CHAPTER 13

RENAL TRANSPLANT OUTCOME BEYOND 5 YEARS

EFFECT OF DONOR AND RECIPIENT FACTORS AND IMMUNOSUPPRESSION

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Most assessments of long term renal transplant outcome have focussed on variables affecting survival beyond one year. Calculations have frequently used the time to median survival starting from 100% at one year (t ½). These have frequently used datasets with only a few years of follow up and the projections have been subject to considerable error. The aim of this study was to use ANZDATA as a unique and large database with follow-up extending to 25 years to assess whether long term outcome had changed over the years and if so, to establish the important contributing variables.

14,261 patients were transplanted between 1963-1999. Only those patients surviving beyond five years were studied in order to focus more clearly on factors operating in the long term. The analysis was confined to primary recipients of living and cadaver donor kidneys, receiving their transplant in Australia between the years 1970-94, resulting in actual five year follow-up on all patients in the study (n=7623). Follow up was to death, graft failure or to September 30, 2000.Outcomes studied were patient survival, patient survival with a functioning graft and graft survival (censored for patient death).

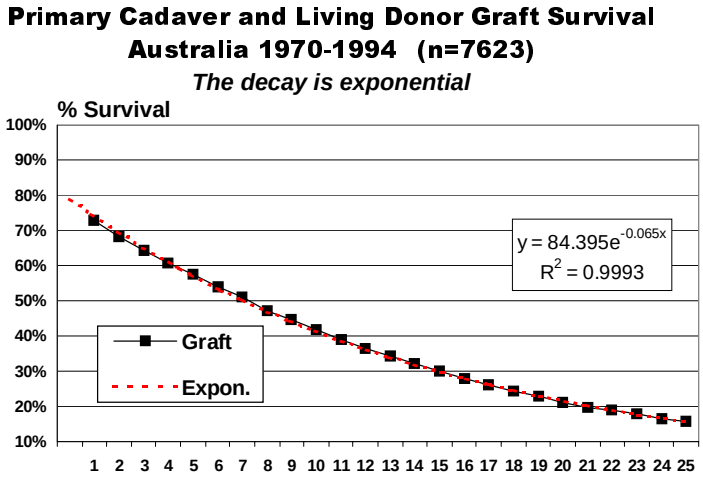


Figure 13.1

The cohort transplanted in the years between 1970-94 in Australia with a primary renal transplant (living or cadaver donor) demonstrated an exponential decay in both the patient and graft survival between one and twenty years at a similar rate of ~2.7%/year. Death censored graft survival decayed at a rate of 1.8%/year.

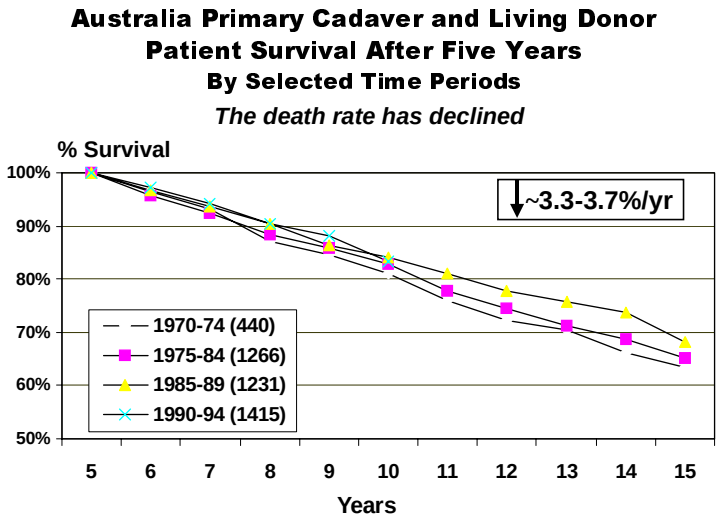


Figure 13.2

Patient survival beyond five years was divided into four time-based cohorts of 1970-74 (n=440 grafts), 1975-84 (n=1266), 1985-89 (n=1231) and 1990-94 (n=1415). There was a minor trend towards improvement in later years. The rate of decay in patient survival beyond five years dropped from 3.7%/year in the 1970-74 cohort to 3.3%/year in the two most recently transplanted groups.

