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Robot-assisted kidney transplantation: analysis of surgical aspects and functional results from its introduction to its standardization

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1. ABBREVIATIONS AND KEYWORDS

Abbreviations.

BMI, body mass index; CRP, C-reactive protein; CT, computed tomography; DGF, delayed graft function; EAU, European Association of Urology; EDTA, ethylene diamine tetra-acetic acid; ERUS, EAU Robotic Urology Section; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GMV, grafts with multiple vessels; GSV, grafts with single vessel; IL-6, interleukin-6; KT, kidney transplantation; NGAL, neutrophil gelatinase-associated lipocalin; OKT, open kidney transplantation; POD, postoperative day; RAKT, robot-assisted kidney transplantation; RWT, rewarming time; SD, Standard Deviation; SIRS, systemic inflammatory response syndrome

Keywords.

Inflammatory Markers; Learning Curve; Kidney Transplantation; Robotic Surgery.

2. SUMMARY

2.1 Summary (English version)

Robot-assisted kidney transplantation:
analysis of surgical aspects and functional results from its introduction to its standardization

INTRODUCTION & BACKGROUND. Kidney transplantation (KT) is the preferred treatment for patients with end-stage renal disease (ESRD) owing to the greater survival rate and better quality of life in comparison to hemodialysis. To date, the open approach has been the gold standard in KT, despite its invasiveness and high morbidity. In order to reduce the morbidity associated with conventional open surgery, the minimally invasive procedure may be a good alternative, particularly in immunocompromised and fragile KT patients and even more importantly in obese recipients due to the higher complication rate. The scientific evidence supporting robot-assisted kidney transplantation (RAKT) is growing rapidly. Since the first description in 2010, RAKT has been shown to be technically feasible in different clinical settings, including living donors, obese patients, deceased donors, and challenging surgical conditions (i.e., patients with previous abdominal surgery, grafts with multiple vessels, and patients with autosomal dominant polycystic kidney disease).

METHODS. In 2016, the European pioneer Dr. Alberto Breda, with the support of the European Association of Urology (EAU), formed the EAU Robotic Urology Section (ERUS) RAKT working group in order to prospectively follow the outcomes of RAKT. In order to report the evolution of RAKT, the manuscript describes the technical details and the surgical steps of this approach. Furthermore, the most relevant studies conducted by the ERUS group are analyzed, focusing on the functional outcomes, the surgical results and the complication rate.
A quantification of the systemic response in open kidney transplantation (OKT) versus RAKT has been explored through the clinical results (immediate vs delayed graft function) and systemic inflammatory markers (C-reactive protein, interleukin-6, and neutrophil gelatinase-associated lipoprotein).
The learning curve required with this innovative approach has been studied, evaluating surgical and functional results and intra- and postoperative complications in the five highest volume centers of the ERUS working group.

MAIN RESULTS. Thanks to the collaboration of this group, *Breda et al.* published the largest multicenter series of RAKT, *Territo et al.* addressed the functional results at 1-year follow-up of patients with grafts from living donors, *Vignolini et al.* developed a RAKT program with grafts from deceased donors, and *Siena et al*. described the technique for RAKT when using grafts with multiple vessels. In light of comparable graft and patient survival, the advantages of RAKT, in terms of incision length, postoperative pain, blood loss, and time to recovery, are supported by robust evidence. In addition, RAKT is associated with a lower risk of specific surgical complications such as postoperative lymphocele and wound infection. Despite this, there is no study comparing the functional results and the quantification of the systemic response in open versus robotic KT. In order to explore this issue, functional results and systemic inflammatory markers were compared in RAKT versus conventional OKT, without significant differences in the kinetics and magnitude of postoperative SIRS according to the surgical approach.
Furthermore, previous experience in RAKT has been shown to have no impact on the learning curve of this emerging technique when the procedure is carried out by surgeons with experience in robotic surgery and vascular anastomosis.

However, consensus has been lacking on the optimal way of determining the learning curve in RAKT. Although RAKT technique has already been standardized by the ERUS working group, analysis of the learning curve remains difficult due to its multifactorial nature and the several variables that have to be considered. In the reported analysis of learning curve in RAKT, experienced surgeons require 35 cases to achieve optimal surgical outcomes.

CONCLUSIONS. In this manuscript, the evolution of RAKT, from its introduction to its standardization, is described. In particular, the most relevant studies conducted by the ERUS group are reported, focusing on the analysis on inflammatory markers in OKT versus RAKT and the learning curve required with this innovative approach.

2.2 Summary (Italian version)

Trapianto renale robotico:
analisi degli aspetti chirurgici e dei risultati funzionali dalla sua introduzione alla sua standardizzazione

INTRODUZIONE. Il trapianto renale (TR) è considerato il trattamento d'elezione per i pazienti affetti da insufficienza renale cronica terminale, grazie al maggior tasso di sopravvivenza e la migliore qualità della vita rispetto all'emodialisi. Ad oggi, l'approccio chirurgico a cielo aperto è considerato il gold standard della chirurgia del TR, nonostante la sua alta invasività e morbilità. Pertanto, la chirurgia minimamente invasiva può essere una valida alternativa, soprattutto in pazienti fragili, immuno-compromessi ed obesi a causa del più alto tasso di complicanze. Le evidenze scientifiche a supporto del trapianto renale robotico (TRR) stanno aumentando rapidamente. Dalla sua prima descrizione nel 2010, si è dimostrato che il TRR è tecnicamente fattibile in diversi contesti clinici, tra cui nel caso di trapianto da donatore vivente e cadavere, nei pazienti obesi nonché in condizioni chirurgiche difficili (pazienti precedentemente sottoposti a chirurgia addominale, reni con vasi multipli e pazienti con malattia renale policistica autosomica dominante).

METODI. Nel 2016, il pioniere europeo della procedura -Dr. Alberto Breda-, con il supporto dell'Associazione Europea di Urologia (EAU), ha creato il gruppo di lavoro dedicato al TRR (gruppo ERUS) al fine di valutare in modo prospettivo i risultati del TRR.
Al fine di riportare l'evoluzione del TRR, vengono descritti i dettagli tecnici e i tempi chirurgici di questo approccio. Inoltre, vengono analizzati gli studi condotti dal gruppo ERUS, con particolare attenzione ai risultati funzionali, ai dati chirurgici ed alle complicanze intra- e post operatorie.
Si è realizzata uno studio sulla quantificazione della risposta infiammatoria del trapianto convenzionale open comparato con il TRR, studiando eventuali differenze in termini di dati funzionali e marcatori infiammatori (proteina reattiva C, interleuchina 6, lipoproteina associata alla gelatinasi neutrofila).
Infine, si è provveduto ad analizzare la "learning curve" richiesta da questa nuova tecnica, valutando i risultati clinico-chirurgici e le complicanze registrate nei 5 centri del gruppo ERUS con più alto volume (maggior numero di TRR).

RISULTATI. Grazie alla collaborazione dei membri di questo gruppo, *Breda et al*. hanno pubblicato la più grande serie multicentrica di TRR; *Territo et al.* hanno analizzato e pubblicato i risultati funzionali ad un anno di follow-up; *Vignolini et al.* hanno dimostrato fattibilità del TRR con reni da donatore cadavere; *Siena et al.* hanno descritto la tecnica del TRR impiegando reni con vasi multipli. Tenendo in considerazione gli analoghi risultati funzionali tra TR a cielo aperto e TRR, i vantaggi di quest'ultimo riguardano la minore lunghezza dell'incisione, il minor dolore post-operatorio, la minore perdita di sangue e il più rapido recupero post-operatorio. Inoltre, il TRR è associato a un minor rischio di complicanze post-operatorie, quali il linfocele e l'infezione della ferita. Ciononostante, ad oggi, non è stato condotto uno studio che paragoni i risultati funzionali e che quantifichi la risposta infiammatoria sistemica nel TR realizzato con tecnica convenzionale e nel TRR. Al fine di valutare questi aspetti, sono stati confrontati i risultati clinico-funzionali e i livelli sierici di marcatori infiammatori sistemici (proteina reattiva C, interleuchina 6, lipoproteina associata alla gelatinasi neutrofila) in pazienti sottoposti a TRR e TR a cielo aperto. Inoltre, le precedenti esperienze in TRR hanno già dimostrato di non avere alcun impatto sulla curva di apprendimento di questa tecnica emergente, quando la procedura viene eseguita da chirurghi con esperienza sia in chirurgia robotica che nella

realizzazione di anastomosi vascolari. Tuttavia, manca un unanime consenso sul modo ottimale di determinare la curva di apprendimento nel TRR. Sebbene tale tecnica sia già stata standardizzata dal gruppo ERUS, l'analisi della curva di apprendimento rimane difficile a causa della sua multifattorialità e delle diverse variabili che devono essere considerate. Pertanto, è stata analizzata la curva di apprendimento nel TRR valutando i risultati chirurgici e funzionali e le complicanze intra e post-operatorie nei cinque centri del gruppo ERUS con più alto volume chirurgico per TRR.

CONCLUSIONI. In questo manoscritto viene descritta l'evoluzione del TRR, dalla sua introduzione alla sua standardizzazione, riportando gli studi più significativi realizzati dal gruppo ERUS. Inoltre, vengono in dettaglio analizzate: la risposta infiammatoria nel TRR e convenzionale; la curva di apprendimento richiesta nel TRR.

3. INTRODUCTION

3.1 Historical overview of kidney transplantation

The first trials of allogenic KT stemmed from the Ukrainian surgeon Yurii Voronoy working in Kherson (Ukraine). He was trained in experimental KT using dogs, and in 1933 he transplanted a kidney from a young man who had died from a brain injury to a patient with renal failure following mercury chloride poisoning. The renal vessels were anastomosed to the vessels of the thigh but the kidney never functioned, probably due to a long warm ischemia time and blood group incompatibility. Voronoy reported five more KTs until 1949, unfortunately also without functional success.

In 1912, the German surgeon G. Schone from Greifswald suggested that immunological factors were responsible for the disappointing results following allogeneic transplantation, creating the term "transplant immunity" and describing in detail the typical histological findings caused by rejection following allogeneic and heterogenic transplantation. However, the background and basics of the underlying immunological details remained obscure until the 1940s, when in Glasgow, Thomas Gibson and Sir Peter Medawar were able to show by experimental skin transplantation that graft rejection was caused by active immunity. In 1943, Medawar and Gibson published their landmark article "The fate of skin homograft's in man" and for their significant works in immunology Medawar was awarded the Nobel Prize in 1960.

In the United States, the history of clinical KT began in 1945 when David Hume, together with two trainee surgeons, Charles Hufnagel and Ernest Landsteiner, in the Peter Bent Brigham Hospital in Boston, transplanted a kidney from a deceased donor, under local anesthesia, to the antecubital region of a female patient with acute renal failure. The patient survived, the native kidneys regained their function, and the non-functioning transplant was removed after 48 h. Ernest Landsteiner was the son of the Austrian-American pathologist Karl Landsteiner (1868–1943), who discovered the ABO blood group system in 1901 and was awarded the Nobel Prize in 1930 "for his discovery of human blood groups".

In 1950, the urologist Richard Lawler and colleagues in Chicago performed the first intra-abdominal KT in a 44-year-old woman with polycystic kidney disease. The serum creatinine of the patient had risen to 2.3 mg/dL. The kidney was implanted orthotopically following one-sided nephrectomy with end-to-end-anastomosis of the graft ureter to the native ureter. Extensive details of the graft function were not reported, except that the transplanted kidney excreted the injected dye indigo carmine on postoperative day 52, thereby proving its function. Two months later, serum creatinine was 1.2 mg/dL. Nine months after the KT, the graft was without function.

In 1954, a team of physicians and surgeons in Boston, led by John Merrill and Joseph Murray, including the urologist John Hartwell Harrison, prepared for a pioneering landmark operation. The 23-year-old the patient Richard Herrick suffered from deteriorating renal function due to glomerulonephritis, with some improvement of his condition after initiation dialysis. Since 1949, a modified Kolff artificial kidney (the Kolff Brigham Artificial Kidney) had been constructed and used at the Brigham Hospital. The medical team was supported by George W. Thorn, Chief of Medicine, and Francis D. Moore, Chief of Surgery. It had been shown that skin transplantation was successful between identical twins, and Richard's brother Ronald, after intensive evaluations including the skin graft test and comparison of finger prints, turned out to be an identical twin. Therefore, the idea of bypassing the barrier of rejection in performing this transplantation between the monozygotic twins seemed to be daring but promising and justified.

The donor kidney was removed by the urologist Hartwell Harrison and the transplantation, done according to the technique developed by R. Küss and his colleagues from Paris and refined by Joseph Murray, was successful, including the reconstruction of the urinary tract by transvesical ureteroneocystostomy in cooperation with H. Harrison. Fortunately, there was immediate onset of renal function. The patient died 8 years after transplantation from a cardiac event. Ronald Herrick died on 29 December 2010 at the age of 79 years, 56 years after the kidney donation to his brother for the first long-term successful kidney transplant.

In 1958, Murray published the results of seven KTs between identical twins. To prove genetic and immunological identity, the potential candidates for transplantation were cross skin grafted and the blood types matched for all known blood groups. As final proof of identity, the presence of a non-reactive skin graft was recorded and observed grossly and stereomicroscopically in the healthy donor after 3 weeks. In a later publication in 1976, Murray reported long-term graft function for up to 20 years and uneventful pregnancies in transplanted women. In 1990, Murray was awarded the Nobel Prize in Physiology or Medicine together with E. Donnall Thomas for their discoveries concerning "organ and cell transplantation in the treatment of human disease". A series of identical twin transplants was performed around the world, in Richmond, New Orleans, Portland, Oregon, Denver, Palo Alto (USA), and Montreal (Canada). On 30 October 1960, M.F.A. Woodruff and colleagues performed the first KT between identical twins in the United Kingdom at Edinburgh Royal Infirmary. By the time of Woodruff's retirement in 1976, 126 more KTs had been performed.

3.2 Kidney transplantation (from deceased and living donors)

End-stage renal disease (ESRD) is defined by an irreversible glomerular filtration rate (GFR) of less than 10 mL/min or a serum creatinine level exceeding 8 mg/dL. While different modalities are available for renal replacement therapy, including hemodialysis and peritoneal dialysis, KT is the preferred treatment for patients affected by ESRD [1].

So far, no guidelines exist for when during the course of chronic kidney progression KT should be performed. Generally speaking, pre-emptive KT is considered more advantageous for patients developing progressive ESRD. It is associated with improved patient and graft survival, a higher return to work rate, and a better quality of life and is more economical when compared with the costs of initiating dialysis. By simply avoiding dialysis, there is no requirement for catheters, fistulas, or lines, which all have potential complications. Furthermore, there is a reduction in dialysis-associated cardiovascular events, including sudden cardiac death and the accelerated progression of heart failure. Despite wide acceptance of the superiority of pre-emptive KT, data on this issue remain controversial [2][3].

Compared with KT from deceased donors, KT from living donors has several advantages, including improved long-term patient survival, better quality of life, better transplant survival, and reduced waiting time for KT [4][5].

Nowadays, around 40% of all KT in the United States and around 20% of all KT in Europe are performed with living donors. Every year, the radio of "emotionally related" living donors to genetically related living donors increases slightly, with most of the living donors currently being family members [6]. In 2005, in EUROTRANSPLANT, approximately 50% of living donors were not genetically related, and in the United States 37.2% of living donors have been reported to be unrelated to the transplant recipient [7]. The advantages of living kidney donation are better results (both long- and short-term) compared with deceased donor grafts, consistent early function and easier management, the avoidance of a long waiting time for transplantation, less aggressive immunosuppressive regimens, emotional gain to the donor, and a global increase in the kidney transplant rate [8]. Living kidney donation is justified if the donor risk is minimal and there is a potential maximum benefit for the recipient. Safety and efficiency must be guaranteed in all the surgical techniques employed, with the lowest possible morbidity for the donor and best functional results for the grafts [8] [9].

When a living donor has two equally functioning kidneys, the left kidney is preferred for donation as the left renal vein is longer than the right renal vein. When the kidney function of both kidneys is different, the lesser functioning kidney is used for donation in order to limit the risks for the donor. Many concerns have been raised regarding the use of the right kidney for living donation, but the literature suggests that right laparoscopic donor nephrectomy is feasible and results in good graft function [10] [11].

3.3 Living donor nephrectomy

As regards the surgical approach for living kidney donation, open donor nephrectomies were carried out for nearly 50 years until the introduction of laparoscopy in 1995 by Ratner *et al.* [12]. Since its first description, the laparoscopic approach for donor nephrectomy has been demonstrated to improve peri- and postoperative outcomes, such as blood loss, pain, hospital stay, and cosmetic results, when compared with open surgery. In 2001, the first series of robot-assisted laparoscopic donor nephrectomy, using the da Vinci® surgical system, was reported by the group of the University of Illinois (Chicago)[13]. They demonstrated that robot-assisted nephrectomy is feasible, safe, and reproducible, providing similar results to the laparoscopic approach [14], [15].

According to the literature, laparoscopic surgery for living donor nephrectomy achieves similar functional results compared with open and robot-assisted living donor nephrectomy, being equally safe for the donor [16] [17]. The most commonly used technique is the minimally invasive trans-peritoneal laparoscopic approach. In figure 1 the linear port configuration described by Harper et al. is shown [18]. It is routinely used in our institution for laparoscopic renal surgery, including the nephrectomy for kidney donation, with the aim of exploiting its ergonomic position for the surgeon and camera holder.

Robot-assisted surgery offers clear advantages over conventional laparoscopy thanks to the use of EndoWrist instruments, three-dimensional view, enhanced visualization of the operative field (×12), and, possibly, a shorter learning curve [19], [20].

Open nephrectomy for donation may offer an advantage in challenging cases such as grafts with multiple vessels and/or vascular anomalies, and prior abdominal surgery. Furthermore, the open approach may be preferred in centers with low experience in laparoscopy and/or a low case volume of living donor nephrectomies [21].

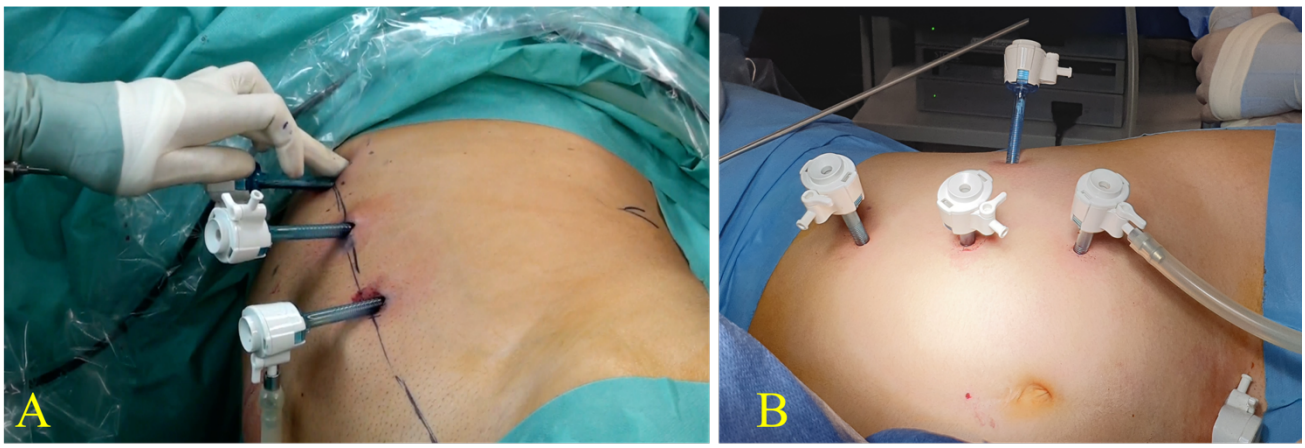


Figure 1. A: Linear port configuration along the left pararectal line, with the camera placed at the most cephalic position (at the 12nd rib level). **B:** An additional trocar is used to raise the kidney during the section of the vessels. A Pfannenstiel incision is mad to introduce endovascular stapler and the 15-mm EndoCatch bag for organ extraction.

3.4 Conventional open kidney transplantation

Despite all the new advances in surgical technology and armamentarium, techniques for KT have remained unchanged during the last few decades, and the open approach remains the gold standard [1] [22].

Back table preparation of the kidney. During kidney preparation, both the renal vein and artery are carefully inspected, including any endothelial damage or atherosclerotic plaques (figure 2). All side branches are ligated and divided and care must be taken to avoid any extensive dissection of the vessels into the hilum, or compromising the vascularization of the proximal ureter or the renal pelvis. Whenever appropriate, any vascular reconstruction that might be necessary can be done at this point (figure 3). This can consist of shortening a long aortic patch in case of multiple renal arteries spread or reconstruction of repairing any damaged vessels. During the bench procedure, renal biopsy can also be performed, if there is doubt about the quality of the parenchyma prior to transplantation.

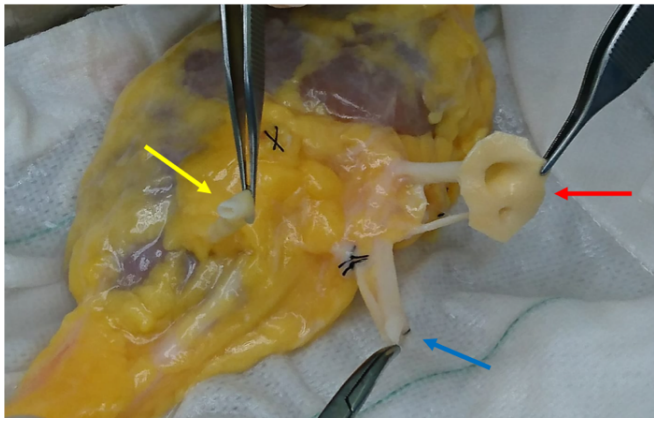


Figure 2. Kidney graft from cadaveric donor. Double renal artery on a Carrel patch (red arrow); renal vein (blue arrow); lower pole artery (yellow arrow).

