Guidance on the Benefits of Pancreas after Kidney (PAK) Transplantation

Contents

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Abstract

A prior publication suggested that a sequential pancreas transplant after a kidney transplant (PAK) is associated with worse short-term patient survival and indifferent long-term patient survival compared to patients on the waitlist,[1] but the data supporting these associations may be subject to an important selection bias due to the waiting list used for analysis and an inadequate follow-up period.[2] In this Organ Procurement and Transplantation Network (OPTN) database analysis, which attempts to correct for these factors, PAK and simultaneous pancreas and kidney (SPK) patient outcomes were similar, and both options represented a significant improvement over the excess patient mortality of uremic diabetic patients on dialysis. Additionally, PAK recipients following living donor kidney transplants seemed to have better pancreas graft survival outcomes than PAK recipients following deceased donor kidney transplants and the best kidney transplant outcomes were observed in the PAK after living donor kidney combination. Thus, PAK transplants are currently underutilized and should be considered as a treatment option for uremic diabetic patients.

Introduction

Beginning in 2004, there has been a profound decline in the number of pancreas transplants performed in the United States.[3] There is a perception in the pancreas transplant community that the overall decline in pancreas transplantation, particularly PAK transplantation, occurred immediately following publication of a study funded by the National Institutes of Health in a Journal of the American Medical Association (JAMA) article published in 2003.[4] This study was a retrospective observational study performed as a query to the OPTN database comparing survival rates at 1 and 4 years post-transplant and the relative risk of death between patients on the waiting list and pancreas transplant recipients. In that study, the authors concluded that patients receiving solitary pancreas transplants, including PAK, had an increased mortality risk compared to those remaining on the waiting list and receiving conventional medical therapy.[5] A subsequent rebuttal study employing a similar study design came to a contradictory conclusion indicating that PAK transplanted recipients did not have increased mortality compared to those waiting for a PAK.[6] Although there have been rebuttals and reviews of the JAMA paper, none seem to have helped increase the number of PAK transplants.

Pancreas transplantation is frequently considered only a life-enhancing rather than a life-saving procedure. However, abundant evidence indicates that, similar to kidney transplantation, successful pancreas transplantation is clearly life-extending.[7] For example, the University of Wisconsin published their experience with one thousand kidney-pancreas transplantations with 22 year follow-up.[8] In this

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[1] Venstrom JM, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. JAMA 2003; 290 (21): 2817-23.

[2] Gruessner RWG, Sutherland DER, Gruessner AC. Mortality assessment for pancreas transplants. Am J Transplant 2004; 4: 2018-2026.

[3] Stratta, Robert J., Jonathan A. Fridell, Angelika C. Gruessner, Jon S. Odorico, and Rainer W.g. Gruessner. Pancreas transplantation: A Decade of Decline. Current Opinion in Organ Transplantation 21, no. 4 (August 2016): 386-92. doi:10.1097/mot.0000000000000319.

[4] Ibid.

[5] Venstrom, 2819-2820.

[6] Gruessner, 2018-2026.

[7] Fridell, Jonathan A., and John A. Powelson. Pancreas after kidney transplantation. Current Opinion in Organ Transplantation 20, no. 1 (February 2015): 113. doi:10.1097/mot.0000000000000160.

[8] Sollinger HW, Odorico JS, Becker YT, D'Alessandro AM, Pirsch JD. One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. Ann Surg. 2009 Oct;250(4):618-30. PubMed PMID: 19730242. Epub 2009/09/05. eng.

report, patient survival following transplantation of both a kidney and a pancreas was dramatically superior to all other options for type 1 diabetic uremic patients, particularly cadaveric renal transplantation and dialysis.[9] Although not evident for the first 4 to 5 years (beyond the 4 year interval of the prior mentioned publications), with the extended follow-up in this particular study the patient survival following simultaneous pancreas and kidney transplantation (SPK) is even remarkably superior to that of Type 1 diabetic uremic recipients undergoing living donor renal transplantation alone, supporting the fact that freedom from diabetes has a clear survival advantage.[10,11] Figure 1 shows the relative patient survival of SPK, live donor kidney (LD), deceased donor kidney (DD), and dialysis (HD) originally shown in the Wisconsin study.