Figure 13.3

Graft survival beyond five years assessed in the same time-based cohorts showed no difference in the annual rate of decline. The rates of decline were surprisingly similar in each of the four time-based cohorts and averaged 4.8%/year.

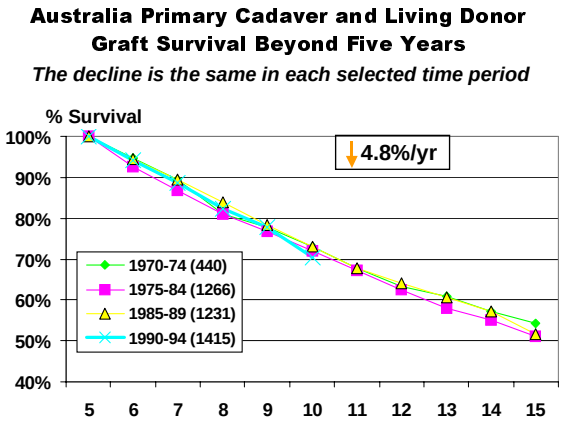


Figure 13.4

The death rate per 100 patient years exposed was shown to decline for the eras 1970-84, 1985-89 and 1990-94. Consistent with the observation seen in the survival analysis the overall death rate decreased from 4.56 deaths/100 patient years (1970-84) to 3.61 (1985-89) and 3.38 (1990-94).

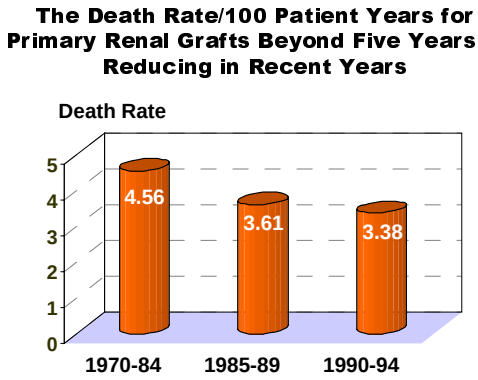


Figure 13.5

A breakdown of the causes of death showed a reduction of 37% in cardio-vascular causes of deaths (2.25 reducing to 1.42 deaths/100 patient years) and a reduction of 23% in the death rate from malignancy (1.06 reducing to 0.82).

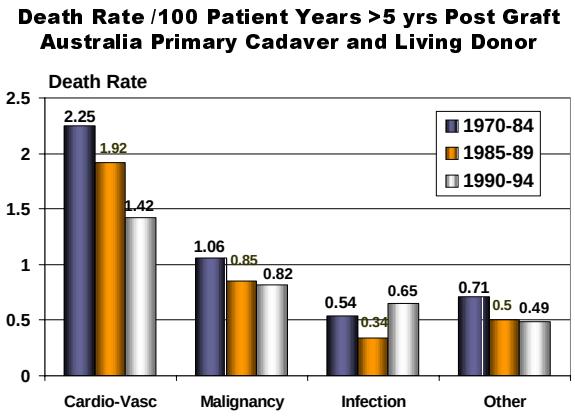
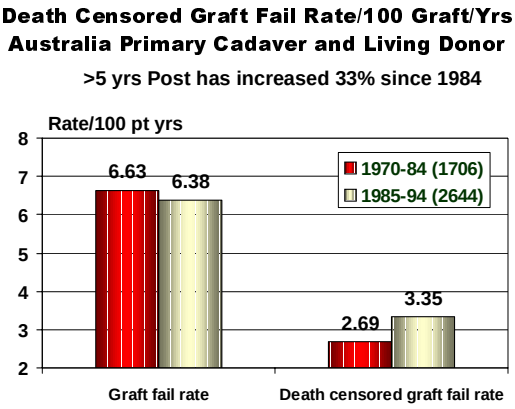


