APPENDIX 1: MALIGNANCY AFTER KIDNEY TRANSPLANTATION

The following editorial represents work that was separate to, but derived from this thesis. This editorial was invited commentary to accompany a research paper published in the same journal issue (Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. *Am J Transplant* 2004; 4:905-913) and was co-written with Clinical Professor Jeremy Chapman with the equal contribution between us.

**Publication details:**


**Contribution of authors**

*ACW* critically appraised the research paper, performed a literature review of the methodology and content area, contributed to drafting the manuscript and revised the manuscript with *JRC*

*JRC*: critically appraised the research paper and wrote the first manuscript draft and revised the manuscript with *ACW*
Cancer After Renal Transplantation: The Next Challenge

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The successful renal transplant recipient faces death from cardiovascular disease, infection and cancer. In Australia, 25% of all patients surviving for 20 years after a transplant will have a cancer (non skin); rising to 65% if one includes skin cancers. Cancer is the cause of death in 70% of those with a non skin cancer and a major cause of morbidity in the long term for renal transplant recipients. It has been well established that the relative risk of cancer is increased in the transplant compared with the normal population. Understanding this phenomenon is thus important if we are to avoid, diagnose early, or effectively treat cancer in renal transplant patients. It may also lead to insights into the impact of immune suppression and cancer surveillance mechanisms in both the dialysis and normal populations. Kasiske et al. in this issue have now contributed to the further understanding of cancer in both the dialysed patient and in the renal transplant recipient.

All sources available for the description of risk of cancer in the transplant population have inherent weaknesses. The registries of renal transplant recipients, such as the Australia and New Zealand Registry (ANZDATA) and the Collaborative Transplant Study (CTS) are affected by varying degrees by under-reporting of cancer, while specific cancer registries relying on voluntary reporting, suffer from inaccessible denominators. Individual series and case reports provide data on the potential behavior of some cancers, but are clearly limited from an epidemiological perspective. Linkage of data from two or more trusted sources is thus attractive, especially where the sources have complementary strengths. This approach has been used in the past to validate registry data (1,2), but Kasiske and colleagues take this further by linking the USRDS with Medicare billing claims for cancer diagnoses.

The analysis confirms the high risk of cancer in the renal transplant population in the United States. The data are limited by the methodology to the first 3 years after transplantation, and to the 47% of total transplant patients who use Medicare and can thus be tracked by the billing system. The analysis shows a very high risk of many cancers compared with the normal, age-matched, US population. The 3-year cumulative incidence is also higher than shown in previous analyses, with 7.4% of patients having a skin and 7.5% a non skin cancer by 3 years. This compares with the ANZDATA rates of approximately 10% and 3% at 3 years; and with the CTS rates of approximately 1% and 2%, respectively. Two features of this US analysis are thus the higher rate of cancer after renal transplantation compared with other reports, and the different ratio of skin to non skin cancer (1:1 in US Medicare claims; compared with 3:1 in the Australian surf).

The risk of cancer in the dialysis and end-stage renal failure population is of course distorted by the incidence of cancers which cause renal failure and by treatment policies which place relatively few patients with cancer on transplant waiting lists and limit the number of patients with metastatic malignant disease that are commenced on dialysis. It is important to look beyond these issues to discern whether uremia predisposes to cancer. This analysis provides confirmation of the impact of dialysis as opposed to transplantation, as the relative risk of cancer increased with the number of years on dialysis. There was also support for this effect from the limited differences in risks between the waiting list and transplanted populations as opposed to the large relative risks compared with the normal population. This concurs with other studies examining cancer risk in the dialysis population and turns some attention away from the role of immunosuppressive agents (3).

The types of cancer that show the largest relative risks for the transplant compared with the waiting list population are kidney, lymphoma, Kaposi's sarcoma and skin, but with reduction in the risk of ovarian and prostate cancer. It is tempting to offer explanatory hypotheses for each of these effects, related either to biological or nonbiological processes. Compared with the normal population, Kaposi's sarcoma, lymphoma, skin and kidney cancers stand out in the US data with more than a 15-fold increase in risk, while melanoma, leukemia, hepatobiliary, and female genital tract have a fivefold increase. Common solid tumors
including gastrointestinal tract, prostate, pancreas, ovary and breast are also increased, but to a lesser degree. These data are at some variance to that seen in CTS and ANZDATA analyses where, for example, breast cancer is not significantly increased. The data have been adjusted for age, but the age-specific relative risks may be informative, with preliminary Australian data showing higher risk ratios in the younger than the older age groups.

Diagnosis and understanding of the relative and absolute risks are only the start of the journey that must be taken in order to reduce the rising impact of cancer on the quality of life and the longevity of transplanted patients. Identifying causes of the increased risks and determining appropriate renal population screening strategies combined with early treatment programs, may impact on mortality and morbidity. The different modes of action of immunosuppressive agents and the early data in randomized studies suggest that sirolimus may lead to fewer cancers (4), while longer term trial (5) and registry data (6) identify specific demographic factors and drug doses associated with increased cancer risk. These data open up the prospect of tailored therapy, targeted not only at the individual's risk of allograft rejection but also their risk of cancer.

References

APPENDIX 2: SUPPORTING DATA FOR CHAPTER 2

Ap 2.1: Search strategies

The following search strategies were used to identify randomised trials for inclusion in the systematic review “Interleukin 2 receptor antagonists for renal transplant recipients”.

