
CTS Collaborative Transplant Study

Newsletter 1:2005

February 1, 2005

We are starting the new year with a **complete update of all CTS website graphs**. Special attention was given to the **liver transplant** section, which has been considerably expanded from previously 66 to **now 247 graphs**. Analysis of your own center's data is based on the latest update you have provided.

The **Data Status Summary**, which was distributed with the November 2004 newsletter, was very well received. We will therefore maintain it as a **regular feature** and you will find it, again, attached to the current printout. The summary allows for quick orientation on your center's registration and follow up status. Please be reminded that a large fraction of incomplete data indicates that the website analysis of **your center's transplants** is currently not sufficient for analysis. This can be remedied by providing a **complete update** in time for the next quarterly sendout. Thank you for your understanding and cooperation.

The question as to why transplants from **unrelated living** kidney donors are performing **better** than transplants from cadaver donors continues to be the subject of discussions. We have pointed out in Newsletter 3:2004 that short ischemia or the absence of an HLA mismatch effect cannot be the reason. The effect of donor age was hinted at in that newsletter, but the repeated inquiries reaching us suggest that the point was not made sufficiently clear. We would therefore like to expand on this issue and provide further support for the **important role of donor age**.

In kidney transplants from **cadaver donors**, donor age is known to be an extremely important factor influencing graft outcome. As shown in Figure 1, graft survival **declines** with each decade of **increasing donor age**. Importantly, the same analysis of donor age in transplants from **related donor** kidney grafts is not nearly as impressive (Figure 2). Whereas transplants from young donors have approximately the same success rate, regardless of whether the donor organ came from a deceased or living donor, grafts from **older donors** clearly are **superior** if the donor was a **living related** donor.

