Proyecto Prometeo II

Cáncer en el trasplantado renal: ¿Se puede prevenir?

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Dossier bibliográfico

Grupo I | **Epidemiología del cáncer en trasplante renal: Incidencia, prevalencia y factores de riesgo**

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Organizado por

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SOCIEDAD ESPAÑOLA DE TRASPLANTE

Con la colaboración de

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Epidemiología del cáncer en trasplante renal: Incidencia, prevalencia y factores de riesgo

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GRUPO 1-Epidemiología del cancer en trasplante renal: Incidencia, prevalencia y factores de riesgo

	Apellidos	Nombre	Hospital	Ciudad	Artículos asignados	Nº Art.
1	Ramos Escorihuela	David	Hospital Universitario La Fe	Valencia	**1. Influence of Current and Previous Smoking on Cancer and Mortality After Kidney Transplantation** Transplantation 2016;100: 227–232 Opelz G, Döhler B **2. Treatment of Kidney Transplant Recipients With ACEi/ARB and Risk of Respiratory Tract Cancer: A Collaborative Transplant Study Report** Am J Transplant. 2011 Nov;11(11):2483-9. Opelz G, Döhler B **3. Epidemiology of de novo malignancies after solidorgan transplantation: Immunosuppression, infection and other risk factors** Best Pract Res Clin Obstet Gynaecol. 2014 Nov;28(8):1251-65. Piselli P, Verdirosi D, Cimaglia C, Busnach G, Fratino L, Ettorre GM, De Paoli P, Citterio F, Serraino D. **4. Polycystic Kidney Disease and Cancer after Renal Transplantation** J Am Soc Nephrol 25: 2335–2341, 2014 Wetmore JB, Calvet JP, Yu AS, Lynch CF, Wang CJ, Kasiske BL, Engels EA **5. Time on Dialysis and Cancer Risk After Kidney Transplantation** Transplantation 2013;95: 114-121 Wong G, Turner RM, Chapman JR, Howell M, Lim WH, Webster AC, Craig JC. **6. Donor Cancer Transmission in Kidney Transplantation: A Systematic Review** Am J Transplant. 2013 Oct;13(10):2645-52 Xiao D, Craig JC, Chapman JR, Dominguez-Gil B, Tong A, Wong G.	**59** **60** **61** **62** **63** **64**

2	Cofan Pujol	Frederic	Hospital Clínic	Barcelona	**1. Outcomes of Solid Organ Transplant Recipients With Preexisting Malignancies in Remission: A Systematic Review and Meta-Analysis** Transplantation 2016;00: 00–00 Acuna SA, Huang JW, Daly C, Shah PS, Kim SJ, Baxter NN. **2. Cytomegalovirus exposure, immune exhaustion and cancer occurrence in renal transplant recipients** Transplantation 25 (2012) 948–955 Courivaud C, Bamoulid J, Gaugler B, Roubiou C, Arregui C, Chalopin JM, Borg C, Tiberghien P, Woronoff-Lemsi MC, Saas P, Ducloux D **3. Cancer Transmission From Organ Donors-Unavoidable But Low Risk** Transplantation 2012;94: 1200-1207 Desai R, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J **4. Impact of Cytomegalovirus on Long-term Mortality and Cancer Risk After Organ Transplantation** Transplantation 2015;99: 1989–1994 Desai R, Collett D, Watson CJ, Johnson PJ, Moss P, Neuberger J **5. Racial/Ethnic Differences in Cancer Risk After Kidney Transplantation** American Journal of Transplantation 2013; 13: 714–720 Hall EC, Segev DL, Engels EA **6. The Risk of Cancer in Recipients of Living-Donor, Standard and Expanded Criteria Deceased Donor Kidney Transplants: A Registry Analysis** Transplantation 2014;98: 1286-1293 Ma MK, Lim WH, Turner RM, Chapman JR, Craig JC, Wong G	**7** **8** **9** **10** **11** **12**

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3	Canal Girol	Cristina	Fundación Puigvert	Barcelona	**1. Malignancies After Kidney Transplantation: Hong Kong Renal Registry** American Journal of Transplantation 2012; 12: 3039–3046 Cheung CY, Lam MF, Chu KH, Chow KM, Tsang KY, Yuen SK, Wong PN, Chan SK, Leung KT, Chan CK, Ho YW, Chau KF. **2. Epidemiology of post-transplant malignancy in Asian renal transplant recipients: a population-based study.** Int Urol Nephrol (2014) 46:833–838 Hsiao FY, Hsu WW **3. Post-transplant malignancy: a burdensome complication in renal allograft recipients in Korea** Clin Transplant 2014: 28: 434–442 Kim JH, Kim SO, Han DJ, Park SK.. **4. Malignancies after renal transplantation in Taiwan: a nationwide population-based study** Nephrol Dial Transplant (2011) 0: 1–7 Li WH, Chen YJ, Tseng WC, Lin MW, Chen TJ, Chu SY, Hwang CY, Chen CC, Lee DD, Chang YT, Wang WJ, Liu HN. **5. Cancer report** 2013 Annual Report - 36th Edition Wong G, Grace B, Clayton P, Craig JC. **6. Cancer-Specific and All-Cause Mortality in Kidney Transplant Recipients With and Without Previous Cancer** Transplantation 2015;99: 2586–2592 Viecelli AK, Lim WH, Macaskill P, Chapman JR, Craig JC, Clayton P, Cohney S, Carroll R, Wong G	**1** **2** **3** **4** **5** **6**

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7	**Pérez Sáez**	**María José**	**Hospital del Mar**	**Barcelona**	**1. Cumulative Doses of T-Cell Depleting Antibody and Cancer Risk after Kidney Transplantation** PLoS One. 2015 Nov 10;10(11):e0139479. doi: 10.1371/journal.pone.0139479. eCollection 2015. Chen JH, Wong G, Chapman JR, Lim WH **2. Antithymocyte Globulin Induction in Living Donor Renal Transplant Recipients: Final Report of the TAILOR Registry** Transplantation. 2012 Aug 27;94(4):331-7 Gaber AO1, Matas AJ, Henry ML, Brennan DC, Stevens RB, Kapur S, Ilsley JN, Kistler KD, Cosimi AB; Thymoglobulin Antibody Immunosuppression in Living Donor Recipients Investigators **3. Association of Antibody Induction Immunosuppression With Cancer After Kidney Transplantation** Transplantation 2015;99: 1051–1057 Hall EC, Engels EA, Pfeiffer RM, Segev DL **4. Effect of Immunosuppression for Primary Renal Disease on the Risk of Cancer in Subsequent Renal Transplantation: A Population-Based Retrospective Cohort Study** Transplantation. 2013 Jan 15;95(1):122-7. Hibberd AD, Trevillian PR, Wlodarczyk JH, Kemp DG, Stein AM, Gillies AH, Heer MK, Sheil AG **5. Acute Rejection, T-Cell-Depleting Antibodies, and Cancer After Transplantation** Transplantation. 2014 Apr 27;97(8):817-25 Lim WH, Turner RM, Chapman JR, Ma MK, Webster AC, Craig JC, Wong G **6. Belatacept for kidney transplant recipients (Review)** Cochrane Database Syst Rev. 2014 Nov 24;11:CD010699 Masson P, Henderson L, Chapman JR, Craig JC, Webster AC **7. The janus face of immunosuppression – de novo malignancy after renal transplantation: the** experience of the Transplantation Center Munich Kidney Int. 2007 Jun;71(12):1271-8. Wimmer CD, Rentsch M, Crispin A, Illner WD, Arbogast H, Graeb C, Jauch KW, Guba M **8. Combined introduction of anti-IL2 receptor antibodies, mycophenolic acid and tacrolimus: effect on malignancies after renal transplantation in a single-centre retrospective cohort study** Nephrol Dial Transplant (2012) 27: 2547–2553 Braconnier P, Del Marmol V, Broeders N, Kianda M, Massart A, Lemy A, Ghisdal L, Le Moine A, Madhoun P, Racapé J, Abramowicz D, Wissing KM. **9. Cancer risk with alemtuzumab following kidney transplantation** Clin Transplant 2013: 27: E264–E271 DOI: 10.1111/ctr.12094 Puttarajappa C, Yabes J, Bei L, Shah N, Bernardo J, McCauley J, Basu A, Tan H, Shapiro R, Unruh M, Wu C	**44** **45** **46** **47** **48** **49** **50** **51** **52**

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Referencias Bibliográficas

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1. Malignancies After Kidney Transplantation: Hong Kong Renal Registry
American Journal of Transplantation 2012; 12: 3039–3046
Cheung CY, Lam MF, Chu KH, Chow KM, Tsang KY, Yuen SK, Wong PN, Chan SK, Leung KT, Chan CK, Ho YW, Chau KF.

Many studies have shown that kidney transplant recipients have a higher incidence of cancers when compared with general population. However, most data on the posttransplant malignancies (PTM) are derived from Western literature and large population-based studies are rare. There is also lack of information about the posttransplant cancer-specific mortality rate. We conducted a population-based study of 4895 kidney transplants between 1972 and 2011, with data from the Hong Kong Renal Registry. Patterns of cancer incidence and mortality in our kidney transplant recipients were compared with those of the general population using standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) respectively. With 40 246 person-years of follow-up, 299 PTM was diagnosed. The SIR of all cancers was 2.94 (female 3.58 and male2.58).Non-Hodgkin lymphoma (NHL), kidney, and bladder cancers had the highest SIRs. The overall SMR was 2.3 (female 3.4 and male 1.7) and the highest SMR was NHL. The patterns of PTM differ among countries. Increases in cancer incidence can now translate into similar increases in cancer mortality. NHL is important in our kidney transplant recipients. Strategies in cancer screening in selected patient groups are needed to improve transplant outcomes.

2. Epidemiology of post-transplant malignancy in Asian renal transplant recipients: a population-based study.

Int Urol Nephrol (2014) 46:833–838

Hsiao FY, Hsu WW

Objective: Using Taiwan's National Health Insurance Research Database, this large population-based study was conducted to explore the incidences and risk factors of post-transplant malignancy in Asian renal transplant recipients.

Patients and methods: A total of 642 patients who firstly underwent renal transplant between January 1, 2000 and December 31, 2008 were identified from a 2 million cohort. The primary endpoint was a subsequent hospitalization with a primary diagnosis of malignancy (ICD-9-CM code: 140.xx-239.xx) after renal transplantation. All patients were followed until the occurrence of endpoints or the end of the study (December 31, 2010), whichever came first. Adjusted risks of post-transplant cancer were analyzed using Cox proportional hazards regression model. All models were adjusted for baseline characteristics, comorbid diseases, transplant year, and exposure to immunosuppressive agents.

Results: Among 642 renal transplant patients, 54 cancers (8.4 %) were identified. The median time between transplant and cancer diagnosis was 46.2 (range 8.5–107.4) months. Cancers of kidney and other unspecified urinary organs was the most common cancer sites, accounted for 18.5 % of the malignancies diagnosed. The next most common cancer sites were trachea, bronchus, and lung (14.8 %), bladder (13.0 %), liver and intrahepatic bile ducts (11.1 %), colon (5.6 %), and prostate (5.6 %). Age at transplantation was a statistically significant risk factor of post-transplant cancer in our study. Increased risks of posttransplant cancer were observed in patients who received immunosuppression agents (cyclosporine (HR 1.26, 95 % CI 0.58–2.77, p = 0.5603), tacrolimus (HR 1.99, 95 % CI 0.66–6.00, p = 0.2197), and mycophenolate (HR 1.00, 95 % CI 0.40–2.45, p = 0.9874)) although the estimates were not statistically significant.

Conclusions: Our population-based cohort study offers additional insight into post-transplant cancers in Asian population. Further studies are warranted to assess the association between specific immunosuppression agents and post-transplant cancers.

3. Post-transplant malignancy: a burdensome complication in renal allograft recipients in Korea
Clin Transplant 2014: 28: 434–442
Kim JH, Kim SO, Han DJ, Park SK..

Cancer has been a serious complication of kidney transplantation ever since the outcome of this procedure improved. The incidence of cancer among kidney transplant (KT) recipients is increasing, and these patients have a higher risk of developing cancer than the general population. The present retrospective cohort study compared the cancer rate of kidney recipients in a single transplantation center in Korea with that in healthy Korean individuals using the standardized incidence ratio (SIR). The medical records of all 2365 patients who underwent renal transplantation between 1989 and 2009 were reviewed retrospectively. During the study period, 136 renal allograft recipients developed 140 malignancies. The cumulative cancer incidence one, five, 10, and 15 yr post-transplantation was 0.60%, 3.24%, 5.69%, and 8.90%, respectively. Non-Hodgkin lymphoma(NHL) and thyroid cancer were the most common cancers after renal transplantation, occurring significantly more frequently than in the general Korean population. The SIR of all cancers was 1.9 (women: 2.4; men: 1.6). Comparison with similar studies in Korea and other countries suggests transplant center-related differences dictate post-transplant malignancy incidence more strongly than ethnic or geographic factors. Early surveillance programs for de novo malignancies after kidney transplantation focusing on kidney-transplantation-related tumors and postoperative time period should be established.

4. Malignancies after renal transplantation in Taiwan: a nationwide population-based study
Nephrol Dial Transplant (2011) 0: 1–7
Li WH, Chen YJ, Tseng WC, Lin MW, Chen TJ, Chu SY, Hwang CY, Chen CC, Lee DD, Chang YT, Wang WJ, Liu HN.

Background: Renal transplantation has been regarded as the treatment of choice for end-stage renal disease. Renal transplantation increases the risk of cancers due to long term immunosuppression. The types of post-transplantation malignancies may vary among different geographic regions and ethnic populations. To date, large population-based studies of post-transplantation malignancies in Asian renal transplant recipients (RTRs) have rarely been reported.
Methods: To investigate the patterns of post-transplantation malignancies in Chinese RTRs, we performed a nationwide population-based cohort study between 1997 and 2008 based on data from the National Health Insurance Database in Taiwan. Patterns of cancer incidence in RTRs were compared with those of the general population using standardized incidence ratios (SIRs).
Results: Among the 4716 RTRs (2475 males and 2241 females; mean age 44.1 6 12.4 years) and 22 556 person- years of observation, 320 post-transplant cancers were diagnosed. The SIR of all cancers was 3.75 (95% confidence interval 3.36–4.18). Women had a higher risk than men for the development of malignancies (SIR 5.04 for women and SIR 2.88 for men). Renal, bladder and liver cancers were the most common cancers, with SIRs of 44.29, 42.89 and 5.07, respectively. When stratified by age, RTRs of young age at transplant (<20 years) had the highest risk of post-transplantation malignancies.
Conclusions: This study demonstrates different patterns of malignancies after renal transplantation in Chinese RTRs, with higher incidences of kidney and bladder cancers. Physicians should be more vigilant in examining RTRs for post-transplantation malignancies especially in younger patients.

5. Cancer report

2013 Annual Report - 36th Edition

Wong G, Grace B, Clayton P, Craig JC.

There is now consistent evidence showing an increased risk of cancer by at least 1.5 and 2-fold for people on dialysis and with kidney transplants, respectively. Cancer is also second to cardiovascular disease as the major cause of mortality and morbidity in these patients. Cancer can occur de novo or recur after transplantation. Patients with a prior cancer are also at risk of developing a new cancer type after transplantation. In this report, we provide the overall and site-specific cancer risks for those on dialysis and with a functioning kidney allograft between 1965 – 2012. We will also present the incidence of disease recurrence and new cancer development among those with a prior cancer. Finally, several new and novel risk factors for cancer after transplantation have been established using data from the ANZDATA Registry. Understanding the potential modifiable risk factors of cancer may enable clinicians, health professionals and decision makers to develop strategies that may prevent and/or halt disease occurrence and progression in the future.

6. Cancer-Specific and All-Cause Mortality in Kidney Transplant Recipients With and Without Previous Cancer

Transplantation 2015;99: 2586–2592

Viecelli AK, Lim WH, Macaskill P, Chapman JR, Craig JC, Clayton P, Cohney S, Carroll R, Wong G

Background: For dialysis patients with a cancer history, a period of surveillance is generally recommended before listing for transplantation. However, the outcomes of patients with cancer recurrence and/or a second primary cancer after transplantation are unknown.
Aim: To determine the prognosis of kidney transplant recipients who developed cancer after transplantation and whether this varied with cancer types (first cancer, recurrence, second primary cancer).
Methods: Using data from the Australian and NewZealand Dialysis and Transplant Registry, we compared the cancer-specific and all-cause mortality among recipients with different cancer types using adjusted Cox proportional hazard models.

Results: Of the 21,415 recipients transplanted between 1965 and 2012, 3%(651 of 21,415) had a previous cancer history. A total of 2840 (13%) recipients developed cancer after the first transplant, of whom 2760 (97.2%) developed a first cancer, 23 (0.8%) experienced cancer recurrence, and 57 (2%) developed a second primary cancer. There were no significant differences in the risks of cancer-specific and all-cause mortality between recipients who developed their first cancer after transplant, those with cancer recurrence (adjusted hazard ratios [aHRs], 0.79; 95% confidence interval [95% CI], 0.38-1.67; P = 0.54 and aHRs, 0.86; 95% CI, 0.45-1.66; P = 0.66, respectively) and recipients who developed a second primary cancer after transplantation (aHRs, 1.01; 95%CI, 0.63-1.62; P = 0.95 and aHRs, 1.16; 95% CI, 0.79-1.69; P = 0.45, respectively).
Conclusion. Among patients with a previous history ofmalignancy, recurrent and second primary cancers are infrequent after renal transplantation. A history of previous malignancy does not have an additive effect on the cancer-specific and overall survival of kidney transplant recipients who develop cancer.

7. Outcomes of Solid Organ Transplant Recipients With Preexisting Malignancies in Remission: A Systematic Review and Meta-Analysis

Transplantation 2016;00: 00–00

Acuna SA, Huang JW, Daly C, Shah PS, Kim SJ, Baxter NN.

Background: Solid organ transplant recipients (SOTR) with a pretransplant malignancy (PTM) are at increased risk for cancer recurrence. However, it is unclear whether differences in survival and incidence of posttransplant de novo malignancies exist between recipients with PTM and those without PTM. We designed a systematic review to synthesize all available evidence assessing these outcomes.

Methods: A systematic search was performed in MEDLINE, EMBASE, and Cochrane Library to identify studies comparing the following outcomes in SOTR by PTM status: (1) all-cause mortality, (2) cancer-specific mortality, and (3) incidence of posttransplant de novo malignancy. Risk of bias was assessed using the Newcastle-Ottawa Scale.

Results: Thirty-two cohort studies were included. Recipients with PTM were at increased risk of all-cause mortality compared to recipients without PTM (pooled hazard ratio [HR], 1.51; 95% confidence interval [CI], 1.27-1.81). Similarly, recipients with PTM were 3 times more likely to die of cancer (pooled HR, 3.13; 95% CI, 2.29-4.27). The pooled HR for developing posttransplant de novo malignancy was also increased (HR, 1.92; 95% CI, 1.52-2.42). The association of all-cause mortality and SOTR with PTM did not vary by transplanted organ.

Conclusions: Pretransplant malignancy is associated with increased risk of all cause mortality, cancer-specific mortality and of developing de novo malignancies after transplantation compared with those without PTM. These results reaffirm the need for careful selection of transplant recipients with PTM. Tailored screening and management strategies should be developed for this group of patients.

8. Cytomegalovirus exposure, immune exhaustion and cancer occurrence in renal transplant recipients

Transplantation 25 (2012) 948–955

Courivaud C, Bamoulid J, Gaugler B, Roubiou C, Arregui C, Chalopin JM, Borg C, Tiberghien P, Woronoff-Lemsi MC, Saas P, Ducloux D

The role of Cytomegalovirus (CMV) in carcinogenesis is controversial. We studied whether CMV may contribute to cancer occurrence in renal transplant recipients. We studied a prospective cohort of 455 consecutive patients who received a kidney transplant between January 1995 and December 2006. All cancers and types of cancers were assessed. Lymphocyte phenotype and cytokines production were analysed according to CMV status in a subset population of this cohort. Mean follow-up was 84 ± 29 months. One hundred and nineteen cancers (26.2%) occurred during the study follow-up. There was a higher cumulated incidence of cancers in CMV-exposed patients (30.4% vs. 20%; P = 0.018). Mean time to cancer occurrence was shorter in CMV-exposed patients than in CMV-native patients (4.7 ± 2.6 vs. 6.7 ± 2.8; P = 0.001). Cox regression analysis revealed that both pretransplant CMV exposure (HR, 1.83; 95% CI, 1.17–2.88; P = 0.009) and post-transplant CMV replication (HR, 2.17; 95% CI, 1.02–4.59; P = 0.044) were risk factors for cancer. Among CD8+ T cells, exhausted T cells assessed as CD57+CD28- were expanded in CMV exposed patients (26 ± 20 vs. 9 ± 8%; P < 0.0001), whereas CD8+CD57+IL2- cells were more frequent in CMV-exposed patients. Our results highly suggest that CMV increases the risk of cancer after transplantation.

9. Cancer Transmission From Organ Donors-Unavoidable But Low Risk
Transplantation 2012;94: 1200-1207
Desai R, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J

Background: Donor origin cancer (DOC) in transplant recipients may be transmitted with the graft (donor-transmitted cancer [DTC]) or develop subsequently from the graft (donor-derived cancer [DDC]).
Methods: Recipients with DOC between January 1, 2001, and December 31, 2010, were identified from the United Kingdom Transplant Registry and database search at transplantation centers.
Results: Of 30,765 transplants from 14,986 donors, 18 recipients developed DOC from 16 donors (0.06%): 3 were DDC (0.01%) and 15 were DTC (0.05%). Of the 15 DTCs, 6 were renal cell cancer; 5, lung cancer; 2, lymphoma; 1, neuroendocrine cancer; and 1, colon cancer. Recipients with DTC underwent explant/excision (11), chemotherapy (4), and radiotherapy (1). Of 15 recipients, 3 (20%) recipients with DTC died as a direct consequence of cancer. Early DTC (diagnosed e6 weeks of transplantation) showed a better outcome (no DTC-related deaths in 11 cases) as opposed to late DTC (DTC-related deaths in 3 of 4 cases). Five-year survival was 83% for kidney recipients with DTC compared with 93% for recipients without DTC (P=0.077). None of the donors resulting in cancer transmission was known to have cancer at donation.

Conclusions: DTC is rare but frequently results in graft loss and death. The risk of cancer transmission cannot be eliminated because, in every case, the presence of cancer was not known at donation. This information will allow informed consent for prospective recipients. Explantation/excision is likely to benefit recipients with localized cancer, but in transplants other than kidney/pancreas, the benefits should be balanced against the risks of retransplantation.

10. Impact of Cytomegalovirus on Long-term Mortality and Cancer Risk After Organ Transplantation

Transplantation 2015;99: 1989–1994

Desai R, Collett D, Watson CJ, Johnson PJ, Moss P, Neuberger J

Background.There is conflicting evidence of the effect of cytomegalovirus (CMV) infection on survival and the risk of cancer after transplantation.

Methods. All recipients of kidney, liver, heart, and lung transplants in the United Kingdom between 1987 and 2007 with known CMV immunoglobulin G status were identified from the U.K. Transplant Registry. Based on the donorrecipient CMV status, recipients were grouped into: donor (D) negative recipient (R) negative (D− R−), D−R+, D + R+ and D + R−. Cancer data were obtained from the Office for National Statistics. The impact of CMV infection on survival and cancer incidence was assessed.

Results. The 10-year posttransplant survival in D−R− recipients (73.6% [95%CI, 72.3, 74.9]) was significantly higher (P < 0.0001) than in other recipients (66.1% [65.3, 66.9]). Compared with the D− R− group, the risk-adjusted hazard of death within 10 years of transplantation for D+ R− group was 14% higher for kidney recipients (P = 0.0495), 13% higher for liver recipients (P = 0.16), 34% higher for heart recipients (P = 0.01), and 35% higher for lung recipients (P = 0.006). The proportion of recipients with a cardiovascular cause of death was higher (P = 0.03) among the recipients exposed to CMV (18%) as compared to the D− R− recipients (16%). The CMV status was not associated with an increased risk of cancer.

Conclusions. The results from this large study demonstrate that CMV is associated with a significantly increased long-term mortality in kidney and cardiothoracic transplant recipients and an increased risk of cardiovascular death but not of posttransplant cancer.

11. Racial/Ethnic Differences in Cancer Risk After Kidney Transplantation
American Journal of Transplantation 2013; 13: 714–720
Hall EC, Segev DL, Engels EA

Transplant recipients have elevated cancer risk, but it is unknown if cancer risk differs across race and ethnicity as in the general population. US kidney recipients (N = 87,895) in the Transplant Cancer Match Study between 1992 and 2008 were evaluated for racial/ethnic differences in risk for six common cancers after transplantation. Compared to white recipients, black recipients had lower incidence of non-Hodgkin lymphoma (NHL) (adjusted incidence rate ratio [aIRR] 0.60, $p<0.001$) and higher incidence of kidney (aIRR 2.09, $p<0.001$) and prostate cancer (aIRR 2.14, $p<0.001$); Hispanic recipients had lower incidence of NHL (aIRR 0.64, $p = 0.001$), lung (aIRR 0.41, $p < 0.001$), breast (aIRR 0.53, $p = 0.003$) and prostate cancer (aIRR 0.72, $p = 0.05$). Colorectal cancer incidence was similar across groups. Standardized incidence ratios (SIRs) measured the effect of transplantation on cancer risk and were similar for most cancers ($p\geq0.1$). However, black and Hispanic recipients had larger increases in kidney cancer risk with transplantation (SIRs: 8.96 in blacks, 5.95 in Hispanics vs. 4.44 in whites), and only blacks had elevated prostate cancer risk following transplantation (SIR: 1.21). Racial/ethnic differences in cancer risk after transplantation mirror general population patterns, except for kidney and prostate cancers where differences reflect the effects of end-stage renal disease or transplantation.

12. The Risk of Cancer in Recipients of Living-Donor, Standard and Expanded Criteria Deceased Donor Kidney Transplants: A Registry Analysis

Transplantation 2014;98: 1286-1293

Ma MK, Lim WH, Turner RM, Chapman JR, Craig JC, Wong G

Background: Kidneys from expanded criteria deceased donors may elicit a strong inflammatory response, predisposing recipients to an increased risk of cancer after transplantation. We aimed to determine the association between donor types and cancer risk after kidney transplantation. **Methods:** Using the Australian and New Zealand Dialysis and Transplant Registry, we assessed the association between different donor types (living donor, standard, and expanded criteria deceased donors) and the risk of cancer after kidney transplantation using adjusted Cox proportional hazard and competing risk models.
Results: Over a median follow-up period of 4.4 years in 7,040 patients (34,684 patient-years), 468 patients (6.6%) developed cancer. The overall risks for cancer were 1,080, 1,444, and 2,018 per 100,000 patient-years for recipients of living donor, standard, and expanded criteria deceased donor kidneys, respectively. Compared to recipients of living donor kidneys, recipients of expanded criteria deceased donor kidneys were at an increased risk of cancer (adjusted hazard ratio [HR], 1.52; 95% confidence interval [95% CI], 1.15Y2.02; P=0.004), particularly for genitourinary cancer (adjusted HR, 1.79; 95% CI, 1.03Y3.10; P=0.038) and post-transplant lymphoproliferative disease (adjusted HR, 2.72; 95% CI, 1.38Y5.37; P=0.004). **Conclusion:** Recipients of expanded criteria deceased donor kidneys are at substantially increased risk of cancer, especially cancers with a viral etiology. Allocation of expanded criteria deceased donor kidneys to potential recipients should balance the harms, such as the excess risk of cancer against the survival gains and quality-of-life benefits associated with transplantation.

13. Risk of human papillomavirus-related cancers among kidney transplant recipients and patients receiving chronic dialysis - an observational cohort study

BMC Nephrology 2013, 14:137

Skov Dalgaard L, Fassel U, Østergaard LJ, Jespersen B, Schmeltz Søgaard O, Jensen-Fangel S

Background: Individuals with end-stage renal disease (ESRD) have excess risk of various cancer types. However, the total burden of human papillomavirus-related cancers remains unknown. **Methods:** We performed a nationwide observational cohort study during 1994–2010. For each person with ESRD, we sampled 19 population controls (without ESRD) matched on age, gender and municipality. Participants were followed until first diagnosis of human papillomavirus-related cancer, death, emigration, or 31 December 2010, whichever came first. Human papillomavirus-related cancers were extracted from Danish medical administrative databases. We considered cancers of the cervix, vulva, vagina, penis, anus, and subsets of head and neck cancers as human papillomavirus-related. We calculated incidence rates of human papillomavirus-related cancer and used Poisson regression to identify risk factors for human papillomavirus-related cancer. **Results:** Among 12,293 persons with ESRD and 229,524 population controls we identified 62 and 798 human papillomavirus-related cancers, respectively. Incidence rates of human papillomavirus-related- cancer were 102 per 100,000 person-years (95% confidence interval [CI]; 79.5-131) among persons with ESRD and 40.8 per 100,000 person-years (95% CI; 38.1-43.7) among population controls. ESRD patients had 4.54 (95% CI, 2.48-8.31) fold increased risk of anal cancer and 5.81 fold (95% CI; 3.36-10.1) increased risk of vulvovaginal cancer. Adjusted for age, comorbidity, and sex, ESRD patients had 2.41 (95% CI; 1.83-3.16) fold increased risk of any human papillomavirus related cancer compared with population controls. Compared with dialysis patients renal transplant recipients had an age-adjusted non-significant 1.53 (95% CI, 0.91-2.58) fold higher risk of human papillomavirus-related cancer.
Conclusions: Persons with ESRD have excess risk of potentially vaccine-preventable human papillomavirus-related cancers.

14. Prevalence of high-risk human papillomavirus cervical infection in female kidney graft recipients: an observational study.

Pietrzak et al. Virology Journal 2012, 9:117

Pietrzak B, Mazanowska N, Ekiel AM, Durlik M, Martirosian G, Wielgos M, Kaminski P

Background: Immunosuppressive therapy protects the transplanted organ but predisposes the recipient to chronic infections and malignancies. Transplant patients are at risk of cervical intraepithelial neoplasia (CIN) and cervical cancer resulting from an impaired immune response in the case of primary infection or of reactivation of a latent infection with human papillomavirus of high oncogenic potential (HR-HPV).

Methods: The aim of this study was to assess the prevalence of HR-HPV cervical infections and CIN in 60 female kidney graft recipients of reproductive age in comparison to that in healthy controls. Cervical swabs were analyzed for the presence of HR-HPV DNA. HR-HPV-positive women remained under strict observation and were re-examined after 24 months for the presence of transforming HR-HPV infection by testing for HR-HPV E6/E7 mRNA. All the HR-HPV-positive patients were scheduled for further diagnostic tests including exfoliative cytology, colposcopy and cervical biopsy.

Results: The prevalence of HR-HPV did not differ significantly between the study group and the healthy controls (18% vs 25%, p = 0.37). There was no correlation between HR-HPV presence and the immunosuppresive regimen, underlying disease, graft function or time interval from transplantation. A higher prevalence of HR-HPV was observed in females who had had ≥2 sexual partners in the past. Among HR-HPV-positive patients, two cases of CIN2+ were diagnosed in each group. In the course of follow-up, transforming HR-HPV infections were detected in two kidney recipients and in one healthy female. Histologic examination confirmed another two cases of CIN2+ developing in the cervical canal.

Conclusions: Female kidney graft recipients of reproductive age are as exposed to HR-HPV infection as are healthy individuals. Tests detecting the presence of HR-HPV E6/E7 mRNA offer a novel diagnostic opportunity in those patients, especially in those cases where lesions have developed in the cervical canal.

15. Surveillance of Nonmelanoma Skin Cancer Incidence Rates in Kidney Transplant Recipients in Ireland

Transplantation 2014;98: 646-652

Bannon FJ, McCaughan JA, Traynor C, O'Brien K, Gavin AT, Maxwell AP, Comber H, Conlon PJ

Background: The incidence of nonmelanomatous skin cancer (NMSC) is substantially higher among renal transplant recipients (RTRs) than in the general population. With a growing RTR population, a robust method for monitoring skin cancer rates in this population is required. **Methods.** A modeling approach was used to estimate the trends in NMSC rates that adjusted for changes in the RTR population (sex and age), calendar time, the duration of posttransplant follow-up, and background population NMSC incidence rates. RTR databases in both Northern Ireland (NI) and the Republic of Ireland (ROI) were linked to their respective cancer registries for diagnosis of NMSC, mainly squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). **Results.** RTRs in the ROI had three times the incidence (PG0.001) of NMSC compared with NI. There was a decline (PG0.001) in NMSC 10-year cumulative incidence rate in RTRs over the period 1994-2009, which was driven by reductions in both SCC and BCC incidence rates. Nevertheless, there was an increase in the incidence of NMSC with time since transplantation. The observed graft survival was higher in ROI than NI (PG0.05) from 1994-2004. The overall patient survival of RTRs was similar in NI and ROI.
Conclusion. Appropriate modeling of incidence trends in NMSC among RTRs is a valuable surveillance exercise for assessing the impact of change in clinical practices over time on the incidence rates of skin cancer in RTRs. It can form the basis of further research into unexplained regional variations in NMSC incidence.

16. Risk Factors for Non-melanoma Skin Cancer in Kidney Transplant Patients in a Spanish Population in the Mediterranean Region

Acta Derm Venereol 2013; 93: 422–427.

Bernat García J, Morales Suárez-Varela M, Vilata JJ, Marquina A, Pallardó L, Crespo J.

Non-melanoma skin cancer (NMSC) is the most frequent malignancy in organ transplant recipients. The aetiology of NMSC after transplant is multifactorial. The aim of this study was to determine the clinical and environmental factors involved in the development of NMSC in a Spanish kidney transplant population from the Mediterranean region. A total of 289 patients who had received a kidney transplant during the period January 1996 to December 2010 were included in the study. Both prospective and retrospective data were used. All patients underwent a structured interview and a complete examination of the skin. After a median follow-up of 72 months (range 12–180 months), 73 of the 289 patients (25.2%) developed 162 tumours. The ratio of basal cell carcinoma to squamous cell carcinoma was 2.21:1. The cumulative incidence of NMSC increased with the duration of immunosuppression, from 20.78% at 5 years, to 37.35% at 10 years to 53.08% at 15 years after transplantation. Age at the time of transplant, phototype and occupational sun exposure were associated with a higher risk of NMSC. NMSC is a significant clinical problem in kidney transplant recipients. This has implications for the development of prevention and surveillance strategies. Clinical and environmental factors may be used to identify those patients who are at risk for NMSC.

17. Nonmelanoma skin cancer after renal transplantation: a single-center experience in 1736 transplantations

International Journal of Dermatology 2011, 50, 1496–1500

Zavos G, Karidis NP, Tsourouflis G, Bokos J, Diles K, Sotirchos G, Theodoropoulou E, Kostakis A.

Background: Renal transplantation is associated with an increased incidence of nonmelanoma skin cancer (NMSC) caused by immunosuppression. Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), the two major histological types of NMSC, exhibit more aggressive biological and clinical courses in renal transplant recipients (RTRs), with higher rates of recurrence and mortality than in the general population.
Methods: We retrospectively analyzed our experience of NMSC in 1736 renal transplantations performed over a 25-year period. All cases of skin cancer after renal transplantation were included except those of skin cancer resulting from melanoma and mesenchymal skin tumors.
Results: In our series, the overall incidence of NMSC after transplantation was 2.2% (n = 39), and SCC represented the most frequent skin malignancy (64.1%), followed by BCC (17.9%), Bowen's disease (10.2%), basosquamous carcinoma (5.1%), and a rare case of invasive sebaceous carcinoma (2.6%). A shift to newer immunosuppressive regimens after the initial diagnosis of NMSC had been implemented in eight cases (20.5%). The recurrence rate after initial treatment was 41% (n = 16), and distant metastatic disease was diagnosed in 15.4% (n = 6) of NMSC patients. The NMSC-specific mortality rate was 25.6% (n = 10).
Conclusions: Nonmelanoma skin cancer remains a significant source of morbidity and mortality in RTRs, and post-transplant surveillance should be increased.

18. Post-Transplantation Lymphoproliferative Disorder After Kidney Transplantation: Report of a Nationwide French Registry and the Development of a New Prognostic Score

American Society of Clinical Oncology. J Clin Oncol 31:1302-1309

Caillard S, Porcher R, Provot F, Dantal J, Choquet S, Durrbach A, Morelon E, Moal V, Janbon B, Alamartine E, Pouteil Noble C, Morel D, Kamar N, Buchler M, Mamzer MF, Peraldi MN, Hiesse C, Renoult E, Toupance O, Rerolle JP, Delmas S, Lang P, Lebranchu Y, Heng AE, Rebibou JM, Mousson C, Glotz D, Rivalan J, Thierry A, Etienne I, Moal MC, Albano L, Subra JF, Ouali N, Westeel PF, Delahousse M, Genin R, Hurault de Ligny B, Moulin B..

Purpose: Post-transplantation lymphoproliferative disorder (PTLD) is associated with significant mortality in kidney transplant recipients. We conducted a prospective survey of the occurrence of PTLD in a French nationwide population of adult kidney recipients over 10 years.
Patients and Methods: A French registry was established to cover a nationwide population of transplant recipients and prospectively enroll all adult kidney recipients who developed PTLD between January 1, 1998, and December 31, 2007. Five hundred patient cases of PTLD were referred to the French registry. The prognostic factors for PTLD were investigated using Kaplan-Meier and Cox analyses.
Results: Patients with PTLD had a 5-year survival rate of 53% and 10-year survival rate of 45%. Multivariable analyses revealed that age 55 years, serum creatinine level 133 mol/L, elevated lactate dehydrogenase levels, disseminated lymphoma, brain localization, invasion of serous membranes, monomorphic PTLD, and T-cell PTLD were independent prognostic indicators of poor survival. Considering five variables at diagnosis (age, serum creatinine, lactate dehydrogenase, PTLD localization, and histology), we constructed a prognostic score that classified patients with PTLD as being at low, moderate, high, or very high risk for death. The 10-year survival rate was 85% for low-, 80% for moderate-, 56% for high-, and 0% for very high–risk recipients.
Conclusion: This nationwide study highlights the prognostic factors for PTLD and enables the development of a new prognostic score. After validation in an independent cohort, the use of this score should allow treatment strategies to be better tailored to individual patients in the future.

19. Associations Between EBV Serostatus and Organ Transplant Type in PTLD Risk: An Analysis of the SRTR National Registry Data in the United States

American Journal of Transplantation 2012; 12: 976–983

Dharnidharka VR, Lamb KE, Gregg JA, Meier-Kriesche HU

In a prior multiorgan transplant database study, recipient Epstein–Barr virus (EBV) seronegativity was not associated with increased risk for posttransplant lymphoproliferative disorders (PTLD) in liver transplants (LTX), at variance with prior single center reports and with data from kidney and heart transplants (KTX and HTX). The Scientific Registry of Transplant Recipients (SRTR) in the United States is the only other registry with data on the required variables for comparison. Our study set comprised 112 756 KTX (580 PTLDs; 0.51%), 13 937 HTX (140 PTLDs; 1.0%) and 40 437 LTX (383 PTLDs; 0.95%) performed January2003 onward. The unadjusted hazard ratio (HR) for PTLD if recipient EBV seronegative was 5.005 for KTX, 6.528 for HTX and 2.615 for LTX ($p < 0.001$ for all). In models adjusted for multiple covariates, the adjusted HR was 3.583 ($p < 0.001$) for KTX, 4.037 ($p < 0.001$) for HTX, 1.479 ($p = 0.03$) for LTX. Interaction models using EBV seropositive KTX as reference group showed significantly higher risk for all other EBV seronegative organ transplant groups and also for EBV seropositive LTX (AHR 2.053, $p < 0.0001$).Recipient EBV seronegativity is still significantly associated with risk for PTLD in LTX, though less so because of higher baseline risk in the EBV seropositive LTX group.

20. Incidence of Post-Transplantation Lymphoproliferative Disease in Andalusia (1990-2009)

Transplantation Proceedings, 45, 3592-3594 (2013)

Govantes MA, Esteve AF, Ramos MT, Gracia De Guindo MC, Sánchez LF, Blanca MA, Rodríguez-Benot A, Blandino MV, De la Nuez PC, Rodríguez DB

Background: Post-transplantation lymphoproliferative disease (PTLD) is a severe complication of renal transplantation (RT) but information about its incidence and predisposing factors is diverse, varying according to geographic area and study period.
Methods: We analyzed the incidence of PTLD after all RT performed at adult transplantation centers in Andalusia from January 1, 1990 to December 31, 2009, recorded in the Andalusian Transplant Co-ordination Information System (SICATA) regional computerized database (n = 5577). We calculated the risk of PTLD using the Kaplan-Meier curve, censoring for organ failure and incidence rate per patient-year of exposure. Log-rank comparisons were made by center (n = 5), decade (1990-1999 vs 2000-2009), age group, recipient gender, hepatitis C virus (HCV) serology, transplantation number, and duration of pre-RT replacement therapy (per quartiles).
Results. We identified 60 cases of PTLD. The pre-RT treatment time was 48.2 ± 60 months; 11.7% were retransplantations, and 10.4% had a positive HCV serology. The median post-RT time before diagnosis of PTLD was 5.98 years. At the time of the database analysis, only 11 patients (18%) were alive with a functioning transplant; 10% had returned to dialysis and 72% had died. The actuarial incidence of PTLD at 1, 5, 10, and 20 years post-RT was 0.2%, 0.5%, 1.6%, and 2.9%, respectively; the exposure rate was 14.71 PTLD/10,000 patient-years (95% confidence interval [CI], 12.3-17.1). Although the incidence tended to be higher in 1990-1999 than 2000-2009 (16.8 vs 12.1 cases/10,000 patient-years), in the actuarial study the difference was far from significant (at 7.5 years, 1.2 vs 0.8%; P = .4). Nor were there significant differences in the curves of incidence per RT center (1%-1.2% of patients) or recipient characteristics.
Conclusions: The cumulative incidence of PTLD in Andalusia in patients with a functioning kidney transplant during 1990-2009 was 2.9% at 20 years. There was no significant variation between the RT centers or over time. No associated factors were identified among the basic recipient variables studied.

21. Risk of diffuse large B-cell lymphoma after solid organ transplantation in the United States

Am J Hematol. 2014 July ; 89(7): 714–720. doi:10.1002/ajh.23726.

Gibson TM, Engels EA, Clarke CA, Lynch CF, Weisenburger DD, Morton LM

Abstract: Non-Hodgkin lymphoma (NHL) arising in the context of immunosuppression is an important adverse outcome following solid organ transplantation. Diffuse large B-cell lymphoma (DLBCL) is the most commonly diagnosed subtype of post-transplant NHL, but few studies of transplant recipients have examined subtype-specific risks. Therefore, we examined DLBCL risk in the Transplant Cancer Match Study, including registry-based cancer ascertainment among 96,615 solid organ transplants performed from 2000–2008. We determined standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) comparing DLBCL risk in transplant recipients to that in the general population, and used multivariable Poisson regression models to assess the impact of potential risk factors. We identified 321 incident cases of DLBCL, over 12 times more than expected based on general population rates (SIR=12.6, 95% CI=11.2–14.0). SIRs were highest in young recipients and those receiving a lung or pancreas/kidney-pancreas transplant, and were greatly elevated for extranodal DLBCLs at the site of the transplant compared to other sites. DLBCL risk was highest in the first year following transplant, and SIRs for early-onset DLBCL risk were elevated in association with EBV negative serostatus and use of polyclonal antibody induction therapy. In conclusion, associations between recipient and transplant factors and post-transplant DLBCL risk suggest a complicated interrelationship among multiple risk factors and timing of disease.

22. Lymphoproliferative Disorders After Adult Kidney Transplant: Epidemiology and Comparison of Registry Report With Claims-Based Diagnoses

Am J Kidney Dis. 58(6):971-980.

Kasiske BL, Kukla A, Thomas D, Wood Ives J, Snyder JJ, Qiu Y, Peng Y, Dharnidharka VR, Israni AK

Background: Posttransplant lymphoproliferative disorder (PTLD) is a major complication of kidney transplant.
Study Design: Retrospective cohort study comparing PTLD incidence rates using US Medicare claims and Organ Procurement and Transplantation Network (OPTN) data, examining risk factors for PTLD in OPTN data, and studying recipient and graft survival after PTLD diagnosis.
Setting & Participants: All adult first-transplant patients who underwent deceased or living donor kidneyonly transplants in 2000-2006 (n _ 89,485) followed up through 3 years posttransplant.
Predictors: Recipient and donor characteristics, HLA mismatches, viral serologic test results, and initial immunosuppression.
Outcomes: OPTN-reported or Medicare claims–based PTLD diagnosis, recipient and graft survival after OPTN-reported PTLD diagnosis.
Measurements: Adjusted HRs for PTLD diagnosis estimated using a Cox proportional hazards model; probability of survival free of all-cause graft failure estimated using the Kaplan-Meier method.
Results: The incidence rate of PTLD during the first posttransplant year was 2-fold higher in Medicare claims (0.46/100 patient-years; 95% CI, 0.39-0.53) than in OPTN data (0.22/100 patient-years; 95% CI, 0.17-0.27).
Factors associated with increased rates of PTLD included older age, white race (vs African American), induction with T-cell– depleting antibodies, Epstein-Barr virus seronegativity at the time of transplant, and cytomegalovirus seronegativity at the time of transplant. The adjusted risk of death with graft function was 17.5 (95% CI, 14.3-21.4) times higher after a report of PTLD, and the risk of death-censored graft failure was 5.5 (95% CI, 3.9-7.7) times higher.
Limitations: Shortcomings inherent in large databases, including inconsistencies in patient follow-up, reporting, and coding practices by transplant centers; insufficient registry data to analyze acute rejection episodes and antirejection treatment; no available data for potential effects of different types of PTLD treatment on patient outcomes.
Conclusions: Despite the limitations of data collected by registries, PTLD clearly is an important complication; both mortality and death-censored graft failure increase after PTLD.

23. Burkitt lymphoma risk in U.S. solid organ transplant recipients

Am J Hematol. 2013 April ; 88(4): 245–250. doi:10.1002/ajh.23385.

Mbulaiteye SM, Clarke CA, Morton LM, Gibson TM, Pawlish K, Weisenburger DD, Lynch CF, Goodman MT, Engels EA

Abstract: Case reports of Burkitt lymphoma (BL) in transplant recipients suggest that the risk is markedly elevated. Therefore, we investigated the incidence of BL in 203,557 solid organ recipients in the U.S. Transplant Cancer Match Study (1987–2009) and compared it to the general population using standardized incidence ratios (SIRs). We also assessed associations with demographic and clinical characteristics, and treatments used to induce therapeutic immunosuppression. BL incidence was 10.8 per 100,000 person-years, representing 23-fold (95%CI 19–28) greater risk than in the general population, and it peaked 3–8 years after the time of transplantation. In adjusted analyses, BL incidence was higher in recipients transplanted when <18 vs. ≥35 years (incidence rate ratio [IRR] 3.49, 95% CI 2.08–5.68) and in those transplanted with a liver (IRR 2.91, 95% CI 1.68– 5.09) or heart (IRR 2.39, 95% CI 1.30–4.31) compared to kidney. BL incidence was lower in females than males (IRR 0.45, 95% CI 0.28–0.71), in blacks than whites (IRR 0.33, 95% CI 0.12– 0.74), in those with a baseline Epstein-Barr virus (EBV)-seropositive versus EBV-seronegative status (IRR 0.34, 95% CI 0.13–0.93), and in those treated with azathioprine (IRR 0.56, 95% CI 0.34–0.89) or corticosteroids (IRR 0.48, 95% CI 0.29–0.82). Tumors were EBV-positive in 69% of 32 cases with results. EBV positivity was 90% in those aged <18 years and 59% in those aged 18+ years. In conclusion, BL risk is markedly elevated in transplant recipients, and it is associated with certain demographic and clinical features. EBV infection was present in most but not all BL cases.

24. Presentación clínica del carcinoma de células renales en el trasplante renal

Arch Esp Urol. 2009 Apr;62(3):207-13; discussion 213.

González-López R, Bueno-Serrano G, Mayor-De Castro J, Vázquez-Escuderos JJ, Díez-Nicolás V, Marcén Letosa R, Pascual Santos J, Burgos Revilla FJ.

Objetivo: Analizar la presentación clínica y la actitud terapéutica ante la afectación del injerto por un Carcinoma de células renales (CCR).
Métodos: Análisis de los casos descritos en nuestro Centro y revisión de la literatura actual.
Resultados: El CCR presenta una incidencia superior en los pacientes trasplantados, afectando en menos del 10% al injerto. La ausencia de inervación hace que habitualmente sea un hallazgo casual durante el seguimiento, aunque su presentación puede llegar a ser como un abdomen agudo en caso de rotura del injerto. El tratamiento convencional es la trasplantectomía, realizándose en los últimos años la nefrectomía parcial con buenos resultados. La modificación de la inmunosupresión es una medida habitual tras el tratamiento.
Conclusiones: La incidencia de CCR post-TR en nuestra serie es del 0,7%, originándose el 22% de los mismos en el injerto. La presentación clínica del CCR primitivo del injerto es variable. La nefrectomía parcial es técnicamente posible y oncológicamente segura en el tratamiento del CCR del injerto renal.

25. Development of Urologic de Novo Malignancies After Renal Transplantation

Transplant Proc. 2014 Jan-Feb;46(1):170-5.

Hevia V, Gómez V, Díez Nicolás V, Alvarez S, Gómez Del Cañizo C, Galeano C, Gomis A, García-Sagredo JM, Marcen R, Burgos FJ

Objectives: The incidence of neoplasms in renal transplant recipients is higher than in general population. The increasing age of donors and recipients also increases the risk of developing malignancies, including genitourinary. The aim of this study is to analyze clinical aspects and management of this complication.

Materials and Methods: We conducted a retrospective analysis of 1365 patients who underwent renal transplantation between 1977 and 2010 who were 44.6 ± 14.9 years old at the time of transplantation. The median follow-up was 95.6 months (range, 18.0-236.0). Data were analyzed for sex, age, time from transplant to diagnosis, location, clinical stage, immunosuppression, treatment, follow-up, and evolution.

