Making Procurement Biopsies Important Again for Kidney Transplant Allocation

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A comment on “Carpenter et al: Procurement biopsies in the evaluation of deceased donor kidneys. Clin J Am Soc Nephrol 2018;13:1876–1885.”

Keywords

Kidney transplantation · Kidney donor profile index · Kidney donor risk index · Pretransplant donor biopsy · Frozen section · Wedge biopsy · Core-needle biopsy

Abstract

Context: Results of procurement biopsies often drive the decision to discard kidneys from deceased donors with advanced age or comorbidities. However, the criteria to perform, process, and score procurement graft biopsies are not standardized. **Subject of Review:** A recent retrospective, single-center study by Carpenter et al. [Clin J Am Soc Nephrol 2018;13:1876–1885] compared the scores obtained from 270 consecutive frozen kidney sections of biopsies at time of procurement with those of paraffin-embedded sections of biopsies at reperfusion and the correlation of both biopsy scores with graft survival. In 116 kidneys, procurement biopsies were repeated, allowing to test the reproducibility of this technique. Procurement biopsies were poorly reproducible, did not correlate with scores obtained with paraffin-embedded reperfusion biopsies, and were not significantly associated with transplant outcomes, while reperfusion biopsies provided an excellent prediction of graft survival. Based

on these findings, the authors suggest “an urgent need to reexamine the role of procurement biopsies during allocation given their high resource requirements and association with discards.” **Second Opinion:** Carpenter’s paper is important because it emphasizes the crucial role of correct histological evaluation of kidney grafts to accurately predict their survival. In this study, procurement biopsies were frozen and read by on-call pathologists, often with no specific training in renal pathology, while reperfusion sections were paraffin embedded and scored by experienced renal pathologists at Columbia University, New York, NY, USA. This methodological difference per se represents an obvious explanation for the poor concordance between the 2 assessments. Use of wedge biopsies in procurement samples versus core-needle samples in reperfusion biopsies may further account for the discrepancies between scores even in seemingly objective measurements, such as the percentage of glomerulosclerosis. Therefore, these data should not mislead us regarding the importance of procurement biopsies to define organ suitability for transplantation. Rather, they should prompt more studies aimed at optimizing the strategies to score these samples properly for optimal organ allocation.

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The Need to Optimize the Use of Marginal Kidneys for Transplantation

The significant benefit of kidney transplantation over dialysis in terms of life quality and expectancy [1] has fueled a progressive expansion of the indications for transplantation in subjects with end-stage kidney disease [2]. This, together with the growing number of individuals who develop end-stage kidney disease every year [3], contrasts with the steady supply of potential donors, despite the implementation of programs to extend criteria for donor selection. As a result, there is a widening gap between patients on transplant waiting lists and those who actually receive an organ [4] (Fig. 1a). This trend has a dramatic impact on patients on transplant waiting lists, as their survival after 5 years on dialysis is below 40% on average [5]. However, the number of discarded kidneys from deceased donors has increased, mostly as a consequence of the aging of the donor pool (Fig. 1b) [4, 6, 7].

This has created a sense of urgency in the transplant community to expand the donor pool by extending criteria for donation by taking into consideration donors who would have been judged unsuitable for transplantation years before. The expanded criteria donor program was established in 2002 in the United States to increase the use of organs from donors with ≥ 60 years or comorbidities [8]. However, since its implementation, the discard rates have further increased [5]. Major determinants of discarded kidneys were donor comorbidities and biopsy findings on wedge biopsy (percentage of glomerulosclerosis) [5] (Fig. 2). Indeed, many studies converged to indicate that expanded criteria donor kidneys provide significantly worse outcomes compared to those achieved with standard kidneys [9].

In 2013, the United Network of Organ Sharing Kidney Transplantation Committee approved a new allocation policy [10] based on the kidney donor risk index (KDRI). The KDRI is a summative score calculated using donor factors, which describes the relative risk of posttransplant graft failure from a particular deceased donor compared to the average donor [11]. The kidney donor profile index (KDPI) is a percentage that is calculated by ranking the KDRI from the 1st to the 100th percentile, with reference to a given Organ Procurement and Transplantation Network donor cohort. For example, a donor with a KDPI of 70% has a higher expected risk of graft failure than 70% of all recovered kidney donors within the last year. However, implementation of the KDPI score to allocate donor organs is still associated with significant kidney discard rates [5].

