

The Role of Procurement Biopsies in Acceptance Decisions for Kidneys Retrieved for Transplant

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Abstract

Background and objectives There is a shortage of kidneys for transplant, and many patients on the deceased donor kidney transplant waiting list would likely benefit from kidneys that are currently being discarded. In the United States, the most common reason given for discarding kidneys retrieved for transplant is procurement biopsy results. This study aimed to compare biopsy results from discarded kidneys with discard attributed to biopsy findings, with biopsy results from comparable kidneys that were successfully transplanted.

Design, setting, participants, & measurements In this retrospective, observational, case-control study, biopsy reports were examined from 83 kidneys discarded in 2010 due to biopsy findings (cases), 83 contralateral transplanted kidneys from the same donor (contralateral controls), and 83 deceased donors randomly matched to cases by donor risk profile (randomly matched controls). A second procurement biopsy was obtained in 64 of 332 kidneys (19.3%).

Results The quality of biopsy reports was low, with amounts of tubular atrophy, interstitial inflammation, arteriolar hyalinosis, and acute tubular necrosis often not indicated; 69% were wedge biopsies and 94% used frozen tissue. The correlation between first and second procurement biopsies was poor; only 25% of the variability (R^2) in glomerulosclerosis was explained by biopsies being from the same kidney. The percentages of glomerulosclerosis overlapped substantially between cases, contralateral controls, and randomly matched controls: $17.1\% \pm 15.3\%$, $9.0\% \pm 6.6\%$, and $5.0\% \pm 5.9\%$, respectively. Of all biopsy findings, only glomerulosclerosis $>20\%$ was independently correlated with discard (cases versus contralateral controls; odds ratio, 15.09; 95% confidence interval, 2.47 to 92.41; $P=0.003$), suggesting that only this biopsy result was used in acceptance decisions. One-year graft survival was 79.5% and 90.7% in contralateral and randomly matched controls, respectively, versus 91.6% among all deceased donor transplants in the Scientific Registry of Transplant Recipients.

Conclusions Routine use of biopsies could lead to unnecessary kidney discards.

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Introduction

There is a shortage of kidneys for transplant, and many patients on the deceased donor kidney transplant waiting list would likely benefit from kidneys that are currently being discarded. In the United States, a donor kidney biopsy is obtained from more than half of all deceased donors, and the biopsy finding is the most common reason given for discarding a kidney recovered for transplant (1).

There are reasons to suspect that routine procurement biopsies may cause more harm than good (2). The quality of procurement biopsies is likely low. Even if the quality were improved to the level of implantation biopsies, the biopsy results may not be reliable enough to predict transplant outcomes and justify decisions regarding kidney acceptance.

The purpose of this study was to compare biopsy results from discarded kidneys with discard attributed to biopsy findings, with biopsy results from comparable kidneys that were successfully transplanted. We

hypothesized that the quality of procurement kidney biopsy reports used in acceptance decisions is low, the percentage of globally sclerotic glomeruli is the predominant biopsy finding used in acceptance decisions, and the extent of overlap in the biopsy results between discarded kidneys and transplanted kidneys is sufficient to call into question the utility of procurement biopsies in acceptance decisions.

Materials and Methods

Patient Protections

This was a joint study of the Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients (SRTR). Approvals were obtained from the US Department of Health and Human Services Health Resources and Services Administration (HRSA). No identifiable patient information was released to investigators outside of OPTN and SRTR.

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Study Design

In this retrospective, observational, case-control study, we included all kidneys discarded in 2010 with available biopsy reports and biopsy findings indicated as the reason for discard (cases), and contralateral kidneys that also had biopsy reports but were transplanted (contralateral controls). In addition, each case was matched by donor risk to another donor from whom at least one kidney was transplanted and whose kidneys were not discarded due solely to biopsy results (randomly matched controls). Thus, there were three study groups: cases, contralateral controls, and randomly matched controls. Cases included kidneys discarded due to biopsy results. Contralateral controls included contralateral kidneys for cases that also underwent biopsy but were transplanted. Randomly matched controls included kidneys from donors matched to cases, both of which were biopsied but not discarded due to the biopsy; matching was based on kidney donor risk index, Public Health Services high-risk status, and hepatitis C virus serology.

Randomly matched controls were matched to cases by identifying the donor kidneys transplanted in the same year (2010) with the same Public Health Services high-risk status (yes or no) and hepatitis C virus serology status (positive or negative), and the most similar kidney donor risk index. The kidney donor risk index is a summary measure of the graft failure risk associated with a particular donor relative to a reference donor (3). The kidney donor profile index is a transformation of the kidney donor risk index into a percentile (0%–100%) based on a recent pool of donors (<http://transplantpro.org/kdpi-calculator-available-on-unet-march-26/>). A higher kidney donor profile index indicates a higher risk of graft failure. Kidneys that were discarded because of the biopsy findings or with no biopsy report available were excluded from the control sampling population, and kidneys that were discarded for reasons other than biopsy findings were not excluded.

Data Collection

We used data from OPTN and SRTR to characterize deceased donor kidneys from 2010 and to analyze graft and patient survival for transplanted kidneys. The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of OPTN, and has been described elsewhere (4). HRSA provides oversight of the activities of the OPTN and SRTR contractors.

Biopsy reports and anatomic information from cases and controls were obtained from DonorNet. Anatomic information included the following: aortic plaque (0, none; 1, mild; 2, moderate; 3, severe; or not available [NA]); renal artery plaque (0, none; 1, mild; 2, moderate; 3, severe; or NA); presence of one or more renal cysts; presence of a capsular tear, hematoma, or both; and abnormal gross appearance of the kidney (yes, no, include free-text comments). Biopsy information included the following: biopsy type wedge or needle, or NA; frozen versus paraffin-embedded tissue; number of glomeruli; number of globally sclerotic glomeruli; whether percentage of globally sclerotic glomeruli was estimated; interstitial fibrosis (0, none, 0%–5%; 1, mild, 6%–25%; 2, moderate, 26%–50%; 3, severe, >50%; or NA); interstitial inflammation (\leq 5%; 1, mild,

6%–25%; 2, moderate, 26%–50%; 3, severe, >50%; or NA); tubular atrophy (0, none; 1, mild, <25% of tubules; 2, moderate, 26%–50%; 3, severe, >50%; or NA); chronic arterial changes (0, none; 1, mild, <25% narrowing; 2, moderate, 26%–50%; 3, severe, >50%; or NA); arteriolar hyalinosis (0, none; 1, mild; 2, moderate; 3, severe; or NA); and acute tubular necrosis (0, none; 1, mild; 2, moderate; 3, severe; or NA).

