

## Long-Term Issues in Renal Transplant Recipients

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### Long-Term Management Issues in Renal Transplant Patients

Working together for the patients' benefit  
*Referral (back) to the Nephrologist*

- Transplant Center ultimately responsible for outcomes
- Increasingly complex patient population
- Increased regulatory requirements
  - CMS, UNOS, SRTA
- Re-building our process of referral
- Your Comments/Questions/Input

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## Long-Term Issues in Renal Transplant Recipients

- Outcomes
- Causes of Graft Failure
- Causes of Patient Death
- Patient Management
  - Immunosuppression
  - Other

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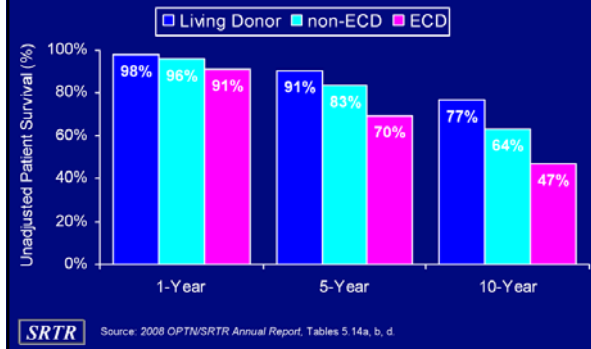
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**Figure III-6. Unadjusted 1-Year (2005-2006), 5-Year (2001-2006), and 10-Year (1996-2006) Kidney Recipient Survival, by Donor Type**




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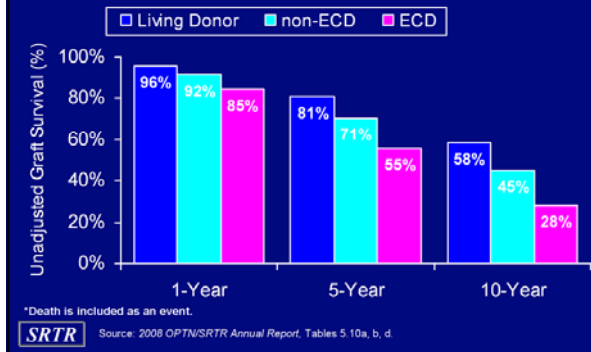
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**Figure III-7. Unadjusted 1-Year (2005-2006), 5-Year (2001-2006), and 10-Year (1996-2006) Kidney Graft Survival\*, by Donor Type**




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### Long-Term Allograft Failure

- ~ 40% fail due to patient death with a functioning graft
- ~60% of allografts surviving > 1 year eventually fail, patient still alive
  - 40% due to “chronic allograft nephropathy”
  - 10-20 % fail from other causes (late acute rejection, recurrent glomerular diseases)

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## Cardiovascular Complications After Renal Transplantation and Their Prevention

Akinlolu O. Ojo  
(*Transplantation* 2006;82: 603–611)

**TABLE 4.** Prevalence of cardiovascular disease according to the presence of proteinuria in kidney transplant recipients in recipients without pretransplant CVD (29)

	RTR with proteinuria	RTR without proteinuria	P value
Posttransplant CVD	35.3.4%	14.6	<0.001
Mean time <sup>a</sup> (years)	4.28 ± 1.3	3.5 ± 1.23	NS

RTR = renal transplant recipients.  
<sup>a</sup> Mean time ± SD from transplantation to the development of a cardiovascular event.

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## Cardiovascular Disease after Renal Transplantation

- Risk factor management
- Optimal screening tests for CAD, treatments are poorly defined in this population

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## Malignancy after Renal Transplantation

- Known higher risk of skin and non-skin solid tumors after renal transplantation
- Independent of induction immunosuppression
- Incidence rises over length of follow-up
  - 2.34 % after 10 years
  - (PTLD: 0.62% after 10 years)
- Higher incidence with Cyclosporine compared with Tacrolimus long-term maintenance (Bustami RT et al. *Transplantation* 2004)
- Lower incidence in patients on Sirolimus (Rapamune<sup>R</sup>)

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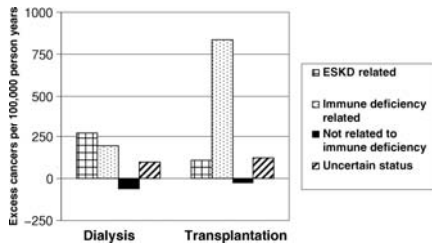
Rate ratios of common cancers in kidney recipients, based on registry analyses, compared with rates in the age- and sex-matched general population