Figure 13.6

The graft failure rate (expressed as failed grafts/100 graft years) was not significantly different when 1706 grafts performed in the pre cyclosporin years 1970-84 (graft fail rate 6.63 grafts/100 graft years) were compared with 2644 grafts performed between 1985-94 (6.38). Removing death as a cause of graft failure shows the graft failure rate to have increased 24% from 2.69 graft failures/100 graft years in 1970-84, to a rate of 3.35 in 1985-94.



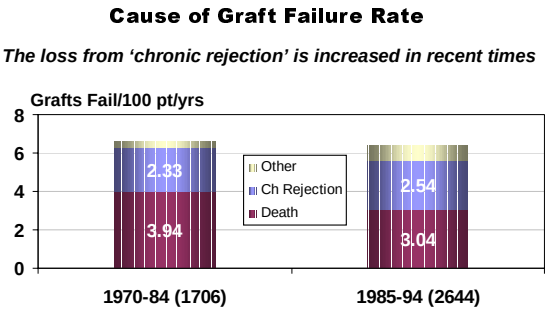


Figure 13.7

This increase is contributed to by a 9% increase in grafts coded as lost from 'chronic rejection' (graft failure rate 2.33 increasing to 2.54). As the coding options in the Registry for failing grafts are restricted and did not include drug toxicity, any slowly failing graft with scarring on a biopsy is likely to have been coded as 'chronic rejection'.

Univariate Analysis	
Living donor source	p=0.0002
Donor age <50 years	p=0.0002
Donor not of 'marginal' status	p=0.002
Recipient never smoked	p=0.0001
Donor death due to trauma	p=0.02
Not treated with Cyclosporin	p=0.0004

Figure 13.8

Individual variables were assessed in five year survivors with a functioning kidney by plotting graft survival curves and using log rank analysis to determine significance of any difference. Univariate analysis of factors proving to significantly favour graft survival is shown.

Donor factors not significantly influencing outcome included oliguria, hypertension, a smoking history or terminal serum creatinine >120umol/L along with delayed graft function >7 days, use of antibody to treat rejection and the primary renal disease.

Cox Multivariate Regression Analysis		
Being on Cyclosporin at five years	1.90 (1.4 - 2.6) [Hazard ratio (95% confidence limits)]	p=0.000
Recipient smoking	1.86 (1.3 - 2.6)	p=0.000
Recipient age <20 years	1.55 (1.1 - 2.1)	p=0.007
Receipint age > 50 years	0.61 (0.5 - 0.8)	p=0.000
Donor age >50 years	1.51 (1.2 - 2.0)	p=0.002
Live donor source	0.67 (0.4 - 1.0)	p=0.05

Figure 13.9

A backwards-stepwise model of Cox multivariate regression analysis showed the factors listed to be associated with a significant effect on death censored graft survival in five year survivors.

The cohort receiving cyclosporin was shown to contain more smokers, to have worse HLA matching, to have received more marginal donors and to have older recipients than the comparative groups. These imbalances were all of marginal statistical significance.

The significantly deleterious effects on graft survival (non death censored) beyond 5 years of cadaveric donor source (fig 13.10), donor age >50 years (fig 13.11), recipient smoking (fig 13.12) and the use of cyclosporin (fig 13.13) are shown.