Figure 1: Patient Survival in Wisconsin Study[12]
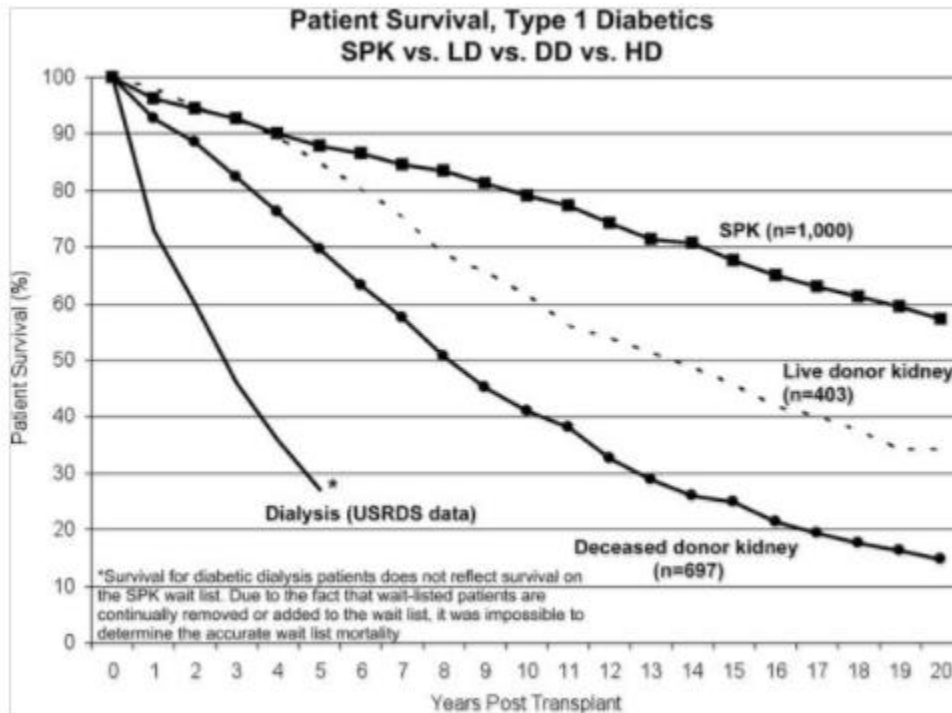
Furthermore, if a suitable diabetic uremic patient is evaluated for transplantation, they would have historically been offered the choice between a SPK transplant or, if they had a suitable living donor, living donor renal transplantation followed by PAK. Since this is the actual starting point, the relevant waiting list survival to consider is actually that of a candidate that requires both a kidney and a pancreas: i.e., on the waitlist for an SPK, not the survival of a renal transplant recipient waiting for a pancreas alone as was used in the JAMA publication.[13] If they ultimately no longer require dialysis and are also not diabetic, there would be a greater patient survival advantage compared to remaining diabetic but free from renal failure.

The study described in this guidance document was intended to reproduce the original study from 2003 adding an additional waiting list comparison group (PAK transplanted group being compared to waitlisted

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[9] Ibid.
[10] Ibid.
[11] Stratta, 390.
[12] Reproduced with permission from Author(s). One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. Annals of Internal Medicine. 2009; vol: 250-4. ©American College of Physicians.
[13] Venstrom, 2818.

SPK candidates), while also looking at kidney and pancreas graft survival and extending the survival analyses to 10 years.

Background

1) Methods

UNOS staff analyzed the OPTN database of candidates who were registered from January 1st, 1995 to December 31st, 2010 for an SPK transplant or a PAK transplant. The analysis excluded pediatric candidates (age < 18) and recipients who had a multi-organ transplant or a previous transplant. Recipients who received a pancreas and a kidney at the same time from two different donors were also excluded from the analysis. After these exclusions, the cohort consisted of 25,361 patients. Of these patients 19,725 were waiting for an SPK and 12,308 received an SPK. Additionally, 5,636 candidates were waiting for a PAK and 3,358 received a PAK. PAK candidates were defined as receiving a kidney and waiting for a pancreas transplant. Pancreas graft outcomes were determined from graft failures defined by individual centers as reported to UNOS.