Cancer site (ICD code)	2006(1) Australia Vajdic	2007(15) Canada Villeneuve	2000(16) Denmark Birkeland	2003(17) Sweden Adami	2004(18) United States Kasiske
All (excluding nonmelanocytic skin)	3.3 (3.1,3.5)	2.5 (2.3,2.7)	3.6 (3.1,4.1)	3.9 (3.6,4.2)	na
Breast (female, C50)	1.0 (0.8,1.3)	1.3 (1.0,1.7)	1.5 (0.7,2.6)	1.0 (0.6,1.5)	1.1 (0.9-1.3)
Colon (C18)	2.4 (1.9,2.9)	1.4 (1.0,1.8)	na	2.4 (1.5,3.5)	na
Cervix (C53)	2.5 (1.5,4.3)	1.6 (0.6,3.4)	na	2.0 (0.7,4.7)	5.7 (4.2-7.2)
Lung (C33-C34)	2.5 (2.0,3.0)	2.1 (1.7,2.5)	na	1.7 (1.1,2.5)	2.8 (2.5-3.0)
Prostate (C61)	1.0 (0.7,1.3)	0.9 (0.6,1.3)	na	1.1 (0.7,1.7)	1.6 (1.4-1.8)
Melanoma (C43)	2.5 (2.1,3.1)	1.9 (1.2,3.0)	1.4 (0.3,3.9)	1.8 (1,3)	6.3 (5.4-7.0)

na = Estimate not available.

Managing Cancer Risk and Decision Making After Kidney Transplantation  
Webster AC et al. *Amer J Transplantation* 2008

The burden of excess cancers by cancer category and type of renal replacement therapy



Stewart, J. H. et al. *Nephrol. Dial. Transplant.* 2009 24:3225-3231; doi:10.1093/ndt/gfp331

Copyright restrictions may apply.

Rectum, breast, ovary, prostate

NDT  
Nephrology Dialysis Transplantation

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

H. Myron Kauffman,<sup>1,4</sup> Wida S. Cherikh,<sup>1</sup> Yulin Cheng,<sup>1</sup> Douglas W. Hanto,<sup>2</sup> and Barry D. Kahn<sup>3</sup>

TABLE 5. Results of the Cox multivariate model—significant risk factors for development of de novo malignancies and de novo non-skin solid malignancies within 903 days of transplant

Variable	Any de novo malignancies		De novo non skin solid	
	RR (95% CI)	P value	RR (95% CI)	P value
SEL/EVL vs. CYA/TAC	0.40 (0.24, 0.64)	0.0001	0.45 (0.24, 0.82)	0.0095
Male vs. female	1.60 (1.32, 1.92)	<0.0001	1.25 (0.98, 1.59)	0.0702
Adult vs. pediatric	3.75 (1.53, 9.17)	0.0038	2.16 (0.87, 5.35)	0.0977
White vs. non-white	3.43 (2.76, 4.26)	<0.0001	1.88 (1.46, 2.43)	<0.0001
Diagnosis category				
Glomerular diseases (baseline)	1.00		1.00	
Tubular & interstitial diseases	1.61 (1.14, 2.28)	0.0067	1.77 (1.09, 2.86)	0.0207
Diabetes	1.18 (0.91, 1.53)	0.2035	1.51 (1.07, 2.14)	0.0194
Hypertensive nephropathies	1.99 (1.54, 2.57)	<0.0001	2.39 (1.70, 3.36)	<0.0001
Polycystic kidney	1.80 (1.37, 2.35)	<0.0001	1.56 (1.03, 2.36)	0.0345
Renovascular & vascular diseases	1.73 (1.18, 2.59)	0.0055	1.59 (0.92, 2.73)	0.0955
All other diagnoses	1.23 (0.86, 1.76)	0.2492	1.68 (1.07, 2.65)	0.0246
History of previous malignancy	2.42 (1.72, 3.40)	<0.0001	2.71 (1.73, 4.24)	<0.0001

(*Transplantation* 2005;80: 883-889)