Figure 13.10

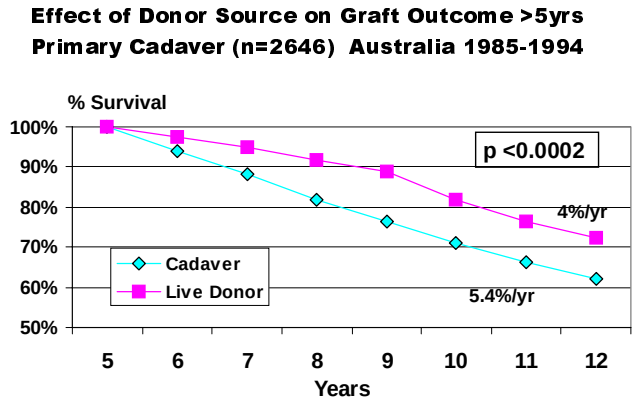


Figure 13.11

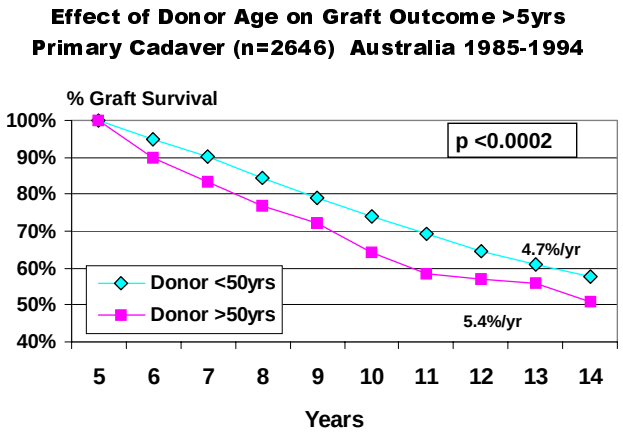


Figure 13.12

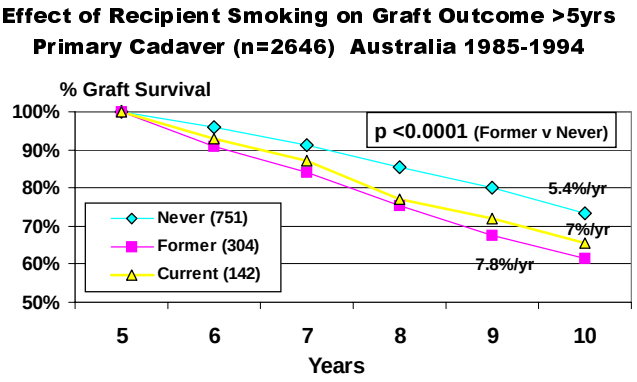
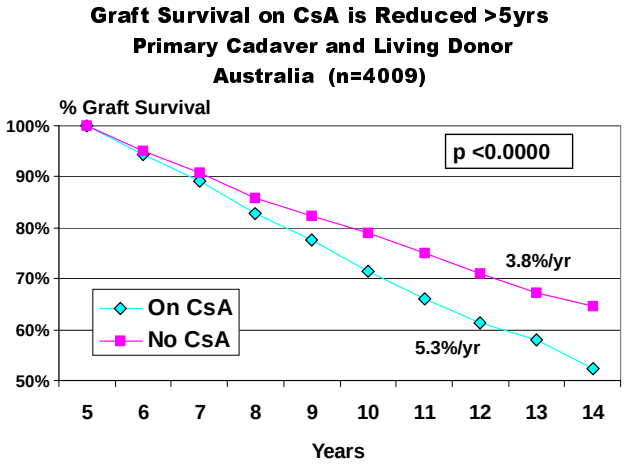


Figure 13.13



Summary

The rate of graft failure in five year renal transplant survivors appears to have been constant over the last 30 years but an analysis reveals that the 'constant' rate is the subject of two opposing influences. The death rate has fallen since 1984 due to an improvement in cardiovascular and malignancy outcome and this gain is countered by an increase in the rate of graft loss from 'chronic rejection' and other causes. The coding for rejection in this database is a surrogate for a slowly failing kidney for any reason which does not exclude drug toxicity. The identified variables impacting on death censored graft outcome include non-discretionary factors such as the donor and recipient age and the source of the kidney and two variables subject to discretion, smoking and the use of cyclosporin.