Skin Cancer after Renal Transplantation

Robert P. Carroll and Graeme R. Russ

Central and Northern Adelaide Renal and Transplantation Service, Adelaide, Australia

Abstract

Nonmelanoma skin cancer is the most common cancer in kidney transplant recipients. The most common nonmelanoma skin cancer is squamous cell cancer, with an incidence of approximately 4% per annum in Northern Europe compared to 30% per year in high ultraviolet exposure areas such as Queensland, Australia. Age at transplantation, duration of immunosuppression, previous ultraviolet exposure, and previous nonmelanoma skin cancer are the key factors defining the risk of developing squamous cell cancer in kidney transplant recipients. Irrespective of geography, there appears to be a small minority of kidney transplant recipients who accrue multiple squamous cell cancers, with concomitant morbidity and mortality of approximately 1% per year. This review focuses on the current evidence available to risk-stratify kidney transplant recipients with regards to squamous cell cancer development, risk of metastasis, and death. In particular we focus on the concept of high-risk squamous cell cancer and tumor thickness as the main determinants of squamous cell cancer metastasis risk. Potential strategies to reduce the incidence of high-risk squamous cell cancer, including immunosuppression dose reduction, conversion to mammalian target of rapamycin inhibitor, and enumeration of regulatory T-cells in peripheral blood of kidney transplant recipients, are discussed. This latter technique may also define those kidney transplant recipients who derive benefit from mammalian target of rapamycin inhibitor conversion, i.e. tailored immunosuppression. It is proposed that the management of high-risk squamous cell cancer in kidney transplant recipients be directed by a multidisciplinary team involving the nephrologist, dermatologist, plastic surgeon, histopathologist, and radiation oncologist. **(Trends in Transplant. 2013;7:23-30)**

Corresponding author: Robert P. Carroll, E-mail: robert.carroll@health.sa.gov.au

Key words

Cancer. Skin. Kidney transplant. Squamous cell carcinoma.

Correspondence to:
Robert P. Carroll
Central and Northern Adelaide Renal
and Transplantation Service,
Royal Adelaide Hospital, North Terrace,
Adelaide SA 5000, Australia
E-mail: robert.carroll@health.sa.gov.au

Introduction

Kidney transplant recipients (KTR) are three-to-five times more likely to develop cancer than the general population and for advanced-stage malignancy have a substantially poorer prognosis[1,2]. For nonmelanoma skin cancer (NMSC) and in particular the most prevalent type of NMSC, cutaneous squamous cell carcinoma (SCC), the increased risk can be 60-250-fold[3-5]. It is expected that half of all white organ transplant recipients will experience NMSC at some point after organ transplantation[6]. In addition, KTR who develop SCC are at an increased risk of developing non-cutaneous cancer[7,8].

Factors associated with squamous cell carcinoma development post renal transplantation

Prospective cohort studies of KTR in Northern Europe have defined SCC incidence at around 3.5% per annum[9]. However, the incidence is substantially higher in high ultraviolet (UV) light exposure environments, such as subtropical Queensland, Australia, where the overall incidence approaches 30% per annum[10]. In addition, whereas KTR in Northern Europe tend to accrue singular tumors per year, those in subtropical Queensland accrue multiple tumors per year[10].

The development of SCC is related to time after transplant. In a prospective study in the UK, 4/230 (1.8%) KTR developed SCC within five years of transplantation. With longer-term follow-up > 10 years, 34/230 (14%) developed at least one SCC, 18/34 (53%) developed more than two SCC, and 5/34 (15%) developed more than five SCC. These figures are similar to other European studies, with 88% of KTR developing multiple SCC within the five-year period following their first SCC[11,12]. It is believed that the time to next SCC after the first SCC is approximately 15 months, and 12 months to develop a third SCC[13-15]. However, in recent controlled trials from Northern Europe and the UK for secondary prevention of SCC in KTR, time to second and subsequent SCC was > 18 and > 24 months, respectively[16,17]. This may also reflect baseline UV exposure as a similar randomized controlled trial in Australia had a median time to next tumor of nine months[18].

