Long-Term Pancreas Allograft Survival in Simultaneous Pancreas-Kidney Transplantation by Era

UNOS registry analysis

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OBJECTIVE — To determine whether short-term improvement in pancreas graft survival with simultaneous pancreas-kidney (SPK) transplants translated into improved long-term survival, then to examine the implications of that determination.

RESEARCH DESIGN AND METHODS — We analyzed data for 14,311 diabetic patients who received a first SPK transplant between October 1987 and November 2007, using Kaplan-Meier analysis for graft survival rates and Cox regression analysis for year-of-transplant effect.

RESULTS — Overall, from 1995 to 2004, 5-year pancreas graft survival stayed about the same (70–71%). Limiting analysis to grafts that survived more than 1 year, 5-year survival from 1987 to 2004 ranged from 80 to 84%. With 1987–1989 as reference, the adjusted hazard ratio for graft failure by year of transplant increased to 1.49 (95% CI 0.97–2.30) in 2000–2004.

CONCLUSIONS — Long-term pancreas graft survival has remained unchanged despite the dramatic decreases in technical failures and early acute rejection rates that have contributed to prolonged SPK graft survival.

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Simultaneous pancreas-kidney (SPK) transplants account for over 78% of current pancreas allografts (1–3). Expectations for SPK started high, especially when technical and immunosuppressive advances yielded marked improvements in 1-year and 3-year graft survival rates through 2004, as shown on the International Pancreas Transplant Registry (IPTR) Web site (2) and by previous studies (3–6). But the focus of these studies, like clinical focus, has been on relatively short-term survival. The question remains: Has that translated into improved long-term—5-year-plus—SPK pancreas graft survival? This study's objective was to determine the answer, then examine the implications. We also examined causes of chronic pancreas graft dysfunction and other factors that may influence evaluation of SPK as therapy for diabetes.

RESEARCH DESIGN AND METHODS

— We analyzed data collected by the United Network for Organ Sharing (UNOS) for 14,311 diabetic patients who received a first SPK transplant between October 1987 and November 2007, including follow-up through November 2007. Patients (n = 147) whose follow-up data were missing were excluded.

Baseline characteristics were compared using the Kruskal-Wallis test for continuous variables, the χ^2 test for categorical variables, Kaplan-Meier analysis and log-rank tests to calculate and compare pancreas graft survival rates, and Cox proportional hazard models to estimate year-of-transplant effect—adjusted for potential confounding factors of donor and recipient demographics, duct management, venous management, preservation time, and number of HLA mismatches. Patients were grouped by date of transplant into five eras: 1987–1989, 1990–1994, 1995–1999, 2000–2004, and 2005–2007. Pancreas graft survival was calculated for the full dataset, then—to minimize effects of first-year technical failure and acute rejection—recalculated for grafts surviving over 1 year. We used STATA version 9.0 (Stata, College Station, TX) for all statistical analyses.

RESULTS

— Compared with other era's recipients, those in 2005–2007 were more likely to be older (41.5 ± 8.4 vs. 34.8 ± 6.6 years in 1987–1989, $P < 0.001$) and male (63.7 vs. 58.0% in 1987–1989, $P = 0.003$), were less likely to be white (73.1 vs. 95.1% in 1987–1989, $P < 0.001$), had more donor-recipient HLA mismatches (4.5 ± 1.2 vs. 4.2 ± 1.2 in 1987–1989, $P < 0.001$), and had younger donors (25.9 ± 10.3 vs. 27.2 ± 1.3 years in 1987–1989, $P < 0.001$).

Although SPK pancreas graft survival improved significantly between 1987 and 1995, it has not improved since 1995 (Fig. 1*A*). These rates were similarly high among recipients transplanted in the eras 1995–1999, 2000–2004, and 2005–2007. Limiting analysis to grafts surviving over 1 year, 5-year SPK survival rates after 1990 were almost identical in the different eras (Fig. 1*B*), and SPK offered much better survival than pancreas-after-kidney (PAK) transplant and pancreas transplant alone (PTA): 10- and 15-year survival was 62 and 40%, respectively, for SPK only 36 and 11% for PAK, and 32 and 18% for PTA (3).