**Medline**

1. Kidney Transplantation/
2. basiliximab.tw.
3. daclizumab.tw.
4. zenapax.tw.
5. cd25.tw.
6. cd 25.tw.
7. bt563.tw.
8. simulect.tw.
9. exp Receptors, Interleukin-2/
10. exp Antibodies, Monoclonal/
11. interleukin-2 receptor$.tw.
13. il2.tw.
14. il 2.tw.
15. il2R.tw.
16. il 2R.tw.
17. il 2 R.tw.
18. monoclonal antibod$.tw.
19. or/2-18
20. 1 and 19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized controlled trials/
24. random allocation/
25. double blind method/
26. single blind method/
27. or/21-26
28. animal/ not (animal/ and human/)
29. 27 not 28
30. clinical trial.pt.
31. exp clinical trials/
32. (clinic$ adj25 trial$).ti,ab.
33. cross-over studies/
34. (crossover or cross-over or cross over).tw.
35. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
36. placebos/
37. placebo$.ti,ab.
38. random$.ti,ab.
39. research design/
40. or/30-39
41. 40 not 28
42. 29 or 41
43. 20 and 40
Appendix 2: Supporting data for chapter 2

**Embase**

1. exp Interleukin 2 Receptor Antibody/
2. basiliximab.tw.
3. daclizumab.tw.
4. dacliximab.tw.
5. cd25.tw.
6. cd 25.tw.
7. bt563.tw.
8. simulect.tw.
9. zenapax.tw.
10. interleukin-2 receptor$.tw.
13. il2.tw.
14. il-2.tw.
15. il2r.tw.
16. il-2r.tw.
17. il-2-r.tw.
18. or/1-17
19. exp Kidney Transplantation/
20. 18 and 19
21. exp clinical trial/
22. comparative study/
23. drug comparison/
24. major clinical study/
25. randomization/
26. crossover procedure/
27. double blind procedure/
28. single blind procedure/
29. placebo/
30. prospective study/
31. ((clinical or controlled or comparative or placebo or prospective or randomi#ed) adj3 (trial or study)).ti,ab.
32. (random$ adj7 (allocat$ or allot$ or assign$ or basis$ or divid$ or order$)).ti,ab.
Appendix 2: Supporting data for chapter 2

33. ((singl$ or doubl$ or trebl$ or tripl$) adj7 (blind$ or mask$)).ti,ab.
34. (cross?over$ or (cross adj1 over$)).ti,ab.
35. ((allocat$ or allot$ or assign$ or divid$) adj3 (condition$ or experiment$ or intervention$ or treatment$ or therap$ or control$ or group$)).ti,ab.
36. or/21-30
37. or/31-35
38. 36 or 37
39. 20 and 38
Appendix 2: Supporting data for chapter 2

Ap 2.2: Complete list of trial reports identified

Systematic reviews are trial based, not report/publication based. Below is an alphabetical list of all trials identified for the systematic review “Interleukin 2 receptor antagonists for renal transplant recipients”. Trials are listed in bold font, with all reports that we identified that pertained to that trial listed below.

Trials are named by taking the first author and year of the ‘index’ publication (the first journal report of the trial we identified). Many trials are reported more than once in medical journals. Other additional and subsequent reports may contribute data to the systematic review, but these data are attributed at trial level, not at the level of each individual report. The trial we nominated as the ‘index’ publication of each trial is marked with a star. This approach is taken to reveal the lineage of a trial in the most transparent manner possible

Ahsan 2002


ATLAS 2003


Appendix 2: Supporting data for chapter 2

**Baczkowska 2002**


**Brennan 2002**


**Daclizumab Double 99**


Appendix 2: Supporting data for chapter 2


Appendix 2: Supporting data for chapter 2


**Daclizumab Triple 98**


**Davies/Lawen 2000**


**de Boccardo 2002**

**Flechner 2000**


**Folkmane 2001**


**Garcia 2002**


**Hourmant 1994**


**Kahan 1999**

Hall M, Kovarik J, Gerbeau C, Schmidt AG. Influence of the duration of IL-2 receptor (IL-2R) blockade on the incidence of acute rejection episodes in renal


Kovarik JM, Gerbeau C, Hall M, Schmidt AG. Influence of the duration of IL-2 receptor (IL-2R) blockade on the incidence of acute rejection episodes in renal transplantation [abstract]. Transplantation 1998;65(12):S179


Appendix 2: Supporting data for chapter 2


Khan 2000


* Kirkman 1989


Appendix 2: Supporting data for chapter 2


Kirkman 1991


Kriaa 1993


Kumar 2002

* Kumar MSA, Hahn J, Adams C, Fa K, Fyfe B, Damask A et al. Steroid avoidance (SA) in kidney transplant recipients treated with Simulect (BMAB), Neoral (CSA) and Cellcept (MMF) - A randomized prospective controlled clinical trial [abstract].
Appendix 2: Supporting data for chapter 2


**Kyllonen 2002**

* Kyllonen L. Induction with Single Bolus ATG or Basiliximab in Cadaveric Kidney Transplantation with Cyclosporine Immunosuppression. *Transplantation* 2002;74 (Suppl 4):466

**Lacha 2001**


**Lebranchu 2002**


Appendix 2: Supporting data for chapter 2


Matl 2001


Mourad 2002


Nair 2001


Appendix 2: Supporting data for chapter 2


Nashan 1997


Appendix 2: Supporting data for chapter 2


**Philosophe 2002**

Appendix 2: Supporting data for chapter 2


**Pisani 2001**


**Ponticelli 2001**


Ponticelli C, Yusim A, Cambi V, Legendre C, Rizzo G, Salvadori M et al. Basiliximab (Simulect) significantly reduces the incidence of acute rejection in
renal transplant patients receiving a triple therapy with azathioprine [abstract]. In: International Congress of the Transplantation Society; 2000 Aug 27-Sep 1; Rome (Italy). 2000:(CD-ROM) Abstract 0114


Pourfarziani 2003


Sandrini 2002


Sheashaa 2003


Shidban 2000


Shidban 2003

**Sollinger 2001**


Appendix 2: Supporting data for chapter 2


**Soulillou/Cantarovich 1990**


**Tullius 2003**


**van Gelder 1995**


**van Riemsdijk 2002**

Hesselink DA, Nguyen H, Wabbijn M, Smak Gregoor PJH, Steyerberg EW, Van Riemsdijk IC et al. Tacrolimus dose requirement in renal transplant recipients is...


APPENDIX 3: SUPPORTING DATA FOR CHAPTER 3

Ap 3.1: Search strategies

The following search strategies were used to identify randomised trials for inclusion in the systematic review “Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients”.