The analysis did not exclude PAK candidates with a creatinine greater than 2 mg/dL. Because creatinine was not a required field before October 1999, excluding candidates with creatinine values above 2 mg/dL would incorrectly assume that all of those with a missing creatinine had values less than 2 mg/dL. Therefore to reduce bias, it is necessary to include all candidates on the waiting list and transplanted before October 1999, regardless of creatinine values.

Social security death master file (SSDMF) supplanted all death data. If transplanted recipients were not reported dead to the OPTN or not located in the SSDMF, then they were considered alive and were censored at 3,650 days. Candidates who were not transplanted were also censored at 3,650 days plus median waiting time to transplant for the anticipated transplant type. The analysis compared outcomes for SPK waiting list candidates to SPK and PAK transplant recipients. Kaplan-Meier log-rank tests were used to test differences in unadjusted waitlist and post-transplant mortality.

The analysis considered the impact of each transplant type:

- Deceased donor kidney alone
- Deceased donor SPK
- Living donor kidney alone
- Living donor kidney followed by a deceased donor pancreas
- Deceased donor kidney followed by a deceased donor pancreas

The impact for each of these transplant types was assessed considering kidney and pancreas graft survival as well as patient mortality. To accurately measure kidney graft survival, the PAK group was subdivided into 4 groups by kidney donor type:

1. Deceased donor kidney and pancreas
2. Deceased donor kidney with no pancreas
3. Living donor kidney and pancreas
4. Living donor kidney with no pancreas

A cox-proportional hazards model was used to determine if receiving a pancreas after a living or a deceased donor transplant impacted kidney graft survival, while a log-rank test was used to determine if receiving a living donor kidney increased graft survival of the pancreas compared to receiving a deceased donor kidney.

A time dependent covariate analysis using cox-proportional hazard model was used to determine survival from listing for each transplant type. The models also allowed piecewise testing of mortality outcomes during 5 specific clinical time periods (0 to 90 days, 91 to 365 days, 1 to 3 years, 3 to 5 years, 5 to 10 years). The modeling followed the transplanted group until death or 10 years post-transplant. For the waitlisted candidates who did not receive a transplant, follow-up

time was 10 years plus median time to transplant for the anticipated transplant type. Hazard ratios were calculated to compare the risk of mortality within each time period, by comparing the average mortality for waitlisted candidates to the average mortality for transplanted recipients. SPK and PAK analyses were adjusted for year of listing and the PAK analysis for kidney donor type (living or deceased).

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc. Cary, NC) and R 3.3.2.

2) Results

The SPK and PAK waitlisted candidate groups were similar, yet based on the large number of subjects, it is not surprising there were differences in the demographics within each group. Table 1 shows the patient demographics for each group. The median age at listing was 40 for SPK candidates and 42 for PAK candidates. For both groups, most candidates were male and Caucasian. The median time to transplant was 430 days for SPKs and 465 days for PAKs.

**Table 1: Demographic Information by Expected Transplant Procedure Type.**

Variable	PAK N=5,636	SPK N=19,725	P overall
Transplanted:			<0.001
No	2,278 (40.4%)	7,417 (37.6%)	
Yes	3,358 (59.6%)	12,308 (62.4%)	
GENDER:			0.016
Female	2,403 (42.6%)	8,053 (40.8%)	
Male	3,233 (57.4%)	11,672 (59.2%)	
Ethnicity:			<0.001
White	4,728 (83.9%)	14,629 (74.2%)	
Black	480 (8.52%)	2,956 (15.0%)	
Hispanic	339 (6.01%)	1,681 (8.52%)	
Asian	43 (0.76%)	229 (1.16%)	
Other	46 (0.82%)	230 (1.17%)	
Listing Age	41.8 (8.10)	40.2 (8.42)	<0.001
ABO:			<0.001
A	2,265 (40.2%)	7,145 (36.2%)	
AB	220 (3.90%)	721 (3.66%)	
B	645 (11.4%)	2,383 (12.1%)	
O	2,506 (44.5%)	9,476 (48.0%)	