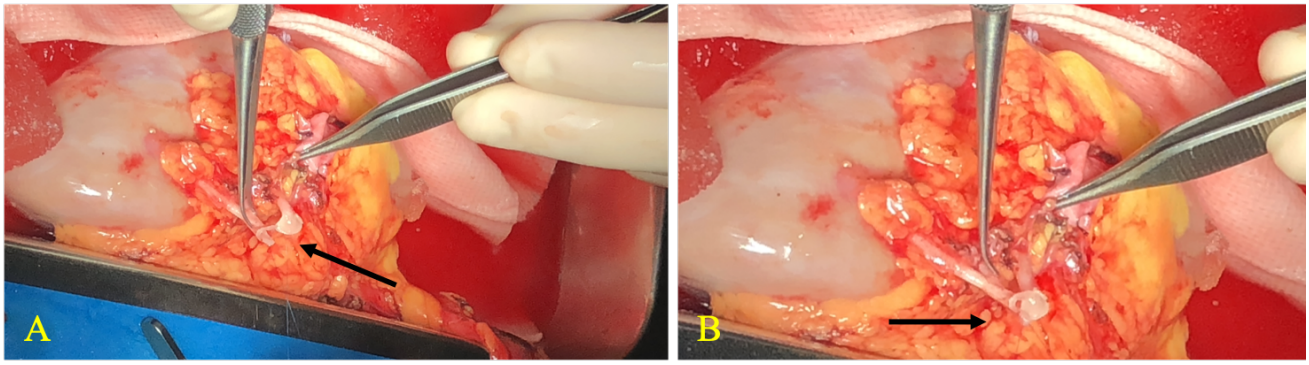


Figure 3. Bench table preparation of the graft from living donation with double artery. In A and B details of reconstruction of the arteries joined as a pantaloon

Creation of the operative field and graft allocation. A conventional OKT is placed in a heterotopic position in one of the lower quadrants through an extraperitoneal approach. An incision is usually made in the right (or left) lower abdominal quadrant (Gibson incision) for access to the retroperitoneal space. Generally, the kidney graft is placed in the right side because of greater accessibility to the iliac external vessels and the inferior vena cava. Currently, the tendency in nearly all conventional KTs is to place the anastomosis in the external iliac vessels, using an end-to-side suture. After the operative field has been created, the graft is placed in the retroperitoneal space to decide upon the best position to perform the anastomosis without moving the kidney. The position of the anastomosis is mainly decided by selecting the best segment on the iliac artery and, in patients with severe atheromatosis plaques, the previous computed tomography (CT) may help in finding the appropriate arterial space. Therefore, the iliac vessels are dissected but this should be limited to the area of the anastomosis. Limited dissection and correct ligation of the perivascular lymph vessels can reduce the incidence of lymphoceles secondary to lymph discharge.

Venous anastomosis. Usually, the vein is the first vessel to be anastomosed. The previously selected site for the anastomosis in the iliac vein is isolated using a Satinsky clamp and a venotomy is performed using a scalpel. It is convenient to have the vein full of blood to avoid any injury in the posterior aspect of the vein when performing the venotomy. The venotomy can be expanded by resecting a small strip of one of the edges. Diluted 4% heparin is instilled in the vein lumen to wash out traces of blood and avoid clot formation. The end-to-side anastomosis is performed using two running sutures of non-absorbable 5/0 or 6/0 monofilament thread. One suture is placed at each pole of the venotomy and two running sutures are carried out on both sides to complete the anastomosis (figure 4). Once the venous anastomosis has been completed, a Bulldog clamp is placed in the proximal end of the graft vein and the Satinsky clamp is released. If any bleeding of the suture or vein occurs, it must be repaired before proceeding to the arterial anastomosis.

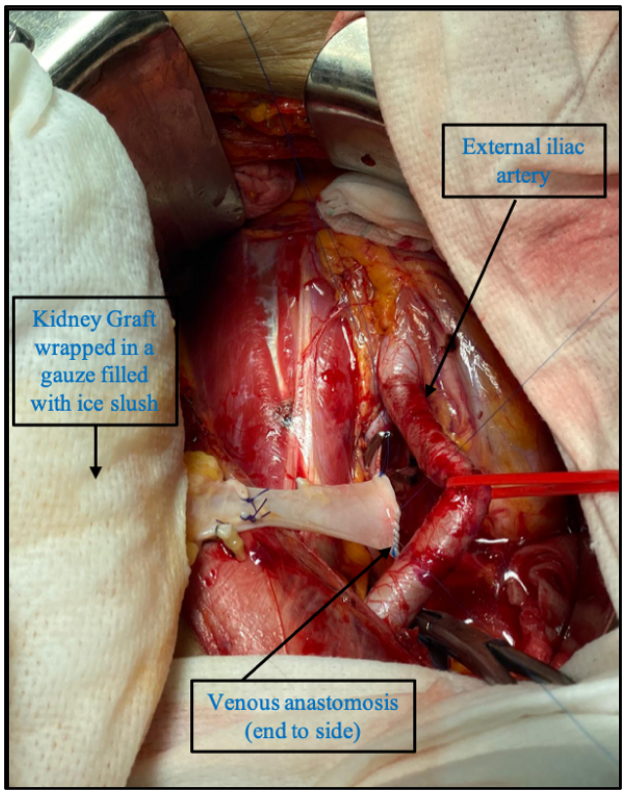


Figure 4. The external iliac vessels are dissected in the right side (right iliac fossa). The venous end-to-side anastomosis is performed using two running sutures of non-absorbable 5/0 or 6/0 monofilament.

Arterial anastomosis. An end-to-side anastomosis of the renal artery to the external iliac artery (or common iliac artery) is usually performed using an appropriately trimmed cuff of aorta attached to the renal artery (the Carrel patch - figure 5). Vascular clamps are applied to the external iliac artery proximally and distally if an end-to-side anastomosis is to be performed, with care taken to avoid clamping diseased segments of artery wherever possible. An arteriotomy appropriately placed is performed in the external iliac artery, and the lumen is flushed out again with heparinized saline; where the donor artery has no Carrel aortic patch, a hole punch is used to create a suitably sized hole for anastomosis. The anastomosis is done with a continuous 5-0 or 6-0 monofilament vascular suture although an interrupted technique may be necessary where no Carrel patch exists. Particular care should be taken to ensure that all the intima on the recipient artery is secured back in position during the anastomosis to prevent a dissection propagating along the distal artery on reperfusion. In very severe cases of calcification of the recipient artery, it may be necessary to carry out a formal endarterectomy of the iliac artery, with the distal intima stitched in place to prevent formation of a flap and subsequent dissection. The figure 6 shows different techniques for arterial anastomosis.

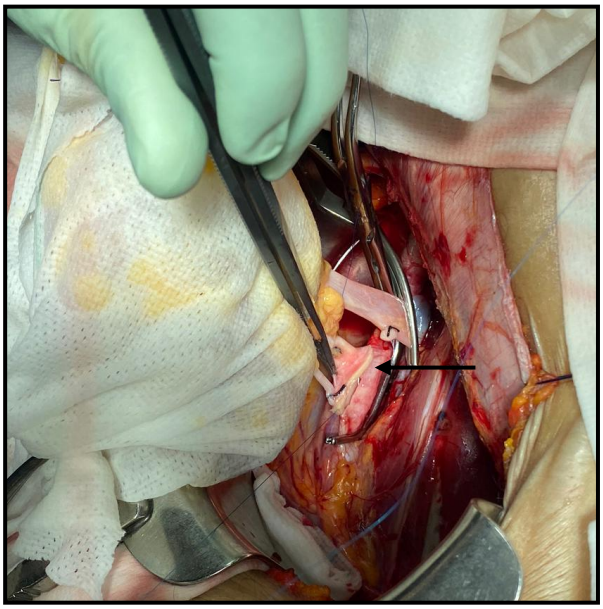


Figure 5. An end-to-side anastomosis of the renal artery to the external iliac artery is performed using the Carrel patch.

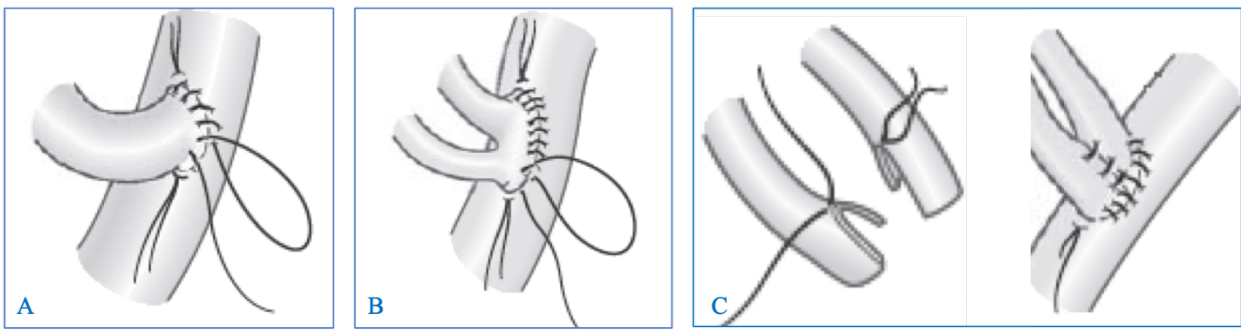


Figure 6. Variations of renal artery anastomosis. **A**: End-to-side anastomosis. **B:** Two renal arteries on a patch. **C:** Two arteries joined as a pantaloon.

Uretero-vesical anastomosis. The Lich-Gregoir extravesical technique protected by a ureteral stent is preferred because it is fast to do, does not require a separate cystotomy, requires less ureteric length, and is associated with fewer urinary tract infections, fewer leaks, and less hematuria than intravesical techniques for minimization of urinary tract complications [22] [23]. Technically, a longitudinal oblique incision is made for approximately 2 cm until the bladder mucosa bulges into the incision. The bladder is partially drained via the urethral catheter, and the mucosa is dissected away from the muscularis on both sides to facilitate later creation of a submucosal tunnel for the ureter. The bladder mucosa is incised and 5-0 monofilament absorbable sutures placed through both ends of the incision. The ureter is brought up to the wound, the mucosal sutures are passed through the toe and heel of the spatulated end, and the ureter is parachuted onto the bladder. The ureter is then anastomosed to the bladder mucosa with running sutures between the ureter and the mucosa of the bladder. Specifically, it is recommended to anchor the toe of the ureter with a horizontal or vertical mattress suture placed in the toe of the ureter and passed submucosally through the seromuscular layer of the bladder and tied about 5 mm distal to the cystotomy. Once the ureteric anastomosis has been completed, the seromuscular layer is closed over the ureter with interrupted absorbable sutures, care being taken to avoid narrowing the ureter in the process (figure 7 and figure 8)

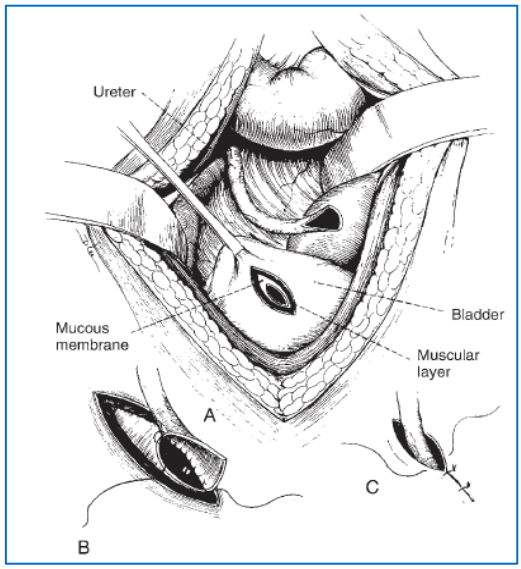


Figure 7. Drawing of the Lich-Gregoir extravesical technique for ureteral reimplantation.

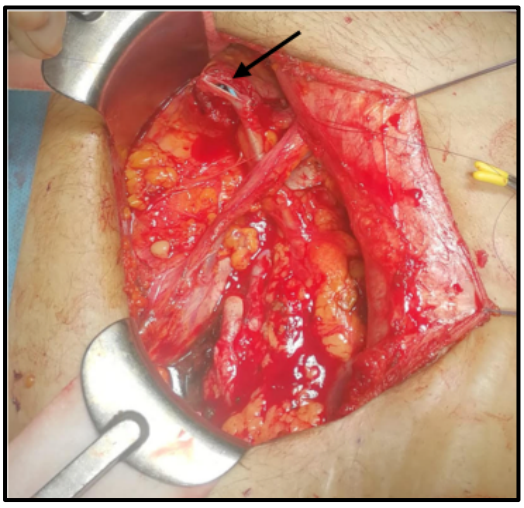


Figure 8. The ureter is to the bladder mucosa with two running sutures with the DJ stent placed into the urinary cavity.

3.5 The minimally invasive approach in kidney transplantation

Kidney transplant recipients are often fragile and immunocompromised, and therefore they have a higher risk of perioperative complications. As is known, perioperative morbidity affects short-term convalescence as well as long-term graft survival.

Minimally invasive surgery (i.e., laparoscopic and robotic surgery) may be a good alternative in order to reduce the morbidity associated with OKT, especially in those patients who are known to have a higher complication rate. In addition, in obese recipients, KT presents several challenges related to surgery: access to the external iliac vessels, surgery and vascular anastomosis time, an increase in the risk of surgical site complications (i.e., wound infection, lymphocele formation), and delayed graft function (DGF) [24][25][26][27]. Consequently, many transplant centers tend to regard obesity as a contraindication to KT.

Considering the above, KT recipients and the obese population affected by ESRD are potentially the ideal candidates for a minimally invasive approach. However, despite the growing evolution of minimally invasive surgery and its widespread impact, KT surgery has remained unchanged since its inception. This could be attributed to the limited exposure of transplant surgeons to minimally invasive techniques, the optimal functional results already obtained with the conventional open approach, and resistance to change among nephrology colleagues.

A few attempts at laparoscopic KT have been reported [28] [29] [30], but the obvious limitations of laparoscopic suturing techniques have precluded widespread adoption of laparoscopy for renal transplantation.

In this scenario, RAKT extends the options for recipients towards minimally invasive techniques. Recently, in a non-randomized comparison between OKT and RAKT, Pein et al. [31] demonstrated that RAKT appears to be safe in selected patients, without influencing graft outcomes or resulting in higher complication rates. While RAKT is currently still not suitable for all recipients, it seems to be an upcoming and promising new approach in KT.

3.6 Laparoscopic kidney transplantation

Laparoscopy represented a revolution in surgery at the end of the twentieth century. Since the first nephrectomy was reported in 1991 by Clayman et al. [32], the complexity of laparoscopic procedures has gradually increased.

In 2004, a group from Johns Hopkins Medical Institutions published a series of four kidney auto-transplantations for treatment of proximal ureteral avulsion. In two cases, laparoscopic implantation was attempted but was abandoned for technical reasons [28]. Probably as a result of the difficulty of the surgical technique, human laparoscopic KT was not successfully performed until 2009, by Rosales et al. [29]. They placed the graft (from living donation) through a 7-cm Pfannenstiel incision. Surgical time was 240 min (53 min for vascular suture), the cold ischemia time was 182 min, and there was immediate urine output.

Since then, a few other attempts have been published. Modi et al. [30] described a series of 72 successful consecutive cases of laparoscopic KT from living donors, with a mean operating time of 224 min. They compared the functional outcomes with those in patients transplanted by open surgery, and reported comparable outcomes in terms of graft and patient survival with a median follow-up of 22 months. They also reported a significant difference in analgesic requirements, which were higher among the latter group. There were some complications in the laparoscopy group, with four patients requiring conversion to open surgery and two grafts lost because of torsion [30].

Nowadays, with the introduction and the progressive spread of robotic surgery, the laparoscopic approach in KT has been abandoned because it is technically very demanding.

3.7 The robotic approach for kidney transplantation

Minimally invasive techniques have recently been introduced to decrease the morbidity and mortality of open surgery, although OKT remains the gold standard. According to the literature, robotic surgery in KT provides technical advantages and functional benefits attributable to the three-dimensional vision, seven degrees of freedom, 12× magnification, and elimination of hand tremor. These great advantages are clear in the context of vascular and reconstructive surgery, allowing more precise vascular anastomosis and ureteral reimplantation [33][34][35].

In 2002 Hoznek et al. [36] described the possibility of performing a robotic anastomosis in KT, and in 2010 the first pure RAKT was performed by Giulianotti et al. in the United States [37].

In Europe, the first RAKT was performed in 2011 by Boggi et al. [38], who carried out the vascular anastomosis robotically and the ureteral reimplantation in open fashion. For this reason, the procedure may be considered a "hybrid RAKT".

In 2014 Menon et al. [39] standardized the technique with the transperitoneal approach and regional hypothermia, known as the Vattikuti-Medanta technique; this represented a collaborative effort of Menon's team and the Medanta Hospital team in India using the IDEAL (idea, development, exploration, assessment, and long-term monitoring) framework. [40]. This IDEAL study entailed three phases, in order to develop the RAKT procedure in an evidence-based manner. In the first phase the importance of preclinical procedural testing was demonstrated [41]; in the second, the surgical technique was described [39]; and finally in the third, patient safety was proved [42]. The authors highlighted that RAKT is a safe technique with possible advantages such as low intra- and postoperative complications, better cosmetic results, and superlative vision that could result in better quality of the vascular and ureteral anastomoses.

Following the IDEAL model, the initial European experience of pure RAKT was reported by Breda et al. [43] and Doumerc et. al [44], who, in 2015, performed the first two procedures in Spain and France respectively. One year later, Breda et al. published a single-center experience on 17 cases of RAKT from living donation [45]. In this initial experience, RAKT was described as an attractive alternative to open surgery. It has been demonstrated to be a feasible, reproducible, and safe technique that offers surgical advantages during the performance of vascular and ureterovesical anastomosis due to a greater degree of freedom in movements and enhanced visualization of the surgical field. In addition, it has been suggested that RAKT decreases the complication rate, hospital stay, and postoperative pain and improves aesthetic results [43] [45] [46].

The standardized RAKT technique will be detailed in Chapter 11. While OKT is an extraperitoneal surgery, in the aforementioned studies on RAKT the procedure was carried out trans-peritoneally. The robotic extraperitoneal approach may potentially reduce gas filling-related consequences for the renal vasculature and the risk of bowel injuries. However, in comparison with an extra-peritoneal approach, the trans-peritoneal procedure offers a greater field exposure while maintaining easier accessibility to iliac vessels for the anastomoses. Recently, in order the explore this issue, Eltemamy et al. [47] investigated the feasibility of single-port robotic extraperitoneal KT, performing a dual KT in a preclinical setting (cadaveric model). As regards graft introduction, it is usually carried out via a periumbilical incision, which is certainly the preferred option for obese patients. On the other hand, the Pfannenstiel incision may reduce the risk of incisional hernia and could be preferred in order to achieve better cosmetic results. A successful single-center experience of RAKT using a Pfannenstiel incision was reported by Ganpule et al. [48] in 26 cases.

4. OVERVIEW OF THE RAKT ACHIEVEMENTS BY THE ERUS GROUP

In 2016 the ERUS RAKT working group was created by Dr. Alberto Breda with the aim of collecting and analyzing data from eight different European centers performing RAKT (**Flowchart 1**).

As extensively detailed in the following chapters of this manuscript, thanks to this multicenter collaboration and the creation of a common online database (Figure 9; *http://www.auoctransplantdataplatform.com*), in 2017 the ERUS working group was able to report the results of 120 patients, demonstrating that RAKT is associated with low complication rates, rapid recovery, and excellent graft function [49]. One year later, Territo et al. [50] addressed the functional results of RAKT from living donors at 1 year of follow-up. Until now, these are the largest series published on RAKT from living donation. Furthermore, the ERUS group was able to analyze different scenarios for RAKT as follows:

- Siena et al. [51] described the technique for RAKT in grafts with multiple vessels.
- The evaluation of RAKT in obese recipients was coordinated by colleagues from the University of Toulouse.
- Vignolini et al. [52] developed a RAKT program with grafts from deceased donors.

In addition to the aforementioned studies analyzing different clinical settings, in this manuscript the following will be reported:

- the cold ischemia device designed and developed with the aim of maintaining the graft at a constant and low temperature (below 20ºC);
- quantification of the systemic response in open versus robotic KT, explored through the clinical results (immediate vs delayed graft function) and systemic inflammatory markers (C-reactive protein, interleukin-6, and neutrophil gelatinase-associated lipoprotein) in robotic versus conventional OKT;
- analysis of the learning curve in RAKT [53].

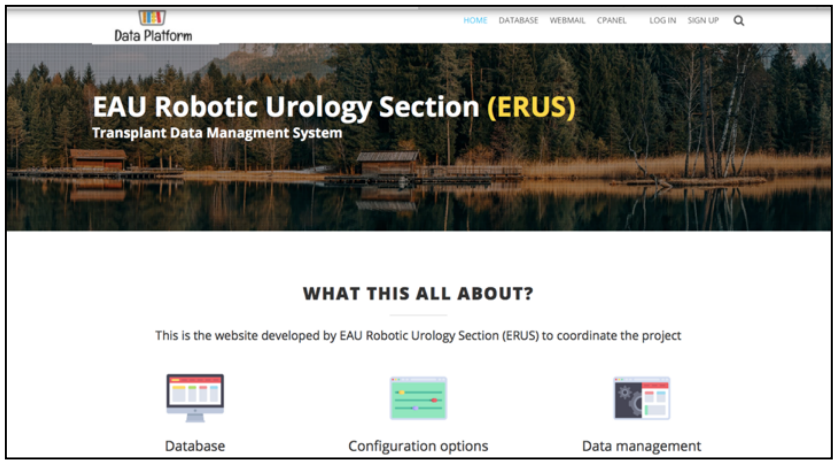


Figure 9. Common online registry (database – ERUS RAKT working group).

Flowchart 1. Development of RAKT and achievements by the ERUS group.