Statistical Analyses

Comparisons of cases with the two distinct control groups (contralateral controls and randomly matched controls) were made separately. For each comparison, only pairs with known results from the case and control kidneys were included in the analysis. When we compared binary biopsy findings in cases with their contralateral controls, Mantel–Haenszel odds ratios and Wald 95% confidence intervals (95% CIs) were derived from conditional logistic regression for matched-pairs data. When we compared continuous/ordinal biopsy findings, the Hodges–Lehmann estimator of the pseudo-median difference between cases and controls (5) was estimated, and differences were compared using the Wilcoxon signed rank test for matched-pairs data. When we compared cases with randomly matched controls, analyses were modified to account for the clustering of control kidneys within donors. Binary biopsy findings were compared using Mantel–Haenszel odds ratios and Wald 95% CIs derived from conditional logistic regression for matched-pairs data with adjustment for kidney laterality. Conditional/ordinal outcomes were compared using the signed rank test for clustered data on the matched case-control differences (6). To compare binary biopsy findings from first and second biopsies from the same kidney, odds ratios were estimated from logistic regression for repeated measures using generalized estimating equations taking into account the nested correlation induced by kidney laterality within donor. Continuous/ordinal outcomes from first/second biopsies of the same kidney were compared using the signed rank test for clustered data on the matched case-control differences (6). Graft and patient survival differences between contralateral and randomly matched controls were examined using Cox proportional hazards analysis. All analyses were carried out with SAS 9.1.3 (SAS Institute, Inc., Cary, NC) and R 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) software.

Results

Donors and Biopsies

Of the 7241 deceased kidney donors in 2010 (Figure 1), two kidneys were transplanted from 5594 deceased kidney donors (77.3%), no kidneys were transplanted from 1067 deceased kidney donors (14.7%), and one kidney was transplanted from 580 deceased kidney donors (8.0%). Of the 580 donors from whom only one kidney was transplanted, one kidney was discarded from 525 donors and the second kidney was not recovered from 55 donors. Of the 525 donors from whom one kidney was transplanted and one discarded, the discard was due to reasons other than biopsy findings for 420 donors (80.0%) and to biopsy findings for 105 donors (20%). Of these 105 donors, biopsy

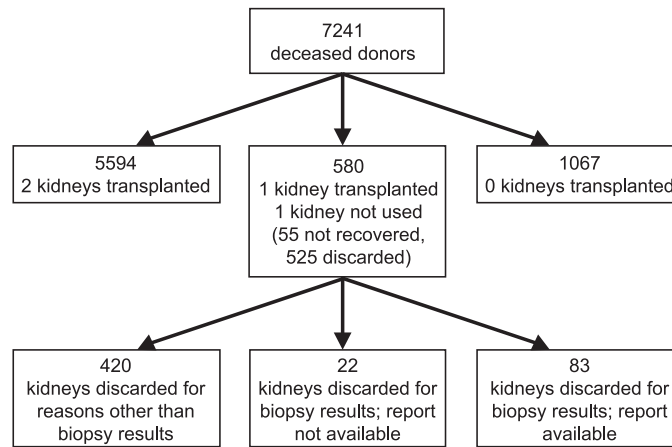


Figure 1. | Study population selection. The figure shows the disposition of kidneys from United States deceased donors in 2010 and their relation to the 83 discarded kidneys in this study.

reports were unavailable for 22 donors (21%) and were available (for both kidneys) for 83 donors (79%).

Thus, 83 kidneys discarded due to biopsy findings (cases) and 83 contralateral transplanted kidneys with biopsy reports (contralateral controls) were available for study. The 83 cases were matched by donor risk profile to 83 deceased donors (randomly matched controls), and 151 kidneys from these controls were transplanted. The kidney donor profile index for the 83 randomly matched control donors was virtually identical to the kidney donor profile index for cases ($76.8\% \pm 17.7\%$; 95% CI, 72.9% to 80.7%). Fifteen kidneys were discarded from randomly matched controls with biopsy not the sole reason for discard.

First and Second Procurement Biopsies of the Same Kidney

Of the 332 kidneys studied, two biopsies of the same kidney occurred in 64 kidneys (19.3%): 24 of 83 kidneys (29%) in cases, 16 of 83 kidneys (19%) in contralateral controls, and 24 of 166 kidneys (14%) in randomly matched controls ($P=0.02$ by the chi-squared test). The reason for obtaining a second biopsy was usually not indicated in the records. In some instances, obtaining a second biopsy may have been routine practice for the accepting organ procurement organization. In other instances, the first biopsy may have shown moderate to severe damage and a second biopsy was obtained to confirm that this was not due to sampling error. The second biopsy was more likely to be a needle core than a wedge biopsy (Table 1, Supplemental Table 1), likely reflecting an effort to obtain better tissue sampling. The second biopsy tended to show greater chronic tubule-interstitial damage than the first biopsy; the second biopsy showed more tubular atrophy and interstitial fibrosis. The percentage of globally sclerotic glomeruli was numerically greater in the first than in the second biopsy, but this difference was not statistically significant (Figure 2, Table 1). The linear trend line equation was $\text{First Biopsy} = 0.4933 \times \text{Second Biopsy} + 6.1434$; $R^2 = 0.2532$; $P < 0.001$; indicating that only 25% of the variability in glomerulosclerosis was explained by biopsies being from the same kidney. For subsequent analyses, the second biopsy was used.

Biopsy Results and Anatomic Abnormalities from Discarded Kidneys Compared with Controls

Of 332 biopsies, 12 biopsies (3.6%) showed <10 glomeruli, 51 biopsies (15.4%) showed 10–24 glomeruli, 122 biopsies (36.8%) showed 25–49 glomeruli, and 147 biopsies (44.3%) showed ≥ 50 glomeruli. There were no differences between cases and controls in the numbers of glomeruli in the biopsies (Tables 2 and 3, Supplemental Tables 2 and 3). The percentage of globally sclerotic glomeruli was reported in all cases and contralateral controls, and in all but two randomly matched control kidneys. Only 2 cases (2.4%), 3 contralateral controls (3.6%), and 12 randomly matched controls (7.2%) did not include a comment in the report regarding the amount of interstitial fibrosis (cases versus randomly matched controls, $P=0.08$). However, a description of the amount of chronic vascular damage was missing in 6 cases (7.2%), 8 contralateral controls (9.6%), and 29 randomly matched controls (17.5%) (cases versus randomly matched controls, $P=0.01$). The amounts of tubular atrophy, interstitial inflammation, arteriolar hyalinosis, and acute tubular necrosis were often not indicated in the biopsy report (Tables 2 and 3).

Cases showed more glomerular sclerosis than contralateral or randomly matched controls ($P < 0.001$) (Tables 2 and 3). However, there was substantial overlap in the percentage of global glomerular sclerosis between cases and controls (Figure 3). In general, histologic differences between cases and contralateral controls (Table 2) were less than differences between cases and randomly matched controls (Table 3).