Medline

1. kidney transplantation/
2. exp tacrolimus/
3. tacrolimus.tw.
4. prograf.tw.
5. FK 506.tw.
6. FK506.tw.
7. Tsukubaenolide.tw.
8. fr-900506.tw.
9. fujimycin.tw.
10. protopic.tw.
11. or/2-10
12. 1 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized controlled trials/
16. random allocation/
17. double blind method/
18. single blind method/
19. or/13-18
20. animal/ not (animal/ and human/)
21. 19 not 20
22. clinical trial.pt.
23. exp clinical trials/
25. cross-over studies/
26. (crossover or cross-over or cross over).tw.
27. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
Appendix 3: Supporting data for chapter 3

28. placebos/
29. placebo$.ti,ab.
30. random$.ti,ab.
31. research design/
32. or/22-31
33. 32 not 20
34. 21 or 33
35. 12 and 34
Appendix 3: Supporting data for chapter 3

Embase

1. exp Tsukubaenolide/
2. prograf?.tw.
3. protopic.tw.
4. tacrolimus.tw.
5. fujimycin.tw.
6. fk506.tw.
7. fk 506.tw.
8. fr-900506.tw.
10. or/1-9
11. exp Kidney Transplantation/
12. 10 and 11
13. exp clinical trial/
14. comparative study/
15. drug comparison/
16. major clinical study/
17. randomization/
18. crossover procedure/
19. double blind procedure/
20. single blind procedure/
21. placebo/
22. prospective study/
23. ((clinical or controlled or comparative or placebo or prospective or randomi#ed) adj3 (trial or study)).ti,ab.
24. (random$ adj7 (allocat$ or allot$ or assign$ or basis$ or divid$ or order$)).ti,ab.
25. ((singl$ or doubl$ or trebl$ or tripl$) adj7 (blind$ or mask$)).ti,ab.
26. (cross?over$ or (cross adj1 over$)).ti,ab.
27. ((allocat$ or allot$ or assign$ or divid$) adj3 (condition$ or experiment$ or intervention$ or treatment$ or therap$ or control$ or group$)).ti,ab.
28. or/13-22
29. or/23-27
30. 28 or 29
31. 12 and 30
Appendix 3: Supporting data for chapter 3

Ap 3.2: Complete list of trial reports identified

Systematic reviews are trial based, not report/publication based. Below is an alphabetical list of all trials identified for the systematic review “Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients”. Trials are listed in bold font, with all reports that we identified as pertaining to that trial listed below.

Trials are named by taking the first author and year of the ‘index’ publication (the first journal report of the trial we identified). Many trials are reported more than once in medical journals. Other additional and subsequent reports may contribute data to the systematic review, but these data are attributed at trial level, not at the level of each individual report. The trial we nominated as the ‘index’ publication of each trial is marked with a star. This approach is taken to reveal the lineage of a trial in the most transparent manner possible.

Agha 2001


Baskin 2002


Busque 2001


Appendix 3: Supporting data for chapter 3

**Campos 2002**


**Charpentier 2002**


**Egfjord 2002**


**El Haggan 2002**


**Heering 1998**

Appendix 3: Supporting data for chapter 3


Ichimaru 2001


Johnson 2000


* Johnson C. Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus cyclosporine (Neoral) with mycophenolate mofetil after cadaveric kidney transplantation. Transplantation 2000;69(5):834-41.

Laskow 1995


**Liu 2003**


**Margreiter 2002**


Dietl H, European Tacrolimus vs. Cyclosporin-Microemulsion Renal Transplantation Study Group. Analysis of Primary and Recurrent Acute Rejections


Sperschneider H, For the European Tacrolimus vs Ciclosporin-ME Study Group. A Large Multicentre Trial To Compare The Efficacy and Safety of Tacrolimus and Ciclosporin-Microemulsion Following Renal [abstract]. In: XVIII International Congress of the Transplantation Society; 2000 Aug 27-Sep 1; Rome (Italy). 2000

Mayer 1997


Appendix 3: Supporting data for chapter 3


Miller 2002
Appendix 3: Supporting data for chapter 3


**Morris-Stiff 1998**


**Nichelle 2002**


**Pirsch 1997**


Jensik SC, FK 506 Kidney Transplant Study Group. Tacrolimus (FK 506) in kidney transplantation: three-year survival results of the US multicenter, randomized,
Appendix 3: Supporting data for chapter 3


273
Appendix 3: Supporting data for chapter 3


**Radermacher 1998**


**Raofi 1999**


**Shapiro 1991**
Appendix 3: Supporting data for chapter 3


**Toz 2001**


**Trompeter 2002**


Appendix 3: Supporting data for chapter 3


Tsinalis 2000


van Duijnhoven 2002


Wang 2000


Weimer 2002


White 2000
Appendix 3: Supporting data for chapter 3


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Appendix 3: Supporting data for chapter 3

**Yang 1999**


**Yu 2000**

APPENDIX 4: SUPPORTING DATA FOR CHAPTER 4

Ap 4.1: Search strategies
The following search strategies were used to identify randomised trials for inclusion in the systematic review “Target of rapamycin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients”.

