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Low percentage of pre-transplant histological evaluation of extended criteria donors in Southern Portugal. Are these biopsies irrelevant or should we change our practice?

Rita Magriço[1], Fernanda Carvalho[2]

[1] Nephrology Department. Hospital Garcia de Orta – Avenida Torrado da Silva, 2801-951 Almada, Portugal
[2] Nephrology Department. Hospital Curry Cabral – Rua Ivone Silva, 18.ª, 1050-083 Lisboa, Portugal

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Kidney transplant offers the possibility of reduced mortality and improved quality of life and is at the top of the list of the most cost-effective interventions in medicine[1]. The cost-effectiveness of kidney transplant when compared to dialysis was studied in the Portuguese Healthcare system, with a cost break-even point for transplantation of 32 months[2].

However, the number of patients waiting for a kidney transplant far outweighs the number of organs available. By the end of 2014, there were 1970 patients waiting for a kidney transplant in Portugal. 43 of these died whilst waiting. It is therefore important to identify ways of improving the number and outcomes of the kidney transplants performed.

THE NUMBER OF HARVESTED KIDNEYS COULD BE INCREASED

Transplantation Units throughout Europe and United States have successfully transplanted kidney grafts from elderly donors (over 70 and even over 80 years old). Age alone is insufficient to predict graft function and therefore should not be used as an exclusion criterion for transplantation. The ideal graft is intended to contain enough nephron mass to allow a good glomerular filtration rate in the recipient. Careful consideration must be given to the comorbidities of the donor, cause of death, macroscopic evaluation of the kidney, kidney ultrasound, serum and urine analysis. Histological analysis of the kidney may help the physician with the difficult decision on whether to proceed with transplantation.

THE NUMBER OF KIDNEYS HARVESTED BUT DISCARDED COULD BE REDUCED BY HISTOLOGICAL ANALYSIS OF THE GRAFT

Although in 2015 there was an 11% increase in the number of transplants performed and a 9.5% increase in the number of donors, up to 30% of the harvested kidneys were discarded. On average, 130 organs per year (mostly kidneys) are harvested in Portugal but discarded. This is mainly due to the age and comorbidities of the donor. If a biopsy of the graft is available, the physician has additional information to decide on whether to proceed with transplantation.

THE CURRENT VALUE OF HISTOLOGICAL EVALUATION OF THE DONOR

A great amount of controversy still exists. In the United States, for example, the Kidney Donor Risk Index (KDRI) is used to decide on the graft's suitability for transplantation. This Index is based on clinical criteria such as the donor's age, height, cause of death, any prior diabetes or hypertension, and serum creatinine. No histological criterion is used. In many European centres, however, a histological evaluation of the donor demonstrating absence of significant organ damage is imperative to proceed with donation.

In 2006, Remuzzi et al. published an article in the *New England Journal of Medicine* concluding that

kidney survival following histologically evaluated grafts was superior to kidney survival following non-histologically evaluated matched recipients who were also older than 60 years old (HR for graft failure in the non-histologically evaluated relative to those evaluated histologically of 3.68, 95% CI 1.29-10.53, p-value=0.02)[3]. In the same study, there were no differences in kidney survival in recipients of histologically evaluated grafts from donors > 60 years old when compared with non-histologically evaluated grafts from donors ≤ 60 years old (6% of patients progressed to dialysis in both groups). The median time of follow-up in this study was 23 months and recipients of histologically evaluated grafts from donors > 60 years old received one or two kidneys (double transplant) according to the degree of histological damage present in the biopsy[3]. This study was largely criticised because it included a relatively small number of patients (62 patients in the group with histologically evaluated grafts). Moreover, most of the patients in this group (54 out of 62) received a double transplant, and it was not clear if the improved outcomes were caused by the improved quality of the graft as evaluated by the kidney biopsy or because these patients received a higher nephron mass.

Subsequently, various studies evaluated graft function and survival according to the characteristics found in the donor's biopsy. These studies gave rise to scoring systems such as the Leuven Donor Risk Score or the Maryland Aggregate Pathology Index. However, in some of these studies donor biopsies were observed retrospectively; the score was not validated in a prospective way or was validated in a small number of patients. Randomized controlled trials which prospectively evaluate patients and graft survival of a significant number of patients are lacking.

ETHICAL IMPLICATIONS

Although it is unclear which histological parameter predicts more accurately graft survival, it is clear that organs with severe histological damage are not suitable for transplantation. These patients evolve with graft dysfunction and post-transplant kidney biopsies show donor-associated severe organ damage. A reflection must be made on whether it is ethical to submit this group of patients to the surgical- and immunosuppression-associated risks when a histological analysis could have detected *a priori* a dismal prognosis. The benefit of histological evaluation is increased in transplantation programmes that look for suitable kidneys among donors with extended clinical criteria.