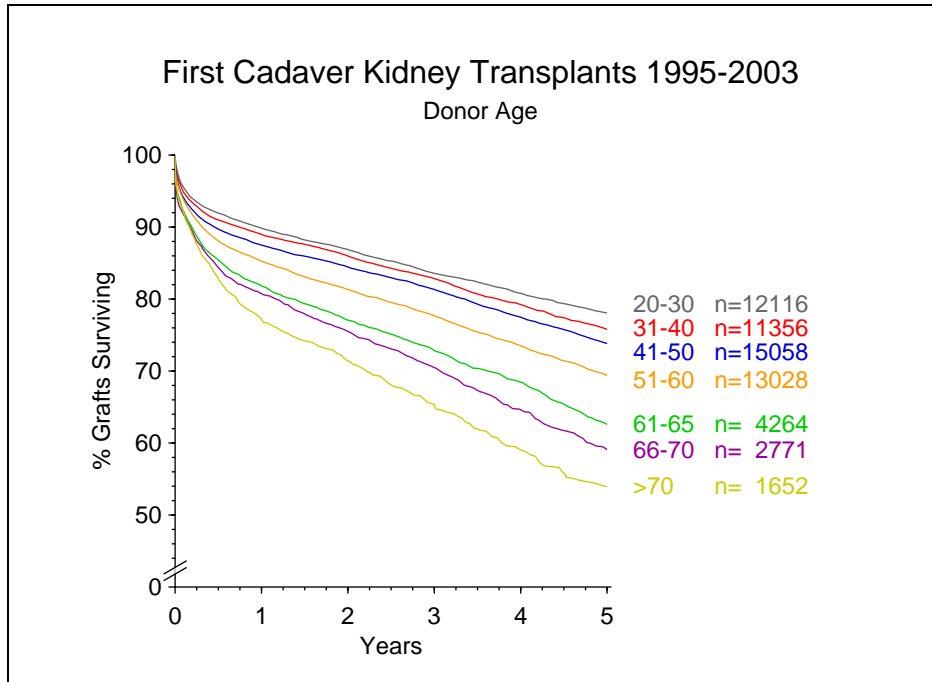


Figure 1

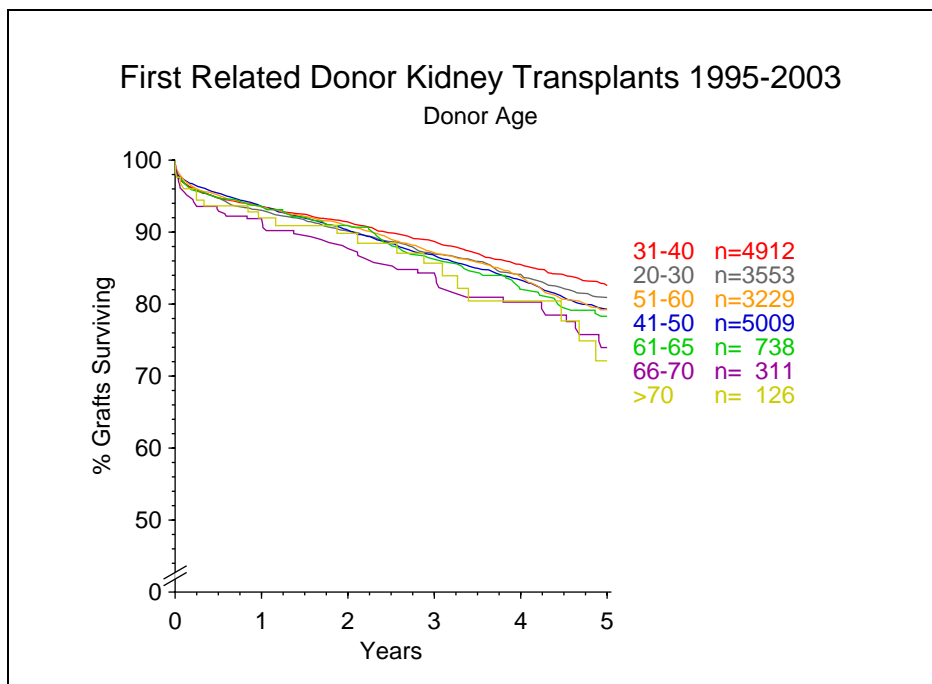


Figure 2

The results of transplants from **living unrelated** donors mirror those from living related donors. Increasing donor age up to the age of 70 is **not** associated with deteriorating graft survival (Figure 3).

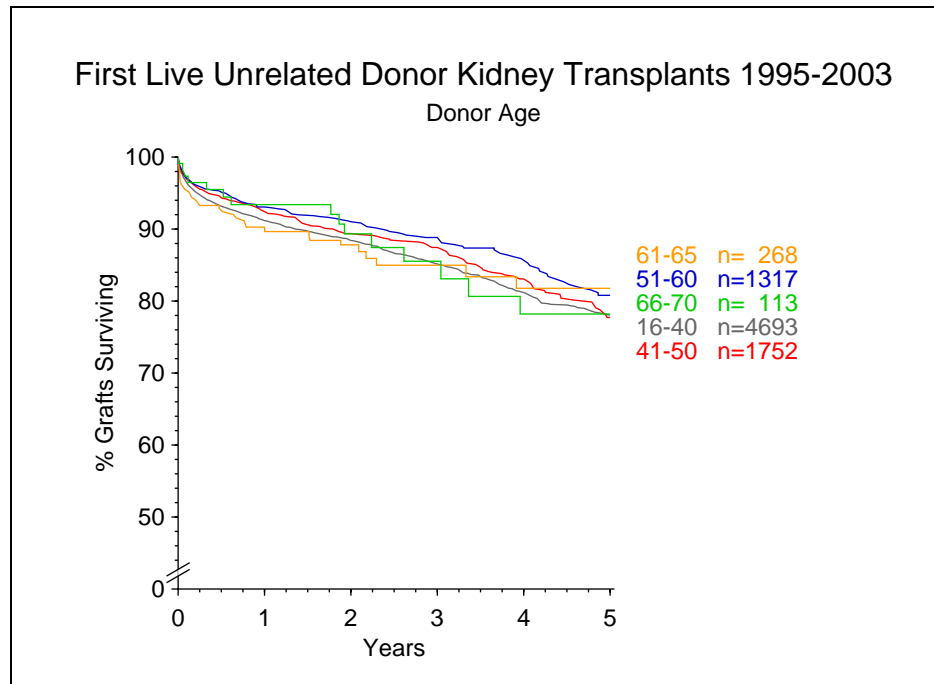


Figure 3

The most likely interpretation of these results is that living donors are **selected** for organ donation based on their **general status of health** (non-hypertensive, non-diabetic, no serious cardiovascular problems, etc.) whereas such selection is not made in the case of cadaver donors. In addition, it is likely that the process of **brain death**, which is associated with the release of cytokines, chemokines, etc., further contributes to the lower success rate of grafts from elderly cadaver donors. These results **contradict** claims that age per se (reduced nephron mass) causes decreased graft survival.