Results: We diagnosed 25 de novo urologic neoplasms (25/1365; 1.8%) in 24 patients, with a median follow-up of 32 months (range, 12.5-51.8) from the diagnosis. Sixteen were male (66.7%) and 8 female (33.3%), with a median age at diagnosis of 59 years (range, 56.0e65.5). The median time between the transplant and the diagnosis of the malignancy was 69 months (range, 40.0-116.5). There were 11 renal cell carcinomas (RCC; 11/25; 44%), 8 in native kidney and 3 in renal allograft; 9 prostate cancers (PCa; 9/25; 36%), 8 localized and 1 metastatic; and 5 transitional cell carcinomas (TCC; 5/25; 20%), 3 in bladder and 2 in renal allograft pelvis. Treatments performed were similar to those used in the nontransplanted population. RCC were treated with radical nephrectomy when affecting the native kidney, partial nephrectomy when affecting the allograft, or immunotherapy when metastatic. Patients with localized PCa were treated with radical prostatectomy, radiotherapy, or androgenic deprivation if there were comorbidities, and those metastatic with hormonal deprivation. Bladder TCCs were treated with transurethral resection or radical cystectomy. Pelvis TCCs affecting the allograft were treated with radical nephroureterectomy of the allograft including bladder cuff and pelvic lymphadenectomy.

Conclusions: There exists an increased incidence of urologic tumors in kidney transplant recipients. Conventional treatments of these tumors are technically feasible. The risk of developing these tumors remains even in the long term. Because of their suitability for curative treatments, it is advisable to perform periodic screening for urologic cancers to achieve an early diagnosis.

26. De novo malignancies in renal transplant recipients: experience at a single center with 1882 transplant patients over 39 yr

Clin Transplant 2013: 27: E30–E36 DOI: 10.1111/ctr.12050

Apel H, Walschburger-Zorn K, Haberle L, Wach S, Engehausen DG, Wullich B.

Purpose: Cancers complicating organ allografts are a major cause of morbidity and mortality after renal transplantation. Different registries have described an overall three to eightfold increase in cancer risk compared with the general population. This retrospective study investigated the incidence and outcome of de novo malignancies following kidney transplantation in a single German kidney transplantation center.

Materials and Methods: Between 1966 and 2005, 1882 patients underwent kidney transplantation at the Erlangen–Nuremberg kidney transplantation center. The incidence and types of post-transplant malignancies were retrospectively analyzed according to the patients' records and the database of the local cancer registry.

Results: We identified 257 malignancies in 231 patients, an overall incidence of 13.7%. The mean follow-up time was 9.9 yr (range, 0.4– 25.5 yr). The observed incidence data corresponded to a 12.1-fold increase in the overall risk of developing a malignant nonskin tumor compared with the nontransplanted population. Urinary tract malignancies represented the most frequent malignancies among the nonskin tumors (32.1%), followed by gastrointestinal tract (30.7%) and gynecological (14%) cancers. When we considered the duration from renal transplantation to tumor detection and tumor-specific survival, there was no difference between patients treated with or without a cyclosporine A-based regimen.

Conclusions: In our study, the overall risk of developing a posttransplant nonskin malignancy was 12.1-fold higher compared with the age-matched general population. Development of solid organ malignancies is one of the most frequent causes of morbidity and mortality in renal transplant recipients; thus, close tumor screening in patients after kidney transplantations is warranted.

27. Post-transplantation Malignancy After Kidney Transplantation in Turkey

Transplant Proc. 2015 Jun;47(5):1418-20.

Keles Y, Tekin S, Duzenli M, Yuksel Y, Yücetin L, Dosemeci L, Sengul A, Demirbaş A, Tuncer M

Objective: Kidney transplantation is the best treatment option for end-stage renal disease patients. Increased incidence of post-transplantation malignancy can be caused by immunosuppressive drugs and some oncogenic infections. The aim of this study is to show the incidence of post-transplantation malignancy in patients who had surgery and were followed up in the Organ Transplant Center, Medical Park Antalya, Antalya, Turkey.
Method: The study was based on 2100 kidney transplantation patients who had surgery between May 2008 and December 2012 and also on 1900 patients who had surgery by members of our team in other centers and who were followed up routinely. In all of our patients, the type of malignancy, the time that malignancy developed, immunosuppressive regimens, and viral status (Epstein-Barr virus and cytomegalovirus) were investigated.
Results: Malignancy was developed in 30 patients (60% of them were male, median age was 52.1 years). Post-transplantation malignancy development time was a median of 5.1 years. The types of malignancies were as follows: non-melanoma skin cancer in 12 patients (40%), urogenital cancer in 7 patients (24%), breast cancer in 4 patients (14%), lymphoproliferative disease in 3 patients (10%), thyroid cancer in 2 patients (6%), and lung cancer in 2 patients (6%).
Discussion: In this study, we did not find any increased post-transplantation malignancy risk in our patients. This finding could be due to the low-dosage immunosuppressive protocols that we used.

28. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008—A Swedish population-based study

Int. J. Cancer: 132, 1429–1438 (2013) VC 2012 UICC

Krynitz B, Edgren G, Lindelöf B, Baecklund E, Brattström C, Wilczek H, Smedby KE

Organ transplant recipients are at increased risk of a wide range of malignancies, especially cutaneous squamous cell carcinomas (SCC). Few previous population-based studies have quantified and compared cancer risks according to graft type and with long-term follow-up. Using nationwide Swedish registers, we identified 10,476 recipients transplanted from 1970 to 2008 and followed them for cancer occurrence. Relative risks of cancer in comparison with the general population were expressed as standardized incidence ratios (SIR) and within the transplanted cohort as incidence rate ratios (IRR). During a total follow-up of 93,432 person-years, patients were diagnosed with 1,175 cancers excluding SCC, and with 2,231 SCC, $SIR_{cancer\ excl\ SCC}$ 2.4 (95% CI, 2.2–2.5); SIR_{SCC} 121 (95% CI, 116–127). Cancer risks were most increased among heart and/or lung recipients $SIR_{cancer\ excl\ SCC}$ 3.3 (95% CI, 2.8–4.0); SIR_{SCC} 198 (95% CI, 174–224), followed by kidney $SIR_{cancer\ excl\ SCC}$ 2.3 (95% CI, 2.1–2.4); SIRSCC 121 (95% CI, 116–127) and liver recipients $SIR_{cancer\ excl\ SCC}$ 2.3 (95% CI, 1.9–2.8); SIR_{SCC} 32 (95% CI, 24–42). During follow-up, risk of cancer excluding SCC remained stable while risk of SCC tripled over 20 years irrespective of graft type, partly due to a subgroup of patients developing new SCCs at a rapidly increasing rate. In summary, posttransplant cancer risk varied by transplanted organ and by cancer site, with the bulk of the excess risk driven by an exceptionally high and accelerating risk of SCC. These findings underscore the importance of regular skin screening in organ transplant recipients.

29. Risk of de novo cancers after transplantation: Results from a cohort of 7217 kidney transplant recipients, Italy 1997–2009

Eur J of Cancer 2013 Jan;49(2):336-44

Piselli P, Serraino D, Segoloni GP, Sandrini S, Piredda GB, Scolari MP, Rigotti P, Busnach G, Messa P, Donati D, Schena FP, Maresca MC, Tisone G, Veroux M, Sparacino V, Pisani F, Citterio F; Immunosuppression and Cancer Study Group

Abstract: To assess incidence and risk factors for de novo cancers (DNCs) after kidney transplant (KT), we carried out a cohort investigation in 15 Italian KT centres.

Seven thousand two-hundred seventeen KT recipients (64.2% men), transplanted between 1997 and 2007 and followed-up until 2009, represented the study group. Person years (PY) were computed from 30 days after transplant to cancer diagnosis, death, return to dialysis or to study closure. The number of observed DNCs was compared to that expected in the general population of Italy through standardised incidence ratios (SIR) and 95% confidence intervals (CI). To identify risk factors, incidence rate ratios (IRR) were computed.

Three-hundred ninety five DNCs were diagnosed during 39.598 PYs, with Kaposi's sarcoma (KS), post-transplant lymphoproliferative disorders (PTLD), particularly non-Hodgkin' lymphoma (NHL), lung, kidney and prostate as the most common types. The overall IR was 9.98/ 1.000 PY, with a 1.7-fold augmented SIR (95% CI: 1.6-1.9). SIRs were particularly elevated for KS (135), lip (9.4), kidney carcinoma (4.9), NHL (4.5) and mesothelioma (4.2). KT recipients born in Southern Italy were at reduced risk of kidney cancer and solid tumors, though at a higher KS risk, than those born in Northern Italy. Use of mTOR inhibitors (mTORi) exerted, for all cancers combined, a 46% significantly reduced risk (95% CI: 0.4–0.7).

Our study findings confirmed, in Italy, the increased risks for cancer following KT, and they also suggested a possible protective effect of mTORi in reducing the frequency of posttransplant cancers.

30. Incidence of Primary and Second Cancers in Renal Transplant Recipients: A Multicenter Cohort Study

Am J Transplant. 2013 Jan;13(1):214-21

Tessari G, Naldi L, Boschiero L, Minetti E, Sandrini S, Nacchia F, Valerio F, Rugiu C, Sassi F, Gotti E, Fonte L, Talamini G, Girolomoni G

Limited data exist about cancer prognosis and the development of second cancers in renal transplant recipients. In a retrospective cohort study on 3537 patients incidence rates of the first and, if any, of a second cancer, and standardized incidence ratios [SIR (95% CI)] were computed. Two hundred and sixty-three (7.5%) patients developed a NMSC, and 253 (7.2%) another type of cancer after a median follow-up of 6.5 and 9.0 years, respectively. A statistically significant excess risk, if compared to an age- and sex-matched reference general population, was observed for Kaposi sarcoma and NMSC, followed by non-Hodgkin lymphoma and carcinoma of cervix uteri; a small number of unusual cancers such as tumors of the salivary glands, small intestine and thyroid also were detected at a level worthy of additional scrutiny. Ten-year survival rate of all noncutaneous cancers was 71.3%, with lower rates for lung carcinoma and non-Hodgkin lymphoma (0% and 41.7%, respectively). Patients with NMSC had an increased risk of developing a second NMSC [SIR 8.3 (7.0–10.0)], and patients with a primary noncutaneous cancer had increased risk of developing a second noncutaneous cancer [SIR 1.8 (1.2–2.8)], if compared to the whole cohort. Our study underscore that the high risk of primary and second cancer in renal transplant recipients, including unusual cancers.

31. Influence of Fractalkine Receptor Gene Polymorphisms V249I-T280M on Cancer Occurrence After Renal Transplantation

Transplantation. 2013 Mar 15;95(5):728-32

Courivaud C, Bamoulid J, Loupy A, Deschamps M, Ferrand C, Simula-Faivre D, Tiberghien P, Chalopin JM, Legendre C, Thervet E, Borg C, Saas P, Ducloux D

Background: Fractalkine (CX3CL1) and its receptor (CX3CR1) are involved in antitumor immunity. Two common single nucleotide polymorphisms of the CX3CR1 gene, V249I and T280M, have been associated with reduced fractalkine signaling characterized by decreased adhesive function, signaling, and chemotaxis of leukocytes. We hypothesized that a renal transplant recipient (RTR) carrying the homozygous I249M280 genotype could experience more cancer due to lower CX3CL1-dependent antitumorigenic effects.
Methods: We studied the association between these polymorphisms and cancer incidence in two independent cohorts of RTR, including a total of 622 patients.
Results: The median follow-up was 8.7 and 7.9 years for the first and second cohorts, respectively. Analysis of 622 patients identified 20 (3.2%) I249M280 homozygous patients, 321 (51.6%) V249T280 homozygous patients, and 281 (45.2%) heterozygous patients. I249M280 homozygotes have an independent increased risk of cancer (hazard ratio [95% confidence interval], 3.3 [1.04Y10.52], P=0.043 for cohort 1 and 9.2 [1.67Y50.91], P=0.011 for cohort 2) compared with other patients. Age and male gender were also risk factors for cancer occurrence.
Conclusions: CX3CR1 gene polymorphism is associated with a higher rate of cancer in RTRs. Such findings may be used to influence immunosuppressive strategies and optimize patient management.

32. Clinical and Genetic Factors Associated With Cutaneous Squamous Cell Carcinoma in Kidney and Heart Transplant Recipients

Transplant Direct. 2015 May;1(4).

Sanders ML, Karnes JH, Denny JC, Roden DM, Ikizler TA, Birdwell KA

Background: Cutaneous squamous cell carcinoma (cSCC) occurs with higher frequency and recurrence rates, increased morbidity and mortality, and more aggressive metastasis in kidney and heart transplant recipients compared to the general population but all transplant recipients do not develop cSCC. In addition, the phenotypic expression of cSCC among transplant recipients can vary between mild disease and extensive recurrent metastatic disease. These clinically observed differences in occurrence and severity of cSCC among transplant recipients suggest the possibility that an underlying genetic component might modify risk.
Methods: We identified 88 white posttransplant cSCC cases (71 kidney and 17 heart) and 300 white posttransplant controls (265 kidney and 35 heart) using a DNA biobank linked with deidentified electronic medical records. Logistic regression was used to determine adjusted odds ratios (OR) for clinical characteristics and single nucleotide polymorphisms (SNP) associated with cSCC in both a candidate SNP and genomewide analysis.
Results: Age (OR, 1.08; 95% confidence interval [95% CI], 1.05-1.11; P < 0.001) and azathioprine exposure (OR, 8.64; 95% CI, 3.92-19.03; P < 0.001) were significantly associated, whereas sex, smoking tobacco use, dialysis duration, and immunosuppression duration were not. Ten candidate SNPs previously associated with nonmelanoma skin cancer in the general population were significantly associated with cSCC in transplant recipients. Genomewide association analysis implicated SNPs in genes previously associated with malignancy, CSMD1 (OR, 3.14; 95%CI, 1.90-5.20) and CACNA1D (OR, 2.67; 95% CI, 1.73-4.10]).
Conclusions: This study shows an association of increasing age and azathioprine exposure with cSCC and confirms a genetic contribution for cSCC development in kidney and heart transplant recipients.

33. Demethylation of the TSDR Is a Marker of Squamous Cell Carcinoma in Transplant Recipients
Am J Transplant. 2014 Nov;14(11):2617-22
Sherston SN, Vogt K, Schlickeiser S, Sawitzki B, Harden PN, Wood KJ.

Malignancy is an important cause of death in transplant recipients. Cutaneous squamous cell carcinoma (cSCC) causes significant morbidity and mortality as 30% of transplant recipients will develop cSCC within 10 years of transplantation. Previously we have shown that high numbers of regulatory T cells (Tregs) are associated with the development of cSCC in kidney transplant recipients (KTRs). Demethylation analysis of the Tregspecific demethylated region (TSDR) provides a more accurate association with cSCC risk after transplantation.
Age, gender and duration of immunosuppression matched KTRs with (n¼32) and without (n=27) cSCC, were re-analyzed for putative clinical and immunological markers of cancer risk. The proportion of FOXP3+ CD4+ cellswas higher in the population with a previous SCC. Major T cell subsets remained stable over time; although B cell, CD8 and CD4 subpopulations demonstrated age-related changes. TSDR methylation analysis allowed clarification of Treg numbers, enhancing the association of high Treg levels in KTRs with cSCC compared to the cSCC-free cohort. These data validate and expand on previous findings in long-term KTRs, and show that immune markers remain stable over time. TSDR demethylation analysis provides a more accurate biomarker of cancer posttransplantation.

34. Human skin carcinoma arising from kidney transplant–derived tumor cells

J Clin Invest. 2013;123(9):3797–3801

Verneuil L, Varna M, Ratajczak P, Leboeuf C, Plassa LF, Elbouchtaoui M, Schneider P, Sandid W, Lebbé C, Peraldi MN, Sigaux F, de Thé H, Janin A

Tumor cells with donor genotype have been identified in human skin cancer after allogeneic transplantation; however, the donor contribution to the malignant epithelium has not been established. Kidney transplant recipients have an increased risk of invasive skin squamous cell carcinoma (SCC), which is associated with accumulation of the tumor suppressor p53 and TP53 mutations. In 21 skin SCCs from kidney transplant recipients, we systematically assessed p53 expression and donor/recipient origin in laser-microdissected $p53^+$ tumor cells. In one patient, molecular analyses demonstrated that skin tumor cells had the donor genotype and harbored a TP53 mutation in codon 175. In a kidney graft biopsy performed 7 years before the skin SCC diagnosis, we found $p53^+$ cells in the renal tubules. We identified the same TP53 mutation in these $p53^+$ epithelial cells from the kidney transplant. These findings provide evidence for a donor epithelial cell contribution to the malignant skin epithelium in the recipient in the setting of allogeneic kidney transplantation. This finding has theoretical implications for cancer initiation and progression and clinical implications in the context of prolonged immunosuppression and longer survival of kidney transplant patients.

35. HLA and Risk of Diffuse Large B-cell Lymphoma After Solid Organ Transplantation

Transplantation. 2015 Dec 4. [Epub ahead of print]

Hussain SK, Makgoeng SB, Everly MJ, Goodman MT, Martínez-Maza O, Morton LM, Clarke CA, Lynch CF, Snyder J, Israni A, Kasiske BL, Engels EA

Background: Solid organ transplant recipients have heightened risk for diffuse large B-cell lymphoma (DLBCL). The role of donor-recipient HLA mismatch and recipient HLA type on DLBCL risk are not well established.
Methods: We examined 172 231 kidney, heart, pancreas, and lung recipients transplanted in the United States between 1987 and 2010, including 902 with DLBCL. Incidence rate ratios (IRRs) were calculated using Poisson regression for DLBCL risk in relation to HLA mismatch, types, and zygosity, adjusting for sex, age, race/ethnicity, year, organ, and transplant number.
Results: Compared with recipients who had 2 HLA-DR mismatches, those with zero or 1 mismatch had reduced DLBCL risk, (zero: IRR, 0.76, 95% confidence interval [95% CI], 0.61-0.95; one: IRR, 0.83; 95% CI, 0.69-1.00). In stratified analyses, recipients matched at either HLA-A, -B, or -DR had a significantly reduced risk of late-onset (>2 years after transplantation), but not early-onset DLBCL, and there was a trend for decreasing risk with decreasing mismatch across all 3 loci (P = 0.0003). Several individual recipient HLA-A, -B, -C, -DR, and -DQ antigens were also associated with DLBCL risk, including DR13 (IRR, 0.74; 95% CI, 0.57-0.93) and B38 (IRR, 1.48; 95% CI, 1.10-1.93), confirming prior findings that these 2 antigens are associated with risk of infection-associated cancers.
Conclusions: In conclusion, variation in HLA is related to susceptibility to DLBCL, perhaps reflecting intensity of immunosuppression, control of Epstein-Barr virus infection among transplant recipients or chronic immune stimulation.

36. Peak Panel Reactive Antibody, Cancer, Graft, and Patient Outcomes in Kidney Transplant Recipients

Transplantation. 2015 May;99(5):1043-50
Lim WH, Chapman JR, Wong G

Background: High levels of pretransplant panel reactive antibodies (PRA) are known to be associated with detrimental effects on graft outcomes, but the association between pretransplant PRA levels and long-termpatient outcomes is unclear.
Methods: Using the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), we assessed the risk of rejection, graft failure, mortality and cancer in kidney transplant recipients with varying peak PRA levels.
Results: In 7,118 kidney transplant recipients between 1997 and 2009, there were a total of 3,171 (44.6%), 3,306 (46.4%), 323 (4.5%), and 318 (4.5%) recipients with peak PRA levels of 0%, 1% to 50%, 51%to 80%, and greater than 80%, respectively. Compared to recipients with 0% peak PRA level, recipients with peak PRA levels greater than 80% were at increased risk of acute rejection (odds ratio, 1.81, 95% confidence interval [95% CI], 1.30–2.35; P < 0.001), death censored graft failure (hazard ratio [HR], 2.06; 95% CI, 1.46–2.91; P < 0.001), all cause mortality (HR, 1.56; 95% CI, 1.15–2.11; P < 0.001) and cancer (HR, 1.94; 95% CI, 1.26–2.97; P = 0.002) in the adjusted models independent of human leukocyte antigen mismatches and initial immunosuppression.
Conclusion: Highly sensitized kidney transplant recipients with peak PRA greater than 80% had a greater risk of rejection, graft failure, cancer and death independent of age and time on dialysis. Strategies to reduce transplant waiting time and avoidance of sensitization in all potential transplant candidates are imperative to improve the overall graft and patient survival.

37. Natural Killer Lymphocytes Are Dysfunctional in Kidney Transplant Recipients on Diagnosis of Cancer

Transplantation 2015 Nov;99(11):2422-30

Peraldi MN, Berrou J, Venot M, Chardiny V, Durrbach A, Vieillard V, Debré P, Charron D, Suberbielle C, Chevret S, Glotz D, Dulphy N, Toubert A

Background: The incidence of cancer is increased after solid organ transplantation. Natural killer (NK) cells are key effectors of the tumor immune response.
Methods: We conducted a cross sectional multicentre matched case–control study including 42 kidney transplant recipients (KTRs) on diagnosis of cancer and 41 KTRs without cancer. Extensive phenotyping of NK cells populations and functional tests of NK cells were performed.
Results: Kidney transplant recipients with cancer had a higher incidence of acute rejection (P = 0.02) and cytomegalovirus (CMV) infection (P = 0.03) than controls. They had more lymphopenia than control KTRs (1020/mm^3 ± 32 vs 1218/mm^3 ± 34; P = 0.001) including a $CD4^+$ lymphopenia (P = 0.01). Total CD3−/ CD56+ NK cell counts were similar in both groups. However, KTRs with cancer had a lower frequency of the cytokine-enriched $CD56^{bright}$ NK cell subset (P = 0.001). The percentage of NK cells expressing NKp46 was decreased in KTRs with cancer (45% vs 53 %, P = 0.001). Furthermore, the ability of NK cells to degranulate $CD107a^+$ cytolytic vesicles was reduced (11% vs 22%; P = 0.02), and the percentage of NK cells secreting IFNγ was decreased (7.5% vs 28.8%; P = 0.01) in KTRs with cancer.
Conclusions: These results reveal an imbalance between NK cell subpopulations and functional NK cell defects in KTRs at the diagnosis of malignancy, including a decreased expression of NKp46 and decreased numbers of NK cells producing INFγ. This study highlights the role of NKp46, a major activating NK cell receptor, which could be considered as a potential marker during immunological follow-up of KTRs.

38. Epidemiology of Posttransplantation Lymphoproliferative Disorder in Adult Renal Transplant Recipients

Transplantation 2013;95: 470-478

Morton M, Coupes B, Roberts SA, Klapper PE, Byers RJ, Vallely PJ, Ryan K, Picton ML

Background: There is little information in the literature describing the relationship between posttransplantation lymphoproliferative disorder (PTLD) incidence and presentation with both recipient Epstein-Barr virus (EBV) serostatus and EBV status of PTLD histology, particularly in the late posttransplantation period.
Methods: This study reports the largest UK single-center, single-organ analysis of PTLD to date in a retrospective cohort study of 80 cases occurring in 4189 adult renal transplant recipients.
Results: The incidence rate was 2.6 cases per 1000 patient-years (95% confidence interval [95% CI], 2.1-3.2) for PTLD, 1.8 (95% CI, 1.4-2.4) for non-Hodgkin's lymphoma, and 0.2 (95% CI, 0.07-4.2) for Hodgkin's lymphoma. Non-Hodgkin's lymphoma occurred at a rate 7.6 times that of the adult general population in England, whereas the rate for Hodgkin's lymphoma was 5.9 times. The incidence of PTLD was highest during the 10th to 14th posttransplantation years. Early-onset disease was associated with EBV-seronegative recipient status, EBV-positive histology, and the involvement of extranodal sites. PTLD occurring in EBV-seronegative recipients was associated with EBV nuclear antigen antibody deficiency, polymorphic disease, and the involvement of extranodal sites. EBV-negative histology occurred in 32% of cases at a median time to presentation of 109 months. PTLD involving the allograft, central nervous system, and skin was uncommon and occurred late.
Conclusion: The incidence of PTLD is highest in the late posttransplantation period. Close clinical surveillance and education for transplant recipients is required for the duration of time while immunosuppressed. Failure to detect EBV DNA in blood should not reassure, particularly in patients with symptoms such as abdominal pain, oropharyngeal complaints, neck lumps, and B-symptoms.

39. Impact of Epstein–Barr virus donor and recipient serostatus on the incidence of post-transplant lymphoproliferative disorder in kidney transplant recipients

Nephrol Dial Transplant (2012) 27: 2971–2979

Sampaio MS, Cho YW, Shah T, Bunnapradist S, Hutchinson IV

Background: Post-transplant lymphoproliferative disorder (PTLD) is a serious complication of transplantation.
Methods: Using the OPTN/UNOS database, primary kidney recipients (2000–2009) were stratified according to transplant type (deceased donor, DD or living donor, LD), donor (D) and recipient (R) Epstein–Barr virus (EBV) serostatus (R+; D+/R− and D−/R−) and recipient age. Incidence and adjusted risk of PTLD and death were compared.
Results: Of the 137 939 primary kidney recipients transplanted between 2000 and 2009, 913 subsequently developed PTLD. In 90 208 recipients with known EBV serostatus, we found a trend toward a decrease in PTLD incidence in years 2007–2009 when compared to 2000–2003. This was due to a significant decrease in PTLD incidence in EBV− recipients. Of those, 61 273 had a known donor serostatus and were further examined. In adults, PTLD incidence (in 1000 person-years) in DD and LD was 7.0 and 7.0 in D+/R−; 3.0 and 2.5 in D−/R− and 1.2 and 1.0 in R+, respectively. The hazard ratio (HR) for PTLD (R+ as reference) in D+/R− (6.2 in DD and 7.2 in LD) was double to thrice than for D−/R− transplants (2.4 in both DD and LD). In pediatric recipients, PTLD incidence in DD and LD was 15.9 and 17.3 in D+/R−; 12 and 18 in D−/R− and 1.2 and 2.2 in R+, respectively. The HR for PTLD was 17.4 and 6.9 in D+/R− and 15.9 and 7.6 in D−/R− in DD and LD, respectively.
Conclusion: A D+/R−, compared with a D−/R− transplant, may contribute to an increase in PTLD incidence of 35 and 42% in adult DD and LD transplants, respectively.

40. Comparative analysis of post-transplant lymphoproliferative disorder after kidney transplantation versus hematopoietic stem cell transplantation

Transpl Int. 2014 Jul;27(7):721-32.

Yoon JH, Lee S, Kim HJ, Lee JW, Min WS, Chung BH, Yang CW, Kim YS, Kim JI, Moon IS, Oh EJ, Park GS, Cho SG

Summary: Post-transplant lymphoproliferative disorder (PTLD) is a major complication caused by immune-suppression after transplantation. Survival outcome is known to be poor and the characteristics are not fully understood because of its rare incidence. This single center retrospective study enrolled 41 adult PTLD patients after kidney-transplantation (KT, n = 28) and hematopoietic stem cell transplantation (HSCT, n = 13) from 1992 to 2012. We compared the characteristics and estimated the survival outcomes according to several factors [age-adjusted-IPI (aaIPI), pathologic subtype, viral status, extranodal manifestation] and added some significant parameters to aaIPI scoring system. Post-HSCT-PTLD patients were younger and showed earlier onset, and viral status was more frequently identified. Ten-year OS of the entire group was 44% but the 10-year OS was not significantly different between post-KT-PTLD and post-HSCT-PTLD (39% vs. 56%, P = 0.860). The time onset of PTLD and viral statuses were not meaningful, however, aaIPI, age > 50, extranodal manifestation and monomorphic subtype were predictive for OS. We used those factors for PTLD-specific scoring which showed intermediate-risk (HR = 7.1, P = 0.019) and high-risk (HR = 16.5, P = 0.001) presented worse OS compared to low-risk subgroup. Although the treatment strategies were heterogenous, this study showed comprehensive PTLD data between KT versus HSCT, and our PTLD-specific scoring might be validated by another larger studies.

41. Incidence and long-term outcomes of squamous cell bladder cancer after deceased donor renal transplantation

Clin Transplant 2013: 27: E665–E668 DOI: 10.1111/ctr.12245

Davis NF, McLoughlin LC, Dowling C, Power R, Mohan P, Hickey D, Smyth G, Eng M, Little DM

Objective: To review the incidence and long-term outcomes of squamous cell carcinoma (SCC) of the bladder in patients after kidney transplantation.

Methods: Between January 1976 and March 2013, five patients from one center (0.0013%) developed SCC of the bladder after undergoing a deceased donor kidney transplant. Their relevant risk factors included long-term self-intermittent catheterization/indwelling catheter (n = 2), smoking history (n = 2), and a prior history of cyclophosphamide treatment for vasculitis (n = 1). Primary outcome variables were overall patient survival and latency period between transplantation and SCC diagnosis.

Results: The duration of long-term follow-up was 94 ± 89 (range: 4–239) months. The latency period between transplantation and bladder SCC was 87 ± 87 (range: 2–228) months, and all five patients were immunosuppressed with tacrolimus, mycophenolate mofetil, and prednisone. Four patients had suspected metastases upon presentation, and one patient presented with organ-confined disease. This patient underwent a radical cystectomy and remains disease free eight months post-operatively. Despite radical treatment, the remaining four patients died from metastatic disease 7 ± 4.4 (range: 2–11) months after their initial diagnosis.

Conclusion: SCC of the bladder has a poor prognosis particularly in renal transplant patients. Early detection with flexible cystourethroscopy in patients with risk factors for SCC may improve long-term outcomes in this patient cohort.

42. Renal Cell Carcinoma in the Native and Allograft Kidneys of Renal Transplant Recipients
J Urol. 2011 Jul;186(1):219-23
Leveridge M, Musquera M, Evans A, Cardella C, Pei Y, Jewett M, Robinette M, Finelli A

Purpose: Renal cell carcinoma develops in renal transplant recipients 30 or more times more commonly than in the general population. We assessed the prevalence, histology and outcome of renal cell carcinoma in a large, single center recipient population.
Materials and Methods: We examined outcomes in patients who underwent renal transplantation at our center to determine the prevalence, histology and outcome of those in whom renal cell carcinoma developed.
Results: A total of 3,568 patients received a renal allograft at our institution between 1966 and 2009. A total of 45 renal cell carcinomas were diagnosed in the native kidney of 39 patients (1.1%) and in 8 (0.2%) renal cell carcinoma developed in the allograft kidney. Mean age at diagnosis was 51.6 and 48.2 years in patients with native kidney and allograft tumors, respectively. The mean interval between transplantation and the native or allograft renal cell carcinoma diagnosis was 10.6 and 12.1 years, respectively. Clear cell renal cell carcinoma was the most common tumor histology in native kidneys, diagnosed in 21 cases, while papillary renal cell carcinoma was diagnosed in 20. Five allograft tumors were papillary renal cell carcinoma and 3 were clear cell renal cell carcinoma. Native kidney tumors were managed by radical nephrectomy in 44 or by observation after biopsy. Allograft tumors were managed by transplant nephrectomy in 3 cases, radio frequency ablation in 3 and partial nephrectomy in 2. At a mean 6.6-year followup 32 patients with native kidney renal cell carcinoma were alive while 7 with allograft tumors were alive at a mean 3.6-year followup.
Conclusions: Renal cell carcinoma is more prevalent in patients with renal transplantation than the general population, although the subtype distribution differs. Excellent survival is seen at more than 6 years after treatment.

43. Bladder Cancer in Renal Allograft Recipients: Risk Factors and Outcomes

Transplant Proc. 2014 Dec;46(10):3466-73.

Medani S, O'Kelly P, O'Brien KM, Mohan P, Magee C, Conlon P

Background: Solid organ transplant recipients have an increased cancer risk owing to immunosuppression and oncogenic viral infections. We report on the incidence and types of bladder cancer in kidney transplant recipients in Ireland, describing possible additional risk factors and outcomes in these patients.

Methods: We identified kidney transplant recipients diagnosed with de novo bladder cancer between January 1, 1994, and July 31, 2012, by integrating data from the Irish National Cancer Registry and National Renal Transplant Registry. We calculated the standardized incidence ratio (SIR) and examined patient and tumor characteristics and 1-year survival rate.

Results: Fifteen patients were diagnosed with de novo bladder cancer during the study period, representing 0.48% of kidney transplant recipients. The SIR was 2.5 (95% CI, 1.4-4.2; $P < .001$). The mean interval between transplantation and diagnosis of bladder tumor was 8.6 years and mean age at time of diagnosis was 55.7 years. Sixty percent of patients were male. The tumor types were transitional cell carcinoma (9 patients), squamous cell carcinoma (3 patients), adenocarcinoma (1 patient), carcinoma in situ (1 patient), and diffuse large B-cell lymphoma (1 patient). Beside immunosuppression, risk factors associated with bladder cancer were urogenital disease (6 patients), cyclophosphamide exposure (2 patients), BK nephropathy (1 patient), analgesic nephropathy (1 patient), and extensive smoking (1 patient). Eight patients underwent radical cystectomy for invasive tumors, with resection of other pelvic organs in 7 patients. Mortality rate within the first year was 40%.

Conclusion: Bladder cancer occurred more commonly in kidney transplant recipients with a predominance of aggressive tumors and a high mortality. In patients with preexisting risk factors such as urologic abnormalities and cyclophosphamide exposure careful assessment before transplantation and vigilant monitoring posttransplantation with a low threshold for cystoscopy may improve outcomes.

44. Cumulative Doses of T-Cell Depleting Antibody and Cancer Risk after Kidney Transplantation
PLoS One. 2015 Nov 10;10(11):e0139479. doi: 10.1371/journal.pone.0139479. eCollection 2015.
Chen JH, Wong G, Chapman JR, Lim WH

Abstract: T-cell depleting antibody is associated with an increased risk of cancer after kidney transplantation, but a dose-dependent relationship has not been established. This study aimed to determine the association between cumulative doses of T-cell depleting antibody and the risk of cancer after kidney transplantation. Using data from the Australian and New Zealand Dialysis and Transplant Registry between 1997–2012, we assessed the risk of incident cancer and cumulative doses of T-cell depleting antibody using adjusted Cox regression models. Of the 503 kidney transplant recipients with 2835 person-years of follow-up, 276 (55%), 209 (41%) and 18 (4%) patients received T-cell depleting antibody for induction, rejection or induction and rejection respectively. The overall cancer incidence rate was 1,118 cancers per 100,000 patient-years, with 975, 1093 and 1377 cancers per 100,000 patient-years among those who had received 1–5 doses, 6–10 doses and >10 doses, respectively. There was no association between cumulative doses of T cell depleting antibody and risk of incident cancer (1–5: referent, 6–10: adjusted hazard ratio (HR) 1.19, 95%CI 0.48–2.95, >10: HR 1.42, 95%CI 0.50–4.02, p = 0.801). This lack of association is contradictory to our hypothesis and is likely attributed to the low event rates resulting in insufficient power to detect significant differences.

45. Antithymocyte Globulin Induction in Living Donor Renal Transplant Recipients: Final Report of the TAILOR Registry

Transplantation. 2012 Aug 27;94(4):331-7

Gaber AO1, Matas AJ, Henry ML, Brennan DC, Stevens RB, Kapur S, Ilsley JN, Kistler KD, Cosimi AB; Thymoglobulin Antibody Immunosuppression in Living Donor Recipients Investigators

Background: The Thymoglobulin Antibody Immunosuppression in LivingDonor Recipients registry was established to assess clinical experience with rabbit antithymocyte globulin (rATG; Thymoglobulin) in living donor renal transplant recipients.
Methods: From 2003 to 2008, US transplant centers prospectively entered information on patients who received rATG induction. In addition to standard United Network for Organ Sharing registry data elements, information was collected regarding immunosuppression, viral prophylaxis, acute rejection, and adverse events.
Results: Data on 2322 patients from 49 transplant centers were enrolled and met inclusion criteria for analysis. Patient and graft survival were 99.3% and 99.0% at 6 months and 98.4% and 98.2% at 12 months as recorded in Thymoglobulin Antibody Immunosuppression in Living Donor Recipients registry and were 91.5% and 83.2% at 5 years by Kaplan-Meier estimates based on linked United Network for Organ Sharing registry records. Freedom from rejection was 93.6% through 5 years. Mean rATG cumulative dose was 5.29 mg/kg. More than one-third of patients (37.6%) were steroid-free at discharge, and nearly half of patients (48%) were steroid-free at 12 months.
Before discharge, 3.2% experienced serious adverse events, with 11 events (0.005%) reported as possibly or probably related to rATG. Incidence of cytomegalovirus infection was 4.2% at 12 months, and 99.1% of patients were posttransplant lymphoproliferative disorder-free through 5 years.
Conclusions: rATG induction in living donor renal transplantation is safe and associated with a low incidence of acute rejection and posttransplantation complications.

46. Association of Antibody Induction Immunosuppression With Cancer After Kidney Transplantation

Transplantation 2015;99: 1051–1057

Hall EC, Engels EA, Pfeiffer RM, Segev DL

Background: Induction immunosuppression is a mainstay of rejection prevention after transplantation. Studies have suggested a connection between antibody induction agents and cancer development, potentially limiting important immunosuppression protocols.
Methods: We used a linkage of U.S. transplantation data and cancer registries to explore the relationship between induction and cancer after transplantation. A total of 111,857 kidney recipients (1987–2009) in the Transplant Cancer Match Study, which links the Scientific Registry for Transplant Recipients and U.S. Cancer Registries, were included. Poisson regression models were used to estimate adjusted incidence rate ratios (aIRR) of non–Hodgkin lymphoma (NHL) and other cancers with increased incidence after transplantation (lung, colorectal, kidney, and thyroid cancers, plus melanoma).
Results: Two thousand seven hundred sixty-three cancers of interest were identified. Muromonab-CD3 was associated with increased NHL (aIRR, 1.37; 95% CI, 1.06–1.76). Alemtuzumab was associated with increased NHL (aIRR, 1.79; 95% CI, 1.02–3.14), colorectal cancer (aIRR, 2.46; 95% CI, 1.03–5.91), and thyroid cancer (aIRR, 3.37; 95% CI, 1.55–7.33). Polyclonal induction was associated with increased melanoma (aIRR, 1.50; 95%CI, 1.06–2.14).
Conclusion: Our findings highlight the relative safety with regard to cancer risk of the most common induction therapies, the need for surveillance of patients treated with alemtuzumab, and the possible role for increased melanoma screening for those patients treated with polyclonal anti–T-cell induction.

47. Effect of Immunosuppression for Primary Renal Disease on the Risk of Cancer in Subsequent Renal Transplantation: A Population-Based Retrospective Cohort Study

Transplantation. 2013 Jan 15;95(1):122-7.

Hibberd AD, Trevillian PR, Wlodarczyk JH, Kemp DG, Stein AM, Gillies AH, Heer MK, Sheil AG

Background: To measure the risk of cancer in renal transplantation for recipients who had previously been treated with immunosuppressive agents for primary renal disease.
Methods: A retrospective population-based cohort study of 5970 renal transplant recipients in Australia registered on the Australia and New Zealand Dialysis and Transplant Registry between 1982 and 1997 and followed until 2007. Data about the incidence of a range of cancer types from this Registry were compared with cancer incidence data for the general population matched for cancer type, year of incidence, age, and gender derived from national cancer records. Outcome measures for each cancer group with or without pretransplantation immunosuppression were cancer-specific standardized incidence ratios and a multivariate hazard ratio (HR) standardized to 1.
Results: For those treated with pretransplantation immunosuppression, the risks for four cancer groups during renal transplantation were significantly increased: anogenital cancer (HR, 3.13; confidence interval [CI], 1.92Y5.11; PG0.0001), non-Hodgkin's lymphoma (HR, 2.37; CI, 1.53-3.68; P=0.0001), breast cancer (HR, 2.52; CI, 1.13-5.61; P=0.024), and urinary tract cancer (excluding kidney) (HR, 1.84; CI, 1.13-3.01; P=0.015). However, the risks of cancer in the oral cavity and pharynx, kidney, thyroid, colon, leukemia, lung, melanoma, prostate, and stomach were not significantly increased.
Conclusions: Pretransplantation immunosuppression for primary renal disease increases the risks of four cancer types in renal transplantation while sparing the others. Patients in whom this treatment is being considered should be informed of these risks.

48. Acute Rejection, T-Cell-Depleting Antibodies, and Cancer After Transplantation

Transplantation. 2014 Apr 27;97(8):817-25

Lim WH, Turner RM, Chapman JR, Ma MK, Webster AC, Craig JC, Wong G

Background: Systemic inflammatory response has been shown to play a vital role in carcinogenesis and tumor progression. Acute rejection is a systemic inflammatory state and may share a common casual pathway for cancer development after transplantation. The increased burden of immunosuppression used in the treatment of acute rejection, particularly the use of T-cell-depleting antibody may further heighten the risk of cancer development. We aimed to determine the association between acute rejection, T-cell-depleting antibody use and cancer risk after kidney transplantation.

Methods: Using the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), we assessed the risk of incident cancer among those who had experienced rejection stratified by the use of T-cell-depleting antibody using adjusted Cox proportional hazard and competing risk models.

Results: A total of 7153 kidney transplant recipients between 1997 and 2009 were included. A total of 467 (6.5%) recipients developed cancers. Recipients who experienced acute rejection and treated with T-cell-depleting antibody were at a 1.4-fold increased risk of cancer (adjusted hazard ratio [HR] 1.42, 95% CI 1.02-1.99, P=0.039) compared with those who did not experience acute rejection. There was an excess risk of genitourinary tract cancers among recipients who had experienced rejection requiring T-cell-depleting antibody compared with recipients who did not experience acute rejection (HR 2.20, 95% CI 1.33-3.66, P=0.007).

Conclusion: Acute rejection requiring T-cell-depleting antibody is a significant risk factor for cancer development in kidney transplant recipients independent of competing events such as age and cardiovascular deaths.

49. Belatacept for kidney transplant recipients (Review)
Cochrane Database Syst Rev. 2014 Nov 24;11:CD010699
Masson P, Henderson L, Chapman JR, Craig JC, Webster AC

Background: Most people who receive a kidney transplant die from either cardiovascular disease or cancer before their transplant fails. The most common reason for someone with a kidney transplant to lose the function of their transplanted kidney necessitating return to dialysis is chronic kidney transplant scarring. Immunosuppressant drugs have side effects that increase risks of cardiovascular disease, cancer and chronic kidney transplant scarring. Belatacept may provide sufficient immunosuppression while avoiding unwanted side effects of other immunosuppressant drugs. However, high rates of post-transplant lymphoproliferative disease (PTLD) have been reported when belatacept is used in particular kidney transplant recipients at high dosage.
Objectives: 1) Compare the relative efficacy of belatacept versus any other primary immunosuppression regimen for preventing acute rejection, maintaining kidney transplant function, and preventing death. 2) Compare the incidence of several adverse events: PTLD; other malignancies; chronic transplant kidney scarring (IF/TA); infections; change in blood pressure, lipid and blood sugar control. 3) Assess any variation in effects by study, intervention and recipient characteristics, including: differences in pre-transplant Epstein Barr virus serostatus; belatacept dosage; and donor-category (living, standard criteria deceased, or extended criteria deceased).
Search methods: We searched the Cochrane RenalGroup's Specialised Register to 1 September 2014 through contact with the Trials' Search Coordinator using search terms relevant to this review.
Selection criteria: Randomised controlled trials (RCT) that compared belatacept versus any other immunosuppression regimen in kidney transplant recipients were eligible for inclusion.
Data collection and analysis: Two authors independently extracted data for study quality and transplant outcomes and synthesized results using random effects metaanalysis, expressed as risk ratios (RR) and mean differences (MD), both with 95% confidence intervals (CI). Subgroup analyses and univariate meta-regression were used to investigate potential heterogeneity.
Main results: We included five studies that compared belatacept and calcineurin inhibitors (CNI) that reported data from a total of 1535 kidney transplant recipients. Of the five studies, three (478 participants) compared belatacept and cyclosporin and two (43 recipients) compared belatacept and tacrolimus. Co-interventions included basiliximab (4 studies, 1434 recipients); anti-thymocyte globulin (1 study, 89 recipients); alemtuzumab (1 study, 12 recipients); mycophenolate mofetil (MMF, 5 studies, 1509 recipients); sirolimus (1 study, 26 recipients) and prednisone (5 studies, 1535 recipients).
Up to three years following transplant, belatacept and CNI-treated recipients were at similar risk of dying (4 studies, 1516 recipients: RR 0.75, 95% CI 0.39 to 1.44), losing their kidney transplant and returning to dialysis (4 studies, 1516 recipients: RR 0.91, 95% CI 0.61 to 1.38), and having an episode of acute rejection (4 studies, 1516 recipients: RR 1.56, 95% CI 0.85 to 2.86). Belatacept-treated kidney transplant recipients were 28% less likely to have chronic kidney scarring (3 studies, 1360 recipients: RR 0.72, 95% CI 0.55 to 0.94) and also had better graft function (measured glomerular filtration rate (GFR) (3 studies 1083 recipients): 10.89 mL/min/1.73 m², 95%CI 4.01 to 17.77; estimated GFR (4 studies, 1083 recipients):MD 9.96 mL/min/1.73 m², 95%CI 3.28 to 16.64) than CNItreated recipients. Blood pressure was lower (systolic (2 studies, 658 recipients): MD -7.51 mm Hg, 95% CI -10.57 to -4.46; diastolic (2 studies, 658 recipients): MD -3.07 mm Hg, 95% CI -4.83 to -1.31, lipid profile was better (non-HDL (3 studies 1101 recipients): MD -12.25 mg/dL, 95% CI -17.93 to -6.57; triglycerides (3 studies 1101 recipients): MD -24.09 mg/dL, 95% CI -44.55 to -3.64),

and incidence of new-onset diabetes after transplant was reduced by 39% (4 studies (1049 recipients): RR 0.61, 95% CI 0.40 to 0.93) among belatacept-treated versus CNI-treated recipients.
Risk of PTLD was similar in belatacept and CNI-treated recipients (4 studies, 1516 recipients: RR 2.79, 95% CI 0.61 to 12.66) and was no different among recipients who received different belatacept dosages (high versus low dosage: ratio of risk ratios (RRR) 1.06, 95% CI 0.11 to 9.80, test of difference = 0.96) or among those who were Epstein Barr virus seronegative compared with those who were seropositive before their kidney transplant (seronegative versus seropositive; RRR 1.49, 95% CI 0.15 to 14.76, test for difference = 0.73).
The belatacept dose used (high versus low), type of donor kidney the recipient received (extended versus standard criteria) and whether the kidney transplant recipient received tacrolimus or cyclosporin made no difference to kidney transplant survival, incidence of acute rejection or estimated GFR. Selective outcome reporting meant that data for some key subgroup comparisons were sparse and that estimates of the effect of treatment in these groups of recipients remain imprecise.
Authors' conclusions: There is no evidence of any difference in the effectiveness of belatacept and CNI in preventing acute rejection, graft loss and death, but treatment with belatacept is associated with less chronic kidney scarring and better kidney transplant function. Treatment with belatacept is also associated with better blood pressure and lipid profile and a lower incidence of diabetes versus treatment with a CNI.
Important side effects (particularly PTLD) remain poorly reported and so the relative benefits and harms of using belatacept remain unclear. Whether short-term advantages of treatment with belatacept are maintained over the medium- to long-term or translate into better cardiovascular outcomes or longer kidney transplant survival with function remains unclear. Longer-term, fully reported and published studies comparing belatacept versus tacrolimus are needed to help clinicians decide which patients might benefit most from using belatacept.

50. The janus face of immunosuppression – de novo malignancy after renal transplantation: the experience of the Transplantation Center Munich

Kidney Int. 2007 Jun;71(12):1271-8.

Wimmer CD, Rentsch M, Crispin A, Illner WD, Arbogast H, Graeb C, Jauch KW, Guba M

After decades of successful organ transplantation clinicians continue to be troubled by the increasing incidence of cancers under maintenance immunosuppression. In this study, we examined rates of malignancies in 2419 renal transplant recipients transplanted in our institution between 1978 and 2005. In renal transplant recipients the cumulative incidence of cancer after 25 years was 49.3% for all tumors and 39.7% excluding non-melanoma skin cancers, compared with 21% for a normal sex- and age-matched population. The most frequent tumors observed were non-melanoma skin cancers (20.5%), kidney cancers (12.0%), and cancers of the pharynx, larynx, or oral cavity (8.2%). The general increase of cancer risk was 4.3-fold. Independent risk factors for the development of a tumor were male gender, older recipient age, the presence of preformed antibodies before transplantation, and the time on immunosuppression. Interestingly, the use of IL-2-receptor antagonists significantly reduced the tumor risk of transplant recipients. The tumor risk between immunosuppressive drugs typically used for maintenance immunosuppression was not significantly different. However, mammalian target of rapamycin (mTOR) inhibitor-based immunosuppressive protocols showed a clear tendency for lower malignancy rates. De novo malignancies following renal transplantation represent a serious problem endangering the prognosis of otherwise successfully transplanted patients. Future studies will have to address whether optimized immunosuppressive regimens including mTOR-inhibitors are capable of reducing the incidence or preventing the development of posttransplant malignancies.

51. Combined introduction of anti-IL2 receptor antibodies, mycophenolic acid and tacrolimus: effect on malignancies after renal transplantation in a single-centre retrospective cohort study

Nephrol Dial Transplant (2012) 27: 2547–2553

Braconnier P, Del Marmol V, Broeders N, Kianda M, Massart A, Lemy A, Ghisdal L, Le Moine A, Madhoun P, Racapé J, Abramowicz D, Wissing KM.

Background: Several studies suggest that the introduction of tacrolimus (TRL), mycophenolic acid (MPA) and interleukin 2 receptor antibodies (IL2Ra) as single drugs more than a decade ago has not increased the risk of malignancy after renal transplantation. However, only limited data are available on their carcinogenic effects when used in combination as a potent immunosuppressive regimen.
Methods: A retrospective single-centre cohort study on 929 adult renal transplant recipients. Investigation of the effect of two consecutive immunosuppressive regimens [1993–98, N = 405, anti-lymphocyte antibodies, cyclosporine and azathioprine (AZA); 1999–2007, N = 524, predominantly IL2Ra, TRL and MPA] on the incidence rate of skin cancer, solid tumours and post-transplant lymphoproliferative disease (PTLD).
Results: In total, 365 malignancies developed among 113 patients. As compared to the previous cyclosporine and AZA-based immunosuppression, the introduction of the new immunosuppressive regimen did not increase the incidence rate of skin cancer [rate ratio 0.84; 95% confidence interval (CI) 0.48–1.46], solid tumours (0.89; 95% CI 0.46–1.67) and PTLD (0.82; 95% CI 0.28–2.21). Patients treated with the more recent regimens less frequently developed multiple skin cancers and invasive squamous cell cancer. Skin cancer after transplantation was strongly associated with the development of solid tumours (odds ratio 5.2; $P < 0.0001$). The introduction of the new immunosuppressive drugs reduced the incidence of first year acute rejection from 34.8 to 13.2% ($P < 0.0001$).
Conclusion: Although significantly more efficient in the prevention of acute rejection, the introduction of TRL, MPA and IL2Ra-based immunosuppression after kidney transplantation was not associated with an increased incidence of skin cancer, solid tumours or PTLD.