Few anatomic abnormalities that would have precluded transplant were noted in the records (Tables 4 and 5, Supplemental Tables 4 and 5). There were no differences between cases and controls in descriptions of aortic and renal artery atherosclerosis. One or more renal cysts were noted more often in cases than in contralateral or randomly matched controls. Overall, fewer cases than contralateral or randomly matched controls were noted to be anatomically normal (Tables 4 and 5).

Independent Histologic and Anatomic Correlates of Discard

We analyzed biopsy results from cases and contralateral controls to determine which factors may have led to the

Biopsy Characteristic	First Biopsy (n=64)	Second Biopsy (n=64)	P Value ^a
Wedge (versus needle)	40/48 (83.3)	10/48 (20.8)	<0.001
Frozen tissue (versus paraffin-embedded tissue)	37/39 (94.9)	37/39 (94.9)	NE
Number of glomeruli assessed	53.8±28.4	49.7±40.0	0.81
Percentage of global sclerosis	11.5±10.7	11.0±10.9	0.84
Biopsy findings, if reported^b			
Tubular atrophy (36 pairs)	0.61±0.73	1.03±0.29	0.01
Interstitial fibrosis (62 pairs)	0.68±0.70	1.02±0.42	0.01
Interstitial inflammation (3 pairs)	1.00±0.00	0.33±0.58	NE
Vascular damage (55 pairs)	0.91±0.82	1.11±0.50	0.19
Arteriolar hyalinosis (3 pairs)	0.33±0.58	0.33±0.58	NE
Acute tubular necrosis (7 pairs)	0.29±0.49	0.29±0.49	NE
Missing biopsy information			
Wedge versus needle biopsy	11/64 (17.2)	5/64 (7.8)	0.14
Tissue processing method not indicated	23/64 (35.9)	4/64 (6.3)	<0.001
Tubular atrophy	23/64 (35.9)	8/64 (12.5)	0.003
Interstitial fibrosis	2/64 (3.1)	0/64 (0.0)	NE
Interstitial inflammation	32/64 (50.0)	57/64 (89.1)	<0.001
Vascular damage	7/64 (10.9)	2/64 (3.1)	0.11
Arteriolar hyalinosis	39/64 (60.9)	54/64 (84.4)	0.01
Acute tubular necrosis	48/64 (75.0)	49/64 (76.6)	0.81

Data are presented as the fraction (%) or mean±SD. NE, not estimable due to too few discordant pairings.
^aP values for binary data were generated from logistic regression for repeated measures using generalized estimating equations and taking into account the nested correlation induced by kidney laterality within donor (5). P values for parametric data were generated from a signed rank test on the matched case-control differences for clustered data (6). See Supplemental Table 1 for details.
^b0, none; 1, mild; 2, moderate; 3, severe.

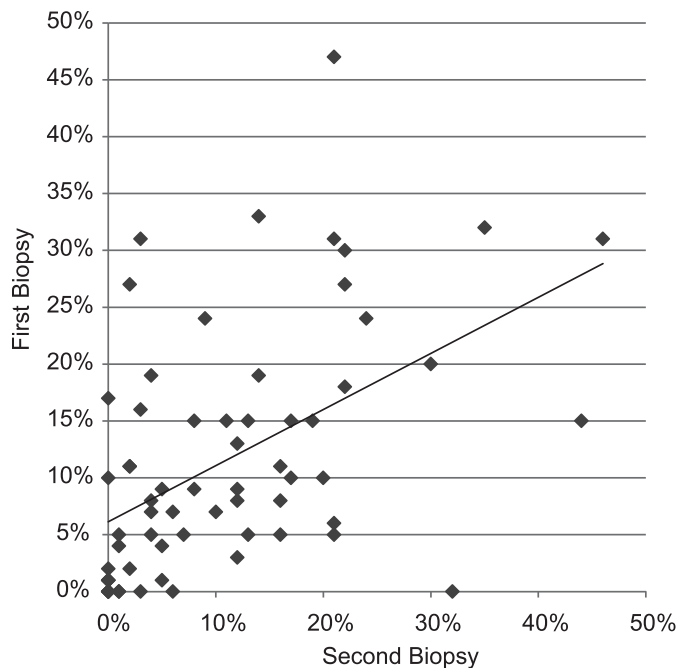


Figure 2. | Comparison of the percentage of globally sclerotic glomeruli in two biopsies from the same kidney. The figure shows the percentage of globally sclerotic glomeruli in first and second biopsies from 64 kidneys that underwent two biopsies. The linear trend equation was $\text{First Biopsy} = 0.4933 \times \text{Second Biopsy} + 6.1434$; $R^2 = 0.2532$; $P < 0.001$.

decision to discard one kidney but not the other. Only a percentage of global glomerular sclerosis >20% was associated with the decision to discard based on biopsy findings (Table 6).

Transplant Outcomes

Unadjusted Kaplan–Meier graft survival was lower in recipients of contralateral control kidneys than in recipients of randomly matched control kidneys (Figure 4). One-

Table 2. Comparison of biopsies from discarded and paired control kidneys from the same donor

Biopsy Characteristic	Kidney Discarded for Biopsy Findings (n=83)	Contralateral Kidney Not Discarded (n=83)	P Value ^a
Wedge (versus needle)	42/63 (66.7)	47/63 (74.6)	0.10
Frozen tissue (versus paraffin-embedded tissue)	49/50 (98.0)	49/50 (98.0)	NE
Number of glomeruli assessed	53.5±40.9	55.2±39.8	0.50
Percentage of global sclerosis	17.1±15.3	9.0±6.6	<0.001
Percentage of global sclerosis >20%	27/83 (32.5)	4/83 (4.8)	<0.001
Biopsy findings, if reported^b			
Tubular atrophy (52 pairs)	1.00±0.56	0.87±0.49	0.08
Interstitial fibrosis (80 pairs)	0.95±0.55	0.78±0.57	0.01
Interstitial inflammation (37 pairs)	0.81±0.57	0.65±0.54	0.07
Vascular damage (75 pairs)	1.01±0.73	0.87±0.62	0.04
Arteriolar hyalinosis (35 pairs)	0.63±0.60	0.69±0.72	NE
Acute tubular necrosis (32 pairs)	0.72±0.81	0.69±0.64	0.85
Missing biopsy information			
Wedge versus needle biopsy	18/83 (21.7)	17/83 (20.5)	0.66
Tissue processing method not indicated	29/83 (34.9)	32/83 (38.6)	0.22
Tubular atrophy	27/83 (32.5)	29/83 (34.9)	0.42
Interstitial fibrosis	2/83 (2.4)	3/83 (3.6)	NE
Interstitial inflammation	43/83 (51.8)	39/83 (47.0)	0.22
Vascular damage	6/83 (7.2)	8/83 (9.6)	NE
Arteriolar hyalinosis	44/83 (53.0)	44/83 (53.0)	1.00
Acute tubular necrosis	47/83 (56.6)	50/83 (60.2)	0.22

Data are presented as the fraction (%) or mean±SD. NE, not estimable due to too few discordant pairings.