On an individual level, the clinical parameters associated with increased risk of SCC posttransplant include: intensity and duration of previous UV exposure; recalled history of blistering sunburn; and age at transplant and previous history of sun damaged skin and NMSC[5,10,19]. At the time of transplant assessment, it is possible to have an evidenced-based approach to predict time to first SCC and therefore advise on the necessary dermatological review periodicity[20]. In fact, after transplantation it is also possible to use similar evidenced-based clinical indices to predict the number of SCC accrued over the next 12 months[10,21].

Metastatic squamous cell skin carcinoma and outcome in kidney transplant recipients

Irrespective of time to develop multiple SCC, there is still a small but significant cohort of KTR who accrue multiple SCC, which are associated with significant morbidity. Up to 3% of KTR populations per year undergo extensive plastic surgical procedures requiring in-patient stays in hospital[9,10]. The KTR populations have an incident mortality of 1-4% for metastatic SCC[10], which is related to the dose of immunosuppression, with heart transplant recipients having the highest SCC-related mortality rates and immunosuppression doses[22].

In prospective studies, in a large cohort of predominantly non-immunosuppressed

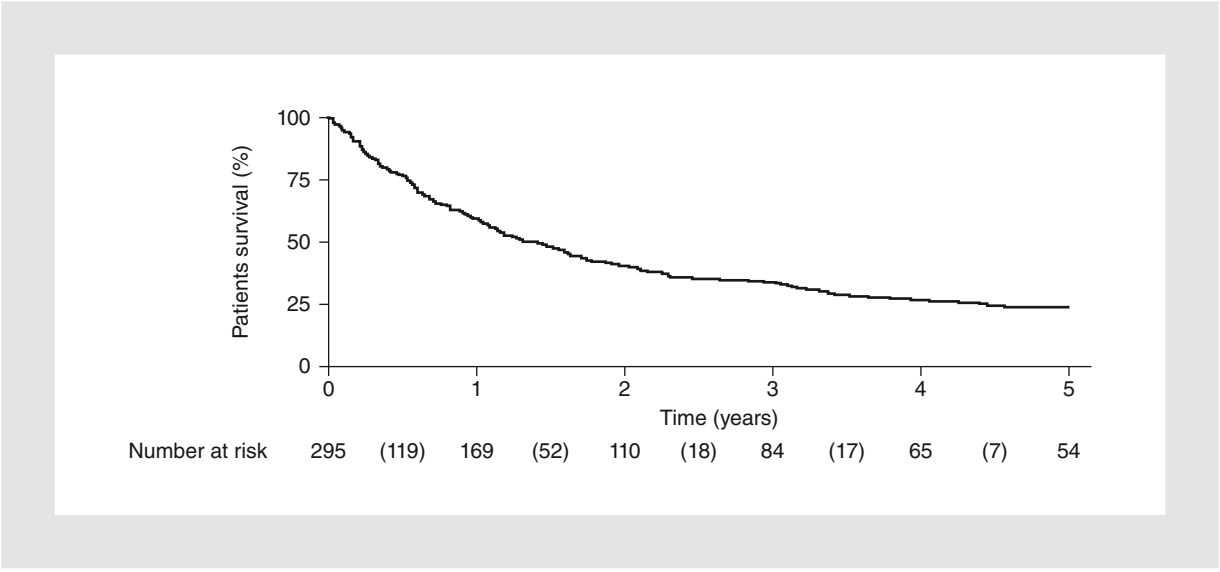

Figure 1. *Kaplan Meier estimate of patient survival after diagnosis of nodal spread of squamous cell cancer skin. Data from kidney transplant recipients registered in the ANZDATA registry from 1990 to 2011 as having nodal spread of squamous cell cancer. Approximately 85% of all deaths relate directly to death from metastatic squamous cell cancer and the remainder predominantly from cardiovascular death.*