Figure 2: SPK Waitlist survival (gray) and post-transplant survival for PAK (blue) and SPK post-transplant recipients (green).
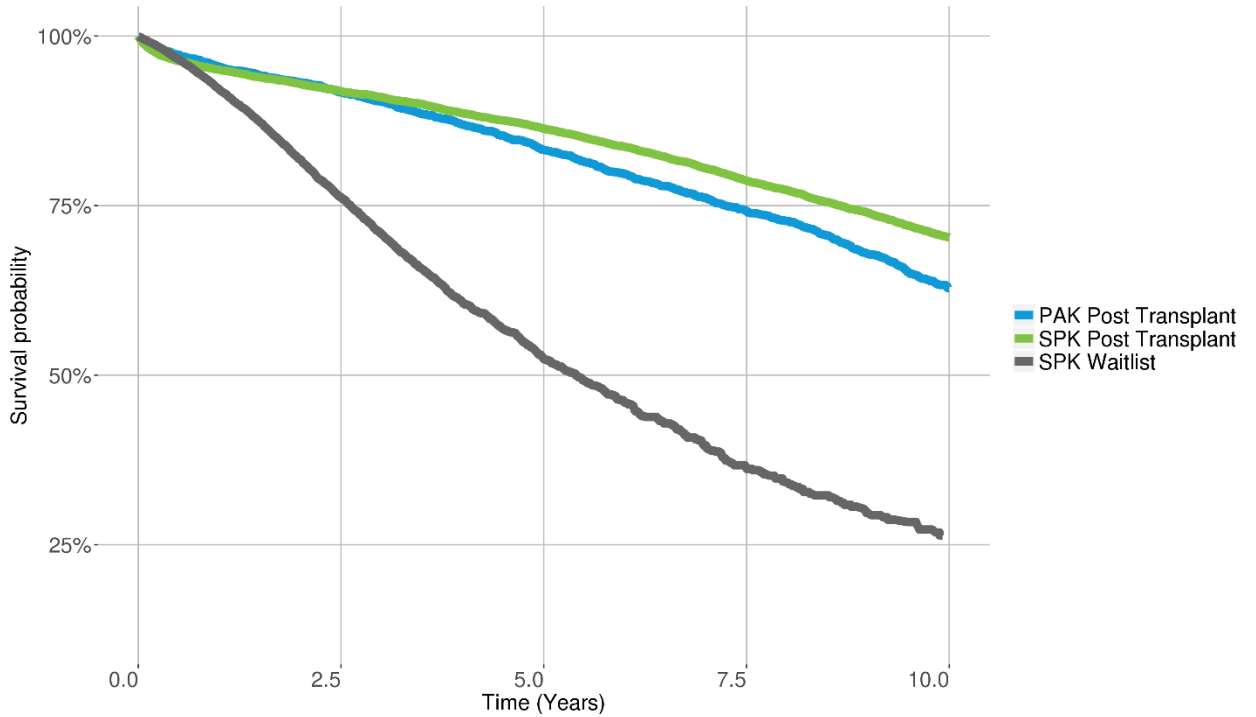
Waitlist and post-transplant survival by transplant procedure type are shown in Figure 2. The 10 year waitlist survival for the SPK waitlist group was dramatically lower than either of the transplanted groups (PAK or SPK). At 10 years, the survival for waitlisted SPK candidates was 26.4%. Post-transplant survival was very similar through 5 years for both groups (82.9% PAK and 86.4% SPK) but diverges thereafter, and at 10 years post-transplant SPK recipients had higher survival than PAK recipients (p < 0.001, PAK 63.2 % and SPK 70.3%). From the graphic above we can see that both transplanted groups had markedly higher patient survival compared to the waitlisted SPK group (PAK TX 63.2% vs. SPK WL 26.4% and SPK TX 70.3% vs SPK WL 26.4%).