52. Cancer risk with alemtuzumab following kidney transplantation

Clin Transplant 2013: 27: E264–E271 DOI: 10.1111/ctr.12094

Puttarajappa C, Yabes J, Bei L, Shah N, Bernardo J, McCauley J, Basu A, Tan H, Shapiro R, Unruh M, Wu C

Abstract: Alemtuzumab has been employed for induction therapy in kidney transplantation with low rates of acute rejection and excellent graft and patient survival. Antibody induction therapy has been linked to increased vulnerability to cancer. Data regarding malignancy rates with alemtuzumab are limited. We studied 1350 kidney transplant recipients (between 2001 and 2009) at the University of Pittsburgh Starzl Transplant Institute, for post-transplant de novo and recurrent malignancy, excluding non-melanoma skin cancer, among patients receiving alemtuzumab, thymoglobulin, and no induction therapies. Of the 1350 patients, 1002 (74.2%) received alemtuzumab, 205 (15.2%) received thymoglobulin, and 122 (9%) received no induction therapy. After excluding cancers occurring within 60 d post-transplantation, 43 (3.25%) malignancies were observed during a median follow-up time of 4.0 yr. The incidence of malignancy was 5.4% (1.09 per 100 patient-years [PY]) with thymoglobulin, 2.8% (0.74 per 100 PY) with alemtuzumab, and 3.3% (0.66 per 100 PY) with no induction (across all groups; p = 0.2342, thymoglobulin vs. alemtuzumab; p = 0.008). Thus, with the exception of non-melanoma skin cancer which we did not evaluate, alemtuzumab induction was not associated with increased cancer incidence post-kidney transplantation when compared to no induction therapy and was associated with lower cancer incidence when compared to thymoglobulin.

53. Spectrum of Cancer Risk Among US Solid Organ Transplant Recipients

JAMA. 2011 Nov 2;306(17):1891-901.

Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ, Wolfe RA, Goodrich NP, Bayakly AR, Clarke CA, Copeland G, Finch JL, Fleissner ML, Goodman MT, Kahn A, Koch L, Lynch CF, Madeleine MM, Pawlish K, Rao C, Williams MA, Castenson D, Curry M, Parsons R, Fant G, Lin M.

Context: Solid organ transplant recipients have elevated cancer risk due to immunosuppression and oncogenic viral infections. Because most prior research has concerned kidney recipients, large studies that include recipients of differing organs can inform cancer etiology.
Objective: To describe the overall pattern of cancer following solid organ transplantation.
Design, Setting, and Participants: Cohort study using linked data on solid organ transplant recipients from the US Scientific Registry of Transplant Recipients (1987-2008) and 13 state and regional cancer registries.
Main Outcome Measures: Standardized incidence ratios (SIRs) and excess absolute risks (EARs) assessing relative and absolute cancer risk in transplant recipients compared with the general population.
Results: The registry linkages yielded data on 175,732 solid organ transplants (58.4% for kidney, 21.6% for liver, 10.0% for heart, and 4.0% for lung). The overall cancer risk was elevated with 10,656 cases and an incidence of 1375 per 100,000 person-years (SIR, 2.10 [95% CI, 2.06-2.14]; EAR, 719.3 [95% CI, 693.3-745.6] per 100,000 person-years). Risk was increased for 32 different malignancies, some related to known infections (eg, anal cancer, Kaposi sarcoma) and others unrelated (eg, melanoma, thyroid and lip cancers). The most common malignancies with elevated risk were non-Hodgkin lymphoma (n = 1504; incidence: 194.0 per 100,000 person-years; SIR, 7.54 [95% CI, 7.17-7.93]; EAR, 168.3 [95% CI, 158.6-178.4] per 100,000 person-years) and cancers of the lung (n = 1344; incidence: 173.4 per 100,000 person-years; SIR, 1.97 [95% CI, 1.86-2.08]; EAR, 85.3 [95% CI, 76.2-94.8] per 100,000 person-years), liver (n = 930; incidence: 120.0 per 100,000 person-years; SIR, 11.56 [95% CI, 10.83-12.33]; EAR, 109.6 [95% CI, 102.0-117.6] per 100,000 person-years), and kidney (n = 752; incidence: 97.0 per 100,000 person-years; SIR, 4.65 [95% CI, 4.32-4.99]; EAR, 76.1 [95% CI, 69.3-83.3] per 100,000 person-years). Lung cancer risk was most elevated in lung recipients (SIR, 6.13 [95% CI, 5.18-7.21]) but also increased among other recipients (kidney: SIR, 1.46 [95% CI, 1.34-1.59]; liver: SIR, 1.95 [95% CI, 1.74-2.19]; and heart: SIR, 2.67 [95% CI, 2.40-2.95]). Liver cancer risk was elevated only among liver recipients (SIR, 43.83 [95% CI, 40.90-46.91]), who manifested exceptional risk in the first 6 months (SIR, 508.97 [95% CI, 474.16-545.66]) and a 2-fold excess risk for 10 to 15 years thereafter (SIR, 2.22 [95% CI, 1.57-3.04]). Among kidney recipients, kidney cancer risk was elevated (SIR, 6.66 [95% CI, 6.12-7.23]) and bimodal in onset time. Kidney cancer risk also was increased in liver recipients (SIR, 1.80 [95% CI, 1.40-2.29]) and heart recipients (SIR, 2.90 [95% CI, 2.32-3.59]).
Conclusion: Compared with the general population, recipients of a kidney, liver, heart, or lung transplant have an increased risk for diverse infection-related and unrelated cancers.

54. Cancer Risk After ABO-Incompatible Living-Donor Kidney Transplantation

Transplantation 2013;96: 476-479

Hall EC, Engels EA, Montgomery RA, Segev DL

Background: Recipients of ABO-incompatible (ABOi) living-donor kidney transplants often undergo more intense immunosuppression than their ABO-compatible counterparts. It is unknown if this difference leads to higher cancer risk after transplantation. Single-center studies are too small and lack adequate duration of follow-up to answer this question.
Methods: We identified 318 ABOi recipients in the Transplant Cancer Match Study, a national linkage between the Scientific Registry of Transplant Recipients and population-based U.S. cancer registries. Seven cancers (non-Hodgkin lymphoma, Merkel cell carcinoma, gastric adenocarcinoma, hepatocellular carcinoma, thyroid cancer, pancreatic cancer, and testicular cancer) were identified among ABOi recipients. We then matched ABOi recipients to ABO-compatible controls by age, gender, race, human leukocyte antigen mismatch, retransplantation, and transplant year.
Results: There was no demonstrable association between ABOi and cancer in unadjusted (incidence rate ratio, 0.83; 95% confidence interval, 0.33Y1.71; P=0.3) or matched control (incidence rate ratio, 0.99; 95% confidence interval, 0.38Y2.23; P=0.5) analyses.
Conclusion: To the extent that could be determined in this registry study, current desensitization protocols are not associated with increased risk of cancer after transplantation.

55. Cumulative Incidence of Cancer After Solid Organ Transplantation

Cancer. 2013 Jun 15;119(12):2300-8.

Hall EC, Pfeiffer RM, Segev DL, Engels EA

Background: Solid organ transplantation recipients have elevated cancer incidence. Estimates of absolute cancer risk after transplantation can inform prevention and screening.
Methods: The Transplant Cancer Match Study links the US transplantation registry with 14 state/regional cancer registries. The authors used nonparametric competing risk methods to estimate the cumulative incidence of cancer after transplantation for 2 periods (1987-1999 and 2000-2008). For recipients from 2000 to 2008, the 5-year cumulative incidence, stratified by organ, sex, and age at transplantation, was estimated for 6 preventable or screen-detectable cancers.
For comparison, the 5-year cumulative incidence was calculated for the same cancers in the general population at representative ages using Surveillance, Epidemiology, and End Results data.
Results: Among 164,156 recipients, 8520 incident cancers were identified. The absolute cancer risk was slightly higher for recipients during the period from 2000 to 2008 than during the period from 1987 to 1999 (5-year cumulative incidence: 4.4% vs 4.2%; P5.006); this difference arose from the decreasing risk of competing events (5-year cumulative incidence of death, graft failure, or retransplantation: 26.6% vs 31.9%; P<.001). From 2000 to 2008, the 5-year cumulative incidence of non-Hodgkin lymphoma was highest at extremes of age, especially in thoracic organ recipients (ages 0-34 years: range, 1.74%-3.28%; aged >50 years; range, 0.36%-2.22%). For recipients aged >50 years, the 5-year cumulative incidence was higher for colorectal cancer (range, 0.33%-1.94%) than for the general population at the recommended screening age (aged 50 years: range, 0.25%-0.33%). For recipients aged >50 years, the 5-year cumulative incidence was high for lung cancer among thoracic organ recipients (range, 1.16%-3.87%) and for kidney cancer among kidney recipients (range, 0.53%-0.84%). The 5-year cumulative incidence for prostate cancer and breast cancer was similar or lower in transplantation recipients than at the recommended ages of screening in the general population.
Conclusions: Subgroups of transplantation recipients have a high absolute risk of some cancers and may benefit from targeted prevention or screening.

56. Cancer after Kidney Transplantation in the United States
Am J Transplant. 2004 Jun;4(6):905-13
Kasiske BL, Snyder JJ, Gilbertson DT, Wang C

Previous reports of cancer after kidney transplantation have been limited by small numbers of patients in single-center studies and incomplete ascertainment of cases in large registries.
We examined rates of malignancies among first-time recipients of deceased or living donor kidney transplantations in 1995–2001 (n = 35 765) using Medicare billing claims.
For most common tumors, e.g. colon, lung, prostate, stomach, esophagus, pancreas, ovary and breast, cancer rates were roughly twofold higher after kidney transplantation compared with the general population. Melanoma, leukemia, hepatobiliary tumors, cervical and vulvovaginal tumors were each approximately fivefold more common. Testicular and bladder cancers were increased approximately threefold, while kidney cancer was approximately 15-fold more common. Kaposi's sarcoma, non-Hogkin's lymphomas, and nonmelanoma skin cancers were more than 20-fold increased than in the general population. Compared with patients on the waiting list, several tumors were more common after transplantation ($p < 0.01$): nonmelanoma skin cancers (2.6-fold), melanoma (2.2-fold), Kaposi's sarcoma (9.0-fold), non-Hodgkin's lymphoma (3.3-fold), cancer of the mouth (2.2-fold), and cancer of the kidney (39% higher). The rates for most malignancies are higher after kidney transplantation compared with the general population. Cancer should continue to be a major focus of prevention in kidney transplantation.

57. Posttransplant Malignancies in Solid Organ Adult Recipients: An Analysis of the U.S. National Transplant Database

Transplantation 2012;94: 990-998

Sampaio MS, Cho YW, Qazi Y, Bunnapradist S, Hutchinson IV, Shah T.

Background: De novo posttransplant malignancy (PTM) is a serious complication of transplantation. Incidences may vary among solid organ transplantations (SOTs) and may take to particular screening recommendations and posttransplantation care.
Methods: Adult recipients, from the U.S. Organ Procurement Transplant Network/United Network for Organ Sharing database (data as of September 3, 2010), of a primary kidney transplantation (KT), liver transplantation (LT), heart transplantation (HT) or lung transplantation (LuT) performed in the United States between 1999 and 2008 were selected. Multiple-organ recipients and those whose grafts failed within 2 weeks after transplantation were excluded. The incidence of PTM (in 1000 person-years) was estimated using the Kaplan-Meier product-limit method and compared with SOT and the general population.
Results: The cohort included 193,905 recipients (123,380 KT; 43,106 LT; 16511 HT; and 10,908 LuT). PTM incidence was 8.03, 11.0, 14.3, and 19.8 in KT, LT, HT, and LuT, respectively. In general, PTM recipients were 3 to 5 years older, mostly whites, and are males in all SOTs. In KT, the type of cancer with the highest incidence was posttransplant lymphoproliferative disorder (PTLD, 1.58%), followed by lung (1.12%), prostate (0.82%), and kidney (0.79%) cancers; in LT, PTLD (2.44%), lung and bronchial (2.18%), primary hepatic (0.91%), and prostate (0.88%) cancers; in HT, lung and bronchial (3.24%) and prostate (3.07%) cancers, and PTLD (2.24%); and in LuT, lung and bronchial cancers (5.94%), PTLD (5.72%), and colorectal cancer (1.38%). PTLD, Kaposi sarcoma, and lung and bronchial cancers were increased in all SOTs, when compared with an older (55- to 59-year-old) population.
Conclusions: Cancer incidence is different among solid organ transplantations, and ratios may be higher than those in the 55- to 59-year-old population.

58. Comparison of cancer diagnoses between the US solid organ transplant registry and linked central cancer registries

Am J Transplant. 2016 Apr 7.

Yanik EL, Nogueira LM, Koch L, Copeland G, Lynch CF, Pawlish KS, Finch JL, Kahn AR, Hernandez BY, Segev DL, Pfeiffer RM, Snyder JJ, Kasiske BL, Engels EA

Abstract: US transplant centers are required to report cancers in transplant recipients to the transplant network. The accuracy and completeness of these data, collected in the Scientific Registry of Transplant Recipients (SRTR), are unknown. We compared diagnoses in the SRTR and 15 linked cancer registries, for colorectal, liver, lung, breast, prostate, and kidney cancers, melanoma, and non-Hodgkin lymphoma (NHL). Among 187,384 transplants, 9323 cancers were documented in the SRTR or cancer registries. Only 36.8% of cancers were in both, with 47.5% and 15.7% of cases additionally documented solely in cancer registries or the SRTR, respectively. Agreement between the SRTR and cancer registries varied (kappa: 0.28 for liver cancer, 0.52-0.66 for lung, prostate, kidney, colorectum and breast cancers). Upon evaluation, some NHLs documented only in cancer registries were identified in the SRTR as another type of post-transplant lymphoproliferative disorder. Some SRTR-only cases were explained by miscoding (colorectal cancer instead of anal cancer, metastases as lung or liver cancers) or missed matches with cancer registries, partly due to out-migration from their catchment areas. Estimated sensitivity for identifying cancer was 52.5% for the SRTR and 84.3% for cancer registries. In conclusion, SRTR cancer data are substantially incomplete, limiting their usefulness for surveillance and research.

59. Influence of Current and Previous Smoking on Cancer and Mortality After Kidney Transplantation

Transplantation 2016;100: 227–232

Opelz G, Döhler B

Background: Evidence is limited regarding the effect of stopping smoking before kidney transplantation.
Methods: Collaborative Transplant Study data from 46 548 recipients of first kidney transplants (1995-2012) were analyzed to 10 years after transplantation.
Results: Compared with patients who had never smoked (n = 31,462), patients who stopped smoking before transplantation (n = 10,291) only had a modestly increased risk of all-cause graft failure (hazard ratio [HR], 1.1; 95% confidence interval [95%CI], 1.0-1.1; P < 0.001) or death (HR,1.1; 95%CI, 1.0-1.2; P < 0.001) and a similar risk of death-censored graft failure (HR,1.0, 95%CI, 1.0-1.1; P = 0.19), but a 40%increase in death from malignancy (HR, 1.4; 95% CI, 1.2-1.7; P < 0.001). The risk of events was generally markedly higher in patients who continued to smoke (n = 4795) versus those who had stopped. For tumors of the lip, oral cavity and pharynx, digestive organs, respiratory tract, female genitalia and urinary tract, HR values increased significantly from never-smoked to former smokers to current smokers. The risk of respiratory tumors or cervical cancer was approximately halved when smoking was stopped versus continued.
Conclusions: This large series provides clear evidence that patients who stop smoking before transplantation experience substantial benefits, including a substantial reduction in certain types of malignancy.

60. Treatment of Kidney Transplant Recipients With ACEi/ARB and Risk of Respiratory Tract Cancer: A Collaborative Transplant Study Report

Am J Transplant. 2011 Nov;11(11):2483-9.

Opelz G, Döhler B

Whether treatment with angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARB) increases the risk of cancer is controversial. Collaborative transplant study data were analyzed according to whether kidney transplant recipients were treated with ACEi/ARB at year 1. Twenty-four thousand and ninety patients were studied of whom 9079 (38%) patients received ACEi/ARB. There were 872 nonskin malignancies during years 2–8 posttransplant, including 107 respiratory/intrathoracic tumors. The standardized incidence ratio (SIR) for all nonskin malignancies was similar between the ACEi/ARB (1.91) and no ACEi/ARB (1.81) groups ($p = 0.42$). For respiratory/ intrathoracic tumors, however, SIR was significantly higher with ACEi/ARB (1.65 vs. 1.09 for no ACEi/ARB, $p=0.033$). Multivariate Cox regression analysis showed that ACEi/ARB treatment was not associated with an increased risk of respiratory/intrathoracic tumors in nonsmokers. In patients with a history of smoking, however, the risk of respiratory/intrathoracic tumors was 2.77 (95% CI 1.19–6.43, $p = 0.018$) in patients without ACEi/ARB treatment as compared to 7.10 (95% CI 3.27–15.4, $p < 0.001$) in patients treated with ACEi/ARB. Our data indicate that in kidney transplant recipients, ACEi/ARB treatment is associated with a significant increase in the rate of respiratory/intrathoracic tumors in the subpopulation of patients with a history of smoking.

61. Epidemiology of de novo malignancies after solidorgan transplantation: Immunosuppression, infection and other risk factors

Best Pract Res Clin Obstet Gynaecol. 2014 Nov;28(8):1251-65.

Piselli P, Verdirosi D, Cimaglia C, Busnach G, Fratino L, Ettorre GM, De Paoli P, Citterio F, Serraino D.

Abstract: Organ transplantation is an increasingly used medical procedure for treating otherwise fatal end-stage organ diseases, and a large number of anti-rejection drugs have been developed to prolong long-term survival of both the individual and the transplanted organ. However, the prolonged use of immunosuppressive drugs is well known to increase the risk of opportunistic diseases, particularly infections and virus-related malignancies. Although transplant recipients experience a nearly twofold elevated risk for all types of de novo cancers, persistent infections with oncogenic viruses are associated with up to hundredfold increased risks. Women of the reproductive age are growing in number among the recipients of solid-organ transplants, but specific data on cancer outcomes are lacking. This article updates evidences linking iatrogenic immunosuppression, persistent infections with oncogenic viruses, other risk factors and post-transplant malignancies. Epidemiological aspects, tumourigenesis related to oncogenic viruses, clinical implications, as well as primary and secondary prevention issues are discussed to offer clinicians and researchers alike an update of an increasingly important topic.

62. Polycystic Kidney Disease and Cancer after Renal Transplantation

J Am Soc Nephrol 25: 2335–2341, 2014

Wetmore JB, Calvet JP, Yu AS, Lynch CF, Wang CJ, Kasiske BL, Engels EA

Abstract: Autosomal dominant polycystic kidney disease (ADPKD), the most common form of polycystic kidney disease (PKD), is a disorder with characteristics of neoplasia. However, it is not known whether renal transplant recipients with PKD have an increased risk of cancer. Data from the Scientific Registry of Transplant Recipients, which contains information on all solid organ transplant recipients in the United States, were linked to 15 population-based cancer registries in the United States. For PKD recipients, we compared overall cancer risk with that in the general population. We also compared cancer incidence in PKD versus non-PKD renal transplant recipients using Poisson regression, and we determined incidence rate ratios (IRRs) adjusted for age, sex, race/ethnicity, dialysis duration, and time since transplantation. The study included 10,166 kidney recipients with PKD and 107,339 without PKD. Cancer incidence in PKD recipients was 1233.6 per 100,000 person-years, 48% higher than expected in the general population (standardized incidence ratio, 1.48; 95% confidence interval [95% CI], 1.37 to 1.60), whereas cancer incidence in non-PKD recipients was 1119.1 per 100,000 person-years. The unadjusted incidence was higher in PKD than in non-PKD recipients (IRR, 1.10; 95% CI, 1.01 to 1.20). However, PKD recipients were older (median age at transplantation, 51 years versus 45 years for non-PKD recipients), and after multivariable adjustment, cancer incidence was lower in PKD recipients than in others (IRR, 0.84; 95% CI, 0.77 to 0.91). The reason for the lower cancer risk in PKD recipients is not known but may relate to biologic characteristics of ADPKD or to cancer risk behaviors associated with ADPKD.

63. Time on Dialysis and Cancer Risk After Kidney Transplantation

Transplantation 2013;95: 114-121

Wong G, Turner RM, Chapman JR, Howell M, Lim WH, Webster AC, Craig JC.

Background: Increasing time on dialysis is an established risk factor for certain cancer types for patients on dialysis, but the relationship between the time on dialysis and cancer risk after transplantation is unclear. We aimed to determine if the length of time on maintenance dialysis before the first kidney transplantation was associated with the risk of site-specific and overall incident cancers after transplantation.

Methods: Using the Australia and New Zealand Dialysis and Transplant Registry, we assessed the association between both all cancers (except for nonmelanocytic skin cancers) and site-specific cancer incidence and the duration on dialysis before the first transplantation using adjusted Cox proportional hazards and competing risk models.

Results: Over a median follow-up of 4.4 years (interquartile range, 1.7-7.7 years), the total cumulative incidence of all cancers after the first kidney transplantation was 15.0 per 1000 patient-years. There was a linear relationship between the duration of dialysis and the risk of cancer after transplantation (P_{trend}=0.02). The excess risks for lung and urinary tract cancers were highest among recipients who had been on dialysis for the longest duration before transplantation (adjusted hazard ratio [95% confidence interval], 3.32 [1.00-11.4]; P=0.05 and 2.57 [1.33-4.95]; P=0.005, respectively).

Conclusion: Increasing time on dialysis is a significant risk factor for common solid organ cancers, such as lung cancer, and urinary tract cancers in kidney transplant recipients, irrespective of age. Strategies to improve cancer surveillance among recipients who had been on dialysis for a longer time may be warranted.

64. Donor Cancer Transmission in Kidney Transplantation: A Systematic Review
Am J Transplant. 2013 Oct;13(10):2645-52
Xiao D, Craig JC, Chapman JR, Dominguez-Gil B, Tong A, Wong G.

Transplantation of any biological material from a donor to a host will carry some inherent risk of disease transmission. Our aims were to summarize the totality of the published evidence about donor cancer transmission among kidney transplant recipients and to determine the cancer-specific survival of these patients. We systematically reviewed all case reports, case series and registry studies that described the outcomes of kidney transplant recipients with donor cancer transmission published to December 2012. A total of 69 studies with 104 donor-transmitted cancer cases were identified. The most common transmitted cancer types were renal cancer (n=20, 19%), followed by melanoma (n=18, 17%), lymphoma (n=15, 14%) and lung cancer (n=9, 9%). Patients with melanoma and lung cancers had the worst prognosis, with less than 50% of recipients surviving after 24 months from transplantation. Recipients with transmitted renal cancers had the best outcomes, with over 70% of recipients surviving for at least 24 months after transplantation. Overall, the risk of donor transmission of cancer appears low, but there is a high likelihood of reporting bias. Our findings support the current recommendations for rejecting organs from donors with a history of melanoma and lung cancer, but suggest that the use of donor kidneys with a history of small, incidental renal cell cancer may be reasonable.

65. Cancers of the Kidney and Urinary Tract in Patients on Dialysis for End-Stage Renal Disease: Analysis of Data from the United States, Europe, and Australia and New Zealand

J Am Soc Nephrol 14: 197–207, 2003

Stewart JH, Buccianti G, Agodoa L, Gellert R, McCredie MR, Lowenfels AB, Disney AP, Wolfe RA, Boyle P, Maisonneuve P.

Abstract: Patients on maintenance dialysis have increased risk for cancer, especially in the kidney and urinary tract. In a retrospective cohort of 831,804 patients starting dialysis during 1980 to 1994 in the United States, Europe, or Australia and New Zealand, standardized incidence ratios (SIR) with 95% confidence intervals (CI) were calculated for kidney and bladder cancers. Risks for cancers of the kidney (SIR 3.6; CI 3.5 to 3.8) and bladder (SIR 1.5; CI 1.4 to 1.6) were increased, relatively more in younger than older patients and more in female patients (kidney: SIR 4.6, CI 4.3 to 4.9; bladder: SIR 2.7, CI 2.4 to 2.9) than male patients (kidney: SIR 3.2, CI 3.0 to 3.4; bladder: SIR 1.3, CI 1.2 to 1.3). SIR for kidney cancer were raised in all categories of primary renal disease, and for bladder cancer in all but diabetes and familial, hereditary diseases. Notably high SIR occurred in toxic nephropathies (chiefly analgesic nephropathy) and miscellaneous conditions (a category that includes Balkan nephropathy), the excess of kidney cancer in these conditions being urothelial in origin. SIR for kidney cancer rose significantly, and those for bladder cancer fell (not reaching significance) with time on dialysis. There was no association with type of dialysis. The pattern of increased risk for renal parenchymal cancer in dialysis patients is consistent with causation through acquired renal cystic disease and of urothelial cancers of the kidney and bladder with the carcinogenic effects of certain primary renal diseases.

66. De Novo Kidney Graft Tumors: Results From a Multicentric Retrospective National Study
American Journal of Transplantation 2012; 12: 3308–3315

Tillou X, Doerfler A, Collon S, Kleinclauss F, Patard JJ, Badet L, Barrou B, Audet M, Bensadoun H, Berthoux E, Bigot P, Boutin JM, Bouzguenda Y, Chambade D, Codas R, Dantal J, Deturmeny J, Devonec M, Dugardin F, Ferrière JM, Erauso A, Feuillu B, Gigante M, Guy L, Karam G, Lebret T, Neuzillet Y, Legendre C, Perez T, Rerolle JP, Salomon L, Sallusto F, Sénéchal C, Terrier N, Thuret R, Verhoest G, Petit J; "Comité de Transplantation de l'Association Française d'Urologie (CTAFU)".

De novo tumors in renal allografts are rare and their prevalence is underestimated. We therefore analyzed renal cell carcinomas arising in renal allografts through a retrospective French renal transplant cohort. We performed a retrospective, multicentric survey by sending questionnaires to all French kidney transplantation centers. All graft tumors diagnosed after transplantation were considered as de novo tumors. Thirty-two centers participated in this study. Seventy-nine tumors were identified among 41 806 recipients (Incidence 0.19%). Patients were 54 men and 25 women with a mean age of 47 years old at the time of diagnosis. Mean tumor size was 27.8 mm. Seventy-four (93.6%), 53 (67%) and 44 tumors (55.6%) were organ confined (T1– 2), low grade (G1–2) and papillary carcinomas, respectively. Four patients died of renal cell carcinomas (5%). The mean time lapse between transplantation and RCC diagnosis was 131.7 months. Thirty-five patients underwent conservative surgery by partial nephrectomy (n = 35, 44.3%) or radiofrequency (n = 5; 6.3%). The estimated 5 years cancer specific survival rate was 94%. Most of these tumors were small and incidental. Most tumors were papillary carcinoma, low stage and low grade carcinomas. Conservative treatment has been preferred each time it was feasible in order to avoid a return to dialysis.

67. De novo renal cell carcinoma of native and graft kidneys in renal transplant recipients
BJU Int. 2011 Jul;108(2):229-34.
Tsaur I, Obermüller N, Jonas D, Blaheta R, Juengel E, Scheuermann EH, Kachel HG, Karalis A, Probst M.

Objective: To access the epidemiological, clinical and survival features of renal transplant patients with de novo renal cell carcinoma of native and graft kidneys.
Patients and Methods: We performed a retrospective examination of the data of 2001 consecutive renal transplant recipients at our centre between November 1979 and January 2010.
Results: In the patient cohort examined, 30 renal cell carcinomas were observed in 26 individuals (incidence 1.5%) with 25 tumours in the native and five in allograft kidneys. Mean tumour size in surgical specimens was 44 ± 36 mm. The rate of papillary cancer was 37.5%. After a mean follow-up of 58.6 ± 62.3 months, 15.4% of the patients died from cancer and 57.7% were in complete remission. Overall and tumour-specific survival rates at 1, 5 and 10 years were 86.1%, 75.1% and 43.8%, and 90.4%, 83.5% and 66.8%, respectively.
Conclusions: Due to increasingly improved survival after renal transplantation, de novo malignancies might soon become the main cause of intermediate- or long-term mortality. Current data support an increased risk of renal cell carcinoma in renal transplant recipients in a particularly aggressive way, but low tendency for metachronous contralateral evolution. With continuous radiological follow-ups, acceptable oncological outcome can be achieved. Graft tumours may have a favourable prognosis.

68. The High Rate of de novo Graft Carcinomas in Renal Transplant Recipients

Am J Nephrol 2013;37:91–96

Viart L, Surga N, Collon S, Jaureguy M, Elalouf V, Tillou X.

Background: To investigate the incidence, the clinical characteristics and outcomes of renal graft carcinomas in the same renal transplant population.
Methods: From April 1989 to April 2012, 1,037 consecutive renal transplantations were performed in our department. Data were collected prospectively in an extensively maintained database. For all recipients, monitoring consisted of clinical examination and an abdominopelvic CT scan or ultrasonography at least once a year.
Results: After 1,037 renal transplantations, 48 men and 14 women (sex ratio 3: 4) with a mean age of 54 years (25.1– 78.9) were included for urological malignancies. Eight graft carcinomas were identified: 7 renal cell carcinomas (5 papillary carcinomas and 2 clear cell carcinomas of the renal graft) and 1 transitional cell carcinoma of the ureteral graft (incidence 0.78%). Nephron-sparing surgery was chosen for 5 patients with good outcomes. All graft renal cell carcinomas were classified as pT1a and the mean size of tumors was 28.4 mm (range 6–45). The 5-year specific survival rate was 100%. No recurrence was observed with a mean follow-up of 36.8 months (4.1–84.3).
Conclusion: Thus confirming an increased risk of de novo graft cancer, close monitoring of renal transplant recipients should be discussed with at least an abdominopelvic ultrasonography and PSA measurement once a year. Renal cell graft carcinomas seemed to be mostly small and of papillary type and low grade.

69. Risk of bladder cancer in renal transplant recipients: a meta-analysis

British Journal of Cancer (2014) 110, 1871–1877

Yan L, Chen P, Chen EZ, Gu A, Jiang ZY

Background: Renal transplantation has been associated with a significantly increased risk of developing cancers during long-term follow-up, but for bladder cancer, this risk is less clear. We therefore performed a meta-analysis to determine whether bladder cancer risk in renal transplant recipients was increased.

Methods: Eligible studies were identified through searches of PubMed and other public resources. Random-effects meta-analyses were used to pool overall estimates for standardised incidence ratios (SIRs). Heterogeneity test, sensitivity analysis, and assessment of publishing bias were also performed.

Results: We identified a 3.18-fold higher SIR (95% confidence intervals (CI): 1.34–7.53, P=0.008) of bladder cancer in patients following renal transplantation compared with the general population, based on data from 79 988 patients with a total follow-up of 308 458 patient-years. When stratified by ethnicity, the SIRs for bladder cancer were 2.00 (95% CI: 1.51–2.65, P=0.001) and 14.74 (95% CI: 3.66–59.35, P<0.001) between European and Asian renal transplant recipients, respectively.

Conclusions: Our study demonstrated that the risk of developing bladder cancer in transplant populations was increased. Such association suggests that physicians should be more vigilant in checking for bladder cancer in transplantation recipient population.

70. A retrospective review of patients with urothelial cancer in 3,370 recipients after renal transplantation: a single‑center experience

World J Urol (2015) 33:713–717

Zhang A, Shang D, Zhang J, Zhang L, Shi R, Fu F, Tian Y

Objective: To summarize the diagnosis, surgical intervention and postoperative management of patients with urothelial cancer (UC) after renal transplants (RTx).
Methods: In our retrospective review of 3,370 RTx recipients in our transplant center from 1974 to 2012, all recipients underwent routine checkups and follow-up. Imaging was performed in all patients suspected of having malignancies, and the histological cell type of the specimen slices was reappraised by pathologists. The data of all recipients with malignancies were retrospectively reviewed to determine clinical characteristics after RTx.
Results: A total of 169 patients of the cohort of 3,370 had malignancies after RTx. Of 180 tumors, 106 tumors were confirmed as UC. Fifty-two patients had taken drugs containing aristolochic acid. The median time to neoplasia after RTx in the group taking aristolochic acid (30 months) was significantly less than in those not taking aristolochic acid (60.3 months). We recommended surgical intervention for RTx recipients with UC, transurethral resection of bladder tumors for patients with solitary or concomitant superficial UC, and radical cystectomy for high-risk bladder UC. We performed simultaneous bilateral or unilateral nephroureterectomy in patients with upper urinary tract UC.
Conclusion: Our results suggest that UC is the predominant tumor in Chinese RTx recipients and that regular urinalysis and imaging are needed in all recipients after RTx, especially women with a history of taking aristolochic acid. Surgical interventions did not increase the risk beyond that in UC patients without RTx.

71. Risk of Hepatobiliary Cancer After Solid Organ Transplant in the United States
Clin Gastroenterol Hepatol. 2014 Sep;12(9):1541-9.
Koshiol J, Pawlish K, Goodman MT, McGlynn KA, Engels EA

Background & Aims: Studies of liver cancer risk in recipients of solid organ transplants generally have been small, yielding mixed results, and little is known about biliary tract cancers among transplant recipients.
Methods: We identified incident hepatobiliary cancers among 201,549 US recipients of solid organs, from 1987 through 2008, by linking data from the US transplant registry with 15 cancer registries. We calculated standardized incidence ratios (SIRs), comparing risk relative to the general population. We also calculated incidence rate ratios (RRs), comparing risk for hepatocellular carcinoma (HCC) and total (intrahepatic and extrahepatic) cholangiocarcinoma among subgroups of recipients.
Results: Of transplant recipients, 165 developed hepatobiliary cancers (SIR, 1.2; 95% confidence interval [CI], 1.0–1.4). HCC risk was increased among liver recipients (SIR, 1.5; 95% CI, 1.0–2.2), especially 5 or more years after transplant (SIR, 1.8; 95% CI, 1.0–3.0). Cholangiocarcinoma was increased among liver (SIR, 2.9; 95% CI, 1.6–4.8) and kidney recipients (SIR, 2.1; 95% CI, 1.3–3.1). HCC was associated with hepatitis B virus (RR, 3.2; 95% CI, 1.3–6.9), hepatitis C virus (RR, 10; 95% CI, 5.9–16.9), and non–insulin-dependent diabetes (RR, 2.5; 95% CI, 1.2–4.8). Cholangiocarcinoma was associated with azathioprine maintenance therapy (RR, 2.0; 95% CI, 1.1–3.7). Among liver recipients, primary sclerosing cholangitis was associated with an increased risk of cholangiocarcinoma, compared with the general population (SIR, 21; 95% CI, 8.2–42) and compared with liver recipients without primary sclerosing cholangitis (RR, 12.3; 95% CI, 4.1–36.4).
Conclusions: Risks for liver and biliary tract cancer are increased among organ transplant recipients. Risk factors for these cancers include medical conditions and potentially medications taken by recipients.

72. Outcomes of Colorectal Cancer Arising in Solid Organ Transplant Recipients

J Gastrointest Surg (2014) 18:599–604

Merchea A, Abdelsattar ZM, Taner T, Dean PG, Colibaseanu DT, Larson DW, Dozois EJ.

Introduction: The incidence of colorectal cancer posttransplantation is unclear. Limited reports exist and have conflicting conclusions. We aimed to review the clinical features and oncologic outcomes of colorectal cancer in transplant recipients at our institution.

Methods: A retrospective review of all patients diagnosed with colorectal cancer after solid organ transplantation between 2000 and 2011 was conducted. Clinical features and outcomes were reviewed.

Results: Twenty of 3,946 patients were identified. The most common single organ transplanted was the kidney (n =8). Six patients had multiorgan transplantation. Median age of diagnosis of cancer was 64.3 years, and median time from transplant to diagnosis of cancer was 8.7 years. Ten patients were symptomatic at presentation. Cancer was identified on routine colonoscopy in seven patients. Tumors were most commonly found in the right colon (n =14, 70 %). Six patients had stage IV disease at presentation. Short-term morbidity was identified in 11 patients. Postoperative mortality occurred in one patient. Median followup was 2.47 years. Overall survival at 5 years was 69 %, and disease-free survival was 68 %. Distant recurrence was seen in 3 (15 %) patients.

Conclusion: Colorectal cancer in these patients is rare, and surgery can be done safely. Vigilant screening must be maintained in this patient population.

73. Increased Incidence of Gastric Cancer in Renal Transplant Recipients

J Clin Gastroenterol 2012;46:e87–e91)

Park JM, Choi MG, Yang CW, Jung CK, Lee SK, Yoon AR, Kim YS, Chung IS.

Objective: The risk of malignancy after transplantation is regarded to be higher than in the general population. The aim of this study was to evaluate the frequency of gastric cancer in renal transplant recipients.
Methods: A total of 820 renal transplantation recipients were invited for gastric cancer screening. Frequencies of gastric cancer in this cohort and in 10,080 asymptomatic subjects were compared. Cancer specimens were examined for Epstein-Barr virus by in situ hybridization.
Results: A total of 509 recipients (mean age, 48.1±10.7 y; men, 56.8%) participated. Fifteen (2.9%) and 10 (0.1%) cases of adenocarcinoma were identified among recipients and controls, respectively ($P<0.001$; odds ratio, 30.58). Early gastric cancer was detected in 9 of the 15 recipients, and 4 of the 9 were treated by endoscopic resection. Recipient age was found to be a significant factor of gastric cancer development. In cancer tissues, Epstein-Barr virus was detected in 5 (33.3%) renal recipients and in 1 (10%) of the controls, respectively.
Conclusions: The frequency of gastric cancer was found to be higher in renal recipients than in controls. Gastric cancer screening should be considered after transplantation, because it would provide cure by minimally invasive treatment.

74. Risk of Colorectal Cancer After Solid Organ Transplantation in the United States

Am J Transplant. 2016 Mar;16(3):960-7

Safaeian M, Robbins HA, Berndt SI, Lynch CF, Fraumeni JF Jr, Engels EA.

Solid organ transplant recipients have increased colorectal cancer (CRC) risk. We assessed CRC risk among transplant recipients and identified factors contributing to this association. The US transplant registry was linked to 15 population-based cancer registries (1987–2010). We compared CRC risk in recipients to the general population by using standardized incidence ratios (SIRs) and identified CRC risk factors by using Poisson regression. Based on 790 cases of CRC among 224 098 transplant recipients, the recipients had elevated CRC risk (SIR 1.12, 95% confidence interval [CI] 1.04 to 1.20). The increase was driven by an excess of proximal colon cancer (SIR 1.69, 95% CI 1.53 to 1.87), while distal colon cancer was not increased (SIR 0.93, 95% CI 0.80 to 1.07), and rectal cancer was reduced (SIR 0.64, 95% CI 0.54 to 0.76). In multivariate analyses, CRC was increased markedly in lung recipients with cystic fibrosis (incidence rate ratio [IRR] 12.3, 95% CI 6.94 to 21.9, vs. kidney recipients). Liver recipients with primary sclerosing cholangitis and inflammatory bowel disease also had elevated CRC risk (IRR 5.32, 95% CI 3.73 to 7.58). Maintenance therapy with cyclosporine and azathioprine was associated with proximal colon cancer (IRR 1.53, 95% CI 1.05 to 2.23). Incidence was not elevated in a subgroup of kidney recipients treated with tacrolimus and mycophenolate mofetil, pointing to the relevance of the identified risk factors. Transplant recipients have increased proximal colon cancer risk, likely related to underlying medical conditions (cystic fibrosis and primary sclerosing cholangitis) and specific immunosuppressive regimens.

75. Malignancy-related mortality following kidney transplantation is common
Kidney Int. 2014 Jun;85(6):1395-403.
Farrugia D, Mahboob S, Cheshire J, Begaj I, Khosla S, Ray D, Sharif A

There is a paucity of studies describing malignancy-related mortality after kidney transplantation. To help quantify this, we extracted data for all kidney-alone transplant procedures performed in England between April 2001 and March 2012. Data linkage analysis was performed between Hospital Episode Statistics and the Office for National Statistics to identify all deaths occurring in this cohort. Among 19,103 kidney transplant procedures analyzed (median follow-up 4.4 years), 2085 deaths occurred, of which 376 (18.0%) were due to malignancy (crude mortality rate 361 malignancy-related deaths per 100,000 person-years). Common sites of malignancy-related death were lymphoma (18.4%), followed by lung (17.6%) and renal (9.8%), with 14.1% unspecified. The risk of malignancy-related death increased with age: under 50 (0.8%), 50–59 (2.5%), 60–69 (4.8%), 70–79 (6.5%) and over 80 years (9.1%). Age- and gender-stratified malignancy related mortality risk difference was higher in the transplant compared with the general population. Cox proportional hazard models identified increased age, pretransplant history of malignancy and deceased-donor kidney transplantation to be independently associated with risk for post-transplant death from malignancy. Thus, malignancy as a cause of postkidney transplantation death is common and requires heightened surveillance.

76. Lung Cancer Prognosis in Elderly Solid Organ Transplant Recipients

Transplantation 2015;99: 2181–2189

Sigel K, Veluswamy R, Krauskopf K, Mehrotra A, Mhango G, Sigel C, Wisnivesky J.

Background: Treatment-related immunosuppression in organ transplant recipients has been linked to increased incidence and risk of progression for several malignancies. Using a population-based cancer cohort, we evaluated whether organ transplantation was associated with worse prognosis in elderly patients with non–small cell lung cancer (NSCLC).

Methods: Using the Surveillance, Epidemiology, and End Results Registry linked to Medicare claims, we identified 597 patients aged 65 years or older with NSCLC who had received organ transplants (kidney, liver, heart, or lung) before cancer diagnosis. These cases were compared to 114,410 untransplanted NSCLC patients. We compared overall survival (OS) by transplant status using Kaplan-Meier methods and Cox regression. To account for an increased risk of non-lung cancer death (competing risks) in transplant recipients, we used conditional probability function (CPF) analyses. Multiple CPF regression was used to evaluate lung cancer prognosis in organ transplant recipients while adjusting for confounders.

Results: Transplant recipients presented with earlier stage lung cancer ($P = 0.002$) and were more likely to have squamous cell carcinoma ($P = 0.02$). Cox regression analyses showed that having received a non-lung organ transplant was associated with poorer OS ($P < 0.05$), whereas lung transplantation was associated with no difference in prognosis. After accounting for competing risks of death using CPF regression, no differences in cancer-specific survival were noted between non-lung transplant recipients and nontransplant patients.

Conclusions: Non-lung solid organ transplant recipients who developed NSCLC had worse OS than nontransplant recipients due to competing risks of death. Lung cancer-specific survival analyses suggest that NSCLC tumor behavior may be similar in these 2 groups.

77. Survival After Cutaneous Melanoma in Kidney Transplant Recipients: A Population-Based Matched Cohort Study

Am J Transplant. 2014 Jun;14(6):1368-75

Vajdic CM, Chong AH, Kelly PJ, Meagher NS, Van Leeuwen MT, Grulich AE, Webster AC

Transplant recipients are at elevated risk of melanoma and may have poorer outcomes than nontransplant 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 were obtained from the National Death Index (1982–2011). Histopathology was compared using conditional logistic regression and overall survival analyzed using Cox proportional hazard models. Compared to melanomas in nontransplant recipients (n¼202), melanomas in transplant recipients (n=75) had a higher Clark's level (p=0.007) and higher American Joint Committee on Cancer pathologic stage (p=0.002), but not Breslow thickness (p=0.11). Posttransplant melanoma conferred higher risk of death (adjusted hazard 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 those in nonrecipients. More aggressive tumor behavior 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.

Proyecto Prometeo II

Grupo II | Evaluación y detección precoz del cáncer pre y postrasplante renal

Referencias Bibliográficas

Organizado por

SET
SOCIEDAD ESPAÑOLA DE TRASPLANTE

Con la colaboración de

NOVARTIS

1. High Prevalence of Colon Adenomas in End Stage Kidney Disease Patients on Hemodialysis Undergoing Renal Transplant Evaluation.

Clin Transplant. 2016 Mar;30(3):256-62.

Saumoy M, Jesudian AB, Aden B, Serur D, Sundararajan S, Sivananthan G, Gambarin-Gelwan M.

Abstract: The aim of this study was to determine whether patients with end-stage kidney disease (ESKD) on hemodialysis (HD) undergoing kidney transplant evaluation are at higher risk for colonic neoplasia than the general population. This is a retrospective cohort study of patients with ESKD who underwent a first screening colonoscopy while undergoing kidney transplant evaluation. Data were collected on the prevalence of adenomatous polyps and advanced adenomas in 70 patients with ESKD and 70 controls, undergoing their first screening colonoscopy, matched for age, gender, and endoscopist. At the time of the colonoscopy, an average time on HD was 3.2 ± 2.9 yr. The prevalence of adenomatous polyps was significantly higher in ESKD on HD (54.3% vs. 32.9%, p = 0.008) than in controls. In a multivariate analysis controlling for other factors, ESKD on HD remained a risk factor for the presence of adenomas (OR 3.06, 95% CI 1.21, 7.73). No colonoscopy-related complications were reported in the patients with ESKD on HD. We demonstrate a significantly higher prevalence of adenomatous polyps in patients with ESKD undergoing a first screening colonoscopy as part of kidney transplant evaluation. In addition, colonoscopy can be safely performed in this population.

2. Utility of Prostate Cancer Screening in Kidney Transplant Candidates.

J Am Soc Nephrol. 2015 Dec 23. pii: ASN.2014121182. [Epub ahead of print]

Vitiello GA, Sayed BA, Wardenburg M, Perez SD, Keith CG, Canter DJ, Ogan K, Pearson TC, Turgeon N.

Abstract: Screening recommendations for prostate cancer remain controversial, and no specific guidelines exist for screening in renal transplant candidates. To examine whether the use of prostate-specific antigen (PSA)-based screening in patients with ESRD affects time to transplantation and transplant outcomes, we retrospectively analyzed 3782 male patients ≥18 years of age undergoing primary renal transplant evaluation during a 10-year period. Patients were grouped by age per American Urological Association screening guidelines: group 1, patients <55 years; group 2, patients 55-69 years; and group 3, patients >69 years. A positive screening test result was defined as a PSA level >4 ng/ml. We used univariate analysis and Cox proportional hazards models to identify the independent effect of screening on transplant waiting times, patient survival, and graft survival. Screening was performed in 63.6% of candidates, and 1198 candidates (31.7%) received kidney transplants. PSA screening was not associated with improved patient survival after transplantation (P=0.24). However, it did increase the time to listing and transplantation for candidates in groups 1 and 2 who had a positive screening result (P<0.05). Furthermore, compared with candidates who were not screened, PSA-screened candidates had a reduced likelihood of receiving a transplant regardless of the screening outcome (P<0.001). These data strongly suggest that PSA screening for prostate cancer may be more harmful than protective in renal transplant candidates because it does not appear to confer a survival benefit to these candidates and may delay listing and decrease transplantation rates.

3. Prostate-specific antigen screening and prostate cancer treatment in renal transplantation candidates: A survey of U.S. transplantation centers.

Urol Oncol. 2016 Feb;34(2):57.e9-13.

Gin GE, Pereira JF, Weinberg AD, Mehrazin R, Lerner SM, Sfakianos JP, Phillips CK.

Introduction: Renal transplantation candidates are a highly screened population. There are currently no guidelines or consensus on prostate cancer (CaP) screening in these patients. In light of the recent United States Preventive Services Task Force recommendations against prostate-specific antigen (PSA) screening, we conducted a survey of transplantation surgeons to gain a better understanding of practice patterns among U.S. centers.
Materials and methods: A 14-question multiple-choice online survey was e-mailed to 195 U.S. renal transplantation centers. The questionnaire assessed CaP screening and treatment practices. The survey also evaluated characteristics of the respondent's institution. Descriptive statistics were used for each of the responses, and associations were made with program characterization using logistic or linear regression models.
Results: A total of 90 surgeons responded, representing 65 of 195 programs (33% response rate). Overall, 89% of respondents reported routinely screening for CaP in renal transplantation candidates and 71% had set guidelines for PSA screening. The most common age to start PSA screening was 50 years (51%) and 79% of respondents reported no age limit to stop PSA screening. Definitive treatment of CaP was required before proceeding to transplantation in 45% of respondents. Active surveillance was a viable option in 67% of responders. Most respondents (73%) replied that the waiting time for eligibility after treatment depended on the CaP stage and risk.
Conclusions: Although most programs have guidelines on PSA screening in renal transplantation candidates, there is still variation nationwide in screening and treatment practices. AS is a viable treatment option in most of the programs. Our results suggest a benefit of a consensus panel to recommend guidelines in this population.

4. Utility of mammography for chronic kidney disease patients undergoing kidney transplant evaluation.

Clin Transplant. 2016 Apr;30(4):445-51.

Stoecker JB, Cote DR, Augustine JJ, Sarabu N, Schulak JA, Sanchez EQ, Humphreville VR, Ammori JB, Woodside KJ.

Abstract: Transplant centers typically require screening mammography (MMG) for women ≥40 during evaluation. American Cancer Society recommends starting annual MMG at 40, while USPSTF recommends biennial MMG at 50. We sought to determine the effect of age and other breast malignancy risk factors on screening MMG in the pre-transplant renal failure population undergoing transplant evaluation.
Methods: We retrospectively examined women ≥40 undergoing kidney transplant evaluation from 2006 to 2012 (n = 541).
Results: Patients aged 40.0-49.9 and ≥50 had similar rates of breast biopsy and breast malignancy. African Americans underwent a higher rate of biopsies (OR 2.391, 95%CI 1.111-5.019, p = 0.026), with a lower rate of biopsy in those already on dialysis at presentation (OR 0.434, 95%CI 0.212-0.888, p = 0.022). Higher breast density (>50% fibroglandular tissue) increased both rate of biopsy (OR 2.876, 95%CI 1.377-6.010, p = 0.005) and malignancy (OR 5.061, 95%CI 1.012-25.315, p = 0.048).
Conclusions: As we found no independent differences in biopsy or malignancy between age groups, it is reasonable for transplant centers to use the same evaluation MMG screening policy for all women ≥40. However, as malignancy risk increased with higher breast density, a lower threshold for additional workup may be warranted in patients with dense breasts or an indeterminate lesion on MMG.

5. Yield of screening colonoscopy in renal transplant candidates.

Can J Gastroenterol Hepatol. 2015 Nov-Dec;29(8):423-6.

AlAmeel T, Bseiso B, AlBugami MM, AlMomen S, Roth LS.