subjects, the most significant clinicopathologic parameter predicting SCC metastasis was tumor thickness with almost no risk of spread < 2.8 mm[23]. Risk of spread was 4% in tumors 2-6 mm, and 16% in those thicker than 6 mm. However, the risk of spread for any stage or grade was three-times higher for patients taking immunosuppression. The aggressiveness of SCC in KTR is reflected in the one-year mortality rate from metastatic SCC in organ transplant recipients, which approaches 60%[23,24], whereas two-year mortality is only 20% in the general population with metastatic SCC[25,26]. This attrition is also reflected in data from the ANZDATA registry shown in figure 1.

The clinical impact of SCC or solid organ cancer on KTR populations is illustrated by registry data showing death from any cancer is in some countries (Australia) becoming the leading cause of death of KTR who have a functioning graft. Death from SCC is one of the largest contributors to cancer death[27].

The primary reason for this clinical predicament is that not only do immunosuppressive drugs suppress immune responses to the allograft, but they may also impair antitumor responses[28-31]. Immunosuppressive agents can have indirect mutagenic effect, leading to the elaboration of the mediators that are pro-carcinogenic[31,32]. These issues will be discussed in the following sections.

Immunosuppressive regimen and squamous cell carcinoma risk

Whereas immunosuppressive exposure leads to a greater risk of SCC[33,34], there are conflicting data regarding the impact of the calcineurin inhibitors (CNI), tacrolimus and cyclosporine, mycophenolate acid, and azathioprine on SCC risk in the context of solid organ transplantation[33,35,36]. The only immunosuppressants consistently associated with reduced *de novo* cancer risk are the mammalian target of rapamycin inhibitors (mTORi)[37,38].

Before it was used in transplantation, azathioprine was associated with malignancy after prolonged treatment of autoimmune disorders[29]. Azathioprine is thought to increase SCC risk due to its incorporation into DNA.

This incorporation causes DNA to absorb more UV energy and creates reactive oxygen species, which are directly mutagenic[39,40]. However, when compared to CNI-based regimens, azathioprine and prednisolone regimens have been associated with fewer skin malignancies[41].

Both cyclosporine and tacrolimus have been shown to promote progression of cancer in mice by increasing synthesis of transforming growth factor beta (TGF-β), interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) in tumor cells, thereby enhancing tumor growth, metastasis, and angiogenesis[29,31,42]. From a preventative perspective, there is only one prospective randomized controlled trial suggesting reduced CNI dose results in fewer cancers developing[34]. In this study, 231 KTR were randomized to low or standard dose cyclosporine. After a follow-up of 66 months, there were 26 NMSC, predominately SCC, in the standard cyclosporine dose group and 17 NMSC in the reduced dose group ($p < 0.05$).

Steroids act primarily by blocking the nuclear factor kappa-B pathway, which can lead to skin malignancy[43,44]. In non-KTR taking oral corticosteroids, there is an increase risk of SCC[45] and Kaposi's sarcoma[46]. In case-control studies, steroid usage has been associated with SCC development in long-term immunosuppressed KTR[47]. Meta-analysis of steroid-free regimens in KTR has shown reduced incidence of cancer after five years, but these observations did not reach statistical significance[48].

The inhibitors of the intracellular mammalian target of rapamycin (mTOR) pathway, sirolimus and everolimus, inhibit the intracellular effects of VEGF, reduce levels of TGF-β, and sensitize tumor cells to apoptosis[49]. There is strong evidence *in vitro* and in animal models that mTORi inhibit malignant transformation. There are three randomized controlled trials involving sirolimus for secondary prevention of SCC in KTR, and these are summarized in table 1 and reviewed elsewhere[50]. Although, in a population-based approached, new SCC was reduced by 40% on conversion to mTORi, there were major issues with tolerability so that only 30-50% of KTR were able to tolerate mTORi in the long term[16-18]. However, in those KTR who tolerated mTORi, the reductions in new SCC approached 60%.