**Medline**

1. exp kidney transplantation/
2. kidney transplant$.tw.
3. renal transplant$.tw.
4. kidney graft$.tw.
5. renal graft$.tw.
6. or/1-5
7. sirolimus/
8. sirolimus.tw.
9. rapamycin.tw.
10. rapamune.tw.
11. ay 22-989.tw.
12. everolimus.tw.
13. SDZ RAD.tw.
14. (RAD or RAD100).tw.
15. certican.tw.
16. or/7-15
17. and/6,16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized controlled trials/
21. random allocation/
22. double blind method/
23. single blind method/
24. or/18-23
25. animals/ not (animals/ and human/)
26. 24 not 25
27. clinical trial.pt.
Appendix 4: Supporting data for chapter 4

28. exp clinical trials/
29. (clinic$ adj25 trial$).ti,ab.
30. cross-over studies/
31. (crossover or cross-over or cross over).tw.
32. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
33. placebos/
34. placebo$.ti,ab.
35. random$.ti,ab.
36. research design/
37. or/27-36
38. 37 not 25
39. 26 or 38
40. and/17,39
Appendix 4: Supporting data for chapter 4

**Embase**

1. Rapamycin/
2. sirolimus.tw.
3. rapamycin.tw.
4. rapamune.tw.
5. everolimus.tw.
6. ay 22989.tw.
7. SDZ RAD.tw.
8. (RAD or RAD100).tw.
9. certican.tw.
10. or/1-9
11. exp kidney transplantation/
12. kidney transplant$.tw.
13. renal transplant$.tw.
14. kidney graft$.tw.
15. renal graft$.tw.
16. or/11-15
17. 10 and 16
18. exp clinical trial/
19. evidence based medicine/
20. outcomes research/
21. crossover procedure/
22. double blind procedure/
23. single blind procedure/
24. prospective study/
25. major clinical study/
26. exp comparative study/
27. placebo/
28. "evaluation and follow up"/
29. follow up/
30. randomization/
31. or/18-30
32. controlled study/ not case control study/
Appendix 4: Supporting data for chapter 4

33. or/31-32
34. (clinic$ adj5 trial$).ti,ab.
35. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
36. random$.ti,ab.
37. placebo$.ti,ab.
38. or/34-37
39. 33 or 38
40. limit 39 to human
41. and/17,40
Ap 4.2: Complete list of trial reports identified

Systematic reviews are trial based, not report/publication based. Below is an alphabetical list of all trials identified for the systematic review “Target of rapamycin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients”. Trials are listed in bold font, with all reports that we identified as pertaining to that trial listed below.

Trials are named by taking the first author and year of the ‘index’ publication (the first journal report of the trial we identified) and any associated trial code number. Many trials are reported more than once in medical journals. Other additional and subsequent reports may contribute data to the systematic review, but these data are attributed at trial level, not at the level of each individual report. The trial we nominated as the ‘index’ publication of each trial is marked with a star. This approach is taken to reveal the lineage of a trial in the most transparent manner possible.

Cohen 2003


Durrbach 2004


Flechnrer 2002 (318)

Flechner SM, Burke JT, Cook DJ, Mastroianni B, Savas K, Goldfarb D, Modlin C, Krishnamurthi V, Novick AC. A randomized prospective trial of sirolimus vs
Appendix 4: Supporting data for chapter 4


Flechner SM, Kurian S, Burke JT, Rollin H. Kidney transplantation with sirolimus and mycophenolate mofetil based immunosuppression preserves renal structure and function at two years compared to calcineurin inhibitor drugs. *Transplantation* 2004;78(2):141.


**Gaber 2002**


**Gallon 2003**
Appendix 4: Supporting data for chapter 4


**Glotz 2005**


**Gonwa 2002 (212)**


**Gonwa 2003 (PSG)**


**Grinyo 2002**


* Grinyo JM, Campistol JM, Paul J, Garcia J, Arias M, Morales JM et al. A randomised, open, multicenter, trial comparing tacrolimus (TAC) withdrawal with TAC dose reduction in de novo renal transplants, receiving sirolimus (SIR), TAC


**Groth 1999 (207)**


**Kahan 1999 (203)**


**Kahan 2000 (301)**


Appendix 4: Supporting data for chapter 4


Appendix 4: Supporting data for chapter 4


**Kahan 2001 (157)**


**Kandaswamy 2005**


Kandaswamy R, Humar A, Sutherland DER, Gillingham K, Matas A. A prospective, randomized study of cyclosporine (csa)/mycophenolate mofetil (mmf) versus tacrolimus (tac)/sirolimus(sir) with rapid discontinuation of prednisone (p) [abstract]. *Transplantation* 2004;78(2 Suppl):32

**Kaplan 2001 (251)**

Appendix 4: Supporting data for chapter 4


Appendix 4: Supporting data for chapter 4


Kramer 2003 (2307)


Rigotti P et al. Excellent graft function in de novo kidney transplant recipients treated with concentration controlled everolimus, reduced neoral exposure and simulect: 6 months analysis [abstract 294]. In: European Society of Transplantation; 2003 Sep; Venice (Italy). 2003


**Kreis 2000 (210)**


**Kumar 2003**

Appendix 4: Supporting data for chapter 4

Kumar M. A prospective randomized study to compare the efficacy and safety of sirolimus (slr) and mycophenolate mofetil (mmf) monitored by protocol biopsies in tacrolimus (tac) based steroid free immunosuppression. *Am J Transplant* 2005;4(Suppl 8):216.

Kumar M. Comparison of efficacy and safety of sirolimus (slr) and mycophenolate mofetil (mmf) as adjunct to calcineurin inhibitor (cni) based steroid free immunosuppression in kidney transplantation. *Am J Transplant* 2004;4(Suppl 8):578.

**Lebranchu 2004 (132)**


**MacDonald 2001 (302)**


Appendix 4: Supporting data for chapter 4


Kahan BD, Jaffe JS. Triglyceride (tg) elevations in renal transplant recipients treated with sirolimus (rapamycin, rapa) added to a cyclosporine (csa)/prednisone (pred) regimen [abstract]. *Transplantation* 1999;67(Suppl):585.


Sindhi R, Lavia MF, Paulin E, Shaw S, Sindhi LA, Livingston R et al. Stimulated response of peripheral lymphocytes may distinguish cyclosporine effect in renal


Machado 2001


Machado 2003


**Miller 2002**


**Paczek 2003 (193)**


**Pascual 2003 (2306)**


**Pescovitz 2004**


**Rostaing 2001**


**Russ 2003 (rapa-tac)**

Russ G, Campbell S, Chadban S, Eris J, O'Connell P, Pussell B et al. The safety and efficacy of reduced- and standard-target concentration tacrolimus plus...