Background: Cardiovascular disease is the most common cause of death among patients with end-stage renal disease undergoing maintenance dialysis. Renal transplantation offers a survival advantage to patients with end-stage renal disease; it is also associated with a three- to fivefold increase in the risk of developing a neoplasm.
Objective: To determine the yield of screening colonoscopy among patients with chronic kidney disease who were considered for renal transplantation.
Methods: Patients were included if they were ≥50 years of age, had chronic kidney disease and were being considered for renal transplantation. They underwent a screening colonoscopy that was performed as part of their pretransplant workup. Data from December 2008 to May 2014 were collected retrospectively for all eligible patients.
Results: During the study period, 433 patients were considered for renal transplantation. Of these, 170 underwent colonoscopies as part of their pretransplant workup. One was excluded because of previous history of colon cancer. Of the 169 procedures performed, ≥1 polyp(s) was diagnosed in 24%. The most common pathological diagnoses were hyperplastic polyp or normal colonic tissue. Fifteen (37%) patients had tubular adenomas and one patient had a sessile serrated adenoma. Advanced adenomas, defined as villous, tubulovillous or high-grade dysplasia, were found in four patients. Adenocarcinoma was diagnosed in one patient.
Conclusion: In a population of asymptomatic potential kidney transplant recipients ≥50 years of age, the prevalence of colorectal adenomatous polyps was 24%. Colonoscopy appeared to be useful as a screening tool in potential transplant recipients.

6. Importance of pre-transplant colonoscopy in renal transplant recipients.

J Clin Med Res. 2014 Dec;6(6):414-21

Therrien A, Giard JM, Hebert MJ, Bouin M.

Background: Current recommendations for colorectal cancer screening for kidney transplant candidates are the same as for the general population. However, few studies have established the prevalence and characteristics of colorectal polyps in this population. The aim of this study is to describe the prevalence and characteristics of colonic lesions detected by pre-transplant colonoscopies in our kidney transplant population.
Methods: A retrospective study was conducted from January 2007 to December 2009 at the Centre Hospitalier de l'Universite de Montreal (Canada). Inclusion criteria are all renal transplant recipients with a test for colorectal cancer screening in the 5 years preceding the transplantation. Patients benefiting of a second transplantation were excluded. The files were reviewed for clinical data, including colonoscopy indication, endoscopic and pathologic results. Advanced lesions were defined as adenomas of 10 mm or greater or with a villous component. Polyps were considered proximal if they were at the level of or above the splenic angle.
Results: This study includes 159 patients. A pre-transplant colonoscopy was performed in 40% (n = 64). Polyps were present in 32.8% (n = 21) of colonoscopies and 66.7% of them showed adenomas. Advanced lesions were present in 6.25% of the exams. Finally, 66.7% of patients with polyps had at least one proximal lesion.
Conclusions: The prevalence of colorectal polyps before transplant is high among renal transplant recipients. The high prevalence of proximal lesions supports the need for total colonoscopy.

7. Health benefits and costs of screening for colorectal cancer in people on dialysis or who have received a kidney transplant.

Nephrol Dial Transplant. 2013 Apr;28(4):917-26.

Wong G, Li MW, Howard K, Hua DK, Chapman JR, Bourke M, Turner R, Tong A, Craig JC.

Background: Despite the higher risk of colorectal cancer (CRC) in people with chronic kidney disease, it remains uncertain whether early detection through screening is cost-effective in this setting. We aimed to determine the costs and health benefits of CRC screening in people on dialysis or who have received a kidney transplant.

Methods: Using a government health perspective, three probabilistic Markov models were constructed to compare the cost-effectiveness and cost-utility of annual immunochemical faecal occult blood test (iFOBT) screening against no-screening in a cohort of 1000 patients (age 50-70 years) on dialysis and with kidney transplants. A series of one-way, multi-way and probabilistic sensitivity analyses were conducted to assess the robustness of the model structure and the extent in which the model's assumptions were sensitive to the uncertainties within the input variables.

Results: The incremental cost-effectiveness ratios (ICERs) of CRC screening compared with no-screening were $138 828 per quality-adjusted life year [QALY; $122 977 per life year saved (LYS)], $121 973 per QALY ($ 85 095 per LYS) and $44 790 per QALY ($25 036 per LYS) for dialysis patients not listed on the transplant waiting list, patients on the transplant waiting list and patients with kidney transplants, respectively. The test specificity of iFOBT, the starting age of screening and cancer prevalence were influential factors that determined the overall cost-effectiveness of screening in this setting.

Conclusion: Screening for CRC using iFOBT may reduce cancer-specific mortality in patients on dialysis and with kidney transplants. However, the benefits and costs of screening CRCs in patients on dialysis, especially for those deemed not suitable for transplantation, greatly exceeded the typical thresholds for acceptable cost-effectiveness.

8. Screening for colorectal cancer and advanced colorectal neoplasia in kidney transplant recipients: cross sectional prevalence and diagnostic accuracy study of faecal immunochemical testing for haemoglobin and colonoscopy.

BMJ. 2012 Jul 25;345:e4657.

Collins MG, Teo E, Cole SR, Chan CY, McDonald SP, Russ GR, Young GP, Bampton PA, Coates PT.

Objective: To investigate whether screening kidney transplant recipients aged over 50 years for colorectal cancer with a faecal immunochemical test for haemoglobin might be justified, by determining the prevalence of advanced colorectal neoplasia and evaluating the diagnostic accuracy of faecal haemoglobin testing compared with colonoscopy in a population of kidney transplant recipients at otherwise average risk.
Design: Cross sectional prevalence and diagnostic accuracy study with index test of faecal haemoglobin and reference standard of colonoscopy.
Setting: Outpatient clinics in metropolitan and regional hospitals in South Australia.
Participants: 229 kidney transplant recipients aged 50 years and over, who were at least 6 months (mean 9.0 (SD 8.4) years) post-transplant and otherwise at average risk of colorectal cancer, completed the study between June 2008 and October 2011.
Interventions: Faecal immunochemical testing (Enterix Insure) for human haemoglobin, followed by colonoscopy with histological evaluation of retrieved samples.
Main outcome measures: Prevalence of advanced colorectal neoplasia, defined as an adenoma at least 10 mm in diameter, villous features, high grade dysplasia, or colorectal cancer; sensitivity, specificity, and predictive values of faecal haemoglobin testing for advanced neoplasia compared with colonoscopy.
Results: Advanced colorectal neoplasia was found in 29 (13%, 95% confidence interval 9% to 18%) participants, including 2% (n=4) with high grade dysplasia and 2% (n=5) with colorectal cancer. Faecal testing for haemoglobin was positive in 12% (n=28); sensitivity, specificity, and positive and negative predictive values for advanced neoplasia were 31.0% (15.3% to 50.8%), 90.5% (85.6% to 94.2%), 32.1% (15.9% to 52.4%), and 90.1% (85.1% to 93.8%). Colonoscopy was well tolerated, with no significant adverse outcomes. To identify one case of advanced neoplasia, 8 (6 to 12) colonoscopies were needed.
Conclusions: Kidney transplant recipients aged over 50 years have a high prevalence of advanced colorectal neoplasia. Faecal haemoglobin screening for colorectal neoplasia has similar performance characteristics in transplant recipients to those reported in general population studies, with poor sensitivity but reasonable specificity. Surveillance colonoscopy might be a more appropriate approach in this population.

9. Long-term follow-up of patients with monoclonal gammopathy of undetermined significance after kidney transplantation.

Am J Nephrol. 2012;35(4):365-71.

Naina HV, Harris S, Dispenzieri A, Cosio FG, Habermann TM, Stegall MD, Dean PG, Prieto M, Kyle RA, Rajkumar SV, Leung N.

Introduction: Long-term data regarding kidney transplantation (KTx) patients with monoclonal gammopathy of undetermined significance (MGUS) are scarce. We evaluated the long-term outcomes of these patients in a single-center retrospective study from the Mayo Clinic, Rochester, Minn., USA.

Methods: Patients who had an MGUS before transplant or developed one after KTx were selected. Monoclonal protein was screened as part of the KTx evaluation by serum protein electrophoresis. Screening for posttransplant lymphoproliferative disorder (PTLD) or MGUS after transplant was not required by protocol. Patients with multiple myeloma, dysproteinemia-related kidney disease or no pretransplant serum protein electrophoresis were excluded.

Results: Between 1963 and 2006, 3,518 patients underwent KTx. MGUS was identified in 42 patients, with 23 before transplant and 19 after transplant. Median follow-up for these patients was 8.5 years (range 0.3-37). Four (17.4%) pretransplant MGUS patients developed a hematologic malignancy: 2 smoldering multiple myeloma and 2 PTLD - an Epstein-Barr virus-positive diffuse large cell lymphoma and a Hodgkin lymphoma. None of the 19 patients who developed an MGUS after transplant progressed to multiple myeloma, but 2 (10.5%) developed Epstein-Barr virus-negative T cell lymphoproliferative disorders at 16 and 26 years after transplant. Median survival was 26.1 and 28.0 years for the pretransplant and posttransplant MGUS groups, respectively.

Conclusion: Progression from true MGUS to multiple myeloma is rare after KTx. KTx appears safe in true MGUS patients if the monoclonal gammopathy was not the cause of the kidney disease. None of the patients progressed to multiple myeloma, but 2 developed smoldering multiple myeloma and several developed PTLD. Further studies are needed to explain the relationship between MGUS and PTLD.

10. HPV-related (pre)malignancies of the female anogenital tract in renal transplant recipients.
Crit Rev Oncol Hematol. 2012 Nov;84(2):161-80.
Hinten F, Meeuwis KA, van Rossum MM, de Hullu JA.

Abstract: Renal transplantations (RTs) are performed routinely in many countries. After RT, the administration of lifelong immunosuppressive therapy is required. As a consequence, renal transplant recipients (RTRs) have a high risk to develop virus-associated (pre)malignancies, such as Human papillomavirus (HPV) related anogenital (pre)malignancies. It is known that the majority of the RTRs are infected with HPV and that these women have a 14-fold increased risk of cervical cancer, up to 50-fold of vulvar cancer and up to 100-fold of anal cancer. Often, treatment of these lesions requires concessions and may be suboptimal as radiation therapy and extensive surgery may damage the renal transplant. Therefore, prognosis may be compromised due to inadequately treated malignancies. Especially for these immunocompromised patients prevention is of utmost importance. Yearly cervical cancer screening for RTRs is advised, but appears to be executed poorly. For the future, optimizing screening and prevention of anogenital (pre)malignancies is an important issue for women after RT. This review gives a broad overview of all aspects regarding HPV-related (pre)malignancies of the female anogenital tract in RTRs.

11. Screening for renal cancer in recipients of kidney transplants.
Nephrol Dial Transplant. 2011 May;26(5):1729-39.
Wong G, Howard K, Webster AC, Chapman JR, Craig JC.

Background: Renal cancer is the most common solid organ cancer in the kidney transplant population with an excess risk ~ 5-fold greater than the general population. It is uncertain whether routine screening for renal cancer is cost-effective. The aim of our study is to estimate the costs and health benefits of ultrasonographic (US) screening for renal cancer in the kidney transplant population.
Methods: A Markov model was developed to compare the costs and benefits in a cohort of kidney transplant recipients (n = 1000, aged 18-69 years), who underwent annual and biennial US screening for renal cancer, compared with a cohort that did not.
Results: For recipients of kidney transplants aged 18-69 years, the incremental cost-effectiveness ratio (ICER) for routine US screening ranged from $252,100/LYS for biennial screening to $320,988/LYS for annual screening. A total of two and one cancer deaths were averted in the annually and biennially screened population, with a relative cancer-specific mortality reduction by 25% and 12.5%, respectively. Using a series of sensitivity analyses, the ICER was most sensitive to the costs and test specificity of ultrasonography, prevalence of disease, and the risk of graft failure in the screened population.
Conclusions: Routine screening for renal cancer may reduce the risk of cancer-related deaths in recipients of kidney transplants. Uncertainties, however, exist in the model's influential variables including the risk of graft failure among those who received contrast-enhanced diagnostic computer tomography. Given the available evidence, routine screening for renal cancers may not be cost-effective for recipients of kidney transplants.

12. Incidence, predictors, costs, and outcome of renal cell carcinoma after kidney transplantation: USRDS experience.

Transplantation. 2010 Oct 27;90(8):898-904.

Hurst FP, Jindal RM, Graham LJ, Falta EM, Elster EA, Stackhouse GB, Agodoa LY, Lentine KL, Salifu MO, Abbott KC.

Introduction: We carried out an analysis of the United States Renal Data System to determine the incidence, risk factors, prognosis, and costs associated with the diagnosis of renal cell carcinoma (RCC) after kidney transplantation.
Methods: This is a retrospective cohort of 40,821 Medicare primary renal transplant recipients transplanted from January 1, 2000, to July 1, 2005, and followed up till December 31, 2005, excluding those with prior RCC or nephrectomy. Kaplan-Meier analysis was performed to determine the time of occurrence of RCC, and Cox regression was used to determine factors associated with RCC.
Results: Three hundred sixty-eight patients were diagnosed with RCC within 3 years after transplant (incidence of 3.16 per 1000 person years). The 3-year incidence of RCC posttransplant was 9.29 per 1000 person years (2.3%) for those with pretransplant cysts and 3.08 per 1000 person years (0.7%) without pretransplant cysts. RCC was diagnosed disproportionately early posttransplant in patients with cysts. Cysts were independently associated with increased risk of RCC, as was male gender, older recipient, donor age, African American recipient, increased time on dialysis and acute rejection within first year posttransplant. RCC was associated with increased risk of mortality with a higher risk with pretransplant cysts. Patients who developed RCC had higher cumulative median costs ($55,456 at 2 years) than those who did not develop RCC ($40,369). There was no "clustering" of RCC in individual states or centers more than would be expected by chance.
Conclusion: RCC was diagnosed disproportionately early in patients with pretransplant renal cysts and was associated with a worse prognosis and increased costs.

13. Native renal cysts and dialysis duration are risk factors for renal cell carcinoma in renal transplant recipients.

Am J Transplant. 2011 Jan;11(1):86-92.

Goh A, Vathsala A.

Abstract: Urinary tract cancers are the third most common cancers in renal transplant recipients (RTX). This study examined the impact of dialysis duration and native renal cyst(s) (NRC) on renal cell carcinoma (RCC) occurrence among 1036 RTX followed-up from 1995 to July 2007. Abdominal ultrasonography was planned within 1-month of transplant, then every 5 years, or 2 years if renal cysts developed. Based on presence and time of development of NRC, RTX were grouped into those with no (No-NRC), new (New-NRC), preexisting (Pre-NRC) and time-indeterminate NRC (TI-NRC). Ten asymptomatic RTX were diagnosed with RCC at a median of 5.8 years posttransplant and had 5-year graft and patient survivals of 90% and 100%, respectively, following appropriate therapy. RCC occurred only in Pre-NRC and TI-NRC who had significantly longer dialysis duration than No- or New-NRC (6.7 ± 3.9 and 3.3 ± 3.2 vs. 2.7 ± 3.1 and 2.6 ± 2.4 years, respectively). These results suggest that NRC and increased dialysis duration are risk factors for RCC posttransplant. Since early treatment of RCC gives excellent outcomes, regular ultrasonography performed within a month of transplantation, then every 5 years for those without cysts and every 2 years for those with cysts for early detection of RCC is recommended.

14. The health and economic impact of cervical cancer screening and human papillomavirus vaccination in kidney transplant recipients.

Transplantation. 2009 Apr 15;87(7):1078-91.

Wong G, Howard K, Webster A, Chapman JR, Craig JC.

Background: The risk of cervical cancer in women who are kidney transplant recipients is increased, but little is known about the effectiveness of screening and human papillomavirus (HPV) vaccination in this group of women. We sought to determine the cost effectiveness of annual screening for cervical cancers using conventional cytology, liquid-based cytology (LBC), and pretransplant HPV vaccination in kidney transplant recipients.
Methods: Three deterministic Markov models were developed to compare the costs and health outcomes in a cohort of women (n=1000) with kidney transplants aged 18 to 69 who underwent annual screening using conventional cytology, LBC, and HPV vaccination in HPV naïve women.
Results: After a screening period of 50 years, the incremental benefits of screening using conventional cytology compared with no screening were 0.05 life years saved (LYS) (18.2 days of lives saved), the incremental costs were $608, giving an incremental cost-effectiveness ratio of $12,160 per LYS. Compared with conventional cytology alone, the incremental cost-effectiveness ratios of annual screening using LBC and HPV vaccination before transplantation (assuming nonwaning efficacy) were $127,000 and $152,333 per LYS, respectively.
Conclusion: The recommended policy of annual screening using conventional cytology is cost effective. The replacement of conventional cytology with LBC is likely to provide minimal survival benefits but considerable costs. Assuming the reported trial-based vaccine efficacy in HPV naïve women, a program of HPV vaccination before kidney transplantation is unlikely to be cost effective. Additional data about the long-term efficacy and safety of HPV vaccination is required before it should be included as standard care of renal transplant recipients.

15. The uptake of cervical cancer screening by renal transplant recipients.
Nephrol Dial Transplant. 2009 Feb;24(2):647-52.
Courtney AE, Leonard N, O'Neill CJ, McNamee PT, Maxwell AP.

Background: Renal transplant recipients are at an increased risk of developing cervical cancer compared to women in the general population. At least annual cervical smear screening is currently recommended, but little information is available regarding the actual uptake of such screening.
Methods: All female renal transplant recipients in one United Kingdom region who were alive with a functioning graft were identified. The uptake and results of cervical smear testing over a 10-year period in this cohort were determined.
Results: Of the 173 women eligible for cervical cancer screening, 18 (10%) undertook the recommended number of screening procedures; 56 (32%) had never had a cervical smear performed. The year of transplantation, age at engraftment and the social deprivation status did not significantly influence the uptake of screening ($P > 0.05$). In those women who were screened, the incidence of smear test abnormalities was 20% in renal transplant recipients compared with 7% in the general population. The cytological findings in the positive smear tests ranged from borderline changes to grade III cervical intraepithelial neoplasia.
Conclusions: The renal transplant population is at higher risk of abnormal cervical cytology, but the uptake of cervical cancer screening is low. The reasons for this low screening rate are unclear, and changes in practice are necessary to improve the uptake of cervical smear testing in women with renal transplants.

16. Cost-effectiveness of breast cancer screening in women on dialysis.

Am J Kidney Dis. 2008 Nov;52(5):916-29.

Wong G, Howard K, Chapman JR, Craig JC.

Background: Breast cancer screening is recommended for women 50 years and older in most developed countries. Women on dialysis therapy have a risk of acquiring breast cancer similar to that for other women, but a greater all-cause mortality rate because of mortality from other competing causes. It is uncertain whether routine screening is cost-effective in women on dialysis therapy. In this study, we determine the costs and health outcomes of annual mammographic breast cancer screening in women on dialysis therapy.
Study design: We performed a cost-effectiveness analysis. Sensitivity and scenario analyses were performed to assess uncertainties in the model's parameter estimates. BASE CASE: A cohort (n = 1,000) of women on dialysis therapy aged 50 to 69 years in Australia. MODEL, PERSPECTIVE, AND TIME FRAME: A deterministic Markov model was developed from the perspective of a health care payer. Patients were followed up over their life time.
Intervention: We compared a cohort of women who underwent annual mammography with a cohort that did not.
Outcomes: Life-years saved (LYS), costs, and incremental cost-effectiveness ratio (ICER).
Results: Average costs for a program of annual screening for a woman on dialysis therapy were $4,805 over 30 years. Incremental costs of screening were $403, and benefits were 0.0037 LYS. Five breast cancer deaths occurred in the screened arm and 6 breast cancer deaths occurred in the unscreened arm, a difference of 1 breast cancer averted by screening, with an estimated ICER of $109,852/LYS. The absolute reduction in breast cancer mortality was 0.1%, with a net gain in life expectancy of 1.3 days. The ICER was strongly dependent on age, with the most favorable ICER approximately $100,000/LYS at age 45 years.
Limitations: Costs and clinical data were obtained from the nonindigenous Australian population and may not be generalizable to African Americans on dialysis therapy and indigenous populations from other countries.
Conclusion: Using the most optimistic assumptions, survival gains expected from screening for breast cancer in women on dialysis therapy are very small. Annual population breast cancer screening should not be recommended for all women on dialysis therapy, but should be an individual decision between the patient and health care provider.

17. Quantitative Epstein-Barr virus shedding and its correlation with the risk of post-transplant lymphoproliferative disorder.

Clin Transplant. 2012 Sep-Oct;26(5):741-7.

Holman CJ, Karger AB, Mullan BD, Brundage RC, Balfour HH Jr.

Abstract: We postulated that quantitative monitoring of Epstein-Barr virus (EBV) shedding after transplantation could distinguish EBV-associated illnesses and predict clinical outcome. EBV DNA was measured in solid organ (SOT) and hematopoietic cell transplants (HCT) using our own real-time TaqMan EBV PCR. The proportion of patients who had EBV DNAemia post-transplant was significantly lower in HCT vs. SOT ($p < 0.001$). Over a 7.5-yr period, post-transplant lymphoproliferative disorder (PTLD) occurred in 66 (5.8%) of 1131 patients who met adequate monitoring criteria. SOT recipients developed PTLD significantly later than HCT recipients (median, 2.8 yr vs. 121 d; $p < 0.001$). PTLD was documented in 53 (14%) of 376 patients who had EBV in ≥1 whole blood sample vs. 13 (2%) of 755 patients who had at least three EBV-negative blood samples and were never positive. PTLD risk in viremic patients increased with the peak quantity of EBV DNAemia ($p < 0.001$). PTLD occurred in 37/333 (11%) of patients with peak blood levels 10(3) - 10(5) copies/mL vs. 16/43 (37%) of patients with levels >10(5) ($p < 0.001$). EBV PCR was predictive in 29 (78%) of 37 patients tested within three wk prior to tissue diagnosis of PTLD, and thus, we conclude that EBV PCR with careful attention paid to changes in EBV DNAemia could lead to earlier diagnosis and treatment of PTLD.

18. Monitoring infection with Epstein-Barr virus among seromismatch adult renal transplant recipients.

Am J Transplant. 2011 May;11(5):1058-63.

Martin SI, Dodson B, Wheeler C, Davis J, Pesavento T, Bumgardner GL.

Abstract: Patients who undergo Epstein-Barr virus (EBV) seromismatch (D+/R-) transplants have a higher risk for the development of post-transplant lymphoproliferative disorder (PTLD). Adult renal transplant recipients at a single institution were prospectively monitored for EBV during the first year post-transplant. Over a 2-year period, 34 patients (7.78%) were identified as being EBV D+/R-recipients. Patients who developed symptoms or had persistent viremia were pre-emptively administered rituximab. Six recipients were discharged without monitoring on the protocol. Of those six, three (50%) developed PTLD and all three lost their grafts. Twenty (60.6%) of the 34 recipients developed viremia during the first year post-transplant. Of the recipients who became viremic, six (30%) received rituximab. None of the six who received rituximab-developed PTLD. We found that recipients who were not monitored on the protocol were more likely to have PTLD and graft loss compared to those who were ($p = 0.008$). Post-transplant monitoring of adults who undergo EBV D+/R-kidney transplants for viremia and symptoms associated with EBV infection may prompt intervention which reduces the incidence of PTLD within the first year. Use of rituximab in preventing PTLD among patients with primary EBV infection requires further prospective study to determine its overall safety and efficacy.

19. CD8+ Immunosenescence Predicts Post-Transplant Cutaneous Squamous Cell Carcinoma in High-Risk Patients.

J Am Soc Nephrol. 2016 May;27(5):1505-15.

Bottomley MJ, Harden PN, Wood KJ.

Abstract: Most morbidity associated with malignancy in long-term renal transplant recipients is due to cutaneous squamous cell carcinoma (SCC). Previously identified measures to stratify SCC risk have limited use, however. We hypothesized that an increased proportion of senescent, terminally differentiated CD8(+) T cells would identify renal transplant recipients at elevated SCC risk. Peripheral blood lymphocytes were isolated from 117 stable transplant recipients at high risk of SCC and analyzed phenotypically by flow cytometry. Participants were followed up prospectively for SCC development. The predictive value of variables was assessed using Cox regression. Age at transplant and enrollment, dialysis duration, and previous disease were predictive of SCC development during follow-up. Previously published clinical phenotype-based risk scores lost predictive value with the removal of age as a covariate. The percentage of CD57-expressing CD8(+) T cells was the strongest immunologic predictor of future SCC and correlated with increasing CD8(+) T cell differentiation. We dichotomized participants into those with a majority (CD57hi) and a minority (CD57lo) of CD8(+) T cells expressing CD57; CD57hi participants were more likely to develop SCC during follow-up (hazard ratio, 2.9; 95% confidence interval, 1.0 to 8.0), independent of potential confounders, and tended to develop earlier recurrence. The CD57hi phenotype was stable with time and associated with increasing age and cytomegalovirus seropositivity. Our results show that the CD57hi phenotype is a strong predictor of SCC development and recurrence in this cohort of long-term, high-risk renal transplant recipients. This information may allow identification of recipients who may benefit from intensive dermatologic screening and immunosuppression reduction.

20. CD57 expression in CD8 T cells and development of cutaneous squamous cell carcinoma in renal transplant recipients: a prospective cohort study.

Lancet. 2015 Feb 26;385 Suppl 1:S23.

Bottomley M, Harden P, Wood K.

Background: Cutaneous squamous cell carcinoma is the most common malignancy in renal transplant recipients and a major cause of morbidity and mortality. Various measures have been proposed to identify recipients at increased risk of developing this cancer to allow targeted intervention. CD57 expression might represent a marker of T-cell exhaustion; we hypothesised that expression could predict development of squamous cell carcinoma in renal transplant recipients, and undertook a prospective cohort study to assess its predictive value.

Methods: Renal transplant recipients with and without previous squamous cell carcinoma (matched by race, age, sex, and immunosuppression duration) were recruited at routine clinical follow-up. Peripheral blood lymphocytes were analysed by flow cytometry. Three previously developed risk scores (Harden, Urwin, and Harwood), based on clinical phenotype, were also evaluated. The outcome event was histologically diagnosed squamous cell carcinoma during the study. Ethics approval was granted by local committee. Hazard ratios (HR) were calculated by Cox regression.

Findings: 57 renal transplant recipients with and 53 without previous squamous cell carcinoma were recruited. During a median follow-up of 309 days (IQR 223-409), 20 recipients developed this cancer (including four with a first diagnosis). On univariate analysis increasing age at enrolment, previous squamous cell carcinoma, having the CD57hi phenotype (≥50% of CD8 T cells expressing CD57), and increasing clinical risk score were predictive of cancer development. However, all three clinical risk scores were no longer predictive when adjusted for age. By contrast, transplant recipients displaying CD57hi were at significantly increased risk of future squamous cell carcinoma compared with CD57lo recipients (≤50% of CD8 T cells expressing CD57) (HR 5·0, 95%CI 1·11-22·3; p=0·04); risk remained significant after adjustment for both age (1·1, 1·0-1·1; p=0·04) and history of previous squamous cell carcinoma (3·5, 1·12-11·2; p=0·04).

Interpretation: Our results show that the CD57hi phenotype is a stronger predictor of squamous cell carcinoma development in long-term, at-risk renal transplant recipients than previously identified clinical phenotypes. This finding could help in the identification of renal transplant recipients at high risk of this cancer, who would benefit from intensive dermatological screening and immunosuppression reduction.

21. Natural Killer Lymphocytes Are Dysfunctional in Kidney Transplant Recipients on Diagnosis of Cancer.

Transplantation. 2015 Nov;99(11):2422-30.

Peraldi MN, Berrou J, Venot M, Chardiny V, Durrbach A, Vieillard V, Debré P, Charron D, Suberbielle C, Chevret S, Glotz D, Dulphy N, Toubert A.

Background: The incidence of cancer is increased after solid organ transplantation. Natural killer (NK) cells are key effectors of the tumor immune response.
Methods: We conducted a cross sectional multicentre matched case-control study including 42 kidney transplant recipients (KTRs) on diagnosis of cancer and 41 KTRs without cancer. Extensive phenotyping of NK cells populations and functional tests of NK cells were performed.
Results: Kidney transplant recipients with cancer had a higher incidence of acute rejection (P = 0.02) and cytomegalovirus (CMV) infection (P = 0.03) than controls. They had more lymphopenia than control KTRs (1020/mm3 +/- 32 vs 1218/mm3 +/- 34; P = 0.001) including a CD4+ lymphopenia (P = 0.01). Total CD3-/CD56+ NK cell counts were similar in both groups. However, KTRs with cancer had a lower frequency of the cytokine-enriched CD56bright NK cell subset (P = 0.001). The percentage of NK cells expressing NKp46 was decreased in KTRs with cancer (45% vs 53 %, P = 0.001). Furthermore, the ability of NK cells to degranulate CD107a+ cytolytic vesicles was reduced (11% vs 22%; P = 0.02), and the percentage of NK cells secreting IFN[gamma] was decreased (7.5% vs 28.8%; P = 0.01) in KTRs with cancer.
Conclusions: These results reveal an imbalance between NK cell subpopulations and functional NK cell defects in KTRs at the diagnosis of malignancy, including a decreased expression of NKp46 and decreased numbers of NK cells producing INF[gamma]. This study highlights the role of NKp46, a major activating NK cell receptor, which could be considered as a potential marker during immunological follow-up of KTRs.

22. The immune phenotype may relate to cancer development in kidney transplant recipients. Kidney Int. 2014 Jul;86(1):175-83.
Hope CM, Grace BS, Pilkington KR, Coates PT, Bergmann IP, Carroll RP.

Abstract: High regulatory T-cell (Treg) numbers predict recurrent cutaneous squamous cell carcinoma in kidney transplant recipients, and the Treg immune phenotype may identify kidney transplant recipients at risk of developing squamous cell carcinoma and/or solid-organ cancer. To investigate this, a total of 116 kidney transplant recipients, of whom 65 had current or past cancer, were immune-phenotyped and followed up prospectively for a median of 15 months. Higher Treg (CD3+CD4+FOXP3+CD25(Hi)CD127(Lo)) proportion and numbers significantly increased the odds of developing cancer (odds ratios (95% CI) 1.61 (1.17-2.20) and 1.03 (1.00-1.06), respectively) after adjusting for age, gender, and duration of immunosuppression. Class-switched memory B cells (CD19+CD27+IgD-) had a significant association to cancer, 1.04 (1.00-1.07). Receiver operator characteristic (ROC) curves for squamous cell carcinoma development within 100 days of immune phenotyping were significant for Tregs, memory B cells, and γδ T cells (AUC of 0.78, 0.68, and 0.65, respectively). After cancer resection, Treg, NK cell, and γδ T-cell numbers fell significantly. Immune-phenotype profiles associated with both squamous cell carcinoma and solid-organ cancer in kidney transplant recipients and depended on the presence of cancer tissue. Thus, immune profiling could be used to stratify kidney transplant recipients at risk of developing cancers to identify those who could qualify for prevention therapy.

23. The benefits of cancer screening in kidney transplant recipients: a single-center experience.
Cancer Med. 2016 Feb;5(2):153-8.
Kato T, Kakuta Y, Abe T, Yamanaka K, Imamura R, Okumi M, Ichimaru N, Takahara S, Nonomura N.

Abstract: The frequency of malignancy is increasing in kidney transplant recipients. Posttransplant malignancy (PTM) is a major cause of long-term graft survival inhibition. In this study, we evaluated the frequency and prognosis of PTM at our center and examined the efficacy of cancer screening. Between 1972 and 2013, 750 patients were followed-up at our center. Annual physical examinations and screenings were performed to detect PTM. We investigated the detail of two distinctive cancer groups: screening-detected cancers and symptom-detected cancers. Seventy-seven PTM were identified during the follow-up period. The mean age at the initial PTM detection was 43.6 ± 12.8 years. The mean interval from transplantation to cancer diagnosis was 134.5 ± 11.3 months. Among the 77 patients, posttransplant lymphoproliferative disease (PTLD) was the most common cancer (19.5%, 15/77), followed by renal cell carcinoma (15.6%, 12/77). Of the cancer cases, 46.8% (36/77) were detected via screening. The most frequently screening-detected cancer was renal cell carcinoma of the native kidney and breast cancer (22.2%, 8/36). However, it was difficult to detect PTLD, urothelial carcinoma, and colorectal cancer via screening. Interestingly, Cox proportional regression analyses revealed nonscreened recipients to be a significant prognostic factor for PTM ($P < 0.001$). This study is the first to report that appropriate screening tests play a key role in early PTM diagnosis and lead to reduce the mortality rate in kidney transplant recipients. These findings support the provision of long-term appropriate screening for kidney transplant recipients.

24. De Novo Malignancies After Transplantation: Risk and Surveillance Strategies.
Med Clin North Am. 2016 May;100(3):551-67.
Doycheva I, Amer S, Watt KD.

Abstract: De novo malignancies are one of the leading causes of late mortality after liver and kidney transplantation. Nonmelanoma skin cancer is the most common malignancy, followed by posttransplant lymphoproliferative disorder and solid organ tumors. Immunosuppression is a key factor for cancer development, although many other transplant-related and traditional risk factors also play a role. In this review, the authors summarize risk factors and outcomes of frequently encountered de novo malignancies after liver and kidney transplantation to stratify recipients at highest risk. Future efforts in prospectively validated, cost-effective surveillance strategies that improve survival of these complex patients are greatly needed.

25. Cancer screening in the United States, 2015: a review of current American cancer society guidelines and current issues in cancer screening.

CA Cancer J Clin. 2015 Jan-Feb;65(1):30-54.

Smith RA, Manassaram-Baptiste D, Brooks D, Doroshenk M, Fedewa S, Saslow D, Brawley OW, Wender R.

Abstract: Each year, the American Cancer Society (ACS) publishes a summary of its guidelines for early cancer detection along with a report on data and trends in cancer screening rates and select issues related to cancer screening. In this issue of the journal, we summarize current ACS cancer screening guidelines. The latest data on utilization of cancer screening from the National Health Interview Survey (NHIS) also is described, as are several issues related to screening coverage under the Affordable Care Act, including the expansion of the Medicaid program.

26. ERBP Guideline on the Management and Evaluation of the Kidney Donor and Recipient. Nephrol Dial Transplant. 2013 Aug;28 Suppl 2:ii1-71.

European Renal Best Practice Transplantation Guideline Development Group.

Abstract not available

27. KHA-CARI: Kidney Health Australia - Caring for Australasians with Renal Impairment. KHA-CARI guideline: recipient assessment for transplantation.

Nephrology (Carlton). 2013 Jun;18(6):455-62.

Campbell S, Pilmore H, Gracey D, Mulley W, Russell C, McTaggart S;

Abstract not available

28. KDIGO clinical practice guideline for the care of kidney transplant recipients.
Am J Transplant. 2009 Nov;9 Suppl 3:S1-155.
Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group.

Abstract: The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the monitoring, management, and treatment of kidney transplant recipients is intended to assist the practitioner caring for adults and children after kidney transplantation. The guideline development process followed an evidence-based approach, and management recommendations are based on systematic reviews of relevant treatment trials. Critical appraisal of the quality of the evidence and the strength of recommendations followed the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach. The guideline makes recommendations for immunosuppression, graft monitoring, as well as prevention and treatment of infection, cardiovascular disease, malignancy, and other complications that are common in kidney transplant recipients, including hematological and bone disorders. Limitations of the evidence, especially on the lack of definitive clinical outcome trials, are discussed and suggestions are provided for future research.

Proyecto Prometeo II

Grupo III

Prevención del cáncer postrasplante renal: de los factores clásicos a la inmunosupresión

Referencias Bibliográficas

Organizado por

SET
SOCIEDAD ESPAÑOLA DE TRASPLANTE

Con la colaboración de

NOVARTIS

1. Clinical Insights for Cancer Outcomes in Renal Transplant Patients

Transplantation Proceedings, 42, S36–S40 (2010)

Alberú J.

Abstract: The long-term fate of renal transplant recipients has remained relatively unchanged over the last 15 years. The cumulative, chronic effects of immunosuppression contribute, to a great extent, to the higher, premature mortality rates linked to cardiovascular disease and malignancy observed in this patient population. Immunosuppression disrupts both antitumor surveillance and antiviral activities, and oncogenic viruses predispose to specific malignancies. Further, some drugs promote carcinogenesis by mechanisms independent of their immunosuppressive effects. In vitro studies have shown that calcineurin inhibitors (CNIs) promote tumor progression by a transforming growth factor--dependent mechanism.

In contrast, in vivo mouse models have demonstrated that mammalian target of rapamycin (mTOR) inhibitors inhibit metastatic tumor growth and angiogenesis. The association between mTOR-inhibitor and reduced malignancy has been demonstrated in several studies. United Network for Organ Sharing registry data demonstrate that an mTOR-inhibitor either with or without a CNI, is associated with a reduced incidence of tumors compared to regimens that do not utilize mTOR-inhibitor Five years after renal transplantation, patients in the Rapamune Maintenance Regimen study who received sirolimus (SRL)-based CNI-free therapy after cyclosporine (CsA) withdrawal at 3 months showed a reduced incidence of malignancy compared with those who continued a regimen including (CsA) In the CONVERT study, patients who converted to SRL displayed a significantly lower malignancy rate (3.8%) at 24 months compared with those who continued CNI based therapy (11%; $P < .001$). A randomized, prospective study to evaluate the effect of conversion to SRL from a CNI, compared with continued CNI, showed that SRL was associated with a lower rate of nonmelanoma skin cancer (NMSC) and a longer time to first biopsy-confirmed new NMSC. An mTOR-inhibitor CNI-free regimen should be considered for transplant recipients at high risk for cancer development and for those who develop malignancies over the posttransplant course.

2. Lower Malignancy Rates in Renal Allograft Recipients Converted to Sirolimus-Based, Calcineurin Inhibitor-Free Immunotherapy: 24-Month Results From the CONVERT Trial
Transplantation 2011;92: 303–310

Alberú J, Pascoe MD, Campistol JM, Schena FP, Rial Mdel C, Polinsky M, Neylan JF, Korth-Bradley J, Goldberg-Alberts R, Maller ES; Sirolimus CONVERT Trial Study Group

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Background: Long-term immunosuppression imposes increased malignancy risk in renal allograft recipients, significantly contributing to overall morbidity and mortality. This study examined malignancy rates in renal allograft recipients at 2 years after conversion to a sirolimus (SRL)-based, calcineurin inhibitor (CNI)-free regimen.
Methods: This open-label, randomized, multicenter study (the CONVERT Trial) randomly assigned 830 patients to SRL conversion (n=555) or CNI continuation (n=275). Patients with history of posttransplant lymphoproliferative disease or known/suspected malignancy within 5 years before screening were excluded. As part of standard safety measurements, subjects were monitored for any malignancy occurrence; both skin and nonskin malignancies were reported, even if the patient discontinued from the therapy. Malignancy rates were analyzed based on exposure time to study drugs (i.e., number of events per 100 person-years of follow-up).
Results: At 2 years postconversion, the total number of malignancies per 100 person-years of exposure was significantly lower among SRL conversion patients compared with CNI continuation (2.1 vs. 6.0, P<0.001). Patients undergoing SRL based, CNI-free therapy had significantly lower rates of the subset of nonmelanoma skin carcinomas through 2 years postconversion (1.2 vs. 4.3, P<0.001). This difference persisted after excluding patients with a history of malignancy before randomization. The rate of all other malignancies was not significantly different between treatment groups (P=0.058).
Conclusion: In renal allograft recipients, SRL-based immunosuppression was associated with a lower rate of malignancy at 2 years postconversion compared with continuation of CNI-based immunosuppression. This reduction was driven by a significant reduction in nonmelanoma skin carcinoma rates; the rate of all other malignancies was numerically lower but did not achieve statistical significance.

3. Monotherapy Rapamycin in Renal Transplant Recipients With Lymphoma Successfully Treated With Rituximab

Transplantation Proceedings, 41, 2435–2437 (2009)

Alexandru S., Gonzalez E., Grande C., Hernandez A., Morales E., Praga M., Andrés A., and Morales J.M.

Abstract: Posttransplantation B-lymphoproliferative (PTBL) disease is a severe complication of organ transplantation, which requires reduction of immunosuppressive treatment. The use of the anti-CD20 monoclonal antibody, Rituximab, improves the survival of these patients. In this setting, maintenance immunosuppressive therapy may represent a challenge. The mammalian target of rapamycin (m-TOR) inhibitor Rapamycin has antiproliferative effects that makes it a safe, efficient option to avoid graft rejection and reduce the malignancy risk. We studied 6 renal recipients (4 men and 2 women) of overall mean age of 50.66 ± 15.89 years who were diagnosed with lymphoma at a mean time of graft function of 137.0 ± 68.00 months. All of the patients were Epstein-Barr–negative. Four received a combination of Rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and 2 received Rituximab only. In all cases complete remission persisted during follow-up of 21.83 ± 8.34 months. The immunosuppressive treatment was switched to the m-TOR inhibitor Rapamycin at therapeutic trough blood levels of 5–8 ng/dL. The mean time of Rapamycin treatment was 15.5 ± 8.96 months. Notably, we observed neither acute rejection nor relapse episodes. Renal function remained stable with no significant proteinuria. The serum creatinine level before switching to Rapamycin was 1.06 ± 0.16 mg/dL and 0.9 ± 0.14 mg/dL 12 months later. However, 1 patient had to stop Rapamycin treatment due to pneumonitis. Our study suggests that immunosuppressant monotherapy with Rapamycin is safe and efficient for renal recipients who develop lymphoma because of its antitumor effects without nephrotoxicity.

4. Cancer incidence after immunosuppressive treatment following kidney transplantation
Critical Reviews in Oncology/Hematology 56 (2005) 71–85
Andrés A.

Abstract: Cancer incidence is increased in renal transplant recipients due to immunosuppressant treatment that should be maintained to prevent and treat acute rejection. Use of new and very potent immunosuppressants has made it possible to reduce acute rejection incidence and improve renal graft survival, although increase of infections and post-transplant neoplasms have become clearer. On the other hand, renal transplant candidates who remain on dialysis have a greater prevalence of neoplasms than the age-matched general population, either because the neoplasm was the cause of their renal failure (multiple myeloma or kidney or urinary tract cancers) or because their renal disease entails a risk for cancer development (acquired cystic disease or analgesic nephropathy).
Practically, all de novo neoplasms have a greater incidence in renal transplant patients. Cutaneous neoplasms are the most prevalent in renal transplant recipients and their incidence increases with transplant time. Post-transplant lymphoproliferative diseases are more frequent in patients who receive greater immunosuppression (antithymocyte/antilymphocyte globulin or OKT3) or are infected de novo by Epstein Barr Virus (EBV) through the transplanted kidney. Kaposi's sarcoma has a high incidence in the renal transplanted population, does not appear in the general population, and is related with Human Herpes Virus 8 (HHV-8) infections. The incidence of tumors in non-functioning native kidneys is especially high in renal transplant due to the presence of acquired cystic disease or analgesic nephropathy.
Gold standards of post-transplant de novo renal neoplasm prevention are modulating immunosuppression and avoiding exposure to sunlight and to different oncogenic viruses (EBV, cytomegalovirus, hepatitis B and C viruses).

5. Long-Term Maintenance of Calcineurin Inhibitor Monotherapy Reduces the Risk for Squamous Cell Carcinomas After Kidney Transplantation Compared With Bi- or Tritherapy

Transplantation Proceedings, 39, 2592–2594 (2007)

Abou Ayache R., Thierry A., Bridoux F., Bauwens M., Belmouaz M., Desport E., and Touchard G.

Abstract: The incidence of skin cancer after organ transplantation is mainly related to type, level, and duration of immunosuppression. The immunosuppressive minimization strategy reduces skin malignancies, but no data are available concerning long-term calcineurin inhibitor (CNI) monotherapy compared with bi- or tritherapy. We studied the benefits of long-term CNI monotherapy (6 years of exposure) with regard to the incidence of squamous cell carcinomas (SCC) and basal cell carcinomas (BCC) compared with bi- or tritherapy, among first renal allograft adult recipients who were more than 6 years posttransplantation. Among 294 renal transplantations performed between 1986 and 1999, 80 patients received CNI monotherapy (MT) and 86 patients bi- or tritherapy (BTT) with a follow-up of more than 6 years. MT patients were older, had longer follow-up, and fewer biopsy-proven acute rejection episodes. The incidence of SCC was 15.9 SCC/1000 patients/year for MT vs 26.2 for BTT ($P = .07$). The incidence was significantly lower for patients older than 40 years (22.4 vs 56, respectively; $P < .01$). The incidence of BCC was 28.3 BCC/1000 patients/year for MT and 10.1 for BTT ($P = .05$), which failed to show a significant difference in patients older than 40 years (39.7 vs 25, respectively; $P = .09$). The ratio of SCC/BCC in MT was maintained around 1/2 over time, while it exceeded 2/1 in BTT after 12 years posttransplantation. Patient survival was comparable between the 2 groups. A higher graft survival rate was observed in the MT group. CNI monotherapy should be considered to be a beneficial, safe immunosuppressive minimization strategy for SCC in selected recipients.

6. Effectiveness of a combination therapy using calcineurin inhibitor and mTOR inhibitor in preventing allograft rejection and post-transplantation renal cancer progression

Cancer Lett. 2012 Aug 28;321(2):179-86

Basu A, Liu T, Banerjee P, Flynn E, Zurakowski D, Datta D, Viklicky O, Gasser M, Waaga-Gasser AM, Yang J, Pal S.

Abstract: Calcineurin inhibitors (CNIs) may promote post-transplantation cancer through altered expression of cytokines and chemokines in tumor cells. We found that there is a potential cross-talk among CNI induced signaling molecules and mTOR. Here, we utilized a murine model of post-transplantation cancer to examine the effect of a combination therapy (CNI + mTOR-inhibitor rapamycin) on allograft survival and renal cancer progression. The therapy prolonged allograft survival; and significantly attenuated CNI-induced post-transplantation cancer progression, with down-regulation of mTOR and S6-kinase phosphorylation. Also, rapamycin inhibited CNI-induced over-expression of the angiogenic cytokine VEGF, and the chemokine receptor CXCR3 and its ligands in post-transplantation tumor tissues.

7. Prevention of Skin Cancer and Reduction of Keratotic Skin Lesions During Acitretin Therapy in Renal Transplant Recipients: A Double-Blind, Placebo-Controlled Study

J Clin Oncol. 1995 Aug;13(8):1933-8.

Bavinck JN1, Tieben LM, Van der Woude FJ, Tegzess AM, Hermans J, ter Schegget J, Vermeer BJ.

Purpose: The purpose of this study was to investigate the effect of acitretin on the development of keratotic skin lesions, and on squamous cell carcinomas and basal cell carcinomas in a group of renal transplant recipients.

Patients and methods: Forty-four renal transplant recipients with more than 10 keratotic skin lesions on the hands and forearms were enrolled onto a randomized, double-blind, placebo-controlled trial to test the possible skin cancer-preventing effect of a 6-month treatment with acitretin 30 mg/d.

Results: No deterioration in renal function occurred in any of the 38 assessable patients treated. During the 6-month treatment period, two of 19 patients (11%) in the acitretin group reported a total of two new squamous cell carcinomas, compared with nine of 19 patients (47%) in the placebo group who developed a total of 18 new carcinomas (chi 2 = 6.27, P = .01). The relative decrease in the number of keratotic skin lesions in the acitretin group was 13.4%, as compared with a relative increase in the placebo group of 28.2% (difference, 41.6%; 95% confidence interval, 11.5 to 71.7). Most patients treated with acitretin had mild mucocutaneous side effects, but these were easily manageable. Some patients experienced mild hair loss. With the exception of three patients, no increase in serum cholesterol or triglyceride above pretreatment levels was observed, and liver function remained unchanged in all patients.

Conclusion: Acitretin 30 mg/d over 6 months had significantly more effect than placebo in the prevention of squamous cell carcinomas and reduced the occurrence of keratotic skin lesions in a group of renal transplant recipients with severe lesions. This effect was most pronounced in patients with a history of squamous cell carcinomas and basal cell carcinomas.

8. Combined introduction of anti-IL2 receptor antibodies, mycophenolic acid and tacrolimus: effect on malignancies after renal transplantation in a single-centre retrospective cohort study

Nephrol Dial Transplant. 2012 Jun;27(6):2547-53

Braconnier P, Del Marmol V, Broeders N, Kianda M, Massart A, Lemy A, Ghisdal L, Le Moine A, Madhoun P, Racapé J, Abramowicz D, Wissing KM.

Background: Several studies suggest that the introduction of tacrolimus (TRL), mycophenolic acid (MPA) and interleukin 2 receptor antibodies (IL2Ra) as single drugs more than a decade ago has not increased the risk of malignancy after renal transplantation. However, only limited data are available on their carcinogenic effects when used in combination as a potent immunosuppressive regimen.

Methods: A retrospective single-centre cohort study on 929 adult renal transplant recipients. Investigation of the effect of two consecutive immunosuppressive regimens [1993-98, N = 405, anti-lymphocyte antibodies, cyclosporine and azathioprine (AZA); 1999-2007, N = 524, predominantly IL2Ra, TRL and MPA] on the incidence rate of skin cancer, solid tumours and post-transplant lymphoproliferative disease (PTLD).

Results: In total, 365 malignancies developed among 113 patients. As compared to the previous cyclosporine and AZA-based immunosuppression, the introduction of the new immunosuppressive regimen did not increase the incidence rate of skin cancer [rate ratio 0.84; 95% confidence interval (CI) 0.48-1.46], solid tumours (0.89; 95% CI 0.46-1.67) and PTLD (0.82; 95% CI 0.28-2.21). Patients treated with the more recent regimens less frequently developed multiple skin cancers and invasive squamous cell cancer. Skin cancer after transplantation was strongly associated with the development of solid tumours (odds ratio 5.2; $P < 0.0001$). The introduction of the new immunosuppressive drugs reduced the incidence of first year acute rejection from 34.8 to 13.2% ($P < 0.0001$).

Conclusion: Although significantly more efficient in the prevention of acute rejection, the introduction of TRL, MPA and IL2Ra-based immunosuppression after kidney transplantation was not associated with an increased incidence of skin cancer, solid tumours or PTLD.

9. Malignancy after Transplantation

Transplantation. 2005 Oct 15;80(2 Suppl):S254-64.

Buell JF, Gross TG, Woodle ES.

Abstract: As newer immunosuppressive regimens have steadily reduced the incidence of acute rejection and have extended the life expectancy of allograft recipients, posttransplant malignancy has become an important cause of mortality. In fact, it is expected that cancer will surpass cardiovascular complications as the leading cause of death in transplant patients within the next 2 decades. An understanding of the underlying pathobiology and how to minimize cancer risks in transplant recipients are essential. The etiology of posttransplant malignancy is believed to be multifactorial and likely involves impaired immunosurveillance of neoplastic cells as well as depressed antiviral immune activity with a number of common posttransplant malignancies being viral-related. Although calcineurin inhibitors and azathioprine have been linked with posttransplant malignancies, newer agents such as mycophenolate mofetil and sirolimus have not and indeed may have antitumor properties. Long-term data are needed to determine if the use of these agents will ultimately lower the mortality due to malignancy for transplant recipients.

