Pathways from Diagnosis to Death from Keratinocyte Cancer in Kidney Transplant Recipients

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Abstract

Background: Kidney transplant recipients are at increased risk of developing and dying from keratinocyte cancer. We aimed to describe the clinical course of keratinocyte cancer-related deaths in a cohort of kidney transplant recipients.

Methods: In kidney transplant recipients transplanted between 1995 and 2014 in Queensland, Australia, we ascertained keratinocyte cancer deaths by searching national transplant and state death registries to March 2020. Deceased transplant recipients’ medical records were reviewed to assess features of the primary lesion of the fatal keratinocyte cancer, metastases, and clinical information before death.

Results: Of 658 kidney transplant recipient deaths, 49 (7%) were due to keratinocyte cancer, and 35 were from squamous cell carcinoma (SCC), primarily from the head and neck (24; 69%). The most common site of metastasis was the lungs (21; 58%). Median time (minimum, maximum) from the diagnosis of primary SCC to metastasis was 5 months (0, 29). After this, the median time to death was 9 months (1, 50).

Conclusion: Fatal keratinocyte cancers overwhelmingly arise on the head and neck, with lungs the most common metastasis site. The short time from diagnosis of primary to death indicates the aggressive nature of these keratinocyte cancers.

Introduction

Kidney transplant recipients receive intense, long-term immunosuppressive therapy to prevent allograft rejection [1]. However, long-term immunosuppression greatly increases the incidence of squamous cell and basal cell carcinomas (SCCs and BCCs), collectively termed...
keratinocyte cancers [1, 2]. SCC tumour incidence in kidney transplant recipients may be increased over 100-fold [3, 4], and BCC tumour incidence increased by around 10-fold [5]. SCCs in kidney transplant recipients are more likely to display features associated with poor prognosis, such as early infiltration with deep tissue involvement, perineural invasion, and lymphatic invasion [6, 7]. There is an increased keratinocyte cancer mortality rate in kidney transplant recipients compared to the general population, and previous studies have estimated standardized mortality ratios ranging from 30- to 52-fold [1, 8, 9]. In Australia, keratinocyte cancer is one of the leading causes of malignancy-related death in the kidney transplant population [9].

We recently conducted a study in Queensland kidney transplant recipients, showing that most keratinocyte cancer-related deaths are due to SCC (74 times the SCC mortality rate in the general population) but that BCC can also be fatal with a doubling of death rate compared with the general population [10]. Despite these greatly increased risks of keratinocyte cancer deaths in transplant recipients, the pathways from diagnosis to death from keratinocyte cancers have rarely been studied. One American multicentre study reported 68 organ transplant recipients (78% kidney recipients) who were diagnosed with 62 metastatic SCCs and 15 other metastatic skin cancers (such as melanoma and Merkel cell carcinoma). These metastatic lesions caused death in 23 (34%) of the transplant recipients on average 2 years after diagnosis of metastatic disease [11]. Primary lesions were mainly SCCs and, of those with a known location, were primarily on the face and scalp [11]. The clinical progression of keratinocyte cancer to mortality has not been studied in kidney transplant recipients in Australia. We aimed to review and describe the clinical details and courses of all keratinocyte cancer-related deaths in this cohort of kidney transplant recipients transplanted in Queensland.

Materials and Methods

Ascertainment of fatal cases of keratinocyte cancer in the study kidney transplant recipients has been described in detail previously [10], but in brief, a database maintained by the Queensland Kidney Transplant Service was used to identify all patients who received one or more solid organ transplants between January 1995 and December 2014 at the Princess Alexandra Hospital, the transplant centre for the state of Queensland. Cause of death information to March 2020 was identified using multiple sources, namely the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA); the Queensland Registry of Births, Deaths, and Marriages; and the Queensland Kidney Transplant Service Data-base. Cause of death information was searched for the terms “squamous, basal, skin” to identify cases where keratinocyte cancer caused or contributed to death.

Available medical records were obtained from the Princess Alexandra Hospital and reviewed to assess the features of the presumed fatal primary keratinocyte cancer and ascertain related metastases and the general circumstances surrounding each death. Supplementary clinical information (medical imaging and pathology reports, discharge summaries, medication summaries, and records of surgical procedures) were accessible from public hospitals around Queensland through a common online portal (The Viewer © Queensland Health). Information from private clinicians (general practitioners, dermatologists, surgeons, oncologists) was available only if the correspondence was filed within the public hospital medical record.

