ORIGINAL ARTICLE

Safety of dual kidney transplantation compared to single kidney transplantation from expanded criteria donors: a single center cohort study of 39 recipients

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SUMMARY

Our objective was to compare the outcomes of dual kidney transplanataion (DKT) to single kidney transplantation (SKT) performed with grafts from expanded criteria donors (ECD) in recipients ≥65 years, focusing on surgical complications. All kidney transplantations (KT) performed between 2006 and 2014 in our institution were analysed. DKT was indicated according to the criteria of the French national Agence de la Biomedecine. Thirty-nine DKT and 155 SKT were included, with a median follow-up of 36 and 26.5 months, respectively. The rate of early surgical revisions was not significantly higher after DKT (23.1% vs 15.5% ($P = 0.2593$)) but more venous graft thromboses (12.8% vs 3.2% ($P = 0.02$)) were reported. The glomerular filtration rate (GFR) 24 months after KT was significantly higher after DKT (45.0 ± 16.3 vs 39.8 ± 13.8 ml/min/1.73m^2; $P = 0.04$) and allowed shorter waiting time without a significant increased risk of surgical revision, excepted for venous graft thrombosis, more frequent after DKT. Graft survivals were not significantly different and GFR was higher after DKT. DKT seems to remain an appropriate strategy to address the growing graft shortage in elderly patients.

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Key words
dual kidney transplantation, extended criteria donor, graft shortage, kidney transplantation, surgical complication

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Introduction

Treatment of end-stage renal disease (ESRD) is a worldwide medical and socioeconomic challenge [1,2]. While kidney transplantation (KT) is considered as the gold standard treatment for ESRD [3–5], graft shortage remains one of the main challenges in occidental countries. Indeed, even though the number of KT is growing, waiting lists keep increasing every year. With limited supplies of organs and an increasing demand for them, many patients do not receive a transplant in time, with a concerning rate of mortality on the waiting list.

Focusing on elderly ESRD patients, demographic analyses show that the number of patients over 65 years old (yo) awaiting KT constantly grows every year in both Europe [6] and US [7] due to an increased life expectancy and a strong prevalence of ESRD in this

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population. For example, in France, the number of recipients ≥70 yo increased 10-fold between 1999 and 2012 [8] and recipients ≥65 yo represented 27.6% of all ESRD population with a functioning graft in 2014 [9]. The risk of mortality of these patients on the waiting list increases with age and waiting time [10] while KT substantially improves their survival [3,11–14] and quality of life [15,16] with cost-effective outcomes [17,18]. In US, Schold *et al.* [19] showed that 46% of candidates ≥60 yo placed on the waiting list would actually die before receiving a transplant.

The first step to address that graft shortage in the elderly patients was to enlarge donors selection criteria (extended criteria donors or ECD) [20–22] in order to comply a double constraint: on the one hand, the need to enlarge the pool of transplants available and on the other hand the growing age and comorbidities of donors over the past several years [23,24]. ECD according to the UNOS (United Network for Organ Sharing) criteria included initially any donor ≥60 yo and those between 50 and 59 yo with at least two of the following risk factors: cerebrovascular cause of death, history of hypertension or serum creatinine value >150 μmol/l at the organ removal [25]. Currently, these ECD represent more than half of the kidney donors pool in Europe [24]. However, the discard rate of ECD is twice that of the standard criteria donors (SCDs) [26,27]. In the US, that rate even approaches 60% for donors ≥65 yo [28]. Kidneys from older donors have a reduction in nephron mass [29,30], a reduced repair capacity and display increased immunogenicity [31]. The UNOS ECD/SCD criteria have been recently refined with the Kidney Donor Risk Index (KDRI) and Profile Index (KDPI). This scoring system, proposed by Rao *et al.* [32], aimed to increase the utilization of marginal kidneys by providing a fine granular characterization of donor quality, based on 10 donor factors and without the need of a transplant biopsy. The KDPI system has also been made part of the "longevity matching" allocation in the US, where the best kidneys are allocated to the recipients with the longest predicted post-transplant survival. To our knowledge, only one study assessed the impact of that new allocation policy on the rate of discarded kidneys [33], with no significant change in the discard rate from "ECD era" to "KDPI era" (18.1% vs. 18.3%, respectively), but an unexpected and harmful "labeling effect" of high risk (KDPI > 85) SCD kidneys which were at increased risk of discard in the KDPI era, although providing a much lower risk of death (at 2 years post-transplant) to their recipients when compared to those remaining on dialysis waiting list.

First described by Johnson *et al.* [34], dual kidney transplantation (DKT) has been developed with the aim of compensating the nephron mass reduction and to use kidneys from very marginal donors that would have been discarded for single kidney transplantation (SKT). It consists in allocating two kidneys from the same donor to a single recipient [35].

In France, DKT has been performed in the context of an observational study, the BIGRE programme, led by the national Agence de la Biomédecine (ABM) since 2003 [36]. The grafts have to present a cold ischemic time <24 h, and must be obtained from a donor ≥65 yo, with a glomerular filtration rate (GFR) calculated with the Cockcroft and Gault formula between 30 and 59 ml/min during the organ removal, and presenting at least one of the following risk factors: history of hypertension, diabetes or vascular disease or death from cerebral stroke. Additional criteria for allocation include: recipient's age ≥65 yo, pre-transplant panel reactive antibody (PRA) <25% and an informed and consenting patient. When GFR is above 59 ml/min, kidneys are allocated for SKT. Below 30 ml/min, kidneys are not eligible for transplantation.

Even if Remuzzi *et al.* [37]. showed better renal function and blood pressure control without exposing to major surgical complications, the safety of DKT compared to SKT is still debated, with varying and conflicting results among studies [37–44]. The aim of our study was to compare the outcomes of DKT performed in our centre according to the BIGRE programme criteria to SKT performed with ECD kidneys implanted into recipients ≥65 yo, with a focus on surgical revisions.

Patients and methods

Donor and recipient selection and allocation criteria

We retrospectively reviewed data of all recipients with a DKT or a SKT performed between February 2006 and June 2014 in University Hospital of Nice, France. Patients ≥65 yo who received a SKT with an ECD kidney were compared to DKT recipients meeting the selection criteria of the ABM BIGRE programme, also ≥65 yo by definition. For each procedure, recipients' characteristics (demographic data, primary renal disease and follow-up time after transplantation) and donors' characteristics (demographic data, comorbidities, cause of death and renal function at removal) were reported. Main information concerning each procedure was noted: waiting time, operating time, ipsilateral or bilateral technique, cold (CIT) and warm (WIT) ischemia

times, number of HLA mismatches, uses of perfusion machine, blood transfusion quantification and length of hospital stay. The peri- and post-operative uses of immunosuppressive therapies were collected. Recipients received polyclonal antilymphocyte antibodies or anti-IL2-R for induction while maintenance immunosuppression consisted of calcineurin inhibitors (CNI), Mycophenolate Mofetil (MMF) or Azathioprine (AZA) and steroids.