Figure 3: Kidney graft survival (left) and pancreas graft survival (right) for SPK and PAK candidate groups
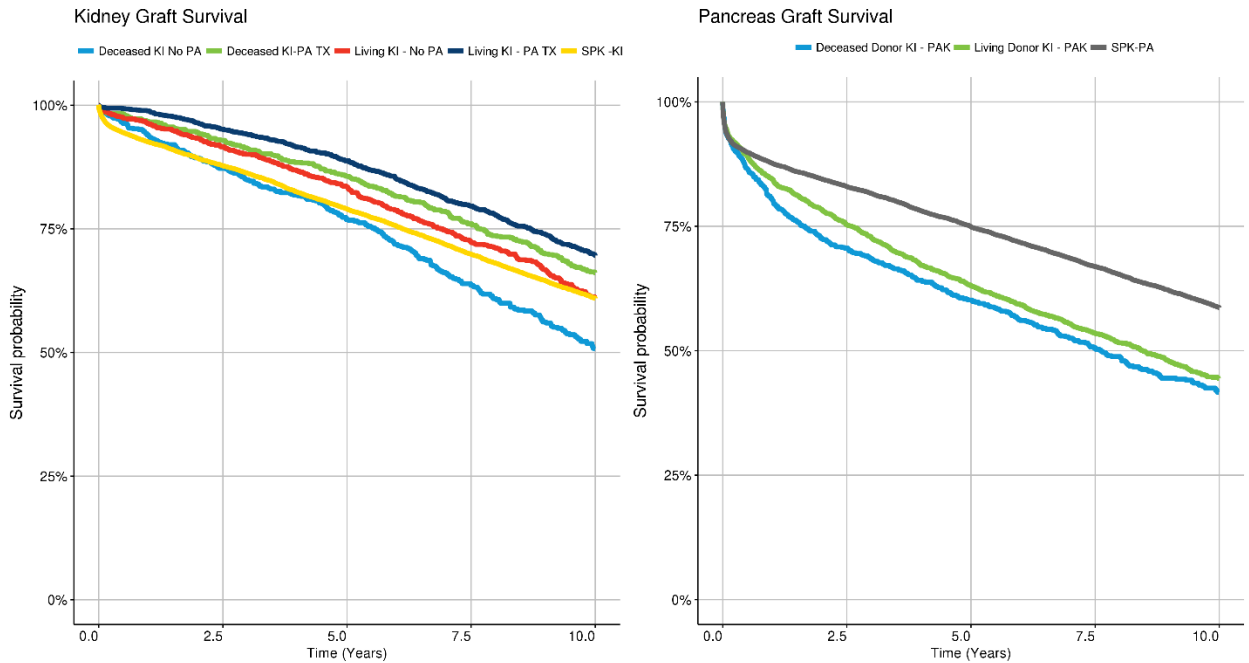

Kidney and pancreas graft survival for both PAK and SPK transplant types are shown in Figure 3. The cox-proportional hazard model comparing kidney donor type (living vs. deceased) and whether PAK candidates received a pancreas shows that receiving a living donor kidney was associated with improved kidney graft survival as expected (p-values < 0.001). Receiving a subsequent pancreas was also associated with improved long term kidney graft survival (p-value < 0.001) versus not receiving a subsequent pancreas transplant, regardless of whether the kidney was from a deceased or living donor. The interaction between donor type and pancreas transplantation was not significant (p-value = 0.09).

Ten-year kidney graft survival was 69.7% for recipients who received a living donor kidney and a pancreas compared to 61.1% for those who only received a living donor kidney. Additionally, 10-year kidney graft survival for recipients who received a deceased donor kidney transplant and then a pancreas was 66.1%, while kidney graft survival for recipients who just received a deceased donor kidney was 50.8%. SPK kidney graft survival was 61% at 10 years. Similarly for pancreas, a cox- proportional hazard model was used to determine if receiving a living donor kidney increased pancreas graft survival. At 10 years, PAK recipients who received a living donor kidney had a pancreas graft survival of 44.4% compared to 41.7% for those PAK recipients who received a deceased donor kidney (p < 0. 001). In comparison, SPK pancreas graft survival was 58.7% at 10 years

Figure 4 shows the hazard ratio of patient survival from listing by SPK and PAK transplant types. Panel one compares SPK recipients to waitlisted (WL) SPK candidates who did not receive a transplant (WL SPK No TX). The second panel compares PAK recipients to waitlisted SPK candidates who did not receive a transplant (WL SPK No TX). This comparison is particularly important because it shows the benefit of receiving a PAK compared to candidates who receive neither a kidney nor a pancreas.