The precise location of the primary keratinocyte cancer, which ultimately caused death, was not always apparent in patients with numerous neoplastic skin lesions. Information regarding primary lesion location and diagnostic details was therefore defined as (i) definite or highly likely: either a locally invasive lesion or a discrete lesion showing high-risk features such as lymphovascular or perineural invasion, with subsequent metastatic deposits in the regional nodal basin, without any other possible culprit lesions that would drain to the regional nodal basin; (ii) probable: lesion with high-risk features in a location with subsequent metastatic deposits in regional lymph nodes; and (iii) unknown. Histopathology reports of primary lesions were ascertained for anatomical location, subtype, and differentiation as applicable, presence of perineural invasion, and lymphovascular invasion. Other information collected included locations of invasion or metastasis (diagnosed on imaging), treatment, and time between transplantation and death; time between primary and metastasis; and time between metastasis and death. The number of skin cancers diagnosed in the 6 months prior to diagnosis of metastatic keratinocyte cancer was also noted from the hospital record.

Demographic characteristics of included and excluded transplant recipients were compared using χ² test for categorical variables (or Fishers’ exact test when cell counts were <5) or Mann-Whitney U-test for non-normally distributed continuous variables. Ethical approval was obtained from the Human Research Ethics Committees of the QIMR Berghofer Medical Research Institute and from the Queensland Health Metro South Ethics Board (LNR/2019/QMS/50370).

Results

Of 2,234 included patients, 658 (29%) were deceased on follow-up in 2020. Forty-nine (7%) died from keratinocyte cancer: 48 (7%) from SCC and 1 (0.2%) from BCC. There were 38 (78%) transplant recipients whose medical records were available. Most died in or after 2015 (26; 68%). Thirty-two (84%) were men, 23 (61%) lived in major cities, their median age at the first transplant was 54 years (range 10–77), and the median age at death was 66.5 (range 39–82). Twenty-eight (74%) had received a single kidney transplant, while nine (25%)
had received more than one kidney transplant, and one had received both cardiac and renal transplant. The 11 kidney recipients who were not included were similar to those included in regard to age at transplant, age at death, and sex, but they were somewhat more likely to have been transplanted before 2005 and to be living in an outer regional area (differences not significant) (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000524120). Fourteen recipients had data available on skin cancers excised in 6 months prior to diagnosis of metastatic keratinocyte cancer in the hospital record, of which there was a median of 4 (minimum 1, maximum 11) BCCs and SCCs diagnosed.

**Clinicopathological Features of Fatal Primary Tumours**

Of the 38 kidney transplant recipients with records available, 37 (97%) deaths were caused by SCC and 1 death was caused by a BCC (3%) (Table 1). Twenty-four had histopathology of the presumed primary lesion available; 16 (42%) were deemed definite or highly likely to be

| Table 1. Fatal primary SCC and BCC characteristics and metastatic locations at death |
|---------------------------------|------------------|------------------|
| **Location**                    | SCC (n = 37)     | BCC (n = 1)      |
| Head and neck<sup>a</sup>       | 25 (68)          | 1 (100)          |
| Upper limb<sup>b</sup>          | 10 (27)          | –                |
| Lower limb<sup>c</sup>          | 2 (5)            | –                |
| **Histopathology (SCC)<sup>d</sup>** |                   |                  |
| Well-differentiated             | 2 (9)            | –                |
| Moderately differentiated       | 7 (30)           | –                |
| Poorly differentiated           | 12 (52)          | –                |
| Other                           | 2 (9)            | –                |
| **Histopathology (BCC)**        |                   |                  |
| Nodular                         | –                | 1 (100)          |
| **Lymphovascular invasion<sup>e</sup>** |                   |                  |
| Yes                             | 10 (43)          | –                |
| No                              | 13 (57)          | –                |
| **Perineural invasion<sup>f</sup>** |                   |                  |
| Yes                             | 6 (26)           | –                |
| No                              | 17 (74)          | –                |
| **Metastasis location**         |                   |                  |
| Distant                         | 27 (73)          | –                |
| Nodal                           | 6 (16)           | –                |
| None                            | 4 (11)           | 1 (100)          |
| **Disease course**              |                   |                  |
| Years from the first transplant to primary lesion (median [min, max])<sup>g</sup> | 10 (1, 37)      | 9 (9, 9)         |
| Years from the first transplant to death (median [min, max])<sup>h</sup> | 12 (3, 39)      | 15 (15, 15)      |
| Months between primary and metastasis (median [min, max])<sup>i</sup> | 5 (0, 29)       | –                |
| Months from metastasis to death (median [min, max])<sup>j</sup> | 8 (1, 29)       | –                |
| **Distant sites of metastasis (in 27 transplant recipients)** |                   |                  |
| Lung or pleura                  | 23 (85)          | –                |
| Bone                            | 7 (26)           | –                |
| Liver                           | 4 (15)           | –                |
| Gastrointestinal                | 2 (7)            | –                |
| Breast                          | 2 (7)            | –                |
| Brain                           | 1 (4)            | –                |