Surgical technique

The surgical technique has already been described by our team in a previous work [45]. For ipsilateral DKT, a pararectal or a Jalaguier–Gibson incision was performed. Anastomoses were made end-to-side on external iliac vessels. The second kidney was placed distally from the first on iliac vessels. Uretero-vesical reimplantations were performed separately with the Campos Freire–Lich-Gregoir technique or together with the Wallace technique and a double J stent was left in place for 6 weeks. Ipsilateral DKT was performed when recipients presented extended calcifications on the contralateral iliac artery, in case of voluminous native polycystic kidney or according to the surgeon's preference when it was feasible. For bilateral DKT, the same technique as SKT was performed on each side of the recipient: pararectal or Jalaguier–Gibson incision, end-to-side anastomoses on iliac vessels and uretero-vesical reimplantations with the Campos–Freire technique. Uretero-ureteral end-to-side anastomosis was performed when the graft ureter was too short.

Surgical complications

We reported all data regarding surgical complications with revision: number and dates of overall surgical revisions, ureteral complications (stenosis, fistulas), vascular complications (arterial and venous thrombosis and stenosis), hemorragic complications (haematomas, number of transfused unit of blood), lymphoceles, abcesses, eventrations, early (<1 month after transplantation) and late surgical revisions, early (<1 month after transplantation) and late graft explantations and deaths directly related to transplantation. The primary endpoint of the study was the early surgical revision rate. We also investigated a potential association between body mass index (BMI) and early surgical revision in DKT recipients by comparing the rates of patients with a BMI $\geq$ 30 kg/m^2 among those that experienced or not an early surgical revision. We reported in this work only complications that led to a surgical or radiological revision, that is, complications classified Clavien-Dindo 3 or more. Only blood transfusions corresponded to Clavien-Dindo 2 complications.

Graft function

Renal function of each patient after transplantation was assessed by measuring serum creatinine (SCr) and calculating GFR using Modification of Diet in Renal Disease (MDRD) at 1, 3, 6, 12 and 24 months. The mean SCr and GFR values were calculated only for patients with functional allografts. Delayed graft function (DGF) was defined by the need of at least one dialysis within the first seven days following the transplantation. We also analysed recipient and graft global and death-censored survivals.

In order to precise the consequences of the early loss of one graft among DKT patients, we analysed SCr, MDRD GFR and death-censored graft survival in two subgroups of DKT: those with early explantation of one graft (DKT 1) and those without explantation (DKT 2). We also compared the outcomes of the DKT 1 group with our SKT group in order to determine wether the remaining graft was useful.

Data sources

All data were extracted from the CRISTAL application, the consultation, hospitalization and operative reports and the CLINICOM software (Intersystems, Cambridge, MA, USA) used in our centre to report all biological and imaging results. The numbers of transfused blood units were collected from the French blood agency (Etablissement Français du Sang) database.

Statistical analysis

Statistical analysis was performed using GRAPHPAD PRISM 6 and R-statistics softwares (GraphPad Software, San Diego, CA, USA). Statistical significance was defined as a P value < 0.05. Results are expressed as percentages for categorical variables, means $\pm$ standard deviations (SD) for variables with a normal distribution and as medians for variables with a nonnormal distribution. Variables' relationships were calculated using an unpaired t test for continuous parametric variables, a Mann–Whitney test for continuous nonparametric variables and a chi-square test or a Fisher's exact test for nominal parametric variables. Survival curves were calculated using the Kaplan–Meier method and compared with the log-rank test.

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Results

Recipients and donors characteristics

Five of the 44 recipients that underwent a DKT in our centre were excluded because of their age <65 yo (Tables 1 and 2). Among the 783 SKT performed during the same period, only 155 met the UNOS ECD criteria. DKT group ($n = 39$) and SKT group ($n = 155$) were similar in terms of sex ratio, recipients age, BMI, history of ESRD or immunosuppressive therapies (excepted for polyclonal antilymphocyte therapies, more frequently used in DKT, contrary to anti-IL2 polyclonal antibodies). The median follow-up time was 36 months in the DKT group vs 26.5 months in the SKT group ($P = 0.1158$).

No significant difference was observed between the two groups regarding donors' demographic characteristics, comorbidities and causes of death. Donors were significantly older in the DKT group (77.1 ± 5.3 yo) compared to the SKT group (72.1 ± 6.3 yo) ($P < 0.0001$) and their renal function at removal was significantly poor in the DKT group, in terms of GFR (62.7 ± 25.1 ml/min/1.73 m^2 vs 88.8 ± 39.3; $P = 0.0001$) and SrC (106.4 ± 48.3 µmol/l vs 83.9 ± 40.4; $P = 0.0033$). The mean CIT was 18 h 18 min ±4 h 02 min for the first kidney (K1) and 19 h 20 min ±4 h 17 min for the second kidney (K2) in the DKT group versus 17 h 23 min ±5 h 11 min in the SKT group ($P = 0.3072$ and $P = 0.0323$ respectively). The mean WIT was 44.8 ± 16.2 min and 42.3 ± 11.9 min in the DKT group versus 50.8 ± 79.1 min in the SKT group (P = ns for both). Perfusion machine was used for three procedures (7.7%) in the DKT group versus seven (4.5%) in the SKT group.

Waiting time and operative data

The median waiting time before transplantation was 2.79 months in the DKT group vs 5.95 months in the SKT group ($P = 0.0022$; Table 3). DKT was performed ipsilaterally in 24 cases and bilaterally in 15 cases. Uretero-vesical reimplantations were performed separately with the Campos Freire–Lich-Gregoir technique in 33 DKT and together with the Wallace technique in four DKT. For two DKT recipients, one transplant's ureter had to be reimplanted on native ureter because of its short length. The mean operating time was 239.8 ± 58.2 min in the DKT group versus 163.7 ± 41.5 in the SKT group ($P < 0.0001$). The mean operating time is still

Table 1. Recipients characteristics.

	DKT ($n = 39$)	SKT ($n = 155$)	P
Demographic data			
Recipients mean age (year ± SD)	70.8 ± 4.4	70.4 ± 3.9	0.2696
Recipients sex (% males)	64.1	75.5	0.1515
Recipients mean BMI (kg/m^2 ± SD)	25.3 ± 4.3	26.2 ± 4.1	0.2115
Anterior kidney transplantations	0 (0%)	9 (5.8)	0.1233
Causes of renal disease (%)			
Diabetes	7 (17.9)	33 (21.3)	0.6448
Hypertensive nephrosclerosis	10 (25.6)	33 (21.3)	0.5587
PKD	2 (5.1)	24 (15.5)	0.0897
Immunologic	4 (10.3)	14 (9.0)	0.8138
Idiopathic/undetermined	11 (28.2)	31 (20.0)	0.2661
Other	5 (12.8)	20 (12.9)	0.989
Immunosuppressive therapy (%)			
Cyclosporin	5 (12.8)	16 (10.3)	0.6536
Tacrolimus	34 (87.2)	135 (87.1)	0.989
Azathioprine	0 (0)	3 (1.9)	0.3812
Mycophenolate	38 (97.4)	146 (94.2)	0.413
Corticoids	39 (100)	144 (92.9)	0.0867
Polyclonal antilymphocyte AB	28 (71.8)	76 (49.0)	**0.0108**
Polyclonal anti-IL2 AB	11 (28.2)	79 (51.0)	**0.0108**
Median follow up time (months)	36.0	26.5	0.1158

DKT and SKT recipients were comparable for all demographic characteristics, history, immunosuppressive treatment and follow-up time.