Pioneers in RAKT: USA & Europe

→ United States of America (USA)

- Hoznek et al. (2002): description of the robotic vascular anastomosis
- Giulianotti et al. (2010): first worldwide experience of RAKT
- Menon et al. (2014): standardization of the RAKT

→ Europe

- Boggi et al. (2011): hybrid RAKT – Italy
- Breda et al. (2015): first pure RAKT – Spain
- Doumerc et al. (2015): first pure RAKT – France

ERUS RAKT working group created in 2016

Studies performed by ERUS RAKT working group

- European experience in RAKT from living donation
- One-year follow-up in RAKT
- RAKT using grafts with multiple vessels
- RAKT in obese recipients
- RAKT program from deceased donors
- Cold ischemia device for KT
- Systemic inflammation response in RAKT vs OKT
- Learning curve in RAKT

Institutions involved in the ERUS working group:

1. Fundaciò Puigvert, Autonomous University of Barcelona, Spain
2. Hospital Clinic, Barcelona, Spain
3. University Hospital of Rangueil, Toulouse, France
4. Ghent University Hospital, Ghent, Belgium
5. University of Florence, Careggi Hospital, Florence, Italy
6. Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
7. Saarland University, Homburg/Saar, Germany
8. Halle University Hospital (Saale), Halle, Germany

5. EUROPEAN EXPERIENCE IN RAKT FROM LIVING DONATION

5.1 Introduction and objectives

The first European Experience in RAKT was published in 2017, in a study that prospectively collected a series of 120 cases of RAKT from living donation performed at eight different European centers [49]. Therefore, from the same collecting European database (figure 9), Territo et al. [50] analyzed the functional results and late complications of RAKT from living donors at 1 year of follow-up.

Here, the surgical procedure is described and standardized. Furthermore, the outcomes of both studies are reported. These are the first and largest reported multicenter prospective studies on RAKT.

5.2 Materials and methods

Preparation of the kidney. After robot-assisted/laparoscopic living donor nephrectomy, the preparation of the kidney is performed at the back table. First, the graft is placed in a basin with slushed ice and perfused with 1 liter of storage solution (Celsior®, or Custodiol®, or Institut Georges Lopez-1®). Next, the graft vessels are carefully dissected. A double-J can be placed in the ureter if preferred. Subsequently, the kidney is wrapped in a gauze filled with slushed ice, with the artery and vein brought out through an opening in the gauze (figure 10). The aim is to keep the donor kidney at a constant low temperature after insertion in the abdominal cavity, until the vascular anastomoses have been completed and the kidney is reperfused. In addition, the gauze can prevent potential graft injury from manipulation with the robot arms. To keep the graft temperature below 20°C intracorporeally, ice is added through the GelPOINT® every 15 min.

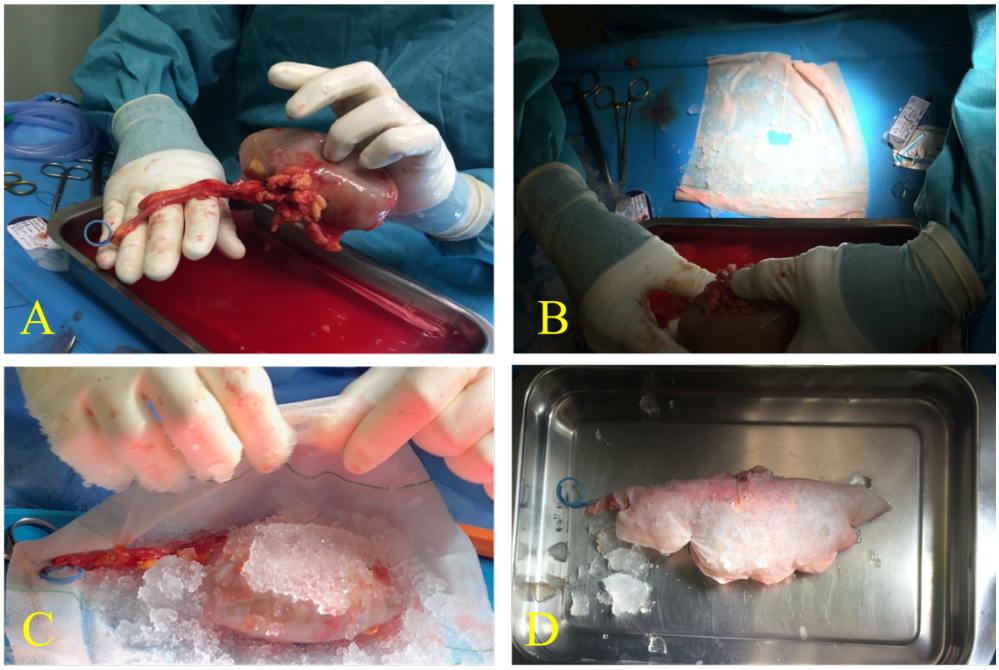


Figure 10. A. A ureteral double J stent is placed in the graft. **B.** A central hole in the gauze from which the artery and vein are outside. **C, D.** The graft is wrapped in a gauze jacket filled with ice slush

*Patient and trocar positioning***.** When using the da Vinci Si® or X® system, the patient is positioned in the lithotomy position according to the Vattikuti Medanta technique When the da Vinci Xi® system is used, the patient is positioned in dorsal decubitus. A 20–30° Trendelenburg position is recommended. The required robotic instruments are: monopolar scissors, Potts scissors, bipolar forceps, prograsp forceps, large needle driver, black diamond micro-forceps, and bulldog clamps. A 12-mm camera port is inserted in the supraumbilical area and a pneumoperitoneum is created. Veress needle puncture, optical trocar access, or the Hasson technique can also be used for access to the abdomen and creation of a pneumoperitoneum. The open approach (Hasson technique) has been reported to result in fewer complications [54]. Three extra robotic 8-mm ports are placed under vision and the robot is docked. Minimal changes in port placement may be made according to the robotic system used (figure 11).

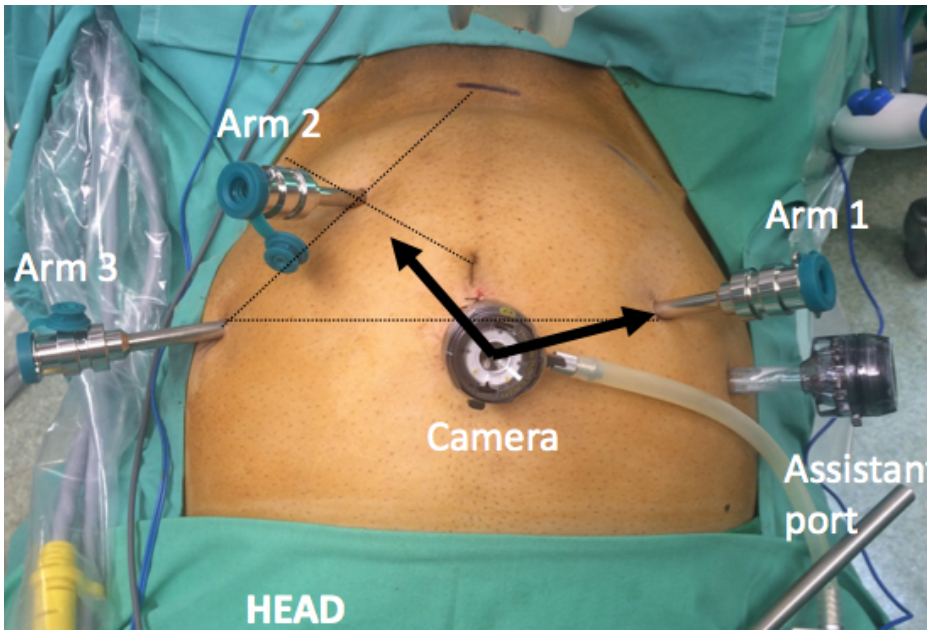


Figure 11. Trocar placement in RAKT using the da Vinci Si® system.

Transplant bed preparation. Accurate dissection of the external iliac vessels is performed. Subsequently, the bladder is prepared for ureteral reimplantation. A retroperitoneal pouch is created by incision of the peritoneum following a transverse line above the level of the appendix and mobilization of the peritoneal flaps. These will be used to cover (retroperitonealize) the graft once the vascular anastomosis has been completed. Although RAKT is a transperitoneal approach, retroperitonealization of the kidney is performed to avoid pedicle torsion and to enable future graft biopsies.

GelPOINT placement and graft introduction. A GelPOINT® device replaces the camera trocar through a 6- to 8-cm (four fingers) periumbilical incision once the transplant bed preparation has been performed. Alternatively, the GelPOINT® device can be introduced from the beginning through a 6- to 8-cm periumbilical incision, containing the camera and an assistant port. This GelPOINT® device is used to introduce the graft in the abdominal cavity and allows for insertion of slushed ice (± 200 ml) via modified Toomey syringes into the abdominal cavity, surrounding the graft surface with the intent of achieving regional hypothermia [i.e., low constant temperature (<20°C) of the graft] (figure 12). Additionally, GelPOINT® is a useful device for fast hand introduction if needed (i.e., in cases of massive bleeding). In selected cases, the graft can be introduced transvaginally as described by a few authors [44]. The AirSeal® system may be used in order to maintain a stable and low-pressure pneumoperitoneum at 8 mmHg.

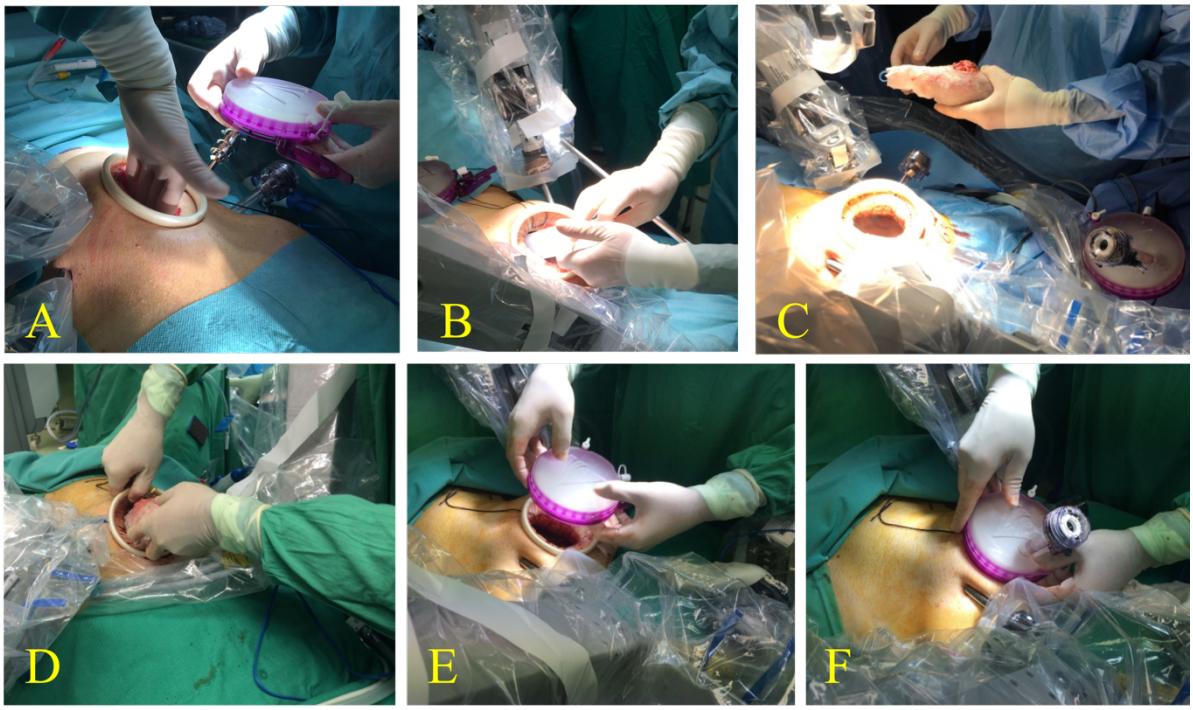


Figure 12. Introduction of the kidney and ice through the GelPOINT®. **A** The GelPOINT® device is placed through a 6- to 8-cm (four fingers) incision. **B.** Ice slush is introduced in the abdominal cavity using modified Toomey syringes. **C, D**. The graft is introduced into the abdominal cavity. **E, F** Once the graft is inside, the GelPOINT® cup is inserted to close the abdomen.

Venous and arterial anastomosis. After clamping of the external iliac vein with robotic bulldog clamps, the distal clamp followed by the proximal clamp, a longitudinal venotomy using cold scissors is performed. An end-to-side anastomosis between the graft renal vein and the external iliac vein is created using a 6/0 Gore-Tex® CV-6 TTc-9 or THc-12 needle continuous suture. At the proximal angle, the suture is tied to secure the posterior wall of the anastomosis watertight and to avoid stenosis; then the continuous suture is completed until the distal angle. Prior to finishing the anastomosis, the lumen is flushed with heparinized solution using a 4.8 Fr ureteric catheter. The catheter may be pulled out by the assistant from outside the abdomen while the surgeon tightens the knot to secure the anastomosis (figure 13). Next, the graft vein is clamped and the bulldog clamps are removed from the external iliac vein and positioned on the external iliac artery, first proximally and then distally. The artery may be incised with the cold scissors or a scalpel at the 1–2 o'clock position. Arteriotomy may be completed using a laparoscopic aortic punch to transform the linear arteriotomy into a circular one. In both arterial and venous anastomosis, the anastomosis is started by passing the needle in the external iliac vessel in an outside–inside direction, then inside–outside through the graft vessel (figure 14). For the venous anastomosis, the knot is tied now and the needle is then passed outside–inside through the renal vein to start the running suture. For the arterial anastomosis, the suture is not tied yet (as for the venous anastomosis), and the needle is passed through the graft artery outside–inside before tying the suture to a loop that is left outside. This is done to prevent a difficult first needle passing in a small arterial lumen. After completing the arterial anastomosis, a clamp is positioned on the graft artery while the external iliac artery is declamped. If no sign of leakage (bleeding) is observed, the graft vein and artery are declamped. The evaluation of the graft perfusion is primarily visual: pink colorization, a pulsatile graft artery, filling of the renal vein, small

bleedings from the renal capsule and urine output are signs of perfusion. Doppler ultrasound evaluation (drop-in ultrasound probe linked to TilePro®) is recommended to verify adequate perfusion of the graft.

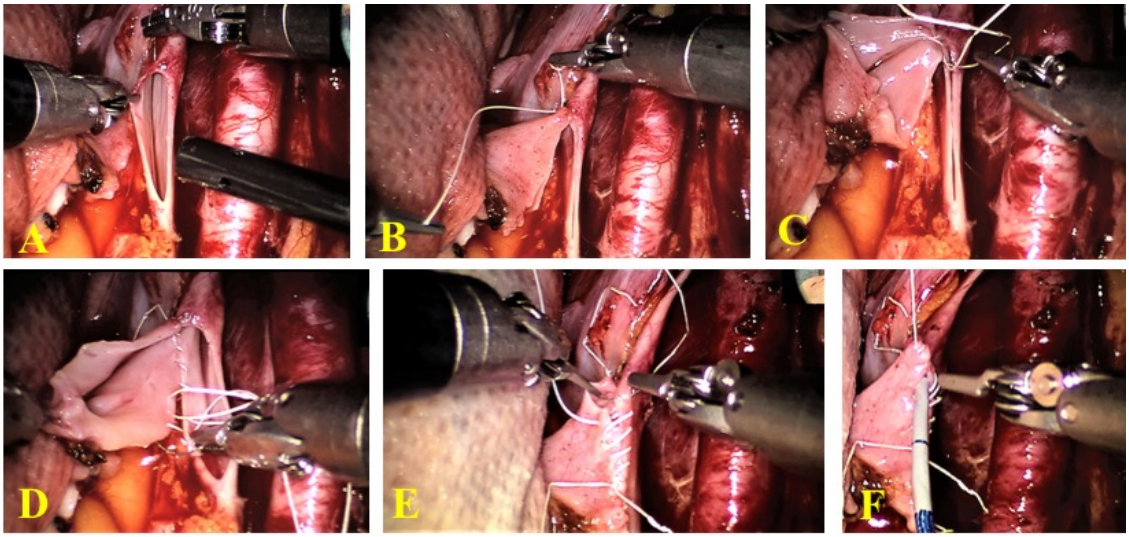


Figure 13. A. The graft renal vein is anastomosed in an end-to-side continuous fashion to the external iliac vein using a 6/0 Gore-Tex®. B, C. At the cranial angle, the suture is knotted to fix the posterior wall of the anastomosis. D, E. The running suture is completed until the caudal angle. F. Before completing the anastomosis, the lumen is flushed with heparinized solution using a 4.8 Fr ureteral catheter.

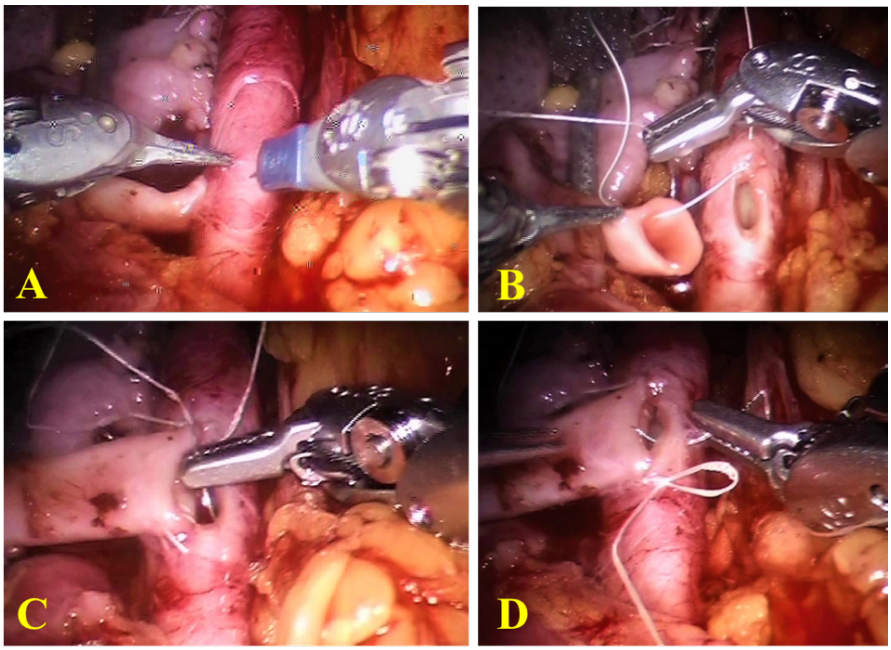


Figure 14. A The robotic scalpel is used to make a linear incision on the iliac artery, converting it into a circular hole with a laparoscopic vascular punch. B. The running suture is carried out using a 6/0 Gore-Tex®; particularly in the caudal tying of an arterial anastomosis, the needle is passed in the external iliac vessel in an outside–inside direction, then outside–inside through the graft vessel. C, D. The running suture is completed until the caudal angle.

Ureteroneocystostomy. After flipping the kidney on the psoas and retroperitonealization of the graft, the ureteroneocystostomy is performed according to the Lich-Gregoir technique using a Monocryl or PDS 5/0 continuous

suture. Care is taken to construct an adequate detrusor tunnel as an antireflux mechanism. A double J stent is inserted to protect the anastomosis. The stent can be removed after 3 weeks (figure 15).

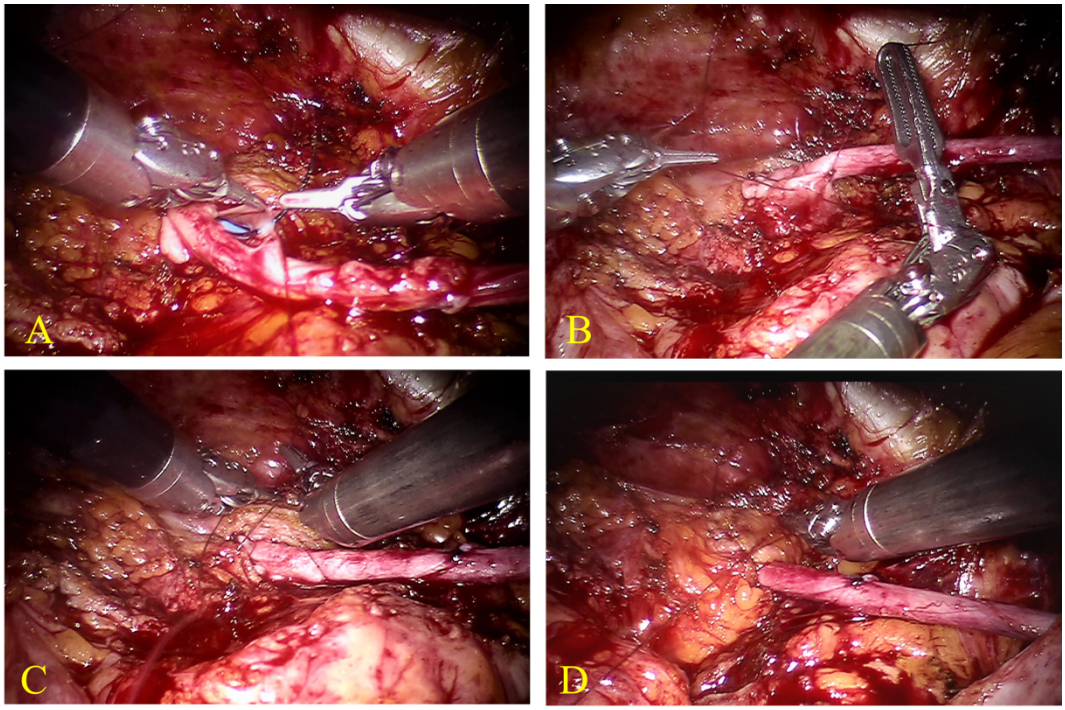


Figure 15. Ureteroneocystostomy performed according to the Lich-Gregoir technique. A and B: Running suture between ureteral and bladder mucosa using 5-0 Monocryl. C and D: Details of the antireflux tunnel.