Figure 4: Patient Survival from Transplant
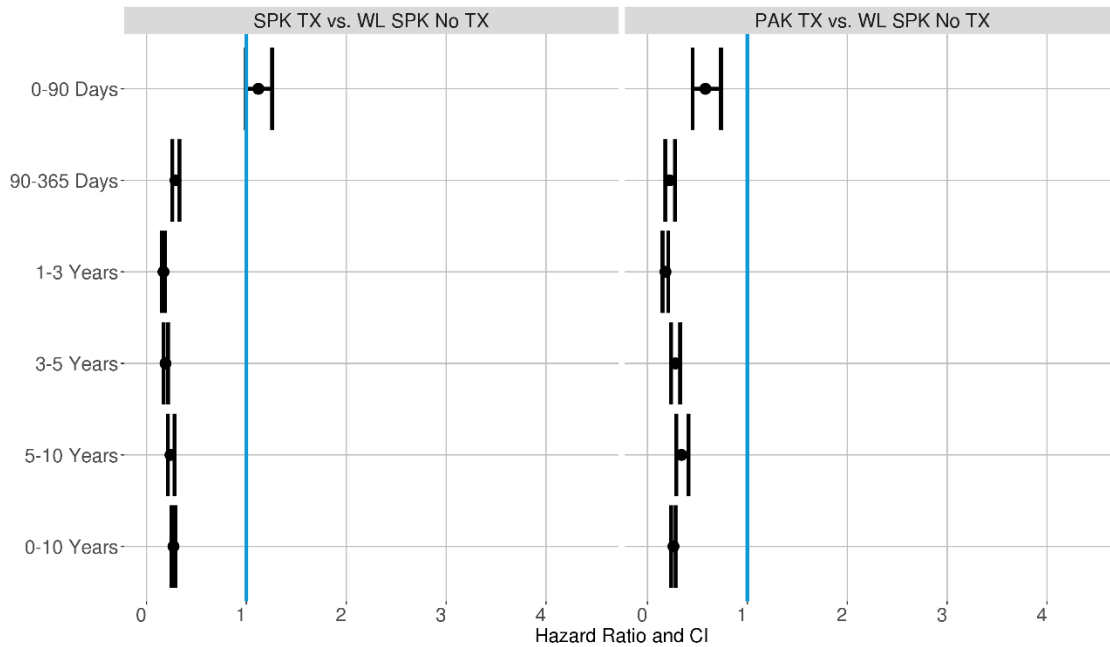
In Figure 4, at each time point the hazard ratio is comparing the number of candidates who died on the waitlist over the number of candidates who were waiting at that time point to the number of recipients who died during that time point over the number of people transplanted in that time frame. A ratio between 0 and 1 indicates a benefit of transplantation compared to staying on the waitlist. A ratio greater than one favors conventional therapies over transplantation. If the confidence intervals overlap with 1, transplantation as a treatment option is considered neutral.

Among the SPK group, survival at 90 days demonstrated no benefit of transplant compared to staying on the waitlist (HR =1.12, CI = [0.996, 1.25]). However, after the first 90 days, there was overwhelming statistical support for getting the SPK transplant from 90 to 365 days (HR =0.29, CI = [0.25, 0.33]), 1 to 3 years (HR =0.17, CI = [0.15, 0.18]), 3 to 5 years (HR =0.19, CI = [0.17, 0.21]), and 5 to 10 years (HR =0.24, CI = [0.21, 0.28]). Among the 7,417 SPK candidates who did not get a transplant 2,881 died compared to 12,308 number of SPK recipients of which 3,049 died.

Although not shown when comparing PAK recipients to PAK candidates (those who received a kidney and are waiting for a pancreas) in the first 90 days, the hazard of death post-surgery was 3.1 CI [2.3-4.0] times greater than staying on the waitlist. Although the hazard ratio for the first 90 days demonstrates that there is an increased risk associated with transplantation, it is important to note that there were only 13 deaths within 90 days of PAK transplant out of 3,358 PAK transplants. From 90 to 365 days the hazard was 1.19 CI [0.92-1.53], and from 1 to 3 years the hazard fell to 1.0 CI [0.81-1.23]. Longer term, the hazard of death from 3 to 5 years was 1.17 CI [0.93-1.45], and from 5 to 10 years was 1.07 CI [0.84-1.37]. Overall 314 died out of 2,278 while waiting for a pancreas after receiving a kidney transplant, compared 953 who died out of the 3,358 post-transplant recipients for PAKs.