DKT, dual kidney transplantation; SKT, single kidney transplantation; SD, standard deviation; PKD, polycystic kidney disease. Bold values are statistically significant ($P < 0.05$).

Table 2. Donors characteristics.

	DKT (n = 39)	SKT (n = 155)	P
Demographic data			
Donors mean age (year ± SD)	77.1 ± 5.3	72.1 ± 6.3	**<0.0001**
Donors sex (% males)	41.0	51.6	0.2372
Sex concordance rates donor-recipients (%)	22 (56.4)	80 (51.6)	0.5918
Female donor for male recipient rates (%)	13 (33.3)	56 (36.1)	0.7444
Donors mean BMI (kg/m^2 ± SD)	25.4 ± 3.9	26.9 ± 4.5	0.0567
Donor/recipient BMI median ratio	0.95	1.02	0.7744
Comorbidities (%)			
Hypertension	20 (51.3)	85 (54.8)	0.6903
Coronary heart disease	6 (15.4)	18 (11.6)	0.5863
Diabetes	7 (17.9)	36 (23.2)	0.4782
Renal disease	5 (12.8)	8 (5.2)	0.1421
Systemic disease	1 (2.6)	0 (0)	0.2010
Smoking	3 (7.7)	27 (17.4)	0.1332
Cause of death (%)			
CerebroCvascular	30 (76.9)	121 (78.1)	0.8781
Cerebral anoxia	2 (5.1)	5 (3.2)	0.6297
Public road accident trauma	1 (2.6)	4 (2.6)	1.0000
Non public road accident trauma	6 (15.4)	22 (14.2)	0.8030
Meningitis	0 (0)	2 (1.3)	1.0000
Others	0 (0)	1 (0.6)	1.0000
Mean serum creatinine at removal (μmol/l ± SD)	106.4 ± 48.3	83.9 ± 40.4	**0.0033**
Mean GFR (MDRD) at removal (ml/min/1.73 m^2 ± SD)	62.7 ± 25.1	88.8 ± 39.3	**0.0001**
Ischemia time			
Cold (h ± SD)			
K1	18h18 min ±4h02 min	17h23 min ±5h11 min	0.3072
K2	19h20 min ±4h17 min		**0.0323**
Warm (min ± SD)			
K1	44.8 ± 16.2	50.8 ± 79.1	0.6603
K2	42.3 ± 11.9		0.5291
Use of perfusion machine (after July 2009)	3 (7.7%)	7 (4.5%)	0.4235

DKT and SKT donors were comparable for all demographic characteristics (excepted age), comorbidities, causes of death and use of perfusion machines. Serum creatinine and GRF were poorer in the DKT group. Cold ischemia time of the second kidney transplanted in DKT was significantly longer.

DKT, dual kidney transplantation; SKT, single kidney transplantation; SD, standard deviation; K1, first kidney transplanted; K2, seconde kidney transplanted. Bold values are statistically significant ($P < 0.05$).

significantly shorter in SKT when compared separately to ipsilateral DKT (219.5 ± 29.5, $P < 0.0001$) and bilateral DKT (272.3 ± 76.9, $P < 0.0001$). The median length of hospital stay was 18 days in both groups ($P = 0.7749$). HLA mismatches were significantly more frequent in DKT (4.4 ± 1.2) than in SKT (3.5 ± 1.1) ($P < 0.0001$).

Surgical complications

A total of 19/39 (48.7%) surgical revisions were reported in the DKT group versus 52/155 (33.6%) in the SKT group ($P = 0.0788$), within a median time of 0.5 day in the DKT group versus 1 day in the SKT group ($P = 0.4516$) and including 9/39 (23.1%) early revisions in the DKT group versus 24/155 (15.5%) in the SKT group ($P = 0.2593$; Table 4; Fig. 1). No significant difference was observed regarding surgical complication-free survival curves ($P = 0.37$). One death out of 39 patients (2.6%) directly related to transplantation was observed in the DKT group versus 4/155 (2.6%) in the SKT group ($P = 0.9954$). In the DKT group, the patient died 10 days after transplantation from a graft haemorrhage after a surgical revision for arterial anastomotic leakage. In the SKT group, one patient died on day 52, after a surgical revision for peritonitis caused by an eventration with bowel occlusion, another on day 55 from an haemorrhagic shock after explantation for venous thrombosis and transplant hematoma. The two remaining deaths in the SKT group occurred on day 14 and at 7 months due to multi-system organ failure

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Table 3. Intra-operative and peri-operative outcomes.

	DKT (n = 39)	SKT (n = 155)	P
Median waiting time (months)	2.79	5.95	**0.0022**
Mean operating time, min ± SD (IC95)	239.8 ± 58.2 (220.9; 258.7)	163.7 ± 41.5 (157.1; 170.3)	**<0.0001**
Median length of hospital stay (days)	18	18	0.7749

Median waiting time on list was significantly shorter in the DKT group. The operating time was significantly longer in DKT but no difference was found regarding the hospitalization length after transplantation.

DKT, dual kidney transplantation; SKT, single kidney transplantation; SD, standard deviation. Bold values are statistically significant ($P < 0.05$).

Table 4. Surgical complications of DKT compared to SKT.