Values are n (%) unless otherwise indicated. <sup>a</sup>Includes seven lesions with unknown primary location but presumed head and neck due to cervical metastasis. <sup>b</sup>Includes two lesions with unknown primary but presumed upper limb due to axillary metastasis. <sup>c</sup>Includes one lesion with unknown primary but presumed lower limb due to groin inguinal metastasis and history. <sup>d</sup>Missing information for 14 SCCs. <sup>e</sup>Missing information for 14 SCCs and 1 BCC. <sup>f</sup>Including 29 cases with a known primary. <sup>g</sup>Including 25 cases with a known primary and known metastasis. <sup>h</sup>Including 35 cases with a known metastasis.
the primary SCC that progressed, while eight (21%) lesions were considered the probable primary lesion. Five recipients had a primary lesion documented in the medical record, although histopathology was unavailable. Nine kidney recipients had unknown primaries. Of these, seven had subsequent metastatic deposits in cervical lymph nodes, and thus a head and neck location was inferred. Two involved the axillary lymph nodes, and an upper limb location was inferred.

Fatal primary SCCs were mainly located on the head and neck (25, 68%) (Table 1). Specific locations were 13 (52%) on the face or ear, 5 (20%) on the scalp, and 7 lesions (28%) of an unknown head and neck location. There were 10 SCC primary lesions of the upper limb with 5 (50%) lesions from the forearm, 3 (30%) from the hand, and 2 (20%) of an unknown upper limb location. There were two lower limb lesions: one on the thigh and one on the left lower leg. Of the 23 primary SCCs with histopathological reports available, most were poorly (12; 52%) or moderately (7; 32%) differentiated. Ten lesions (45%) showed lymphovascular invasion, and six (27%), perineural invasion. The single fatal BCC lesion was located on the right cheek and was of the nodular subtype, with an expansile growth pattern reported (Table 1).

Clinical Courses of Fatal Keratinocyte Cancers

The pathway of fatal SCCs typically involved spread to regional lymph node basins and then to distant organs (Fig. 1). Most SCC deaths were associated with distant metastasis (27; 73%). Four SCC deaths (11%) had no known nodal or distant metastasis, with the cause of death being secondary to deep local invasion. The single BCC death occurred from extensive local invasion, leading to a fungating facial tumour, sepsis, and eventual death.

Of the 27 transplant recipients who died with known distant metastasis, the most common site was the lungs or pleura (21; 85%) (Fig. 1). The median time (minimum, maximum) from transplantation to diagnosis of primary fatal SCC was 10 years (1, 37), and for the BCC case, this was 9 years. Time from diagnosis of primary SCC to first diagnosis of metastasis was 5 months (0, 29), and the median time (minimum, maximum) from diagnosis of metastasis to death was 8 months (1, 29) (Table 1).

Thirty-two transplant recipients had immunosuppressant medication information available. Most had changes to their immunosuppressant medications after diagnosis of locally advanced or metastatic disease, with 22 (71%) having a reduction in immunosuppressive medication dosage. Three (10%) switched to mammalian tar-
get of rapamycin inhibitor therapy. Three (10%) were commenced on either acitretin or nicotinamide (Table 2).

Thirty-one kidney transplant recipients had information on radiation or medical oncology treatment. Most patients where SCC was the cause of death received radiation therapy as part of their treatment (26; 87%). Seven (23%) were prescribed either chemotherapy or epidermal growth factor receptor inhibitor therapy. The transplant recipient where BCC was the cause of death received radiotherapy to the primary lesion, and no chemotherapy was given (Table 2).