^aP values for binary data were generated from logistic regression for repeated measures using generalized estimating equations and taking into account the nested correlation induced by kidney laterality within donor (5). P values for parametric data were generated from a signed rank test on the matched case-control differences for clustered data (6). See Supplemental Table 2 for details.

^b0, none; 1, mild; 2, moderate; 3, severe.

year graft survival was 79.5% and 90.7% in contralateral and randomly matched control kidneys, respectively. The unadjusted relative risk of graft failure in contralateral control kidneys compared with randomly matched control kidneys was 1.98 (95% CI, 1.12 to 3.52), and the relative risk adjusted for recipient age, sex, race, and kidney donor risk index was 2.06 (95% CI, 1.14 to 3.72). One-year patient survival was 89.2% and 97.4% in contralateral and randomly matched control kidneys, respectively (Figure 4). The unadjusted relative risk of death in contralateral compared with randomly matched control kidneys was 2.54 (95% CI, 1.12 to 5.74), and the relative risk adjusted for recipient age, sex, race, and kidney donor risk index was 2.76 (95% CI, 1.20 to 6.78).

Among recipients with functioning grafts at 12 months after transplant, the estimated GFR, estimated by the Chronic Kidney Disease Epidemiology Collaboration equation (7), was 50.0±23.1 ml/min per 1.73 m² in contralateral control kidneys (n=68) and 51.4±20.7 ml/min per 1.73 m² in randomly matched control kidneys (n=139) (P=0.67). At 12 months, 7 acute rejection episodes had occurred in recipients of contralateral control kidneys (all biopsy confirmed) and 12 had occurred in recipients of randomly matched control kidneys (11 biopsy confirmed).

Discussion

Due to the shortage of deceased donor kidneys, it is critical that kidneys suitable for transplant not be discarded unnecessarily. In 2011, 2587 kidneys retrieved for transplant in the United States were subsequently discarded (1).

Of these, 966 kidneys (37.3%) were discarded due to biopsy findings, the most common reason for discard. In 2012, 50.4% of deceased donor kidneys removed for transplant underwent a procurement biopsy (personal communication, D.E.S., based on OPTN data as of March 1, 2013).

A large number of studies have examined how well kidney biopsy findings correlate with post-transplant outcomes. Most single-center studies have examined “implantation” biopsies obtained at the time of transplant surgery (8–40). These biopsies have usually been paraffin embedded, carefully stained, and interpreted by renal pathologists. Different scoring systems have been used to assess the amount of chronic damage (11,15,23,27,29,32,33,39,40). Morphometry has also been used to determine the amount of chronic damage in the transplanted kidney as accurately as possible (23,25,32). Nevertheless, these studies have generally failed to show strong correlations between histologic findings of implantation biopsies and kidney graft survival.

Although there are exceptions (41), most studies of procurement biopsies have analyzed the limited data collected in registries (42–45). Often, the only information available in registry studies is the percentage of globally sclerotic glomeruli. Like studies of implantation biopsies, studies examining the association of procurement biopsy findings with post-transplant outcomes have produced conflicting results (41–44).

Unlike implantation biopsies obtained under optimal conditions, procurement biopsies are generally obtained using frozen sections that are often interpreted by a general pathologist without special training in reading kidney

Table 3. Comparison of biopsies from discarded kidneys and randomly matched controls

Biopsy Characteristic	Kidney Discarded for Biopsy Findings (n=83)	Randomly Matched Control (n=166)	P Value ^a
Wedge (versus needle)	34/51 (66.7)	72/101 (71.3)	0.55
Frozen tissue (versus paraffin-embedded tissue)	32/33 (97.0)	57/65 (87.7)	NE
Number of glomeruli assessed (164 pairs)	53.8±41.1	51.4±32.9	0.86
Percentage of global sclerosis (164 pairs)	17.1±15.4	5.0±5.9	<0.001
Percentage of global sclerosis >20%	27/83 (32.5)	5/166 (3.0)	<0.001
Biopsy findings, if reported^b			
Tubular atrophy (80 pairs)	1.07±0.47	0.60±0.54	<0.001
Interstitial fibrosis (150 pairs)	0.97±0.52	0.54±0.56	<0.001
Interstitial inflammation (38 pairs)	0.75±0.55	0.45±0.50	0.04
Vascular damage (127 pairs)	1.05±0.76	0.64±0.63	0.001
Arteriolar hyalinosis (24 pairs)	0.38±0.51	0.58±0.65	0.51
Acute tubular necrosis (18 pairs)	0.78±0.97	0.28±0.46	0.22
Missing biopsy information			
Wedge versus needle biopsy	18/83 (21.7)	38/166 (22.9)	0.79
Tissue processing method not indicated	29/83 (34.9)	64/166 (38.6)	0.51
Tubular atrophy	27/83 (32.5)	51/166 (30.7)	0.72
Interstitial fibrosis	2/83 (2.4)	12/166 (7.2)	0.08
Interstitial inflammation	43/83 (51.8)	85/166 (51.2)	0.92
Vascular damage	6/83 (7.2)	29/166 (17.5)	0.01
Arteriolar hyalinosis	44/83 (53.0)	99/166 (59.6)	0.27
Acute tubular necrosis	47/83 (56.6)	119/166 (71.7)	0.01

Data are presented as the fraction (%) or mean±SD. NE, not estimable due to too few discordant pairings.

^aP values for binary data were generated from logistic regression for repeated measures using generalized estimating equations and taking into account the nested correlation induced by kidney laterality within donor (5). P values for parametric data were generated from a signed rank test on the matched case-control differences for clustered data (6). See Supplemental Table 3 for details.

^b0, none; 1, mild; 2, moderate; 3, severe.