5.3. Results

Surgical data, functional results, and complications. In the series of 120 RAKTs, the median estimated blood loss was 150 ml, with a median hemoglobin of 110 mg/dl preoperatively and 101, 95, and 98 mg/dl on postoperative days (POD) 1, 3, and 7, respectively. Two patients were converted to OKT owing to low blood flow at Doppler ultrasound evaluation immediately after skin closure and they accounted for the longest operative times. In terms of functional results, Breda et al. [49] demonstrated an excellent graft function (median eGFR at 30 days was 58 ml/min) (Table 1). In addition, the authors, did not find a correlation between total operative time or rewarming time (RWT – i.e., the time between removal of the kidney from the cold storage and start of reperfusion while continuously adding ice slush) and post-operative creatinine or eGFR (table 2 and table 3). The median hospital stay was 7 days (range 4–8 days). The median double-J dwell time was 28 days (range 14–60 days). Five cases (4.2%) of DGF were reported. Postoperative complications, recorded according to the Clavien-Dindo classification, are summarized in table 4.
Territo et al. [50] demonstrated that the functional results at 1 year of follow-up were not statistically different from the functional results at 1 month of follow-up (figure 16 and figure 17).
Follow-up changes in biomarkers (creatinine and eGFR), analyzed using the Wilcoxon test, are reported in table 5. In particular, at 1 year of follow-up, the median serum creatinine was 131 μmol/L (IQR 107–164) with a median eGFR of 57.4 ml/min per 1.73 m^2 (IQR 45–69). The complication rate remained low. As far as graft survival is concerned, three cases of graft loss occurred due to massive arterial thrombosis within the first postoperative week as mentioned above. No late vascular complications or cases of incisional hernia were recorded. Late complications comprised one case of ureteral stenosis and one case of graft pyelonephritis.

		Pre-operative	**Postoperative**			
			Day 1	**Day 3**	**Day 7**	**Day 30**
Creatinine (μmol/L)	Median (IQR)	517.0 (230.4)	288.7 (201.5)	155.0 (101.2)	131.5 (63.0)	130.0 (59.3)
eGFR (ml/min/1.73 m^2)	Median (IQR)	10.0 (6.0)	21.2 (14.6)	45.0 (32.3)	52.6 (24.2)	58.0 (27.8)
All comparisons (p value^{1,2,3,4}) are statistically significant (< 0.001)						
p value^1=Preoperative vs Day 7						
p value^2=Day 1 vs Day 7						
p value^3=Preoperative vs Day 30						
p value^4=Day 1 vs Day 30						

Table 1. Preoperative functional data and evaluation of postoperative functional results of 120 RAKTs from living donation [49].

		Pearson correlation	*p-value*
Day 1	**Creatinine (umol/L)**	-0.114	*0.237*
	eGFR (ml/min/1.73 mq)	0.123	*0.208*
Day 7	**Creatinine (umol/L)**	-0.001	*0.993*
	eGFR (ml/min/1.73 mq)	-0.096	*0.322*
Day 30	**Creatinine (umol/L)**	0.074	*0.446*
	eGFR (ml/min/1.73 mq)	-0.101	*0.297*
Difference POD 7 – POD 1	**Creatinine (umol/L)**	0.161	*0.094*
	eGFR (ml/min/1.73 mq)	-0.247	***0.012***
Difference POD 30 – POD 1	**Creatinine (umol/L)**	0.183	*0.059*
	eGFR (ml/min/1.73 mq)	-0.190	*0.054*

Table 2. Correlation between operating time and analytical variables at POD 1, 7, 30 and difference (POD 7 – POD 1; POD 30 - 1).

		Rewarming time (min)			
		<=48 (n=37) mean (sd) median (IQR)	**48-55** (n=33) mean (sd) median (IQR)	**>=55** (n=41) mean (sd) median (IQR)	***p-value***
POD 1	**Creatinine (umol/L)**	338.1 (187.37) 305.70 (232.6)	349.69 (236.21) 291.3 (145)	328.36 (179.32) 278.95 (201.05)	*0.862*
	eGFR (ml/min/1.73 mq)	23.07 (13.35) 20.91 (16.64)	21.80 (15.67) 19.40 (8.4)	26.92 (17.5) 22.05 (15.22)	*0.227*
POD 7	**Creatinine (umol/L)**	154.84 (104.51) 123.2 (56.4)	219.63 (267.13) 118.0 (63.8)	168.43 (97.80) 145 (62.4)	*0.551*
	eGFR (ml/min/1.73 mq)	57.26 (22.99) 53 (36.08)	45.28 (20.10) 48 (26.1)	53.03 (21.76) 53 (22.5)	*0.112*
POD 30	**Creatinine (umol/L)**	147.92 (89.49) 120 (46.25)	156.81 (94.36) 130 (41.50)	135.66 (40.0) 137 (60)	*0.587*
	eGFR (ml/min/1.73 mq)	65.5 (22.93) 64 (25.5)	51.63 (20.52) 51 (28)	61.36 (20.96) 55 (30.4)	***0.040***
Difference POD 1 – POD 7	**Creatinine (umol/L)**	-183.25 (180.8) -140.8 (188.3)	-128.61 (122.33) -143.5 (82.73)	-158.99 (139.68) -140.8 (153.15)	*0.931*
	eGFR (ml/min/1.73 mq)	33.8 (20.12) 31.55 (27.07)	22.40 (20.04) 25.50 (25.43)	26.18 (18.09) 27.55 (26.80)	*0.125*
Difference POD 30 – POD 1	**Creatinine (umol/L)**	-185.40 (197.40) -136.85 (202.53)	-152.13 (117.63) -144 (92.35)	-193.68 (162.87) -147 (201.15)	*0.883*
	eGFR (ml/min/1.73 mq)	44.08 (25.46) 42.80 (30.12)	29.03 (20.16) 30.15 (24.35)	35.02 (19.58) 32.90 (18.53)	***0.012***

Table 3. Correlation between the rewarming time and the analytical variables at POD 1, 7, 30 and the difference (POD 7 – POD 1; POD 30 – POD 1).

COMPLICATION	RAKTs (n=120) No. (%)	CLAVIEN–DINDO CLASSIFICATION GRADE	RAKTs (n=120) No. (%)
Wound infection	1 (0.8)		
Bleeding (observation)	1 (0.8)	Grade I	5 (4.2)
Ileus	3 (2.5)		
Deep venous thrombosis	1 (0.8)	Grade II	4 (3.3)
Bleeding requiring blood transfusion	3 (2.5)		
		Grade III	
Lymphocele	1 (0.8)	III a	1 (0.8)
Arterial thrombosis	3 (2.5)	III b	8 (6.7)
Bleeding requiring surgical exploration	5 (4.2)		
		Grade IV	
None		IV a	0 (0)
None		IV b	0 (0)
None		Grade V	0 (0)
Total			**18 (15)**

Table 4. Postoperative complications, recorded according to the Clavien-Dindo classification, in a series of 120 RAKTs [49].

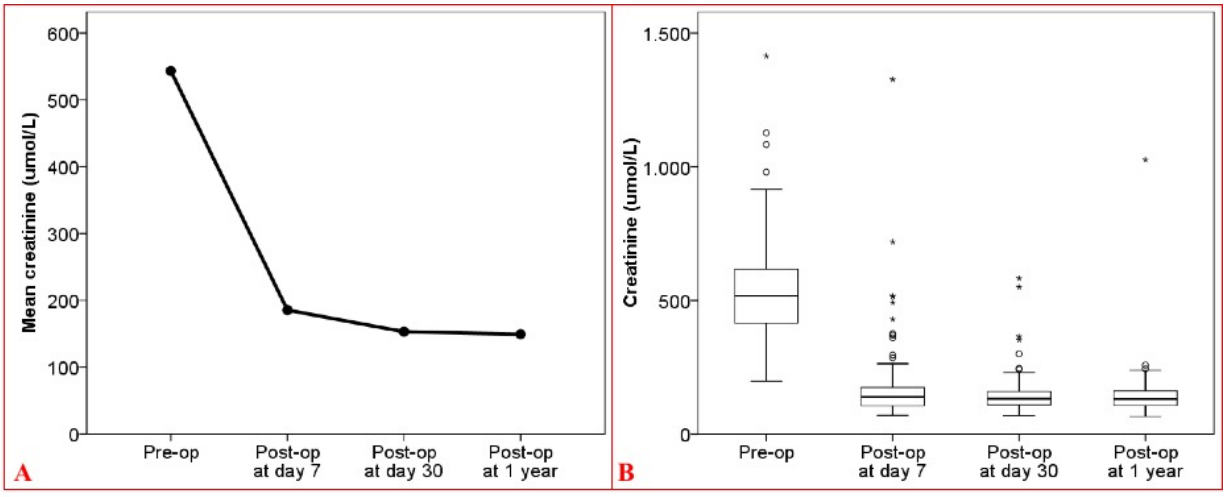


Figure 16. **A:** Trend with respect to serum creatinine over time. Values are shown at four time points: preoperative, POD 7, POD 30, and 1 year. **B:** In each box plot, the central horizontal line indicates the median value, and the lower and upper box horizontal lines indicate the 25th and 75th percentiles. Whiskers above and below the box indicate the 90th and 10th percentiles. Circles and asterisks indicate outliers and extremes values, respectively.

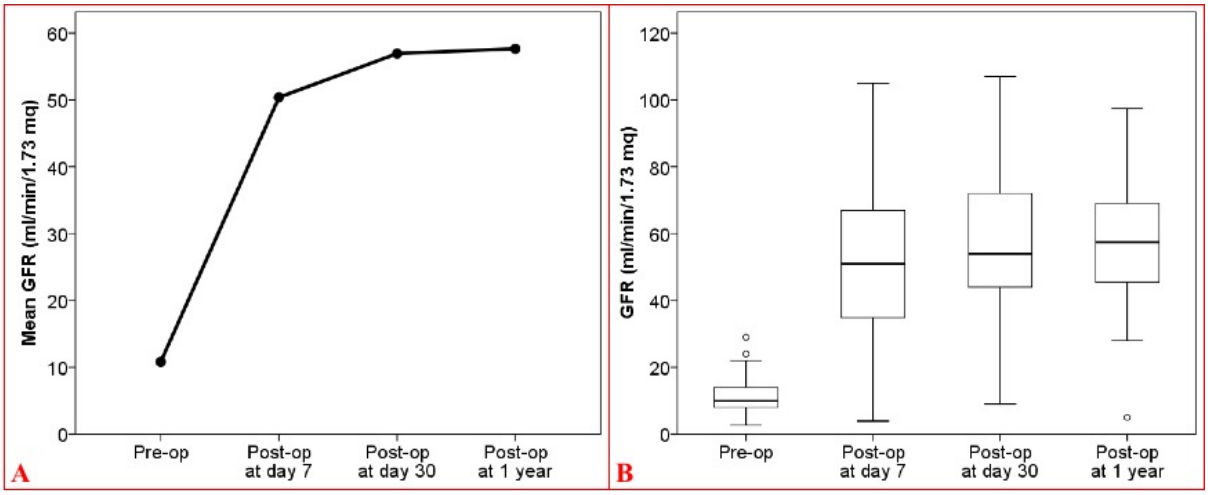


Figure 17. **A:** Trend with respect to eGFR over time. Values are shown at four time points: preoperative, POD 7, POD 30, and 1 year. **B:** In each box plot, the central horizontal line indicates the median value, and the lower and upper box horizontal lines indicate the 25th and 75th percentiles. Whiskers above and below the box indicate the 90th and 10th percentiles. Circles indicate outliers.

	Time point	***Median (IQR)***	***Wilcoxon signed ranks test***		
			p value preop vs POD 7	***p value POD 7 vs POD 30***	***p value POD 30 vs 1 year***
Creatinine (µmol/L)	Preoperative	517 (415–616)	<0.001	0.65	0.78
	POD 7	138.8 (105.6–180)			
	POD 30	132 (110–160)			
	Postop 1 year	131 (107–164)			
eGFR (ml/min/1.73 m^2)	Preoperative	10 (8–14)	<0.001	0.011	0.91
	POD 7	21 (13–29)			
	POD 30	54 (44–72)			
	Postop 1 year	57.4 (45–69)			

Table 5. Recipient serum creatinine and GFR at pre-operative and post-operative time points

5.4. Discussion

The typical technical advantages of robotic surgery are related to the use of articulated instruments, a three-dimensional view, superb magnification (12 x), and good surgeon ergonomics. Furthermore, correct use of the da Vinci robotic system possibly provides benefits in terms of patient outcomes, including a significant decrease in blood loss, a low postoperative complication rate, and shorter hospital stay. From a technical point of view other advantages of RAKT are related to the quality of the vascular anastomosis.

In terms of functional outcomes, the most important aspect to consider in KT performed from living donors is patient and graft survival. For open KT the rate of DGF from living donors has been reported to be up to 4%, while the reported prevalence of arterial graft thrombosis is between 0.5% and 3.5% [22]. In the multicenter study [49], five cases (4.2%) of DGF and three cases (2.5%) of arterial thrombosis with graft loss were observed. These results are in line with the literature on open KT. Notably, three cases of graft loss due to arterial thrombosis during the first postoperative week were reported in these series (2.5%). This complication might be associated with technical errors during the learning curve.

In addition, RAKT is associated with a lower risk of specific surgical complications such as postoperative lymphocele. In fact, the intraperitoneal window left during RAKT allows natural drainage of lymph into the peritoneal space. In addition, the wound infection rate seems to be very low, with only one case (0.8%) reported in a patient with diabetes and hypertension.

As far as ureteral stenosis is another complication in recipients of renal transplants from living donors, with an incidence of 0.6%–10.5% [22]. It is usually caused by surgical technique or compromise of the ureteral blood supply during surgery. The low complication rate with RAKT compared with the literature for open KT may be related to both selection biases (i.e. well selected graft from living donation) as well as the technical benefits of the robotic approach in terms of more precise vascular and ureteral suture.

Urinary tract infection (UTI) and acute pyelonephritis often occur in KT, increasing morbidity and mortality in renal transplant recipients. The reported incidence ranges from 25% to 75%

According to the literature, incisional hernia is not a rare complication in open KT, with an incidence of up to 5.4% [22]. Risk factors include the type of incision, the immunosuppressive treatment, wound infections, impaired tissue quality due to renal disease, and neuromuscular trauma owing to the operation. In our series, no cases of incisional hernia were reported, emphasizing the benefits of the robotic approach in terms of the smaller surgical incision and the use of the GelPOINT device to introduce the graft into the abdominal cavity. We believe that both the small incision and the device may strongly decrease the abdominal trauma, explaining the absence of this kind of complication.

To our knowledge, these are the first and largest series in the literature on graft survival, functional results, and postoperative complications related to RAKT [49] [50]. RAKT from living donation is a safe procedure and, in a properly selected group of patients, it seems to provide a low complication rate with maintenance of excellent graft function at 1 year follow-up. Overall, these are key benefits for KT recipients, who are fragile, immunocompromised patients with a higher risk of surgical complications.

6. RAKT USING GRAFTS WITH MULTIPLE VESSELS

6.1 Introduction and objectives

Anatomic variations in the renal vasculature are common, being reported in 25%–40% of kidneys. Supernumerary or accessory renal arteries and, to a lesser extent, renal veins, represent the most common variations [55].

Grafts with multiple vessels (GMV) pose a technical challenge for KT. Several retrospective studies, using different techniques for vascular reconstruction, have demonstrated the feasibility and safety of KT using GMVs [56][57. However, a recent review reported increased risks of complications, DGF, and lower 1-year graft survival using GMVs, despite the fact that long-term outcomes were comparable to those of KT using grafts with single vessels (GSV) [58]. Moreover, previous studies have reported a potential increased rate of ureteral complications for grafts with accessory lower pole arteries, although this is still matter of controversy [59][60][61].

The previously discussed advantages of robotic technology for accurate vascular anastomoses are crucial also in cases of KT using GMV (figure 18). In these cases, the surgeon may decide to perform either extracorporeal reconstruction of graft vessels according to the specific graft and recipient anatomic characteristics. Moreover, robotic surgery may allow performance of precise vascular anastomoses even in case of multiple vessels of very small caliber.

To date, no studies have reported surgical technique and outcomes of RAKT using GMVs. Herein the ERUS working group experience with RAKT using GMVs from living donors is described, focusing on technical feasibility and perioperative and early functional outcomes.

6.2 Materials and methods

In terms of methodology, prospective multi-institutional data were collected by the ERUS working group using the common database on RAKT in order to select consecutive patients undergoing RAKT from living donors using GMVs between July 2015 and January 2018. Patients undergoing RAKT using GSVs served as controls. In the case of GMVs, ex vivo vascular reconstruction techniques were performed during bench surgery according to the case-specific anatomy. Intraoperative outcomes and early (30-day) postoperative complications and functional results were the main study endpoints. Multivariable logistic regression analysis evaluated potential predictors of suboptimal renal function at 1 month.

Technically, after retrieval, the graft was defatted and perfused with cold storage solution as in conventional OKT. In the case of GMVs, the following reconstruction techniques have been employed according to the case-specific vascular anatomy: a) conjoined (side-to-side) arterial anastomosis (in a pantaloon fashion – figure 19), in cases of multiple renal arteries of almost equal caliber; b) reimplantation (end-to-side) of a polar artery into the main renal artery, or c) a combination of these techniques in the presence of ≥3 renal arteries and/or complex vascular anatomy. Finally, small accessory renal arteries supplying the upper pole and with a diameter of less than 2–3 mm were ligated during bench surgery. Grafts with one artery and one vein after ligation of small accessory arteries were not considered grafts with multiple vessels. In one graft with two renal veins, a conjoined (side-to-side) venous anastomosis was performed in a pantaloon fashion to create a common venous ostium for subsequent single venous anastomosis to the external iliac vein. The second graft with multiple renal veins (n=2) in our series was found in a patient with a duplication of the inferior vena cava. In this case, the two renal veins were left intact on a caval patch and the patch anastomosed to the external iliac vein.

6.3 Results

RAKT from living donors using kidneys with multiple arteries and veins was first reported by Siena et al. in 2018 [62]. As far as the results are concerned, overall 148 RAKTs were performed during the study period. Among these, GMVs were used in 21 (14.2%); in all cases, single arterial and venous anastomoses could be performed after vascular reconstruction (figure 20). Median anastomoses and rewarming times (RWT) did not differ significantly between the GMV and GSV groups. Total and cold ischemia times were significantly higher in the GMV cohort (112 vs 88 min, p=0.004 and 50 vs 34 min, p=0.003, respectively – figure 21). Overall complication rate and early functional outcomes were similar among the two groups. No major intra- or postoperative complications were recorded in the GMV cohort. At the multivariable analysis, only the donor age was a significant predictor of sub-optimal renal function on POD 30, whereas the use of GMVs was not significantly associated with suboptimal renal function at 1 month (table 6).

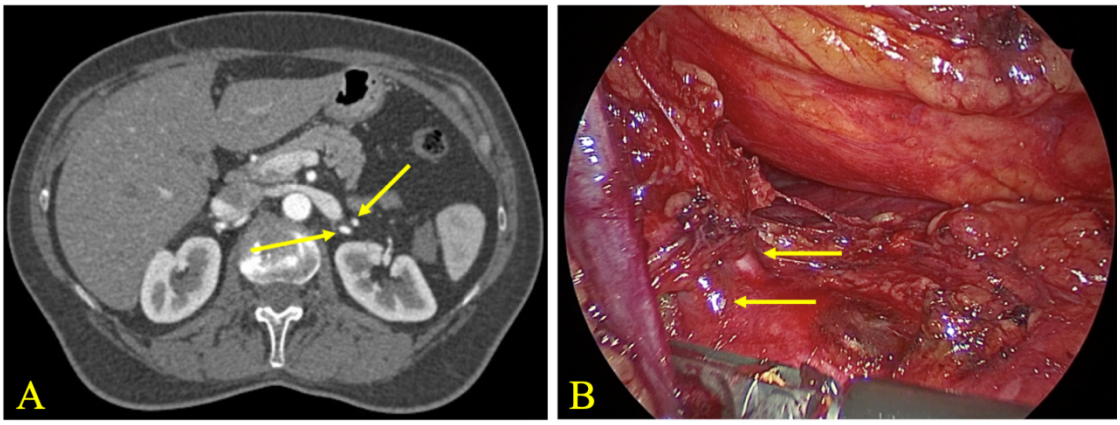


Figure 18. A. CT scan showing a double artery in the left kidney. **B**. Laparoscopic dissection of the left renal arteries in preparation for the living donor nephrectomy.

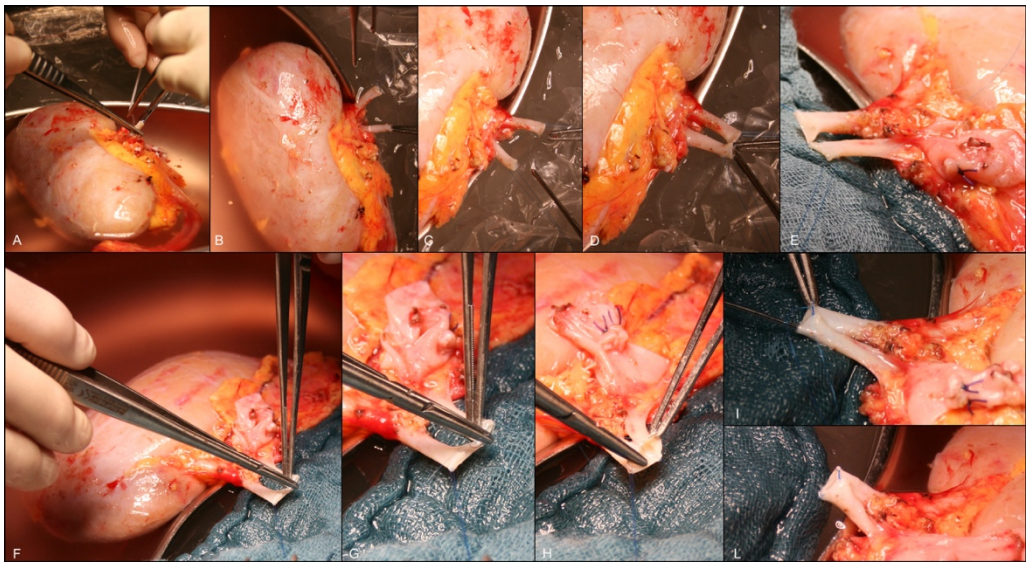


Figure 19. Bench table preparation of the graft with a double artery for subsequent RAKT, detailing the reconstruction of the arteries joined side-to-side in a pantaloon fashion.