The CTS **Steroid Withdrawal Study**, which had the primary goal of finding out whether **long-term maintenance on steroid-free immunosuppression** could be successful, has now reached 8 years of reliable follow up. We recently completed an analysis of the available data and a manuscript is currently in press with the American Journal of Transplantation. The key survival results are illustrated in Figures 4 and 5. Because the study was **prospective but not randomized**, we had to compare the outcome in study patients with that of **matched controls** from the general CTS data base. The procedure was carried out in a very conservative fashion, selecting controls that had characteristics **at least as good as or better** than those of the study group. Although a full accounting of the details would go beyond the usual content of our newsletter, they will be contained in the forthcoming official publication. Considering the intention of our study, it would have been completely satisfactory if the outcome of study patients and controls had been identical. However, to our surprise, we found that patients in whom steroids were withdrawn did **significantly better** (Figures 4 and 5). Baseline immunosuppression consisted of **cyclosporine in 94 % of the patients**, indicating that these results are representative for cyclosporine-treated patient cohorts. Whether azathioprine or MMF was administered in addition to cyclosporine did not result in a significant difference.

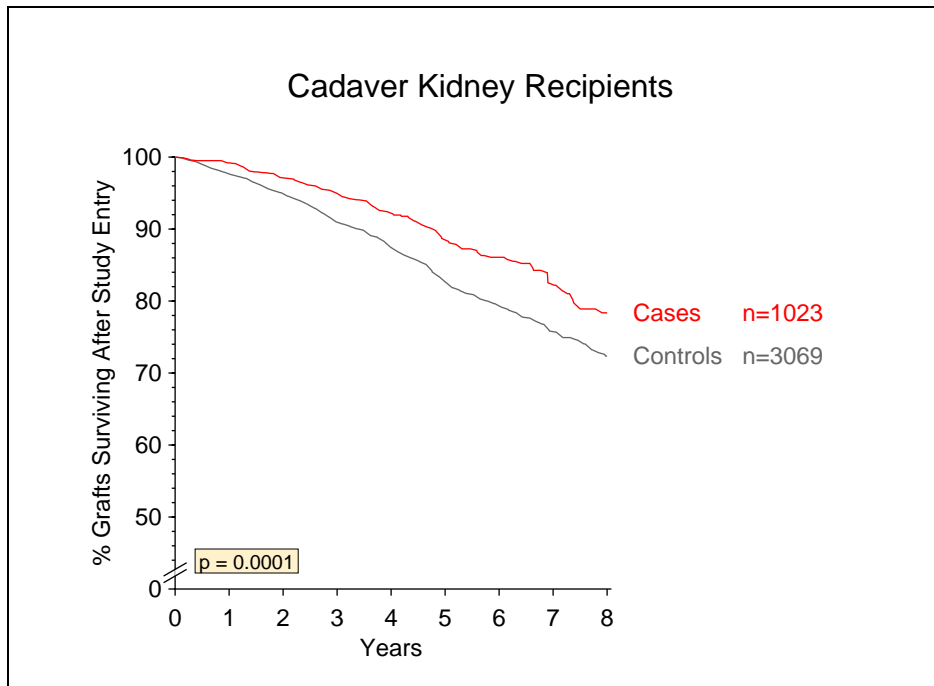


Figure 4

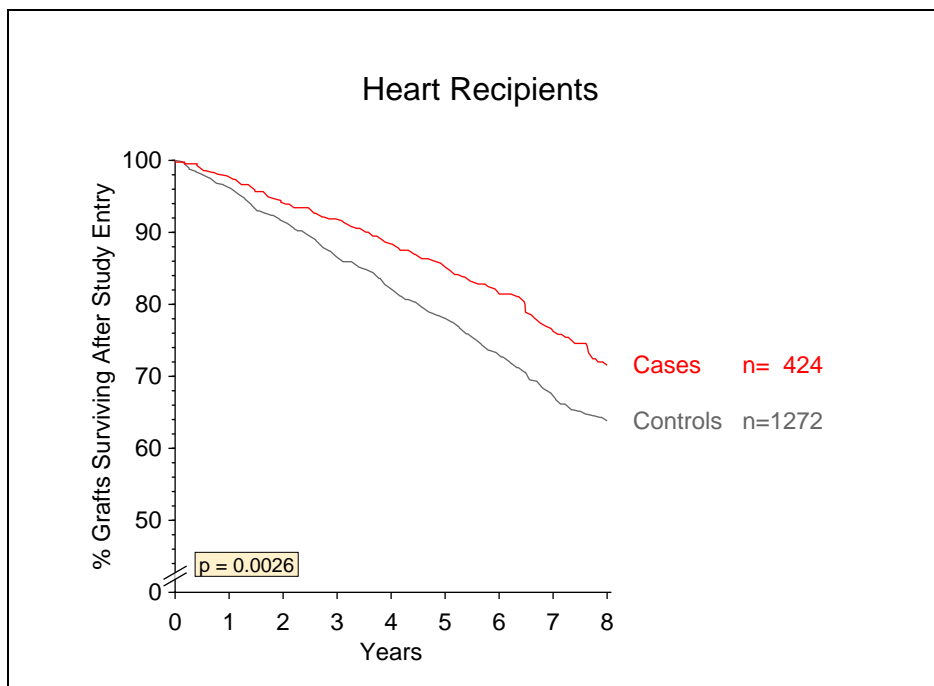


Figure 5

A number of additional findings, of great interest, emerged: The need for **rejection treatment** was **not higher** in patients in whom steroids were withdrawn as compared to control patients who continued on steroids. However, it must be pointed out that all patients in the current study had received **steroids for a minimum of six months** and steroids were **withdrawn slowly** according to the consensus protocol (Newsletter 3:1994). There was also no significant difference in the evolution of **serum creatinine** between controls and kidney recipients in whom steroids were withdrawn.

In an analysis of secondary outcome parameters, we found **small but significant advantages** in steroid-free patients with respect to **hypertension** and **hypercholesteremia**. Disappointingly, there was no difference in the rate of osteonecrosis. Perhaps the most interesting results were obtained in the analysis of posttransplant development of osteoporosis and cataracts. Whereas a significant advantage of steroid withdrawal was not apparent in the overall series, those patients in whom steroids were withdrawn **during