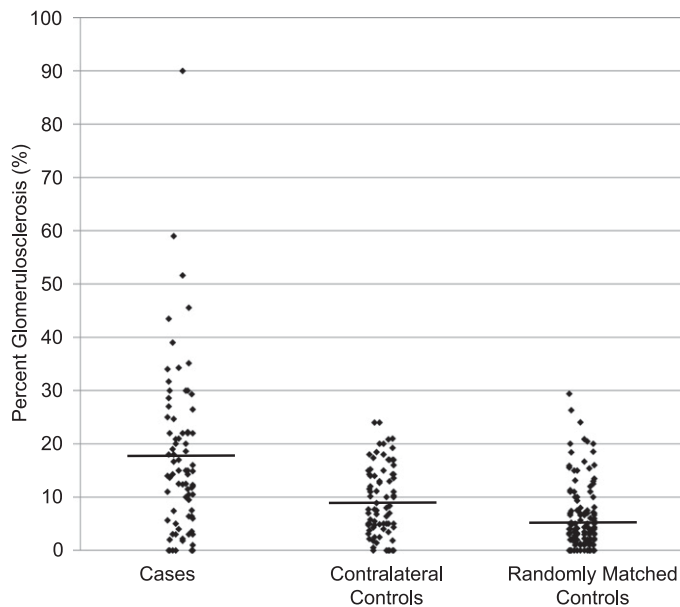


Figure 3. | Percentage of globally sclerotic glomeruli in discarded kidneys (cases), transplanted contralateral kidneys from the same donor (contralateral controls), and randomly matched controls. Horizontal lines indicate group means: 17.0%, 9.0%, and 5.0% for cases, contralateral controls, and randomly matched controls, respectively. *P*<0.001 for cases versus contralateral controls and for cases versus randomly matched controls.

biopsies. The results may be reported to a surgeon not trained in renal pathology, who then must decide whether to accept the kidney for a particular patient.

We found that the quality of biopsy reports used in acceptance decisions was poor. Most biopsies were wedge biopsies; studies have shown that core needle biopsies are

Biopsy Characteristic	Kidney Discarded for Biopsy Findings (n=83)	Randomly Matched Control (n=166)	P Value ^a
Aortic plaque (49 pairs) ^b	1.49±1.14	1.45±1.12	NE
Aortic plaque not mentioned	32/83 (38.6)	28/83 (33.7)	0.18
Renal artery plaque (55 pairs) ^b	0.75±0.99	0.75±1.02	1.00
Renal artery plaque not mentioned	26/83 (31.3)	24/83 (28.9)	0.42
Cysts noted	27/83 (32.5)	18/83 (21.7)	0.05
Capsular tear/hematoma noted	2/83 (2.4)	2/83 (2.4)	1.00
Normal, no anatomic abnormalities	29/83 (34.9)	37/83 (44.6)	0.05

Data are presented as the fraction (%) or mean±SD. NE, not estimable due to too few discordant pairings.
^aP values for binary data were generated from logistic regression for repeated measures using generalized estimating equations and taking into account the nested correlation induced by kidney laterality within donor (5). P values for parametric data were generated from a signed rank test on the matched case-control differences for clustered data (6). See Supplemental Table 4 for details.
^b0, none; 1, mild; 2, moderate; 3, severe.

Biopsy Characteristic	Kidney Discarded for Biopsy Findings (n=83)	Randomly Matched Control (n=166)	P Value ^a
Aortic plaque (61 pairs) ^b	1.37±1.29	1.30±1.01	0.93
Aortic plaque not mentioned	32/83 (38.6)	64/166 (33.6)	0.99
Renal artery plaque (78 pairs) ^b	0.63±0.86	0.82±1.05	0.61
Renal artery plaque not mentioned	26/83 (31.3)	57/166 (34.3)	0.56
Cysts noted	27/83 (32.5)	22/166 (13.3)	<0.001
Capsular tear/hematoma noted	2/83 (2.4)	3/166 (1.8)	0.75
Normal, no anatomic abnormalities	29/83 (34.9)	91/166 (54.8)	0.001

Data are presented as the fraction (%) or mean±SD.
^aP values for binary data were generated from logistic regression for repeated measures using generalized estimating equations and taking into account the nested correlation induced by kidney laterality within donor (5). P values for parametric data were generated from a signed rank test on the matched case-control differences for clustered data (6). See Supplemental Table 5 for details.
^b0, none; 1, mild; 2, moderate; 3, severe.

Percentage of Glomerulosclerosis	Discarded Kidney (n=83)	Contralateral Kidney (n=83)	Conditional Odds Ratio for Discard	P Value ^a
0.0	8 (9.6)	10 (12.1)	Reference	–
0.1–5.0 (n=35)	12 (14.5)	23 (27.7)	0.93 (0.22 to 3.89)	0.92
5.1–10.0 (n=25)	8 (9.6)	17 (20.5)	1.03 (0.22 to 4.78)	0.97
10.1–20.0 (n=57)	28 (33.7)	29 (34.9)	2.42 (0.56 to 10.44)	0.23
>20.0 (n=31)	27 (32.5)	4 (4.8)	15.09 (2.47 to 92.41)	0.003

Data are presented as n (%) or odds ratio (95% confidence interval).
^aP values were generated from a signed rank test on the matched case-control differences for clustered data (6).

superior to wedge biopsies (46,47). Almost all biopsies were processed using frozen tissue. The number of glomeruli is often used as an indicator of biopsy adequacy, and Wang *et al.* found that biopsies with at least 25 glomeruli were better predictors of graft survival (13). In this study, 63 of 332 biopsies (19%) showed <25 glomeruli and only 146 of 332 (43.9%) showed ≥50. At least 90% of biopsies reported the amount of interstitial fibrosis and

chronic arterial damage (Tables 2 and 3), but one-third did not mention chronic tubular atrophy, and half did not comment on the presence or absence of arteriolar hyalinosis or the amount of interstitial inflammation. Two-thirds of biopsies failed to comment on the presence, absence, or severity of acute tubular necrosis.

A comparison of two biopsies from the same kidney demonstrated significant differences (Table 1), calling into