**Discussion**

Unique to this study is the identification of the clinical course of fatal keratinocyte cancers in kidney transplant recipients. Sixty-eight percent of fatal primary SCC lesions were located on the head and neck, as opposed to 33% of SCCs located on the head and neck in the Queensland population [12]. SCC lesions predominately caused death through distant metastasis to the lungs, but there was also a tendency of head and neck lesions that caused extensive local invasion, and this was also the case for the single fatal BCC on the face.

The location of the primary lesions was mainly sun-exposed areas. Sun protection is an essential measure for keratinocyte cancer prevention in transplant recipients. Ultraviolet protection with sunscreen use has been shown to reduce the risk of SCCs in transplant recipients [13]. Ulrich et al. [13] randomized and followed 120 solid organ transplant recipients over 24 months. Transplant recipients in the intervention group, who had received free broad-spectrum sunscreen for the study, had decreased development of SCC compared to the control group [13].

The higher incidence of keratinocyte cancers, especially SCCs, is well described in kidney transplant recipients [3, 14]. In this study, the multiplicity of skin cancers in these transplant recipients could not be captured in all patients as keratinocyte cancers are not collected through the national registry [15]. Nonetheless, of the 14 transplant recipients with data available, a total of 65 SCCs and BCCs were diagnosed in the 6 months before diagnosis of a metastatic keratinocyte cancer. This high number of skin cancers reflects the experience of Caucasian transplant recipients in Queensland, Australia [16]. Multidisciplinary transplant clinics, including transplant physicians, dermatologists, surgical teams, and general practitioners, may reduce hospital visit burden and facilitate streamlined services to improve clinic adherence and follow-up while also providing an opportunity for sun protection reinforcement [16, 17].

As well as being more frequent, SCCs in the kidney transplant population may be more aggressive, with higher rates of invasion, recurrence, and mortality than SCCs in the general population. Smith et al. [6] compared the histological features of 601 SCCs from 518 immunocompetent individuals with 231 SCCs from 79 organ trans-

| Treatment                        | SCC (n = 37) | BCC (n = 1) |
|----------------------------------|--------------|------------|
| Radiation therapya               |              |            |
| Yes                              | 26 (87)      | 1 (100)    |
| Primary and metastatic           | 7 (23)       | –          |
| Primary only                     | 1 (3)        | 1 (100)    |
| Metastatic only                  | 16 (53)      | –          |
| Unknown                          | 2 (7)        | –          |
| No                               | 4 (14)       | –          |
| Chemotherapya                    | 7 (23)       | –          |
| No                               | 23 (77)      | 1 (100)    |
| Medication changesb              |              |            |
| Immunosuppressant medication reduction  | 22 (71)    | –          |
| Acitretin/nicotinamide commenced  | 3 (10)       | –          |
| Immunosuppressant change to include mammalian target of rapamycin inhibitor | 3 (10) | – |
| No change                        | 8 (26)       | 1 (100)    |

Values are n (%). a Unknown for 7 SCC cases. b Unknown for 6 SCC cases.
plant recipients (53 were kidney recipients). They found that a significantly higher proportion of SCCs from organ transplant recipients had poor prognostic histological features such as the presence of an angiogenic component, loss of cellular adhesion, and greater tumour thickness [6]. Lott et al. [7] compared SCC features in 193 organ transplant recipients (of whom 100 were kidney recipients) and 308 immunocompetent controls and found that SCCs in transplant recipients were more likely to feature deep tissue involvement, perineural invasion, and lymphatic invasion.

In the present study, histological features of fatal keratinocyte cancers were noted. A high proportion showed poor to moderate differentiation and lymphovascular invasion. Two SCC cases had features of aggressive spindle cell type. Interestingly, there is no evidence that BCCs in kidney transplant recipients have more aggressive features, with one study describing a greater predominance of superficial BCCs in a transplant population [18]. Systemic immunosuppression affects SCCs and BCCs differently for reasons not fully understood.

The clinical course of metastatic keratinocyte cancer in kidney transplant recipients has been described in one other study. A multicentre study of the clinical course of 62 metastatic SCCs in 68 American organ transplant recipients (52 were kidney recipients) by Martinez et al. [11] also found a head and neck predominance, with the lung being the most common site of distant metastasis. A notable difference in this study was the timing between primary lesion and diagnosis of metastasis; in Martinez et al.’s [11] paper, this was 1.4 years, while this was only 5 months in this study. Martinez et al. [11] reviewed metastatic cases, while this study reviewed fatal cases, and thus the difference in time to metastasis likely reflects the greater aggressiveness and more rapid spread of fatal lesions.