Quantifying Nephron Mass to Decide Organ Suitability

The poorer survival of older kidneys has been initially attributed to a greater susceptibility to ischemia-reperfusion injury and delayed graft function, which in turn may expose the allograft to a higher risk of acute rejection and graft failure [12–14]. An additional and probably crucial determinant of earlier function loss of kidneys from older donors is an imbalance between the number of viable nephrons supplied with the graft and the metabolic demand of the recipient. Therefore, a standardized assessment of pretransplant donor biopsies has been proposed to estimate nephron mass [15]. This estimate allows distinction between kidneys that would provide outcomes similar to standard organs and those that should be discarded [16]. Histological evaluation can also identify kidneys with suboptimal nephron mass that should not be transplanted alone but may be suitable if used in dual transplantation (transplantation of both kidneys from one donor into the same recipient).

This strategy has been tested in a matched-cohort study in which graft outcomes of 62 recipients of kidneys from donors older than 60 years allocated to single or dual transplantation based on pretransplant histological evaluation were compared with 124 matched recipients of single kidney grafts from donors younger than 60 years [17]. Results showed that renal function at 3 years was similar between recipients of single or dual grafts allocated according to procurement biopsy and recipients of single grafts from younger donors. Allocation of grafts from donors older than 60 years based on kidney biopsy significantly increased long-term survival compared with that of 124 recipients of grafts from similarly old donors allocated solely on the basis of standard clinical criteria [17]. Of note, a multivariable analysis indicated that allocation based on procurement biopsy predicted improved long-term graft survival independently from other classical factors potentially affecting graft outcome, such as gender, age, weight, cold-ischemia time, and the number of HLA mismatches [17]. A subsequent analysis showed that even kidneys from donors older than 70 years provide excellent outcomes if allocated to single or dual transplantation on the basis of pretransplant biopsy results [18].

Pretransplant biopsy may be particularly important to optimize the use of organs with high KDPI (the KDRI and KDPI do not include biopsy information in their algorithm) [19]. A multicenter controlled study showed that kidneys from octogenarian donors allocated to single or

Fig. 1. Patients on the waiting lists for kidney transplants and rates of kidney discard according to donor age. **a** Increase incidence of ESRD patients on active waiting list (above) compared with steady incidence of kidney transplant. **b** Rates of kidneys recovered for

transplant and not transplanted by age (years). From the Scientific Registry of Transplant Recipients (<https://www.srtr.org/reports-tools/srtroptn-annual-data-report/>; accessed January 31, 2019).

Fig. 2. Common causes of kidney discard in the US. Bars represent percent of 36,700 kidneys discarded between the 2000 and 2015. From the Scientific Registry of Transplant Recipients (<https://www.srtr.org/reports-tools/srtroptn-annual-data-report/>; accessed January 31, 2019).

dual transplantation after a pretransplant biopsy provided comparable 7-year outcomes as single standard-criteria kidney transplants [20]. Most of these very old kidneys may have been discarded by a United Network of Organ Sharing center based on their KDPI scores (96–100%). Importantly, recipients of very old kidneys had remark-

ably shorter waiting times than recipients of younger grafts [20].

A retrospective analysis compared the outcomes of 442 marginal kidney transplants (median KDPI: 93%) allocated as single or dual transplants based on pretransplant biopsy, with those of 248 single standard transplant controls (median KDPI: 36%). At 40 months posttransplant, graft survival was similar between marginal and standard kidney transplants [21].

Overall, data from multiple groups [19] converge to indicate that kidneys from donors older than 60 years with a KDPI higher than 85% can be used safely, provided that the kidneys are selected and allocated on the basis of pretransplant histologic findings [22]. It has been estimated that an allocation strategy based on pretransplant donor biopsy would increase by over 20% the incidence of renal transplants from donors with marginal KDPI (80–100), which would translate into an overall increase of 4% considering the entire pool of donors [21].

The Issue of Correct Histological Analysis

Allocation of marginal kidneys on the basis of pretransplant biopsies is grounded on the assumption that biopsy interpretation is reproducible and that changes observed in the collected samples are representative of those in the whole kidney.

In a recent study, Carpenter et al. [23] analyzed the reproducibility and prognostic capability of procurement

biopsies. These authors compared 270 procurement frozen section biopsy reports with those retrospectively obtained from reperfusion paraffin-embedded biopsies. Repeated procurement biopsies from 116 grafts allowed the authors to examine also the reproducibility of sequential frozen section biopsies. Results showed the lack of correlation between procurement and reperfusion biopsies. In only 64% of cases ($\kappa = 0.25$), the same score category was maintained, with a high discrepancy for glomerulosclerosis, which had only 63% agreement ($\kappa = 0.15$), compared to interstitial fibrosis/tubular atrophy and vascular disease that had agreement rates of 82 and 80%, respectively. These data led the authors to question the utility of procurement biopsy—at least if performed and scored as it is generally done—to define eligibility of organs for transplantation.