In subgroup analysis, there was also a suggestion that mTORi are not beneficial for secondary prevention of SCC in KTR with more than two SCC[16,17]. This leads to questions as to how to manage KTR with aggressive SCC who do not tolerate mTORi or continue to accrue high-risk lesions whilst on therapy.

Unfortunately, there are only limited case series data showing that immunosuppressive dose reduction after SCC reduces the chance of death from metastatic SCC, the likelihood of metastasis, or subsequent SCC development[51,52]. Around two-thirds of KTR will develop fewer SCC after reduction or cessation of immunosuppression, and therefore the converse is also true; that after drug cessation one-third of KTR can still accrue SCC.

For those who have failed to derive benefit from the aforementioned options, there is evidence that adding low-dose capecitabine to preexisting immunosuppressive regimens is efficacious[53]. In this study of 15 solid organ transplant patients, new SCC development fell to a third of pretreatment levels, with a discontinuation rate of 33% at one year.

In our local experience (n = 4) we have found that cessation of antiproliferative and partial reduction in prednisolone and sirolimus and the addition of capecitabine has been efficacious in reducing the number of new SCC and the severity of the histological

Table 1. Randomized controlled trials of sirolimus conversion for secondary prevention of squamous cell carcinoma in kidney transplant recipients

	Campbell, et al.[18]	Euvrard, et al.[17]	De Fijter, et al.[6]
Cohort size	n = 87	n = 120	n = 155
Age	59	62	> 55 (58%)
Duration immunosuppression (months)	115 (24-243)	148 (18-565)	216 (48-382)
Longitude subtropical (23°)	20-35° South	40-50° North	50-55° North
Concurrent antiproliferative	33/39 (80%)	47/64 (75%)	0/72 (0%)
Median number of SCC	2 (0-9)	3 (2-15)	64% (2-9)*
Mean sirolimus level	7.9-10.3	7.5-17.0	7.1-9.4
Concurrent prednisolone use	29/39 (75%)	37/64 (57%)	71/71 (100%)
Proportion affected by new SCC Sirolimus vs. controls	41 vs. 70%	22 vs. 39%	47 vs. 56%
Number SCC per person per year Sirolimus vs. controls	0.88 vs. 1.71	NC	0.82 vs. 1.38
Median time to first SCC in controls	9 months	Only 40% affected	18 months
Rate ratio	0.53	NC	0.51 (95% CI: 0.32-0.82)
Relative risk time to first SCC	NC	0.56 (95% CI: 0.32-0.98)	0.76 (95% CI: 0.48-1.2)

Values in brackets = ranges.
*Mean (± 2 SD) – as median and range not stated.
SCC: squamous cell carcinoma; NC: not collected.

features. One patient was unable to tolerate capecitabine. There have been no deteriorations in graft function with this alteration in the drug regimen.

Future options

As in the general population, UV exposure increases the risk of SCC in KTR[20,54,55]. Ultraviolet light is directly mutagenic to DNA, in particular inducing p53 mutations[56]. The p53 is a tumor suppressor gene, it is responsible for inducing apoptosis in cells with irretrievably damaged DNA, and is the prime mechanism preventing epidermal carcinogenesis[57]. Around 90% of SCC have this mutation and are therefore resistant to apoptosis[26].

Importantly, UV light is also immunosuppressive[58,59] and induces keratinocytes to secrete IL-10, which in turn prevents Langerhans cells from activating T-cells[60,61]. Post UV exposure to the skin, Langerhans cells in the epidermis migrate to local lymph nodes and undergo apoptosis[58,62]. The migrating Langerhans cells contain pyrimidine dimers, specific to UV-induced damage, and are functionally impaired, with reduced major histocompatibility complex class II, intercellular adhesion molecule-1, and B7 expression[63,64]. These UV-induced antigen-presenting cells are involved in the suppression of cutaneous immunity and can generate regulatory T-cells (T_{reg})[65,66]. These cells are thought to play a part in the defective cell-mediated immunity of patients with SCC[67]. Indeed, SCC development correlates with susceptibility to UV-induced suppression of cutaneous cell-mediated immunity[67-69].