**Stallone 2003**


**Stegall 2003**


Appendix 4: Supporting data for chapter 4


van Hooff 2003

301

**Vitko 2001 (201)**


Kovarik JM, Kaplan B, Tedesco SH, Kahan BD, Dantal J, McMahon L, Berthier S, Hsu C-H, Rordorf C. Pharmacokinetics of an everolimus-cyclosporine


Appendix 4: Supporting data for chapter 4


**Vitko 2004 (TERRA)**


APPENDIX 5: SUPPORTING DATA FOR CHAPTER 5

Ap 5.1: Search strategies

The following search strategies were used to identify randomised trials for inclusion in the systematic review “Monoclonal and polyclonal antibody therapy for treating acute rejection in kidney transplant recipients”.

Medline

1. kidney transplantation/
2. ((kidney or renal) adj (transplant$ or recipient$)).tw.
3. 1 or 2
4. exp antibodies, monoclonal/
5. monoclonal antibod$.tw.
6. (polyclonal adj3 antibod$).tw.
7. exp antilymphocyte serum/
8. antilymphocyte.tw.
9. alg.tw.
10. lymphocyte$ antibod$.tw.
11. lymphocyte antiserum$.tw.
12. muromonab cd$.tw.
13. thymoglobulin$.tw.
14. antithymocyte.tw.
15. atg.tw.
16. okt3.tw.
17. okt 3.tw.
18. thymocyte antibod$.tw.
19. thymocyte antiserum$.tw.
20. or/4-19
21. 3 and 20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized controlled trials/
25. random allocation/
26. double blind method/
27. single blind method/
28. or/22-27
Appendix 5: Supporting data for chapter 5

29. animals/ not (animals/ and human/)
30. 28 not 29
31. clinical trial.pt.
32. exp clinical trials/
33. (clinic$ adj25 trial$).ti,ab.
34. cross-over studies/
35. (crossover or cross-over or cross over).tw.
36. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
37. placebos/
38. placebo$.ti,ab.
39. random$.ti,ab.
40. research design/
41. or/31-40
42. 41 not 29
43. 30 or 42
44. 21 and 43
**Embase**

1. exp kidney transplantation/
2. exp monoclonal antibody/
3. monoclonal antibod$.tw.
4. (polyclonal adj3 antibod$).tw.
5. lymphocyte antibody/
6. antilymphocyte$.tw.
7. lymphocyte antibod$.tw.
8. lymphocyte antiserum$.tw.
9. alg.tw.
10. muromonab-cd3/
11. muromonab cd 3.tw.
12. muromonab cd3.tw.
13. okt3/
14. okt3.tw.
15. okt 3.tw.
16. atg$.tw.
17. thymocyte antibody/
18. antithymocyte$.tw.
19. thymocyte antibod$.tw.
20. thymocyte antiserum$.tw.
21. or/2-20
22. 1 and 21
23. exp clinical trial/
24. comparative study/
25. drug comparison/
26. major clinical study/
27. randomization/
28. crossover procedure/
29. double blind procedure/
30. single blind procedure/
31. placebo/
32. prospective study/
Appendix 5: Supporting data for chapter 5

33. (((clinical or controlled or comparative or placebo or prospective or randomi#ed) adj3 (trial or study)).ti,ab.

34. (random$ adj7 (allocat$ or allot$ or assign$ or basis$ or divid$ or order$)).ti,ab.

35. ((singl$ or doubl$ or trebl$ or tripl$) adj7 (blind$ or mask$)).ti,ab.

36. (cross?over$ or (cross adj1 over$)).ti,ab.

37. (((allocat$ or allot$ or assign$ or divid$) adj3 (condition$ or experiment$ or intervention$ or treatment$ or therap$ or control$ or group$))).ti,ab.

38. or/23-32

39. or/33-37

40. 38 or 39

41. 22 and 40
Appendix 5: Supporting data for chapter 5

Ap 5.2: Complete list of trial reports identified

Systematic reviews are trial based, not report/publication based. Below is an alphabetical list of all trials identified for the systematic review “Monoclonal and polyclonal antibody therapy for treating acute rejection in kidney transplant recipients”. Trials are listed in bold font, with all reports that we identified as pertaining to that trial listed below.

Trials are named by taking the first author and year of the ‘index’ publication (the first journal report of the trial we identified) and any associated trial code number. Many trials are reported more than once in medical journals. Other additional and subsequent reports may contribute data to the systematic review, but these data are attributed at trial level, not at the level of each individual report. The trial we nominated as the ‘index’ publication of each trial is marked with a star. This approach is taken to reveal the lineage of a trial in the most transparent manner possible.

**Baldi 2000**


**Barenbrock 1994**


**Birkeland 1975**


**Casadei 1998**

Casadei D, Rial M, Argento J, Goldberg J, Raimondi E. Preliminary results from a randomized and prospective study about immunoglobulin (IVIg) high doses vs. MoAb in the rescue of steroid resistant rejections [abstract]. *J Am Soc Nephrol* 1997;8(Program & Abstracts):677A.


**Filo 1980**


**Gaber 1998**


Gaber LW, For the US Multicenter Thymoglobulin Study Group. Correlation of post treatment renal allograft biopsies to rejection reversal [abstract]. American Society
Appendix 5: Supporting data for chapter 5

of Transplant Physicians ~ ASTP 1997;16th Annual Meeting; May 10-14; Chicago (USA):238


Appendix 5: Supporting data for chapter 5


Woodle S, Moore LW for the Thymoglobulin Multicenter Study Group. 12 month intent to treat analysis of the double blind, randomized multicenter thymoglobulin vs ATGAM trial for the treatment of acute rejection following renal transplantation [abstract]. *Transplantation* 1998;65(12):191

**Glass 1983**


**Goldstein 1985**


**Hesse 1990**


Appendix 5: Supporting data for chapter 5

**Hilbrands 1996**


**Hoitsma 1982**


**Hourmant 1985**


**Howard 1977**


**Johnson 1989**


**Mariat 1998**


Mariat C, Alamartine E, Laurent-Pilonchery B, Diab N, de Filippis JP, Berthoux F. Randomized prospective study comparing low-dose OKT3 to low-dose