	DKT (n = 39)	SKT (n = 155)	OR (IC95)	P
Surgical complications				
Ureteral				
Stenoses	4 (10.3%)	15 (9.7%)	1.07 (0.33; 3.42)	0.9134
Fistulas	1 (2.6%)	3 (1.9%)	1.33 (0.13; 13.19)	0.8050
Plasties or reimplantations	0 (0%)	13 (8.4%)	0.13 (0.01; 2.30)	0.0612
Vascular				
Arterial stenoses	3 (7.7%)	9 (5.8%)	1.35 (0.35; 5.25)	0.6621
Arterial thomboses	0 (0%)	2 (1.3%)	0.78 (0.04; 16.53)	0.4758
Venous thromboses	5 (12.8%)	5 (3.2%)	4.41 (1.21; 16.10)	**0.0154**
Hemorragic				
Hematomas	6 (15.4%)	34 (21.9%)	0.65 (0.25; 1.67)	0.3661
Intraoperative RBC (mean ± SD)	0.77 ± 0.99 (0.45; 1.09)	0.40 ± 0.88 (0.26; 0.54)		**0.0073**
Postoperative RBC (mean ± SD)	2.62 ± 2.50 (1.81; 3.43)	1.95 ± 2.56 (1.54; 2.36)		**0.044**
Intraoperatively transfused patients	16 (10.3%)	30 (19.3%)	0.48 (0.25; 0.92)	**0.02**
Postoperatively transfused patients	30 (76.9%)	86 (55.5%)	2.67 (1.19; 6.01)	**0.01**
Surgical revisions for bleeding	3 (7.7%)	17 (11.0%)	0.68 (0.19; 2.44)	0.5477
Drained lymphoceles	2 (5.1%)	5 (3.2%)	1.62 (0.30; 8.69)	0.5691
Drained abcesses	0 (0%)	2 (1.3%)	0.78 (0.04; 16.53)	0.4758
Eventrations	3 (7.7%)	8 (5.2%)	1.54 (0.39; 6.07)	0.5413
Transplantectomies				
Early	5 (12.8%)	9 (5.8%)	2.39 (0.75; 7.58)	0.1303
Late	1 (2.6%)	3 (1.9%)	1.33 (0.13; 13.19)	0.8050
Total	6 (15.4%)	12 (7.7%)	2.17 (0.76; 6.20)	0.1414
Early surgical revisions	9 (23.1%)	24 (15.5%)	1.64 (0.69; 3.88)	0.2593
Total surgical revisions	19 (48.7%)	52 (33.6%)	1.88 (0.92; 3.83)	0.0788
Median time to revision (days)	0.5	1		0.4516
Deaths directly related to transplantation	1 (2.6%)	4 (2.6%)	0.99 (0.11; 9.15)	0.9954

No significant difference was found regarding the rate of early revisions. The only significant differences reported concerned graft venous thrombosis, higher in DKT. And the number of patients transfused lower introperatively but higher postoperatively in the DKT group.

DKT, dual kidney transplantation; SKT, single kidney transplantation. Bold values are statistically significant ($P < 0.05$).

caused by sepsis (post-operative pneumonia and urinary infection respectively). No significant difference was found regarding ureteral complications, arterial stenosis and thrombosis, drained lymphoceles, abscesses, eventrations, haematomas and early or late explantations between the two groups. Among the five early explantations of one graft in the DKT group, four were performed because of a graft venous thrombosis and one per-operatively because of a bad condition of graft vein. Regarding the nine early transplantectomies in the SKT group, five were performed because of graft venous thrombosis associated with graft hematoma, two were

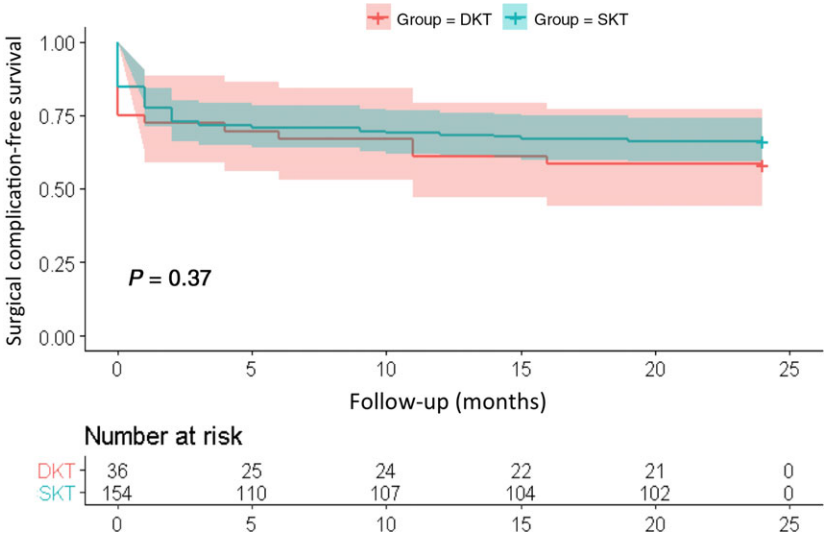

Figure 1 Surgical complication-free survival in DKT compared to SKT. DKT: dual kidney transplantation, SKT: single kidney transplantation. No significant difference was found regarding surgical complication-free survival in the two groups by Kaplan–Meier analysis.

performed on day 12 and day 18 for graft arterial thrombosis, one on day 10 for a defective renal perfusion caused by a transplant malposition and one on day 3 for a transplant gas embolism caused by a perfusion machine dysfunction.

The rate of venous thrombosis was statistically higher in the DKT group (n = 5; 12.8%) compared to the SKT group (n = 5; 3.2%; P = 0.0154). Peroperatively, 16 patients (10.3%) were transfused in the DKT group versus 30 (19.3%) in the SKT group (P = 0.02). Postoperatively, more patients were transfused postoperatively after DKT (30 (76.9%)) than after SKT (86 (55.5%)) (P = 0.01). No significant difference was found between the rates of recipients with a BMI ≥30 kg/m^2 among DKT that experienced an early surgical revision (22.2%) or not (13.3%) (P = 0.52). No significant difference was observed by comparing surgical complication-free survivals between the two groups.

Three eventrations (12.5%) occurred after ipsilateral DKT. When compared to bilateral DKT (no eventration, P = 0.27) and SKT (eight patients (5.2%), P = 0.16), no significant difference was found. Three venous thromboses (12.5%) occurred after ipsilateral DKT. When compared to bilateral DKT, no difference was found (two thromboses (13.3%), P = 0.94), whereas a significant difference was found versus SKT (five venous thromboses (3.2%), P = 0.04), almost as when SKT is compared to bilateral DKT (P = 0.06).

Survivals and graft functions

Kaplan–Meier survival curves did not show statistical difference regarding global recipient survival (P = 0.12) (Fig. 2a), global graft survival (P = 0.081; Fig. 2b) and death-censored graft survival (P = 0.63; Fig. 2c). At 12, 24 and 36 months, respectively, recipient survival was 97.4%, 97.4% and 97.4% in the DKT group versus 92.7%, 87.1% and 84.8% in the SKT group, graft survival was 97.4%, 97.4% and 85.3% in the DKT group versus 85.5%, 78.5% and 76.3% in the SKT group and death-censored graft survival was 100%, 100% and 87.6% in the DKT group versus 91.3%, 88.7% and 88.7% in the SKT group. Five out of 39 patients experienced delayed graft function (12.8%) in the DKT group versus 7/155 patients (4.5%) in the SKT group (P = 0.0543; Table 5). There was a statistically significant better renal function in the DKT group at all steps, both for Scr and GFR, with a mean SCr at 12 months of 148.9 ± 102.7 µmol/l in the DKT group versus 170.4 ± 109.8 in the SKT group (P = 0.0022) and a mean MDRD GFR at 12 months of 46.7 ± 19.2 ml/min/1.73 m^2 in the DKT group versus 40.0 ± 15.6 in the SKT group (P = 0.04; Table 5). GFR seemed to be stable in time in DKT recipients, whereas it showed a trend to increase in SKT. In order to precise GFR evolution, we compared GFR at 1 month with GFR at 24 months in each group. Mean GFR at 12 months was significantly higher in the SKT group (39.8 vs 33.3 ml/min/1.73 m^2; P < 0.0001) but not in the DKT group. Among the DKT, five recipients, the "DKT 1" subgroup experienced an early loss of one graft. This led to a nonsignificant decrease in renal function in the DKT 1 subgroup compared to the DKT 2 subgroup (Table 6; Fig. 3a) and to the SKT group (Table 7; Fig. 3b). The death-censored graft survival of DKT 1 subgroup was neither significantly different from that of DKT 2 subgroup (P = 0.2848; Fig. 3a) nor from that of SKT group (P = 0.4873; Fig. 3b). Finally, after a median follow-up