10. Randomized Controlled Trial of Sirolimus for Renal Transplant Recipients at High Risk for Nonmelanoma Skin Cancer

Am J Transplant. 2012 May;12(5):1146-56

Campbell SB, Walker R, Tai SS, Jiang Q, Russ GR.

Abstract: Sirolimus has antineoplastic effects and may reduce skin cancer rates in kidney transplant patients. This prospective, multicenter, randomized, open-label, controlled trial randomized 86 kidney transplant recipients (≥1 year posttransplant) with history of nonmelanoma skin cancer (NMSC) to continue calcineurin inhibitor (CNI) or convert to sirolimus. Patients were stratified by number of NMSC lesions (0-5, 6-20) in previous year. Primary end point was number of biopsy-confirmed new NMSC lesions per patient-year. Yearly NMSC rate was significantly lower with sirolimus (1.31 vs. 2.48 lesions/patient-year; p = 0.022). Squamous cell carcinoma occurred at a lower rate in the sirolimus versus CNI group (p = 0.038); basal cell carcinoma rate was similar in both. A lower proportion of patients receiving sirolimus developed new or recurrent NMSC (56.4% vs. 80.9%; p = 0.015) or new squamous cell carcinoma (41.0% vs. 70.2%; p = 0.006). No sirolimus patients and one CNI continuation patient experienced acute rejection. Incidence of treatment-emergent adverse events was similar between groups; however, discontinuation rates related to adverse events were significantly higher with sirolimus (46.2% vs. 0%; p < 0.001). In kidney transplant recipients with history of NMSC, conversion from CNI to sirolimus reduced rates of NMSC, without increasing acute rejection risk.

11. Minimizing the Risk of Posttransplant Malignancy
Transplantation. 2009 Apr 27;87(8 Suppl):S19-22
Campistol JM.

Abstract: Nowadays cancer represents the second main cause of death in renal transplant patients with normal function of the graft. The incidence is 10 to 20 times higher than normal population. Calcineurin inhibitor therapy contributes to the increase in the development of neoplasia. Important evidence could bring a preventive effect of mammalian target of rapamycin in skin cancer, Kaposi's sarcoma, and renal cell carcinoma.

12. Ridurre al minimo il rischio di neoplasie post-trapianto
G Ital Nefrol 2010; 27 (S50): S81-S85
Campistol JM.

Minimizing the risk of cancer in transplant patients Recent improvements in immunosuppressive therapies have reduced the incidence of acute rejection and increased patient survival. These agents may however contribute to higher rates of mortality due to an increased risk of cardiovascular disease or malignancy. Transplant patients are in an immunocompromised state, and have a reduced ability to combat the development of malignancy. The higher risk for the activity of oncoviruses may also contribute to the higher incidence and the specific tumor types seen.
Some immunosuppressants may have a direct oncogenic effect. In vitro data have demonstrated that calcineurin inhibitors (CNIs) may have a direct effect on tumor growth and the development of metastases. In contrast, mTOR inhibitors have demonstrated in vitro antitumoral properties, perhaps via a potent antiangiogenic effect.
Recent studies and registry analyses have confirmed that mTOR inhibitors are associated with a reduced incidence of malignancies. UNOS data demonstrated that an mTOR inhibitor, with or without a CNI, is associated with a reduced incidence of cancer compared to regimens without mTOR inhibitors. The Rapamune Maintenance Regimen study demonstrated that patients receiving sirolimus-based, CNI-free therapy after CsA withdrawal at 3 months had a reduced incidence of malignancy at 5 years post-transplant compared with those who continued a regimen including CsA. In the CONVERT study, patients converted to sirolimus had significantly lower malignancy rates (3.1%) at 24 months compared with those who continued CNI-based therapy (9.8%, $p<0.001$). The elimination of CNIs and the introduction of sirolimus may therefore have a role in reducing the risk of cancer in post-transplant patients.
Conflict of interest: None

13. Practical recommendations for the early use of m-TOR inhibitors (sirolimus) in renal transplantation

Transpl Int. 2009 Jul;22(7):681-7.

Campistol JM, Cockwell P, Diekmann F, Donati D, Guirado L, Herlenius G, Mousa D, Pratschke J, San Millán JC.

Abstract: m-TOR inhibitors (e.g. sirolimus) are well-tolerated immunosuppressants used in renal transplantation for prophylaxis of organ rejection, and are associated with long-term graft survival. Early use of sirolimus is often advocated by clinicians, but this may be associated with a number of side-effects including impaired wound-healing, lymphoceles and delayed graft function. As transplant clinicians with experience in the use of sirolimus, we believe such side-effects can be limited by tailored clinical management. We present recommendations based on published literature and our clinical experience. Furthermore, guidance is provided on sirolimus use during surgery, both at transplantation and for subsequent operations.

14. Acitretin and skin cancer in kidney transplanted patients. Clinical and histological evaluation and immunohistochemical analysis of lymphocytes, natural killer cells and Langerhans cells in sun exposed and sun protected skin

Clin Transplant 2005: 19: 115–121

Carneiro RV1, Sotto MN, Azevedo LS, Ianhez LE, Rivitti EA.

Background: Renal transplanted recipients have an increased incidence of actinic keratosis and skin cancer.
Methods: In order to examine the chemoprophylatic effects of low-dose acitretin on keratosis and skin cancer development we submitted 13 renal transplanted patients who presented actinic keratosis to acitretin therapy (20 mg/d) for 12 months. The patients were assessed at monthly intervals during the first 6 months and every 2 months until the 12th month for new skin lesions and for acitretin toxicity. Normal skin biopsies of sun exposed and sun protected areas were taken for histopathological examination and submitted to immunohistochemistry technique to demonstrate CD4+ and CD8+ T lymphocytes, natural killer (NK) cells and Langerhans' cells which were counted and compared before, after 6 and 12 months of the treatment.
Results: There was an improvement of actinic keratosis in all patients. Only one patient developed new skin cancer. Side-effects were well tolerated and no significant biochemical effects were observed. There were no differences in the microscopic aspects of the skin and in the number of CD4+ and CD8+ T lymphocytes and NK cells. There was a significant increase in the number of epidermal Langerhans' cells after 12 months of acitretin therapy.
Conclusions: The data obtained permit us to conclude that low dose acitretin therapy is safe, well tolerated and partially effective in chemoprophylaxis of skin cancer in renal transplant recipients. The increase in epidermal Langerhans' cells observed may be an expression of the immunomodulatory effect of acitretin.

15. Non-Melanoma Skin Cancer Incidence and Risk Factors After Kidney Transplantation: A Canadian Experience

Transplantation. 2008 Aug 27;86(4):535-41.

Comeau S, Jensen L, Cockfield SM, Sapijaszko M, Gourishankar S.

Background: Non-melanoma skin cancer (NMSC) after kidney transplantation is common and can result in significant morbidity and mortality. Incidence and risk factors for NMSC can vary between geographic locations and there is no literature describing the incidence or risk factors for NMSC in Canada.
Methods: The purpose of this retrospective cohort study was to determine the incidence of NMSC, the time of development of NMSC, and risk factors (including sun exposure history) for NMSC in kidney transplant recipients between 1990 and 2003 in our center (n=926).
Results: We observed a 9.7% incidence of NMSC lesions after kidney transplant with a median time of development of a first NMSC lesion of 4 years. Risk factors for NMSC (multivariate analysis) include older men (>45 years), a history of posttransplant warts, and longer duration of residence in a northern climate.
Conclusion: We conclude that NMSC is common after kidney transplantation in a northern climate and these individuals require disease prevention-specific education, more vigilant surveillance and early referral and treatment.

16. Cytomegalovirus-Induced γδ T Cells Associate with Reduced Cancer Risk after Kidney Transplantation

J Am Soc Nephrol. 2010 Jan; 21(1): 181–188.

Couzi L, Levaillant Y, Jamai A, Pitard V, Lassalle R, Martin K, Garrigue I, Hawchar O, Siberchicot F, Moore N, Moreau JF, Dechanet-Merville J, Merville P.

Abstract: An increase in the number of blood γδ T cells follows cytomegalovirus (CMV) infection in kidney transplant recipients. These cells react against CMV-infected cells and tumor epithelial cells in vitro. We hypothesized that these CMV-induced γδ T cells play a protective role against cancer in kidney transplant recipients. We performed a longitudinal case-control study involving 18 recipients who developed cancer between 2 and 6 yr after transplantation and 45 recipients who did not. The median percentage of γδ T cells among total lymphocytes in patients with malignancies was significantly lower compared with that in control patients at 6, 12, and 18 mo before the diagnosis of cancer. Patients with a γδ T cell percentage of more than 4% were protected from cancer. An increase of the $V\delta2^{neg}$ γδ T cell subset significantly associated with lower incidence of cancer only in recipients who experienced pre- or postgraft CMV infection. Finally, a retrospective follow-up of 131 recipients for 8 yr revealed that CMV-naive recipients had an approximately 5-fold higher risk of cancer compared with CMV-exposed patients. In summary, these results suggest a protective role of CMV exposure against cancer in kidney transplant recipients.

17. Cardiovascular disease and neoplasms after pancreas transplantation
Lancet. 1998 Jul 4;352(9121):65; author reply 66.
Secchi A, Caldara R, La Rocca E, Fiorina P, Di Carlo V.

With respect to Edmond Ryan's April 11 commentary1 on the clinical indications of pancreas transplantation, we would briefly report our experience. Since 1985 we have enrolled 333 insulin-dependent diabetic patients to the kidney-pancreas transplantation programme: 107 patients received kidney-pancreas (KP) transplantation (25 duct-obstruction [KPS group], 82 bladder diversion [KPW group]); 34 patients received kidney transplantation alone (KA group; pancreas not available); and 192 patients remained on the waiting-list (WL group).

18. Evolution of hepatitis B management in kidney transplantation

World J Gastroenterol. 2014 Jan 14;20(2):468-74

Yap DY, Chan TM.

Abstract: Chronic hepatitis B virus (HBV) infection adversely influences the clinical outcomes of renal transplant recipients owing to increased hepatic complications. Management of HBV infection in kidney transplant recipients presents a challenge to clinicians, especially in endemic regions. Interferon precipitates renal allograft dysfunction. Treatment with lamivudine, the first oral nucleoside analogue available, resulted in effective viral suppression, reduced liver-related complications, and improved patient survival so that medium-term data showed comparable patient survival rates between hepatitis B surface antigen-positive and HBsAg-negative kidney transplant recipients in the era of effective antiviral therapies. Entecavir has replaced lamivudine as first-line therapy for treatment-naïve subjects in view of the propensity for drug resistance with the latter. Management of HBV infection in kidney transplant patients needs to take into consideration the nephrotoxicity of nucleoside/tide analogues such as adefovir and tenofovir. Prevention of HBV-related complications in kidney transplant recipients starts much earlier prior to transplantation, with vaccination of patients with chronic kidney disease and donor-recipient matching with regard to HBV status. In addition to anti-viral treatment, patients with chronic HBV infection must have regular surveillance for liver cancer and assessment for the development of cirrhosis.

19. Skin cancers in organ transplant recipients.
Ann Transplant. 1997;2(4):28-32.
Euvrard S1, Kanitakis J, Pouteil-Noble C, Claudy A, Touraine JL.

Abstract: Organ transplant recipients on immunosuppressive therapy are prone to skin cancers, especially squamous cell carcinomas developing on sun-exposed areas. Their frequency increases with time after transplantation reaching 40-70% of the patients after 20 years. Squamous cell carcinomas tend to be multiple and may have a life-threatening course. Most studies concern kidney transplant recipients but new data are now available on recipients of other organs. Carcinogenic factors include mainly immunosuppressive treatments, UV light and human papillomaviruses; the role of genetic factors is more equivocal. Melanomas and other rare tumors such as Merkel cell tumors or sarcomas are also increased. Surgical excision with histological examination represents the treatment of choice. When lesions become multiple and/or aggressive, additional therapeutic methods are necessary, such as topical or oral retinoids and in some cases, reduction of the immunosuppressive treatment. Radiotherapy should be reserved to limited cases. Prevention must be undertaken by a regular dermatological examination and sun protection.

20. Sirolimus and Secondary Skin-Cancer Prevention in Kidney Transplantation

N Engl J Med. 2012 Jul 26;367(4):329-39

Euvrard S, Morelon E, Rostaing L, Goffin E, Brocard A, Tromme I, Broeders N, del Marmol V, Chatelet V, Dompmartin A, Kessler M, Serra AL, Hofbauer GF, Pouteil-Noble C, Campistol JM, Kanitakis J, Roux AS, Decullier E, Dantal J; TUMORAPA Study Group.

Background: Transplant recipients in whom cutaneous squamous-cell carcinomas develop are at high risk for multiple subsequent skin cancers. Whether sirolimus is useful in the prevention of secondary skin cancer has not been assessed.

Methods: In this multicenter trial, we randomly assigned transplant recipients who were taking calcineurin inhibitors and had at least one cutaneous squamous-cell carcinoma either to receive sirolimus as a substitute for calcineurin inhibitors (in 64 patients) or to maintain their initial treatment (in 56). The primary end point was survival free of squamous-cell carcinoma at 2 years. Secondary end points included the time until the onset of new squamous-cell carcinomas, occurrence of other skin tumors, graft function, and problems with sirolimus.

Results: Survival free of cutaneous squamous-cell carcinoma was significantly longer in the sirolimus group than in the calcineurin-inhibitor group. Overall, new squamous-cell carcinomas developed in 14 patients (22%) in the sirolimus group (6 after withdrawal of sirolimus) and in 22 (39%) in the calcineurin-inhibitor group (median time until onset, 15 vs. 7 months; P=0.02), with a relative risk in the sirolimus group of 0.56 (95% confidence interval, 0.32 to 0.98). There were 60 serious adverse events in the sirolimus group, as compared with 14 such events in the calcineurin-inhibitor group (average, 0.938 vs. 0.250). There were twice as many serious adverse events in patients who had been converted to sirolimus with rapid protocols as in those with progressive protocols. In the sirolimus group, 23% of patients discontinued the drug because of adverse events. Graft function remained stable in the two study groups.

Conclusions: Switching from calcineurin inhibitors to sirolimus had an antitumoral effect among kidney-transplant recipients with previous squamous-cell carcinoma. These observations may have implications concerning immunosuppressive treatment of patients with cutaneous squamous-cell carcinomas. (Funded by Hospices Civils de Lyon and others; TUMORAPA ClinicalTrials.gov number, NCT00133887.).

21. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.6.2. Cancer risk after renal transplantation. Skin cancers: prevention and treatment.

Nephrol Dial Transplant. 2002;17 Suppl 4:31-6.

EBPG Expert Group on Renal Transplantation.

Guidelines: D. Due to the high prevalence of skin cancers after organ transplantation, it is highly recommended to inform patients about self-awareness. E. Primary prevention should include the avoidance of sun exposure, use of protective clothing and use of an effective sunscreen (protection factor >15) for unclothed body parts (head, neck, hands and arms) in order to prevent the occurrence of squamous-cell carcinoma. This is the most frequent skin tumour in transplant recipients, and its preferential location is the head. F. Recipients with pre-malignant skin lesions (warts, epidermodysplasia verruciformis or actinic keratoses) should be referred early to a dermatologist for active treatment and close follow-up. G. All skin cancers should be completely removed by a dermatologist with appropriate techniques, such as electro-desiccation with curettage, cryotherapy or surgical excision. H. Secondary prevention for recipients should include close follow-up by a dermatologist (at least every 6 months), the use of topical retinoids to control actinic keratoses and to diminish squamous-cell carcinoma recurrence, and reduction of immunosuppression whenever possible. I. In recipients with multiple and/or recurrent skin cancers, the use of systemic retinoids, such as low-dose acitretin, could be recommended for months/years, if well tolerated, in addition to further reduction in immunosuppression whenever possible.

22. De Novo Immunosuppression With Mammalian Target of Rapamycin Inhibitors and Posttransplantation Malignancy in Focus

Transplant Proc. 2009 Jul-Aug;41(6 Suppl):S42-4

Flechner S., Friend P., Campistol J., Weir M., Diekmann F., and Russ G.

This article provides an overview of the main points arising from a panel discussion following 4 discussion workshops on two themes. The first theme examined the indications for de novo immunosuppression with mammalian target of rapamycin (mTOR) inhibitors. The second explored the management of the risks of posttransplantation malignancy.

23. Risk Factors for Non-melanoma Skin Cancer in Kidney Transplant Patients in a Spanish Population in the Mediterranean Region

Acta Derm Venereol. 2013 Jul 6;93(4):422-7.

Bernat García J, Morales Suárez-Varela M, Vilata JJ, Marquina A, Pallardó L, Crespo J.

Abstract: Non-melanoma skin cancer (NMSC) is the most frequent malignancy in organ transplant recipients. The aetiology of NMSC after transplant is multifactorial. The aim of this study was to determine the clinical and environmental factors involved in the development of NMSC in a Spanish kidney transplant population from the Mediterranean region. A total of 289 patients who had received a kidney transplant during the period January 1996 to December 2010 were included in the study. Both prospective and retrospective data were used. All patients underwent a structured interview and a complete examination of the skin. After a median follow-up of 72 months (range 12-180 months), 73 of the 289 patients (25.2%) developed 162 tumours. The ratio of basal cell carcinoma to squamous cell carcinoma was 2.21:1. The cumulative incidence of NMSC increased with the duration of immunosuppression, from 20.78% at 5 years, to 37.35% at 10 years to 53.08% at 15 years after transplantation. Age at the time of transplant, phototype and occupational sun exposure were associated with a higher risk of NMSC. NMSC is a significant clinical problem in kidney transplant recipients. This has implications for the development of prevention and surveillance strategies. Clinical and environmental factors may be used to identify those patients who are at risk for NMSC.

24. Skin cancer surveillance in renal transplant recipients: re-evaluation of U.K. practice and comparison with Australian experience

Br J Dermatol. 2009 Jan;160(1):177-9.

Garg S, Carroll RP, Walker RG, Ramsay HM, Harden PN

Background: Nonmelanoma skin cancer (NMSC) is the most common tumour following solid organ transplantation. In 2000 a survey of U.K. centres managing renal transplant recipients (RTRs) showed that only 21% offered skin cancer surveillance.
Objectives: The survey was repeated in 2006 in the U.K. and Australia. The aims were to determine if U.K. practice had changed since 2000, to define skin cancer surveillance practice in Australian RTRs and to compare this with that in the U.K.
Methods: Questionnaires were sent to 84 U.K. and 45 Australian centres providing long-term RTR follow-up.
Results: Fifty-six (67%) U.K. centres caring for 82% (n = 16 349) of the RTR population replied. Sixty-six per cent provided annual skin cancer surveillance and 39% offered full skin examination (FSE) compared with 21% and 20% in 2000. Eighty-one per cent of surveillance was performed by nondermatologists (n = 30), nine (30%) of whom had received formal training for the role. Thirty-one (69%) Australian centres covering 86% (n = 5392) of the RTR population responded. Ninety-seven per cent provided skin cancer surveillance, and 61% offered FSE. Forty per cent (n = 12) of skin cancer surveillance was conducted by nondermatologists. Two nondermatologists had received formal training.
Conclusions: Despite a substantial improvement in the provision of skin cancer surveillance for RTRs in the U.K. between 2000 and 2006, only 39% of units offer FSE. In contrast, virtually all Australian centres offer annual skin cancer surveillance, with more dermatology involvement. Lack of training for nondermatologists involved in skin cancer surveillance is evident in both countries. The availability of dermatologists and the variation in NMSC risk between the populations may explain the different practices observed.

25. Can Immunosuppressive Strategies Be Used to Reduce Cancer Risk in Renal Transplant Patients?

Transplant Proc. 2010 Nov;42(9 Suppl):S32-5.

Geissler E.K.

Abstract: The risk of renal transplant recipients developing a malignancy is increasingly recognized as a major issue impacting long-term overall survival. As immunosuppression is thought to contribute to the development of cancer but is therapeutically required to protect against kidney rejection, reducing cancer in this setting is a challenging objective. An important question is whether there is a selective difference between pharmacological immunosuppressants regarding effects on malignancy. Both experimental and clinical studies thus far suggest that calcineurin inhibitors tend to promote tumor development; mycophenolic acid prodrugs such as mycophenolate mofetil have exhibited some capacity to inhibit tumors, but the concentrations needed for this effect are well above levels sustainable in transplant recipients. In contrast to these immunosuppressive substances, despite its potent immunosuppressive effects, rapamycin has demonstrated an impressive ability to inhibit de novo tumor development, as well as reduce tumor growth once cancer is already established. The antitumor effects of rapamycin are being studied extensively and appear to stem from the central role that the mammalian target of rapamycin molecule plays in basic cellular processes such as cell growth and proliferation, which are also essential for neoplasm development. Pilot trials and retrospective analyses of clinical data, especially using sirolimus, are highly suggestive that rapamycin can inhibit tumors in the clinical transplant setting. Prospective clinical trials are currently underway that will bring definitive answers as to whether rapamycin treatment can act simultaneously as an immunosuppressive and anticancer agent, with the aim of reducing the long-term problem of posttransplant malignancy.

26. Monitoring immunosuppression with measures of NFAT decreases cancer incidence

Clin Immunol. 2009 Sep;132(3):305-11

Giese T, Sommerer C, Zeier M, Meuer S.

Abstract: Long-term immunosuppression causes a significantly increased risk for the development of malignancies in transplanted patients. A link between immunosuppression and incidence of cancer is well documented and involves the effect of immunosuppression on anti-tumor surveillance and antiviral adaptive immune responses. We present a 67-year-old patient with a history of recurrent non-melanoma skin cancer. After adjustment of immunosuppressive therapy under close pharmacodynamic control, the development of new malignant lesions could be prevented. The availability of a quantitative, quick laboratory test for an assessment of the individual functional activity of immunocompetent cells that are crucial for transplant rejection, defense against viral infection, and tumor surveillance along with the ability to adjust doses of immunosuppressive agents such that patients are largely protected against malignant disease and/or viral infection are important. NFAT-regulated gene expression measured in peripheral blood allowed us to predict "safe" immunosuppression. Thus patients could maintain a stable allograft function. This represents a breakthrough in transplantation medicine and advances our attempts to individualize treatment in transplanted patients.

27. Calcineurin inhibitor-free immunosuppression based on antithymocyte globulin and mycophenolate mofetil in cadaveric kidney transplantation: results after 5 years

Transpl. Int (2003) 16: 820-827

Grinyó JM, Gil-Vernet S, Cruzado JM, Caldés A, Riera L, Serón D, Rama I, Torras J.

Abstract: Kidney grafts from suboptimal donors are more likely to suffer the nephrotoxic side-effects of cyclosporine than kidneys from standard donors. In an attempt to avoid the use of cyclosporine, we carried out a prospective study in low-immunological risk recipients of suboptimal kidneys, using an immunosuppressive protocol combining Thymoglobuline in induction with a bi-therapy of mycophenolate mofetil (MMF) and steroids. Patients with panel reactive antibodies (PRA) <50% receiving a first renal transplant from a suboptimal donor (age >or=50, non heart beating, arterial hypertension, or acute renal failure) or a kidney at risk of delayed graft function (DGF) because of a prolonged cold ischaemia time (CIT) of 24 h or more, were eligible for this trial. Between September 1996 and December 1999, 30 patients were enrolled for the trial and treated with MMF 2 g orally, pre-operatively, and 3 g daily, post-operatively; Thymoglobuline 2 mg/kg IV pre-operatively, 1.5 mg/kg IV the next day, and for doses of 1 mg/kg IV given on alternate days; and prednisolone 0.25 mg/kg per day, reduced progressively from the end of the first month to 0.1 mg/kg per day by 3 months post-transplant. Cyclosporine was added only if rejection grade II or higher, or a reduction in MMF below 1 g daily, occurred. Ten patients (30%) suffered from DGF, and one kidney suffered primary non function. Seven patients (24%) suffered acute rejection (six were biopsy proven, 3 grade I and 3 grade II). MMF dosage was reduced in 28 patients because of adverse events, and calcineurin inhibitors were introduced in 16 patients. There were 14 episodes of opportunistic infection (cytomegalovirus (CMV 10), Herpes zoster 2, Listeria monocytogenes 1, Pseudomonas aeuruginosa 1), and 7 malignancies (skin 2, thyroid 1, lung 1, Kaposi's sarcoma 2, post-transplantation lymphoproliferative disorder 1). Mean serum creatinine was 178, 199, 213, and 218 micromol/l at 1, 2, 3 and 5 years after transplantation, respectively. Actuarial patient and graft (after censoring for death) survival was 94% and 83% after 1 year and 79% and 65% after 5 years, respectively. These results show that with the combination of MMF, Thymoglobuline and steroids the use of cyclosporine can be delayed, and in a few cases completely avoided, with good efficacy in terms of prevention of rejection and recovery of renal function. Regardless of acceptable patient and graft survival, side-effects of MMF at the doses used in this protocol were common and led to overimmunosuppression in the long-term. Starting MMF at low dose, MPA monitoring and probably CMV prophylaxis may improve the results of this regimen.

28. Sun protection education for diverse audiences: need for skin cancer pictures
J Cancer Educ. 2015 March ; 30(1): 187–189
Guevara Y, Gaber R, Clayman ML, Gordon EJ, Friedewald J, Robinson JK.

Abstract: Sun protection education is needed for kidney transplant recipients, whose increased risk of skin cancer could be ameliorated with sun protection. Cognitive interviews with 24 participants equally stratified among non-Hispanic White, non-Hispanic Black, and Hispanic/Latino kidney transplant recipients were performed to evaluate a sun protection education workbook. Study participants were recruited over the phone using a registry of 700 kidney transplant recipients. Participants included 12 women and 12 men with a median age of 52. In 16 of the cognitive interviews with non-Hispanic Blacks and Hispanic/Latinos, pictures of skin cancer were requested by the participants in order to see the appearance of skin cancer. Kidney transplant recipients with skin of color did not consider themselves at risk to develop skin cancer and wanted to see examples of skin cancer occurring on people with skin of color. Based on these results, the workbook was modified to include pictures of squamous cell carcinoma on varying skin tones. Then, 8 participants evaluated the revised workbook in cognitive interviews and found the photographs acceptable and necessary to demonstrate the severity of skin cancer and personalize their risk of developing skin cancer. The participants progressed from having knowledge of skin cancer to believing that they could develop skin cancer because they observed skin cancers on people with their skin tone. Using pictures of skin cancers occurring on people with similar skin tone may heighten a kidney transplant recipients' sense of vulnerability and possibly improve the use of sun protection.

29. Cumulative Incidence of Cancer After Solid Organ Transplantation

Cancer. 2013 June 15; 119(12): 2300–2308

Hall EC, Pfeiffer RM, Segev DL, Engels EA.

Background: Solid organ transplantation recipients have elevated cancer incidence. Estimates of absolute cancer risk after transplantation can inform prevention and screening.
Methods: The Transplant Cancer Match Study links the US transplantation registry with 14 state/regional cancer registries. The authors used nonparametric competing risk methods to estimate the cumulative incidence of cancer after transplantation for 2 periods (1987-1999 and 2000-2008). For recipients from 2000 to 2008, the 5-year cumulative incidence, stratified by organ, sex, and age at transplantation, was estimated for 6 preventable or screen-detectable cancers. For comparison, the 5-year cumulative incidence was calculated for the same cancers in the general population at representative ages using Surveillance, Epidemiology, and End Results data.
Results: Among 164,156 recipients, 8520 incident cancers were identified. The absolute cancer risk was slightly higher for recipients during the period from 2000 to 2008 than during the period from 1987 to 1999 (5-year cumulative incidence: 4.4% vs. 4.2%; $P = .006$); this difference arose from the decreasing risk of competing events (5-year cumulative incidence of death, graft failure, or retransplantation: 26.6% vs. 31.9%; $P < .001$). From 2000 to 2008, the 5-year cumulative incidence of non-Hodgkin lymphoma was highest at extremes of age, especially in thoracic organ recipients (ages 0-34 years: range, 1.74%-3.28%; aged >50 years; range, 0.36%-2.22%). For recipients aged >50 years, the 5-year cumulative incidence was higher for colorectal cancer (range, 0.33%-1.94%) than for the general population at the recommended screening age (aged 50 years: range, 0.25%-0.33%). For recipients aged >50 years, the 5-year cumulative incidence was high for lung cancer among thoracic organ recipients (range, 1.16%-3.87%) and for kidney cancer among kidney recipients (range, 0.53%-0.84%). The 5-year cumulative incidence for prostate cancer and breast cancer was similar or lower in transplantation recipients than at the recommended ages of screening in the general population.
Conclusions: Subgroups of transplantation recipients have a high absolute risk of some cancers and may benefit from targeted prevention or screening.

30. Association of Antibody Induction Immunosuppression with Cancer After Kidney Transplantation

Transplantation. 2015 May;99(5):1051-7.

Hall EC, Engels EA, Pfeiffer RM, Segev DL.

Background: Induction immunosuppression is a mainstay of rejection prevention after transplantation. Studies have suggested a connection between antibody induction agents and cancer development, potentially limiting important immunosuppression protocols.
Methods: We used a linkage of U.S. transplantation data and cancer registries to explore the relationship between induction and cancer after transplantation. A total of 111,857 kidney recipients (1987-2009) in the Transplant Cancer Match Study, which links the Scientific Registry for Transplant Recipients and U.S. Cancer Registries, were included. Poisson regression models were used to estimate adjusted incidence rate ratios (aIRR) of non-Hodgkin lymphoma (NHL) and other cancers with increased incidence after transplantation (lung, colorectal, kidney, and thyroid cancers, plus melanoma).
Results: Two thousand seven hundred sixty-three cancers of interest were identified. Muromonab-CD3 was associated with increased NHL (aIRR, 1.37; 95% CI, 1.06-1.76). Alemtuzumab was associated with increased NHL (aIRR, 1.79; 95% CI, 1.02-3.14), colorectal cancer (aIRR, 2.46; 95% CI, 1.03-5.91), and thyroid cancer (aIRR, 3.37; 95% CI, 1.55-7.33). Polyclonal induction was associated with increased melanoma (aIRR, 1.50; 95% CI, 1.06-2.14).
Conclusion: Our findings highlight the relative safety with regard to cancer risk of the most common induction therapies, the need for surveillance of patients treated with alemtuzumab, and the possible role for increased melanoma screening for those patients treated with polyclonal anti-T-cell induction.

31. Sirolimus for secondary SCC prevention in renal transplantation
Nat Rev Nephrol. 2012 Dec;8(12):687-9.
Halleck F, Budde K.

A recently published study suggests that sirolimus is an attractive treatment option for the prevention of secondary skin cancer in kidney transplant recipients. However, before we think about switching all patients with a previous skin cancer (or with any other malignancy) to sirolimus, we should have a closer look at the data.

32. Alemtuzumab Induction in Renal Transplantation

N Engl J Med 2011;364:1909-19.

Hanaway MJ, Woodle ES, Mulgaonkar S, Peddi VR, Kaufman DB, First MR, Croy R, Holman J; INTAC Study Group.

Background: There are few comparisons of antibody induction therapy allowing early glucocorticoid withdrawal in renal-transplant recipients. The purpose of the present study was to compare induction therapy involving alemtuzumab with the most commonly used induction regimens in patient populations at either high immunologic risk or low immunologic risk.

Methods: In this prospective study, we randomly assigned patients to receive alemtuzumab or conventional induction therapy (basiliximab or rabbit antithymocyte globulin). Patients were stratified according to acute rejection risk, with a high risk defined by a repeat transplant, a peak or current value of panel-reactive antibodies of 20% or more, or black race. The 139 high-risk patients received alemtuzumab (one dose of 30 mg, in 70 patients) or rabbit antithymocyte globulin (a total of 6 mg per kilogram of body weight given over 4 days, in 69 patients). The 335 low-risk patients received alemtuzumab (one dose of 30 mg, in 164 patients) or basiliximab (a total of 40 mg over 4 days, in 171 patients). All patients received tacrolimus and mycophenolate mofetil and underwent a 5-day glucocorticoid taper in a regimen of early steroid withdrawal. The primary end point was biopsy-confirmed acute rejection at 6 months and 12 months. Patients were followed for 3 years for safety and efficacy end points.

Results: The rate of biopsy-confirmed acute rejection was significantly lower in the alemtuzumab group than in the conventional-therapy group at both 6 months (3% vs. 15%, P<0.001) and 12 months (5% vs. 17%, P<0.001). At 3 years, the rate of biopsy-confirmed acute rejection in low-risk patients was lower with alemtuzumab than with basiliximab (10% vs. 22%, P=0.003), but among high-risk patients, no significant difference was seen between alemtuzumab and rabbit antithymocyte globulin (18% vs. 15%, P=0.63). Adverse-event rates were similar among all four treatment groups.

Conclusions: By the first year after transplantation, biopsy-confirmed acute rejection was less frequent with alemtuzumab than with conventional therapy. The apparent superiority of alemtuzumab with respect to early biopsy-confirmed acute rejection was restricted to patients at low risk for transplant rejection; among high-risk patients, alemtuzumab and rabbit antithymocyte globulin had similar efficacy. (Funded by Astellas Pharma Global Development; INTAC ClinicalTrials.gov number, NCT00113269.).

33. Recommendations for Outpatient Monitoring of Kidney Transplant Recipients

Am J Kidney Dis. 2006 Apr;47(4 Suppl 2):S22-36.

Hariharan S

Abstract: Clinical and laboratory outpatient monitoring is an important tool in the prevention and management of complications associated with kidney transplantation and immunosuppressive therapy. In the absence of standard protocols for outpatient surveillance of kidney transplant recipients, recommendations for frequency and type of monitoring are determined by the likelihood of problems that are unique to the individual transplant recipient and the particular posttransplantation period. In addition, it is imperative to maintain the transplant recipient's overall health by screening for conditions or diseases that can be linked to prior renal disease, immunosuppressive therapies, and general health maintenance.

34. Evidencias clínicas sobre el uso de los fármacos anti-mTOR en el trasplante renal

Nefrologia 2011;31(1):27-34

Hernández D., Martínez D., Gutiérrez E., López V., Gutiérrez C., García P., Cobelo C., Cabello M., Burgos D., Sola E., González-Molina M.

Resumen: Los fármacos inhibidores de la calcineurina (ICN) constituyen los pilares de la moderna inmunosupresión en el trasplante renal. Sin embargo, contribuyen significativamente a la pérdida crónica de los injertos renales y a la elevada morbimortalidad en esta población por sus efectos deletéreos sobre el injerto renal, el perfil cardiovascular y la patología tumoral. Los fármacos anti-mTOR, sirolimus (SRL) y everolimus (EVE), son potentes inmunosupresores con capacidad antiproliferativa y antimigratoria, propiedades que les confieren un potencial papel protector en la disfunción del injerto, en la optimización de la función renal y en la aparición de tumores. En efecto, ensayos clínicos controlados y estudios observacionales de conversión han demostrado el efecto beneficioso de estos fármacos en términos de función renal, sin incremento significativo de las tasas de rechazo agudo. En esta revisión se analizan las evidencias del empleo de los fármacos anti-mTOR en los siguientes aspectos clínicos de los pacientes con trasplante renal: 1) prevención de la disfunción inmunológica precoz y preservación de la función renal en el uso de novo y conversión precoz o tardía; 2) disfunción crónica del injerto renal; 3) efectos cardiovasculares; 4) diabetes de novo postrasplante, y 5) patología tumoral de novo.

35. Malignome nach Nierentransplantation: Stellenwert eines jährlichen radiologischen Screeningprogramms

Fortschr. Röntgenstr. 163.3 (1995) 250-255

Heinz-Peer G., Mostbeck G. H., Banyai S., Ilelbich Th., Turetschek K., und Kainberger F.

(Article in German)

Purpose: To evaluate the prevalence of malignant neoplasms after renal transplantation by means of a radiological screening programme and to determine the role of some clinical and demographic parameters concerning pathogenesis of these malignancies. Material and methods: Between November 1992 and June 1994 in a prospective study 504 consecutive renal allograft recipients (331 m, 173 f) aged 51 ± 13 years underwent routine abdominal ultrasound examinations including the renal transplant and p. a. and lateral chest x-rays once a year.
Results: This screening programme revealed 11 malignant neoplasms in 11 patients (2.2 %). We detected 6 renal cell carcinomas (RCQ in the patient's native kidneys, two RCCs in two renal allografts, two non-Hodgkin-lymphomas in the liver and the renal allograft, respectively, and one ovarial carcinoma. Patients with renal cell carcinomas in the native kidneys were significantly older than allograft recipients without tumors. The presence of acquired cystic kidney disease (ACKD) seems to be an additional risk for the development of RCC. There were no significant differences in the time on dialysis, the time with functional renal allograft, and the immunosuppressive therapy.
Conclusion: Yearly abdominal ultrasound screening including the renal allograft is a valuable tool for the early detection of neoplasms in asymptomatic renal allograft recipients. However, routine yearly chest x-rays should not be performed in renal allograft recipients without preexisting tumours.

36. Incidence of cancer in kidney-transplant recipients: A long-term cohort study in a single center

Cancer Epidemiol. 2011 Apr;35(2):105-11.

Wisgerhof HC, van der Geest LG, de Fijter JW, Haasnoot GW, Claas FH, le Cessie S, Willemze R, Bouwes Bavinck JN.

Abstract: In a long-term cohort study, we calculated cancer incidences and survival rates after the development of these cancers in kidney-transplant recipients. The cancer incidences were compared with those in the general population. The occurrence of cancer was recorded in all patients who received kidney transplantation between 1966 and 2006. The median follow-up time was more than 9 years with a maximum of almost 40 years. Altogether 327 (17%) of 1906 patients developed cancer after transplantation: 142 (7%) had non-cutaneous malignancies; 178 (9%) cutaneous squamous-cell carcinomas and 138 (7%) basal-cell carcinomas. The cumulative incidence of any cancer was 13%, 33% and 47% after 10, 20 and 30 years, respectively. The incidences of cancers of the oral cavity, stomach, female genital organs, kidney, thyroid gland, leukemias and lymphomas, and cutaneous squamous-cell carcinoma were significantly increased with a highest standardized morbidity ratio of 40 for cutaneous squamous-cell carcinomas. Survival rates after non-cutaneous malignancies were 57%, 43% and 36% and after non-melanocytic skin cancer 99%, 90% and 77% after 1, 3 and 5 years, respectively. The increased incidence of non-cutaneous malignancies after kidney transplantation is associated with a high mortality. Prevention of cancer after kidney transplantation should be a major focus of future research.

37. HPV-related (pre)malignancies of the female anogenital tract in renal transplant recipients
Crit Rev Oncol Hematol. 2012 Nov;84(2):161-80.
Hinten F, Meeuwis KA, van Rossum MM, de Hullu JA.

Abstract: Renal transplantations (RTs) are performed routinely in many countries. After RT, the administration of lifelong immunosuppressive therapy is required. As a consequence, renal transplant recipients (RTRs) have a high risk to develop virus-associated (pre)malignancies, such as Human papillomavirus (HPV) related anogenital (pre)malignancies. It is known that the majority of the RTRs are infected with HPV and that these women have a 14-fold increased risk of cervical cancer, up to 50-fold of vulvar cancer and up to 100-fold of anal cancer. Often, treatment of these lesions requires concessions and may be suboptimal as radiation therapy and extensive surgery may damage the renal transplant. Therefore, prognosis may be compromised due to inadequately treated malignancies. Especially for these immunocompromised patients prevention is of utmost importance. Yearly cervical cancer screening for RTRs is advised, but appears to be executed poorly. For the future, optimizing screening and prevention of anogenital (pre)malignancies is an important issue for women after RT. This review gives a broad overview of all aspects regarding HPV-related (pre)malignancies of the female anogenital tract in RTRs.

38. Update on the pathogenesis of post-transplant skin cancer in renal transplant recipients
British Journal of Dermatology 2008 158, pp217–224
Ho W.L. and Murphy G.M.

Summary: Remarkable advances in the field of transplantation over the last several decades have benefited many thousands of patients. Five-year survival ranges from 90% for a live donor renal transplant to 85% for a cadaveric renal transplant. However, with this success come the complications of chronic immunosuppression. Lifelong immunosuppressive treatment for adequate graft function results in reduction of immunosurveillance, with increased risk of various cancers leading to substantial morbidity and mortality in these patients. This review discusses multifactorial intrinsic and extrinsic factors contributing to the pathogenesis of skin cancers in renal transplant recipients and reviews potential solutions.

39. De novo cancer avoidance after renal transplantation: A case-control study on low-dose sirolimus combined with a calcineurin inhibitor

J Formos Med Assoc. 2015 Jun;114(6):526-31

Chen KH, Lee CY, Wu FL, Yang CY, Yeh CC, Hu RH, Tsai MK.

Background/purpose: Full-dose sirolimus (SRL) therapy without a calcineurin inhibitor (CNI) reduces the incidence of malignancy after renal transplantation, but with significant side effects. We hypothesized that de novo therapy with low-dose SRL combined with a CNI could still prevent cancer in renal transplant recipients.

Methods: A retrospective case-control study was performed to assess the cancer incidence among renal transplant patients who had undergone surgery in our transplant centers between January 2000 and June 2012. Patients who received low-dose SRL and a CNI (SRL group, n = 189) were compared with patients receiving conventional CNI-based therapy in the same hospitals (Conventional group, n = 271).

Results: The 5-year graft and patient survival rates were comparable between the two groups. Seven patients in the SRL group and 24 patients in the Conventional group developed malignancies during mean follow-up periods of 68.2 ± 37.5 months and 81.7 ± 51.4 months, respectively. The cancer incidence at 5 years was significantly lower in the SRL group (1.9%), than that in the Conventional group (6.7%; p = 0.04). By multivariate analyses, SRL therapy (p = 0.04), male sex (p = 0.04), and younger age (p = 0.01) were significantly associated with a lower risk of malignancy after kidney transplantation.

Conclusion: De novo therapy with low-dose SRL combined with a CNI was associated with reduced risk of post-transplant cancer in renal transplant recipients. De novo cancer prevention using a low-dose proliferation signal inhibitor such as SRL could be effective for renal transplant recipients.

40. Immunosuppressive treatment after solid organ transplantation and risk of post-transplant cutaneous squamous cell carcinoma

Nephrol Dial Transplant. 2010 Aug;25(8):2764-71

Ingvar A, Smedby KE, Lindelöf B, Fernberg P, Bellocco R, Tufveson G, Höglund P, Adami J.

Background: The risk of cutaneous squamous cell carcinoma (CSCC) is found to be substantially increased after organ transplantation. The association with specific immunosuppressive regimens has been previously investigated, but results are not concordant. We aimed to clarify the relationship between separate immunosuppressive drugs, drug load, timing and risk of post-transplant CSCC.
Methods: A population-based nested case-control study was performed in the Swedish organ transplantation cohort (n = 5931). All patients who developed CSCC during the follow-up (1970-97) were eligible as cases (n = 207). Controls (n = 189) were randomly selected from the cohort and individually matched to the cases on follow-up time, age at and calendar period of transplantation. Exposure information was collected through extensive and standardized review of medical records.
Results: The median time to CSCC was 6.7 years. Post-transplant azathioprine (Aza) treatment considerably increased the risk of CSCC during all time periods analysed, and the risk augmented with increasing dose and duration. Patients who after the entire follow-up period had received a high accumulated dose of Aza had an 8.8-fold increased risk of CSCC in multivariate analysis ($P < 0.0001$), compared to patients never treated with Aza. Additionally, a high accumulated dose of corticosteroids during the same period conferred a 3.9-fold elevated risk of CSCC ($P = 0.09$), compared to the lowest accumulated dose of corticosteroids. Cyclosporine treatment was not associated with the risk of CSCC post-transplantation.
Conclusions: This study provides evidence that Aza treatment, but not cyclosporine treatment, is strongly associated with post-transplant CSCC risk. The results suggest that the risk of CSCC after organ transplantation is not only an effect of the immunosuppressive load *per se*.

41. Specialist dermatology clinics for organ transplant recipients significantly improve compliance with photoprotection and levels of skin cancer awareness

Br J Dermatol. 2006 November ; 155(5): 916–925

F. Ismail, L. Mitchell, D. Casabonne, A. Gulati, R. Newton, C.M. Proby, and C.A. Harwood

Background: Organ transplant recipients (OTRs) have 100-fold increased risk of developing squamous cell carcinomas. Cumulative exposure to ultraviolet radiation is the main risk factor and there is evidence that lack of dermatological surveillance may be responsible for poor levels of knowledge and photoprotection among OTRs.

Objectives: This study evaluated whether routine consultation in a specialist OTR dermatology clinic improves understanding of skin cancer risk and compliance with photoprotection measures.

Methods: A cross-sectional questionnaire-based study was performed in a specialist OTR dermatology clinic at Bart's and the London NHS Trust, London, U.K. The subjects were 399 white-skinned patients under surveillance in a renal transplant clinic, who were sent a postal questionnaire from the renal transplant clinic. The main outcome measures were responses to the questionnaire regarding photoprotective practices and skin cancer risk awareness.

Results: Two hundred and ninety-two of 399 (73%) responded, of whom 89% had previously attended the specialist dermatology clinic. Ninety-six per cent recalled receiving photoprotection advice at least once (85% from dermatologists); 92% reported use of sunscreen; 88% specifically dressed to photoprotect themselves; 96% directly avoided sun exposure during summer; 68% were aware that an increased risk of skin cancer was the reason that extra photoprotective measures were important after a transplant. Photoprotective measures and level of skin cancer awareness were significantly lower in those responders who had never attended the specialist clinic. No obvious bias was identified among nonresponders.

Conclusions: Skin cancer awareness and compliance with photoprotective measures in our patient population is generally greater than previously reported, suggesting that delivery of educational messages regarding skin cancer may be improved if provided in a specialist dermatological setting.

42. Post-transplant lymphoproliferative disorders after live donor renal transplantation
Clin Transplant 2005: 19: 668–673
Jain M, Badwal S, Pandey R, Srivastava A, Sharma RK, Gupta RK.

Abstract: The development of post-transplant lymphoproliferative disorders (PTLD) is a well-recognized complication of solid organ transplantation in patients receiving immunosuppressive therapy. The literature on PTLD in live renal allograft recipients is scarce and most of the data pertains to PTLD in cadaveric transplants. As live donor grafts form the mainstay of transplantation programme in India, this study was carried out to define the profile of PTLD in live donor renal allograft recipients. On retrospective evaluation, nine cases of PTLD amongst 1700 live donor allograft recipients from January 1989 to August 2004, were detected at a tertiary care hospital in north India. The clinicopathological features of these cases were evaluated. Mean age at diagnosis of PTLD was 38 yr with median post-transplant latency period of 7 yr. All cases were from extrarenal sites, five being in ileum/jejunum, three in retroperitoneal lymph nodes and one in epididymus. All cases received cyclosporin, azathioprine and prednisolone in varying combinations as immunosuppressive therapy. One case was treated for rejection by anti-thymocyte globulin. Seven patients were seronegative for Epstein–Barr virus at the time of diagnosis. All were B-cell monomorphic PTLD, classifiable as B-cell diffuse large cell lymphomas, with five extranodal and three nodal lymphomas. Management included reduction in immunosuppression, acyclovir therapy, surgical excision and chemotherapy. On follow-up, four patients died, two presented with recurrence, two were in remission and one was lost to follow-up. This study comprising of live related/unrelated renal allograft recipients observed late onset high grade monomorphic PTLD with paucity of early onset polymorphic lesions. Long post-transplant latency period, aggressive behaviour and poor response to treatment necessitate long-term cancer surveillance to facilitate early detection and newer therapeutic strategies to improve the outcome in these patients.

43. Advanced native kidney renal cell carcinoma in renal transplant recipients: role of sirolimus as dual anti-cancer and anti-rejection agent

Clinical Nephrology, Vol. 79 – No. 2/2013 (154-160)

Javaid M M., Chowdhury S, Henderson A and Olsburgh J

Abstract: The incidence of native kidney renal cell carcinoma (RCC) in renal transplant recipients is 15 times higher than the general population. These tumors are often found incidentally when imaging is performed for another indication. At that stage tumors are usually small and asymptomatic but it is possible that they may escape detection until a more advanced stage. Early stage RCC can be treated with radical nephrectomy but the treatment of advanced RCC may be more complicated and is associated with a poorer prognosis. RCC in context of renal transplant presents a special therapeutic challenge; balancing treatment of a potentially lethal malignancy in a redundant organ whilst maintaining good allograft function. We describe 2 cases of advanced renal cell carcinoma of native kidneys in renal transplant recipients and present our experience with sirolimus as a dual immunosuppressive and anti-tumor agent.

44. High graft protection and low incidences of infections, malignancies and other adverse effects with intraoperative high dose ATG-induction: A single centre cohort study of 760 cases

Ann Transplant, 2013: 18: 9-22

Kaden J, Völp A, Wesslau C

Background: In 1990 we introduced the intra-operative single high-dose induction (HDI) with ATG-Fresenius as a novel renal sparing concept. The aim of this analysis was to compare both the long-term patient and graft survival and the incidences of adverse effects in recipients treated with standard triple-drug therapy (TDT) alone or with an additional HDI with ATG-F.
Material/Methods: A total of 760 renal transplant recipients receiving either TDT, consisting of steroids, azathioprine and cyclosporine (n=238) or TDT + 9mg/kg ATG-F intra-operatively (n=522) were included in this retrospective analysis.
Results: Compared to the TDT cohort the graft and patient survival over the entire ten year period was significantly prolonged in the TDT+HDI cohort. In contrast, main adverse effects (TDT+HDI vs. TDT) such as malignancies (4.4 vs. 2.1%), PTLD (0.4 vs. 0.4%), CMV diseases (18.6 vs. 15.5%), Herpes zoster infections (2.9 vs. 1.3%), bacterial pneumonias (3.1 vs. 1.3%) and post-operative thrombocytopenia $<50\times10^3/\mu l$ (0.5 vs. 1.3%) did not significantly differ between the two immunosuppressive regimens. Only CMV-IgM seroconversions occurred significantly more in the HDI cohort (39.3 vs. 23.5%). The absolute numbers of CD3, CD4 and CD8 cell counts were significantly reduced in TDT+ATG-F HDI cohort only over a time period of about five days.
Conclusions: This world-wide largest single-centre cohort analysis clearly shows the superiority of the HDI with ATG-F compared to TDT alone in improving long-term graft survival without increasing the risk for infections, malignancies or other adverse effects.