This interaction of cell-mediated immunity of T_{reg} cells has been found to predict

aggressive behavior of cancer in the general population[70]. Indeed, the predominance of T_{reg} cells in SCC from KTR compared to SCC from non-immunosuppressed subjects has been hypothesized as one of the reasons cancer is more aggressive in KTR[71].

Indeed, we have also investigated whether T_{reg} cells in peripheral blood are a marker of increased SCC risk. In the United Kingdom KTR populations, the number of T_{reg} cells in peripheral blood was additive with previous SCC history in predicting those with KTR at risk of developing new SCC[47]. In addition, we have also shown that KTR converted to mTORi who have increased number of T_{reg} cells are those KTR who continue to accrue SCC in spite of conversion to mTORi. T_{reg} testing may predict those who do not derive benefit from conversion to mTORi[72].

Conclusions

All of these data assume KTR with SCC have regular dermatological follow-up and the recommendations here are for the transplant physician to consider manipulations in immunosuppression in high-risk situations. The transplant physician is reminded to consider post-surgical radiotherapy for any high-risk lesion in their KTR to prevent recurrent of SCC[73].

In summary, SCC is a major clinical problem for a minority of KTR, and previous SCC is one of the major risk factors for new SCC development. In KTR with high-risk lesions (invading deep reticular dermis or > 2.8 mm thick), the risk of metastasis and death is not insubstantial and some thought to manipulation of immune suppression should be considered.

The mTORi have offered some hope, but they are not always well tolerated and may not be efficacious in those with multiple SCC. Capecitabine offers some hope and "simple" dose reduction in those with high-risk lesions may be safe, though there is always the risk of precipitating rejection.

References

1. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant. 2004;4:905-13.
2. Birkeland SA, Lokkegaard H, Storm HH. Cancer risk in patients on dialysis and after renal transplantation. Lancet. 2000;355:1886-7.
3. Zeier M, Hartschuh W, Wiesel M, Lehnert T, Ritz E. Malignancy after renal transplantation. Am J Kidney Dis. 2002;39:E5.
4. Buell JF, Hanaway MJ, Thomas M, Alloway RR, Woodle ES. Skin cancer following transplantation: the Israel Penn International Transplant Tumor Registry experience. Transplant Proc. 2005;37:962-3.
5. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med. 2003;348:1681-91.
6. de Fijter JW. Use of proliferation signal inhibitors in nonmelanoma skin cancer following renal transplantation. Nephrol Dial Transplant. 2007;22(Suppl 1):i23-6.
7. Tessari G, Naldi L, Boschiero L, et al. Incidence of primary and second cancers in renal transplant recipients: a multicenter cohort study. Am J Transplant. 2013;13:214-21.
8. Wisgerhof HC, van der Geest LG, de Fijter JW, et al. Incidence of cancer in kidney-transplant recipients: a long-term cohort study in a single center. Cancer Epidemiol. 2011; 35:105-11.
9. Ramsay HM, Reece SM, Fryer AA, Smith AG, Harden PN. Seven-year prospective study of nonmelanoma skin cancer incidence in U.K. renal transplant recipients. Transplantation. 2007;84:437-9.
10. Carroll RP, Ramsay HM, Fryer AA, Hawley CM, Nicol DL, Harden PN. Incidence and prediction of nonmelanoma skin cancer post-renal transplantation: a prospective study in Queensland, Australia. Am J Kidney Dis. 2003;41:676-83. **Large prospective study of SCC incidence in high-risk population.*
11. Bouwes Bavinck JN, Euvrard S, Naldi L, et al. Keratotic skin lesions and other risk factors are associated with skin cancer in organ-transplant recipients: a case-control study in The Netherlands, United Kingdom, Germany, France, and Italy. J Invest Dermatol. 2007;127:1647-56.
12. Euvrard S, Kanitakis J, Decullier E, et al. Subsequent skin cancers in kidney and heart transplant recipients after the first squamous cell carcinoma. Transplantation. 2006;81: 1093-100.
13. Liddington M, Richardson AJ, Higgins RM, et al. Skin cancer in renal transplant recipients. Br J Surg. 1989;76;1002-5.
14. Lindelof B, Sigurgeirsson B, Gabel H, Stern RS. Incidence of skin cancer in 5356 patients following organ transplantation. Br J Dermatol. 2000;143:513-9.
15. Tessmer CS, Magalhães LV, Keitel E, et al. Conversion to sirolimus in renal transplant recipients with skin cancer. Transplantation. 2006;82:1792-3.
16. Hoogendijk-van den Akker JM, Harden PN, Hoitsma AJ, et al. Two-year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus. J Clin Oncol. 2013 [Epub ahead of print]. ***Largest randomized controlled trial of mTORi for secondary prevention of SCC.*
17. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Eng J Med. 2012;367:329-39.
18. Campbell SB, Walker R, Tai SS, Jiang Q, Russ GR. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. Am J Transplant. 2012;12:1146-56.