**Midtvedt 1996**


**Midvedt 2003**


**Shield 1979**


**Streem 1983**


**Theodorakis 1998**

Theodorakis J, Schneeberger H, Illner WD, Stangl M, Zanker B, Land W. Aggressive treatment of the first acute rejection episode using first-line anti-

**Waid 1992**


Appendix 6: ANZDATA Cancer report

APPENDIX 6: ANZDATA CANCER REPORT

Over the period of my PhD candidature, and whilst developing my research themes, I was the Clinical Epidemiology fellow at the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA). The report presented here was published as a chapter of the 27th annual ANZDATA report and represents the preliminary work behind the studies presented in chapters 6 and 7

Publication details


Contribution of authors

ACW conceived and designed the analysis plan for the report, prepared and analysed the data, interpreted the results and wrote and revised the manuscript.

JRC contributed to the conception of the study, advised on interpretation and presentation of the results and revision of the manuscript.
This report summarises the cancer (excluding non-melanocytic skin cancer) experience of patients treated for end stage renal failure in Australia and New Zealand from 1983 until September 2003.

The first part of the report summarises the relative risk of cancer for patients on dialysis or after at least one kidney transplant, when compared to the general population of Australia. The criteria and methods used for these new analyses are different from those used previously in ANZDATA reports, and have been developed to increase the generalisability of the results and to better reflect observed clinical experience of renal units across Australia and New Zealand.

These analyses are calculated using the method of indirect standardisation by age, gender and calendar year from 1980 – 2003, using national Australian cancer rates supplied by the Australian Institute of Health and Welfare (AIHW). In practical terms this means that the analyses take into account changes in risk that may occur through differences in the age and gender distribution between the ESRF population and that of the referent general population, and also differences that may have occurred over time, and so the final calculation is adjusted for these differences. Previous ANZDATA reports analyses have been restricted to comparing cancer risk of ESRF patients to the incidence experienced in the South Australian population at more limited time points.

The number of observed cases of cancer at each site is calculated from data supplied from renal units treating ESRF patients across Australia and New Zealand. The expected number of cancers is calculated from data supplied to the National Cancer Statistics Clearing House (NCSCH). Individual States and Territories in Australia are required by legislation to maintain a registry of all new cases of cancer in Australian residents. The NCSCH receives data from these cancer registries, and summary data is available from the AIHW website (www.aihw.gov.au/cancer/nesc/index). Results of these analyses are presented as standardised incidence ratios (SIR) with 95% confidence intervals (CI), which can be interpreted like risk ratios or relative risk; a value of SIR = 1 is equivalent risk, SIR = 0.5 is half the risk, SIR = 2 is double the risk etc. The breadth of the 95% CI reflects the precision of the SIR estimates, and those with 95% CI which do not cross 1 can be regarded as statistically significant.

Figure 10.1 shows the risk of cancer experienced by the 33,822 patients undergoing dialysis therapy in Australia and New Zealand between 1980 and 2003, compared to that experienced by the Australian general population. The period of risk for a dialysis patient starts on the day of first dialysis treatment and ends at either (first) transplantation, death or last known follow-up, which ever occurs sooner. Periods of time spent on dialysis after a failed (first) transplant are not considered in this figure (see below). Incident cancers diagnosed at any time after the first day of dialysis are summed in the observed totals. Prior ANZDATA reports have excluded those cancers diagnosed within three months of commencing dialysis therapy, however, for these calculations we opted to include all cancers not known on the date of first dialysis. Site specific cancers are reported in groupings used by the AIHW, and not as previously using those of the South Australian Cancer Registry.

Figure 10.2 shows the risk of cancer experienced by the 13,077 patients who underwent at least one renal transplant in Australia and New Zealand between 1980 and 2003, compared to that experienced by the Australian general population. For these calculations the period of risk for each patient starts on the day of transplantation and continues until death or last known follow-up. Patients have not been removed from the analysis at the time of graft failure as we felt it was important to provide clinicians with an idea of lifetime risk of cancer following transplantation, and also because risk of malignancy is unlikely to return to pre-transplant levels following graft failure. Observed cancers are all those reported at any time after the date of first transplantation, and include those occurring after graft failure, and those that occurred after a subsequent transplant; following a ‘once transplanted always transplanted’ rule.

The second section of this report examines the cumulative risk of a cancer (excluding non-melanocytic skin cancers) with time for patients with ESRF. Figure 10.3 shows the cumulative risk of at least one cancer (excluding non-melanocytic skin cancer) for those undergoing dialysis therapy in Australia and New Zealand, by time on dialysis.

The numbers tabulated below the graph shows the number of patients remaining at risk as time progresses. Dialysis patients cease to be at risk from the day of first transplant, death or last known follow-up, which ever is earlier. Similarly Figure 10.4 shows the lifetime risk of at least one cancer (excluding non-melanocytic skin cancer) following a kidney transplant. Figure 10.5 shows cumulative risk of at least one cancer (excluding non-melanocytic skin cancer) for transplanted patients.
Appendix 6: ANZDATA Cancer report

CANCER REPORT

whilst their first graft continues to function. For these calculations patients cease to be at risk at graft failure, death or last known follow-up, which ever occurs sooner. For Figures 10.3 to 10.5, the curve for the expected number of cancers (excluding non-melanocytic skin cancer) is calculated from the risk experienced by the general population of the same age and gender distribution.

The third part of this report explores the absolute risk of cancer (excluding non-melanocytic skin cancers) for patients after undergoing their first renal transplant. Using data from all 14,354 recipient patients undergoing a transplant from 1963 – 2003, with median follow-up of 7.0 years (interquartile range 2.7–13.2), predictors of post-transplant malignancy (excluding non-melanocytic skin cancer) were investigated. These included age at transplantation, gender, donor source, era of transplantation and primary kidney disease. Each potential predictor was examined alone (univariate analysis) and those that demonstrated a significant relationship with diagnosis of a post-transplant malignancy were entered into a multivariate Cox proportional hazards model, to demonstrate the effect of each predictor after allowing for the effect of other predictors. Results were then stratified by predictors demonstrating significant effect modification, and reported as hazard ratios (HR) with 95% CI. A HR can be interpreted as a risk ratio or relative risk.