45. Malignancy in Kidney Transplant Recipients

Drugs 2008; 68 Suppl. 1: 11-19

Kapoor A

Abstract: Post-transplant malignancy morbidity and mortality are important limitations in kidney transplantation. The incidence of malignancy has been estimated at 20% after 10 years of chronic immunosuppression. The aetiology of post-transplant malignancy is multifactorial, with the increased risk for malignancy in transplant recipients correlating with overall exposure to immunosuppression. Strategies to understand and minimize the risk of developing malignancy in the transplant population are needed. Calcineurin inhibitors (CNIs) have been linked with posttransplant malignancies, while mammalian target of rapamycin (mTOR) inhibitors have shown antineoplastic activities. The dual efficacy of sirolimus as an immunosuppressive and antitumour agent has been demonstrated experimentally and clinically. Clinical studies have demonstrated a lower incidence of new malignancies after renal transplantation in recipients receiving immunosuppression with mTOR inhibitors compared with CNIs. Therapeutic protocols involving mTOR inhibitors may protect an allograft from immunological rejection, while at the same time addressing the problem of cancer in this high-risk population. Newer sirolimus analogues, such as temsirolimus, have become a focus in pure oncological research and are being evaluated for antineoplastic effects on a variety of malignancies in clinical trials.

46. Cancer after Kidney Transplantation in the United States

Am J Transplant. 2004 Jun;4(6):905-13.

Kasiske BL, Snyder JJ, Gilbertson DT, Wang C.

Abstract: Previous reports of cancer after kidney transplantation have been limited by small numbers of patients in single-center studies and incomplete ascertainment of cases in large registries. We examined rates of malignancies among first-time recipients of deceased or living donor kidney transplantations in 1995-2001 (n = 35 765) using Medicare billing claims. For most common tumors, e.g. colon, lung, prostate, stomach, esophagus, pancreas, ovary and breast, cancer rates were roughly twofold higher after kidney transplantation compared with the general population. Melanoma, leukemia, hepatobiliary tumors, cervical and vulvovaginal tumors were each approximately fivefold more common. Testicular and bladder cancers were increased approximately threefold, while kidney cancer was approximately 15-fold more common. Kaposi's sarcoma, non-Hodgkin's lymphomas, and nonmelanoma skin cancers were more than 20-fold increased than in the general population. Compared with patients on the waiting list, several tumors were more common after transplantation ($p < 0.01$): nonmelanoma skin cancers (2.6-fold), melanoma (2.2-fold), Kaposi's sarcoma (9.0-fold), non-Hodgkin's lymphoma (3.3-fold), cancer of the mouth (2.2-fold), and cancer of the kidney (39% higher). The rates for most malignancies are higher after kidney transplantation compared with the general population. Cancer should continue to be a major focus of prevention in kidney transplantation.

47. Cervical dysplasia and cancer developing in women on immunosuppression therapy for renal homotransplantations

Cancer. 1970 Nov;26(5):1048-52.

Kay S, Frable WJ, Hume DM.

A study of cervical changes has been made of 28 female patients over the age of I I years who have received renal transplants for end-stage kidney disease. Three of these patients have shown cellular abnormalities on Papanicolaou smears. One patient showed mild dysplasia in only one mear, but the other 2 have shown persistent atypicalities and one of the 2 developed in-situ epithelioma proven by cervical conization. While definite proof that the cervical changes are due to immunosuppressive therapy is lacking, a plea is made to subject all transplanted patients to routine cervical smears and to record all features of dysplasia and frank malignancy in order that proper assessment of their significance may be made in the future.

48. Retinoids to prevent skin cancer in organ transplant recipients
Lancet. 1991 Nov 30;338(8779):1407.
Kelly JW, Sabto J, Gurr FW, Bruce F.
This article does not have an abstract to display.

49. Cancer Mortality in Kidney Transplantation
Am J Transplant. 2009 Aug;9(8):1868-75.
Kiberd BA1, Rose C, Gill JS.

Abstract: Immunosuppression is associated with an increased risk of cancer in kidney transplant recipients compared to the general population. It is less clear whether standardized cancer mortality ratios (SMRs) are also increased. This study's hypothesis is that SMRs are not increased because of competing risks of death. During the median follow-up of 5.05 years (Q1-Q3: 2.36-8.62), there were 1937 cancer deaths and 36 619 noncancer deaths among 164 078 first kidney-only transplant recipients captured in the United States Renal Data System between January 1990 and December 2004. The observed cancer death rate was 206 per 100 000 patient-years compared to an expected rate of 215 per 100,000 patient-years in the general population. The overall age- and sex-adjusted SMR was only 0.96 (95% CI 0.92-1.00). However, patients <50 years had SMRs significantly greater than unity while patients >60 had SMRs lower than unity. Up to 25% of cancer-related deaths occurred after allograft failure. These findings challenge the notion that cancer is a major cause of premature death in all kidney transplant recipients and has implications for design of cancer prevention strategies in kidney transplant recipients.

50. The role of mammalian target of rapamycin inhibitors in the management of posttransplant malignancy

Clin Transplant 2014: 28: 635–648

Klintmalm GB., Saab S., Hong JC. and Nashan B.

Abstract: Post-transplant malignancies, which occur either de novo or as cancer recurrences, are due to chronic exposure to immunosuppressive agents and are often more aggressive than those that develop in the nontransplant setting. Mammalian target of rapamycin (mTOR) inhibitors have antitumor and immunosuppressive effects. The dual effects of this class of agents may provide adequate immunosuppression to prevent organ rejection while simultaneously reducing the risk of post-transplant malignancy. mTOR inhibitors have become established approved agents for treating renal cell carcinoma and other cancers and, as reviewed herein, accumulating experience among organ transplant recipients collectively points toward a potential to prevent the development of de novo malignancies of various types in the post-transplant period. To date, most research efforts surrounding mTOR inhibitors and cancer control in the transplant population have been in the area of skin cancer prevention, but there have also been interesting observations regarding regression of post-transplant Kaposi's sarcoma and post-transplantation lymphoproliferative disorder that warrant further study.

51. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data

BMJ. 2014 Nov 24;349:g6679.

Knoll GA, Kokolo MB, Mallick R, Beck A, Buenaventura CD, Ducharme R, Barsoum R, Bernasconi C, Blydt-Hansen TD, Ekberg H, Felipe CR, Firth J, Gallon L, Gelens M, Glotz D, Gossmann J, Guba M, Morsy AA, Salgo R, Scheuermann EH, Tedesco-Silva H, Vitko S, Watson C, Fergusson DA.

Objective: To examine risk of malignancy and death in patients with kidney transplant who receive the immunosuppressive drug sirolimus.
Design: Systematic review and meta-analysis of individual patient data.
Data sources: Medline, Embase, and the Cochrane Central Register of Controlled Trials from inception to March 2013.
Eligibility: Randomized controlled trials comparing immunosuppressive regimens with and without sirolimus in recipients of kidney or combined pancreatic and renal transplant for which the author was willing to provide individual patient level data. Two reviewers independently screened titles/abstracts and full text reports of potentially eligible trials to identify studies for inclusion. All eligible trials reported data on malignancy or survival.
Results: The search yielded 2365 unique citations. Patient level data were available from 5876 patients from 21 randomized trials. Sirolimus was associated with a 40% reduction in the risk of malignancy (adjusted hazard ratio 0.60, 95% confidence interval 0.39 to 0.93) and a 56% reduction in the risk of non-melanoma skin cancer (0.44, 0.30 to 0.63) compared with controls. The most pronounced effect was seen in patients who converted to sirolimus from an established immunosuppressive regimen, resulting in a reduction in risk of malignancy (0.34, 0.28 to 0.41), non-melanoma skin cancer (0.32, 0.24 to 0.42), and other cancers (0.52, 0.38 to 0.69). Sirolimus was associated with an increased risk of death (1.43, 1.21 to 1.71) compared with controls.
Conclusions: Sirolimus was associated with a reduction in the risk of malignancy and non-melanoma skin cancer in transplant recipients. The benefit was most pronounced in patients who converted from an established immunosuppressive regimen to sirolimus. Given the risk of mortality, however, the use of this drug does not seem warranted for most patients with kidney transplant. Further research is needed to determine if different populations, such as those at high risk of cancer, might benefit from sirolimus.

52. Canadian Society of Transplantation and Canadian Society of Nephrology Commentary on the 2009 KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients

Am J Kidney Dis. 2010 Aug;56(2):219-46

Knoll GA, Blydt-Hansen TD, Campbell P, Cantarovich M, Cole E, Fairhead T, Gill JS, Gourishankar S, Hebert D, Hodsman A, House AA, Humar A, Karpinski M, Kim SJ, Mainra R, Prasad GV.

KDIGO (Kidney Disease: Improving Global Outcomes) is an international initiative to develop and implement clinical practice guidelines. In November 2009, KDIGO published its guideline for the management of kidney transplant recipients. This guideline was extremely comprehensive and spanned more than 150 pages. The Canadian Society of Transplantation (CST) and the Canadian Society of Nephrology (CSN) congratulate KDIGO, members of the guideline work group, and the evidence review team for producing such a thorough and exhaustive document. This guideline will be of great value to health professionals involved in the management of kidney transplant recipients.

53. Long-term safety and efficacy of antithymocyte globulin induction: use of integrated national registry data to achieve ten-year follow-up of 10-10 Study participants

Trials (2015) 16:365

Lentine KL, Schnitzler MA, Xiao H and Brennan

Background: Rabbit antithymocyte globulin (rATG, Thymoglobulin®) is the most common induction immunosuppression therapy in kidney transplantation. We applied a database integration strategy to capture and compare long-term (10-year) outcome data for US participants in a clinical trial of rATG versus FDA-approved basiliximab.

Methods: Records for US participants in an international, 1-year, randomized clinical trial comparing rATG and basiliximab induction in deceased donor kidney transplantation were integrated with records from the US national Organ Procurement and Transplantation (OPTN) registry using center, transplant dates, recipient sex, and birthdates. The OPTN captures center-reported acute rejection, graft failure, death, and cancer events, and incorporates comprehensive death records from the Social Security Death Master File. Ten-year outcomes according to randomized induction regimen were compared by Kaplan–Meier analysis (two-sided P).

Non-inferiority of rATG was assessed using a one-tailed equivalence test (a-priori equivalence margins of 0–10 %).

Results: Of 183 US trial participants, 89 % (n = 163) matched OPTN records exactly; the remainder were matched by extending agreement windows for transplant and birthdates. Matches were validated by donor and recipient blood types. By Kaplan–Meier analysis, 10 years post-transplant, freedom from acute rejection, graft failure, or death was 32.6 % and 24.0 % in the rATG and basiliximab arms, respectively (P = 0.09). The incidence of acute rejection with rATG versus basiliximab induction was 21.0 % versus 32.8 % (P = 0.07). Patient survival (52.5 % versus 52.2 %, P = 0.92) and graft survival (34.3 % versus 30.9 %, P = 0.56) rates were numerically and statistically similar for both arms. Comparison of the composite outcome meets non-inferiority criteria even with a 0 % equivalence margin (one-sided P = 0.04). With a 10 % equivalence margin, the odds that rATG is no worse than basiliximab for 10-year risk of the composite endpoint are >99 %.

Conclusions: Ten years post-transplant, rATG induction has comparable efficacy and safety to FDA-approved basiliximab. Integration of clinical trial records with national registry data can enable long-term monitoring of trial participants in transplantation, circumventing logistical and cost barriers of extended follow-up.

54. Switching from Tacrolimus to Sirolimus Halts the Appearance of New Sebaceous Neoplasms in Muir-Torre Syndrome

Am J Transplant. 2007 Feb;7(2):476-9.

Levi Z, Hazazi R, Kedar-Barnes I, Hodak E, Gal E, Mor E, Niv Y, Winkler J.

Abstract: Little is known about the effects of immunosuppression on patients with hereditary nonpolyposis colorectal cancer (HNPCC). We describe a kidney transplant recipient with unrecognized Muir-Torre syndrome in whom the administration of a tacrolimus-based regimen led to the eruption of multiple sebaceous tumors. The patient was later found to harbor an MSH2 mutation. Switching to a sirolimus-based regimen resulted in arrest of the disease. When the patient was switched back to tacrolimus, new facial lesions rapidly appeared. Switching again to sirolimus resulted again in halting the appearance of new lesions. This finding is in line with the known antiangiogenic activity of sirolimus and reports on the regression of cutaneous Kaposi's sarcoma in kidney transplant recipients switched from another immunosuppressive regimen to sirolimus. Further studies on the potential use of sirolimus for the treatment of de novo tumors in immunosuppressed kidney transplant recipients with HNPCC are warranted.

55. Basiliximab or Antithymocyte Globulin for Induction Therapy in Kidney Transplantation: A Meta-analysis

Transplantation Proceedings, 42, 1667–1670 (2010)

Liu Y, Zhou P, Han M, Xue CB, Hu XP, and Li C.

Objective: To compare efficacy and safety of basiliximab versus antithymocyte globulin (ATG) for induction therapy in kidney transplantation.
Methods: A literature search of the MEDLINE, EMBASE, CBMdisc, and Cochrane databases was used to identify randomized controlled trials that compared basiliximab and ATG for induction therapy in kidney transplantation. Inclusion criteria comprised: prospective randomized controlled clinical trials, follow-up time 12 months, randomized comparisons of ATG versus basiliximab as induction therapy in kidney transplantation. Meta-analytical techniques were applied to identify differences in outcomes between the two agents.
Results: A total of six studies involving 853 patients were identified. No differences between ATG and basiliximab were seen in terms of biopsy-proven rejection (relative risk [RR] 1.15, 95% confidence interval [CI] 0.88–1.52, P = .31), delayed graft function (RR 1.02, 95% CI 0.69–1.51, P= .93), graft loss (RR 1.15, 95% CI 0.73–1.80, P = .55), and patient death (RR 1.22, 95% CI 0.65–2.30, P = .54). But basiliximab had a lower incidence of infection (RR 0.87, 95% CI 0.78–0.97, P= .02) and neoplasm (RR 0.29, 95% CI 0.09–0.97, P = .04).
Conclusions: Basiliximab is as effective as ATG for induction therapy in kidney transplantation, whereas basiliximab has a lower incidence of infection. Basiliximab may be a safer and preferable option for induction therapy in kidney transplantation.

56. Conversion to Sirolimus in Posttransplant Renal Neoplasms

Transplantation Proceedings, 39, 2264–2266 (2007)

Lopez V, Gutierrez C, Cabello M, Burgos D, Sola E, and Gonzalez-Molina M

Background: Calcineurin inhibitors (CNIs) have been associated with the development of posttransplant malignancies, especially lymphoma and solid organ tumors. Sirolimus (SRL) has been shown to inhibit the growth of tumor cell lines in vitro and in vivo and has proven effective in clinical practice for the treatment of Kaposi's sarcoma. Organ transplant patients treated with CNIs who develop a tumor may thus benefit from conversion to SRL.
Patients and methods. From December 2001 to May 2006, 25 patients who developed a tumor were converted from a CNI-based immunosuppressive regimen to SRL. We analyzed the evolution of the tumor, renal function, and the adverse effects resulting from the change of immunosuppression.
Results: The mean follow-up was 19 months. Creatinine clearance (Cockcroft-Gault) increased from 59.5 ± 21.7 to 66.0 ± 24.2 mL/min at 12 months (P = .4) and serum cholesterol from 176.7 ± 46.8 to 216.4±40.3 mg/dL (P = .01). Proteinuria rose from 0.3 ± 0.1 to 1.3 ± 0.9 g/24 hours (P = .004). Adverse events included anemia, thrombocytopenia, and oral ulcers in 20% of cases, cutaneous eruption and gastrointestinal alterations in 12%, and edema in 24%. Four (16%) patients had improved blood pressure readings. Six (24%) patients died and one experienced an acute rejection episode after conversion to SRL. Nineteen (76%) patients displayed a favorable evolution with no evidence of tumor progression.
Conclusions: Conversion to SRL stabilized tumor progression in 76% of long-term renal transplant patients who developed a neoplasm over a mean follow-up of 19 months. Moreover, renal function improved. The most important adverse effects were increased cholesterol and proteinuria.

57. Tumours after kidney transplantation

Curr Opin Urol. 2003 Mar;13(2):105-9.

Lutz J, Heemann U.

Purpose of review: With the improved long-term outcome of renal allograft recipients, malignant tumours or cardiovascular disease become increasingly important. Malignant tumours develop in 15-20% of graft recipients after 10 years, and thus contribute substantially to the morbidity and mortality of these patients. In contrast to the general population, skin tumours and lymphoproliferative disorders are the most frequent malignancies in transplant recipients. Malignancies can develop in three ways: de-novo occurrence in the recipient; recurrent malignancy in the recipient; or transmission of malignancy from the donor.
Recent findings: The immunosuppressive strategies after renal transplantation differ with respect to the development of malignancies, with cell-depleting antibodies being the highest risk, whereas newer immunosuppressants such as rapamycin could possess anti-tumour potential. The relationship of chronic viral infections to skin tumours and lymphoproliferative diseases has become clearer during recent years. Concomitantly, experience in the management of such diseases has grown. Furthermore, as older donors are accepted, awareness of the possibility of transferring malignancies from the donor to the recipient must increase.
Summary: Malignancies are a major contributor to morbidity and mortality among kidney transplant recipients as such diseases gain importance with longer graft survival. Immunosuppression and chronic viral infections in combination with the transmission of malignant cells from the donor or recurrent malignancies contribute to the increased incidence of cancer. In kidney transplant recipients, screening before and after transplantation and an individualized choice of immunosuppression are thus mandatory.

58. Cohort Profile: The Skin Cancer After Organ Transplant Study

Int J Epidemiol. 2013 Dec;42(6):1669-77.

Madeleine MM, Johnson LG, Daling JR, Schwartz SM, Carter JJ, Berg D, Nelson K, Davis CL, Galloway DA.

Abstract: The Skin Cancer after Organ Transplant (SCOT) study was designed to investigate the link between genus beta human papillomavirus (HPV) and squamous cell skin cancer (SCSC). We focused on a population receiving immunosuppressive therapy for extended periods, transplant patients, as they are at extremely high risk for developing SCSC. Two complementary projects were conducted in the Seattle area: (i) a retrospective cohort with interview data from 2004 recipients of renal or cardiac transplants between 1995 and 2010 and (ii) a prospective cohort with interview data from 328 people on the transplant waiting lists between 2009 and 2011. Within the retrospective cohort, we developed a nested case-control study (172 cases and 337 control subjects) to assess risk of SCSC associated with markers of HPV in SCSC tumour tissue and eyebrow hair bulb DNA (HPV genotypes) and blood (HPV antibodies). In the prospective cohort, 135 participants had a 1-year post-transplant visit and 71 completed a 2-year post-transplant visit. In both arms of the cohort, we collected samples to assess markers of HPV infection such as acquisition of new types, proportion positive for each type, persistence of types at consecutive visits and number of HPV types detected. In the prospective cohort, we will also examine these HPV markers in relation to levels of cell-mediated immunity. The goal of the SCOT study is to use the data we collected to gain a more complete understanding of the role of immune suppression in HPV kinetics and of genus beta HPV types in SCSC. For more information, please contact the principal investigator through the study website: http://www.fhcrc.org/science/phs/cerc/The_SCOT_Study.html.

59. High Grade, Synchronous Colon Cancers After Renal Transplantation: Were Immunosuppressive Drugs to Blame?

Am J Gastroenterol. 1999 Nov;94(11):3359-61.

Trivedi MH1, Agrawal S, Muscato MS, Metzler MH, Marshall JB.

Abstract: Recipients of renal transplants are known to have an increased incidence of cancer, which is believed to be related to the use of immunosuppressive drugs used to prevent rejection. Although the risks of lymphoma and Kaposi's sarcoma are clearly increased in this setting, the association with colon cancer is controversial. We report a 44-yr-old woman, 20 yr post-renal transplant, and with no family history of colorectal cancer or polyps, who was found to have synchronous, poorly differentiated colon cancers associated with extensive abdominal lymph node, bone marrow, and bone (skull) metastasis. The long term immunosuppressive drugs that she had received may have been an important factor in her tumor development and/or progression. Our case and literature review suggest a possible mild, increased risk of colon cancer development in patients after renal transplantation.

60. Immunosuppressive Drugs in Kidney Transplantation: Impact on Patient Survival, and Incidence of Cardiovascular Disease, Malignancy and Infection

Drugs 2009; 69 (16): 2227-2243

Marcen R

Abstract: Renal transplant recipients have increased mortality rates when compared with the general population. The new immunosuppressive drugs have improved short-term patient survival up to 95%at 1–2 years, but these data have to be confirmed in long-term follow-up. Furthermore, no particular regimen has proved to be superior over others with regard to patient survival.

Cardiovascular diseases are the most common cause of mortality in renal transplant recipients and while no immunosuppressive drug has been directly associated with cardiovascular events, immunosuppressive drugs have different impacts on traditional risk factors. Corticosteroids and ciclosporin are the agents with the most negative impact on weight gain, blood pressure and lipids. Tacrolimus increases the risk of new-onset diabetes mellitus. Sirolimus and everolimus have the most impact on risk factors for post-transplant hyperlipidaemia. Modifications in immunosuppression could improve the cardiovascular profile but there is little evidence regarding the beneficial effects of these changes on patient outcomes.

Malignancies are also an increasing cause of mortality, overtaking cardiovascular disease in some series. Induction therapy, azathioprine and calcineurin inhibitors (CNIs) are probably the immunosuppressive agents most linked with post-transplant malignancies. Mycophenolate mofetil (MMF) has no negative impact on the incidence of malignancies. Target of rapamycin (mTOR) inhibitors have antioncogenic properties and they are associated with a lower incidence of malignancies. In addition, these agents have been recommended for use to decrease the dose or withdrawal of CNIs in patients with malignancies.

Infections are still an important cause of morbidity and mortality in renal transplant recipients. Some immunosuppressive agents such as MMF increase the incidence of cytomegalovirus infection and the need for prophylactic measures in risk recipients. The use of potent immunosuppressive therapy has resulted in the appearance of BK virus nephropathy, which progresses to graft failure in a high percentage of patients. Although first associated with tacrolimus and MMF immunosuppression, recent data suggest that BK nephropathy appears with any kind of triple therapy.

In conclusion, reducing risk factors for patient death should be a major target to improve outcomes after renal transplantation. Effort should be made to control cardiovascular diseases, malignancies and infections with improved use of immunosuppressive drugs. Preliminary results with belatacept suggest its safety and efficacy, and open new perspectives in the immunosupppression of *de novo* renal transplant recipients.

61. Belatacept for kidney transplant recipients (Review)
Cochrane Database Syst Rev. 2014 Nov 24;11:CD010699
Masson P, Henderson L, Chapman JR, Craig JC, Webster AC.

Background: Most people who receive a kidney transplant die from either cardiovascular disease or cancer before their transplant fails. The most common reason for someone with a kidney transplant to lose the function of their transplanted kidney necessitating return to dialysis is chronic kidney transplant scarring. Immunosuppressant drugs have side effects that increase risks of cardiovascular disease, cancer and chronic kidney transplant scarring. Belatacept may provide sufficient immunosuppression while avoiding unwanted side effects of other immunosuppressant drugs. However, high rates of post-transplant lymphoproliferative disease (PTLD) have been reported when belatacept is used in particular kidney transplant recipients at high dosage.
Objectives: 1) Compare the relative efficacy of belatacept versus any other primary immunosuppression regimen for preventing acute rejection, maintaining kidney transplant function, and preventing death. 2) Compare the incidence of several adverse events: PTLD; other malignancies; chronic transplant kidney scarring (IF/TA); infections; change in blood pressure, lipid and blood sugar control. 3) Assess any variation in effects by study, intervention and recipient characteristics, including: differences in pre-transplant Epstein Barr virus serostatus; belatacept dosage; and donor-category (living, standard criteria deceased, or extended criteria deceased).
Search methods: We searched the Cochrane Renal Group's Specialised Register to 1 September 2014 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.
Selection criteria: Randomised controlled trials (RCT) that compared belatacept versus any other immunosuppression regimen in kidney transplant recipients were eligible for inclusion.
Data collection and analysis: Two authors independently extracted data for study quality and transplant outcomes and synthesized results using random effects meta-analysis, expressed as risk ratios (RR) and mean differences (MD), both with 95% confidence intervals (CI). Subgroup analyses and univariate meta-regression were used to investigate potential heterogeneity.
Main results: We included five studies that compared belatacept and calcineurin inhibitors (CNI) that reported data from a total of 1535 kidney transplant recipients. Of the five studies, three (478 participants) compared belatacept and cyclosporin and two (43 recipients) compared belatacept and tacrolimus. Co-interventions included basiliximab (4 studies, 1434 recipients); anti-thymocyte globulin (1 study, 89 recipients); alemtuzumab (1 study, 12 recipients); mycophenolate mofetil (MMF, 5 studies, 1509 recipients); sirolimus (1 study, 26 recipients) and prednisone (5 studies, 1535 recipients).Up to three years following transplant, belatacept and CNI-treated recipients were at similar risk of dying (4 studies, 1516 recipients: RR 0.75, 95% CI 0.39 to 1.44), losing their kidney transplant and returning to dialysis (4 studies, 1516 recipients: RR 0.91, 95% CI 0.61 to 1.38), and having an episode of acute rejection (4 studies, 1516 recipients: RR 1.56, 95% CI 0.85 to 2.86). Belatacept-treated kidney transplant recipients were 28% less likely to have chronic kidney scarring (3 studies, 1360 recipients: RR 0.72, 95% CI 0.55 to 0.94) and also had better graft function (measured glomerular filtration rate (GFR) (3 studies 1083 recipients): 10.89 mL/min/1.73 m^2, 95% CI 4.01 to 17.77; estimated GFR (4 studies, 1083 recipients): MD 9.96 mL/min/1.73 m^2, 95% CI 3.28 to 16.64) than CNI-treated recipients. Blood pressure was lower (systolic (2 studies, 658 recipients): MD -7.51 mm Hg, 95% CI -10.57 to -4.46; diastolic (2 studies, 658 recipients): MD -3.07 mm Hg, 95% CI -4.83 to -1.31, lipid profile was better (non-HDL (3 studies 1101 recipients): MD -12.25 mg/dL, 95% CI -17.93 to -6.57; triglycerides (3 studies 1101 recipients): MD -24.09 mg/dL, 95% CI -44.55 to -3.64), and incidence of new-onset diabetes after transplant was reduced

by 39% (4 studies (1049 recipients): RR 0.61, 95% CI 0.40 to 0.93) among belatacept-treated versus CNI-treated recipients.Risk of PTLD was similar in belatacept and CNI-treated recipients (4 studies, 1516 recipients: RR 2.79, 95% CI 0.61 to 12.66) and was no different among recipients who received different belatacept dosages (high versus low dosage: ratio of risk ratios (RRR) 1.06, 95% CI 0.11 to 9.80, test of difference = 0.96) or among those who were Epstein Barr virus seronegative compared with those who were seropositive before their kidney transplant (seronegative versus seropositive; RRR 1.49, 95% CI 0.15 to 14.76, test for difference = 0.73).The belatacept dose used (high versus low), type of donor kidney the recipient received (extended versus standard criteria) and whether the kidney transplant recipient received tacrolimus or cyclosporin made no difference to kidney transplant survival, incidence of acute rejection or estimated GFR. Selective outcome reporting meant that data for some key subgroup comparisons were sparse and that estimates of the effect of treatment in these groups of recipients remain imprecise.

Authors' conclusions: There is no evidence of any difference in the effectiveness of belatacept and CNI in preventing acute rejection, graft loss and death, but treatment with belatacept is associated with less chronic kidney scarring and better kidney transplant function. Treatment with belatacept is also associated with better blood pressure and lipid profile and a lower incidence of diabetes versus treatment with a CNI. Important side effects (particularly PTLD) remain poorly reported and so the relative benefits and harms of using belatacept remain unclear. Whether short-term advantages of treatment with belatacept are maintained over the medium- to long-term or translate into better cardiovascular outcomes or longer kidney transplant survival with function remains unclear. Longer-term, fully reported and published studies comparing belatacept versus tacrolimus are needed to help clinicians decide which patients might benefit most from using belatacept.

62. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies

Clin Transplant 2004: 18: 446–449

Mathew T, Kreis H, Friend P

Abstract: We examined the rates of malignancy at 2 yr after transplantation in renal allograft patients receiving sirolimus (SRL) in continuous combination with cyclosporine (CsA), SRL as base therapy or SRL maintenance therapy after early withdrawal of CsA. A total of 1295 patients were enrolled in two double-blind studies comparing SRL with azathioprine (AZA) or placebo administered in continuous regimens with CsA. In two other trials (n = 161), SRL given as base therapy was compared with CsA. In the fifth trial, patients were randomly assigned at 3 months to either remain on CsA + SRL therapy (n = 215) or to have CsA eliminated with SRL being continued in concentration-controlled doses (n = 215). At 2 yr after transplantation, patients receiving SRL in continuous combination with CsA had a significantly lower incidence of skin cancer compared with patients receiving placebo. Patients receiving SRL as base therapy had no malignancies compared with a 5% incidence in those receiving CsA. The incidence of malignancy was significantly lower in patients receiving concentration- controlled SRL with elimination of CsA compared with those who remained on CsA + SRL. Based on the currently available data, patients receiving SRL-based therapy without CsA or SRL maintenance therapy after early CsA withdrawal have lower rates of malignancy in the first 2 yr after renal transplantation. SRL immunotherapy may be beneficial in protecting renal transplant patients from skin cancer even when given in combination with CsA.

63. The Clinical Course of Kidney Transplant Recipients After 20 Years of Graft Function
American Journal of Transplantation 2015; 15: 734–740
McCaughan JA and Courtney AE

There is a growing population of kidney transplant recipients who have survived 20 years with a functioning graft. This study identified the factors associated with prolonged survival and described the clinical course of recipients after two decades of transplant function. All recipients transplanted in Northern Ireland between 1968 and 1993 were included (n=706) and data were collected prospectively. At 20 years, 25% had a functioning transplant; in multivariate analysis younger recipient age and living donation were associated with 20-year survival. The median recipient survival beyond two decades was 13.3 years; cancer was the commonest cause of death. De novo malignancy developed in 37% of recipients and cardiovascular disease in 27% after 20 years of graft function. The median graft survival after 20 years was 9.3 years; 69% of graft loss was due to death with a functioning transplant. Advances in kidney transplantation have improved the long-term survival of both graft and recipient. After two decades the majority of patients die with a functioning graft. The focus of management in long-term survivors may need to be on the prevention of cancer and cardiovascular disease to allow further improvements in graft and recipient survival.

64. Skin cancer chemoprophylaxis in renal transplant recipients: 5 years of experience using low-dose acitretin

British Journal of Dermatology 1999; 140: 656–660.

McKenna DB and Murphy GM

Summary: Renal transplant recipients have an increased risk of developing skin cancers, which are often multiple and aggressive. Frequently, these tumours develop on a background of widespread epidermal dysplasia. Systemic retinoids are known inhibitors of skin cancer but reports of their use in renal transplant patients are limited. We describe our experience using 0·3 mg/kg daily of acitretin in 16 patients over a 5-year period. Overall, there was a significant reduction in the number of new tumours excised in 12 of 16 patients during treatment compared with the same pretreatment interval. A significant chemoprophylactic effect was shown for up to 4 years of treatment. Patients with five or more tumours prior to acitretin benefited most. Two patients discontinued treatment because of side-effects and two patients developed hyperlipidaemia. Two patients with end-stage graft failure proceeded to haemodialysis. The introduction of low-dose acitretin proved to be a useful strategy in the long-term reduction of skin cancer in renal transplant recipients with multiple skin cancers and extensive epidermal dysplasia.

65. Sunscreen Use Before and After Transplantation and Assessment of Risk Factors Associated With Skin Cancer Development in Renal Transplant Recipients

Arch Dermatol. 2005;141:978-982

Moloney FJ, Almarzouqi E, O'Kelly P, Conlon P, Murphy GM

Objective: To determine the degree of compliance with sunscreen use among renal transplant recipients before and after transplantation and to determine risk factors associated with skin carcinogenesis.

Design: Single-observer study with structured interview using a standardized questionnaire. Medical records and histology reports were examined for details of prior skin cancer. Cox proportional hazards regression was used for analysis of risk factors for developing skin cancer after transplantation.

Setting: Patients attending Beaumont Hospital, the national renal transplantation center in Dublin, Ireland.

Patients: The study population comprised 270 patients (182 male and 88 female). Main Outcome Measures: Patients' use of sunscreens before and after transplantation relative to known skin cancer risk factors and subsequent skin carcinogenesis.

Results: Prior to transplantation, 68.5% of patients never applied sunscreen on a sunny day compared with 25.9% after transplantation. Patients 50 years or younger were more likely to always apply sunscreen both before and after transplantation (P=.01), as were female patients prior to transplantation (P=.02). Those patients who participated in an outdoor recreation were more likely to subsequently develop nonmelanoma skin cancer (P=.04), as were those older than 50 years (P=.001) and those with a history of 2 or more painful sunburns (P=.03).

Conclusions: Transplant recipients are poorly compliant with the use of sunscreens both before and after transplantation. Compliance is poorest in those groups at higher risk of nonmelanoma skin cancer.

66. Keratinocyte cancer prevention with ACE inhibitors, angiotensin receptor blockers or their combination in renal transplant recipients

Clinical Nephrology, Vol. 73 – No. 6/2010 (439-445)

Moscarelli L, Zanazzi M, Mancini G, Rossi E, Caroti L, Rosso G, Bertoni E and Salvadori M

Background: Skin cancer (SC) is the most frequent malignancy after renal transplantation (RT), especially squamous and basal cell carcinoma. The observation that angiotensin II is a potent angiogenic and growth factor raises the possibility that blocking its effects could reduce the incidence of skin cancer.
Objectives: To evaluate the incidence of keratinocyte cancer in RT recipients, the timing of occurrence of the skin events after RT; to compare the incidence of SC in our RT recipients and in RT patients on angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers therapy (ARBs) and their combination. Risk factors were also evaluated.
Results: During follow up, 52 of 565 patients (9.2%), 38 males 14 females, developed SC at a median time of 59 months (range 29 – 74) after RT. 12 of 52 patients (23%) with SC were on ACEi, ARBs therapy or their combination. The incidence was significantly lower in user patients compared to non user (5.6% and 11.4% respectively). BCC was the most frequent type of keratinocyte cancer in non users and in users. No association with incidence of BCC or SCC was observed for other classes of antihypertensive drugs (calcium antagonists, β-blockers, α-blockers).
Conclusion: This study confirms that RT patients are at high risk of SC. The use of ACEi or ARBs is associated with an approximately two-fold reduced risk of Keratinocyte cancers compared to non users in RT recipients. We did not observe an association between the incidence of SC and the use of other classes of antihypertensive drugs. Any chemoprotective effect of these agents may reflect inhibition of the growth factor activity of angiotensin II. Use of ACEi or ARBs, when this is possible, should be considered in RT patients with multiple risk factors.

67. Maintenance Immunosuppression with Target-of- Rapamycin Inhibitors is Associated with a Reduced Incidence of De Novo Malignancies

Transplantation 2005;80: 883–889

Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD.

Background: Immunosuppressive drug therapy has been identified as one etiological factor in the increased incidence of and deaths from malignancies in renal transplant recipients. In animal models, calcineurin inhibitors have a positive growth effect, whereas target-of-rapamycin (TOR) inhibitors have a negative growth effect on malignant cells.
Methods: A multivariate analysis of posttransplant malignancies in 33,249 deceased donor primary solitary renal recipients reported by 264 kidney transplant programs to the Organ Procurement and Transplantation Network database from July 1, 1996 to December 31, 2001 was performed. Data were censored at 963 days to allow comparable follow-up time among drug treatment groups. The incidence and relative risks of any de novo malignancy (skin and solid) and for non-skin solid malignancies in patients receiving TOR inhibitors compared to patients receiving calcineurin inhibitors were the primary endpoints.
Results: The incidence rates of patients with any de novo posttransplant malignancy were 0.60% with sirolimus/everolimus alone, 0.60% with sirolimus/everolimus + cyclosporine/tacrolimus, and 1.81% with cyclosporine/tacrolimus ($P<0.0001$); the rates with a de novo solid tumor were 0%, 0.47%, and 1.00%, respectively. In the Cox regression model the relative risk associated with sirolimus/everolimus immunosuppression for any de novo cancer was 0.39 (95% CI: 0.24-0.64; $P=0.0002$) and for de novo solid cancer was 0.44 (0.24-0.82; $P=0.0092$). Other significant risk factors were male sex, adult age group, white race, and history of a malignancy.
Conclusions: Maintenance immunosuppression with the TOR inhibitor drugs, sirolimus and everolimus, is associated with a significantly reduced risk of developing any posttransplant de novo malignancy and non-skin solid malignancy.

68. Orally Active Vitamin D for Potential Chemoprevention of Posttransplant Malignancy
Cancer Prev Res (Phila). 2012 Oct;5(10):1229-35.
Obi Y, Ichimaru N, Hamano T, Tomida K, Matsui I, Fujii N, Okumi M, Kaimori JY, Yazawa K, Kokado Y, Tsubakihara Y, Nonomura N, Rakugi H, Takahara S, Isaka Y.

Abstract: Posttransplant malignancy (PTM) is a limiting factor both for patient and allograft survival in kidney transplant recipients (KTRs). We hypothesized that active vitamin D compounds (AVD) could reduce PTM development in KTRs. Ambulatory KTRs in a Japanese prospective cohort were followed from August 2007 to November 2010. The outcome of interest was newly diagnosed PTM. A propensity score (PS) of having received AVDs was estimated using 26 clinically relevant factors. We used the Cox proportional hazards model with stratification by PS tertiles on the assumption that baseline hazard functions differ among tertiles. As sensitivity analyses, we used inverse probability weighting and PS matching. Among 218 participants, the median age was 50 (interquartile range [IQR], 40 to 59) years, 63.3% were male, median time since transplantation was 11.2 (IQR, 5.2 to 17.1) years, and mean estimated GFR was 41.3 (SD, 15.6) mL/min per 1.73 m^2. At baseline, 42.2% had been treated with AVDs mainly for glucocorticoid-induced osteoporosis. AVDs used were calcitriol (58.7%) and alfacalcidol (41.3%). During follow-up, PTM developed in 5.4% of 92 AVD users and 8.7% of 126 nonusers. Poor vitamin D status was common in the participants, but the serum 25-hydroxyvitamin D level was not significantly associated with PTM in Cox regression analysis. After stratifying patients by PS tertiles, we found that AVDs were significantly associated with a lower risk of PTM (HR 0.25 [0.07 to 0.82]). Sensitivity analyses yielded similar results. AVDs are potential chemopreventive agents against PTM in KTRs.

69. Effect of cytomegalovirus prophylaxis with immunoglobulin or with antiviral drugs on post-transplant non-Hodgkin lymphoma: a multicentre retrospective analysis

Lancet Oncol. 2007 Mar;8(3):212-8

Opelz G1, Daniel V, Naujokat C, Fickenscher H, Döhler B.

Background: Post-transplant non-Hodgkin lymphoma is a feared complication of immunosuppressive treatment and is associated with high mortality. Most post-transplant lymphomas develop from the uncontrolled proliferation of Epstein-Barr-virus (EBV)-infected B lymphocytes. No reliable methods for the prevention of EBV infection and lymphoma are available. We aimed to elucidate the effect of prophylactic treatment for cytomegalovirus (CMV) infection on the incidence of post-transplant lymphomas.

Methods: In a multicentre retrospective study, we analysed the incidence of post-transplant non-Hodgkin lymphoma in 44 828 recipients of deceased-donor kidney transplants who were reported to the scientific registry of the Collaborative Transplant Study. Patients had received antiviral drugs (aciclovir or ganciclovir) or anti-CMV immunoglobulin to prevent CMV infection according to the transplant centres' protocols, or no CMV prophylaxis. Standardised incidence ratios (SIR) of lymphoma were calculated and compared by χ^2 analyses

Findings: During the first post-transplantation year, 30 255 patients who did not receive CMV prophylaxis developed lymphomas at SIR 26.4. Lymphoma incidence in 12 470 patients who received antiviral treatment was nearly identical (SIR 24.2, p=0.62) to that in patients who did not receive CMV prophylaxis. However, 2103 patients who received anti-CMV immunoglobulin showed a complete absence of lymphomas in the first after-transplantation year (SIR 0; p=0.012 vs no treatment, p=0.016 vs antivirals). In the subsequent 5 years of follow-up, new cases of lymphoma developed at similar rates in all three groups (p=0.97).

Interpretation: These findings suggest that prophylactic anti-CMV immunoglobulin prevents the development of early post-transplant non-Hodgkin lymphoma in kidney-graft recipients. Prophylactic treatment with antiviral drugs does not reduce the risk of post-transplant lymphoma.

70. Pediatric Kidney Transplantation: Analysis of Donor Age, HLA Match, and Posttransplant Non-Hodgkin Lymphoma: A Collaborative Transplant Study Report

Transplantation 2010;90: 292–297

Opelz G and Döhler B

Background: The impact and relationship of donor age, human leukocyte antigen (HLA) matching, and posttransplant non-Hodgkin lymphoma in pediatric kidney recipients are not completely understood.

Methods: We analyzed Collaborative Transplant Study data from 9209 pediatric kidney transplant recipients to examine the effects of donor age and HLA match on graft survival and the relationship between HLA match and occurrence of non-Hodgkin lymphoma.

Results: Survival rates using donors aged 11 to 17, 18 to 34, or 35 to 49 years were similar. Cox regression analysis showed that two HLA-DR mismatches were associated with lower graft survival in transplants performed during 1988 to 1997 ($P<0.001$) but not during the 1998 to 2007 period ($P=0.95$). A hierarchical relationship was observed for the effect of increasing numbers of combined HLA-A+B+DR mismatches on graft survival during the 1988 to 1997 ($P<0.001$) and the 1998 to 2007 period ($P<0.001$). An association between two HLA-DR mismatches and non-Hodgkin lymphoma was demonstrated by multivariate analysis (hazard ratio for 2 vs. 0–1 DR mismatches 2.04, $P=0.021$), and the result was consistent during both 10-year periods.

Conclusion. We recommend that (1) kidneys from deceased donors up to 49 years be allocated to children, (2) an acceptable HLA-A+B+DR match be attempted in patients with relatively common HLA phenotypes, and (3) transplants with two HLA-DR mismatches be avoided to reduce the risk of posttransplant non-Hodgkin lymphoma.

71. Influence of Current and Previous Smoking on Cancer and Mortality After Kidney Transplantation

Transplantation 2016;100: 227–232

Opelz G and Döhler B

Background: Evidence is limited regarding the effect of stopping smoking before kidney transplantation.
Methods: Collaborative Transplant Study data from 46 548 recipients of first kidney transplants (1995-2012) were analyzed to 10 years after transplantation.
Results: Compared with patients who had never smoked (n = 31,462), patients who stopped smoking before transplantation (n = 10,291) only had a modestly increased risk of all-cause graft failure (hazard ratio [HR], 1.1; 95% confidence interval [95%CI], 1.0-1.1; P < 0.001) or death (HR,1.1; 95%CI, 1.0-1.2; P < 0.001) and a similar risk of death-censored graft failure (HR,1.0, 95%CI, 1.0-1.1; P = 0.19), but a 40%increase in death from malignancy (HR, 1.4; 95% CI, 1.2-1.7; P < 0.001). The risk of events was generally markedly higher in patients who continued to smoke (n = 4795) versus those who had stopped. For tumors of the lip, oral cavity and pharynx, digestive organs, respiratory tract, female genitalia and urinary tract, HR values increased significantly from never-smoked to former smokers to current smokers. The risk of respiratory tumors or cervical cancer was approximately halved when smoking was stopped versus continued.
Conclusions: This large series provides clear evidence that patients who stop smoking before transplantation experience substantial benefits, including a substantial reduction in certain types of malignancy.

72. Benefits and harms of statin therapy for persons with chronic kidney disease: A systematic review and meta-analysis

Ann Intern Med. 2012 August 21; 157(4): 263–275

Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF.

Background: Statins have uncertain benefits in persons with chronic kidney disease (CKD) because individual trials may have insufficient power to determine whether treatment effects differ with severity of CKD.
Purpose: To summarize the benefits and harms of statin therapy for adults with CKD and examine whether effects of statins vary by stage of kidney disease.
Data sources: Cochrane and EMBASE databases (inception to February 2012).
Study selection: Randomized trials comparing the effects of statins with placebo, no treatment, or another statin on mortality and cardiovascular outcomes.
Data extraction: Two independent reviewers extracted data and assessed risk of bias.
Data synthesis: Eighty trials comprising 51099 participants compared statin with placebo or no treatment. Treatment effects varied with stage of CKD. Moderate- to high-quality evidence indicated that statins reduced all-cause mortality (relative risk [RR], 0.81 [95% CI, 0.74 to 0.88]), cardiovascular mortality (RR, 0.78 [CI, 0.68 to 0.89]), and cardiovascular events (RR, 0.76 [CI, 0.73 to 0.80]) in persons not receiving dialysis. Moderate- to high-quality evidence indicated that statins had little or no effect on all-cause mortality (RR, 0.96 [CI, 0.88 to 1.04]), cardiovascular mortality (RR, 0.94 [CI, 0.82 to 1.07]), or cardiovascular events (RR, 0.95 [CI, 0.87 to 1.03]) in persons receiving dialysis. Effects of statins in kidney transplant recipients were uncertain. Statins had little or no effect on cancer, myalgia, liver function, or withdrawal from treatment, although adverse events were evaluated systematically in fewer than half of the trials.
Limitation: There was a reliance on post hoc subgroup data for earlier stages of CKD.
Conclusion: Statins decrease mortality and cardiovascular events in persons with early stages of CKD, have little or no effect in persons receiving dialysis, and have uncertain effects in kidney transplant recipients.

73. HMG CoA reductase inhibitors (statins) for kidney transplant recipients (Review)
Cochrane Database Syst Rev. 2014 Jan 28;1:CD005019
Palmer SC, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, Hegbrant J, Strippoli GF.

Background: People with chronic kidney disease (CKD) have higher risks of cardiovascular disease compared to the general population. Specifically, cardiovascular deaths account most deaths in kidney transplant recipients. Statins are a potentially beneficial intervention for kidney transplant patients given their established benefits in patients at risk of cardiovascular disease in the general population. This is an update of a review first published in 2009.
Objectives: We aimed to evaluate the benefits (reductions in all-cause and cardiovascular mortality, major cardiovascular events, myocardial infarction and stroke, and progression of CKD to requiring dialysis) and harms (muscle or liver dysfunction, withdrawal, cancer) of statins compared to placebo, no treatment, standard care, or another statin in adults with CKD who have a functioning kidney transplant.
Search methods: We searched the Cochrane Renal Group's Specialised Register to 29 February 2012 through contact with the Trials Search Coordinator using search terms relevant to this review.
Selection criteria: We included randomised controlled trials (RCTs) and quasi-RCTs that compared the effects of statins with placebo, no treatment, standard care, or statins on mortality, cardiovascular events, kidney function and toxicity in kidney transplant recipients.
Data collection and analysis: Two authors independently extracted data and assessed risk of bias. Treatment effects were expressed as mean difference (MD) for continuous outcomes (lipids, glomerular filtration rate (GFR), proteinuria) and relative risk (RR) for dichotomous outcomes (major cardiovascular events, mortality, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, elevated muscle or liver enzymes, withdrawal due to adverse events, cancer, end-stage kidney disease (ESKD), acute allograft rejection) together with 95% confidence intervals (CI).
Main results: We identified 22 studies (3465 participants); 17 studies (3282 participants) compared statin with placebo or no treatment, and five studies (183 participants) compared two different statin regimens. From data generally derived from a single high-quality study, it was found that statins may reduce major cardiovascular events (1 study, 2102 participants: RR 0.84, CI 0.66 to 1.06), cardiovascular mortality (4 studies, 2322 participants: RR 0.68, CI 0.45 to 1.01), and fatal or non-fatal myocardial infarction (1 study, 2102 participants: RR 0.70, CI 0.48 to 1.01); although effect estimates lack precision and include the possibility of no effect. Statins had uncertain effects on all-cause mortality (6 studies, 2760 participants: RR 1.08, CI 0.63 to 1.83); fatal or non-fatal stroke (1 study, 2102 participants: RR 1.18, CI 0.85 to 1.63); creatine kinase elevation (3 studies, 2233 participants: RR 0.86, CI 0.39 to 1.89); liver enzyme elevation (4 studies, 608 participants: RR 0.62, CI 0.33 to 1.19); withdrawal due to adverse events (9 studies, 2810 participants: RR 0.89, CI 0.74 to 1.06); and cancer (1 study, 2094 participants: RR 0.94, CI 0.82 to 1.07).Statins significantly reduced serum total cholesterol (12 studies, 3070 participants: MD -42.43 mg/dL, CI -51.22 to -33.65); low-density lipoprotein cholesterol (11 studies, 3004 participants: MD -43.19 mg/dL, CI -52.59 to -33.78); serum triglycerides (11 studies, 3012 participants: MD -27.28 mg/dL, CI -34.29 to -20.27); and lowered high-density lipoprotein cholesterol (11 studies, 3005 participants: MD -5.69 mg/dL, CI -10.35 to -1.03).Statins had uncertain effects on kidney function: ESKD (6 studies, 2740 participants: RR 1.14, CI 0.94 to 1.37); proteinuria (2 studies, 136 participants: MD -0.04 g/24 h, CI -0.17 to 0.25); acute allograft rejection (4 studies, 582 participants: RR 0.88, CI 0.61 to 1.28); and GFR (1 study, 62 participants: MD -1.00

mL/min, CI -9.96 to 7.96).Due to heterogeneity in comparisons, data directly comparing differing statin regimens could not be meta-analysed. Evidence for statins in people who have had a kidney transplant were sparse and lower quality due to imprecise effect estimates and provided limited systematic evaluation of treatment harm.

Authors' conclusions: Statins may reduce cardiovascular events in kidney transplant recipients, although treatment effects are imprecise. Statin treatment has uncertain effects on overall mortality, stroke, kidney function, and toxicity outcomes in kidney transplant recipients. Additional studies would improve our confidence in the treatment benefits and harms of statins on cardiovascular events in this clinical setting.