19. Ramsay HM, Fryer AA, Hawley CM, Smith AG, Harden PN. Non-melanoma skin cancer risk in the Queensland renal transplant population. Br J Dermatol. 2002;147:950-6.
20. Urwin HR, Jones PW, Harden PN, et al. Predicting risk of nonmelanoma skin cancer and premalignant skin lesions in renal transplant recipients. Transplantation. 2009; 87:1667-71.
21. Harwood CA, Mesher D, McGregor JM, et al. A surveillance model for skin cancer in organ transplant recipients: a 22-year prospective study in an ethnically diverse population. Am J Transplant. 2013;13:119-29.
22. Vanacker A, Fabre G, Van Dorpe J, Peetermans WE, Maes B. Aggressive cutaneous squamous cell carcinoma associated with prolonged voriconazole therapy in a renal transplant patient. Am J Transplant. 2008;8:877-80.
23. Brantsch KD, Meisner C, Schönfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9:713-20. ***Large prospective study of the risk factor for metastasis of SCC.*
24. Martinez JC, Otley CC, Stasko T, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients: a multicenter collaborative study. Arch Dermatol. 2003; 139:301-6.
25. Oddone N, Morgan GJ, Palme CE, et al. Metastatic cutaneous squamous cell carcinoma of the head and neck: the Immunosuppression, Treatment, Extranodal spread, and Margin status (ITEM) prognostic score to predict outcome and the need to improve survival. Cancer. 2009; 115:1883-91.
26. Carucci JA. Cutaneous oncology in organ transplant recipients: meeting the challenge of squamous cell carcinoma. J Invest Dermatol. 2004;123:809-16.
27. Buell JF, Gross TG, Woodle ES. Malignancy after transplantation. Transplantation. 2005;80:S254-64.
28. Koehl GE, Andrassy J, Guba M, et al. Rapamycin protects allografts from rejection while simultaneously attacking tumors in immunosuppressed mice. Transplantation. 2004;77:1319-26.
29. Guba M, Graeb C, Jauch KW, Geissler EK. Pro- and anticancer effects of immunosuppressive agents used in organ transplantation. Transplantation. 2004;77:1777-82.
30. Thibaudin D, Alamartine E, Mariat C, Absi L, Berthoux F. Long-term kinetic of T-lymphocyte subsets in kidney-transplant recipients: influence of anti-T-cell antibodies and association with posttransplant malignancies. Transplantation. 2005;80:1514-17.
31. Hojo M, Morimoto T, Maluccio M, et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature. 1999;397:530-4.
32. Maluccio M, Sharma V, Lagman M, et al. Tacrolimus enhances transforming growth factor-beta1 expression and promotes tumor progression. Transplantation. 2003; 76:597-602.
33. Jensen P, Hansen S, Møller B, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol. 1999;40:177-86.
34. Dantal J, Hourmant M, Cantarovich D, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. Lancet. 1998;351:623-8. ***The only randomized controlled trial of immunosuppression dose reduction to reduce the risk of cancer and skin cancer in transplantation.*
35. Robson R, Cecka JM, Opelz G, Budde M, Sacks S. Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. Am J Transplant. 2005;5:2954-60.
36. Ulrich C, Stockfleth E. Azathioprine, UV light, and skin cancer in organ transplant patients--do we have an answer? Nephrol Dial Transplant. 2007;22:1027-9.
37. Campistol JM, Eris J, Oberbauer R, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. J Am Soc Nephrol. 2006;17:581-9.
38. Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. Clin Transplant. 2004;18:446-9.