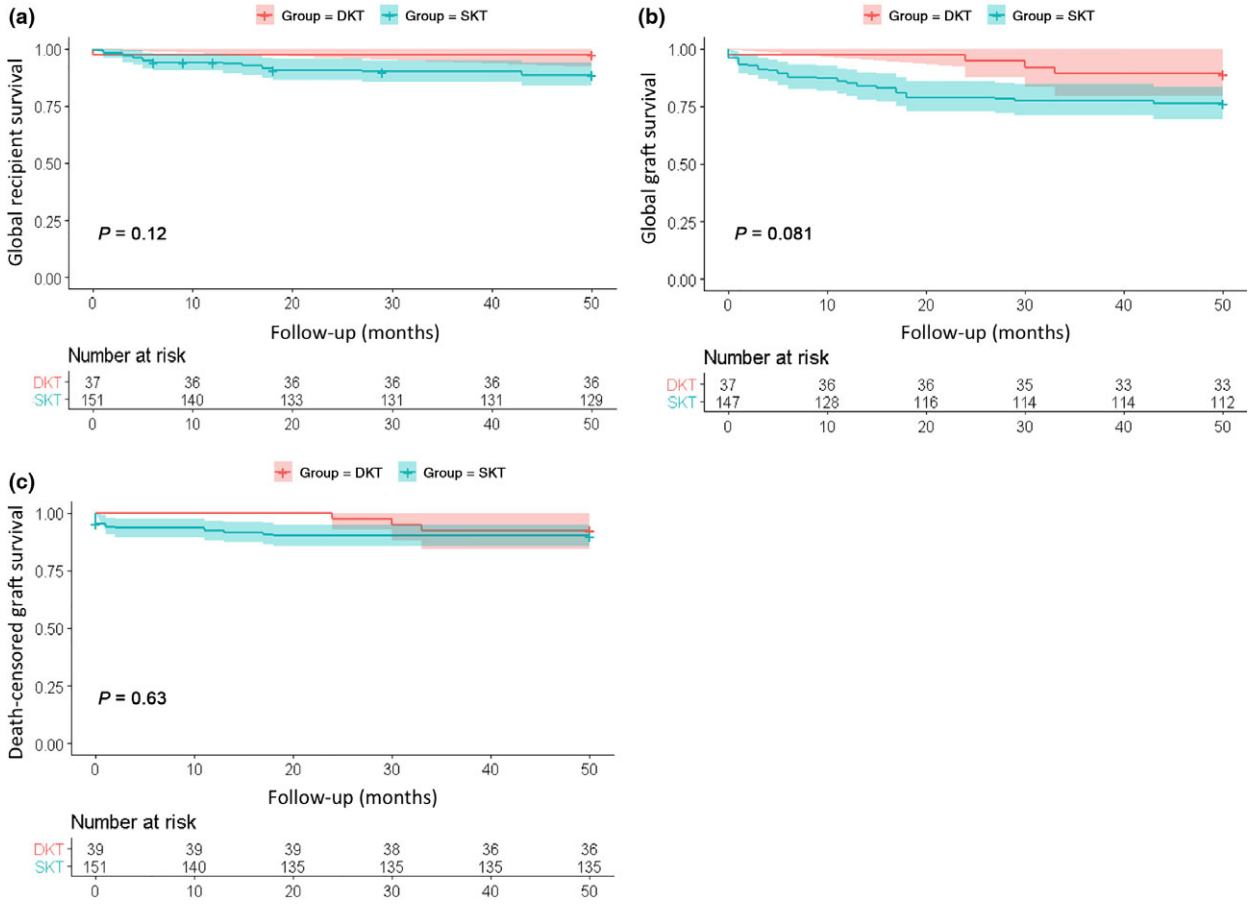

Figure 2 Recipient (a), graft global (b) and death-censored (c) survivals in DKT compared to SKT. DKT: dual kidney transplantation, SKT: single kidney transplantation. No significant difference was found regarding global recipient survival, global graft survival and death-censored graft survival between DKT and SKT by Kaplan–Meier analysis.

time of 36 months in the DKT 1 subgroup, only one patient returned to dialysis after early loss of one graft.

Discussion

Johnson *et al.* [35] first reported in 1996 the interest of DKT to increase the utilization of kidneys from older donors. Remuzzi *et al.* [37] published in 1999 the first prospective controlled multicentric trial, which compared DKT to SKT performed with ECD kidneys. Despite positive outcomes reported, the safety of that technique is still controversial. This may explain the absence of an international DKT allocation system that would define specific donors and recipients' criteria to homogenize practices among KT centres [46–48].

Our study is to our knowledge the first that compares, as extensively, surgical complications between DKT and SKT using the ABM allocation kidney system. Our results suggest that, in elderly patients, DKT strategy could be globally equivalent to SKT performed with ECD kidneys.

Recipient populations of our two groups (DKT and SKT) were comparable. In contrast, donor's age was significantly lower and donor serum creatinine significantly higher in the SKT group compared to the DKT group. Theses differences were expected because we compared here two strategies that use kidneys differing by definition in their donor GFR at removal, and also in the donor age: the BIGRE programme includes only kidneys from donors ≥65 yo for DKT while the UNOS ECD SKT criteria include also some kidneys from donors <65 yo. Rates of uses of perfusion machines are low in both groups because the first use of machine in our centre occurred only from 2013. The higher rate of HLA mismatches in DKT was also expected because HLA compatibility is not a priority criterion in the decision DKT allocation. CIT for the first kidney in DKT was longer than in SKT. We cannot assign the responsibility for that to the DKT attribution circuit, that is not longer than the conventional circuit, despite the small number of centres that perform DKT and the

Table 5. Renal function of DKT compared to SKT.