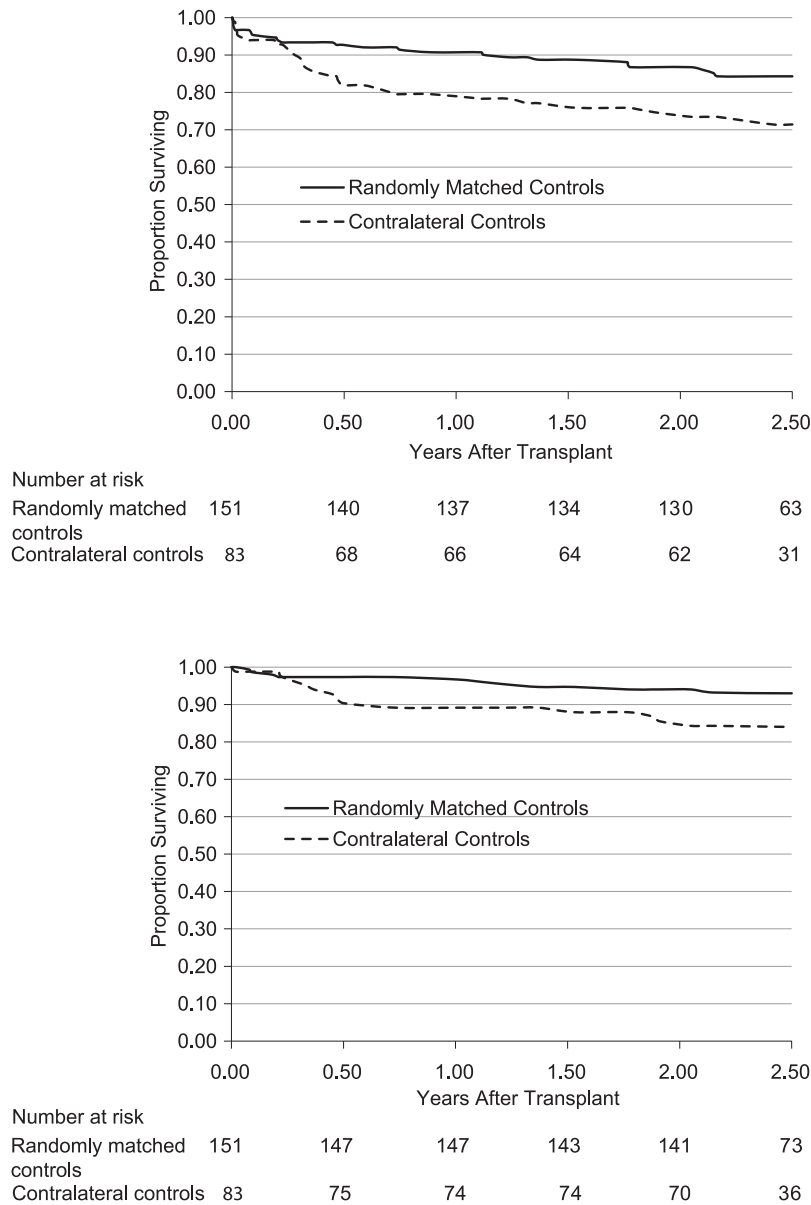


Figure 4. | Graft (top) and patient (bottom) survival for recipients of contralateral control kidneys and randomly matched control kidneys. Unadjusted Kaplan–Meier survival curves are shown.

question the reliability of biopsies for making acceptance decisions. Notably, the percentage of glomerulosclerosis in the 64 pairs of biopsies from the same kidney was substantially discordant (Figure 2).

The most important findings in this study are the overlap in biopsy findings between kidneys that were discarded and kidneys that were transplanted, and that glomerulosclerosis $\geq 20\%$ was the only biopsy finding independently predictive of discard. To the best of our knowledge, ours is the first controlled study to compare biopsy findings between discarded kidneys and matched transplanted kidneys. Although the difference in the percentage of globally sclerotic glomeruli was statistically significant, there was substantial overlap between groups (Figure 3). Glomerulosclerosis $> 20\%$ is often used as a marker of severe chronic kidney damage. This tradition can be traced to a

very small study of implantation biopsies published in 1995 (10). In the present study, 32.5% of discarded kidneys were reported to have $> 20\%$ glomerulosclerosis (Table 2). Similarly, there was substantial overlap, albeit with some statistically significant differences, in most other histologic parameters between cases and controls (Tables 2 and 3).

Graft survival of kidneys contralateral to kidneys that had been discarded due to biopsy findings was worse than graft survival of deceased donor kidneys with a comparable kidney donor risk index (Figure 4). Rates of acute rejection were low in both control groups. Among recipients with functioning grafts at 12 months, estimated GFR was approximately 50 ml/min per 1.73 m². A 1-year graft survival of 80%, compared with 91.6% for all deceased donor recipients in the United States in 2010 (1), may be acceptable for many patients.

There are important caveats to this study. The biopsies from discarded kidneys that were contralateral to the transplanted kidneys may not represent all biopsies from discarded kidneys. It is also possible that the quality of biopsies and their utility could be improved. However, numerous studies have shown poor correlation of implantation biopsies with transplant outcomes, despite these implantation biopsies being performed under optimal conditions.

A reasonable conclusion from this and other studies is that the widespread practice of routinely obtaining procurement biopsies should be abandoned, as has been successfully done in Europe (2). If abandoning routine procurement biopsies is not acceptable in the United States, then perhaps a randomized controlled trial could be designed to more precisely determine the benefits and harms of procurement biopsies. In such a trial, the quality of procurement biopsies could be maximized by using needle rather than wedge biopsies, obtaining three adequate cores, requiring at least 25 glomeruli in the biopsy for it to be considered adequate, replacing frozen tissue with rapid paraffin embedding whenever possible, and using a standardized reporting form to encourage adequate reporting of all important biopsy elements.

In summary, the results of this study suggest that the information obtained from procurement biopsies is of low quality and may lead to unnecessary discard of transplantable kidneys. The practice of obtaining routine procurement biopsies should either be abandoned or more critically reexamined in appropriately designed clinical trials.

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Disclosures

None.

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See related editorial, "Procurement Biopsies in Kidneys Retrieved for Transplantation," on pages 443–444.

Supplemental Material

Table S1. Details of Analysis for Table 1: Comparison of Two Biopsies from the Same Kidney

Table S2. Details of Analysis for Table 2: Comparison of Biopsies from Discarded and Paired Control Kidneys from the Same Donor

Table S3. Details of Analysis for Table 3: Comparison of Biopsies from Discarded Kidneys and Randomly Matched Controls

Table S4. Details of Analysis for Table 4: Comparison of Anatomical Abnormalities from Discarded and Paired Control Kidneys from the Same Donor

Table S5. Details of Analysis for Table 5: Comparison of Anatomical Abnormalities from Discarded Kidneys and Randomly Matched Controls

Supplemental Material

Table S1. Details of Analysis for Table 1: Comparison of Two Biopsies from the Same Kidney