the first post-transplant year** developed **osteoporosis and cataracts at a strikingly lower rate** than patients in whom steroids were withdrawn at a later time-point. The result stresses the importance of withdrawing steroids **relatively early** after transplantation. However, the low rejection rate in our study cohort suggests that the policy of treating all patients with steroids for a minimum of 6 months may have had a benefit with respect to the incidence of rejection.

We are very grateful to the CTS participants who supported this important project, which clearly established that **long-term maintenance** treatment on a **steroid-free cyclosporine** regimen yields **excellent results**.

Participants in the steroid withdrawal study:

Kidney Transplants: Barcelona, Spain, Hospital del Mar (Dr. Lloveras); Hospital Vall D'Hebron (Dr. Callis); Belo Horizonte, Brazil (Dr. Salamao Filho); Botucato, Brazil (Dr. Carvalho); Buenos Aires, Argentina, Cemic (Dr. Moreno), Instituto de Nefrologia (Dr. Casadei), Sanatorio Mitre, (Dr. Agost Carreno); Cardiff, UK (Dr. Moore); Cologne, Germany (Dr. Arns); Heidelberg, Germany (Dr. Tönshoff); Izmir, Turkey (Dr. Gurkan); Jena, Germany (Dr. Sperschneider); Ljubljana, Slovenia (Dr. Kandus); Mannheim, Germany (Dr. Schnülle); Marburg, Germany (Dr. Lange); Munich, Germany (Dr. Kuhlmann); New Lambton, Australia (Dr. Hibberd); Nottingham, UK (Dr. Rigg); Oviedo, Spain (Dr. Gomez); Pato Branco, Brazil (Dr. Engel); Portland, Oregon, USA (Dr. Norman); Prague, Czech Republic (Dr. Ivaskova); Quebec, Canada (Dr. Lachance); Santander, Spain (Dr. Arias); St. Gallen, Switzerland (Dr. Garzoni); Szeged, Hungary (Dr. Szenohradzski); Tours, France (Dr. Lebranchu); Ulm, Germany (Dr. Abendroth); Valencia, Spain (Dr. Sanchez-Plumed); Zürich, Switzerland (Dr. Binswanger, Dr. Weber).

Heart Transplants: Edmonton, Canada (Dr. Modry); Essen, Germany (Dr. Jakob); Lausanne, Switzerland (Dr. Seydoux); London, Canada (Dr. McKenzie); Melbourne, Australia (Dr. Esmore); Montreal, Canada (Dr. Carrier); Oklahoma City, USA (Dr. Nelson); Paris, France (Dr. Amrein); Perth, Australia (Dr. O Driscoll); Prague, Czech Republic (Dr. Malek); Sydney, Australia (Dr. Keogh); Vancouver, Canada (Dr. Ignaszewski); Zürich, Switzerland (Dr. Turina).

I would like to conclude this first newsletter of the year with my usual **appeal for honest and complete reporting**. Our study goals are strictly scientific and we can learn from past experience only if each contributor provides good quality data. **Thanks are due to all of you for your magnificent support of this international research project.**

Sincerely yours,

Gerhard Opelz

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