



Do elderly recipients really benefit from kidney transplantation?



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ABSTRACT

Data from the nineties showed that even older individuals had a survival advantage with kidney transplantation compared to dialysis. Consequently, we are increasingly wait-listing high-risk patients in terms of age and comorbidities. However, times are changing. Due to severe organ shortage we now use more often expanded criteria donor kidneys with less favorable outcomes, while at the same time survival on dialysis is improving. The question therefore rises again if elderly patients really benefit from transplantation nowadays. At least for the U.S., recent data still suggest an overall survival benefit with transplantation in older recipients but the risks vary greatly with the health status of the recipient and with the type of donor. Especially for transplant centers outside of the U.S., recent large studies are lacking. Because of continuing changes in both donor and recipient characteristics as well as dialysis outcomes, a permanent area-specific reassessment of data is needed. In this review we describe the important evolutions in transplant and dialysis care over the last 20 years and provide an overview on recent data comparing survival on dialysis versus transplantation in the elderly.

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1. Introduction

Kidney transplantation is considered to be the preferred therapy for most patients with end-stage renal disease (ESRD) and has shown to be superior to dialysis in terms of long-term mortality risk [1,2]. This was first clearly demonstrated in the landmark study by Wolfe et al. using data from the United States Renal Data System (USRDS) on more than 250,000 incident dialysis patients between 1991 and 1997 [1]. Although the survival advantage of transplantation was most pronounced in younger patients, all age categories gained additional years of life with a transplant compared to dialysis. Even those patients who were transplanted at the age between 60 and 74 years had a relative risk of mortality of 0.39 (95% CI 0.33–0.47, at 18 months after transplantation) compared to those remaining on the waiting list, and their projected life span increased from 6 to 10 years. The findings of this study have encouraged the option of kidney transplantation for relatively older individuals and have consequently led to a strong proportional increase of this age group among transplant recipients over the last two decades [3,4]. However, now 20 years after the Wolfe study, the question on whether elderly patients really benefit from transplantation rises again. First, in the “Wolfe-era” patients were mainly transplanted with good quality, standard criteria donor (SCD) kidneys and not with organs from expanded criteria donors (ECD) or from donors after cardiac death (DCD) as we often use nowadays [3,4]. Second, improved management of chronic kidney disease and improved dialysis care has led to better survival on dialysis [5,6]. Third, survival on dialysis as well as survival

after transplantation is different in Europe and in the United States, which makes it difficult to extrapolate conclusions from studies performed in one continent to another [7,8]. Lastly, the success of kidney transplantation has incited us to push the limits, and we are currently wait-listing high-risk patients in terms of age and/or co-morbidities who would previously not have been considered for transplantation. As a result, the elderly population undergoing transplantation nowadays may include much frailer patients with more co-morbidities compared to those in the Wolfe-study. In this review we describe the important evolutions in transplant and dialysis care over the last 20 years and provide an overview on recent data comparing survival on dialysis versus transplantation in the elderly.

2. Older recipient age

The number of incident ESRD patients has risen strongly over the last two decades [5,6]. This growth is almost completely determined by older adults, which suffer predominantly from ESRD caused by hypertension and diabetes [5]. Simultaneously, we have seen a steady increase of older candidates being transplanted without a corresponding increase in the number of younger transplants. Consequently, the proportion of recipients ≥ 65 years old has risen from about 10–15% to 20–30% over the last decade in Western-Europe and the United States [3,4]. Eurotransplant, for example, responsible for the allocation of donor organs in Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia, reports a rise in the median age of deceased donor transplant recipients from 45 years in 1990 to 55 years in 2013 [3]. Current recipients are not only older, but are also more likely to have more pre-transplant co-morbidities [9].

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3. Organ shortage: lower quality donors

Organ shortage has become of great concern. More patients are being listed for transplantation each year, with only a moderate increase in the number of living or standard criteria deceased donors. As a result, kidneys that previously would not have been considered for transplantation because of inferior quality are now frequently used, such as organs from older donors. Consequently, there has been a dramatic increase in donor age. Eurotransplant, for example, reports an increase of median deceased donor age from 36 years in 1990 to 53 years in 2013 [3]. Patients and transplant physicians are increasingly facing the difficult choice of either accepting an older kidney or to wait for a better offer, while keeping in mind that longer waiting times on dialysis are associated with a worse post-transplant graft and patient survival [10]. In addition, donor age alone may not be a sufficient parameter to estimate organ quality, as the severity of atherosclerotic damage and remaining nephron mass could be highly variable independent of donor age. In an attempt to better predict graft quality, Port et al founded the concept of expanded criteria donors (ECD) [11]. ECDs are defined as those 60 years or older, or those aged 50–59 years with at least 2 of the following conditions: history of hypertension, creatinine level > 1.5 mg/dL, or cerebrovascular cause of death [11]. By definition, ECD kidneys show inferior graft survival compared with SCD kidneys, with a relative risk of graft failure of > 1.7 [11]. Despite these less favorable outcomes, we are increasingly transplanting patients with these ECD kidneys, reasoning that their use may still outweigh the risks inherent to a prolonged time on dialysis. The exact number of ECD is not provided in the Eurotransplant 2013 report, but even considering the age-criterion alone, we can conclude that in Western-Europe at least a quarter of all deceased donors used for a transplant can now be classified as ECD [3]. In the US this proportion lies around 20% [4].