39. O'Donovan P, Perrett CM, Zhang X, et al. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Science. 2005;309:1871-4.
40. Young AR, Sheehan JM, Chadwick CA, Potten CS. Protection by ultraviolet A and B sunscreens against in situ dipyrimidine photolesions in human epidermis is comparable to protection against sunburn. J Invest Dermatol. 2000;115:37-41.
41. McGeown MG, Douglas JF, Middleton D. One thousand renal transplants at Belfast City Hospital: post-graft neoplasia 1968-1999, comparing azathioprine only with cyclosporin-based regimes in a single centre. Clin Transpl. 2000;193-202.
42. Dantal J, Soulillou JP. Immunosuppressive drugs and the risk of cancer after organ transplantation. N Engl J Med. 2005;352:1371-3.
43. Dajee M, Lazarov M, Zhang JY, et al. NF-kappaB blockade and oncogenic Ras trigger invasive human epidermal neoplasia. Nature. 2003;421:639-43.
44. Lazarov M, Green CL, Zhang JY, Kubo Y, Dajee M, Khavari PA. Escaping G1 restraints on neoplasia--Cdk4 regulation by Ras and NF-kappa B. Cell Cycle. 2003;2:79-80.
45. Karagas MR, Cushing GL, Greenberg ER, Mott LA, Spencer SK, Nierenberg DWI. Non-melanoma skin cancers and glucocorticoid therapy. Br J Cancer. 2001;85:683-6.
46. Trattner A, Hodak E, David M, Sandbank M. The appearance of Kaposi sarcoma during corticosteroid therapy. Cancer. 1993;72:1779-83.
47. Carroll RP, Segundo DS, Hollowood K, et al. Immune phenotype predicts risk for posttransplantation squamous cell carcinoma. J Am Soc Nephrol. 2010;21:713-22.
48. Pascual J, Zamora J, Galeano C, Royuela A, Quereda C. Steroid avoidance or withdrawal for kidney transplant recipients. Cochrane Database Syst Rev. 2009;CD005632.
49. Guba M, von Breitenbuch P, Steinbauer M, et al. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med. 2002;8:128-35.
50. Carroll RP, Chapman JR. Can the risk of skin cancer after transplantation be reduced by mTOR inhibitors? Am J Kidney Dis. 2013 [Epub ahead of print].
51. Otley CC, Coldiron BM, Stasko T, Goldman GD. Decreased skin cancer after cessation of therapy with transplant-associated immunosuppressants. Arch Dermatol. 2001;137:459-63.
52. Moloney FJ, Kelly PO, Kay EW, Conlon P, Murphy GM. Maintenance versus reduction of immunosuppression in renal transplant recipients with aggressive squamo us cell carcinoma. Dermatol Surg. 2004;30:674-8.
53. Jirakulaporn T, Endrizzi B, Lindgren B, Mathew J, Lee PK, Dudek AZ. Capecitabine for skin cancer prevention in solid organ transplant recipients. Clin Transplant 2011;25:541-8. ***One of the only manuscripts to show the risk and benefits of immunosuppression dose reduction in high-risk lesion – informative even though small cohort of patients.*
54. Ramsay HM, Fryer AA, Hawley CM, Smith AG, Nicol DL, Harden PN. Factors associated with nonmelanoma skin cancer following renal transplantation in Queensland, Australia. J Am Acad Dermatol. 2003;49:397-406.
55. Ramsay HM, Fryer AA, Reece S, Smith AG, Harden PN. Clinical risk factors associated with nonmelanoma skin cancer in renal transplant recipients. Am J Kidney Dis. 2000;36:167-76.
56. Kullavanijaya P, Lim HW. Photoprotection. J Am Acad Dermatol. 2005;52:937-58.
57. Raj D, Brash DE, Grossman D. Keratinocyte apoptosis in epidermal development and disease. J Invest Dermatol. 2006;126:243-57.
58. Schwarz T. Mechanisms of UV-induced immunosuppression. Keio J Med. 2005;54:165-71.
59. Fisher MS, Kripke ML. Further studies on the tumor-specific suppressor cells induced by ultraviolet radiation. J Immunol. 1978;121:1139-44.