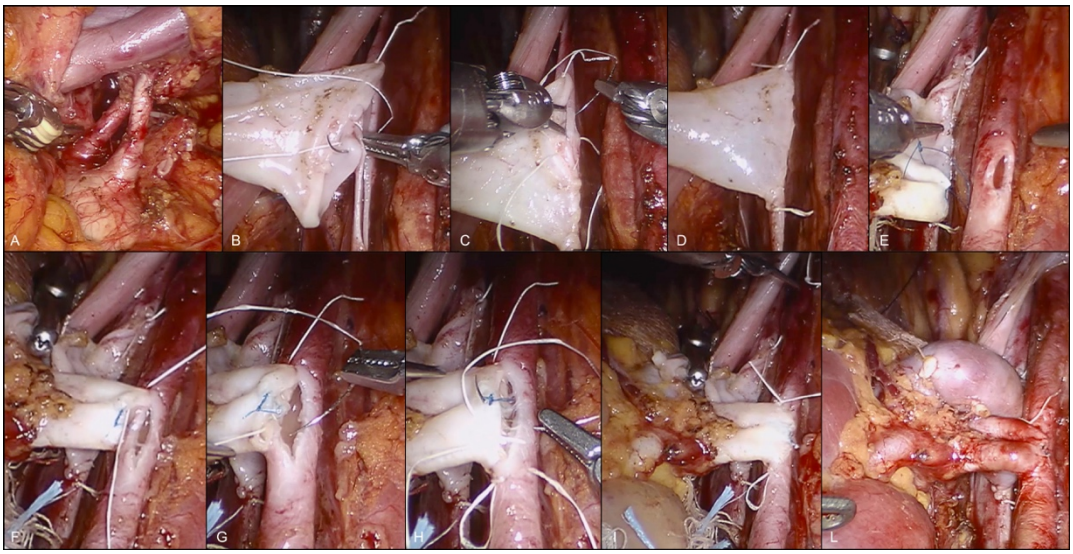
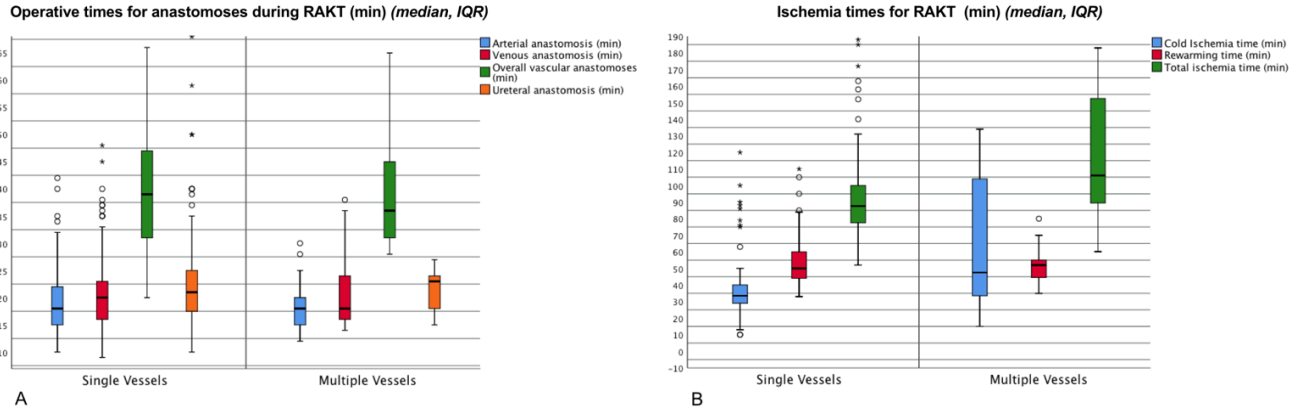


Figure 20. Surgical details of RAKT using GMV (double artery joined side-to-side in a pantaloon fashion)



Anastomosis	Overall (n=148)	Single vessels (n=127)	Multiple vessels (n=21)	p
Arterial	18 (15-21)	18 (15-22)	18 (15-20)	0,7
Venous	20 (16-24)	20 (16-24)	18 (16-24)	0,7
Uretero-vesical	21 (18 - 25)	21 (18-25)	23 (18-24)	0,7

	Overall (n=148)	Single vessels (n=127)	Multiple vessels (n=21)	p
Cold ischemia	35 (30 - 43)	34 (29-40)	50 (34 - 76)	0,003
Rewarming time (with ice slush)	50 (44-57)	50 (43-59)	52 (45 - 55)	0,8
Total ischemia	89 (80 - 106)	88 (78 - 100)	112 (90 - 138)	0,004

Figure 21. RAKT results using GSM vs GMV. **A**. Operative time, including vascular anastomosis (arterial and venous time) and ureterovesical reimplantation. **B.** Ischemia time, including cold ischemia, rewarming time, and total ischemia.

		eGFR < 45 ml/min at POD 30	
		OR (95%CI)	**p**
Donor Age (5 y-fold)		1.46 (1.06-2.01)	**0.02**
Donor BMI		0.79 (0.64-1.08)	0.3
Donor preoperative eGFR (5 ml/min-fold)		0.98 (0.84-1.15)	0.8
Recipient Age (5 y-fold)		1.01 (0.81-1.48)	0.5
Recipient BMI		1.05 (0.89-1.28)	0.5
Graft with multiple vessels (reference: grafts with single vessels)		3.21 (0.70-14.70)	0.1
Console time		1.01 (0.99-1.02)	0.5
Warm ischemia time		1.06 (0.67-1.67)	0.8
Cold ischemia time		1.03 (0.99-1.02)	0.7
Rewarming time		0.94 (0.86-1.03)	0.1
RAKT number	**>20 vs <10**	0.17 (0.02-1.25)	0.08
	>20 vs 10-20	0.67 (0.15-2.74)	0.5

Table 6. Multivariate analysis to evaluate the predictors of sub-optimal renal function on POD 30

6.4 Discussion

This is the largest European multicenter study on RAKT from living-donors using grafts with multiple vessels. A key finding of this study is that RAKT using GMVs from living donors is technically feasible. Using appropriate vascular reconstruction techniques and a standardized operative protocol for RAKT [49], it was possible to perform *single* arterial and venous anastomoses in most cases, thereby reducing rewarming time and total ischemia time. Accordingly, time to complete vascular anastomoses, as well as overall console time and rewarming time, did not significantly differ between RAKTs using grafts with multiple or single vessels. Notably, the robotic platform facilitates the performance of vascular anastomoses thanks to the articulated instruments, three-dimensional view and optimal surgeon ergonomics.

A second finding of this study is that RAKT using GMVs from living donors appears to be safe, achieving optimal early (30-d) postoperative outcomes, with no reported major intra- or postoperative complications. Also, estimated blood loss, length of hospital stay, recipient's Hb values and overall complications rate were comparable to RAKTs using GSV.

A third key finding is that, despite longer cold and total ischemia times, probably reflecting a longer time required for extracorporeal bench vascular reconstruction, RAKT using GMVs from living donor provided optimal early functional results that were comparable to those of RAKT using GSVs.

Therefore, in experienced hands, RAKT using grafts with multiple vessels was technically feasible and achieved optimal perioperative and early functional outcomes that were comparable to those of RAKT using grafts with conventional vascular anatomy. However, larger studies with longer follow-up are needed to standardize the surgical technique and confirm the long-term safety of RAKT using grafts with multiple vessels.

7 RAKT IN OBESE RECIPIENTS

7.1 Introduction and objectives

KT in obese patients presents several challenges related to surgery: access to the external iliac vessels, surgery and vascular anastomosis time, an increase in the risk of surgical site complications, and DGF. Several studies reported technical difficulties of the KT surgery in obese recipients with traditional open approach and a higher post-operative complication rate, including wound dehiscence, infection, lymphocele formation and DGF [24][25][26][27]. Consequently, many transplant centers tend to contraindicate obese recipients of KT. However, compared to remaining on a waiting list, KT in obese recipients improves long-term survival and enhances quality of life, even though obesity is strongly associated with reduced long-term patient survival and graft failure, unlike non-obesity [63] [64].

The first case of RAKT in an obese recipient was reported by Giulianotti et al. in 2010 [65] and the first two cases of European RAKT in obese recipients who were ineligible for OKT open transplantation were published in 2017 by Doumerc et al. [66]. Furthermore, recent studies [67][68][69] have evaluated the feasibility and safety of RAKT in obese recipients in comparison with OKT. However, no studies have evaluated the feasibility and safety of RAKT in obese versus non-obese recipients.

The main objective of this study, from the ERUS group, was to compare minor (Clavien I-II) and major (Clavien ≥III) intra- and postoperative complications in obese recipients (≥30 kg/m^2 BMI), overweight recipients (<30 / ≥25 kg/m^2 BMI) and non-overweight recipients (<25 kg/m^2 BMI). The secondary objective was to compare functional results (DGF, eGFR) between obese, overweight, and non-overweight recipients.

7.2. Materials and methods

Consecutive patients undergoing RAKT with regional hypothermia were selected at the 8 European Centers included in the ERUS-RAKT Project. We defined overweight and obesity as having a body mass index (BMI= weight in kg/m^2 height) ≥ 25 kg/m^2 and ≥ 30 kg/m^2, respectively.

Variables collected in the prospective database included recipient characteristics, graft characteristics, intraoperative parameters and postoperative parameters, with a 30-day follow-up.

The recipient data that were collected included: age (years), gender, BMI (kg/m^2), pre-emptive transplantation, median dialysis duration (days), preoperative creatinine level (μmol/l), glomerular function rate (eGFR) (ml/min/1.73 m^2), hemoglobin level (g/dl) and a medical history of high blood pressure.

The intraoperative data reviewed were: operative time, console time, arterial anastomosis time, venous anastomosis time, ureterovesical anastomosis time, warm ischemia time, cold ischemia time, estimated blood loss, rate of conversion to open surgery, and intraoperative complications. Intraoperative complications included intraoperative vascular injuries and the need for vascular anastomosis revision. The postoperative parameters collected included: serum creatinine (μmol/l), eGFR (ml/min/1.73 m^2) and hemoglobin (g/dl) on postoperative days (POD) 1, 3, 7, and 30.

7.3 Results

A total of 169 RAKTs from living-donor were performed from July 2015 to September 2018. 32 (18.9%) recipients were obese, 66 (39.1%) recipients were overweight and 71 (42.0%) recipients were non-overweight.

Console time did not statistically differ between obese, overweight and non-overweight recipients. Median times to complete arterial, venous and uretero-vesical anastomoses did not statistically differ between obese, overweight and non-overweight recipients (figure 22). There were no major intra-operative complications in either study group. Conversion to open surgery occurred in 1 obese recipient due to a difficult graft placement, in 2 overweight recipients because of intra-operative bleeding and no conversion occurred in non-overweight recipients (p=0.3). Minor and major postoperative complications rate were similar in either study group. The intra-operative parameters were summarized in table 7.

One-year eGFR was similar in all groups (45.1 ± 18.1 versus 48.6 ± 20.5 versus 48.7 ± 19.2 ml/min in obese, overweight and non-overweight recipient groups, respectively, p=0.9). The table 8 summarized the post – operative functional results and the complications in the population group analyzed (obese, overweight and non-overweight recipients). Only the number of arteries was an independent predictive factor of suboptimal renal function in the multivariate analysis (table 9).

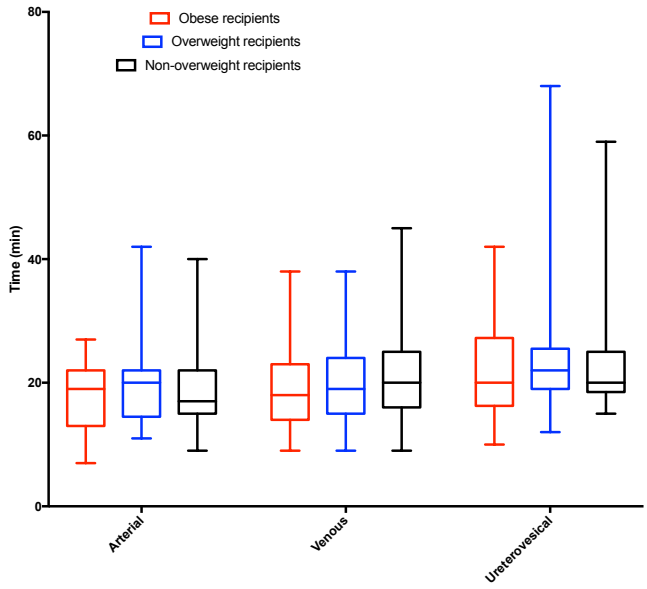


Figure 22. Box Plot Showing arterial, venous and ureterovesical anastomosis time in obese, overweight and non-overweight recipients

	Overall population n= **169**	**Obese recipients** (≥30 kg/m^2 BMI) n= **32**	**Overweight recipients** (<30 / ≥25 kg/m^2 BMI) n= **66**	**Non-overweight recipients** (<25 kg/m^2 BMI) n= **71**	***p***
Console time (min) *Mean +/- SD*	159.1 ± 51.2	147.4 ± 49.9	159.8 ± 53.8	161.6 ± 49.1	0.6
Arterial anastomosis time (min) *Mean +/- SD*	19.1 ± 6.5	18.4 ± 5.1	19.9 ± 7.3	18.7 ± 6.3	0.4
Venous anastomosis time (min) *Mean +/- SD*	20.8 ± 7.3	19.8 ± 7.2	21.2 ± 8.0	20.8 ± 6.7	0.7
Ureterovesical anastomosis time (min) *Mean +/- SD*	23.3 ± 8.8	23.3 ± 9.0	23.1 ± 8.0	23.5 ± 9.6	1
Cold ischemia time (min) *Mean +/- SD*	73.7 ± 110.8	92.2 ± 147.4	59.0 ± 57.6	81.3 ± 132.7	0.4
Estimated blood loss (ml) *Mean +/- SD*	135.3 ± 82.0	118 ± 78.6	141.4 ± 95.4	139.3 ± 67.1	0.5
Intraoperative complications *-Major (Clavien ≥ III) (n, %)* *-Bleeding (requiring blood transfusions) (n, %)*	 -0 (0%) -4 (2.4%)	 -0 (0%) -1 (3.1%)	 -0 (0%) -2 (3.0%)	 -0 (0%) -1 (1.4%)	 1 0.8
Conversion to open surgery *(n, %): reason*	3 (1.8%)	1 (3.1%): difficult graft placement	2 (3.0%): intraoperative bleeding	0 (0%)	0.3

Table 7. Intra-operative parameters in the groups analyzed (obese, overweight and non-overweight recipients).

	Overall population n= **169**	**Obese recipients** (≥30 kg/m^2 BMI) n= **32**	**Overweight recipients** (<30 / ≥25 kg/m^2 BMI) n= **66**	**Non-overweight recipients** (<25 kg/m^2 BMI) n= **71**	***p***
Creatinine (µmol/l)					
POD 1	349.8 ± 196.1	393.5 ± 191.5	357.9 ± 204.5	320.6 ±187.6	0.2
POD 3	210.1 ± 186.9	291.1 ± 213	217.7 ± 218.7	162.6 ± 110.6	**0.005**
POD 7	233.6 ± 770.6	222.6 ± 178.6	169.3 ± 174.1	303.2 ± 120	0.6
POD 30	146.8 ± 90.4	149.1 ± 60.7	165.7 ± 129.8	127.5 ± 49.2	0.2
1-year	149.1 ± 123.7	133.1 ± 38.5	174.4 ± 198.4	135.1 ± 37.4	0.5
Delta creatinine, POD 3 – pre-operative (µmol/l) *Mean +/- SD*	-363.4 ± 222.1	-306.5 ± 226.1	-358.8 ± 228.8	-394.6 ± 211.3	0.2
Delta creatinine, POD 7 – pre-operative (µmol/l) *Mean +/- SD*	-401.6 ± 257.7	-385.4 ± 237.3	-410 ± 220.2	-400.9 ± 301.2	0.9
Delta creatinine, POD 30 – pre-operative (µmol/l) *Mean +/- SD*	-396.8 ± 226.9	-445.3 ± 229.1	-362.3 ± 256.1	-393.6 ± 195.2	0.4
Delta creatinine, 1-year – pre-operative (µmol/l) *Mean +/- SD*	-399.7 ± 251.7	-483.4 ± 258.7	-384 ± 290.4	-376.2 ± 215.7	0.5
eGFR (ml/min/1.73m^2)					
POD 1	22.5 ± 15.0	17.8 ± 11.2	22.3 ± 15.0	24.9 ± 16.1	0.1
POD 3	45.3 ± 23.3	34.7 ± 24.6	43.7 ± 20.8	52.3 ± 23.1	**0.002**
POD 7	58.1 ± 66.2	42.2 ± 24.6	63.3 ± 100.3	60.5 ± 19.4	0.3
POD 30	60.2 ± 22.4	50.7 ± 19.0	58.0 ± 22.0	69.0 ± 22.4	**0.003**
1-year	58.9 ± 19.0	54.4 ± 16.6	57.7 ± 21.1	62.2 ± 18.5	0.5
Delta eGFR, POD 3 – pre-operative (ml/min) *Mean +/- SD*	35.7 ± 23.6	25.4 ± 24	34.8 ± 21.4	41.7 ± 24.0	**0.01**
Delta eGFR, POD 7 – pre-operative (ml/min) *Mean +/- SD*	44.1 ± 22.9	33.1 ± 23.7	43.0 ± 22.6	50.4 ± 20.9	**0.004**
Delta eGFR, POD 30 – pre-operative (ml/min) *Mean +/- SD*	49.9 ± 22.3	41.3 ± 19.5	49.0 ± 20.9	56.5 ± 23.9	**0.03**
Delta eGFR, 1-year pre-operative (ml/min) *Mean +/- SD*	48.0 ± 19.2	45.1 ± 18.1	48.6 ± 20.5	48.7 ± 19.2	0.9
DGF rate *n (%)*	26 (15.4%)	6 (18.8%)	11 (16.7%)	9 (12.7%)	0.6
Delta Hb values (g/dl)					
POD 1	-0.7 ± 1.8	-0.6 ± 1.3	-0.3 ± 2.0	-1.1 ± 1.9	**0.05**
POD 3	-1.3 ± 1.8	-1.2 ± 1.4	-1.1 ± 1.9	-1.6 ± 1.8	0.2
POD 7	-1.1 ± 1.9	-1.2 ± 1.8	-0.9 ± 1.9	-1.4 ± 1.9	0.3
POD 30	1.3 ± 2.6	0.4 ± 1.6	0.9 ± 2.7	1.9 ± 2.7	0.2
Post-operative pain (VAS scale)					
12h	3.5 ± 1.9	2.8 ± 1.6	3.9 ± 1.8	3.8 ± 2.1	0.1
24h	2.5 ± 1.7	2.3 ±1.7	2 ± 1.4	3.0 ± 1.8	0.1
48h	1.7 ± 1.6	1.0 ± 1.1	1.4 ± 1.3	2.5 ± 2.0	**0.01**
JJ stent removal. POD *Mean +/- SD*	32.2 ± 14.4	26.4 ± 15.7	33.5 ± 16.7	32.4 ± 11.1	0.2
Early postoperative complications (POD 30)					

(Clavien-Dindo classification)					
I	3 (infections)	1 (infection)	1 (infection)	1 (infection)	0.8
-Wound infection	1 (ileus)	0 (ileus)	1 (ileus)	0 (ileus)	0.5
-Postoperative ileus					
II	1 (PE)	1 (PE)	0 (PE)	0 (PE)	0.1
-Pulmonary embolism					
-Bleeding requiring transfusions	5 (transfusions)	0 (transfusions)	2 (transfusions)	3 (transfusions)	0.5
IIIa					
-Nephrostomy tube placement	2 (nephrostomies)	1 (nephrostomy)	1 (nephrostomy)	0 (nephrostomy)	0.4
-Percutaneous drainage of pelvic lymphocele	1 (percutaneous drainage)	0 (percutaneous drainage)	0 (percutaneous drainage)	1 (percutaneous drainage)	0.5
IIIb					
-Graft nephrectomy (reason: vascular thrombosis)	3 (graft nephrectomies)	0 (graft nephrectomy)	1 (graft nephrectomy)	2 (graft nephrectomies)	0.6
-Surgical re-exploration (reason: bleeding [n = 2])	2 (re-exploration)	1 (re-exploration)	1 (re-exploration)	0 (re-exploration)	0.4
-Radiologic embolization	2 (radiologic embolization)	0 (radiologic embolization)	0 (radiologic embolization)	2 (radiologic embolization)	0.2

Table 8. Post – operative functional results and complications in the groups analyzed (obese, overweight and non-overweight recipients).

	Odds Ratio	**95% CI**	**Z**	***p***
Age	0.99	0.98-1.00	0.144	0.1
BMI	0.98	0.96-1.00	0.28	0.3
Number of Arteries	0.71	0.55-0.94	0.01	**0.02**

Table 9. Multivariate Analysis of Preoperative Criteria Evaluating Suboptimal Renal Function on POD 30 (eGFR<45 ml/min/1.73 m^2)

7.4 Discussion

The study addresses outcomes and safety solely of the robotic approach, based on BMI groups. Considering BMI as a measure of weight and serum creatinine as a measure of muscle mass, the study found that BMI >35 was associated with increased graft failure and high pre-transplant serum creatinine reduced risk of graft failure. Thus, BMI alone is likely not sufficient as a preoperative assessment of recipients, and transplant surgeons should perform a surgical evaluation of surgical feasibility, with measure of surgical depth.

In this series, the DGF incidence in the overall population was 15.4%, which is higher than the DGF incidence reported in other RAKT studies in obese recipients [24] [25] [26] [27]. One of the explanations could be the difficulty to clinically assess the need for dialysis in these patients and to standardize dialysis indications between the different centers. Thus, consequently, there was probably an over-indication of dialysis within the first week after the transplantation. Furthermore, a possible influence of prolonged pneumoperitoneum on the DGF incidence has to be consider. Indeed, the potential graft damage of pneumoperitoneum and is not fully known.