A few remarks should be made concerning the use of ECDs. First, the dichotomous classification of SCD versus ECD strongly oversimplifies the highly heterogeneous pool of donors. For example, a kidney from a 60-year-old otherwise healthy man with a healthy lifestyle dying in a cycling accident is hardly comparable to a kidney from a 50-year-old donor combining hypertension, a high creatinine and death from a cerebrovascular accident, although both donors would be defined as ECDs. There is an incremental risk of allograft failure when a donor combines the four risk factors that are used for the definition of ECD, with adjusted hazard ratios rising from 1.7 up to 2.69 [12]. In other words, a more graded evaluation would be advisable when considering an ECD offer. Some ECD kidneys will lead to an acceptable transplant function while others will do poorly. The simplistic binary ECD versus SCD comparison used in several studies makes it difficult to extrapolate conclusions found in an overall cohort for decision-making in individual cases. A more refined organ quality scoring system such as the Kidney Donor Risk Index (KDRI) may help clinicians to better predict the outcome for a particular kidney offer [13,14].

Second, even when a shorter graft survival of an ECD kidney would be considered to be acceptable in a specified setting, for instance for elderly transplant candidates who inherently have a shorter life expectancy, a worse patient survival in recipients of ECD kidneys may not be considered acceptable [15,16]. A recent systematic review by Pascual et al. indeed confirmed that all available multicentre or registry reports show significantly worse patient survival with ECD versus SCD transplantation [16]. This has led to the widespread agreement that we should avoid transplanting younger patients with an ECD kidney. It seems reasonable to preferentially allocate those kidneys to the older candidates. However, will these elderly patients benefit from such policy? Transplanting frailer patients with poorer quality organs may result in a sizeable increase of perioperative morbidity and mortality. Especially for this subgroup of patients, the question rises if their survival with an ECD kidney would be superior compared to maintenance of dialysis treatment.

One of the first initiatives on a very large scale to allocate in an old-to-old approach is the Eurotransplant Seniors Program (ESP). Launched

in 1999, the ESP algorithm allocates kidneys from donors age 65 years or older to recipients age 65 years or older within a narrow geographic area without considering donor HLA matching in order to minimize cold ischemia time. A 5-year analysis published in 2008, showed that since the initiation of ESP, more elderly donors have become available and waiting time for elderly patients has decreased [17]. Not surprisingly, patient and graft survival in the ESP cohort was lower than for elderly recipients of a kidney from younger donors through the regular allocation scheme. Five-year patient survival in the ESP group was 60% while this was 74% for the any-to-old group ($P < 0.001$). Nonetheless, the 5-year patient survival of 60% in the ESP group could be considered to be acceptable. Indeed, recipients > 65 years in the U.S. had a similar patient survival at that time even when they were transplanted with much younger donors [18]. However, without a correct control group, we cannot know whether old-for-old recipients would have been better off if they would have stayed on dialysis.

4. Transplantation versus dialysis

An important and difficult methodological issue concerns the appropriate choice of a control group of dialysis patients, in order to be able to assess the true benefit of transplantation versus dialysis per se. Indeed, the ESRD population includes a large proportion of frail patients of high age and/or with severe co-morbidities. Particularly in these elderly patients, only a selected group of fitter patients will be deemed eligible for transplantation. In the Wolfe study, for example, annual death rates in the overall dialysis group were 16.1/100 patient-years versus 6.3/100 patient-years for the waitlisted dialysis patients [1]. Comparing outcomes of transplant patients with the dialysis population as a whole, would result in a very substantial selection bias, while comparing them with the waitlisted subgroup of dialysis patients would be much more appropriate.

Since the Wolfe study in 1999, several investigators have re-evaluated the patient survival with transplantation versus dialysis in more recent cohorts. Table 1 summarizes studies published since 1999 including recipients older than 60 years and waitlisted dialysis patients as control group.

Recent large studies have been mainly performed in the U.S. Rao et al. reported on outcomes of 5667 dialysis patients of 70 years or older who were placed on the U.S. kidney transplant waiting list between 1990 and 2004 [19]. Overall, patients who received a kidney transplant had a 41% lower risk of death than similar patients who remained on the waiting list (RR = 0.59; 95% CI, 0.53–0.65). Even those who were transplanted with an ECD kidney had a lower mortality risk than their waitlisted counterparts (RR = 0.75; 95% CI, 0.65–0.86). However, although long-term outcomes seem to favor transplantation, the peri-operative period is associated with significant excess mortality. Gill et al. have quantified the early post-transplant risk of death according to recipient and donor characteristics [20]. They included all U.S. ESRD patients above 65 years of age who were waitlisted for a first kidney transplant between 1995 and 2007. Patients were classified as low, intermediate or high cardiovascular risk according to their co-morbid disease conditions. The authors showed that peri-operative mortality was strongly dependent not only on recipient co-morbid conditions but also on the type of donor. For example, due to the excessive death rate early on, the time to equal survival for high-risk recipients of an ECD kidney versus patients on dialysis was calculated to be 521 days, which compares poorly with those who received a graft from a SCD (368 days) or a LD (130 days). This study confirms that transplanting high-risk patients with low-quality kidneys leads to a particularly high early mortality and underlines the importance of careful selection of patients and good counseling about transplant options. However, for all risk groups, transplantation was associated with a long-term survival advantage. Most other recent studies also support the benefit of transplantation in elderly recipients, even with the use of lower quality

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