The rapid progression from primary lesion to metastasis highlights the need for frequent skin examination in transplant recipients. This is essential to diagnose lesions early to reduce the incidence of advanced keratinocyte cancers [19, 20]. A Canadian study of 10,183 solid organ transplant recipients (62% kidney) transplanted between 1994 and 2012 found that adherence to regular dermatology assessments in the post-transplant period (a median of 5.4 years) was associated with a 34% reduction in the occurrence of advanced keratinocyte cancer [21].

A minority of transplant recipients in this study received either epidermal growth factor inhibitor therapy or chemotherapy. While platinum-based chemotherapy can be offered in metastatic SCC [22], the treatment is limited by nephrotoxicity and is cautiously used in a kidney transplant population [23]. Radiation therapy provides a renal-safe option for either adjuvant or palliative treatment, reflected by the predominance of radiation therapy used for treatment in this study [24]. Of interest, most kidney transplant recipients reduced their immunosuppressive medications. Immunosuppression is the major reason why transplant recipients suffer increased morbidity and mortality from keratinocyte cancers, with possible mechanisms that include the reduction of immunosurveillance of malignant cells [25], increased oncogenic viral infection [26], and some immunosuppressive agents being carcinogenic themselves [27]. The reduction of immunosuppression has been shown to reduce the incidence of keratinocyte cancer, for example, in kidney transplant recipients who return to dialysis due to graft failure [28]; however, there is no established evidence that the reduction of immunosuppression improves survival in metastatic disease. A retrospective study of 55 kidney transplant recipients with malignancy (both haematological and solid organ) compared the survival of transplant recipients who had a reduction in their immunosuppression doses with those that did not [29]. The authors found that the group with a dose reduction had worse survival. This is unlikely to be causal as transplant recipients with advanced malignancy were more likely to have immunosuppressant dose reduction [29].

No kidney transplant recipient in this study received an immune checkpoint inhibitor to treat metastatic or advanced SCC. These therapies can effectively treat recurrent advanced or metastatic cutaneous SCC; however, trials have excluded the transplant population as there is a concern for rejection [30, 31]. In the kidney transplant population with cutaneous malignancies, there are a small number of case reports that have described a variety of outcomes such as effective treatment of malignancy with graft failure and return to dialysis [32], poor treatment of malignancy and graft failure [33], and effective treatment of malignancy with a functioning graft [34]. The risks versus benefits of checkpoint inhibitor use for advanced or metastatic cutaneous SCC in the kidney transplant population are unclear. The usage of these agents for KTRs is slowly increasing, and further studies are needed.

A strength of this study was the detailed chart review used to obtain the clinical course of fatal keratinocyte cancers in our retrospective cohort of kidney transplant recipients. However, reliance on medical records avail-
able in the transplant hospital was also the major limitation, resulting in missing information from multiple medical providers whose records were unavailable.

In conclusion, our study of Queensland kidney transplant recipients shows that disproportionately more fatal keratinocyte cancers occur on the head and neck than other sites and that time from diagnosis of the primary to metastasis and death may be relatively short. Keratinocyte cancer deaths were frequently associated with distant metastasis to the lungs or pleura. Sun protection and regular skin cancer assessment are paramount for the prevention and early detection of keratinocyte cancers. Further research is needed to investigate innovative treatments of locally advanced or metastatic keratinocyte cancer in today’s kidney transplant population.

Key Message
FATAL KERATINO CYTE CANCERS IN KIDNEY TRANSPLANT RECIPIENTS ARE OVERWHELMINGLY SQUAMOUS CELL CARCINOMAS, BUT BASAL CELL CARCINOMAS CAN ALSO KILL.

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Statement of Ethics
Ethical approval was obtained from the Metro South and QIMR Berghofer Human Research Ethics Committees (LNR/2019/QMS/50370).

Conflict of Interest Statement
There are no conflicts of interest to declare.

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E.X.S. contributed to writing of the paper, performance of the research, and data analysis. K.K. contributed to research design and data analysis. S.C. contributed to research design and writing of the paper.
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Data Availability Statement
The data that support the findings of this study are available from the corresponding author, upon reasonable request.
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