74. Anal cancer in renal transplant patients
Int J Colorectal Dis (2007) 22: 1–5
Patel HS, Silver AR, Northover JM.

Purpose: A comprehensive literature review was performed to examine the prevalence of anal cancer, anal intraepithelial neoplasia (AIN) and anal human papillomavirus (HPV) infection in renal transplant recipients who are at risk of anal cancer due to iatrogenic immunosuppression.
Methods: Pertinent articles were identified from searches performed on the National Center for Biotechnology Information database using the following keywords: anal cancer, AIN, screening, renal transplant (or kidney transplant), organ transplant recipients and post-transplant malignancies.
Results: The prevalence of AIN is 20% in renal transplant patients. The prevalence of anal HPV infection in established transplant patients is 47%, and the prevalence of anal HPV infection in new transplant patients is 23%. The relative risk for anal cancer in renal transplant patients is 10.
Conclusions: As compared to HIV-positive male patients who practise anal intercourse, renal transplant patients showed a modest rise in relative risk for anal cancer. Screening programmes to detect AIN in HIV-positive patients who practise anal intercourse have been introduced on a preliminary basis in sexual health clinics in the US and may become standard practise in this population. The case for screening in renal transplant patients is unclear and would merit further investigation, especially with reference to the prevalence of anal HPV infection in this population. It may transpire that renal transplant patients would benefit more from HPV prophylaxis rather than screening for AIN.

75. Cancer incidence in kidney transplant recipients: a study protocol

BMC Cancer. 2009 Aug 22;9:294.

Pita-Fernandez S, Valdes-Cañedo F, Pertega-Diaz S, Seoane-Pillado MT, Seijo-Bestilleiro R.

Background: Different publications show an increased incidence of neoplasms in renal transplant patients. The objective of this study is to determine the incidence of cancer in the recipients of renal transplants performed in the A Coruña Hospital (Spain) during the period 1981-2007.

Methods/design: During the study period 1967 kidney transplants were performed, corresponding to 1710 patients. Patients with neoplasms prior to the transplant will be excluded (n = 38). A follow-up study was carried out in order to estimate cancer incidence after transplantation.

For each patient, information included donor and recipient characteristics, patients and graft survival and cancer incidence after transplantation. Incident cancer is considered as new cases of cancer after the transplant with anatomopathological confirmation. Their location will be classified according to the ICD-9.

The analysis will be calculated using the indirect standardisation method. Age-adjusted cancer incidence rates in the Spanish general population will be obtained from the Carlos III Health Institute, the National Epidemiology Centre of the Ministry of Science and Technology. Crude first, second and third-year post-transplantation cancer incidence rates will be calculated for male and female recipients. The number of cases of cancer at each site will be calculated from data in the clinical records. The expected number of cancers will be calculated from data supplied by the Carlos III Health Institute. For each tumour location we will estimate the standardized incidence ratios (SIRs), using sex-specific cancer incidence rates, by dividing the incidence rate for the transplant patients by the rate of the general population. The 95% confidence intervals of the SIRs and their associated p-values will be calculated by assuming that the observed cancers follow a Poisson distribution. Stratified analysis will be performed to examine the variation in the SIRs with sex and length of follow-up.

Competing risk survival analysis methods will be applied to estimate the cumulative incidence of cancer and to identify variables associated to its occurrence.

Discussion: Information about cancer incidence in kidney transplant patients could be useful to adapt the guidelines on post-kidney transplant follow-up on tumour screening, and evaluate the impact of intervention measures for the prevention of cancer in these patients.

76. High-risk human papillomavirus in non-melanoma skin lesions from renal allograft recipients and immunocompetent patients

Br J Cancer. 2011 Apr 12;104(8):1334-41.

Reuschenbach M, Tran T, Faulstich F, Hartschuh W, Vinokurova S, Kloor M, Krautkrämer E, Zeier M, von Knebel Doeberitz M, Sommerer C.

Background: High-risk human papillomaviruses (HR-HPVs) can be detected in a proportion of non-melanoma skin cancers. Data on prevalence are inconclusive, but are essential to estimate the relevance of HR-HPV, particularly with regard to prophylactic HPV vaccines for skin cancer prevention.
Methods: High-risk human papillomavirus DNA was investigated in 140 non-melanoma skin lesions from 54 immunocompetent patients and 33 immunosuppressed renal allograft recipients. Expression of $p16^{INK4a}$, a marker for HR-HPV oncogene expression in the uterine cervix, and of p53 and pRB was evaluated immunohistochemically.
Results: The highest prevalence of HR-HPV was found in squamous cell cancer (SCC) (46.2% (6 out of 13) in immunosuppressed and 23.5% (4 out of 17) in immunocompetent patients). High-risk human papillomavirus positivity was accompanied by diffuse $p16^{INK4a}$ expression in most SCC ($P<0.001$) and basal cell cancers ($P=0.02$), while almost all SCC in situ were $p16^{INK4a}$ positive irrespective of HR-HPV presence ($P=0.66$). Diffuse $p16^{INK4a}$ expression was associated with lack of pRB expression ($P=0.001$). p53 was strongly expressed in 40.0% (56 out of 140) of the lesions irrespective of HR-HPV presence.
Conclusion: High-risk human papillomavirus can be detected in lesions of keratinised squamous epithelia. The association of HR-HPV with diffuse $p16^{INK4a}$ expression might indicate HR-HPV oncogene expression in a proportion of lesions. Overexpression of p53 suggests p53 pathway alterations in HR-HPV-positive and -negative lesions.

77. Efficacy of a Sun Protection Workbook for Kidney Transplant Recipients: A Randomized Controlled Trial of a Culturally Sensitive Educational Intervention

Am J Transplant. 2014 December ; 14(12): 2821–2829

Robinson JK, Guevara Y, Gaber R, Clayman ML, Kwasny MJ, Friedewald JJ, Gordon EJ.

Abstract: A culturally sensitive educational intervention that encouraged sun protection behaviors among kidney transplant recipients (KTRs) was developed and the short-term efficacy was evaluated. Non-Hispanic White, Hispanic/Latino and non-Hispanic Black patients, who received a transplant 2-24 months prior to the study, were randomized into two study groups: intervention versus standard of care. Electronic reminders tailored to the weather conditions were sent every 2 weeks by text message or email. Self-reported surveys and biologic measurements were obtained prior to the intervention and 6 weeks later. Among the 101 study participants, there was a statistically significant increase in knowledge, recognition of personal risk of developing skin cancer, willingness to change sun protection behavior and self-reported performance of sun protection in participants receiving the intervention in comparison with those receiving standard of care ($p < 0.05$). The pigment darkening of the sun-exposed forearm and sun damage of the forearm and sunburns/skin irritation from the sun were significantly less in participants receiving the intervention ($p < 0.05$). Providing sun protection education at the beginning of summer with reminders tailored to weather conditions helped KTRs adopt sun protection practices. This sun protection program for KTRs may be incorporated into the care provided by the nephrologist or transplant surgeon.

78. Beneficial effect of low-dose systemic retinoid in combination with topical tretinoin for the treatment and prophylaxis of premalignant and malignant skin lesions in renal transplant recipients

Transplantation. 1995 Mar 15;59(5):714-9.

Rook AH, Jaworsky C, Nguyen T, Grossman RA, Wolfe JT, Witmer WK, Kligman AM.

Abstract: Renal transplant recipients experience a greatly increased frequency of neoplastic skin lesions, including aggressive squamous cell carcinomas. Recent reports suggest that high doses of systemic retinoids may exert a chemotherapeutic and chemoprophylactic effect. Similarly, topical retinoid, especially tretinoin, has also been shown to be anti-tumoragenic in various settings. Because of the serious toxicity of high-dose systemic retinoid, a protocol was developed that combined topical tretinoin with low-dose etretinate (10 mg daily) for the treatment of frequently occurring dysplastic skin lesions in renal transplant recipients. Seven patients elected to receive combined tretinoin and etretinate therapy, and 4 were treated with tretinoin alone. Clinical evaluations were performed monthly. By 3 months of therapy, 9 of 11 patients exhibited at least a 25% decrease in the number of neoplastic growths. After 6 months, 6 of 8 evaluable patients, including 2 of 3 individuals receiving tretinoin alone, exhibited at least a 50% decrease. Three of 4 patients on the combined regimen and 2 of 3 receiving tretinoin alone for at least 9 months, exhibited a significant decrease in the rate of development of new squamous cell cancers. At the start of treatment, epidermal specimens were almost completely devoid of Langerhans cells ($CD1^+$ cells). Their density increased greatly and in proportion to the duration of therapy. Long term topical tretinoin with or without low-dose oral etretinate seems to be an effective regimen to suppress the development of new tumors and to reduce the numbers of existing lesions in renal transplant recipients.

79. Conversión a sirolimus

Nefrologia. 2006;26 Suppl 2:52-63.

Ruiz JC, Alonso A, Arias M, Campistol JM, González Molina M, González Posada JM, Grinyo JM, Morales JM, Oppenheimer F, Sánchez Fructuoso A, Sánchez-Plumed J.

This article does not have an abstract to display.

80. Management of the Well Renal Transplant Recipient: Outpatient Surveillance and Treatment Recommendations

Semin Dial. 2005 Nov-Dec;18(6):520-8.

Salifu MO, Tedla F, Markell MS.

Abstract: Although renal transplantation offers survival and quality of life advantages as a renal replacement therapy, a substantial proportion of transplant recipients develop worsening of preexisting medical diseases or new complications, including sequelae of rejection, new onset diabetes after transplantation (NODAT), hyperlipidemia, opportunistic infections, cancer, and other systemic diseases secondary to immunosuppression. Management of these problems can be a complex endeavor due to medication interactions that often affect immunosuppression levels. However, successful management of the chronic medical problems associated with renal transplantation can prolong the life span of the graft and the patient.

81. Linfomi nel trapianto renale
G Ital Nefrol 2010; 27 (S50): S46-S50
Sandrini S, Valerio F, Insalaco M
Artículo en Italiano

Kidney transplantation and lymphomas

Abstract: Post-transplant lymphoproliferative disease (PTLD) accounts for 30% of nonskin cancers after kidney transplants. Diffuse large B-cell lymphoma is the most frequent form of PTLD. The incidence of PTLD increases over time: from 1.2% at 5 years to 6.8% at 20 years. Its late occurrence is therefore not unusual.
Moreover, not only is it more frequent but also more serious than the early type because of the lower responsiveness to therapy. Epstein-Barr virus (EVB) infection is one of the most important risk factors for this disease, along with the use of antilymphocyte agents, which should be avoided in EVB-negative patients. During the first year after transplant, EBV-PCR monitoring can be helpful for the early diagnosis of EBV-associated PTLD, especially in children. No effective strategy has yet been reported for the prevention of late PTLD. Interruption of immunosuppression is the first step of therapy, but it is rarely effective by itself. Rituximab (4-8 doses) is widely used and is successful in about 50% of cases. Chemotherapy becomes essential in relapsed or refractory disease, but it significantly increases the risk of life-threatening infections. The mortality rate is around 50% 12 months after diagnosis, often due to the side effects of chemotherapy.

82. To convert or not to convert: lessons from the CONVERT trial
Nat Rev Nephrol. 2009 Jul;5(7):371-3
Bunnapradist S, Vincenti F.

Abstract: In participants of the CONVERT trial, which enrolled recipients of kidney transplants, conversion of immunosuppressive therapy from calcineurin inhibitors to sirolimus did not improve renal function. More importantly, the intervention was detrimental among patients with impaired kidney function and/or proteinuria. Sirolimus conversion resulted, however, in lower rates of malignancy.

83. Conversion From Calcineurin Inhibitors to Sirolimus Maintenance Therapy in Renal Allograft Recipients: 24-Month Efficacy and Safety Results From the CONVERT Trial

Transplantation 2009;87: 233–242

Schena FP, Pascoe MD, Alberu J, del Carmen Rial M, Oberbauer R, Brennan DC, Campistol JM, Racusen L, Polinsky MS, Goldberg-Alberts R, Li H, Scarola J, Neylan JF; Sirolimus CONVERT Trial Study Group.

Background: The efficacy and safety of converting maintenance renal transplant recipients from calcineurin inhibitors (CNIs) to sirolimus (SRL) was evaluated.
Methods: Eight hundred thirty renal allograft recipients, 6 to 120 months posttransplant and receiving cyclosporine or tacrolimus, were randomly assigned to continue CNI (n=275) or convert from CNI to SRL (n=555). Primary endpoints were calculated Nankivell glomerular filtration rate (GFR; stratified at baseline: 20-40 vs. >40 mL/min) and the cumulative rates of biopsy-confirmed acute rejection (BCAR), graft loss, or death at 12 months. Enrollment in the 20 to 40 mL/min stratum was halted prematurely because of a higher incidence of safety endpoints in the SRL conversion arm.
Results: Intent-to-treat analyses at 12 and 24 months showed no significant treatment difference in GFR in the baseline GFR more than 40 mL/min stratum. On-therapy analysis of this cohort showed significantly higher GFR at 12 and 24 months after SRL conversion. Rates of BCAR, graft survival, and patient survival were similar between groups. Median urinary protein-to-creatinine ratios ($U_{Pr/Cr}$) were similar at baseline but increased significantly after SRL conversion. Malignancy rates were significantly lower at 12 and 24 months after SRL conversion. Post hoc analyses identified a subgroup with baseline GFR more than 40 mL/min and $U_{Pr/Cr}$ less than or equal to 0.11, whose risk-benefit profile was more favorable after conversion than that for the overall SRL conversion cohort.
Conclusions: At 2 years, SRL conversion among patients with baseline GFR more than 40 mL/min was associated with excellent patient and graft survival, no difference in BCAR, increased urinary protein excretion, and a lower incidence of malignancy compared with CNI continuation. Superior renal function was observed among patients who remained on SRL through 12 to 24 months, particularly in the subgroup of patients with baseline GFR more than 40 mL/min and $U_{Pr/Cr}$ less than or equal to 0.11.

84. Ano-Genital Neoplasia in Renal Transplant Patients
Ann Transplant. 1997;2(4):59-66.
Sillman FH, Sentovich S, Shaffer D.

Abstract: Ano-genital neoplasia is about 20 x more common in renal transplant patients than the general population. Neoplasms in the immunosuppressed are more morbid and mortal because: patients are younger; tumors are more undifferentiated; they have more and larger foci; more sites are involved; neoplasms tend to persist, recur and progress; and there are more complications from treatments. Intraepithelial neoplasia engenders some morbidity. Invasion is rarer, but when it occurs, it is always morbid, and all too often mortal. Invasive ano-genital cancer is primarily preventable because the lower genital and anal tracts are accessible to inspection, cytologic screening, endoscopy and biopsy. Prime prevention is avoiding infection with the Human Papilloma Virus (HPV). Next best is detecting HPV/intraepithelial neoplasia early with frequent inspection, cytology and liberal biopsies; and then removing any condylomas or intraepithelial neoplasia that develop.

85. High-Resolution Anoscopy in the Diagnosis of Anal Cancer Precursor Lesions in Renal Graft Recipients

Ann Surg Oncol. 2008 May;15(5):1470-5

Tramujas da Costa e Silva I1, de Lima Ferreira LC, Santos Gimenez F, Gonçalves Guimarães RA, Botinelly Fujimoto L, Barbosa Cabral CR, Venturim Mozzer R, de Souza Atala L.

Background: Renal graft recipients are one of the population groups known to be at high risk of developing anal cancer. This study investigated the presence of subclinical anal squamous intraepithelial lesions and the diagnostic ability of high-resolution anoscopy in detecting these lesions in renal graft recipients followed-up in Manaus.
Methods: In a cross-sectional study, 50 renal graft recipients were interviewed and submitted to high-resolution anoscopy with biopsies of acetowhite lesions or of the anal transition zone mucosa when acetowhitening was absent. Considering the histopathological reports of the examined anal specimens as the gold standard, the diagnostic validation and precision measures of high-resolution anoscopy were calculated as well as the prevalence of anal squamous intraepithelial lesions in the studied population.
Results: In 42 renal graft recipients with satisfactory histopathological readings, prevalence of anal squamous intraepithelial lesions or condyloma acuminatum (ASIL-ACU) was 23.81%. Sensitivity of high-resolution anoscopy was 100%; specificity, 65.63%; positive predictive value, 47.62%; negative predictive value, 100%; and kappa coefficient, 0.48.
Conclusions: With a prevalence of 23.81% of subclinical ASIL-ACU lesions, the studied renal graft recipients had all these lesions detected by high-resolution anoscopy, notwithstanding most anal transition zone acetowhitened biopsied areas did not reveal histopathological aspects of anal cancer precursor lesions or condyloma acuminatum. Therefore, greater experience with the diagnostic tool was felt necessary to enhance its positive predictive value, specificity and diagnostic precision.

86. Prevention of Cytomegalovirus in Organ Transplant Recipients: Cross Roads Between Antiviral and Antitumor Immunity

Transplantation. 2010 Aug 27;90(4):360-1.

Singh N

This article does not have an abstract to display.

87. Sirolimus and Skin-Cancer Prevention in Kidney Transplantation

N Engl J Med. 2012 Oct 18;367(16):1565; author reply 1565-6.

Smak Gregoor PJ.

This article does not have an abstract to display.

88. Protection from Cancer in Kidney Transplant Patients by γδ T Cells: Role of CMV Infection?
J Am Soc Nephrol 21: 11–13, 2010.
Söderberg-Naucleér S.
This article does not have an abstract to display.

89. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.6.3. Cancer risk after renal transplantation. Solid organ cancers: prevention and treatment.

Nephrol Dial Transplant. 2002;17 Suppl 4:32, 34-6.

EBPG Expert Group on Renal Transplantation.

Abstract: Guidelines: J. All renal transplant recipients should have regular ultrasonography of their native kidneys (when applicable) for screening of renal cell carcinomas, which are observed at much higher incidence in both dialysed and transplant patients. K. Guidelines published for screening and prevention of solid organ cancers in the general population should be strictly applied to transplant recipients, who are in general at higher cancer risk, but would benefit equally or even greater. L. All male renal transplant recipients aged 50 and over should have a yearly prostate specific antigen (PSA) test prior to a regular digital rectal examination. M. All female renal transplant recipients should have a yearly cervical (PAP) smear together with regular pelvic examination and regular mammography, according to national recommendations where available. N. All renal transplant recipients should undergo a faecal occult-blood testing as a screening for colorectal cancer and other (pre-malignant) lesions, according to national recommendations where available. O. In all these conditions, it is recommended to reduce immunosuppression whenever possible.

90. Controlling the incidence of infection and malignancy by modifying immunosuppression
Transplantation. 2001 Dec 27;72(12 Suppl):S89-93.
Soulillou JP, Giral M.

Abstract: Long-term outcomes in renal transplantation have improved over the years but are still a matter of concern. Because patients typically require lifelong immunosuppression, the risks of cancer and infection associated with immunosuppressive agents continue to demand attention. Physicians strive endlessly to find the right balance between the level of immunosuppression required to prevent rejection and the level that will minimize dose-dependent side effects. Data presented in this paper suggest that some renal transplant recipients might have more than necessary immunosuppression during maintenance therapy and that reducing the immunosuppressant dose can decrease cancer incidence, without worsening long-term patient or allograft survival. Additionally, data were examined suggesting that immunosuppressive agents might be associated with different risks for cancer, specifically, the potential advantage of reduced cancer risk for sirolimus and sirolimus derivatives in comparison with standard immunosuppressive agents. Although promising, these preliminary results are from preclinical studies, and further study is warranted.

91. Management and prevention of post-transplant malignancies in kidney transplant recipients
Clin Kidney J. 2015 Oct;8(5):637-44.
Stallone G, Infante B, Grandaliano G.

Abstract: The central issue in organ transplantation remains suppression of allograft rejection. Thus, the development of immunosuppressive drugs has been the key to successful allograft function. The increased immunosuppressive efficiency obtained in the last two decades in kidney transplantation dramatically reduced the incidence of acute rejection. However, the inevitable trade-off was an increased rate of post-transplant infections and malignancies. Since the incidence of cancer in immunosuppressed transplant recipients becomes greater over time, and the introduction of new immunosuppressive strategies are expected to extend significantly allograft survival, the problem might grow exponentially in the near future. Thus, cancer is becoming a major cause of morbidity and mortality in patients otherwise successfully treated by organ transplantation. There are at least four distinct areas requiring consideration, which have a potentially serious impact on recipient outcome after transplantation: (i) the risk of transmitting a malignancy to the recipient within the donor organ; (ii) the problems of previously diagnosed and treated malignancy in the recipient; (iii) the prevention of de novo post-transplant malignant diseases and (iv) the management of these complex and often life-threatening clinical problems. In this scenario, the direct and indirect oncogenic potential of immunosuppressive therapy should be always carefully considered.

92. Transmission of donor melanoma by organ transplantation
Lancet Oncol 2010; 11: 790–96
Strauss DC, Thomas JM.

Abstract: Transplant-related malignancies are a major contributor to morbidity and mortality in the organ-recipient population, and most often develop de novo in the immunosuppressed recipient or as recurrent malignancy after transplantation. The least common scenario, and a rare event, is a recipient malignancy derived from the donor organ. Melanoma is one of the most often reported and lethal donor-derived malignancies with a high transmission rate. Donor transmission of melanoma might be related to the biology of melanoma, with regard to tumour dormancy, late recurrence, circulating tumour cells, and the destiny of some micrometastases. Melanoma-cell dormancy explains the late recurrence that can occur after the initial treatment of melanoma, and may be relevant to our understanding and management of some melanoma micrometastasis in the sentinel node. The high incidence of circulating tumour cells in early melanoma should be considered in the context of the transmission of melanoma by apparent disease-free organ donors following removal of a primary melanoma up to 32 years before. This scenario suggests that melanoma cells can remain dormant at distant sites for decades (and possibly forever) in immunocompetent patients, only to reactivate after transplantation into an immunosuppressed recipient. Potential organ donors should be carefully screened for a history of melanoma, and excluded. The current recommendation for treatment of donor-related melanoma includes withdrawal of immunosuppression, graft rejection, and explantation of the allograft after rejection has been established. In non-renal transplant patients with life-sustaining organs, withdrawal of immunosuppression and graft rejection is not feasible, and reduction of immunosuppression or urgent retransplantation are the only possible salvage strategies. The transmission of malignancy by organ donation could be considered "nature's own experiment", but raises questions that our current understanding of the biology of melanoma cannot answer.

93. Induction Therapies in Live Donor Kidney Transplantation on Tacrolimus and Mycophenolate With or Without Steroid Maintenance

Clin J Am Soc Nephrol. 2015 Jun 5;10(6):1041-9.

Tanriover B, Zhang S, MacConmara M, Gao A, Sandikci B, Ayvaci MU, Mete M, Tsapepas D, Rajora N, Mohan P, Lakhia R, Lu CY, Vazquez M.

Background and objectives: Induction therapy with IL-2 receptor antagonist (IL2-RA) is recommended as a first line agent in living donor renal transplantation (LRT). However, use of IL2-RA remains controversial in LRT with tacrolimus (TAC)/mycophenolic acid (MPA) with or without steroids.

Design, setting, participants, & measurements: The Organ Procurement and Transplantation Network registry was studied for patients receiving LRT from 2000 to 2012 maintained on TAC/MPA at discharge (n=36,153) to compare effectiveness of IL2-RA to other induction options. The cohort was initially divided into two groups based on use of maintenance steroid at time of hospital discharge: steroid (n=25,996) versus no-steroid (n=10,157). Each group was further stratified into three categories according to commonly used antibody induction approach: IL2-RA, rabbit anti-thymocyte globulin (r-ATG), and no-induction in the steroid group versus IL2-RA, r-ATG and alemtuzumab in the no-steroid group. The main outcomes were the risk of acute rejection at 1 year and overall allograft failure (graft failure or death) post-transplantation through the end of follow-up. Propensity score-weighted regression analysis was used to minimize selection bias due to non-random assignment of induction therapies.

Results: Multivariable logistic and Cox analysis adjusted for propensity score showed that outcomes in the steroid group were similar between no-induction (odds ratio [OR], 0.96; 95% confidence interval [95% CI], 0.86 to 1.08 for acute rejection; and hazard ratio [HR], 0.99; 95% CI, 0.90 to 1.08 for overall allograft failure) and IL2-RA categories. In the no-steroid group, odds of acute rejection with r-ATG (OR, 0.73; 95% CI, 0.59 to 0.90) and alemtuzumab (OR, 0.53; 95% CI, 0.42 to 0.67) were lower; however, overall allograft failure risk was higher with alemtuzumab (HR, 1.27; 95% CI, 1.03 to 1.56) but not with r-ATG (HR, 1.19; 95% CI, 0.97 to 1.45), compared with IL2-RA induction.

Conclusions: Compared with no-induction therapy, IL2-RA induction was not associated with better outcomes when TAC/MPA/steroids were used in LRT recipients. r-ATG appears to be an acceptable and possibly the preferred induction alternative for IL2-RA in steroid-avoidance protocols.

94. Analysis of Factors that Influence Survival with Post-Trasplant Lymphoproliferative Disorder in Renal Transplant Recipients: The Israel Penn International Transplant Turmor Registry Experience

Am J Transplant. 2005 Apr;5(4 Pt 1):775-80.

Trofe J, Buell JF, Beebe TM, Hanaway MJ, First MR, Alloway RR, Gross TG, Succop P, Woodle ES.

Abstract: Significant mortality is associated with post-transplant lymphoproliferative disorder (PTLD) in kidney transplant recipients (KTX). Univariate/multivariate risk factor survival analysis of US PTLD KTX reported to Israel Penn International Transplant Tumor Registry from November 1968 to January 2000 was performed. PTLD presented 18 (median) (range 1-310) months in 402 KTX. Death rates were greater for those diagnosed within 6 months (64%) versus beyond 6 months (54%, p = 0.04). No differences in death risk for gender, race, immunosuppression, EBV, B or T cell positivity were identified. Death risk increased for multiple versus single sites (73% vs. 53%, hazards ratio (HR) 1.4). A 1-year increase in age increased HR for death by 2%. Surgery was associated with increased survival (55% vs. 0% without surgery) (p < 0.0001). Patients with allograft involvement, treated with transplant nephrectomy alone (n = 20), had 80% survival versus 53% without allograft removal (n = 15) (p < 0.001). Overall survival was 69% for allograft involvement alone versus 36% for other organ involvement plus allograft (n = 19 alive) (p < 0.0001). Death risk was greater for multiple site PTLD and increasing age, and risks were additive. Univariate analysis identified increased death risk for those not receiving surgery, particularly allograft involvement alone.

95. Cutaneous Melanoma Is Related to Immune Suppression in Kidney Transplant Recipients
Cancer Epidemiol Biomarkers Prev. 2009 Aug;18(8):2297-303.
Vajdic CM, van Leeuwen MT, Webster AC, McCredie MR, Stewart JH, Chapman JR, Amin J, McDonald SP, Grulich AE.

Abstract: Melanoma incidence is increased after organ transplantation, but there is uncertainty as to why this occurs. Diagnoses of invasive melanoma were ascertained in 8,152 kidney transplant recipients (1982-2003) by linking national Australian population-based registers, the Australia and New Zealand Dialysis and Transplant Registry, and the Australian National Cancer Statistics Clearing House. Incidence rate ratios (IRR) and standardized incidence ratios were used to compare melanoma risk during periods of transplant function and failure. Standardized incidence ratios were also computed by time since transplantation. Risk factors were examined using multivariate Poisson regression. Linkage identified 82 melanomas (134/100,000 person-years). Incidence was lower after resumption of dialysis and reduction of immune suppression than during transplant function [IRR, 0.09; 95% confidence interval (95% CI), 0.01-0.66]. During first transplant function, melanoma (n = 74) relative risk peaked in the second year and declined linearly thereafter (P trend = 0.03). During first transplant function, risk was positively associated with increasing year of age (IRR, 1.05; 95% CI, 1.03-1.07) and receipt of lymphocyte-depleting antibody (IRR, 1.73; 95% CI, 1.05-2.84). Female sex (IRR, 0.57; 95% CI, 0.35-0.94), non-Caucasian race (IRR, 0.15; 95% CI, 0.02-1.05), and increasing time since transplantation (P trend = 0.06) were inversely associated with risk. The incidence pattern and risk factor profile for melanoma after transplantation strongly suggest that the current receipt, intensity, and possibly the recency of iatrogenic immunosuppression increase melanoma risk. Melanoma risk was also associated with proxy indicators of high personal sun exposure and sensitivity. These findings show the marked influence of immunologic control over melanoma incidence.

96. Cancer after renal transplantation
Curr Opin Nephrol Hypertens 16:523–528.
Vasudev B and Hariharan S

Purpose of review: Prolonged waiting times for renal transplantation, an increase in the average age of recipients, decreased acute rejection rates due to use of newer potent immunosuppressives and improving long-term transplant survival have raised concerns in the transplant community regarding posttransplant cancer. In view of the fact that transplant recipients are living longer, it is of paramount importance that we continue to translate discoveries at the bench to the bedside and document cancers in the posttransplant recipient registries. Analysis of data will help in optimizing patient management.
Recent findings: Recent evidence indicates that sirolimus is associated with a decreased incidence of posttransplant de-novo cancer and remission of Kaposi's sarcoma and nonmelanoma skin cancer. Mycophenolate mofetil has been shown to have an antiproliferative activity against leukemia and lymphoma and an anti-tumor effect against colon and prostate cancer.
Clinically it has been shown to be associated with a reduced incidence of cancers like posttransplant lymphoproliferative disorder.
Summary: Appropriate selection of transplant candidates, pretranspant and posttransplant cancer surveillance and judicious evidence-based use of newer immunosuppressants may help reduce the incidence and improve the outcome of posttransplant cancer.

97. Five-Year Safety and Efficacy of Belatacept in Renal Transplantation

J Am Soc Nephrol. 2010 Sep; 21(9): 1587–1596.

Vincenti F, Blancho G, Durrbach A, Friend P, Grinyo J, Halloran PF, Klempnauer J, Lang P, Larsen CP, Mühlbacher F, Nashan B, Soulillou JP, Vanrenterghem Y, Wekerle T, Agarwal M, Gujrathi S, Shen J, Shi R, Townsend R, Charpentier B.

Abstract: Belatacept is a first-in-class co-stimulation blocker in development for primary maintenance immunosuppression. A Phase II study comparing belatacept with cyclosporine (CsA) for prevention of acute rejection and protection of renal function in kidney transplant recipients demonstrated similar efficacy and significantly higher measured GFR at 1 year for belatacept, but the incidence of posttransplantation lymphoproliferative disorder was higher. Here, we present the results for the extension of this trial, which aimed to assess long-term safety and efficacy of belatacept. Seventy-eight of 102 patients who were receiving belatacept and the 16 of 26 who were receiving CsA completed the long-term extension period. GFR remained stable in patients who were receiving belatacept for 5 years, and the incidences of death/graft loss or acute rejection were low. The frequencies of serious infections were 16% for belatacept and 27% for CsA, and neoplasms occurred in 12% of each group. No patients who were treated with belatacept and one patient who was treated with CsA developed posttransplantation lymphoproliferative disorder during the follow-up period. Serious gastrointestinal disorders occurred more frequently with belatacept (12% belatacept *versus* 8% CsA), and serious cardiac disorders occurred more frequently with CsA (2% belatacept *versus* 12% CsA). Pharmacokinetic analyses showed consistent exposure to belatacept over time. CD86 receptor saturation was higher in patients who were receiving belatacept every 4 weeks (74%) compared with every 8 weeks (56%). In conclusion, this study demonstrated high patient persistence with intravenous belatacept, stable renal function, predictable pharmacokinetics, and good safety with belatacept over 5 years.

98. Mortality from infections and malignancies in patients treated with renal replacement therapy: data from the ERA-EDTA registry

Nephrol Dial Transplant (2015) 30: 1028–1037

Vogelzang JL, van Stralen KJ, Noordzij M, Diez JA, Carrero JJ, Couchoud C, Dekker FW, Finne P, Fouque D, Heaf JG, Hoitsma A, Leivestad T, de Meester J, Metcalfe W, Palsson R, Postorino M, Ravani P, Vanholder R, Wallner M, Wanner C, Groothoff JW, Jager K.

Background: Infections and malignancies are the most common non-cardiovascular causes of death in patients on chronic renal replacement therapy (RRT). Here, we aimed to quantify the mortality risk attributed to infections and malignancies in dialysis patients and kidney transplant recipients when compared with the general population by age group and sex.
Methods: We followed 168 156 patients included in the ERA-EDTA registry who started RRT in 1993-2007 until 1 January 2012. Age- and cause-specific mortality rates per 1000 person-years (py) and mortality rate ratios (MRRs) compared with the European general population (WHO) were calculated. To identify risk factors, we used Cox regression.
Results: Infection-related mortality was increased 82-fold in dialysis patients and 32-fold in transplant recipients compared with the general population. Female sex, diabetes, cancer and multisystem disease were associated with an increased risk of infection-related mortality. The sex difference was most pronounced for dialysis patients aged 0-39 years, with women having a 32% (adjusted HR 1.32 95% CI 1.09-1.60) higher risk of infection-related mortality than men. Mortality from malignancies was 2.9 times higher in dialysis patients and 1.7 times higher in transplant recipients than in the general population. Cancer and multisystem disease as primary causes of end-stage renal disease were associated with higher mortality from malignancies.
Conclusion: Infection-related mortality is highly increased in dialysis and kidney transplant patients, while the risk of malignancy-related death is moderately increased. Young women on dialysis may deserve special attention because of their high excess risk of infection-related mortality. Further research into the mechanisms, prevention and optimal treatment of infections in this vulnerable population is required.

99. Bladder cancer in patients after organ transplantation

Curr Opin Urol. 2010 Sep;20(5):432-6

Wallerand H1, Ravaud A, Ferrière JM.

Purpose of review: Bladder cancer development in organ transplant recipients remains a complex problem to manage as it has been demonstrated that the clinical course seems worse than in the general population. Most of the reports on bladder cancer after organ transplantation were done for kidney transplantation. Both virally and nonvirally are involved in bladder tumor development. The immunosuppressed status of the transplant recipients renders the screening, the therapeutic management, and the post-treatment surveillance very difficult.
Recent findings: With the increase of organ transplantation, especially renal transplantation, graft survival, and age of donor and recipient, urological cancer, including bladder cancer, become a critical problem affecting the survival. The advent of the new immunosuppressed drugs, mTOR inhibitors, leads to the hope of improving both survivals of the graft and of the recipients.
Summary: The molecular pathway P13K/Akt/mTOR is frequently activated during human solid tumor development and progression. However, mTOR inhibitors are also used in order to avoid renal allograft rejection. The combination of both actions could significantly improve graft and organ recipient survival and could provide progresses in targeted therapy management of bladder cancer.

100. Characteristics of Neoplasm Occurrence and the Therapeutic Effect of Sirolimus in South Chinese Kidney Transplant Recipients

Transplantation Proceedings, 38, 3536–3539 (2006)

Wang CX, Liu LS, Chen LZ, Chen SY, Wu PG, Fei JG, Qiu J, Deng SX, Zheng KL, Ji YL, Zhu LY, Shen QR, He XS.

Abstract: Kidney transplantation (KTx) recipients are at a higher risk of oncogenesis when compared to the general population. Sirolimus (SRL), a potent immunosuppressant, has shown promising antineoplastic effects in vitro and in vivo. This study retrospectively analyzed the neoplasm occurrence and the efficiency of SRL on unresectable malignancies in South Chinese KTx recipients. Thirty-three (1.64%) of 2017 patients who received KTx from January 1984 to December 2004 developed neoplasms at 4 to 117 months posttransplant, mostly in digestive organs (33.3%), the hematologic system (15.2%), or the skin (12.1%). The most common type was liver cancer (24.2%), followed by skin cancer, lymphoma, and thyroid cancer (9.1%). The median survival times were 41.5 and 6.0 months for those who did (n = 10) receive radical surgery or did not (n = 23), respectively. The 20-month survival rates were 70.0% versus 13.0% ($P < .01$). For unresectable patients, the median survival time of those treated with SRL (n = 8) was 14.5 months compared to 3.0 months for those who did not (n = 15). The survival rates at 12^{th} and 20^{th} months were 75.0% and 37.5% in the SRL group and 6.7% and 0% in the non-SRL group ($P < .05$). In conclusion, when compared with Western studies, a lower incidence and unique location pattern (liver cancer-dominant) are characteristics of de novo posttransplant neoplasms in South Chinese KTx recipients. Early diagnosis and feasible radical surgery are favorable for prognosis, and SRL is a treatment of choice for KTx recipients with neoplasms.

101. Managing Cancer Risk and Decision Making After Kidney Transplantation
Am J Transplant. 2008 Nov;8(11):2185-91.
Webster AC, Wong G, Craig JC, Chapman JR.

Abstract: Kidney transplant recipients are at higher risk of cancer at most sites, and cancer after transplantation causes considerable morbidity and mortality. To optimize long-term patient outcomes, clinicians balance the prospect of graft failure and dialysis, with competing risks of diabetes, cardiovascular and cerebrovascular disease and the risk of malignancy. In this paper we critically examine the assumptions underpinning primary prevention, immunization, chemoprevention and screening programs, and highlight considerations when applying evidence to the kidney transplant population, and suggest a clinical research agenda that aims to define a rational approach to managing posttransplant cancer risk.

102. Oncologic Issues and Kidney Transplantation: A Review of Frequency, Mortality, and Screening

Adv Chronic Kidney Dis. 2014 Jan;21(1):106-13.

Asch WS, Bia MJ.

Abstract: Kidney transplant recipients are at increased risk for development of malignancy compared with the general population, and malignancies occur at an earlier age. This increased risk, as expressed by the standard incidence ratio (SIR), varies widely, but it is highest in malignancies triggered by oncogenic viruses. For other cancers, this increased risk is the direct consequence of immunosuppressants promoting tumor growth and lowering immune system tumor surveillance. In this review, we briefly discuss the common malignancies with increased risk after kidney transplantation, explore the pros and cons associated with screening, and summarize current prevention and treatment recommendations.

103. The janus face of immunosuppression – *de novo* malignancy after renal transplantation: the experience of the Transplantation Center Munich

Kidney Int. 2007 Jun;71(12):1271-8. Epub 2007 Feb 28.

Wimmer CD, Rentsch M, Crispin A, Illner WD, Arbogast H, Graeb C, Jauch KW, Guba M.

Abstract: After decades of successful organ transplantation clinicians continue to be troubled by the increasing incidence of cancers under maintenance immunosuppression. In this study, we examined rates of malignancies in 2419 renal transplant recipients transplanted in our institution between 1978 and 2005. In renal transplant recipients the cumulative incidence of cancer after 25 years was 49.3% for all tumors and 39.7% excluding non-melanoma skin cancers, compared with 21% for a normal sex- and age-matched population. The most frequent tumors observed were non-melanoma skin cancers (20.5%), kidney cancers (12.0%), and cancers of the pharynx, larynx, or oral cavity (8.2%). The general increase of cancer risk was 4.3-fold. Independent risk factors for the development of a tumor were male gender, older recipient age, the presence of preformed antibodies before transplantation, and the time on immunosuppression. Interestingly, the use of IL-2-receptor antagonists significantly reduced the tumor risk of transplant recipients. The tumor risk between immunosuppressive drugs typically used for maintenance immunosuppression was not significantly different. However, mammalian target of rapamycin (mTOR) inhibitor-based immunosuppressive protocols showed a clear tendency for lower malignancy rates. De novo malignancies following renal transplantation represent a serious problem endangering the prognosis of otherwise successfully transplanted patients. Future studies will have to address whether optimized immunosuppressive regimens including mTOR-inhibitors are capable of reducing the incidence or preventing the development of posttransplant malignancies.

104. The Health and Economic Impact of Cervical Cancer Screening and Human Papillomavirus Vaccination in Kidney Transplant Recipients

Transplantation. 2009 Apr 15;87(7):1078-91.

Wong G, Howard K, Webster A, Chapman JR, Craig JC.

Background: The risk of cervical cancer in women who are kidney transplant recipients is increased, but little is known about the effectiveness of screening and human papillomavirus (HPV) vaccination in this group of women. We sought to determine the cost effectiveness of annual screening for cervical cancers using conventional cytology, liquid-based cytology (LBC), and pretransplant HPV vaccination in kidney transplant recipients.
Methods: Three deterministic Markov models were developed to compare the costs and health outcomes in a cohort of women (n=1000) with kidney transplants aged 18 to 69 who underwent annual screening using conventional cytology, LBC, and HPV vaccination in HPV naïve women.
Results: After a screening period of 50 years, the incremental benefits of screening using conventional cytology compared with no screening were 0.05 life years saved (LYS) (18.2 days of lives saved), the incremental costs were $608, giving an incremental cost-effectiveness ratio of $12,160 per LYS. Compared with conventional cytology alone, the incremental cost-effectiveness ratios of annual screening using LBC and HPV vaccination before transplantation (assuming nonwaning efficacy) were $127,000 and $152,333 per LYS, respectively.
Conclusion: The recommended policy of annual screening using conventional cytology is cost effective. The replacement of conventional cytology with LBC is likely to provide minimal survival benefits but considerable costs. Assuming the reported trial-based vaccine efficacy in HPV naïve women, a program of HPV vaccination before kidney transplantation is unlikely to be cost effective. Additional data about the long-term efficacy and safety of HPV vaccination is required before it should be included as standard care of renal transplant recipients.

105. Screening for renal cancer in recipients of kidney transplants

Nephrol Dial Transplant (2011) 26: 1729–1739

Wong G, Howard K, Webster AC, Chapman JR, Craig JC.

Background: Renal cancer is the most common solid organ cancer in the kidney transplant population with an excess risk ~ 5-fold greater than the general population. It is uncertain whether routine screening for renal cancer is cost-effective. The aim of our study is to estimate the costs and health benefits of ultrasonographic (US) screening for renal cancer in the kidney transplant population.

Methods: A Markov model was developed to compare the costs and benefits in a cohort of kidney transplant recipients (n = 1000, aged 18-69 years), who underwent annual and biennial US screening for renal cancer, compared with a cohort that did not.

Results: For recipients of kidney transplants aged 18-69 years, the incremental cost-effectiveness ratio (ICER) for routine US screening ranged from $252,100/LYS for biennial screening to $320,988/LYS for annual screening. A total of two and one cancer deaths were averted in the annually and biennially screened population, with a relative cancer-specific mortality reduction by 25% and 12.5%, respectively. Using a series of sensitivity analyses, the ICER was most sensitive to the costs and test specificity of ultrasonography, prevalence of disease, and the risk of graft failure in the screened population.

Conclusions: Routine screening for renal cancer may reduce the risk of cancer-related deaths in recipients of kidney transplants. Uncertainties, however, exist in the model's influential variables including the risk of graft failure among those who received contrast-enhanced diagnostic computer tomography. Given the available evidence, routine screening for renal cancers may not be cost-effective for recipients of kidney transplants.

106. mTOR Inhibitors: A Myth, a Cure for Cancer or Something in Between?
American Journal of Transplantation 2011; 12: 1075–1076
Wong G, Chapman JR, Craig JC.
This article does not have an abstract to display.

107. Post-transplant malignancy: reducing the risk in kidney transplant recipients
Expert Opin Pharmacother. 2011 Aug;12(11):1719-29.
Wu C, Shapiro R.

Introduction: The growing and aging of the end-stage kidney disease population, and improvements in short-term kidney transplant outcomes, have increased the number of patients receiving and living with kidney transplants who are at risk for the long-term complications of transplantation. Cancer has become a major cause of death following kidney transplantation, increasing the need to better understand the risk of post-transplant malignancy and to adapt patient management to minimize that risk.
Areas covered: This paper reviews the scope of the problem of post-transplant malignancy, its pathogenesis, and strategies for prevention, with attention to the impact of various immunosuppressive strategies. A Medline search was conducted, reviewing English-language publications from 1948 to February 2011.
Expert opinion: Post-transplant malignancy, one of the most common causes of death following transplantation, is linked to both modifiable and non-modifiable risk factors. The current armamentarium of pharmacotherapy and the possibilities for immunologic monitoring in the future hold the potential for tailoring post-transplant care to minimize the risk of post-transplant malignancy without sacrificing graft survival to optimize outcomes following transplantation.

108. Topical Photodynamic Therapy for Prevention of New Skin Lesions in Renal Transplant Recipients

Acta Derm Venereol. 2006;86(1):25-8.

Wulf HC, Pavel S, Stender I, Bakker-Wensveen CA.

Abstract: Preclinical data suggest that topical methyl aminolevulinate photodynamic therapy may have potential in preventing new skin lesions in transplant recipients. An open intra-patient randomized study investigated the prevention potential of this treatment in 27 renal transplant patients with actinic keratoses and other skin lesions in two circular contralateral areas (5 cm diameter). The treatment area surface was debrided and methyl aminolevulinate cream (160 mg/g) was applied for 3 h prior to illumination by non-coherent red light (570-670 nm, light dose 75 J/cm^2). The control area was not treated. The mean time to occurrence of the first new lesion was significantly longer in treated than control areas (9.6 vs 6.8 months, treatment difference 2.9 [95% confidence interval 0.2 to 5.5] months, p = 0.034). Over 12 months, 62% (16/26) of treated areas were free from new lesions compared with 35% (9/26) in control areas. These findings indicate that topical methyl aminolevulinate photodynamic therapy is a promising preventive treatment against new skin lesions in immunosuppressed patients.

109. Individualization of Immunosuppressive Therapy. III. Sirolimus Associated With a Reduced Incidence of Malignancy

Transplantation Proceedings, 38, 358–361 (2006)

Yakupoglu Y.K., Buell J.F., Woodle S., and Kahan B.D.

Objective: We examined the occurrence of neoplasms among 1008 renal transplant recipients treated with a sirolimus-cyclosporine (CsA) ± prednisone (Pred) regimen.
Methods: A comprehensive database of demographic, laboratory, clinical, and histopathologic features of these patients all followed in our transplant center was analyzed using Student t test and Mann-Whitney U test for continuous and chi-square test for categorical variables. Comparisons were performed with information in the Israel Penn International Transplant Tumor Registry (IPITTR).
Results: During the mean patient follow-up of 62.3 ± 26.1 months (range 27.1 to 131), 36 tumors occurred in 35 patients (3.6%) at 32.5 ± 29.8 months. The most common neoplasms were skin tumors (2.4%), a value that was significantly lower than the 6% rate observed with CsA-azathioprine-Pred treatment. Also, the 0.4% incidence of posttransplant lymphoproliferative disorders and 0.2% incidence of renal cell carcinomas were less than half of those previously reported with a combination of tacrolimus and mycophenolate mofetil. The distribution of tumor types was similar to that reported to the IPITTR. The mean trough drug concentrations in affected recipients at the time of diagnosis were within the putative target ranges.
Conclusion: Renal transplant recipients treated with the sirolimus-CsA ± Pred combination showed a low incidence of tumors of similar types as those encountered with other regimens.

110. Potent Immunosuppression for ABO-Incompatible Renal Transplantation May Not Be a Risk Factor for Malignancy

Transplantation Proceedings, 44, 210–213 (2012)

Yamamoto T, Kawaguchi T, Watarai Y, Tujita M, Hiramitsu T, Nanmoku K, Goto N, Katayama A, Kobayashi T, and Uchida K

Abstract: ABO-incompatible (ABOi) renal transplantation has been increasing, but malignant tumor is a troubling complication of kidney transplantation due to potent immunosuppression.
Few previous studies, however, have demonstrated that potent immunosuppression for ABOi living-donor renal transplantation (LDRT) is a risk factor for malignancy. In the present research, data on 252 LDRT patients ftom 2003 to 2008 were retrospectively analyzed to clarify whether ABOi LDRT was associated with malignancy. A potent immunosuppressive regimen for ABOiLDRT consisted of splenectomy, cyclophosphamide, and double-filtration plasmapheresis to minimize the risk of antibody-mediated rejection, in addition to conventional immunosuppresssants including calcineurin inhibitor, prednisolone, and anti-CD25 monoclonal antibody. A total of 11 incidences of malignancy were observed during a median follow-up of 48 months. The incidence rates in ABO-compatible (ABOc; n = 189) and ABOi (n = 63) LDRT groups were 4.2 % (8/189) and 4.8 % (3/63), respectively. Kaplan-Meier survival analysis showed no statistical difference in event-free survival for malignancy between ABOc and ABOiLDRT groups (log-rank P = .73). Multivariable Cox regression analyses identified no associations of malignancy with ABOi LDRT or any immunosuppressant use. In conclusion, our investigation suggested that potent immunosuppression with splenectomy and cyclophosphamide for ABOi LDRT may not be a risk fietor for malignancy.

111. Variation in Cancer Incidence among Patients with ESRD during Kidney Function and Nonfunction Intervals

J Am Soc Nephrol 27: 1495–1504, 2016

Yanik EL, Clarke CA, Snyder JJ, Pfeiffer RM, and Engels EA

Abstract: Among patients with ESRD, cancer risk is affected by kidney dysfunction and by immunosuppression after transplant. Assessing patterns across periods of dialysis and kidney transplantation may inform cancer etiology. We evaluated 202,195 kidney transplant candidates and recipients from a linkage between the Scientific Registry of Transplant Recipients and cancer registries, and compared incidence in kidney function intervals (time with a transplant) with incidence in nonfunction intervals (waitlist or time after transplant failure), adjusting for demographic factors. Incidence of infection-related and immune-related cancer was higher during kidney function intervals than during nonfunction intervals. Incidence was most elevated for Kaposi sarcoma (hazard ratio [HR], 9.1; 95% confidence interval (95% CI), 4.7 to 18), non-Hodgkin's lymphoma (HR, 3.2; 95% CI, 2.8 to 3.7), Hodgkin's lymphoma (HR, 3.0; 95% CI, 1.7 to 5.3), lip cancer (HR, 3.4; 95%CI, 2.0 to 6.0), and nonepithelial skin cancers (HR, 3.8; 95%CI, 2.5 to 5.8). Conversely, ESRD-related cancer incidence was lower during kidney function intervals (kidney cancer: HR, 0.8; 95%CI, 0.7 to 0.8 and thyroid cancer: HR, 0.7; 95%CI, 0.6 to 0.8).With each successive interval, incidence changed in alternating directions for non-Hodgkin's lymphoma, melanoma, and lung, pancreatic, and nonepithelial skin cancers (higher during function intervals), and kidney and thyroid cancers (higher during nonfunction intervals). For many cancers, incidence remained higher than in the general population across all intervals. These data indicate strong short-term effects of kidney dysfunction and immunosuppression on cancer incidence in patients with ESRD, suggesting a need for persistent cancer screening and prevention.

112. Sirolimus and Non-melanoma Skin Cancer Prevention after Kidney Transplantation: A Meta-analysis

Asian Pacific J Cancer Prev, 13 (9), 4335-4339

Gu YH, Du JX, Ma ML.

Background: Whether sirolimus is useful in the prevention of non-melanoma skin cancer (NMSC) remains unclear and we therefore performed this meta-analysis of randomized controlled trials to test the hypothesis that Sirolimus-based immunosuppression is associated with a decrease in NMSC.

Methods: The main outcomes were NMSC, squamous-cell carcinoma and basal-cell carcinoma. The pooled risk ratio (RR) with its 95% confidence interval (95%CI) were used to assess the effects.