		DKT (n = 39)	SKT (n = 155)	P
Delayed graft function rates (%)	OR: 3.11 (0.93; 10.40)	12.8%	4.5%	0.0543
Mean serum creatinine, μmol/l ± SD (IC95)				
M1		147.2 ± 64.1 (124.9; 169.6)	202.1 ± 105.9 (183.3; 220.8)	**0.0001**
M3		152.7 ± 97.5 (119.2; 186.2)	178.2 ± 73.7 (165.4; 191.0)	**0.0007**
M6		139.2 ± 64.8 (116.2; 182.1)	176.9 ± 79.5 (163.1; 190.7)	**0.0004**
M12		148.9 ± 102.7 (115.2; 190.7)	170.4 ± 109.8 (151.0; 189.8)	**0.0022**
M24		156.5 ± 124.7 (113.0; 200.0)	157.9 ± 46.4 (148.5; 167.4)	**0.0096**
Mean GFR (MDRD), ml/min/1.7 3 m^2 ± SD (IC95)				
M1		44.0 ± 16.7 (38.1; 49.9)	33.3 ± 15.2 (30.5; 36.1)	**0.0003**
M3		46.9 ± 18.4 (40.3; 53.4)	36.9 ± 13.4 (34.4; 39.3)	**0.0017**
M6		46.9 ± 17.6 (40.6; 53.3)	38.1 ± 15.1 (35.3; 40.8)	**0.0059**
M12		46.7 ± 19.2 (40.2; 53.3)	40.0 ± 15.6 (37.1; 42.9)	**0.0413**
M24		45.0 ± 16.3 (39.2; 50.7)	39.8 ± 13.8 (36.9; 42.6)	**0.0397**

No significant difference was found regarding delayed graft function rates, but DKT presented better functional outcomes in terms of serum creatinine and GFR from 1 month (M1) to 24 months (M24) after transplantation.

DKT, dual kidney transplantation; SKT, single kidney transplantation; GFR, glomerular filtration rate. Bold values are statistically significant ($P < 0.05$).

Table 6. Renal function of DKT with (DKT 1) and without (DKT 2) early explantation of one graft.

	DKT 1 (n = 5)	DKT 2 (n = 34)	P
Mean serum creatinine (μmol/l ± SD)			
M1	171.0 ± 85.6	144.9 ± 63.0	0.6364
M3	133.7 ± 33.6	154.5 ± 101.5	0.9008
M6	151.0 ± 40.6	138.0 ± 67.1	0.2674
M12	151.5 ± 58.6	148.6 ± 107.3	0.4406
M24	178.7 ± 93.5	154.3 ± 128.3	0.3762
Mean GFR (MDRD) (ml/min/1.73 m^2 ± SD)			
M1	32.0 ± 16.1	45.2 ± 16.5	0.2824
M3	37.7 ± 12.9	47.8 ± 18.8	0.3576
M6	33.0 ± 11.1	48.3 ± 17.7	0.0919
M12	36.0 ± 10.1	48.1 ± 19.7	0.1721
M24	31.0 ± 10.2	46.4 ± 16.2	0.0887

Overall, DKT 2 recipients tend to present better functional outcomes from 1 month (M1) to 24 months (M24) after transplantation compared to DKT2, but the difference is not statistically significant.

potential high risk of discarded kidneys. The only explanation that remains is the preparation of the contralateral kidney, even if its duration is in most cases much shorter than 55 min.

We found no significant difference between DKT and SKT groups regarding either the number of deaths or the number of graft explantations. We chose the early surgical revision rate as the primary endpoint on the one hand for its relevance in the context of the assessment of the safety of a surgical technique because the vast majority of surgical complications that compromise recipient or graft survival occur in the first month and on the other hand in order to minimize the impact of the difference in median follow-up times between the two groups (36 months in the DKT group vs 26.5 in the SKT) on our main outcome. This primary endpoint is comparable between the two groups, as well as the recipient's surgical complication-free survivals. The rate of postoperative venous thrombosis was significantly higher in DKT, as well as the operative time. Peroperatively, less patients were transfused in the DKT group. That significant difference could be attributed to surgeon experience. Indeed, in our centre, DKT is exclusively reserved to trained surgeons, probably limiting the hemorrhagic risk. On the contrary, we observed significantly more postoperative transfusions after DKT. We can explain that by the higher hemoglobin threshold indicating a blood transfusion in the DKT population, weaker and running a higher risk of heart and vascular diseases.

There was no significant difference regarding the overall surgical revision rate, early explantations and graft and death-censored graft survival. Finally, in our series of DKT, a high recipient BMI (≥30 kg/m^2) was not significantly associated with a higher risk of early surgical revision, which is consistent with other studies [49–51] regarding SKT. As expected, mean operating time was considerably longer in the DKT group compared to the SKT group (239.8 vs 163.7 min respectively), particularly when grafts were placed bilaterally (data not shown).

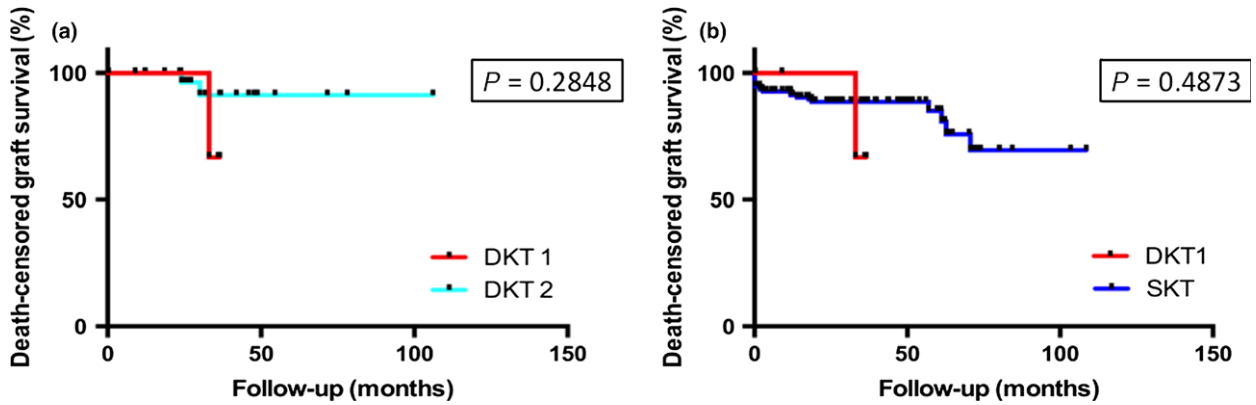

Figure 3 Death-censored graft survivals in DKT1 compared to DKT2 (a) and to SKT (b). DKT1: DKT with early explantation of one graft, DKT2: DKT without explantation. No significant difference was found regarding death-censored graft survival when DKT1 is compared to DKT2 or to SKT by Kaplan–Meier analysis.

Table 7. Renal function of DKT with early explantation of one graft (DKT1) compared to SKT.

	DKT 1 (n = 5)	SKT (n = 155)	P
Mean serum creatinine (μmol/l ± SD)			
M1	171.0 ± 85.6	202.1 ± 105.9	0.5459
M3	133.7 ± 33.6	178.2 ± 73.7	0.2744
M6	151.0 ± 40.6	176.9 ± 79.5	0.7282
M12	151.5 ± 58.6	170.4 ± 109.8	0.6021
M24	178.7 ± 93.5	157.9 ± 46.4	0.9894
Mean GFR (MDRD) (ml/min/1.73 m^2 ± SD)			
M1	32.0 ± 16.1	33.3 ± 15.2	0.9461
M3	37.7 ± 12.9	36.9 ± 13.4	0.8717
M6	33.0 ± 11.1	38.1 ± 15.1	0.5864
M12	36.0 ± 10.1	40.0 ± 15.6	0.6483
M24	31.0 ± 10.2	39.8 ± 13.8	0.2942

No significant difference was found regarding functional outcomes from 1 month (M1) to 24 months (M24) in DKT recipients that experienced an explantation of one graft when compared to SKT.