Moreover, in our study, the number of arteries was an independent predictive factor of suboptimal renal function (eGFR <45 ml/min/1.73 m^2) on POD 30 in the multivariate analysis. In case of GMV, an *ex-situ* vascular reconstruction was performed according to the graft vascular anatomy: (1) conjoined (side-to-side) arterial anastomosis, (2) reimplantation (end-to-side) of a polar artery into the main artery, or (3) combination of these techniques in the event of greater than or equal to three renal arteries and/or complex vascular anatomy.

Finally, several centers have proposed bariatric surgery before transplantation to optimize recipients and reduce time on the waiting list. Another advantage of RAKT is that transplant surgery does not have to be delayed by first performing bariatric surgery. In fact, RAKT can be performed as soon as the donor and recipient are medically cleared and weight loss can be encouraged after the transplantation.

The present study is the first in the literature to describe intra- and postoperative complications as well as one-year functional results related to RAKT performed in obese, overweight, and non-overweight recipients. Particularly, in the obese population, RAKT provides an optimal graft function with a low complication rate. However, further studies and larger series are needed to confirm long-term functional outcomes.

8 RAKT USING GRAFTS FROM DECEASED DONORS

8.1 Introduction and objectives

To date, the vast majority of RAKT procedures worldwide have been performed from living donors, raising concerns regarding the generalizability of RAKT outcomes in the broader and more challenging scenario of deceased donors. While it has been shown that the learning curve for elective RAKT (i.e., living donor RAKT) may be minimal for surgeons with extensive experience in robotic surgery (regardless of their background in OKT) [70] [71], RAKT from deceased donors faces unique technical and logistical challenges. Indeed, due to the timeframe of organ preservation, it can be considered an unforeseeable "emergency" robotic procedure, which requires a structured multidisciplinary framework.

To fill this gap and move the field forward, the University of Florence group has recently developed a RAKT program from deceased donors aiming to safely and progressively increase the pool of patients who may benefit from minimally invasive KT [52].

The cornerstones of this program are: a) an extensive experience in OKT and robotic urologic surgery (including radical prostatectomy, radical nephrectomy, partial nephrectomy, radical cystectomy, dismembered pyeloplasty, and ureteral reconstructive surgery); b) a codified technique for RAKT [49]; c) a structured modular training in RAKT, including e-learning, simulation, dry lab, wet lab, and training on animal models [72]; d) the availability of a multidisciplinary team (comprising urologists, anesthesiologists, nephrologists, and radiologists, as well as operating room support staff and nurses) with experience in KT and robotic surgery; and e) the opportunity to perform RAKT at night-time and/or during the weekend in a dedicated operating room [52].

8.2 Materials and methods.

Selection criteria for RAKT from deceased donors. Exclusion criteria for RAKT from deceased donors include:

a) age <18 years;

b) severe comorbidities with contraindications for robotic surgery;

c) significant atherosclerotic plaques at the level of the external iliac vessels;

d) highly complex vascular graft anatomy (likely to require multiple anastomoses);

e) multiple previous abdominal surgeries;

f) previous KT.

Decision-making process to assess the feasibility of RAKT from deceased donors. A key element of the RAKT program from deceased donors is also represented by the decision-making process aiming to assess the feasibility of RAKT in light of the patient-, graft-, and robotic team-related factors [52]. Accordingly, the decision to proceed with an "emergency" RAKT from a deceased donor relies on a careful balance of the potential advantages of robotic surgery (for both the patient and the surgeon) and the logistical challenges of setting up the operating room and the robotic surgical team in a fixed timeframe, respecting the recipient's selection criteria and the maximal thresholds of cold ischemia time. Specifically, planning RAKT from deceased donors follows a prespecified decision-making process, including the opportunity to perform RAKT according to the surgeon's personal experience and the availability of an expert bedside assistant as well as expert robotic operating room nursing staff. Then, after the recipient has been admitted to the Nephrology Unit for the pretransplant clinical work-up (which systematically includes a CT angiogram of the abdomen to check for severe atherosclerotic plaques at the external iliac vessels), the surgeon checks that the recipient's inclusion criteria are met. Finally, at the time of bench surgery, the graft is carefully inspected to ensure that no exclusion criteria for RAKT are present (i.e., highly complex vascular anatomy requiring multiple vascular anastomoses).

The University of Florence technique. The surgical steps of RAKT using grafts from deceased donors do not differ from the procedure using grafts from living donors, described previously. However, some modifications were adopted at the University of Florence in comparison with the standardized technique reported by Breda et al. [49]. In more detail, two landmark stiches are placed on the upper and lower sides of the graft vein, while one landmark stich is placed on the upper side of the graft artery, to facilitate the subsequent orientation of the graft inside the abdominal cavity. A Pfannenstiel rather than a periumbilical incision is performed to set in place the GelPOINT® device (or the Alexis® wound retractor). Intraoperative indocyanine green fluorescence videography (i.e., FireFly® technology in the DaVinci Xi platform) is routinely used to assess the graft and ureteral reperfusion [73].

8.3 Results

Surgical data, functional results, and complications. The University of Florence group published results on 17 RAKTs from deceased donors [52] and have now performed 19 cases, all successfully completed without need for open conversion. In the vast majority of cases (n=17), RAKT was performed in the right iliac fossa. The graft was introduced using the GelPOINT® device (or the Alexis® port) in 14 (73.7%) cases through a Pfannenstiel incision, while in five (26.3%) it was introduced through a periumbilical incision.

Median eGFR at hospital discharge (median 12 days postoperatively) was 47.2 ml/min/1.73 m^2 (IQR 28.9–59.4), while median eGFR at a median follow-up of 15 months was 58.6 ml/min/1.73 m^2 (IQR 40.0–80.4). Overall, five (26%) patients required dialysis during the first postoperative week, including one due to primary non-function after RAKT from an uncontrolled donation after cardiac death, one due to graft nephrectomy as a result of arterial thrombosis, one due to suspected acute rejection treated with intravenous corticosteroids, and two due to DGF. At a median follow-up of 15 months, all patients are alive and two are still on dialysis.

As far as intraoperative complications are concerned, one case of intraoperative bleeding not requiring transfusion was recorded, requiring the positioning of an additional 5-mm port to increase exposure and help aspiration.

In terms of postoperative complications, three patients (16%) suffered a high-grade (Clavien-Dindo grade III) complication: transplant renal artery stenosis requiring percutaneous angioplasty in one patient, percutaneous placement of a nephrostomy tube for hydronephrosis in one, and arterial graft thrombosis requiring graft nephrectomy in one. A progressive improvement of renal function was recorded at all time points during the postoperative period.

Although larger studies with longer follow-up are needed to confirm these findings and compare the outcomes of RAKT from deceased donors with those from living donors, this preliminary experience outlines that:

- the development of a RAKT program is feasible in centers experienced in robotic surgery and OKT;
- RAKT from deceased donors is feasible from both a technical and a logistical perspective;
- RAKT from deceased donors appears to achieve favorable early postoperative and functional outcomes.

8.4 Discussion

So far, no study has reported on the outcomes of RAKT in the broader setting of deceased donors, which requires a well-structured decision-making process aiming to optimize organization of the emergency robotic operating room, respecting the recipient's inclusion criteria, and ensuring adequate cold ischaemia times. Indeed, performance of RAKT requires extensive planning and logistic coordination of several teams (i.e. urologists, nephrologists, operating room staff, etc.), as well as availability of the robotic platform even at night-time or during weekends. For this reasons, a highly trained multidisciplinary team and the opportunity of a dedicated flexible operating room for RAKT are mandatory.

Extending the number of robotic transplantations performed by urological centers experienced in robotic surgery and using grafts from deceased donors would be key to increase the pool of recipients that may benefit from minimally invasive surgery and would allow the refinement of the indications and limits of this procedure.

A specific challenge in the case of RAKT from deceased donors is represented by the management of the Carrel's patch for arterial anastomosis (figure 23). From a technical point of view, and thanks to the robotic platform, removing the Carrel's patch may provide significant advantages for the surgeon. These include: a) the opportunity to perform a shorter arteriotomy; b) a more anatomic anastomosis thanks to the similar caliber of the graft renal artery and external iliac artery, and c) the reduced risk of atherosclerotic plaques at the level of the graft renal artery (as compared with Carrel's aortic patch). The preliminary experience with robotic KT using grafts from deceased donors suggests that, mirroring the technique used in the setting of living donation, performance of arterial anastomosis *without* Carrol's patch (figure 23) is technically feasible and appears safer especially in the presence of atherosclerotic plaques at the level of the renal artery's ostium [74].

A key finding from the present study is that building a RAKT programme for both living and deceased donors is feasible in centers with a high-volume of robotic urological procedures and experience in open KT. On the other hand, performance of RAKT in the setting of deceased donors may reduce the pressures on the surgical team that are inherently associated with a RAKT living-donor programme. However, further research is needed to evaluate the learning curve of RAKT from deceased donors and compare it with that of RAKT from living donors.

This study represent the first experience with RAKT using grafts from deceased donors at a referral academic center after development of a structured RAKT programme. This preliminary experience might prompt adoption of dedicated RAKT programmes at other high-volume robotic centers and increase use of grafts from deceased donors, extending the pool of recipients undergoing minimally invasive KT.

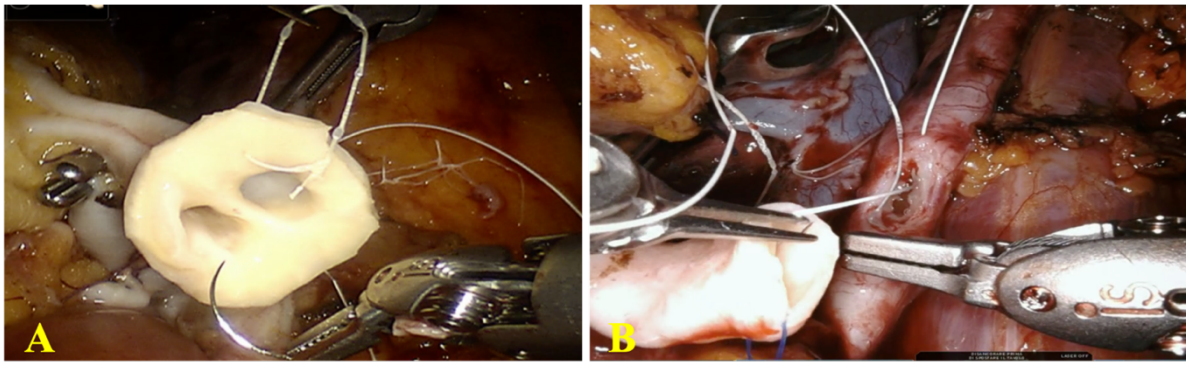


Figure 23. RAKT from cadaveric donor. In A and B arterial anastomosis *with* and *without* Carrol's patch, respectively

9 COLD ISCHEMIA DEVICE FOR KIDNEY TRANSPLANTATION: IDEAL PHASES 0 AND 1

9.1 Introduction and objectives

In both open and robotic KT, the most important aim is patient and graft survival. According to the literature, graft function may be affected by ischemia/reperfusion injury and the ischemia time [75]. Furthermore, there is a long-term detrimental association between DGF and graft survival [76] [77]. In order to protect the graft during vascular anastomosis in KT and avoid the risk of ischemia/reperfusion injury and, consequently, DGF, ice slush is commonly used to maintain a low temperature. However, few literature data have been published on this issue. In the standard RAKT procedure, Menon et al. [39] reported that the graft temperature should be kept below 20°C before graft revascularization. In order to achieve this temperature, the authors described the use of a gauze filled with ice slush to cover the graft and modified Toomey syringes to introduce ice slush into the abdominal cavity on the kidney surface while performing vascular anastomosis. With this technique to generate regional hypothermia, the potential risk associated with the RWT – i.e., the time between removal of the kidney from cold storage and beginning of reperfusion after conclusion of vascular anastomosis, while the graft is exposed to the intraperitoneal temperature (38ºC) – is strongly minimized [39]. In the multicenter series of 120 RAKTs from living donation, Breda et al. [49] found that the RWT (median 50 min) did not impair renal function. However, the authors did report five cases of DGF (4.2%); in OKT the rate of DGF from living donors has been reported to be up to 4% [78]. Another potential concern relates to potential injury generated by the ice slush as a result of development of local or systemic hypothermia. In particular, ileus has been reported to be a potential complication of local hypothermia, demonstrating that the ice slush could damage bowel function [79].

Following the IDEAL model for surgical innovation [80][81][82], a cold ischemia device was designed, developed, and tested. The aim of the device is to maintain the graft at a constant and low temperature (below 20ºC), avoiding introduction of ice slush into the abdominal cavity and consequently reducing the risk of complications related to regional hypothermia. This device could be used in both open and robotic KT.

9.2 Materials and methods

In *IDEAL phase 0*, the cold ischemia device was designed and developed in collaboration with bioengineers from GRENA Ltd. (design and development of the device). The device was tested in the dry lab using porcine kidneys to determine whether it could keep a kidney at a constant low temperature. This testing was performed using 15 porcine kidneys: in five the device was used (group 1), in five a gauze jacket filled with ice slush was used (group 2), and in five no covering was used (group 3). The three groups of kidneys were introduced into a closed box with a predetermined temperature of 37.5°C, simulating the temperature of the abdominal cavity. The temperature was evaluated at scheduled timepoints: T0 (baseline), T1 (1st minute), T2 (5th minute), T3 (10th minute), T4 (15th minute), T5 (20th minute), T6 (25th minute), T7 (30th minute), T8 (35th minute), T9 (40th minute), T10 (45th minute), and T11 (50th minute). The IDEAL phase 0 is shown in the figure 24.

In *IDEAL phase 1*, the cooling system was evaluated in six pigs undergoing open (n= 3) and robotic (n=3) KT, with attention to maneuverability, feasibility, major adverse reactions, and possible technical changes to the device (figure 25).

Data was reported as mean and standard deviation (SD). Comparisons between groups at each timepoint were performed using analysis of variance. Post-hoc pairwise comparisons were also analysed. For all the tests, a difference with a p-value <0.05 was determined to be significant. The statistical package SPSS (V 23) was used.

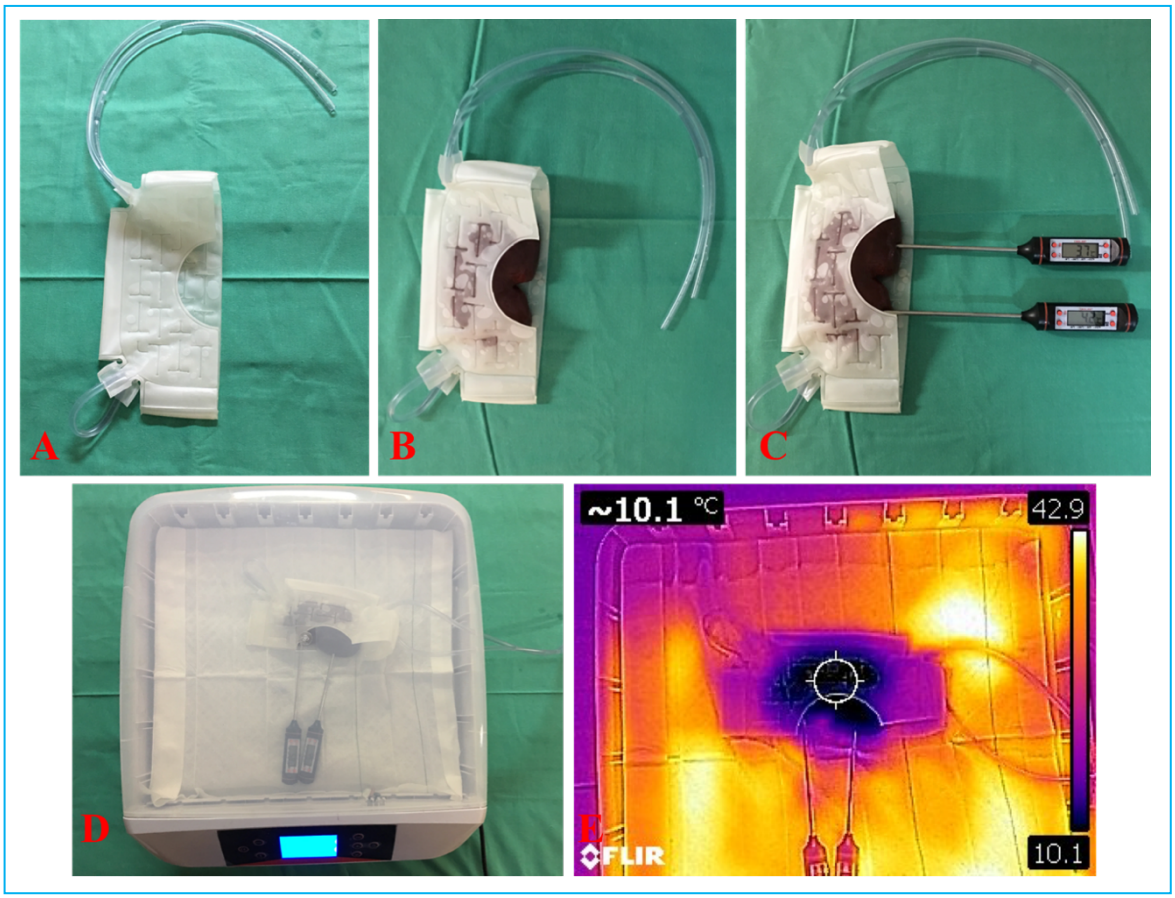


Figure 24. **A** Cold ischemia device; **B** porcine kidney inside the cold ischemia device; **C** thermometers for renal temperature measurement; **D** closed box with a predetermined temperature (37.5ºC) and thermometers to measure renal temperature; **E** the temperature is also measured with a FLIR© C2 IR thermal camera

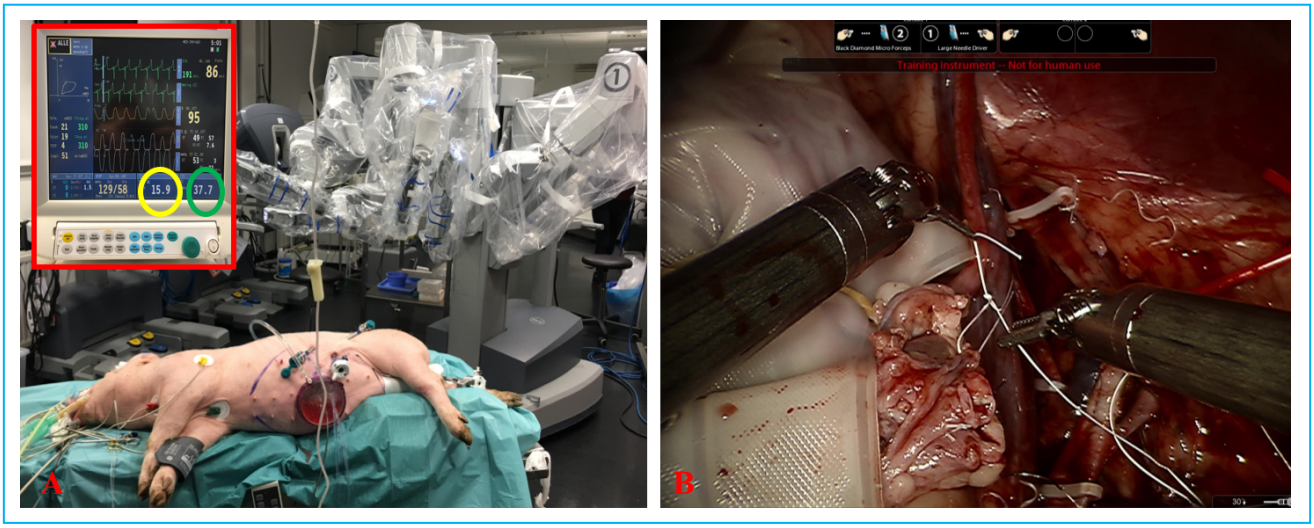


Figure 25. **A** The graft with the device is placed in the porcine abdominal cavity through the gel point; the renal and porcine temperatures are measured, as shown in the yellow and green circles, respectively. **B** Performance of RAKT using the cold ischemia device

9.3 Results

In the dry lab (IDEAL phase 0), the cold ischemia device proved able to maintain a low kidney temperature and was superior to both the gauze jacket filled with ice slush and no covering. Comparison between the three groups, and especially group 1 vs group 3 and group 1 vs group 2, showed a statistically significant difference (analysis of variance, p=0.002) in the absolute values of temperatures at T11 (50th minute) (table 9).

When the absolute change in temperature at specific timepoints was analysed, statistically significant differences were observed between group 1 and group 3 (T0 vs T6, p<0.05), between group 1 and group 2 (T6 vs T11, p<0.05) and in particular comparing group 1 vs the others at T11 vs T0 (all, p<0.05) (Table 10).

In the porcine model (IDEAL phase 1), the cooling device allowed maintenance of a low and constant temperature during both open and robotic procedures, with a mean temperature at T11 of 10.8°C (SD 0.2) and 14.9°C (SD 0.1) during open and robotic KT, respectively (figure 26). Furthermore, it permitted performance of vascular anastomosis without any increase in the surgical time. Specifically, the mean duration of vascular anastomosis was 42 min and 45 min in open and robotic KT, respectively. No major adverse reactions related to the device were reported.