	First Biopsy, Fraction or Mean \pm SD (<i>n</i> = 64)	Second Biopsy, Fraction or Mean \pm SD (<i>n</i> = 64)	Odds Ratio (First vs. Second Biopsy, 95% CI, <i>P</i>) ¹	Pseudomedian Paired Difference (First – Second Biopsy) (<i>P</i>) ²
Type of biopsy, if indicated				
Wedge (vs. needle)	40/48 (83.3%)	10/48 (20.8%)	19.00 (0.7.69-46.96, < 0.001)	--
Tissue processing, if indicated				
Frozen tissue (vs. paraffin-embedded)	37/39 (94.9%)	37/39 (94.9%)	NE	--
Number of glomeruli assessed (64 pairs)	53.8 \pm 28.4	49.7 \pm 40.0	--	6.00 (0.81)
Percent global sclerosis (%) (64 pairs)	11.5 \pm 10.7	11.0 \pm 10.9	--	0.50 (0.84)
Biopsy findings, if reported				
Tubular atrophy ³ (36 pairs)	0.61 \pm 0.73	1.03 \pm 0.29	--	-1.00 (0.01)
Interstitial fibrosis ³ (62 pairs)	0.68 \pm 0.70	1.02 \pm 0.42	--	-1.00 (0.01)
Interstitial inflammation ² (3 pairs)	1.00 \pm 0.00	0.33 \pm 0.58	--	NE
Vascular damage ³ (55 pairs)	0.91 \pm 0.82	1.11 \pm 0.50	--	0.00 (0.19)
Arteriolar hyalinosis ³ (3 pairs)	0.33 \pm 0.58	0.33 \pm 0.58	--	NE
Acute tubular necrosis ³ (7 pairs)	0.29 \pm 0.49	0.29 \pm 0.49	--	NE
Missing biopsy information (%)				
Wedge versus needle biopsy	11/64 (17.2%)	5/64 (7.8%)	2.45 (0.75-8.04, 0.14)	--
Tissue processing method not indicated	23/64 (35.9%)	4/64 (6.3%)	8.41 (2.81-25.24, < 0.001)	--
Tubular atrophy	23/64 (35.9%)	8/64 (12.5%)	3.93 (1.61-9.61, 0.003)	--
Interstitial fibrosis	2/64 (3.1%)	0/64 (0.0%)	NE	--
Interstitial inflammation	32/64 (50.0%)	57/64 (89.1%)	0.12 (0.05-0.32, < 0.001)	--
Vascular damage	7/64 (10.9%)	2/64 (3.1%)	3.81 (0.73-19.91, 0.11)	--
Arteriolar hyalinosis	39/64 (60.9%)	54/64 (84.4%)	0.29 (0.12-0.69, 0.01)	--
Acute tubular necrosis	48/64 (75.0%)	49/64 (76.6%)	0.91 (0.46-1.83, 0.81)	--

¹Odds ratios estimated from logistic regression for repeated measures using generalized estimating equations and taking into account the nested correlation induced by kidney laterality within donor (1).

²Hodges-Lehmann estimator of the pseudomedian; signed rank test on the matched case-control differences for clustered data (2).

³0 = none, 1 = mild, 2 = moderate, 3 = severe.

SD, standard deviation; CI, confidence interval; NE, not estimable due to too few discordant pairs.

Table S2. Details of Analysis for Table 2: Comparison of Biopsies from Discarded and Paired Control Kidneys from the Same Donor

Biopsy Characteristic	Kidney Discarded for Biopsy Findings (<i>n</i> = 83)	Comparison to Contralateral Kidney Not Discarded (<i>n</i> = 83)		
	Fraction (%) or Mean ± SD	Fraction (%) or Mean ± SD	Conditional Odds Ratio for Discard (95% CI, <i>P</i>) ¹	Pseudomedian Paired Difference (Discarded Kidney – Control Kidney) (<i>P</i>) ²
Type of biopsy, if indicated				
Wedge (vs. needle)	42/63 (66.7%)	47/63 (74.6%)	0.17 (0.02-1.38, 0.10)	--
Tissue processing, if indicated				
Frozen tissue (vs. paraffin-embedded)	49/50 (98.0%)	49/50 (98.0%)	NE	--
Number of glomeruli assessed (83 pairs)	53.5 ± 40.9	55.2 ± 39.8	--	-2.00 (0.50)
Percent global sclerosis (83 pairs) (%)	17.1 ± 15.3	9.0 ± 6.6	--	8.00 (< 0.001)
Percentage global sclerosis > 20%	27/83 (32.5%)	4/83 (4.8%)	8.67 (2.62-28.63, < 0.001)	--
Biopsy findings, if reported				
Tubular atrophy ³ (52 pairs)	1.00 ± 0.56	0.87 ± 0.49	--	1.00 (0.08)
Interstitial fibrosis ³ (80 pairs)	0.95 ± 0.55	0.78 ± 0.57	--	1.00 (0.01)
Interstitial inflammation ³ (37 pairs)	0.81 ± 0.57	0.65 ± 0.54	--	1.00 (0.07)
Vascular damage ³ (75 pairs)	1.01 ± 0.73	0.87 ± 0.62	--	0.74 (0.04)
Arteriolar hyalinosis ³ (35 pairs)	0.63 ± 0.60	0.69 ± 0.72	--	NE
Acute tubular necrosis ³ (32 pairs)	0.72 ± 0.81	0.69 ± 0.64	--	0.35 (0.85)
Missing biopsy information				
Wedge versus needle biopsy	18/83 (21.7%)	17/83 (20.5%)	1.50 (0.25-8.98, 0.66)	--
Tissue processing method not	29/83 (34.9%)	32/83 (38.6%)	0.25 (0.03-2.24, 0.22)	--

indicated				
Tubular atrophy	27/83 (32.5%)	29/83 (34.9%)	0.50 (0.09-2.73, 0.42)	--
Interstitial fibrosis	2/83 (2.4%)	3/83 (3.6%)	NE	--
Interstitial inflammation	43/83 (51.8%)	39/83 (47.0%)	2.33 (0.60-9.02, 0.22)	--
Vascular damage	6/83 (7.2%)	8/83 (9.6%)	NE	--
Arteriolar hyalinosis	44/83 (53.0%)	44/83 (53.0%)	1.00 (0.25-4.00, 1.00)	--
Acute tubular necrosis	47/83 (56.6%)	50/83 (60.2%)	0.25 (0.03-2.24, 0.22)	--

¹Mantel-Hanzel odds ratio and Wald 95% CIs derived from conditional logistic regression for matched pairs data. NE indicates not estimable due to 0 discordant pairs in at least 1 discordant grouping (1).

²Hodges-Lehmann estimator of the pseudomedian; Wilcoxon signed rank test for matched pairs data testing the null hypothesis that the median difference is 0 (2).

³0 = none, 1 = mild, 2 = moderate, 3 = severe.

SD, standard deviation; CI, confidence interval; NE, not estimable due to too few discordant pairs.

Table S3. Details of Analysis for Table 3: Comparison of Biopsies from Discarded Kidneys and Randomly Matched Controls