**Switch to a Sirolimus-Based Immunosuppression in Long-Term Renal Transplant Recipients: Reduced Rate of (Pre-)Malignancies and Nonmelanoma Skin Cancer in a Prospective, Randomized, Assessor-Blinded, Controlled Clinical Trial**

Salgo R, et al *Am J Transplant.* 2010

Forty-four RTR (mean age 59.9 years, mean duration of immunosuppression 229.5 months) with skin lesions were randomized to sirolimus or continuation of their original immunosuppression. .... Already the **6-month-assessment showed significant superiority of sirolimus-therapy**; a stop of progression, even regression of preexisting premalignancies ( $p < 0.0005$ ). This effect was increased at month 12 ( $p < 0.0001$ ). Nine patients developed histologically confirmed NMSC: one in the sirolimus group, eight in the control group,  $p = 0.0176$ .

Sirolimus-based immunosuppression in RTR, even when established many years after transplantation, can delay the development of premalignancies, induce regression of preexisting lesions and decelerate the incidence of new NMSC.

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**LONG TERM ALLOGRAFT FAILURE**

“Chronic Rejection” (1970’s-1990’s)



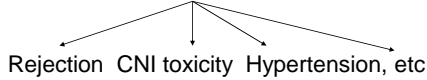
CNI era: *not all graft loss is immunologic*



“Chronic Allograft Nephropathy” (past decade)



Grafts are lost for specific reasons




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**“Chronic Allograft Nephropathy”**

- Still has value as a **clinical** descriptive term, in the absence of a definite pathological/clinical diagnosis
  - Slow decline in allograft function over a period of years, often associated with nephrotic range proteinuria, resulting in allograft failure
- Specific pathological diagnosis whenever possible
  - Immunologic damage
  - Calcineurin inhibitor toxicity
  - Hypertension, Diabetes
  - Glomerular disease (recurrent, *de novo*)

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### "Identifying specific causes of allograft loss"

El-Zoughby, Stegall, et al. *Am J Transplantation* 2009

- 50 month follow-up, overall 25% graft failure
  - 10.4% death with function
  - 14.6% graft failure (nearly 40% immunologic causes \*)
    - glomerular disease 36.6%
      - » recurrent disease 40%
      - » transplant glomerulopathy 40% \*
    - IF/TA 30.7%
      - » CNI toxicity alone 2.1%
      - » Immunologic 27.6% \*
      - » BK polyoma virus 23.4%
      - » Pyelonephritis 14.8%
      - » "idiopathic" 19.1% \*
    - Medical surgical problems 16.3%
    - Acute rejection 11.8% \*
    - Unknown 4.6%

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### Chronic (active) antibody-mediated rejection

- Relatively newly recognized entity, due to C4d staining
- Clinically, often indistinguishable from other causes of progressive long-term allograft failure, although may be associated with acute deteriorations of function
- Formal pathological definition Banff '05, '07
- Diagnosis
  - Anti-donor antibodies
  - Appropriate histology
    - Transplant glomerulopathy/C4d+ staining
  - Allograft dysfunction
- Treatment: poorly defined, generally unsuccessful
  - Plasmapheresis, IVIg, Rituximab
  - Adjustment of maintenance immunosuppression

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### Anti-donor antibodies and "chronic rejection" (Terasaki)

- Anti-HLA antibodies are *the major causative factor* in chronic allograft failure
  - At the time of allograft failure ~90% patients have anti-HLA antibodies
  - The consistent absence of any anti-HLA antibodies is strongly associated with excellent long-term outcomes
  - Detailed analysis shows many, if not most, of these anti-HLA antibodies are donor specific
  - Of those with equivalent degrees of chronic allograft damage, patients with evidence of anti-donor antibodies (+C4d staining) at any time have a 3 year survival of 64% vs. 87% for those with no evidence of anti-donor antibodies

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## Long-term Management Issues *Over vs. Under Immunosuppression ?*

- Monitor drug levels/doses
- Monitor allograft function (creatinine, proteinuria)
  - Virtually every failing allograft should have a biopsy at some time, preferably earlier rather than later
- Cardiovascular disease prevention/management
  - BP, proteinuria, allograft function, lipid management
- Malignancy screening (recommended, proven benefit in transplant patients unclear)
  - Dermatological exam annually
  - Per guidelines
    - Pap
    - Mammogram
    - PSA
    - Colonoscopy
    - (Kidney – no recommendation)

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