	T0 Mean (SD)	**T1 Mean (SD)**	**T2 Mean (SD)**	**T3 Mean (SD)**	**T4 Mean (SD)**	**T5 Mean (SD)**	**T6 Mean (SD)**	**T7 Mean (SD)**	**T8 Mean (SD)**	**T9 Mean (SD)**	**T10 Mean (SD)**	**T11 Mean (SD)**
Device (group 1)	3.1 (0.8)	3.5 (1)	4.9 (1.9)	7.7 (3.5)	10.5 (4)	12.4 (4.1)	14 (3.9)	15.1 (3.4)	16.8 (3.2)	17.7 (2.7)	19 (2)	19.9 (1.9)
Gauze jacket (group 2)	3.1 (0.3)	3.6 (0.5)	5.5 (0.8	8.2 (0.8)	11.2 (1.1)	13.9 (1.9)	16.2 (2.1)	18.4 (2.4)	20.1 (2.8)	22.4 (3.2)	24.4 (3.7)	26.1 (3.7)
No device nor gauze (group 3)	3.8 (0.7)	4.7 (0.9)	7.7 (2.3)	11.2 (3.3)	14.6 (3.3)	17.6 (3.1)	19.9 (3.2)	21.8 (3)	23.5 (2.8)	24.6 (2.7)	25.8 (2.3)	27 (2)
P value*	0.178	0.072	0.071	0.152	0.116	0.063	0.035[a]	0.013[a]	0.012[a]	0.008[ab]	0.005[ab]	0.002[ab]

Table 9. Absolute values of temperature (°C) at each timepoint.

* P value for difference between the three groups at each timepoint (*analysis of variance*).

Post-hoc pairwise comparisons: [a] group 1 vs group 3, p<0.05; [b] group 1 v. group 2, p<0.05; [c] group 3 vs group 2, p<0.05.

	Change from T0 at T6 Mean (SD)	Change from T6 at T11 Mean (SD)	Change from T0 at T11 Mean (SD)
Device (group 1)	10.9 (3.1)	6 (2)	16.8 (1.2)
Gauze jacket (group 2)	13.1 (2.1)	9.8 (2.7)	23 (3.8)
No device nor gauze (group 3)	16 (2.6)	7.1 (1.5)	23.2 (1.6)
P value*	0.028[a]	0.039[b]	0.002[ab]

Table 10. Absolute change in temperature (°C) at each timepoint

* P value for difference between the three groups at each timepoint (*analysis of variance*).

Post-hoc pairwise comparisons: [a] group 1 vs group 3, $p<0.05$; [b] group 1 vs group 2, $p<0.05$; [c] group 3 vs group 2, $p<0.05$.

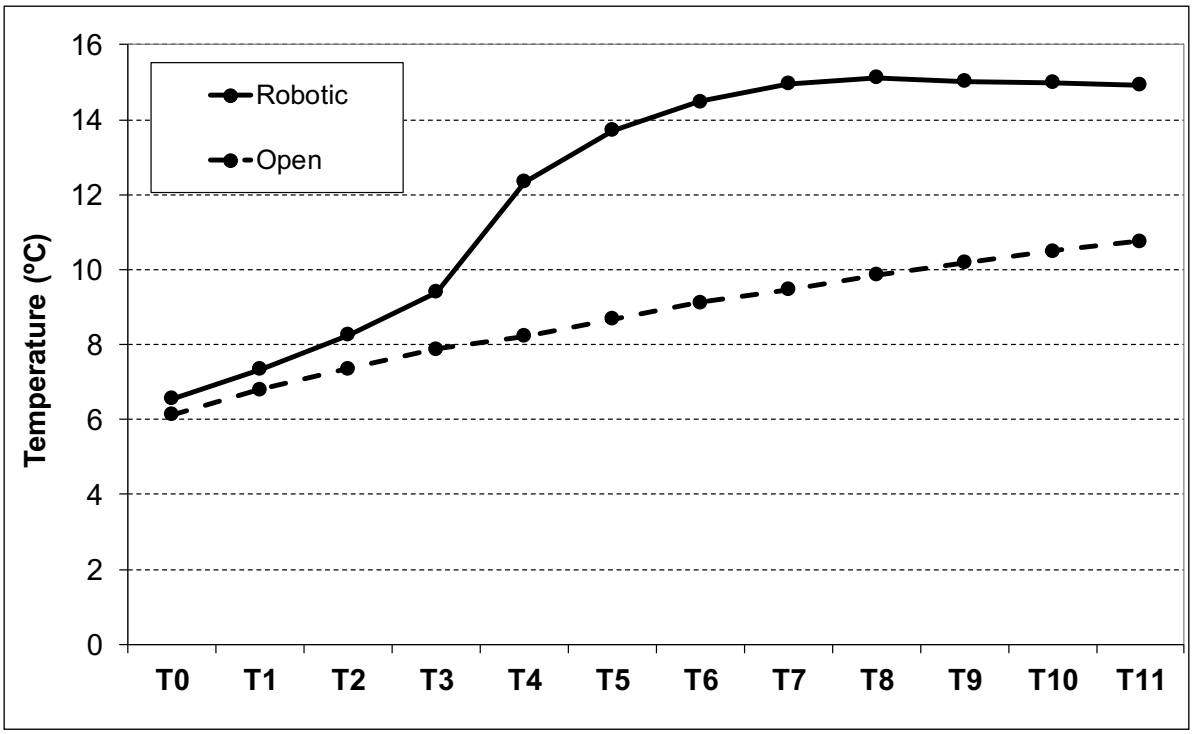


Figure 26. Absolute values in temperature at each timepoint. P value for the difference between the two areas under the curves <0.001 (unpaired t test).

9.4 Discussion

This is a novel technique that addresses the prior limitations of minimally invasive recipient surgery and reduces the risk of complications related to regional hypothermia. The goal is to develop a model that will allow outcomes reaching the standard achieved by open surgery from the very first patients.

The closed environment created by robotic assisted surgery with a temperature of about 38°C justified the concept that an efficient intracorporal cooling device should be utilized. The temperature required to achieve optimal renal protection during KT is below 20°C and several factors indicate that temperature control is of crucial importance in RAKT [39][41]. A regional hypothermia technique for RAKT that was intended to avoid graft impairment during the rewarming time was described by Menon et al. in their IDEAL phase 2a study [39]. They used a gauze jacket filled with ice slush to wrap the kidney during vascular anastomosis, with continuous addition of ice slush for intraperitoneal cooling of the graft. The limitation of this cooling approach is the gradual intra-abdominal melting of ice and the only partial control of the kidney temperature due to incomplete graft covering with ice, which might result in renal allograft impairment when there is an extended vascular anastomosis time. One of the potential injuries related to the use of ice slush is local and/or systemic hypothermia. Breda et al. [49] observed three cases of ileus that could have been caused by intraperitoneal ice cooling. Potentially, the cold ischemia device would be able to prevent this complication by covering the entire renal surface, maintaining a constant low temperature, and isolating the graft from the surrounding abdominal organs. In the IDEAL phase 0 of the study, we evaluated whether the device was able to maintain the kidney at a low and constant temperature after being inserted into a closed box with a predetermined temperature of 37.5°C. The kidneys of group 1, in which the device was used, had a mean final temperature at T11 (50 min) of 19.9°C (SD 1.9), compared with mean final temperatures of 26.1°C (SD 3.7) and 27°C (SD 2) in groups 2 (gauze jacket filled with ice slush) and group 3 (no covering), respectively. Moreover, the change in temperature during the 50 minutes from T0 to T11 was better in group 1 than in groups 2 and 3 ($p=0.002$). In the IDEAL phase 1, we tested the device in the animal model, evaluating not only its ability to maintain a constant temperature below 20°C (to minimize the damage related to the warm ischemia), but also the complications or surgical limitations related to use of the device. As shown in figure 24, the device allows access to the renal hilum, enabling vascular anastomosis in both open and robotic KT to be performed without any increase in duration or surgical difficulties. Specifically, the mean duration of vascular anastomosis was 42 and 45 min in open and robotic KT, respectively. At T11, the cooling system was found to keep the kidney temperature to a mean of 10.8°C (SD 0.2) and 14.9°C (SD 0.1) during open and robotic KT, respectively. No major adverse reactions related to the device were reported.

One limitation of this study is the absence of evaluation of functional outcomes owing to the typical occurrence of acute renal failure in the porcine model of autotransplantation, which is attributable to ischemia/reperfusion injury and thrombogenic features of the model. However, it was in any case not the aim to evaluate the functional results of the graft in this study.

These preliminary results show that the cold ischemia device is able to maintain a constant low temperature of the graft. In terms of maneuverability and feasibility of the surgical procedure, it allows performance of vascular anastomosis within a satisfactory length of time in both open and robotic KT.

10 POSTOPERATIVE SYSTEMIC INFLAMMATORY SYNDROME IN RAKT VERSUS OKT

10.1 Introduction and objectives

The advantages in terms of excellent graft function, benefits in postoperative pain, hospital stay, and aesthetic results were reported in the aforementioned studies on RAKT from living donors [43][45][46][49].

According to the literature, any surgical procedure generates a cascade of reactions initially stimulated by the release of pro-inflammatory cytokines, resulting in postoperative systemic inflammatory response syndrome (SIRS) [83].

Regarding KT, several studies have demonstrated that immediately following open transplantation, an inflammatory response, which includes also neutrophil gelatinase-associated lipocalin (NGAL), is associated with prolonged warm and cold ischemia and reperfusion injury [84][85]. In particular, NGAL protein has also been reported as an inflammatory biomarker in patients with ESRD, with its increasing level strongly associated with acute kidney injury and DGF after KT [86][87].

Among the inflammatory markers, interleukin-6 (IL-6) is also associated with the magnitude of tissue injury and SIRS. Previous studies having reported that postoperative levels of IL-6 are lower in minimally invasive surgery, corresponding to a reduced magnitude of SIRS and a lower invasiveness of surgery [88].

Surgical invasiveness can be evaluated both by clinical parameters and/or by quantification of systemic biologic responses such as metabolic responses, hormonal responses, and cytokine production. Various studies have reported that minimally invasive surgery substantially reduced SIRS owing to small incisions, less tissue manipulation, and less bleeding [89].

Despite this, so far there has been no study on quantification of the systemic response in RAKT and, other than that, there are no studies available comparing RAKT with conventional OKT.

The aims of this prospective study were to compare the systemic inflammatory response syndrome [in terms of serum levels of IL-6, C-reactive protein (CRP) and NGAL] and functional results between RAKT and OKT.

10.2 Materials and methods

This was a prospective, comparative study including consecutive RAKT and OKT performed in two European centers [Fundació Puigvert, Spain and University Hospital Halle (Saale), Germany] between January 2017 and December 2018. All KTs were from living donors and all recipients had pre-emptive KT. ABO-incompatible living donor KTs were excluded. The measurements of inflammatory markers and functional results were collected in a dedicated database. The study adhered to the tenets of the Declaration of Helsinki. The study was approved by the ethics committee of Fundació Puigvert. The study also guaranteed compliance at all times with Law 15/1999 for the Protection of Personal Data (Spanish Government). Patients were informed about the study and the surgical procedure. Informed consent was obtained from all patients prior to inclusion in the study.

Surgical technique, immunosuppression therapy and collection of the samples. RAKT and OKT surgical technique have been previously described. Immunosuppressive induction therapy included steroids, tacrolimus, and mycophenolate mofetil for all patients. All blood samples were drawn from a peripheral venous line on induction and at the following postoperative time points: H1, H6, H12, H24, H48, H72, and POD 5 corresponding respectively to T0, T1, T2, T3, T4, T5, T6, and T7, respectively. Whole blood samples were poured into vacutainer tubes containing ethylene diamine tetra-acetic acid (EDTA) or serum gel. The serum gel samples were centrifuged and then refrigerated. The EDTA samples were immediately refrigerated, subsequently centrifuged at 1400*g* for 10 min, and then immediately frozen at -20 °C until assayed. Laboratory analyses were performed in one batch at Halle University Hospital (Saale), Halle, Germany.

Measurement of inflammatory markers. The serum levels of IL-6, CRP and NGAL were determined using commercially available kits. IL6 and CRP determinations were performed on a Siemens Immulite 1000® (Siemens Healthcare Diagnostics) according to the manufacturer's instructions. NGAL measurements were obtained using the human Lipocalin-2/NGAL kit from R&D Systems. The serum levels of IL-6 and CRP were determined at time points T0–T7. Time points T1 and T2 were excluded from the determination of the serial levels of NGAL because its value as a predictor of acute kidney injury and DGF has been reported not to peak until at least 12h following KT.

Functional assessment of kidney graft. Functional results were evaluated in terms of serum creatinine level and eGFR on POD 1, 3, and 7. DGF was defined as the need for dialysis within the first postoperative week. Slow graft function was defined as a serum creatinine >250 umol/L on POD 7.

Statistical analysis. To assess the hypothesis that RAKT is associated with a lower SIRS compared with OKT, we designed a trial that had a 90% power at a double-sided significance level of 5%, to show a difference in the average maximal value of IL-6 and CRP of at least 15% between OKT and RAKT. We planned to enrol a minimum of 42 patients (21 in each arm). Data were analysed using Xlstat® software version 2018.5 (Addinsoft, Paris, France). Categorical variables are presented as frequencies and continuous variables as the mean ± SD. Demographic data were analysed via unpaired *t*-test, and a non-parametric Mann-Whitney test was used for intergroup comparisons of biomarkers. Point-to-point analysis was performed to compare the mean values of the biomarkers (IL-6, CRP, NGAL) in the OKT and RAKT groups at each time point as well as the maximum values for IL-6 and CRP and the minimum values for NGAL. Data were considered as significantly different if a p value <0.05 was obtained.

10.3 Results

Patient characteristics and surgical data. A total of 49 consecutive patients undergoing KT from living donors were enrolled from January to December 2017: 25 RAKT and 24 OKT. The demographic characteristics of both patient groups are reported in table 11. Mean age was 53±15 (20–74) and 49±14 (22–72) years in the OKT and the RAKT groups, respectively (p=0.74). Other characteristics were similar between the OKT and RAKT groups: mean BMI, gender, preoperative serum creatinine and eGFR, conservation of the graft (warm and cold ischemia, RWT), and operating time (all p>0.05).

Functional outcomes. The mean values of serum creatinine and eGFR on POD1, 3, and 7 are reported in Table 4. We noted no significant differences in the postoperative values of serum creatinine and eGFR between the OKT and RAKT groups (all p>0.05 at POD 1, 3, and 7; table 12) DGF was not observed in any case. Slow graft function was observed in 1/24 RAKT vs 2/20 in OKT (p=0.58). We noted one severe complication (Clavien-Dindo grade III) in the RAKT group: arterial bleeding in the hilum of the graft that could not be controlled robotically. GelPOINT® was removed and the arterial bleeding was identified in the fat of the hilum and was ligated through the abdominal incision of the GelPOINT®. We considered this complication as a conversion to open surgery (Clavien-Dindo grade III) although no enlargement of the abdominal incision was performed.

Inflammatory response in RAKT vs OKT. The mean serum levels of IL-6, CRP and NGAL at each time point are reported in table 13 (analysis and intergroup comparison at each time point).

- IL-6 increased rapidly after surgery, with a peak between 1 and 6 h postoperatively, which corresponded to an increase from the baseline value (T0) of ×8.3±2.4 for OKT vs ×13.4±4.5 for RAKT (p=0.14). The average of the IL-6 peak was 31±4 pg/mL with OKT vs 38±5 pg/mL with RAKT (p=0.27) (Figure 1). IL-6 then decreased continuously during the postoperative period, with a persistent elevation on POD 5 (T7) of ×3.7±0.9 for OKT vs ×3.6±1.1 for RAKT compared with baseline (T0) (p=0.85). The comparison of the IL-6 rates at each time point (from T0 to T7) showed no significant differences between OKT and RAKT (all p>0.05) (table 13 and figure 27).

- CRP increased after surgery, with a peak between 24 and 48 h postoperatively which corresponded to an increase from baseline value (T0) of ×26.4±10.3 for OKT vs ×30.1±17.8 for RAKT (p=0.67). IL-6 then decreased during the postoperative period, with a persistent elevation on POD 5 (T7) of ×17.5±0.7 for OKT vs ×11.5±5.9 for RAKT compared with baseline (T0) (p=0.67). Comparison of CRP rates at each time point (from T0 to T7) showed no significant differences between OKT and RAKT (all p>0.05) (table 13 and figure 28)

- NGAL significantly decreased postoperatively and reached a plateau from POD 1 to POD 5 (T3 to T7) that corresponded to a mean reduction of 2.1±0.2 from baseline value (T0) in OKT vs 2.5±0.3 in RAKT. The comparison of NGAL at each time point (from T0 to T7) showed no significant differences between OKT and RAKT (all p>0.05) (table 13 and figure 29).

As reported in table 14, correlations (Pearson's correlation coefficient) between postoperative kinetics of IL-6 and CRP on the one hand, and CRP and NGAL on the other, were demonstrated in the entire cohort as well as in the OKT and RAKT groups. However, no significant correlation was observed between NGAL and IL-6.

	OKT (n=24)	**RAKT (n=25)**	**P value**
Age (years, mean ± SD)	53±15	49±14	0.74
BMI (mean ± SD)	25±4	25±4	0.95
Gender (M/F)	13/7 (65%/35%)	16/8 (67%/33%)	0.90
Preoperative serum creatinine (µmol/L, mean ± SD)	480±156	458±151	0.12
Preoperative eGFR (mean ± SD)	10±3	12±3	0.41
Operative time, from incision to closure (min, mean ± SD)	240±10	249±47	0.22
Warm ischemia time (min, mean ± SD)	4.8±0.9	3.7±1.0	0.09
Cold ischemia time (min, mean ± SD)	34±8	37±16	0.72
Rewarming time (min, mean ± SD)	60±14	61±14	0.96

Table 11. Demographic characteristics of patients and surgical data.

		OKT (n=24)	**RAKT (n=25)**	**P value**
Serum creatinine (µmol/L, mean ± SD)	POD 1	377±156 [124–687]	294±159 [88–750]	0.13
	POD 3	213±109 [88–544]	202±146 [68–774]	0.82
	POD 7	161±62 [83–272]	158±86 [75–487)	0.90
eGFR (mean ± SD)	POD 1	17±10 [7–41]	24±11 [8–63]	0.09
	POD 3	28±15 [8–70]	36±16 [9–86]	0.15
	POD 7	50±32 [22–139]	47±17 [14–83]	0.74

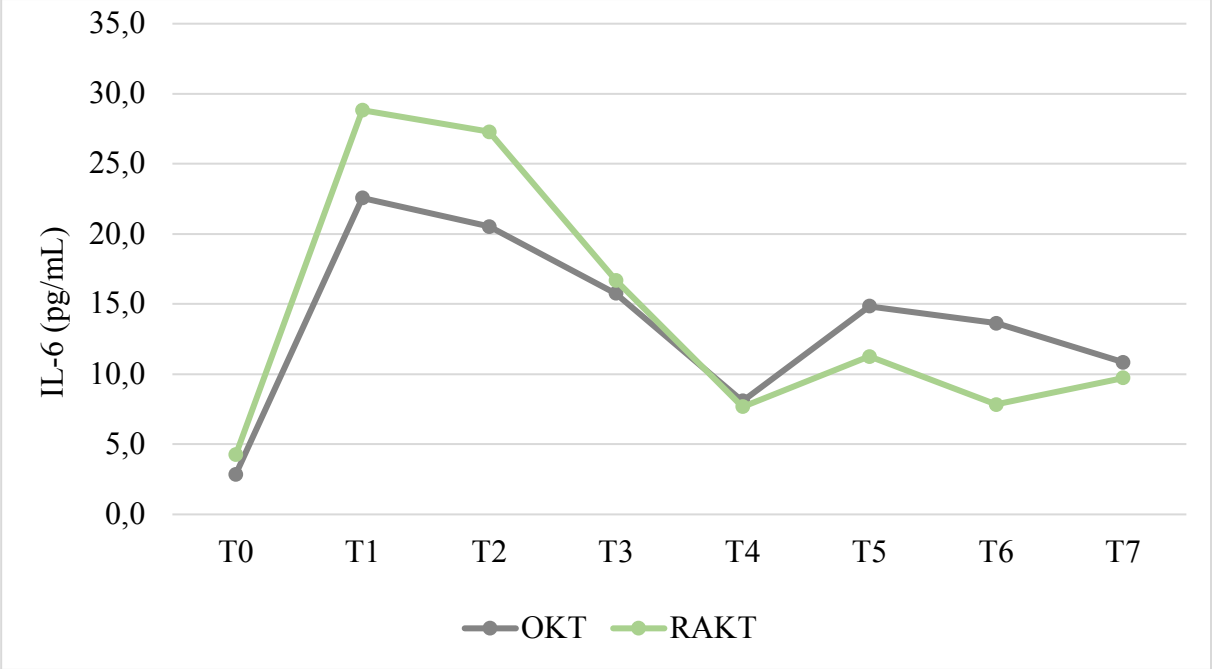
Table 12. Functional results in RAKT versus OKT.

Inflammatory marker	Time point	Procedure		P value (bilateral)
		OKT	RAKT	
IL-6 (pg/mL)	T0	2.9±0.3	4.2±1.0	0.24
	T1	22.6±3.3	28.8±4.8	0.32
	T2	20.5±2.5	39.0±8.2	0.06
	T3	15.1±2.6	16.7±2.6	0.66
	T4	7.8±1.0	7.0±1.2	0.62
	T5	13.5±3.7	10.5±2.5	0.49
	T6	13.6±4.6	7.6±1.1	0.15
	T7	10.9±1.7	9.1±2.0	0.51
CRP (mg/L)	T0	5.4±1.6	4.7±1.3	0.72
	T1	7.6±3.0	4.5±1.5	0.34
	T2	21.8±9.2	14.7±6.1	0.50
	T3	39.3±4.1	42.7±7.4	0.70
	T4	39.9±7.0	64.9±10.6	0.07
	T5	43.9±9.6	46.9±10.1	0.84
	T6	47.0±14.7	40.1±11.0	0.74
	T7	28.5±7.2	37.3±14.2	0.56
NGAL (ng/mL)	T0	462.2±53.6	432.9±37.6	0.65
	T3	265.6±27.9	207.3±15.6	0.12
	T4	223.1±23.8	187.0±14.2	0.41
	T6	263.1±57.5	175.5±10.3	0.29
	T7	243.0±27.0	191.0±12.8	0.16

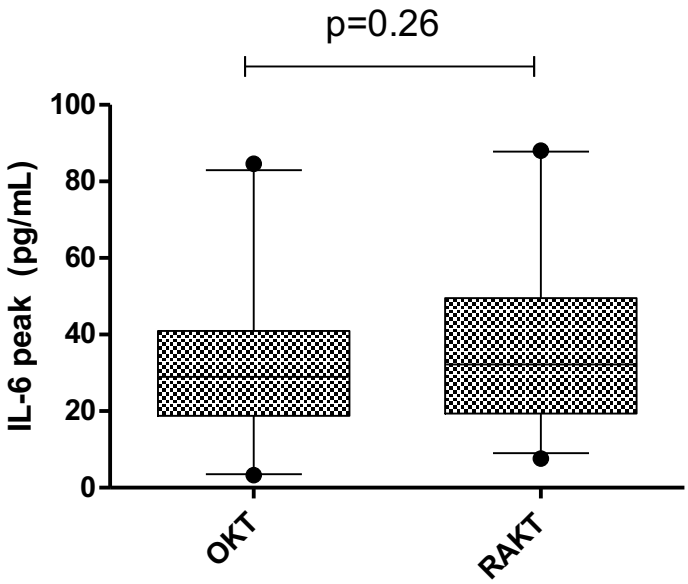
Table 13. Analysis and intergroups comparison (OKT vs RAKT) of inflammatory markers concentrations at each time point.