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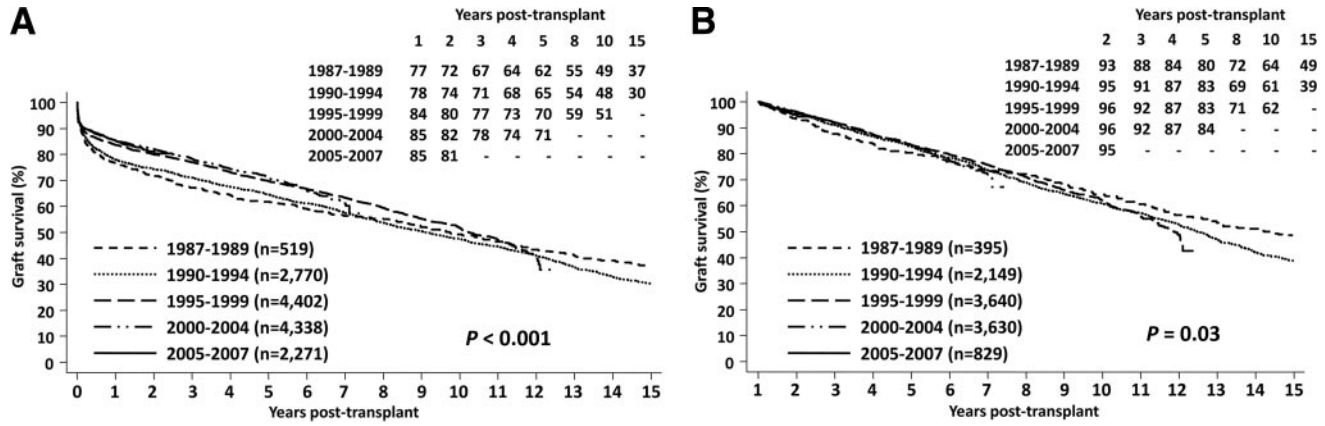

Figure 1—*A: Pancreas graft survival by era for all transplants, 1987–2007: UNOS registry analysis.* B*: Pancreas graft survival by era for transplants surviving more than 1 year, 1987–2007: UNOS registry analysis.*

Looking only at grafts surviving over 1 year—and after considering potential confounders—there was a mild risk association (slight increase in graft-loss rate) for recent-era transplants compared with those in 1987–1989. By year of transplant, adjusted hazard ratio for overall loss of grafts surviving over 1 year in eras 1990–1994, 1995–1999, 2000–2004, and 2005–2007 was 1.20 (95% CI 1.03–1.41), 1.17 (0.99–1.39), 1.26 (1.04–1.54), and 1.49 (0.97–2.30), respectively.

During the first year, posttransplant technical failures caused 66% of graft losses. As posttransplant time progressed, chronic rejection quickly replaced technical failure as the major cause of graft loss. Chronic rejection caused 50% of graft losses between 1–10 years and 54% after 10 years.

CONCLUSIONS — After 1990, graft survival rates were strikingly similar during this study's different eras. Pancreas survival showed no long-term improvement, and risk of failure for grafts surviving over 1 year increased slightly for recent transplants.

SPK transplantation and pancreas transplantation in general may be undergoing clinical reevaluation. According to the Organ Procurement and Transplantation Network (OPTN), the total number of SPK, PAK, and PTA procedures has declined each year from 1,484 in 2004 to 1,233 reported so far for 2009. With some fluctuations, SPK transplants have declined from 915 in 2000 (a spike of 924 in 2006) to 854 (so far) in 2009 (1).

Yet SPK offers distinct quality-of-life (QOL) benefits: freedom from self-administered insulin, more stable blood glucose levels, and no risk of hypoglycemia (7–9). Furthermore, right now there seems to be no realistic alternative that affords the same QOL as SPK for type 1 diabetic patients with end-stage renal disease. Survival is comparable for living-donor kidney transplants and SPK transplants (10), but kidney transplants alone offer diabetic individuals only marginal QOL improvement in freedom from insulin injection or having more stable glycemic control; and the supply of living donor kidneys is still limited.

The 1-year-survived chronic pancreas graft failure rate at 10 and 15 years was lowest with SPK (28 and 60%, respectively) compared with PAK (64 and 89%) and PTA (68 and 82%) (3)—an important consideration because monitoring of function or biopsy of an SPK kidney may also provide warning of possible pancreas graft chronic rejection early enough for more timely and effective intervention, a benefit not obtained with PAK or, obviously, PTA (11). This predictive feature of SPK is slightly compromised because, although (excluding first-year graft failures) 5-year pancreas and kidney survivals were comparable (84 and 83%, respectively), 10-year survival was 63% (pancreas) and 59% (kidney) (3). Nevertheless, early warning should, intuitively, result in improved long-term graft survival. The reason it has not is because, as of now, there is no established, even remotely definitive treatment for chronic rejection—which, as we have shown above, is the major long-term cause of graft dysfunction and loss.

That leads to the real implication of our study's new finding. There will evidently be no "natural" improvement in long-term pancreas graft survival that might be expected after such great short-term improvement. So the next step must be the same level of concentration on elucidating the mechanism of chronic rejection and developing a therapy as effective as that for reducing short-term graft loss.

Meanwhile, the clinical decision as to whether the QOL benefits and predictive feature of SPK offset any contraindications should be weighed for each patient, individually, and the new knowledge that, right now, long-term survival has not improved constituting one more factor to be weighed.

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