 (22.5)
2.01-4.0	10 (28.6)	25 (11.5)
>4.0	7 (20.0)	22 (10.1)

*Range of values presented to protect privacy due to small cell size.
†Acral lentiginous, lentigo maligna melanoma, nevoid, spindle cell, amelanotic, desmoplastic.
‡Stages T1 through T4 only.

Our findings of higher stage and mortality after posttransplant melanoma are consistent with population-based studies in the United States, Sweden, and Australia.[6-9] The Swedish study found a 4-fold higher odds of metastatic melanoma at diagnosis among transplant recipients,[8] and the US study found double the odds of regional (but not distant) metastasis compared with the general population.[6] Transplant-related immunosuppression appears to contribute a 2- to 3-fold increased risk of melanoma-specific mortality, based on our study and others.[7-9,26]

The more advanced stage and worse prognosis observed for posttransplant melanoma in our cohort are likely due to accelerated melanoma growth in the context of impaired immune surveillance.[27,28] It is unlikely that the worse outcomes of posttransplant melanoma are due to a delay in melanoma diagnosis relative to the nontransplant population because transplant recipients have more frequent contact with the health care system as part of routine posttransplant care.

Among transplant recipients, melanoma had a significant impact on overall survival. Depending on the cancer stage, the all-cause mortality rate was 2- to 8-fold higher in transplant recipients with melanoma versus those without melanoma. To our knowledge, this study is the first to show increased mortality even for early-stage tumors that otherwise have an excellent prognosis in the immunocompetent population. An Australian population-based study found lower survival in transplant recipients with melanoma compared with transplant recipients without melanoma but did not report results stratified by stage.[7]

Although the increased mortality after melanoma in our transplant cohort is primarily attributable to cancer metastasis, it is also possible that changes made to immunosuppression regimens in response to the melanoma diagnosis could have led to increased mortality from graft rejection. However, the proportion of transplant recipients dying of causes other than melanoma was not significantly higher in those with melanoma than in those without melanoma, suggesting that graft rejection was not a major contributor to the increased mortality observed in our transplant cohort.

Although guidelines do not recommend regular skin cancer screening in the nontransplant population,[29] our findings highlight the importance of frequent skin cancer screening in the immunosuppressed transplant population with the aim of promoting earlier diagnosis and better outcomes. Adherence to annual dermatology assessment has been associated with reduced morbidity and mortality from keratinocyte carcinoma in transplant recipients.[30] However, skin cancer screening rates are suboptimal in this high-risk population. Less than 3% of transplant recipients in Ontario were found to have seen a dermatologist at least annually,[30] as recommended by posttransplant care guidelines.[31] Only half of transplant care providers in Canada reported arranging annual skin examinations for their patients.[32] Studies in other countries have also found poor adherence to skin cancer screening.[33-37]

Table III. Melanoma-specific mortality in transplant recipients compared with the nontransplant population (matched by age, sex, and melanoma diagnosis year)

	Melanoma-specific mortality			
Variable	Unadjusted hazard ratio (95% CI)	Unadjusted *P* value	Adjusted hazard ratio (95% CI)	Adjusted *P* value
Transplant (yes vs no)	3.01 (1.56-5.79)	.001	1.93 (1.03-3.63)	.040
Melanoma stage (advanced vs T1/T2)	7.83 (3.96-15.47)	<.001	7.20 (3.46-15.00)	<.001
Residence (urban vs rural)	0.73 (0.31-1.73)	.474	0.59 (0.24-1.46)	.253
Income quintile (4-5 vs 1-3)	0.69 (0.39-1.21)	.191	0.86 (0.45-1.62)	.639

CI, Confidence interval.

Table IV. All-cause mortality in transplant recipients with versus without melanoma, stratified by melanoma stage

	All-cause mortality			
Melanoma stage (reference: no melanoma)	Unadjusted hazard ratio (95% CI)	Unadjusted *P* value	Adjusted hazard ratio (95% CI)*	Adjusted *P* value
T1/T2	2.73 (1.42-5.26)	.003	2.18 (1.13-4.21)	.020
T3/T4	6.83 (3.96-11.77)	<.001	4.07 (2.36-7.04)	<.001
III/IV	9.21 (4.38-19.34)	<.001	7.92 (3.76-16.70)	<.001
Unknown	3.07 (0.99-9.52)	.052	2.98 (0.96-9.26)	.059

CI, Confidence interval.
*Adjusted for age, sex, race, urban residence, income quintile, transplant year, and graft organ type.

Reduction of immunosuppression should be considered for transplant recipients who develop melanoma, given the increased risk of mortality across all stages. A 2006 expert consensus panel considered it reasonable to reduce immunosuppression by varying amounts depending on the stage, number, and prognosis of skin cancers.[38] There are case reports of patients who achieved regression or remission of advanced melanoma after discontinuation or reduction of immunosuppressive therapy.[39-41] A retrospective, multicenter cohort study found no statistically significant difference in the proportion of transplant recipients who died after alteration of immunosuppressive regimens (8.8%) compared with no alteration (17.8%), although the analysis was based on small numbers.[42] Further research is required to evaluate how best to balance the risk of melanoma-specific mortality in the context of continued immunosuppression versus the risk of graft loss due to reduction in immunosuppression.

A limitation of our study was that the administrative databases did not contain data on immunosuppressant drugs, as is the case with previous population-based studies. However, our use of survival analysis methods accounted for the duration of immunosuppression, a key measure of immunosuppressant exposure. We also note that there is no available measure of overall immunosuppression level for comparisons across patients because drug combinations and dosages vary greatly between patients. Another limitation is that our ascertainment of melanoma metastasis relied on pathology reports in the Ontario Cancer Registry. We did not have access to clinical records, meaning that we were not able to identify metastasis diagnosed solely on clinical examination or imaging without biopsy confirmation. This misclassification would have led to an underestimation of the incidence of stage III or IV melanoma. Furthermore, the staging criteria of tumor ulceration and mitotic rate were inconsistently reported in pathology reports during the study period. We therefore used only Breslow thickness, the strongest prognostic factor, to define the tumor stage for localized melanomas.

The interplay between melanoma and immunosuppression leads to significantly worse survival in the transplant population. Further study of preventive and therapeutic interventions, including reduction of immunosuppression, is needed to help inform treatment decisions for this high-risk population. Skin cancer screening and patient education as part of routine posttransplant care may be warranted to promote early detection and prevention.[31]

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