When comparing PAK recipients to SPK waitlisted candidates who did not receive a transplant there was support for PAK transplant at each time interval. Specifically, at 90 days the hazard was 0.58 CI [0.45-0.73], then until one year (90 to 365 days) the hazard was HR = 0.22 CI [0.17-0.27], after one year (1 to 3 years) the hazard was 0.18 CI [0.15-0.20]; at 3 to 5 years it was 0.28 CI [0.23-0.32] and the 5 to 10 year hazard was 0.34 CI [0.28-0.41]. A total of 953 recipients died after PAK transplants out of 3,358 transplants at 10 years compared to 2,881 SPK candidates out of 7,417 SPK candidates who were waiting for a transplant.

Figure 4 indicates that PAK transplant recipients who receive both organs have an increased survival advantage compared to uremic candidates who receive neither a pancreas nor a kidney (2nd panel). Moreover, compared to uremic diabetic waitlisted patients, SPK and PAK recipients showed similar overall patient survival benefits (1st panel versus 2nd panel, Figure 4).

Recommendation

From a patient survival outcome perspective, PAK transplants are an excellent alternative to SPK transplants for uremic diabetic patients, particularly if the SPK waiting time is expected to be > 1 year and the recipient has potential living kidney donors. Given the potential benefits of receiving a PAK for uremic diabetic patients, as well as the risks of staying on the waitlist, we recommend the use of PAK transplants for candidates who qualify and would benefit.

Conclusion

PAK and SPK result in similar patient survival, and both outcomes are superior to kidney transplantation alone.[14] Ultimately, achieving dialysis and insulin independence should be the goal for type 1 diabetic uremic patients seeking transplantation therapy, as this provides the optimal patient survival benefit.[15] If achieving dialysis and insulin independence is the ultimate goal, patients should be offered either: 1) living donor kidney followed by pancreas transplantation if medically suitable and no contraindications have developed in the interim, or 2) SPK transplantation, if no living donor is available, the patient desires one operation or the expected waiting time is short. Both options provide excellent kidney graft survival and the possibility of potential preemptive kidney transplantation, and freedom from diabetes. In centers and regions where the waiting times for an SPK can be quite long, a PAK transplant can afford a patient a much shorter period on the waiting list (patient survival beyond one year on the SPK waiting list deteriorates rapidly). Every combination of a living donor kidney transplant followed by a PAK would also result in a donor kidney returning to the cadaveric donor pool for kidney transplant recipients. Elimination of dialysis and insulin requirements should be the dual goals for all medically suitable patients with uremic type-1 diabetes, whether that is achieved with a PAK or SPK.

This guidance extends beyond the original JAMA publication by extending the time frame from 4 to 10 years and looking at a new comparison for the PAK group (PAKs vs WL SPK candidates). PAK transplants are missed opportunities to offer appropriate candidates pancreas transplantation. The decline in PAK transplantation is clearly a leading contributor to the decreased volume trend in pancreas transplantation overall and represents an important opportunity for increasing the number of pancreas transplants.

A general limitation of the analysis is picking an appropriate comparison group for transplanted PAK recipients. There can be several different comparisons groups such as kidney alone transplants with diabetes and no intent to get a pancreas, waitlisted SPK candidates, or candidates who received a kidney and are waiting a pancreas. The analyses here expand on previous analyses by including two of the three comparison groups mentioned above (comparing PAK to waitlisted SPK groups and to waitlisted PAK candidates). Additionally, only those who are healthy enough to get a PAK are included in the PAK transplanted group, which can bias the results because it does not include the patients that had a kidney graft loss before the pancreas transplant. However, even with these limitations the results still indicate that PAK transplants are appropriate for specific diabetic uremic candidates who are expected to have a long wait time for an SPK transplant. Quickly receiving a kidney will mitigate mortality and getting the pancreas after the kidney transplant will increase the kidney graft survival for PAK recipients.

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[14] Gruessner, 2024-2025.

[15] Fridell, 113.