60. Rivas JM, Ullrich SE. Systemic suppression of delayed-type hypersensitivity by supernatants from UV-irradiated keratinocytes. An essential role for keratinocyte-derived IL-10. J Immunol. 1992;149:3865-71.
61. Rivas JM, Ullrich SE. The role of IL-4, IL-10, and TNF-alpha in the immune suppression induced by ultraviolet radiation. J Leukoc Biol. 1994;56:769-75.
62. Schwarz T. Biological effects of UV radiation on keratinocytes and Langerhans cells. Exp Dermatol. 2005; 14:788-9.
63. Aberer W, Schuler G, Stingl G, Honigsmann H, Wolff K. Ultraviolet light depletes surface markers of Langerhans cells. J Invest Dermatol. 1981;76:202-10.
64. Dittmar HC, Weiss JM, Termeer CC, et al. In vivo UVA-1 and UVB irradiation differentially perturbs the antigen-presenting function of human epidermal Langerhans cells. J Invest Dermatol. 1999;112:322-5.
65. Wood KJ, Sakaguchi S. Regulatory T cells in transplantation tolerance. Nat Rev Immunol. 2003;3:199-210.
66. Vink AA, Shreedhar V, Roza L, Krutmann J, Kripke ML. Cellular target of UVB-induced DNA damage resulting in local suppression of contact hypersensitivity. J Photochem Photobiol. 1998;B44:107-11.
67. Yoshikawa T, Rae V, Bruins-Slot W, Van den Berg JW, Taylor JR, Streilein JW. Susceptibility to effects of UVB radiation on induction of contact hypersensitivity as a risk factor for skin cancer in humans. J Invest Dermatol. 1990;95:530-6.
68. Kelly DA, Young AR, McGregor JM, Seed PT, Potten CS, Walker SL. Sensitivity to sunburn is associated with susceptibility to ultraviolet radiation-induced suppression of cutaneous cell-mediated immunity. J Exp Med. 2000; 191:561-6.
69. Cooper KD, Oberhelman L, Hamilton TA, et al. UV exposure reduces immunization rates and promotes tolerance to epicutaneous antigens in humans: relationship to dose, CD1a-DR+ epidermal macrophage induction, and Langerhans cell depletion. Proc Natl Acad Sci USA. 1992;89:8497-501.
70. Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proc Natl Acad Sci USA. 2005;102:18538-43.
71. Carroll RP, Segundo DS, Hollowood K, et al. Immune phenotype predicts risk for posttransplantation squamous cell carcinoma. J Am Soc Nephrol. 2010;21:713-22.
72. Carroll RP, Hester J, Wood KJ, Harden PN. Conversion to sirolimus in kidney transplant recipients with squamous cell cancer and changes in immune phenotype. Nephrol Dial Transplant. 2013;28:462-5.
73. Veness MJ, Harris D. Role of radiotherapy in the management of organ transplant recipients diagnosed with non-melanoma skin cancers. Australas Radiol. 2007;51:12-20.