Biopsy Characteristic	Kidney Discarded for Biopsy Findings (<i>n</i> = 83)		Comparison to Randomly Matched Controls (<i>n</i> = 166 kidneys)	
	Fraction (%) or Mean ± SD	Fraction (%) or Mean ± SD	Conditional Odds Ratio for Discard (95% CI, <i>P</i>) ¹	Pseudomedian Paired Difference (Discarded Kidney – Control Kidney) (<i>P</i>) ²
Type of biopsy, if indicated				
Wedge (vs. needle)	34/51 (66.7%)	72/101 (71.3%)	0.77 (0.32-1.82, 0.55)	--
Tissue processing, if indicated				
Frozen tissue (vs. paraffin-embedded)	32/33 (97.0%)	57/65 (87.7%)	NE	--
Number of glomeruli assessed (164 pairs)	53.8 ± 41.1	51.4 ± 32.9	--	1.00 (0.86)
Percent global sclerosis (164 pairs) (%)	17.1 ± 15.4	5.0 ± 5.9	--	11.00 (< 0.001)
Percentage global sclerosis > 20%	27/83 (32.5%)	5/166 (3.0%)	25.53 (6.04-107.85, < 0.001)	--
Biopsy findings, if reported				
Tubular atrophy ³ (80 pairs)	1.07 ± 0.47	0.60 ± 0.54	--	1.00 (< 0.001)
Interstitial fibrosis ³ (150 pairs)	0.97 ± 0.52	0.54 ± 0.56	--	1.00 (< 0.001)
Interstitial inflammation ³ (38 pairs)	0.75 ± 0.55	0.45 ± 0.50	--	1.00 (0.04)
Vascular damage ³ (127 pairs)	1.05 ± 0.76	0.64 ± 0.63	--	1.00 (0.001)
Arteriolar hyalinosis ³ (24 pairs)	0.38 ± 0.51	0.58 ± 0.65	--	-0.50 (0.51)
Acute tubular necrosis ³ (18 pairs)	0.78 ± 0.97	0.28 ± 0.46	--	1.00 (0.22)
Missing biopsy information				

Wedge versus needle biopsy	18/83 (21.7%)	38/166 (22.9%)	0.90 (0.42-1.95, 0.79)	--
Tissue processing method not indicated	29/83 (34.9%)	64/166 (38.6%)	0.81 (0.43-1.53, 0.51)	--
Tubular atrophy	27/83 (32.5%)	51/166 (30.7%)	1.13 (0.56-2.29, 0.72)	--
Interstitial fibrosis	2/83 (2.4%)	12/166 (7.2%)	0.23 (0.05-1.18, 0.08)	--
Interstitial inflammation	43/83 (51.8%)	85/166 (51.2%)	1.03 (0.56-1.92, 0.92)	--
Vascular damage	6/83 (7.2%)	29/166 (17.5%)	0.25 (0.09-0.72, 0.01)	--
Arteriolar hyalinosis	44/83 (53.0%)	99/166 (59.6%)	0.72 (0.40-1.30, 0.27)	--
Acute tubular necrosis	47/83 (56.6%)	119/166 (71.7%)	0.42 (0.22-0.80, 0.01)	--

¹Mantel-Hanzel odds ratio and Wald 95% confidence intervals derived from conditional logistic regression for matched pairs data with adjustment for laterality of the case and control kidneys (1).

²Hodges-Lehmann estimator of the pseudomedian; signed rank test on the matched case-control differences for clustered data (2).

³0 = none, 1 = mild, 2 = moderate, 3 = severe.

SD, standard deviation; CI, confidence interval; NE, not estimable due to too few discordant pairs.

Table S4. Details of Analysis for Table 4: Comparison of Anatomical Abnormalities from Discarded and Paired Control Kidneys from the Same Donor

Anatomical Characteristic	Kidney Discarded for Biopsy Findings ($n = 83$)		Comparison to Contralateral Kidney Not Discarded ($n = 83$)	
	Fraction (%) or Mean \pm SD	Fraction (%) or Mean \pm SD	Conditional Odds Ratio for Discard (95% CI, P) ¹	Pseudomedian Paired Difference (Discarded Kidney – Control Kidney) (P) ²
Aortic plaque ³ (49 pairs)	1.49 \pm 1.14	1.45 \pm 1.12	--	NE
Aortic plaque not mentioned	32/83 (38.6%)	28/83 (33.7%)	3.00 (0.61-14.86, 0.18)	--
Renal artery plaque ³ (55 pairs)	0.75 \pm 0.99	0.75 \pm 1.02	--	0.00 (1.00)
Renal artery plaque not mentioned	26/83 (31.3%)	24/83 (28.9%)	2.00 (0.37-10.92, 0.42)	--
Cysts noted	27/83 (32.5%)	18/83 (21.7%)	2.80 (1.01-7.77, 0.048)	--
Capsular tear/hematoma noted	2/83 (2.4%)	2/83 (2.4%)	1.00 (0.14-7.10, 1.00)	--
Normal, no anatomic abnormalities	29/83 (34.9%)	37/83 (44.6%)	0.27 (0.08-0.98, 0.046)	--

¹Mantel-Hanzel odds ratios and Wald 95% CIs derived from conditional logistic regression for matched pairs data (1).

²Hodges-Lehmann estimator of the pseudomedian; Wilcoxon signed rank test for matched pairs data testing the null hypothesis that the median difference is 0 (2).

³0 = none, 1 = mild, 2 = moderate, 3 = severe.

SD, standard deviation; CI, confidence interval; NE, not estimable due to too few discordant pairs.

Table S5. Details of Analysis for Table 5: Comparison of Anatomical Abnormalities from Discarded Kidneys and Randomly Matched Controls

Anatomical Characteristic	Kidney Discarded for Biopsy Findings (<i>n</i> = 83)		Comparison to Randomly Matched Controls (<i>n</i> = 166 kidneys)	
	Fraction (%) or Mean ± SD	Fraction (%) or Mean ± SD	Conditional Odds Ratio for Discard (95% CI, <i>P</i>) ¹	Pseudomedian Paired Difference (Discarded Kidney – Control Kidney) (<i>P</i>) ²
Aortic plaque ³ (61 pairs)	1.37 ± 1.29	1.30 ± 1.01	--	0.00 (0.93)
Aortic plaque not mentioned	32/83 (38.6%)	64/166 (33.6%)	1.00 (0.53-1.89, 0.99)	--
Renal artery plaque ³ (78 pairs)	0.63 ± 0.86	0.82 ± 1.05	--	-0.50 (0.61)
Renal artery plaque not mentioned	26/83 (31.3%)	57/166 (34.3%)	0.81 (0.41-1.63, 0.56)	--
Cysts noted	27/83 (32.5%)	22/166 (13.3%)	3.87 (1.83-8.18, < 0.001)	--
Capsular tear/hematoma noted	2/83 (2.4%)	3/166 (1.8%)	1.33 (0.22-7.98, 0.75)	--
Normal, no anatomic abnormalities	29/83 (34.9%)	91/166 (54.8%)	0.35 (0.19-0.66, 0.001)	--

¹Mantel-Hanzel odds ratio and Wald 95% CIs derived from conditional logistic regression for matched pairs data with adjustment for laterality of the case and control kidneys (1).

²Hodges-Lehmann estimator of the pseudomedian; signed rank test on the matched case-control differences for clustered data (2).

³0 = none, 1 = mild, 2 = moderate, 3 = severe.

SD, standard deviation; CI, confidence interval.

References

1. Hollander M, Wolfe DA: Nonparametric Statistical Methods, 2nd ed. John Wiley & Sons, 1999
2. Datta S, Satten GA: A signed-rank test for clustered data. *Biometric* 64:501-507, 2008