The rate of total surgical complications varies greatly between series of DKT reported (13.9–70.4%, Ref. 38,41,43,45,52–54). When compared to our DKT outcomes (48.7%), only Fernandez-Lorente *et al.* [38] and Snanoudj *et al.* [41] reported higher rates, with 58.0% and 70.4% of surgical complications, respectively. Our global rate of explantations of one graft (15.4%) is similar than reported in other studies (2.4–29.4%, Ref. 39,41,43,45,53–59), as well as the rates of ureteral stenoses (10.3% vs 0–11.1%, Ref. 38,39,41,43,56,58–63), ureteral fistulas (2.6% vs 0–17% Ref. 37–39,41, 43–45,53,55,56,59,62,64,65), hematomas (15.4% vs 1–35.5%, Ref. 37,41,45,55,62,63), drained lymphoceles (5.1% vs 1.3–18.6%, Ref. 39,44,56,58,59,61–63,65) and eventrations (7.7% vs 5–12.5%, Ref. 41,43,56,61,62).

We tried to investigate the impact of the placement of grafts in DKT on the rates of eventrations and venous thromboses. In our series, even if there seems to be a trend toward a higher frequency of eventrations after an ipsilateral placement, we cannot conclude because of a lack of statistical power. Regarding venous thromboses, no difference was found when ipsilateral DKT is compared to bilateral DKT, whereas a significant difference was found versus SKT, almost as when SKT is compared to bilateral DKT. This outcome is very controversial in the few studies on that topic which does not allow any reliable conclusion. Some authors argue that the ipsilateral procedure, sometimes wrongly considered as less safe, has the advantage of a shorter operating time, a decreased cold ischemia time and leaves the contralateral iliac fossa available for further retransplantation procedures [60,66]. On the contrary, Timsit *et al.* [55] highlighted a significant risk of graft thrombosis when unilateral implantation is performed (P = 0.035). They explained that finding by the compression induced by the two allografts trapped in the iliac fossa, creating a compartment syndrome and by the need to compromise in allograft implantation, probably leading to a suboptimal positioning of vessels, encouraging early thrombosis [67].

Our results show that the occurrence of venous thrombosis is more associated with grafting an additional transplant (fourfold risk), implying longer operating time and multiplication of vascular sutures, than with its placement, as suggested by Snanoudj *et al.* [68], who underlined that when the number of vascular anastomosis performed is taken into consideration, which is twice for DKT, there is no significant increase in thrombosis associated with DKT among the different studies. The significantly higher risk of graft thrombosis in DKT

compared to SKT is also reported by Andrès *et al.* [44] (fourfold risk) and Snanoudj *et al.* [41] (threefold risk). Focusing on venous graft thrombosis, De Serres *et al.* [40] and Snanoudj *et al.* [41] found respectively a twofold and a fivefold increase in DKT compared to SKT, but not statistically significant. Currently, few risk factors of venous graft thrombosis have been established. Possible causes include damage to the renal vein, its twist on implantation or graft positioning, small or multiple veins, the extension of a deep venous thrombosis and of course the recipient's history (thrombophylia, obesity...) [69]. There are neither evidence-based nor consensus guidelines on the use of immediate postoperative thromboprophylaxis to prevent renal allograft vascular thrombosis because of the lack of powerful studies [70] and contradictory results of prospective studies [71–73].

Regarding graft survival, most of studies that compared DKT to SKT found no significant difference, even after 4 [42], 5 [74] and 8 years [75]. However, Fernandez-Lorente *et al.* [38] found a 10-year cumulative graft survival higher in their SKT group and a review of UNOS registry data [76] showed that DKT resulted in a 15% lower graft survival at 3 years and a higher rate of primary nonfunction, when compared to SKT from donors older than 55 years, whereas Stratta *et al.* [52] reported more recently significant better graft survival until 4 years in DKT. Other DKT series reported graft survival rates at 1 (82–100% Ref. 37,39,41,42,45,52–56,59,61–63,74,75,77,78) and 3 years (76–95%, Ref. 39,41,42,53,54,58–64,74,75) are comparable to ours (respectively 100% and 87.6%), as well as the recipient survival rates at 1 (89.7–100%, Ref. 38,39,41,42,44,52, 54–56,59,61–63,75,77,78) and 3 years (80–97.5%, Ref. 39,41,42,54,58–63,75), both at 97.4% in our series.

Regarding renal function after transplantation (Scr, GFR, DGF), some studies did not find significant differences between DKT and SKT [38,40,41,43] while others found better renal function in DKT [37,39,44,52]. In our DKT group, Scr and MDRD GFR were significantly better until 24 months after surgery. Fernandez-Lorente *et al.* [38] found similar outcomes to ours with a 5-year follow-up, although statistical significance was vanishing 5 years after transplantation. In our series, a trend to increase in GFR after SKT has been observed, whereas GFR remains stable after DKT. That finding was also reported by Snanoudj *et al.* [41]. This increase might reflect compensatory post-transplant hyperfiltration, one of the factors involved in post-transplant chronic nephropathy. In this context, DKT could be a protective factor against post-transplant chronic nephropathy. Our DGF rate in DKT (12.8%) is lower than that reported in most of other studies (13–56.1%, Ref. 38,39,39–44,52,54,56,57,60–62,64,65,74,75,78), these results being probably related to the use of anti-thymocyte globulin for immunosuppressive therapy induction in most of DKT (71.8%) in our centre. However, mean values of serum creatinine and GFR seem to be similar at 12 months (respectively 148.9 vs 119–159 μmol/l [38,41,43,44,52,54,56–58,61,62,74,75,77,78] and 46.7 vs 42–55 ml/min, Ref. 38,40,41,43,52,53,55,57,62,64).

We have no recent experience of kidney transplantation with arterial anastomosis on vascular prosthesis in our centre. None of the recipients of our series benefited from that technique, which was nevertheless reported in our centre previously [79]. However, in case of important atheromatous iliac artery, renal transplantation after or simultaneously to vascular prosthesis implantation has been many times reported [79–83], with a higher morbidity [79] and a graft loss rate around 10% [79,81]. If we take for granted that the ipsilateral DKT causes more graft venous thrombosis, we have to actually balance the increased morbidity of the multiplication of arterial anastomosis on vascular prosthesis in case of bilateral access with the increased risk of graft venous thrombosis in case of single access. In this particular challenging issue, the second option seems more reasonable, especially as the higher rates of venous thrombosis in ipsilateral access have only been reported in one study in a statistically significant manner [55].