Of the 14,354 recipients, 1412 (9.8%) had ≥1 non-skin cancer. In univariate analysis there was a significantly increased risk of cancer with increasing age at transplantation (trend P = 0.0001), for females (P < 0.002), cadaveric donors (P < 0.0001), those with primary disease other than diabetes (P = 0.003) and those transplanted after 1985 (P < 0.001). However, when allowing for all effects in the multivariate model, gender, age and primary renal disease were significant predictors of cancer.

Figure 10.1

<table>
<thead>
<tr>
<th>Site of Cancer</th>
<th>Observed Cancer</th>
<th>Expected Cancer</th>
<th>Standardised Incidence Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Registrable Cancers</td>
<td>1469</td>
<td>861.91</td>
<td>1.70</td>
<td>1.62 1.79</td>
</tr>
<tr>
<td>Head, Neck and Lip</td>
<td>26</td>
<td>10.73</td>
<td>2.47</td>
<td>1.68 3.02</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>22</td>
<td>12.16</td>
<td>1.81</td>
<td>1.19 2.75</td>
</tr>
<tr>
<td>Stomach</td>
<td>32</td>
<td>23.00</td>
<td>1.34</td>
<td>0.95 1.90</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>9</td>
<td>2.40</td>
<td>3.76</td>
<td>1.05 7.22</td>
</tr>
<tr>
<td>Colon</td>
<td>144</td>
<td>134.11</td>
<td>1.07</td>
<td>0.97 1.26</td>
</tr>
<tr>
<td>Liver</td>
<td>21</td>
<td>7.43</td>
<td>2.83</td>
<td>1.84 4.34</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>7</td>
<td>6.44</td>
<td>1.19</td>
<td>0.92 2.20</td>
</tr>
<tr>
<td>Pancreas</td>
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<td>19.44</td>
<td>1.08</td>
<td>0.70 1.66</td>
</tr>
<tr>
<td>Nasal Cavity</td>
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<td>1.44</td>
<td>2.08</td>
<td>0.57 6.46</td>
</tr>
<tr>
<td>Larynx</td>
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<td>8.78</td>
<td>0.91</td>
<td>0.46 1.62</td>
</tr>
<tr>
<td>Trachea, Bronchus and Lung</td>
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<td>109.49</td>
<td>1.71</td>
<td>1.49 1.99</td>
</tr>
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<td>Other Thoracic Organs</td>
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<td>0.74</td>
<td>4.68</td>
<td>1.30 12.53</td>
</tr>
<tr>
<td>Bone and Articular Cartilage</td>
<td>4</td>
<td>1.01</td>
<td>3.95</td>
<td>1.48 10.53</td>
</tr>
<tr>
<td>Malignant</td>
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<td>71.18</td>
<td>1.24</td>
<td>1.00 1.62</td>
</tr>
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<td>Mesotheloma</td>
<td>11</td>
<td>5.72</td>
<td>1.92</td>
<td>1.07 3.47</td>
</tr>
<tr>
<td>Kaposi's Sarcoma</td>
<td>8</td>
<td>0.76</td>
<td>10.46</td>
<td>5.23 20.92</td>
</tr>
<tr>
<td>Connective and Other Soft Tissue</td>
<td>6</td>
<td>5.33</td>
<td>1.13</td>
<td>0.51 2.91</td>
</tr>
<tr>
<td>Breast</td>
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<td>1.36</td>
<td>1.23 1.57</td>
</tr>
<tr>
<td>Vulva</td>
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<td>4.02</td>
<td>1.81 0.06</td>
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<tr>
<td>Vagina</td>
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<td>0.56</td>
<td>6.05</td>
<td>1.95 18.76</td>
</tr>
<tr>
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<td>6.64</td>
<td>3.01</td>
<td>1.04 8.67</td>
</tr>
<tr>
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<td>13.72</td>
<td>1.09</td>
<td>0.60 1.81</td>
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<td>13</td>
<td>10.16</td>
<td>1.28</td>
<td>0.74 2.26</td>
</tr>
<tr>
<td>Other Female Genital Organs</td>
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<td>- -</td>
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<td>1.90</td>
<td>0.92 3.60</td>
</tr>
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<td>0.62</td>
<td>0.50 0.76</td>
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<td>Testis</td>
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<td>0.00</td>
<td>- -</td>
</tr>
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<td>Kidney, Ureter and Urethra</td>
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<td>24.74</td>
<td>7.96</td>
<td>0.93 9.16</td>
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<td>3.89</td>
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<td>0.00</td>
<td>- -</td>
</tr>
<tr>
<td>Brain and Central Nervous System</td>
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<td>12.22</td>
<td>1.90</td>
<td>1.10 2.72</td>
</tr>
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<td>Thyroid Gland</td>
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<td>5.48</td>
<td>6.02</td>
<td>4.28 8.47</td>
</tr>
<tr>
<td>Other Endocrine Glands</td>
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<td>8.82</td>
<td>3.31 23.90</td>
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<td>1.89</td>
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<td>1.06 1.86</td>
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<td>1.43 13.78</td>
</tr>
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<td>8.11</td>
<td>0.59 9.98</td>
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<td>21.05</td>
<td>0.78</td>
<td>0.48 1.25</td>
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</table>

Analysis of 33,822 Patients (87,039 person-years), Standardised for Age, Gender and Calendar Year with Australian General Population

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Figure 10.2


Analysis of 13,077 Patients (110,395 person years), Standardised for Age, Gender and Calendar Year with Australian Population