Results: 5 randomized trials involving a total of 1499 patients receiving kidney transplantation were included. Patients undergoing Sirolimus-based immunosuppression had much lower risk of NMSC (RR = 0.49, 95%CI 0.32-0.76, P = 0.001). Subgroup analyses by tumor type showed that Sirolimus-based immunosuppression significantly decreased risk of both squamous-cell carcinoma (RR = 0.58, 95%CI 0.43-0.78, P < 0.001) and basal-cell carcinoma (RR = 0.56, 95%CI 0.37-0.85, P = 0.006). The quality of evidence was high for NMSC, and moderate for squamous-cell carcinoma and basal-cell carcinoma. No evidence of publication bias was observed.

Conclusion: High quality evidence suggests that Sirolimus-based immunosuppression decreases risk of non-melanoma skin cancer, and Sirolimus has an antitumoral effect among kidney-transplant recipients.

113. Resurfacing the back of the hand as treatment and prevention of multiple skin cancers in kidney transplant recipients

J Am Acad Dermatol 1994;31:760-4.

van Zuuren EJ, Posma AN, Scholtens RE, Vermeer BJ, van der Woude FJ, Bouwes Bavinck JN.

Background: Skin cancer is a serious problem in renal transplant recipients. In some patients numerous skin cancers develop on the back of the hand. Instead of repeated excisions, a more radical procedure may be necessary. For these patients a new surgical therapy is available: resurfacing the back of the hand.
Objective: Our purpose was to clinically evaluate this new procedure.
Methods: Eleven kidney transplant recipients who underwent resurfacing of the back of the hand were analyzed in a retrospective follow-up study. With this surgical procedure the skin of the entire dorsum of the hand is excised and split-skin grafts harvested from thigh and buttock skin are then placed. Information was gathered from the medical records and questionnaires, and by physical examination.
Results: The mean follow-up time was 4.7 years. No recurrences of skin cancer were observed in the transplanted skin. The cosmetic appearance was acceptable, and there were few side effects.
Conclusion: Resurfacing the back of the hand can be a successful treatment for carefully selected patients with multiple skin cancers on the back of the hand and can be used prophylactically in patients with severely actinically damaged skin.

114. Low Dose Isotretinoin In The Prophylaxis Of Skin Cancer In Renal Transplant Patients
Transplantation. 1996 Jan 15;61(1):173.
Bellman BA, Eaglstein WH, Miller J.
This article does not have an abstract to display.

115. Interleukin-10 And Posttransplant Lymphoproliferative Disorder After Kidney Transplantation

Transplantation. 1999 Mar 27;67(6):876-81.

Birkeland SA, Bendtzen K, Møller B, Hamilton-Dutoit S, Andersen HK.

Background: Posttransplant lymphoproliferative disorder (PTLD) is a life-threatening complication of transplantation, which comprises a morphologically and clinically heterogeneous spectrum of B-lymphocyte diseases. Risk factors include primary or reactivated Epstein-Barr virus (EBV) infection, and the type and duration of immunosuppression. Interleukin-10 (IL-10) is a pleiotropic cytokine, produced primarily by T-helper 2 (Th2) lymphocytes in the later stages of T-cell activation, suggested to play a role in EBV-associated PTLD. We recently reported preliminary findings on IL-10 in relation to the development of PTLD in three kidney transplanted patients. The study now includes nine patients that could be followed before and/or after the occurrence of lymphoma.
Methods: Nine patients with lymphomas (eight PTLDs and one Hodgkin's disease) were diagnosed among 268 consecutive renal transplantations (1990-1997). All were treated with cyclosporine with an initial 10-day course of antilymphocyte globulin, supplemented from 1995 with mycophenolate mofetil. Serum antibodies against EBV were detected using recombinant antigens. A double sandwich enzyme-linked immunosorbent assay using rabbit antibodies to purified human recombinant IL-10 was employed; the assay is specific for human natural and viral IL-10.
Results: Three patients experienced primary EBV infection, five reactivated EBV infections, and one did not change EBV status. Three patients had a fulminant course and died with EBV-associated PTLD confirmed post mortem. The other six are alive and are apparently cured. Treatment was immediate discontinuation of immunosuppression (in all PTLDs) and long-term high-dose aciclovir in all but one. Two patients have maintained excellent graft function for 3 and 2 years, respectively, without immunosuppression and are now in a state of operational tolerance. In three of four cases with initial lymphoma, EBV infection (primary or reactivation) preceded the increase in IL-10. In all four cases, the IL-10 increase preceded the PTLD diagnosis. In six cases, IL-10 could be followed after treatment showing either immediate zero or a decrease to zero.
Conclusion: IL-10 seems to play a role in EBV-associated PTLD. Moreover, IL-10 may have an important role in transplant tolerance by inducing long-lasting anergy to donor- and host-specific alloantigens, perhaps caused by down-regulation of Th1 cytokines in the graft. If substantiated, this may provide new insight into the pathogenesis of PTLD introducing new strategies for prevention and therapy of PTLD, and for the induction of tolerance in transplanted patients.

116. Dermatology's Role in Treating Sexually Transmitted Diseases
Arch Dermatol. 2006 Sep;142(9):1231-2.
Poonawalla T, Uchida T, Diven DG.
This article does not have an abstract to display.

117. Hodgkin's disease after transplantation

Transplantation. 1996 Jan 15;61(1):71-6.

Garnier JL, Lebranchu Y, Dantal J, Bedrossian J, Cahen R, Assouline D, Jaccard A, Fetissoff F, Moreau A, Martin X, Delsol G, Berger F, Touraine JL.

Abstract: Hodgkin's disease (HD) has seldom been reported after transplantation. Epstein-Barr virus (EBV) is present in about 50% of Reed-Sternberg cells in HD developing in immunocompetent individuals, but is more frequently found in HD of acquired immune deficiency syndrome patients. We report 7 cases of HD that occurred in transplant recipients. Clinical and pathological data and studies of EBV reveal specific features of HD after transplantation. Six patients received kidney transplants and 1 patient received combined kidney and pancreas transplantation. Immunosuppressive therapy consisted of cyclosporine, steroids, azathioprine, and antilymphocyte globulins. One patient received, in addition, anti-CD3 mAb therapy and an EBV+ B cell lymphoma developed. Retrospective EBV serological data from patients were collected. Tumors were classified according to pathology. EBV studies were conducted by immunohistochemical methods with monoclonal antibodies to EBV-latent membrane protein (LMP) or EBV-nuclear antigen 2 (EBNA2), and by in situ hybridization for latent nuclear EBV-early RNAs (EBERs). The mean lapse of time between transplantation and HD was 49 months. Six patients presented with enlarged lymph nodes and 1 patient presented with liver involvement. HD was classified as IA in 2 patients, IIA in 3 patients, IIIB in 1 patient, and IVB in 1 patient. Four patients had primary EBV infection after graft, before HD, and the others reactivated latent EBV infection. Histological subtypes were mixed cellularity in 6 cases and lymphocytic depletion in 1 case. Latent EBV infection was detected with EBERs in all tumors. Reed-Sternberg cells expressed LMP, and were negative for EBNA2 expression. Six patients were treated: 2 patients at stage I received radiotherapy, and relapsed within 1 year with a more advanced stage of HD; chemotherapy was indicated as primary therapy in 5 patients, and as salvage therapy in 2 patients; it was associated with radiotherapy in 4 patients. Immunosuppressive therapy was reduced in all patients. Four patients were alive and in complete remission 18, 25, 31, and 67 months after chemotherapy, with a functioning graft in 3 patients. Two patients died of infection. Mixed cellularity is the most frequent histological subtype observed in HD occurring in transplant patients. EBV is present in all Reed-Sternberg cells. Posttransplant HD shows similarities with human immunodeficiency virus-associated HD. These facts argue for a role of EBV infection and immunosuppression in the progression of HD after transplantation.

118. Neoplasias malignas en receptores de trasplante renal

Rev Invest Clin. 2005 Mar-Apr;57(2):225-9.

Gómez-Roel X1, León-Rodríguez E.

Abstract: Malignancy following renal transplantation is an important medical problem during the long-term follow-up. The overall incidence of cancer at this group of patients is 3 to 5 times higher than the expected incidence in general population by age. The most common malignancies are skin carcinomas and lymphomas. There is retrospective experience in many reports about the association between the intensity of immunosuppression and the higher frequency of malignancy, besides other factors. In our Institution we found similar experience than other series, with 8.28%, of development of malignancies in a follow-up of 7.28 years. We found lower latency with three-drug immunosuppression than with two. To reduce the development of malignancies after renal transplantation must be one of the objectives in future immunossuppressive therapy, mainly in the setting of new immunosuppressive drugs like rapamycin.

119. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.6.2. Cancer risk after renal transplantation. Skin cancers: prevention and treatment.

Nephrol Dial Transplant. 2002;17 Suppl 4:31-6.

EBPG Expert Group on Renal Transplantation.

Abstract: Guidelines: D. Due to the high prevalence of skin cancers after organ transplantation, it is highly recommended to inform patients about self-awareness. E. Primary prevention should include the avoidance of sun exposure, use of protective clothing and use of an effective sunscreen (protection factor >15) for unclothed body parts (head, neck, hands and arms) in order to prevent the occurrence of squamous-cell carcinoma. This is the most frequent skin tumour in transplant recipients, and its preferential location is the head. F. Recipients with pre-malignant skin lesions (warts, epidermodysplasia verruciformis or actinic keratoses) should be referred early to a dermatologist for active treatment and close follow-up. G. All skin cancers should be completely removed by a dermatologist with appropriate techniques, such as electro-desiccation with curettage, cryotherapy or surgical excision. H. Secondary prevention for recipients should include close follow-up by a dermatologist (at least every 6 months), the use of topical retinoids to control actinic keratoses and to diminish squamous-cell carcinoma recurrence, and reduction of immunosuppression whenever possible. I. In recipients with multiple and/or recurrent skin cancers, the use of systemic retinoids, such as low-dose acitretin, could be recommended for months/years, if well tolerated, in addition to further reduction in immunosuppression whenever possible.

120. Development of cancer in transplantation patients.
Adv Surg. 1978;12:155-91.
Penn I.
This article does not have an abstract to display.

Proyecto Prometeo II

Grupo IV

Cáncer en la población pediátrica: enfermedad linfoproliferativa postrasplante

Referencias Bibliográficas

Organizado por

SET
SOCIEDAD ESPAÑOLA DE TRASPLANTE

Con la colaboración de

NOVARTIS

1. Mortality after pediatric kidney transplantation in England--a population-based cohort study.
Pediatr Transplant. 2014 Feb;18(1):16-22. doi: 10.1111/petr.12173. Epub 2013 Oct 18.
Farrugia D, Cheshire J, Mahboob S, Begaj I, Khosla S, Ray D, Sharif A.

Abstract: The aim of this study was to explore mortality after pediatric kidney transplantation in England over the last decade. We used data from HES to select all kidney transplant procedures performed in England between April 2001 and March 2012. Data linkage analysis was performed with the ONS to identify all deaths occurring among this study cohort. Data for 1189 pediatric recipients were compared to 17 914 adult recipients (number of deaths, 33 vs. 2052, respectively, $p < 0.001$), with median follow-up 4.4 yr (interquartile range 2.2–7.3 yr). There was no difference in mortality within the pediatric cohort; age 0–1 (n = 25, patient survival 100.0%), age 2–5 (n = 198, patient survival 96.0%), age 6–12 (n = 359, patient survival 97.5%), and age 13–18 (n = 607, patient survival 97.4%), respectively ($p = 0.567$). The most common causes of death were renal (n = 8, 24.2%), infection (n = 6, 18.2%), and malignancy (n = 5, 15.2%). All deaths from malignancy were secondary to PTLD. In a fully adjusted Cox regression model, only white ethnicity was significantly associated with risk of pediatric mortality post-kidney transplantation (hazard ratio 2.7, 95% confidence interval [1.0–7.3], $p = 0.047$). To conclude, this population-based cohort study confirms low mortality after pediatric kidney transplantation with short follow-up.

2. Missed viral surveillance testing visits associate with full blown viral diseases in children receiving kidney transplants.

Pediatr Transplant. 2013 Mar;17(2):129-32. doi: 10.1111/j.1399-3046.2012.01773.x. Epub 2012 Aug 20.

Al Khasawneh E, Araya CE, Dharnidharka VR.

Abstract: Surveillance testing for major viral infections such as CMV, EBV, and BKV early in their natural history course may allow for early intervention and prevention of FBVD, but the testing is expensive and optimal interval/frequency are uncertain. At our center we initiated routine monthly viral surveillance for CMV, EBV, and BKV in July 2008 for the first 12 months post-transplant. Here, we retrospectively analyzed for outcome of the patients who missed three or more surveillance tests in the first 12 months post-transplant vs. those who did not. Of 21 patients, five missed three or more surveillance tests. Two of those five developed FBVD (one BKV nephropathy and one EBVPTLD).None of the 16 patients with more regular surveillance testing developed FBVD. The incidence of viral replication was similar in both groups. The odds ratio for FBVD if viral surveillance tests were missed was 23.57 (p-value of 0.047). In this small group of contemporaneous patients on identical immunosuppression, those patients who missed regular viral surveillance were more likely to develop FBVD. Prospective randomized trials to confirm the benefit of regular viral testing are recommended.

3. Immunosuppressive TOR kinase inhibitor everolimus (RAD) suppresses growth of cells derived from posttransplant lymphoproliferative disorder at allograft-protecting doses.

Transplantation. 2003 May 27;75(10):1710-7.

Majewski M, Korecka M, Joergensen J, Fields L, Kossev P, Schuler W, Shaw L, Wasik MA.

Background: Posttransplant lymphoproliferative disorders (PTLDs) represent a life-threatening complication of standard immunosuppressive therapy.
The impact of novel, rapamycin-related immunosuppressive drugs on the pathogenesis of PTLDs remains undefined.
Methods: We tested the effect of everolimus (RAD, Novartis Pharma AG, Basel, Switzerland) on human PTLD-derived cells using in vitro assays and an in vivo severe combined immunodeficiency disease mouse xenotransplant model.
Results: Everolimus profoundly inhibited the proliferation, cell-cycle progression, and survival of the PTLD-1 cell line established from a pulmonary PTLD. Equally profound inhibition of PTLD-1 growth was achieved in vivo at well-tolerated everolimus doses of 0.5 to 5 mg/kg per day. Five mg/kg per day of everolimus, given once per day, inhibited PTLD-1 tumor volume gain by more than 10-fold in treated mice compared with untreated mice. Because the subsequent pharmacokinetic analysis indicated rapid everolimus absorption, distribution, and clearance in mice (with a half-life of 3 to 6 hr and maximum drug blood concentration reached after 0.5 to 1 hr), treatment was changed to a twice-daily regimen. Everolimus given twice daily at 0.5 mg/kg per dose inhibited tumor-volume gain by more than 60-fold and at 0.25 mg/kg per dose by more than 10-fold. Similar everolimus doses were required to prevent graft rejection in a mouse heart allotransplantation model; the highest dose tested (1.5 mg/kg twice daily) resulted in long-term graft survival in all mice that underwent transplantation.
Conclusions: Everolimus displays a potent inhibitory effect on PTLD-derived cells in vitro and in vivo in a dose range leading to prevention of allograft rejection and may prove effective in both the prevention and treatment of PTLDs in transplant patients.

4. Constitutive activation of mTOR signaling pathway in post-transplant lymphoproliferative disorders.

Lab Invest. 2007 Jan;87(1):29-39. Epub 2006 Oct 30.

El-Salem M, Raghunath PN, Marzec M, Wlodarski P, Tsai D, Hsi E, Wasik MA.

We examined activation of the mTOR signaling pathway in situ in the primary, normal reactive and patientderived post-transplant lymphoproliferative disorder (PTLD) tissue samples. We accomplished this analysis by immunohistochemistry on formalin-fixed, paraffin-embedded specimens using a set of highly specific antibodies that permitted us to determine phosphorylation status of the key serines in the mTOR target proteins. Our results demonstrate that the mTOR signaling pathway is activated in reactive tissue in a highly distinct fashion with positive, typically enlarged cells being present primarily in the germinal center and, to a lesser degree, in interfollicular areas with mantle zone being conspicuously negative. We could demonstrate mTOR activation in the lesional cells in the entire spectrum of PTLD subtypes, regardless of their Epstein–Barr virus genome expression status. These data demonstrate the ubiquitous activation of the mTOR signaling pathway in PTLD and indicate that mTOR inhibitors may be effective in treatment and, notably, prevention of PTLDs given their immunosuppressive properties. Furthermore, our results define potential biomarkers of the therapeutic response. Because the constitutive mTOR activation has also been identified in cells isolated from other hematologic malignancies, the ability to examine the in vivo mTOR signaling may have implications reaching beyond the PTLD field.

5. Long-term side effects of treatment with mTOR inhibitors in children after renal transplantation.

Pediatr Nephrol. 2013 Aug;28(8):1293-8. doi: 10.1007/s00467-013-2459-y. Epub 2013 Apr 13.

Kranz B, Wingen AM, Vester U, König J, Hoyer PF.

Background: mTOR inhibitors (mTORI) have emerged as alternative and additive immunosuppressive agents in pediatric renal transplantation (pRTx). Their immunosuppressive, anti-proliferative, and anti-neoplastic mechanisms have been described to be effective, whereas some side effects are alarming. In particular, growth and pubertal development are of concern. The aim of this study was to look for long-term side effects of mTORI therapy in pRTx.

Patients and methods: The retrospective analysis focused on side effects, growth, and pubertal development under mTORI therapy in 31 children. Eighteen children were routinely monitored for estradiol, testosterone, LH, and FSH levels.

Results: The occurrence of bacterial infections, lymphoceles, myelosuppression, and the course of overall linear growth was comparable with other pediatric renal transplant cohorts.

According to the clinical puberty status, all but one patient showed normal age-related development in parallel to normal serum hormone levels. Only one patient experienced cytomegaly virus infection under mTORI, no posttransplant lymphoproliferative disorders (PTLD) occurred.

Conclusions: Long-term mTORI therapy is safe in pRTx. No negative impact on growth and pubertal development was observed.

6. Malignancies after pediatric kidney transplantation: more than PTLD?

Pediatr Nephrol. 2014 Sep;29(9):1517-28. doi: 10.1007/s00467-013-2622-5. Epub 2013 Sep 24.

Mynarek M, Hussein K, Kreipe HH, Maecker-Kolhoff B.

Abstract Post-transplant lymphoproliferative disease (PTLD) is the most frequent malignant complication of transplantation in childhood. Even with modern post-transplant immunosuppressive strategies, 1–2 % of all kidney transplant recipients will develop PTLD within the first 5 years after transplantation, and the risk remains high even thereafter as long as immunosuppression is required. In addition to PTLD, adult kidney transplant recipients have an increased incidence of other immunosuppression-related malignancies, such as nonmelanoma skin cancer or Kaposi's sarcoma. It is foreseeable that pediatric transplant recipients will face similar complications during their adult life. Not only immunosuppression but also other risk factors have been identified for some of these malignancies. Strategies addressing these risk factors during childhood may contribute to life-long cancer prevention. Furthermore, early recognition and regular screening may facilitate early diagnosis and treatment, thereby reducing transplant-related morbidity. In this review we focus on malignant complications after renal transplantation and discuss known risk factors. We also review current screening strategies for malignancies during post-transplant follow-up.

7. A population-based study of 135 lymphomas after solid organ transplantation: The role of Epstein-Barr virus, hepatitis C and diffuse large B-cell lymphoma subtype in clinical presentation and survival.

Acta Oncol. 2014 May;53(5):669-79. doi: 10.3109/0284186X.2013.844853. Epub 2013 Oct 28.

Kinch A, Baecklund E, Backlin C, Ekman T, Molin D, Tufveson G, Fernberg P, Sundström C, Pauksens K, Enblad G.

Background: Epstein-Barr virus (EBV) plays a major role in the development of post-transplant lymphoproliferative disorder (PTLD), but there is an increasing awareness of EBV-negative PTLD. The clinical presentation of EBV-negative PTLD has not been as well characterised as EBV-positive cases. Further, there is limited knowledge on the clinical importance of diffuse large B-cell lymphoma (DLBCL) cell of origin subtype post-transplant.

Materials and methods: We studied the role of EBV, hepatitis C (HCV) and DLBCL subtype in clinical presentation and survival in 135 posttransplant lymphomas diagnosed 1980 – 2006 in a population-based cohort of 10 010 Swedish solid organ transplant recipients. The lymphomas were re-evaluated according to WHO 2008, examined for EBV, and clinical data were collected from medical records.

Results: Lymphoma incidence rate was 159/100 000 person-years and is also reported by lymphoma subtype. EBV-negative lymphomas constituted 48% and were associated with HCV infection ($p = 0.02$), bone marrow involvement ($p = 0.001$), and T-cell phenotype ($p = 0.002$). Among DLBCL, 78% were of non-germinal centre subtype, which was associated with EBV-positivity (69%, $p = 0.001$), early occurrence ($p = 0.03$), heart/liver/lung/pancreas recipients ($p = 0.02$), anti-T-cell globulin ($p = 0.001$), and tacrolimus treatment ($p = 0.02$). DLBCL subtypes had similar overall survival. Five-year overall survival was 42% in all treated patients. Independent poor prognostic factors were older age, B symptoms, ECOG 2-4, kidney/pancreas/heart recipients, T-cell lymphoma, and HCV-infection.

Conclusions: With long follow-up, a large part of PTLD is EBV-negative, due to a high proportion of T-cell lymphomas and low of polymorphic PTLD. EBV-negative PTLD have a different clinical presentation. HCV may play an aetiological role in late-onset PTLD and was revealed as a new prognostic factor for inferior survival that needs to be confirmed in larger studies. The heavier immunosuppression in non-kidney transplantations seems to play a role in the development of nongerminal centre DLBCL. DLBCL cell of origin subtype lacks prognostic importance in the transplant setting.

8. Cancer-infection interface in children after transplantation: posttransplant lymphoproliferative disorder and Epstein-Barr virus infection.

Curr Opin Organ Transplant. 2013 Oct;18(5):549-54. doi: 10.1097/MOT.0b013e3283651b0d.

Fujieda M1, Hattori M.

Purpose of review: To summarize the association between posttransplant lymphoproliferative disorder (PTLD), which is the most frequent cause of posttransplantation tumors in children, and Epstein–Barr virus (EBV) infection.

Recent findings: Most PTLD cases present as proliferation of EBV-infected B cells, because EBV-naive patients have no EBV-specific cytotoxic lymphocytes to control the infected cells. The monitoring of EBV loads in whole blood, as well as in plasma by PCR, represents a useful method for early diagnosis and timely treatment. A program of EBV control by molecular EBV monitoring coupled with lymphocyte phenotype analysis is recommended. Pre-emptive reduced immunosuppression may prevent PTLD, and improved therapeutic options may also contribute to milder PTLD phenotype and improved clinical course.

Summary: A recent trend is that PTLD incidence and high-grade histological findings have decreased because of appropriate immunosuppressive maintenance doses, monitoring of EBV, and preemptive treatment. More sensitive, specific tools for the detection of EBV replication and prophylactic methods are required to establish a definitive strategy for the prevention of PTLD after transplantation.

9. Donor or recipient origin of posttransplant lymphoproliferative disorders following solid organ transplantation.

Am J Transplant. 2014 Dec;14(12):2838-45. doi: 10.1111/ajt.12990. Epub 2014 Oct 10.

Kinch A, Cavelier L, Bengtsson M, Baecklund E, Enblad G, Backlin C, Thunberg U, Sundström C, Pauksens K.

Previous studies of donor or recipient origin of posttransplant lymphoproliferative disorders (PTLDs) following solid organ transplantation (SOT) have either been small or with selected patient groups. We studied tumor origin in a population-based cohort of 93 patients with PTLD following SOT. Tumor origin of PTLD tissue was analyzed by fluorescence in situ hybridization of the sex chromosomes in cases of sex mismatch between donor and recipient (n=41), or HLA genotyping in cases of identical sex but different HLA type (n=52). Tumor origin of PTLD could be determined in 67 of the 93 cases. All 67 PTLDs were of recipient origin. They were found in recipients of kidney (n=38), liver (n=12), heart (n=10) and lung (n=7). The most common recipient-derived lymphomas were monomorphic B-cell PTLDs (n=45), monomorphic T cell PTLDs (n=9), indolent lymphomas (n=6), and polymorphic PTLD (n=4). Half of the recipient-derived PTLDs were Epstein–Barr virus-positive. Twelve of the recipient-derived PTLDs were located in the grafts: in four cases exclusively and in eight cases in combination with disseminated disease outside the graft. Tumor origin was indeterminable in 26 cases, probably due to low DNA quality. We conclude that the vast majority of PTLDs after SOT was of recipient origin.

10. Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies.

Curr Hematol Malig Rep. 2013 Sep;8(3):173-83. doi: 10.1007/s11899-013-0162-5.

Al-Mansour Z, Nelson BP, Evens AM.

Abstract: Post-transplant lymphoproliferative diseases (PTLD) are heterogeneous lymphoid disorders ranging from indolent polyclonal proliferations to aggressive lymphomas that complicate solid organ or hematopoietic transplantation. Risk factors have been identified, including viral infections, degree of immunosuppression, recipient age and race, allograft type, and host genetic variations. Clinically, extra-nodal disease is common, with 10–15 % presenting with central nervous system (CNS) disease. Most PTLD cases are B cell (5–10 % T/NK cell or Hodgkin lymphoma), while approximately one-third are EBV-negative. World Health Organization (WHO) diagnostic categories are: early lesions, polymorphic, and monomorphic PTLD; although in practice, a clear separation is not always possible. Therapeutically, reduction in immunosuppression remains a mainstay, and recent data has documented the importance of rituximab +/− combination chemotherapy. Therapy for primary CNS PTLD should be managed according to immunocompetent CNS paradigms. Finally, novel treatment strategies for PTLD have emerged, including adoptive immunotherapy and rational targeted therapeutics (e.g., targeting downstream signaling pathways of virus-encoded latent membrane protein-2A).

11. The expression of Epstein-Barr virus latent proteins is related to the pathological features of post-transplant lymphoproliferative disorders.

Am J Pathol. 1995 May;146(5):1113-20.

Delecluse HJ, Kremmer E, Rouault JP, Cour C, Bornkamm G, Berger F.

Transplant recipients are at increased risk for the development of post-transplant lymphoproliferative disorders (PTLDs). PTLDs harbor genomes of the Epstein-Barr virus, a herpesvirus that immortalizes B cells in vitro. At least five viral proteins are required for immortalization. Two of them are particularly important. Latent membrane protein (LMP) has transforming activity in fibroblasts, and Epstein-Barr antigen (EBNA)2transactivates the expression of numerous cellular and viral genes. To determine whether the expression of EBNA2 and LMP is related to the histological and clinical presentation of PTLD, we tested their expression in 14 Epstein-Barr virus-positive cases. Using monoclonal antibodies to EBNA2 and LMP on paraffin sections, we found an expression of both proteins in 2 of 3 polymorphic PTLD and in 7 of8 cases of monomorphic, large cell PTLD, without plasmacytic differentiation. One polymorphic and one large cell PTLD expressed IMP only. LMP and EBNA2 were found particularly in immunoblasts. The number of positive cells was extremely variable in the different cases as well as within the same biopsy. Three cases of PTLD had morphological and phenotypical features of plasmacytomas and did not stain for EBNA2 or LMP. This suggests that the expression ofEBNA2 and LMP is related to the differentiation stage of the infected cells and that other viral or cellular proteins may contribute to tumor growth.

12. The value of (18) F-FDG PET in pediatric patients with post-transplant lymphoproliferative disorder at initial diagnosis.

Pediatr Transplant. 2015 Dec;19(8):932-9. doi: 10.1111/petr.12611. Epub 2015 Oct 30.

Vali R, Punnett A, Bajno L, Moineddin R, Shammas A.

Abstract: PTLD is a serious complication of both solid organ and BMT. This study assessed whether ^{18}F-FDG PET, when added to CT scan, had additional value in the initial evaluation of PTLD in pediatric patients and whether PET/CT at baseline can reliably guide biopsy. This retrospective study evaluated 34 consecutive pediatric patients (14 female), aged 3.5–17.0 yr (mean age: 9.9 yr, s.d.: 4.9 yr), who had undergone ^{18}F-FDG PET/CT from May 2007 to December 2014 at initial diagnosis of PTLD following heart (n = 13), lung (n = 8), kidney (n = 4), liver (n = 3), liver and bowel (n = 3), and bone marrow (n = 3) transplantation. PTLD was diagnosed histopathologically in 33 patients and was based on clinical findings, elevated EBV, and imaging and follow-up results in one patient. On lesion-based analysis, ^{18}F-FDG PET showed more lesions than conventional CT scan (168 vs. 134), but CT revealed 22 lesions negative on PET. On per patient analysis, PET detected more lesions in 13 patients, CT identified more abnormalities in seven, and both showed the same number of lesions in 14. Adding ^{18}F-FDG PET to CT scans upstaged the disease in seven patients (20.5%). A combination of ^{18}F-FDG PET and CT was also useful in guiding biopsy, being positive in 36 of 39 samples (92.3%). These findings indicated that ^{18}F-FDG PET and CT are complementary at initial staging of pediatric PTLD and that ^{18}F-FDG PET/CT scanning can guide biopsies.

13. Lymph Node Flow Cytometry as a Prompt Recognition of Ultra Early Onset PTLD: A Successful Case of Rituximab Treatment.

Case Rep Hematol. 2015;2015:430623. doi: 10.1155/2015/430623. Epub 2015 Mar 24.

Li X, Li N, Yang T, Chen Z, Hu J.

Ultra early posttransplantation lymphoproliferative disorder (PTLD) is a rare and fatal complication after hematopoietic stem cell transplantation (HSCT). Here we report, by lymph node (LN) flowcytometry, that we early recognized ultra early PTLD after an HLA-matched sibling allo-HSCT followed by a successful treatment with anti-CD20 antibody (rituximab) in a patient in progress disease for angioimmunoblastic T-cell lymphoma (AITL).The patient was conditioned with a reduced intensity conditioning (RIC) regimen. One week after transplantation, the patient developed high fever, generalized fatigue, high Epstein-Barr virus (EBV) load, and LN enlargement. An LN lymphocyte suspension and peripheral blood flowcytometry was performed to find majority of LN lymphocytes highly expressed CD20. By highly suspicious PTLD, 4 doses of rituximab (375mg/m2 qw) were given immediately followed by reducing and withdrawing immunosuppressant reagent. PTLD was later confirmed by pathology. The patient had good response to rituximab, showing absence of fever, reduction in LN size, and no detectable EBV-DNA. Twenty months after HSCT, the patient remains well without evidence of AITL and PTLD. The current report is one of the earliest cases of PTLD after HSCT. Taken together, by LN flowcytometry as a prompt recognition, rituximab can be an effective preemptive therapy for ultra early developed PTLD.

14. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial

Lancet Oncol 2012132196–206.206

Trappe R, Oertel S, Leblond V, Mollee P, Sender M, Reinke P, et al.

Background: Post-transplantation lymphoproliferative disorder (PTLD) develops in 1–10% of transplant recipients and can be Epstein–Barr virus (EBV) associated. To improve long-term efficacy after rituximab monotherapy and to avoid the toxic effects of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy seen in first-line treatment, we initiated a phase 2 trial to test whether the subsequent use of rituximab and CHOP would improve the outcome of patients with PTLD.

Methods: In this international multicentre open-label phase 2 trial, treatment-naive adult solid-organ transplant recipients diagnosed with CD20-positive PTLD who had failed to respond to upfront immunosuppression reduction received four courses of rituximab (375 mg/m² intravenously) once a week followed by 4 weeks without treatment and four cycles of CHOP every 3 weeks. In case of disease progression during rituximab mono therapy, CHOP was started immediately. Supportive therapy with granulocyte-colony stimulating factor after chemotherapy was mandatory and antibiotic prophylaxis was recommended. The primary endpoint was treatment efficacy measured as response rates in all patients who completed treatment with rituximab and CHOP, per protocol, and response duration, in all patients who completed all planned therapy and responded. Secondary endpoints were frequency of infections, treatment-related mortality, and overall survival. This study is registered at ClinicalTrials.gov, number NCT01458548.

Findings: 74 patients were enrolled between Dec 12, 2002 and May 5, 2008, of whom 70 patients were eligible to receive treatment. PTLD was of late type in 53 (76%) of 70 patients, monomorphic in 67 (96%) of 70, and histologically EBV associated in 29 (44%) of 66 cases. Four of 70 patients did not receive CHOP. 53 of 59 patients had a complete or partial response (90%, 95% CI 79–96), of which 40 (68%, 55–78) were complete responses. At data cutoff (June 1, 2011) median response duration in the 53 patients who had responded to treatment had not yet been reached (>79·1 months). The main adverse events were grade 3–4 leucopenia in 42 of 62 patients (68%, 55–78) and infections of grade 3–4 in 26 of 64 patients (41%, 29–53). Seven of 66 patients (11%, 5–21) had CHOP-associated treatment related mortality. Median overall survival was 6·6 years (95% CI 2·8–10·4; n=70).

Interpretation: Our results support the use of sequential immunochemotherapy with rituximab and CHOP in PTLD.

15. How I treat posttransplant lymphoproliferative disorders.

Blood. 2015 Nov 12;126(20):2274-83. doi: 10.1182/blood-2015-05-615872. Epub 2015 Sep 17.
Dierickx D, Tousseyn T, Gheysens O.

Posttransplant lymphoproliferative disorder (PTLD) is a potentially fatal disorder arisingafter solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT). Iatrogenically impaired immune surveillance and Epstein-Barr virus (EBV) primary infection/reactivation are key factors in the pathogenesis. However, current knowledge on all aspects of PTLD is limited due to its rarity, morphologic heterogeneity, and the lack of prospective trials. Furthermore, the broad spectrum of underlying immune disorders and the type of graft represent important confounding factors.
Despite these limitations, several reviews have been written aimed at offering a guide for pathologists and clinicians in diagnosing and treating PTLD. Rather than providing another classical review on PTLD, this “How I Treat” article, based on 2 case reports, focuses on specific challenges, different perspectives, and novel insights regarding the pathogenesis, diagnosis, and treatment of PTLD. These challenges include the wide variety of PTLD presentation (making treatment optimization difficult), the impact of EBV on pathogenesis and clinical behavior, and the controversial treatment of Burkitt lymphoma (BL)-PTLD.

16. Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies.

Curr Hematol Malig Rep. 2013 Sep;8(3):173-83. doi: 10.1007/s11899-013-0162-5.

Al-Mansour Z, Nelson BP, Evens AM.

Abstract: Post-transplant lymphoproliferative diseases (PTLD) are heterogeneous lymphoid disorders ranging from indolent polyclonal proliferations to aggressive lymphomas that complicate solid organ or hematopoietic transplantation. Risk factors have been identified, including viral infections, degree of immunosuppression, recipient age and race, allograft type, and host genetic variations. Clinically, extra-nodal disease is common, with 10–15 % presenting with central nervous system (CNS) disease. Most PTLD cases are B cell (5–10 % T/NK cell or Hodgkin lymphoma), while approximately one-third are EBV-negative. World Health Organization (WHO) diagnostic categories are: early lesions, polymorphic, and monomorphic PTLD; although in practice, a clear separation is not always possible. Therapeutically, reduction in immunosuppression remains a mainstay, and recent data has documented the importance of rituximab +/− combination chemotherapy. Therapy for primary CNS PTLD should be managed according to immunocompetent CNS paradigms. Finally, novel treatment strategies for PTLD have emerged, including adoptive immunotherapy and rational targeted therapeutics (e.g., targeting downstream signaling pathways of virus-encoded latent membrane protein-2A).

17. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy.

Lancet. 1984;1(8377):583–587

Starzl TE, Nalesnik MA, Porter KA, Ho M, Iwatsuki S, Griffith BP, et al.

Summary: Post-transplant lymphomas or other lymphoproliferative lesions, which were usually associated with Epstein-Barr virus infections, developed in 8, 4, 3, and 2 recipients, respectively, of cadaveric kidney, liver, heart, and heart-lung homografts. Reduction or discontinuance of immunosuppression caused regression of the lesions, often without subsequent rejection of the grafts. Chemotherapy and irradiation were not valuable. The findings may influence policies about treating other kinds of posttransplantation neoplasms.

18. Maintaining calcineurin inhibition after the diagnosis of post-transplant lymphoproliferative disorder improves renal graft survival.

Kidney Int. 2014 Jan;85(1):182-90. doi: 10.1038/ki.2013.253. Epub 2013 Jun 26.

Serre JE, Michonneau D, Bachy E, Noël LH, Dubois V, Suberbielle C, Kreis H, Legendre C, Mamzer-Bruneel MF, Morelon E, Thaunat O.

Post-transplant lymphoproliferative disorder (PTLD) is an uncontrolled proliferation of transformed lymphocytes fostered by immunosuppression. In addition to chemotherapy, treatment of PTLD includes a reduction of maintenance immunosuppression. Patients with PTLD have an increased risk of graft loss, suggesting that reduced immunosuppression strategy needs to be optimized with regard to graft outcome. Here we retrospectively reviewed 101 cases involving PTLD to identify the risks associated with graft loss. During a median follow-up of 70 months, 39 patients died and 21 lost their graft. Multivariate analysis found that an eGFR under 30 ml/min per 1.73m2 at PTLD diagnosis, a biopsy-proven acute rejection episode following reduction of immunosuppression, and the absence of calcineurin inhibition in maintenance immunosuppression are independent risk factors for allograft loss. Neither the type of PTLD nor the chemotherapy regimen was predictive of allograft failure. Histological analysis of graft biopsies showed that maintaining calcineurin inhibition after the diagnosis of PTLD reduced the risk of developing de novo anti-HLA antibodies and humoral rejection. Remarkably, calcineurin inhibitor maintenance was neither associated with higher mortality nor with worse progression-free survival. Thus, maintaining calcineurin inhibition at a reduced dose after the diagnosis of PTLD seems safe and may improve renal graft outcome, possibly through better control of the recipient's humoral immune response.

19. Virus-associated hemophagocytic syndrome in renal transplant recipients: report of 2 cases from a single center.

Case Rep Hematol. 2015;2015:876301. doi: 10.1155/2015/876301. Epub 2015 Mar 8.

Nanmoku K, Yamamoto T, Tsujita M, Hiramitsu T, Goto N, Katayama A, Narumi S, Watarai Y, Kobayashi T, Uchida K.

Virus-associated hemophagocytic syndrome (HPS) is a potentially fatal complication of immunosuppression for transplantation. However, it presents with heterogeneous clinical symptoms (fever, disturbed consciousness, and hepatosplenomegaly) and laboratory findings (pancytopenia, elevated hepatic enzyme levels, abnormal coagulation, and hyperferritinemia), impeding diagnosis. Case 1: A 39-year-old female developed fever 4 years after ABO-incompatible living-related renal transplantation. Laboratory findings revealed thrombocytopenia, elevated hepatic enzymes, Epstein-Barr virus (EBV) DNA seropositivity, and hyperferritinemia. EBV-associated HPS was confirmed by bone marrow aspiration. Steroid pulse therapy and etoposide were ineffective. Disseminated intravascular coagulation resulted in multiple organ failure, and the patient died 32 days after disease onset. Case 2: A 67-year-old male was admitted with rotavirus enteritis a month after living-unrelated renal transplantation. He developed sudden-onset high fever, disturbance of consciousness, and tachypnea 8 days after admission. Laboratory findings revealed elevated hepatic enzyme levels, hyperkalemia, and hyperferritinemia. Emergency continuous hemodiafiltration ameliorated the fever, and steroid pulse therapy improved abnormal laboratory values. Varicella-zoster virus meningitis was confirmed by spinal tap. Acyclovir improved consciousness, and he was discharged 87 days after admission. Fatal virus-associated HPS may develop in organ transplant patients receiving immunosuppressive therapy. Pathognomonic hyperferritinemia is useful for differential diagnosis.

20. Autoimmune haemolytic anaemia associated with Epstein Barr virus infection as a severe late complication after kidney transplantation and successful treatment with rituximab: case report.

BMC Nephrol. 2015 Jul 18;16:108. doi: 10.1186/s12882-015-0096-3.

Hamilton AJ, Webb LH, Williams JK, D'Souza RJ, Ngu LS, Moore J.

Background: Autoimmune haemolytic anaemia (AIHA) is a rare complication following kidney transplantation and usually occurs early in its course. It is characterised by autoantibodies or alloantibodies directed against red blood cells (RBCs).

Case presentation: We describe a 44 year old woman who presented 5 years after kidney transplantation with profound transfusion dependent warm AIHA. Investigations confirmed an IgG autoantibody against RBCs and high titre Epstein-Barr virus (EBV) viraemia. The patient was at higher risk for EBV disease being seronegative at the time of transplantation but had detectable EBV capsid IgG antibody at the time of presentation. The haemolysis was refractory to high dose steroid and intravenous immunoglobulin. There was a rapid and complete resolution of both the anaemia and the viraemia following rituximab therapy, with no adverse events. Twenty-six units of blood were required during the course of treatment.

Conclusions: To our knowledge this is the first reported case of EBV associated AIHA in a renal transplant recipient. It highlights a rare pathology associated with post-transplant EBV infection, of broad interest to transplant physicians, haematologists, and microbiologists, and the effective novel use of monoclonal anti-CD20 therapy.

21. Post-transplantation lymphoproliferative disorder in pediatric kidney-transplant recipients - a national study.

Pediatr Transplant. 2012 Sep;16(6):619-26. doi: 10.1111/j.1399-3046.2012.01731.x. Epub 2012 Jun 18.

Cleper R, Ben Shalom E, Landau D, Weissman I, Krause I, Konen O, Rahamimov R, Mor E, Bar-Nathan N, Frishberg Y, Davidovits M.

Abstract: PTLD is the most common malignancy in pediatric kidney-transplant recipients. We examined the prevalence, clinical features, and outcome of PTLD in Israel. Twelve (4.4%) of 272 pediatric (<19 yr) kidney-transplant recipients retrieved from a search of the NIKTR for 1991-2008 had acquired PTLD at a median of 3.2 yr post-transplantation. PTLD-affected patients were younger at transplantation (4.2 vs. 12.5 yr, p = 0.02), had a higher rate of OKT3 therapy for acute rejection (25% vs. 4%, p = 0.015), and 5/12 were EBV-seropositive at transplantation. Graft dysfunction was the presenting sign in six (50%). PTLD was predominantly abdominal (83%) and B-cell type (67%); T-cell PTLD occurred exclusively in EBV-seropositive patients. Treatment consisted of immunosuppression cessation (6/12, 50%), antiviral agents (7/12, 58%), anti-CD20 monoclonal antibodies (4/12, 33%), and chemotherapy (6/12, 50%). Survival was 100% in the EBV-naïve patients and 40% in the EBV-seropositive patients. Graft loss occurred in three of eight survivors (37.5%). PTLD-associated mortality risk was older age: 11.2 vs. 3.4 yr, longer dialysis: 15 vs. 6.5 months, T-cell type disease (75%), later PTLD onset: 6.35 vs. 1.9 yr post-transplantation and era of transplantation (43% mortality before vs. 20% after 2001). Pretransplantation EBV-seronegative status might confer a survival benefit with early detected PTLD. EBV-seropositive patients are at risk for aggressive late-onset lethal PTLD.

22. Non-post-transplant lymphoproliferative disorder cancers in children after organ transplantation.

Pediatr Transplant. 2013 Dec;17(8):707-9. doi: 10.1111/petr.12165. Epub 2013 Sep 30.

Dharnidharka VR, Kulsum-Mecci N.

(Abstract not available)

23. Solid tumors following kidney transplantation in children.

Pediatr Transplant. 2013 Dec;17(8):726-30. doi: 10.1111/petr.12166.

Smith JM, Martz K, McDonald RA, Harmon WE.

Abstract: Kidney transplant recipients have an increased risk of cancer. Data on non-LPD malignancies (solid tumors) in pediatric renal transplant recipients are limited. We performed a cohort study using the NAPRTCS transplant registry to describe the incidence of non-LPD malignancy compared with the general pediatric population. The observed incidence rate of non-LPD malignancy in the NAPRTCS transplant registry was 72.1 per 100,000 person-years (SIR 6.7; 95% CI, 5.3, 8.5); a 6.7-fold increased risk compared with the general pediatric population (10.7 cases per 100,000 person-years). Non-LPD malignancy was diagnosed in 35 subjects at a median of 726 days post-transplant. The most common type of malignancy was renal cell carcinoma. The increased risk of non-LPD malignancy was seen in all patients regardless of age, gender, race, etiology of end-stage kidney disease, and transplant era. The specific type of immunosuppression was not identified as a risk factor. In this first large-scale study of North American pediatric renal transplant recipients, we observed a 6.7-fold increased risk of non-LPD malignancy compared with the general pediatric population. Further examination of this unique patient population may provide greater insight into the impact of transplant and immunosuppression on malignancy risk.

24. Epstein-Barr virus-associated smooth muscle tumors in children following solid organ transplantation: a review.

Pediatr Transplant. 2015 Mar;19(2):235-43. doi: 10.1111/petr.12426. Epub 2015 Jan 9.

Jossen J, Chu J, Hotchkiss H, Wistinghausen B, Iyer K, Magid M, Kamath A, Roayaie S, Arnon R.

Abstract: EBV-SMT are a rare entity following organ transplantation. Given the rarity of the tumor, there is no standard approach to diagnosis and treatment. A literature search identified 28 reported cases of EBV-SMT in addition to our own experience with one case. The aim of this review is to summarize the existing data regarding pathogenesis, diagnosis, and treatment.

25. Multiple bilateral fibroadenomas of the breasts requiring mastectomy in a renal transplant patient.

Clin Nephrol. 2004 Feb;61(2):151-4.

Kanaan N, Goffin E.

Abstract: Fibroadenomas of the breast have been reported in female renal graft recipients and associated with the use of cyclosporin A (CsA). We report the case of a young patient given CsA who developed multiple bilateral fibroadenomas of the breasts 3 years after renal transplantation, leading to bilateral mastectomy. We discuss the association of CsA with fibroadenomas, the mechanisms by which the drug can act and review the literature. Based on these observations, an early conversion from CsA to tacrolimus should be considered; further observations are needed to assess the reversibility of the breast(s) lesions after such immunosuppressive regimen switch.

26. Characteristic imaging features of breast fibroadenomas in women given cyclosporin A after renal transplantation.

J Clin Ultrasound. 2004 Feb;32(2):69-77.

Son EJ, Oh KK, Kim EK, Cho N, Lee JD, Kim SH, Jung WH.

Purpose: This retrospective study was conducted to determine the characteristic imaging and histopathologic features of breast fibroadenomas in kidney-transplant recipients given chronic cyclosporin A immunosuppressive therapy after the transplantation and to compare these characteristics with those from a control group.
Methods: From January 1, 1990, through December 31, 1999, 486 women underwent renal transplantation at our institution. All patients subsequently received immunosuppressive therapy with cyclosporin A and prednisolone. Ten (2%) of these women had developed breast fibroadenomas during this chemotherapy. We compared the data obtained on this group's fibroadenomas with those obtained from those in the control group, which comprised 100 women with fibroadenomas but who had never undergone organ transplantation or immunosuppressive therapy.
Results: Twenty-two fibroadenomas developed in the 10 transplant recipients. Eight of those 10 had multiple lesions, and 7 were affected bilaterally. The mean diameter of the fibroadenomas was 4.2 +/- 2.5 cm. Mammographically, the lesions were round or oval high-density masses with well-circumscribed margins and no calcification or spiculation. Sonographically, the lesions were relatively highly echogenic and had a lower ratio of the longitudinal to the anteroposterior diameter (L /AP) than did those in the control group. Histopathologically, the features of these lesions were generally typical of fibroadenomas, but some were more typical of malignant lesions. Among the 100 control patients, 146 fibroadenomas developed; 33 women had multiple lesions, and 12 were affected bilaterally. Their fibroadenomas had a mean diameter of 2.1 +/- 1.5 cm, and the imaging features of these lesions were typical of fibroadenomas.
Conclusions: The fibroadenomas that developed in kidney-transplant recipients given chronic cyclosporin A and prednisolone immunosuppressive therapy had a tendency to be multiple, bilateral, and larger than those that developed in the control patients. These fibroadenomas also exhibited some imaging features that differed from those of typical fibroadenomas that develop in women who have not undergone organ transplantation or immunosuppressive therapy.

27. The Seville expert workshop for progress in posttransplant lymphoproliferative disorders.
Transplantation 2012, 94(8): 784-93.
Glotz D, Chapman JR, Dharnidharka VR, Hanto DW, Castro MC, Hirsch HH

Abstract: Posttransplant lymphoproliferative disorders (PTLDs) are associated with significant morbidity and mortality among solid-organ transplant patients, but approaches to diagnosis and management vary considerably. An international multidisciplinary panel evaluated current understanding of risk factors and classification systems and developed recommendations to aid in PTLD prevention. We considered evidence on PTLD risk factors including Epstein-Barr virus serostatus and immunosuppression and identified knowledge gaps for future research. Recommendations address prophylactic and preemptive strategies to minimize PTLD development, including modulation of immunosuppression and antiviral drug regimens. Finally, new classification criteria were outlined that may help facilitate standardized reporting and improve our understanding of PTLD.

28. Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United states.

Am J Hematol 2011; 86 (2): 206-9.

Quinlan SC, Pfeiffer RM, Morton LM, Engels EA.

Abstract: Solid-organ transplant recipients have an elevated risk for some malignancies because of the requirement for immunosuppression [1]. In particular, non-Hodgkin's lymphoma (NHL) is common and comprises one end of a spectrum of post-transplant lymphoproliferative disorder (PTLD) ranging from benign hyperplasia to lymphoid malignancy [2]. PTLD risk is influenced by the type of organ transplanted, the age and Epstein-Barr virus (EBV) serostatus of the transplant recipient, and the intensity of immunosuppression [3-9]. PTLD incidence is high immediately after transplantation, decreases subsequently, and then rises again 4-5 years from transplantation [10,11]. This incidence pattern suggests the presence of separate early-onset and late-onset PTLD subtypes. Early-onset PTLDs tend to be EBV-positive and, when extranodal, are more likely than late-onset PTLDs to be localized to the transplanted organ [12,13]. Late-onset PTLD is less likely to be associated with EBV and, overall, is more likely than early-onset PTLD to be extranodal [13,14]. The Scientific Registry of Transplant Recipients (SRTR) includes data on a large number of solid-organ transplant recipients in the United States and information on malignancies diagnosed post-transplantation. We used these data to conduct a retrospective cohort study among kidney transplant recipients to examine differences in risk factors between early-onset PTLD and late-onset PTLD.

Acreditación

Acreditación solicitada a la
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