Currently, ECD kidneys are allocated in DKT according to clinical, biological or histological features, depending on the preference of each centre. Despite the proposed criteria from both retrospective [43,44] and prospective studies [37,40,65] and the defined UNOS [42] and ABM [21] policies, selection of donors for DKT is still controversial. No simple and efficient allocation criteria that would result in similar outcomes in SKT and DKT are currently available to clinicians. On the one hand, we have to be sure that the two kidneys selected for DKT will be at least as efficient as one ECD kidney selected for SKT. On the other hand, there is always a risk to allocate for DKT two kidneys that would have been suitable for SKT separately [58,84]. That potential waste of resources, also suggested by Moore *et al.* [43] and Alfrey *et al.* [85], could partly explain the decreasing use of that strategy during the last decade [77], even if transplants selected for DKT are often considered as those that "nobody wants" for SKT [22]. Thus, it appears difficult to assess the positive or negative impact of DKT on the pool of organs available [46–48].

The allocation system based on preimplantation biopsy has been supported by many studies that showed better outcomes by discarding kidneys with severe histopathological anomalies [65,86]. Nevertheless, Impedovo *et al.* [63] observed a mean Remuzzi–Karpinsky score significantly better for SKT than DKT, with similar graft survivals in the two groups, suggesting that the algorithm using histologic features to allocate ECD kidneys for DKT may be too protective and probably requires further refinement.

A French prospective study, led by Snanoudj *et al.* [41], compared the ABM allocation system [21], used in our centre, and mainly based on the GFR at organ removal, to three other systems, based, among others, on histological criteria: that of Remuzzi *et al.* [65], of Andres *et al.* [44] and the UNOS criteria [42]. The authors concluded that the ABM criteria were as relevant as the histological criteria, regarding GFR values at 1 year. Moreover, as underlined by Timsit *et al.* [55], the preimplantation histological assessment of kidneys (6 h for processing of samples) requires the availability of a pathologist, often during nights and weekends to avoid an further increase in cold ischemic time.

Composite scores, including clinical, perioperative and histologic features, have also been proposed to allocate kidneys for DKT [87]. Balaz *et al.* [56] used both eGFR and histologic features, associated with additional parameters, to select kidneys allocated for DKT. Anglicheau *et al.* [88] showed in a retrospective study that the most predictable score for GFR at 1 year was a composite score including donor serum creatinine, donor hypertension and percentage of glomerulosclerosis. In addition, Snanoudj *et al.* [41] showed that in the DKT group, but not in the SKT group, there was an association between the percent of glomerulosclerosis, Remuzzi's score and a low 1-year eGFR. This association suggests that data from preimplantation biopsies could improve the prediction of 1-year renal function based on the donor's eGFR in kidneys eligible for DKT.

Finally, Klair *et al.* [89] tried to better define which kidney would fit a SKT or a DKT using the KDRI/KDPI scoring and found that a KDRI >2.2 was the cut-off value that conferred significantly better overall graft survival with DKT, with a discard rate of 41% in that category of transplants. Tanriover *et al.* [90] found that kidneys with KDPI > 90% were associated with increased odds of discard (OR = 1.99, 95% CI 1.74-2.29) compared to ones with KDPI <80% and that DKTs of KDPI > 90% were associated with lower overall allograft failure (HR = 0.74, 95% CI 0.62-0.89) and better patient survival (HR = 0.79, 95% CI 0.64-0.98) compared to single ECD kidneys with KDPI > 90%. Indeed, we can assume that a KDPI > 90% (KDRI-UNOS > 2) seems to be the more relevant threshold to allocate ECD kidneys for DKT and that this scoring system will probably play a role in deceased donor kidney allocation policies across Europe in the near future.

In our centre, the global median waiting time before KT (14 months) is relatively short when compared to other centres in France, and even shorter for elderly recipients that participate in the BIGRE programme, without being removed from the conventional SKT waiting list. Our significantly shorter waiting time in DKT underlines its interesting role in increasing the pool of available organs by allocating kidneys that "nobody wants" for SKT. To date, the shortest median time before DKT transplantation, reported by Balaz *et al.* [56], was 5.4 months, whereas we found a median time of 2.8 months (mean of 6.6 months) between waiting list booking and KT. That difference could be explained by the multiplicity of allocation criteria used among studies, and suggests a relative permissiveness of the ABM criteria used here. Unfortunately, the waiting times before transplantation were not mentioned in the two other studies using the ABM criteria [41,55].

Among the five DKT recipients of our series that experienced an early loss of one graft ("DKT 1" subgroup), in most of cases because of a venous thrombosis (4/5), only one patient returned to dialysis after a median follow-up time of 36 months. Moreover, this led to a nonsignificant decrease in renal function in the DKT 1 subgroup compared to the 34 DKT recipients that did not experience an early loss of one graft ("DKT 2" subgroup) and the death-censored graft survival of DKT 1 subgroup was neither significantly different from that of DKT 2 subgroup nor from that of SKT group. Of course, we do not have enough statistical power to conclude but we did not experience a loss of both two grafts in DKT, and the remaining graft seemed to be enough in most of cases to avoid a return to dialysis. That finding raises two conflicting questions: Is the higher risk of venous thrombosis balanced by a potential functional remaining graft in case of transplantectomy? Have we allocated transplants for DKT that would have been more suitable for two SKT using the ABM criteria, maybe too protective ? Thus far, it is difficult to resolve that dilemma, but if we consider that DKT is not more risky than SKT, the priority in the context of increasing graft shortage would be to reserve the best ECD kidneys only for SKT and thus to improve our allocation criteria, as done in the US with the KDRI/KDPI scoring system [89].

We have to temper our results by the lack of power of the analysis because of the small size of our samples. Other limitations of our study are the inaccurate estimation of GRF by serum-based formulas and the difficulty to extrapolate the results of single centre study, using a national allocation policy. In addition, a reliable comparison to other DKT cohorts published appears difficult, mainly because of the wide heterogeneity of DKT allocation criteria used.

In conclusion, dispite the limitations of our study, our work contributes to the global effort to assess the safety of DKT. Our results suggest that, despite an increased risk for venous graft thrombosis, DKT could provide comparable or superior functional outcomes (no significant difference in graft survivals and higher GFR) to SKT in recipients ≥65 years old, and allow shorter waiting time on list without an increased risk of surgical revision. That technique seems to be safe when the recipient is correctly selected. In the context of increasing graft shortage, we do not think that DKT has to be reserved to expert centres, especially when bilateral technique is performed, but rather to experienced surgeons in order to limit the operating time and the increased risk of venous thrombosis. Even if there is no consensus, the additional risk of thrombosis has to be taken in account in the decision of post-operative anticoagulation. Thus, DKT seems to remain an appropriate strategy to address the growing graft shortage in elderly patients, particularly in front of the increasing part of "very extended" criteria donors (≥80 yo). However, our results need to be confirmed in a larger multicentric study, ideally prospective, with a multivariate analysis. Thus far, that scientific issue can be answered if research groups finally pool their data and perform individual patient data meta analyses.

Authorship

LM: designed the study, collected the data and wrote the paper. LA, MD and JA: contributed important reagents. IB: reviewed and completed the statistical analysis. TY and DC: designed the study. CB: collected the data. HQ, BT and JJ: performed the procedures.

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Conflicts of interest

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