The study provides important results and offers the opportunity to discuss the significance of histological evaluation of the graft and how it should be performed. First, the score of the reperfusion biopsies, determined by some of the most experienced renal pathologists, was an independent predictor of graft survival, even after adjustment for KDRI, recipient age, and dialysis vintage. Lack of correlation between procurement biopsies and graft outcomes, therefore, implies that the inappropriate scoring of these samples (done on frozen sections likely by less experienced pathologists) prevents the correct prediction of graft survival. Unfortunately, the fact that different pathologists analyzed differently processed samples (frozen procurement biopsies versus paraffin-embedded reperfusion biopsies) prevents any formal conclusion on the role of the pathologist experience in proper biopsy scoring in this cohort. In a prospective study, Azancot et al. [24] correlated scores of paraffin-embedded donor biopsies provided by on-call pathologists with those retrospective performed by a single renal pathologist blinded to clinical outcomes. The agreement between scores assigned by experienced renal and on-call pathologists was highly dependent on the training in renal histology of on-call pathologist. Importantly, only the evaluation of renal biopsies by the renal pathologist was significantly and independently associated with graft function and survival.

Processing of the bioptic samples is also crucial. The reliability of histology scoring is enhanced when paraffin-embedded sections are used instead of frozen sections and when a critical number of glomeruli are included in the bioptic sample [25]. Evidence indicates a good correspondence between bioptic paraffin-embedded samples

and matched untransplanted kidneys (k index for correspondence: 0.73), provided that at least 10 glomeruli per biopsy are available and needle rather than wedge biopsies are considered [26]. In contrast, frozen samples are harder to interpret due to the technical difficulties of getting good quality sections and staining of tissue, which will all influence the interpretation of the section by the pathologist [27–29].

Remarkably, in Carpenter' study, even seemingly quantitative measurements like the percentage of glomerulosclerosis were poorly reproducible between procurement and reperfusion biopsies. This somehow surprising finding may partially account for the fact that the association between glomerulosclerosis at the time of transplant and graft survival is not a consistent finding across studies [30–32], possibly as a consequence of variable quantification. An additional source of bias in Carpenter' study is represented by the prevalent use of wedge biopsy in procurement biopsies versus needle core biopsies at reperfusion. As the authors correctly point out, wedge biopsies contain disproportionately high subcapsular parenchyma and may result in overrepresentation of glomerulosclerosis, interstitial fibrosis, and tubular atrophy compared to needle core biopsies [26]. This sampling issue is likely a contributor to the increased rate of discards attributed to biopsy findings, especially in instances of unilateral discards [5].

In summary, different training of the scoring pathologists, sample processing (frozen versus paraffin-embedded sections), and sampling techniques (wedge versus core-needle biopsy) may account for the lack of correlation between reperfusion and procurement biopsies. However, these findings should not lead to the misleading conclusion that procurement biopsies are of little use to predict graft outcomes. Conversely, strong independent association between post-reperfusion score and graft outcomes highlights the importance of histological evaluation to define whether a graft should be transplanted (either alone or in couple) or discarded.

As pointed out also by the authors of the paper, efforts should be undertaken to improve the predictive value of procurement biopsies and randomized controlled studies are needed to better define the scores to decide what grafts should be transplanted (either alone or in couple) and which ones should be discarded.

Sampling and biopsy processing are as important (and challenging) as having trained pathologists constantly available to read the biopsies. To facilitate standardization, a clear scoring system should be defined, similar to

the one generated and validated by the dual kidney transplant group [16, 17]. Telepathology, a consultation tool between an off-site and expert kidney pathologists in central hospitals, may represent an option for those centers where trained renal pathologists are not available [33–35].

Second Opinion

Histological evaluation of kidney grafts is instrumental for optimal allocation of marginal kidneys. Carpenter's paper [23] brings to our attention the crucial importance of proper tissue collection, processing, and evaluation for a correct scoring. Sampling biases, erroneous biopsy processing, and reading of samples by inexperienced pathologists may significantly impair the capability of procurement biopsies to predict graft outcomes. Heterogeneity across studies in the way procurement biopsies are performed may account for the variability in

the reported associations between procurement biopsy scores and graft outcomes. More studies are needed to optimize procedures for procurement biopsies and to identify strategies for their implementation in the clinical practice.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

A.A. and P.C.: conceived the article contents, prepared the manuscript, and endorsed the final draft submitted.

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