<table>
<thead>
<tr>
<th>Site of Cancer</th>
<th>Observed Cancer</th>
<th>Expected Cancer</th>
<th>S. Incidence Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Registrable Cancers</td>
<td>1545</td>
<td>495.08</td>
<td>3.12</td>
<td>2.97 - 3.28</td>
</tr>
<tr>
<td>Head, Neck and Lip</td>
<td>63</td>
<td>22.77</td>
<td>2.77</td>
<td>2.16 - 3.54</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>25</td>
<td>8.34</td>
<td>4.73</td>
<td>3.28 - 6.80</td>
</tr>
<tr>
<td>Stomach</td>
<td>15</td>
<td>12.07</td>
<td>1.24</td>
<td>0.75 - 2.06</td>
</tr>
<tr>
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<td>2.01</td>
<td>0.65 - 6.23</td>
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<td>2.07</td>
<td>4.78</td>
<td>2.05 - 7.99</td>
</tr>
<tr>
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<td>3.21</td>
<td>1.98</td>
<td>1.37 - 4.58</td>
</tr>
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<td>9.36</td>
<td>1.72</td>
<td>1.65 - 2.81</td>
</tr>
<tr>
<td>Nasal Cavity</td>
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<td>0.02</td>
<td>5.41</td>
<td>2.26 - 13.00</td>
</tr>
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<td>Larynx</td>
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<td>5.54</td>
<td>1.99</td>
<td>1.19 - 3.59</td>
</tr>
<tr>
<td>Trachea, Bronchus and Lung</td>
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<td>1.69 - 2.42</td>
</tr>
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<td>10.66</td>
<td>4.76 - 23.02</td>
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<td>0.51 - 3.59</td>
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<td>6.73</td>
<td>2.10 - 20.66</td>
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<td>Connective and Other Soft Tissues</td>
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<td>3.10</td>
<td>1.79 - 5.56</td>
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<td>69.82</td>
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<td>1.01 - 1.94</td>
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<td>4.04 - 8.81</td>
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<td>Corpus Uteri</td>
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<td>5.25</td>
<td>1.05</td>
<td>1.16 - 2.93</td>
</tr>
<tr>
<td>Ovary</td>
<td>8</td>
<td>7.56</td>
<td>1.06</td>
<td>0.53 - 2.12</td>
</tr>
<tr>
<td>Other Female Genital Organs</td>
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<td>0.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Penis and Other Male Genital Organs</td>
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<td>5.62</td>
<td>17.01</td>
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</tr>
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<td>0.97</td>
<td>0.74 - 1.27</td>
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<td>4.36</td>
<td>0.00</td>
<td>-</td>
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<td>5.11</td>
<td>4.14 - 6.38</td>
</tr>
<tr>
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<td>4</td>
<td>1.59</td>
<td>2.67</td>
<td>1.07 - 7.12</td>
</tr>
<tr>
<td>Brain and Central Nervous System</td>
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<td>2.99</td>
<td>1.67</td>
<td>1.02 - 2.72</td>
</tr>
<tr>
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<td>5.56</td>
<td>4.53</td>
<td>3.11 - 6.61</td>
</tr>
<tr>
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<td>0.43</td>
<td>3.52</td>
<td>2.40 - 5.07</td>
</tr>
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<td>70</td>
<td>16.74</td>
<td>4.18</td>
<td>3.31 - 5.28</td>
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<td>231</td>
<td>30.74</td>
<td>10.16</td>
<td>8.03 - 14.58</td>
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<tr>
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<td>0.25</td>
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<td>1.61 - 4.42</td>
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<tr>
<td>Leukaemia</td>
<td>32</td>
<td>12.28</td>
<td>2.61</td>
<td>1.64 - 3.69</td>
</tr>
</tbody>
</table>

but both donor source (P = 0.25) and era (P = 0.87) were not. There was strong evidence of interaction between age and gender (P = 0.02), meaning that the effect of gender on cancer risk varied depending on age at transplantation, and that at different ages, the difference between risk for each gender would not be constant. For men compared to women <35 years at transplantation HR 0.78 (0.63-0.96), 35-44 years HR 0.75 (0.60-0.93), 45-54 years HR 1.00 (0.81-1.22) and >=55 years HR 1.13 (0.90-1.40).

Figure 10.6 summarises the results of this analysis, aiming to give clinicians a clear estimate of a patient’s risk of developing a cancer (excluding non-melanocytic skin cancer) by gender and age at transplantation. This information should be useful for pre-transplant counselling, and to enable clinicians to identify those groups at higher risk of developing a malignancy.
Appendix 6: ANZDATA Cancer report

Figure 10.3
\[ \text{Cumulative Risk of at Least One Cancer} \]
\[ \text{(Excluding Non-Melanocytic Skin Cancer)} \]
\[ \text{Whilst on Dialysis} \]

Patients become at risk at time of first dialysis treatment, and cease to be at risk at time of first transplant, death or last known follow-up. Expected curve is calculated for a general population of the same age and sex distribution.

Figure 10.4
\[ \text{Lifetime Cumulative Risk of at Least One Cancer} \]
\[ \text{(Excluding Non-Melanocytic Skin Cancer)} \]
\[ \text{After First Transplant} \]

Patients become at risk at time of first transplant, and cease to be at risk at time of death or last known follow-up. Expected curve is calculated for a general population of the same age and sex distribution.

Figure 10.5
\[ \text{Cumulative Risk of at Least One Cancer} \]
\[ \text{(Excluding Non-Melanocytic Skin Cancer)} \]
\[ \text{Whilst Graft Continues to Function} \]

Patients become at risk at time of first transplant, and cease to be at risk at time of graft failure, death or last known follow-up. Expected curve is calculated for a general population of the same age and sex distribution.

Figure 10.6
\[ \text{Absolute Cancer Risk in the Clinical Setting.} \]
\[ \text{Adjusted risk of >=1 cancer} \]
\[ \text{(excluding non-melanocytic skin cancer)} \]
\[ \text{By time after First Kidney Transplant} \]

<table>
<thead>
<tr>
<th>Years since Transplant</th>
<th>Risk of Non-skin Cancer by age at Transplantation (%)</th>
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