IS A SUBOPTIMAL GRAFT WORSE THAN DIALYSIS?

The decision on whether to proceed with transplantation must take into account the characteristics of each individual. All patients would do better with a fully compatible kidney from a living donor, which is not available in a large number of cases.

Because the demand for kidney transplantation is higher than the number of organs available, kidneys from extended-criteria donors are used. Due to the comorbidities present in these donors (increased age, hypertension, death from cardiovascular cause, increased creatinine), graft survival is worse than in donors without these criteria.

However, even these transplants may be advantageous. In fact, previous studies demonstrate that recipients of extended-criteria donor kidneys live longer than patients who remain on dialysis[4]. However, the short-term risk of mortality is higher with transplantation and a cautious risk-benefit evaluation must be carried out in each candidate.

PATHOLOGICAL ANALYSIS

Important requisites need to be met when collecting, processing and interpreting a kidney biopsy of a potential donor.

Specimens can be obtained by needle core biopsy or by wedge biopsy (performed on the surgical bench, with a scalp). Wedge biopsies generally obtain a larger number of glomeruli but sometimes over-represent subcapsular tissue. On the other hand, some needle biopsies are performed after introducing the needle in the graft, and only renal medulla is obtained. An adequate specimen must contain at least 25 glomeruli, from the outer cortex deep into the medulla, in order to include at least one arcuate artery.

Usually, kidney biopsies are paraffin-embedded. This process takes several hours and the biopsy is normally ready for observation by the pathologist the following day. When a kidney donor becomes available, it is important to reduce the cold ischaemic time. For

purposes of kidney donor evaluation, frozen sections are prepared. These may be available up to thirty minutes after they arrive at the Pathology Service.

There is a satisfactory correlation between the results found in biopsies observed in frozen sections when compared to paraffin-embedded sections. Frozen sections present artefacts and an experienced renal pathologist is required to interpret the results. There is inter-observer variability on the histological score obtained when evaluating a biopsy[5]. In many Transplantation Units these biopsies are sometimes analysed by general pathologists, since a renal pathologist is not available at all times. Additionally, the changes identified must be considered in the context of the characteristics of each sample. Glomerulosclerosis and fibrosis due to vascular disease may be over-represented in the outer cortex and arteriosclerosis can be better evaluated in larger-calibre arteries. Areas of extensive fibrosis may correspond to a focal scar and are not representative of the remainder of the kidney.

THE NUMBER OF PRE-TRANSPLANTATION BIOPSIES PERFORMED IN SOUTHERN PORTUGAL IS RESIDUAL

Between 2002 and 2014 around 400 transplants per year were performed in Portugal (transplantation incidence between 34 and 55.8 pmp). From 2010 to 2014, approximately 50% of donors died from stroke and more than 20% were over 60 years old. The number of expanded-criteria donors is thus high and tends to increase over the years.

Recently, the authors searched for registries of all renal biopsies performed before transplantation in the regions of Lisbon and the Tagus Valley (comprising all the units harvesting organs south to Coimbra). Since the beginning of the performance of these biopsies 14 years ago (from 2002 to 2015), only kidneys of 35 donors were submitted to histological analysis before proceeding with the allocation algorithm. Considering the high number of extended-criteria donors, the percentage of pre-transplantation biopsies performed to grafts of these donors was expected to be significantly higher. Because the number of patients submitted to biopsy is very small, it is not possible to compare the clinical outcomes in those histologically analysed with the remainder. However, as the number of biopsies performed is residual, it is highly probable that elderly donors who could have suitable kidneys are discarded *a priori* for kidney transplantation (by Coordination Units or by on-call nephrologists) and that a number of transplant recipients have significant graft dysfunction due to severe organ damage already present in the donor.

In the specimens reviewed by the authors, the capacity to identify histological changes when analysing a frozen versus a biopsy processed in paraffin was also assessed. As described in the literature, in the samples observed there was also a high correlation between both techniques when observed by an experienced renal pathologist.

There are several reasons why this analysis is performed in a residual number of cases. There is a small number of pathologists in Southern Portugal with the required expertise to perform this analysis. Additionally, these biopsies often need to be analysed outside usual working hours.

Further studies are needed to accurately define the number of kidneys that are not being harvested due to criteria such as age alone. The number of kidneys harvested but discarded by on-call nephrologists because a pre-transplantation biopsy is not available should also be clarified. Some of these organs could be suitable for transplantation. Finally, it is important to quantify the number of patients who have significant graft dysfunction due to severe damage already present in the donor. These data could help us design appropriate strategies to improve the number and quality of the kidneys available.

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Corresponding author:
Rita Aires Magriço
Rua Luís Pastor de Macedo, Lote 17/18 3.º D
rita.magrico@yahoo.com