	RAKT	OKT	Total (OKT+RAKT)
CRP/IL-6	0.53 (0.37 to 0.65) P<0.01	0.70 (0.58 to 0.80) P<0.01	0.61 (0.51 to 0.69) P<0.01
CRP/NGAL	-0.35 (-0.51 to -0.17) P<0.01	-0.03 (-0.23 to 0.18) P=0.79	-0.21 (-0.34 to -0.07) P<0.01
IL-6/NGAL	-0.07 (-0.26 to 0.12) P=0.44	-0.06 (-0.24 to 0.15) P=0.56	-0.07 (-0.21 to 0.07) P=0.31

Table 14. Correlation between changes in serum levels of inflammatory markers in different surgical approaches (Pearson's correlation coefficient).

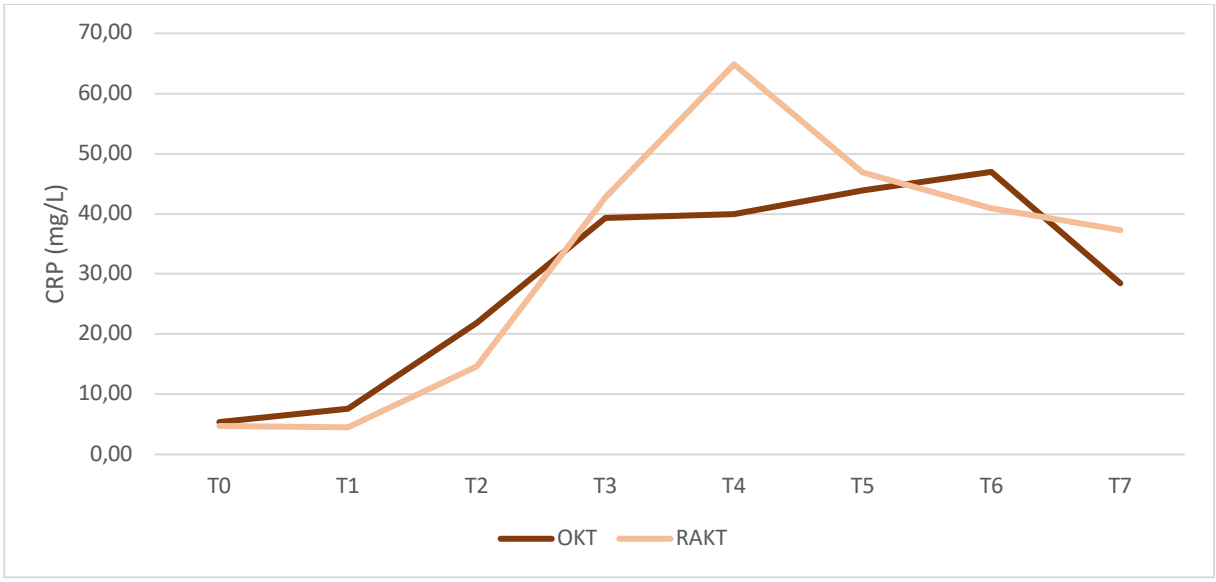


A.

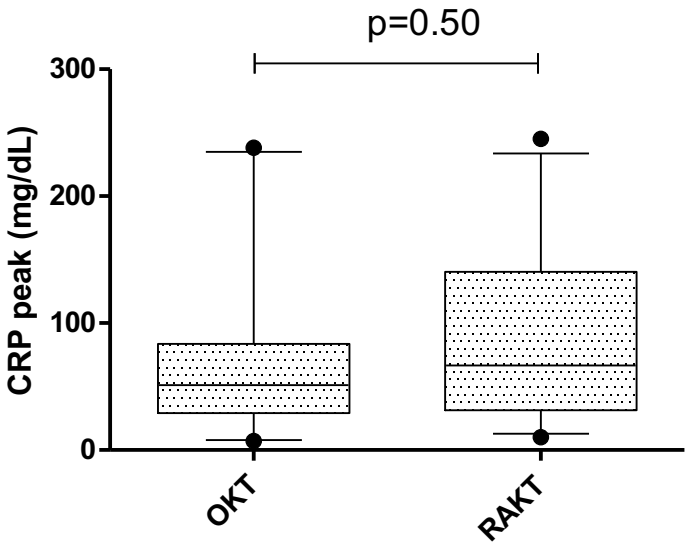


B.

Figure 27. A. Point-to-point serum concentration of IL-6 at T0 to T7 in the RAKT and OKT patient groups. **B.** Peak concentrations of IL-6 in the two groups. Graphs show mean values with 95% confidence intervals.

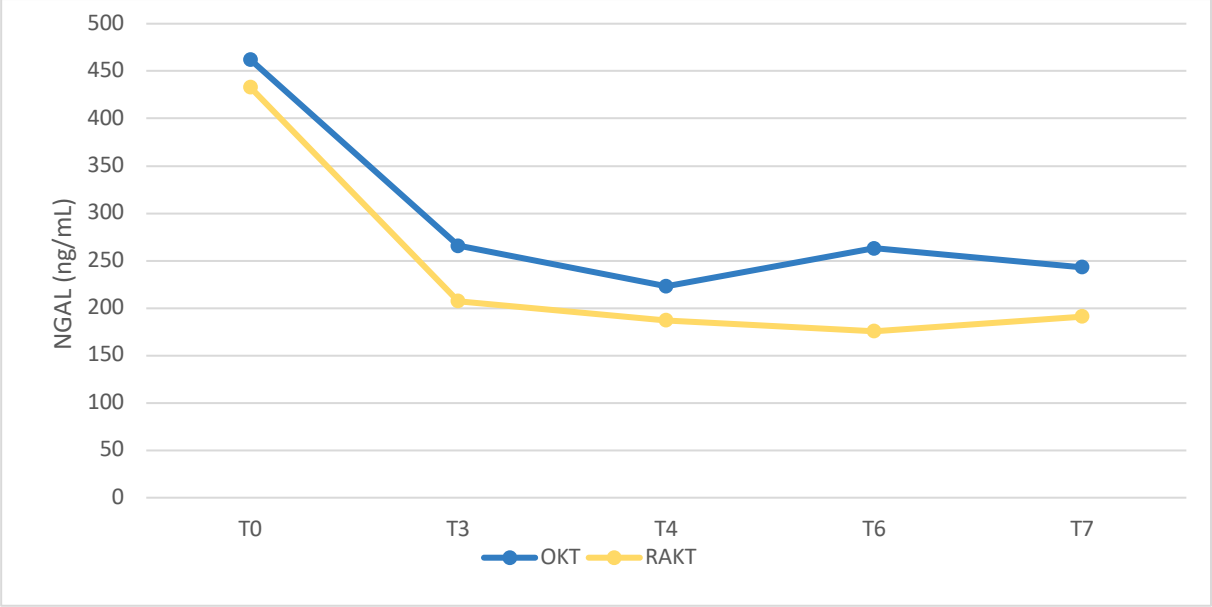


A.



B.

Figure 28. A. Point-to-point serum concentration of CRP at T0 to T7 in the RAKT and OKT patient groups. **B.** Peak concentrations of CRP in the two groups. Graphs show mean values with 95% confidence intervals



A

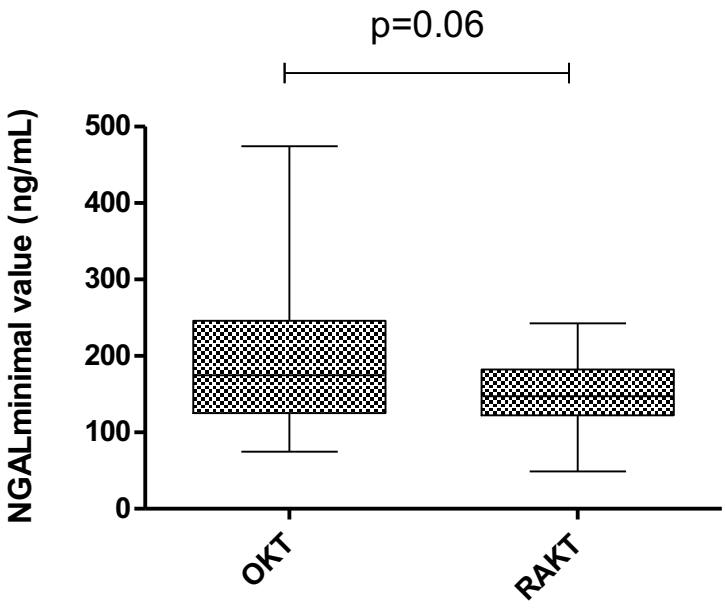


Figure 29. A. Point-to-point serum concentration of NGAL at T0, T3, T4, T6, and T7 in the RAKT and OKT patient groups. **B.** Peak concentrations of NGAL in the two groups. Graphs show mean values with 95% confidence intervals

10.4 Discussion

SIRS is a complex physiological reaction that occurs after surgery with an intensity that is proportional to the invasiveness of the procedure. During surgery, the inflammatory reaction is initially local, with the release of inflammatory cytokines into the surgical site to activate the healing process and fight infectious agents. The inflammatory reaction is secondarily generalized by the release of inflammatory cytokines, in particular IL-6, into the bloodstream and triggers a global response – SIRS [90].

SIRS is therefore a complex phenomenon involving protein synthesis by the liver, neutrophil mobilization from the bone marrow, activation and differentiation of T cells, increase in body temperature, and steroid production by the hypothalamus–hypophyseal axis. SIRS is regulated by a set of pro-inflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukins 1, 8, 12, and 18 [90] [91] [92].

IL-6 and CRP are the two most studied inflammatory markers postoperatively. In a recent systematic review including a total of 14,362 surgical procedures, Watt et al. [88] reported that the postoperative peak of IL-6 and CRP occurred respectively at 24–48 h and 24–72 h after the surgery and that the peak values of IL-6 and CRP were correlated to the degree of tissue damage and invasiveness of surgery. Thus, the magnitude of the IL-6 peak after minor surgery (hernia repair, cholecystectomy), intermediate surgery (total hip replacement, knee prosthesis, colorectal resection), and major surgery (aneurysm repair of the abdominal aorta, cardiac surgery, or extensive liver resection) were respectively 13–77, 140–321, and 248–428 pg/mL Similarly, CRP magnitude was also correlated with the invasiveness of surgery, with a postoperative maximum value of 40–52 mg/L in minor surgery, 74–123 mg/L in intermediate surgery, and 163–186 mg/L in major surgery [88].

In this prospective study comparing OKT with RAKT in pre-emptive living donor KT, there were no significant differences in the kinetic and magnitude of postoperative SIRS according to the surgical approach. However, KT presents major differences with non-transplant surgery which can have a drastic impact on the magnitude of postoperative SIRS: the "graft versus host" allo-immunological response and the need for immediate immunosuppressive treatment [91].

In KT, postoperative prescription of steroids and other immunosuppressive therapies can significantly reduce the magnitude of postoperative SIRS and therefore eliminate any difference that could exist between the open and robotic approaches in our study [93].

According to the literature, comparison of postoperative SIRS between open and minimally invasive surgery shows no difference or equivocal results in a majority of surgical procedures. In fact, when compared with open surgery, the laparoscopic or minimally invasive approach proved to be associated with a significant reduction in SIRS (meaning a significant decrease of CRP and IL-6 peaks). These results in favor of minimally invasive surgery could be explained by smaller skin incisions, less tissue manipulation, and an immunomodulatory effect of CO_2 infused in the peritoneal cavity during laparoscopy [88] [89].

In the present study, the RAKT technique included the insertion of the renal transplant via mini umbilical medial laparotomy. The size of the skin incision was adapted to the size of the transplant but was larger than the single diameter of the transplant itself since the transplant was inserted with a pack of ice slush. Furthermore, in our study, the favorable morphotype of the patients included in both arms (robotic and open) probably decreased the difference in abdominal incision length between the open and robotic approaches and therefore probably favored the open approach.

However, the open approach would be at a disadvantage in cases of obese patients or an unfavorable morphotype owing to the need for a larger abdominal incision while the morphotype of the patient has little impact on the abdominal incision with RAKT. Since previous studies have suggested that BMI is associated with increased values of inflammatory markers and reported favorable outcomes of RAKT in obese patients [94], we can assume that the difference in postoperative SIRS could be significantly in favor of RAKT in obese patients.

Several factors other than tissue trauma and surgical approach could be associated with the magnitude of postoperative SIRS: advanced age, associated comorbidities such as chronic renal failure, and hemodialysis are predictive of an increase in postoperative SIRS. Therefore, one of reasons why the robotic pathway was not associated with a significant reduction in postoperative SIRS in our study could be that we included a homogeneous population of optimal recipients in both arms – young patients (mean 51±14), in pre-emptive renal transplantation and ABO compatible – and that no major postoperative complication occurred. We were therefore unable to identify any predictive clinical factors for increased postoperative SIRS.

This study questions the main determinants of SIRS after KT. The phenomenon of ischemia–reperfusion and early physiological alloimmune responses are probably of great importance [95][96][97][98].

Another reason why postoperative SIRS was low in our study could be that only living donor renal transplantations, meaning short cold ischemia times and reduced ischemia–reperfusion reaction, were included. The difficulty and uncertainty of maintaining a low temperature of the renal transplant during the performance of graft anastomosis, in the closed, warm, and humid atmosphere of pneumoperitoneum is of one the most significant concerns related to RAKT [46] [99] [100] [101]. In reporting non-different kinetics and peaks of inflammatory markers as well as similar functional outcomes between the robot-assisted and open approaches, this study did not confirm this hypothesis and indicated that RAKT is not inferior to the standard open approach with experienced surgeons.

Although prospective and comparative, our study had some limitations related to the low number of patients and the huge number of confounding factors inherent in KT that can potentially influence postoperative SIRS (homogeneity of the population, absence of major complications, and immunosuppressive treatments).

Finally, in this prospective study comparing OKT with RAKT in pre-emptive living donor renal transplantation, no significant differences in the kinetics and magnitude of postoperative SIRS according to the surgical approach were noted. As regards the functional outcomes (i.e., early functional results), they were similar and no major complications occurred. Therefore, in selected patients and when performed by skilled surgeons, the robotic approach does not compromise the outcome of living donor KT.

11. LEARNING CURVE IN RAKT: RESULTS FROM THE ERUS WORKING GROUP

11.1 Introduction and objectives

The ERUS working group has already demonstrated the feasibility of RAKT when the procedure is carried out by surgeons with both experience in OKT and robotic surgical skills. However, RAKT remains a complex procedure. Technical mistakes may lead to graft loss, as was reported in the very early experience of every pioneer center in RAKT. Nevertheless, RAKT has proved to offer less morbidity, cosmetic benefit, and similar graft function results compared with OKT.

In this study [53], we analyzed the learning curve in RAKT, evaluating surgical and functional results and intra- and postoperative complications in the five highest volume centers of the ERUS working group. The second objective of the study was to evaluate the reproducibility of the learning curve.

11.2 Materials and methods

Study design. Data from the ERUS RAKT working group database were collected, involving the 5 Centers that performed more than 20 RAKTs each: Fundaciò Puigvert (Barcelona), Hospital Clinic (Barcelona), Careggi Hospital (Florence), Ghent University Hospital (Ghent), and Bakirkoy Research Hospital (Istanbul). In each center the procedures were performed by a single surgeon skilled in both OKT and robotic surgeries (>100 procedures), such as partial nephrectomies, radical prostatectomies, and pyeloplasty. To compare the learning curves for RAKT, the surgical procedures were categorized as follows: group 1, first 10 surgeries of each center; group 2, 11–20 surgeries; group 3, more than 20 surgeries.

Surgical technique. Standardization of the surgical technique of RAKT was reported by Menon et al. [39]. Subsequently, Breda et al. [49] described technical variations that were adopted by the ERUS RAKT working group. The technique has been already detailed in this manuscript.

Study variables. The variables analyzed included the correlation between the learning curve and surgical results (console time, vascular anastomosis, RWT), functional results, intra- and postoperative complications. RWT was defined as the time between the peritoneal insertion of the kidney and the start of reperfusion. The functional outcomes taken into account were serum creatinine and eGFR at POD 7 and 30 and at 1 year. The early (30-day) post-operative complication rate was reported according to the Clavien-Dindo classification.

Statistical evaluation. Continuous variables were presented as mean and SD, while absolute frequencies and percentages were used to describe the qualitative variables. Student's t-test was used for comparison of quantitative variables. The target and SD values for Shewhart control charts were set by referring to the functional outcomes of procedures reported by Breda et al. [49] (+2SD = alert line, +3SD = alarm line). The values of RAKTs with RWT <48 min were chosen (table 15). Cumulative summation graphs were generated to assess the learning curve, which is considered complete when the curve reaches a plateau. Linear regressions were performed to compare the learning curves of the different surgeons. p values <0.05 were considered statistically significant. The statistical package SPSS V 25 and GraphPad Prism were used.

Minutes	Mean (SD)	Mean + SD	Mean + 2SD	Mean + 3 SD
Rewarming time	40.6 (4)	44.6	48.6	52.6
• Arterial anastomosis	16.5 (3.6)	20.1	23.7	27.3
• Venous anastomosis	17.4 (2.7)	20.1	22.8	25.5
• Non-anastomotic time	8.4 (3.2)	11.6	14.8	18
Ureterocystoneostomy	18.5 (4.8)	23.3	28.1	32.9
eGFR (POD 30-preoperative)	55 (10)	45	35	25

Table 15. Target (mean), alert values (mean + 2SD) and alarm values (mean + 3SD).

11.3 Results

Descriptive characteristics. A total of 183 patients submitted to RAKT were included in the study. Demographic, surgical, and functional data and groups' comparison are reported in table 16.

			Total cases	Group 1	Group 2	Group 3	Group 1 vs 2*	Group 2 vs 3*
			(n=183)	1-10 (n=50)	11-20 (n=50)	>20 (n=83)		
Baseline characteristics	Age (years)		43 [±13]	41[±13]	45 [±14]	44 [±13]		
	Gender, n (%)	Male	62%	54%	70%	62%	0.15	0.45
		Female	38%	46%	30%	38%		
	BMI (kg/m^2)		25 [±4]	24 [±5]	25 [±4]	24 [±4]	0.14	0.07
	Past surgical history, n (%)	Abdominal surgery	17%	70%	69%	66%	0.99	0.42
		Non-abdominal surgery	73%	30%	31%	33%		
	Pre-emptive renal transplantation, n (%)		57%	68%	87%	57%	0.65	0.07
Surgical Results	Total operative time (min)		228 [±56]	287 [±75]	240 [±55]	228 [±56]	<0.01	0.31
	Warm ischemia time (min)		3 [±2]	3 [±2]	3 [±1]	2 [±1.8]	0.98	0.61
	Cold ischemia time (min)		56 [±127]	158 [±280]	237 [±372]	56 [±126]	0.23	< 0.01
	Rewarming time (min)		51 [±12]	60 [±16]	50 [±7]	46 [±10]	< 0.01	<0.01
	Total ischemia time (min)		106 [±154]	209 [±268]	279 [±355]	106 [±154]	0.27	<0.01
	Arterial anastomosis time (min)		17 [±4]	20 [±7]	17 [±4]	17 [±4]	0.01	0.67
	Venous anastomosis time (min)		18 [±3]	22 [±7]	18 [±4]	18 [±3]	<0.01	0.74
	Vascular anastomosis time (min)		36 [±8]	42 [±13]	35 [±8]	36 [±8.5]	<0.01	0.98
	Ureterovesical anastomosis time (min)		20 [±15]	27 [±10]	20 [±7]	20 [±6]	<0.01	0.22
	Estimated blood loss (ml)		153 [±88]	124 [±71]	119 [±73]	150 [±88]	0.74	0.03
Functional results	Creatinine (µmol/L)	Preoperative	526 [±214]	560 [±186]	565 [±260]	500 [±169]	0.92	0.09
		POD 7	163 [±127]	186 [±163]	178 [±131]	135 [±96]	0.78	0.03
		POD 30	108 [±88]	131 [±85]	52 [±19]	132 [±97]	0.30	0.30
		1 year	135 [±102]	123 [±140]	145 [±48]	121 [±31]	0.44	0.06
	eGFR (ml/min/1.73 m^2)	Preoperative	11 [±4]	10.36 [±4]	10 [±4]	11 [±4]	0.53	0.40
		POD 7	54 [±22]	51 [±23]	50 [±22]	58 [±21]	0.83	0.03
		POD 30	57 [±21]	58 [±22]	52 [±19]	61 [±21]	0.21	0.03
		1 year	58 [±18]	59 [±18]	52 [±19]	64 [±20]	0.06	<0.01

Table 16. Descriptive characteristics (demographic, surgical, and functional data) and groups' comparison.

Shewhart control charts. Control charts are reported in figure 30. Arterial anastomosis time was below the alarm/alert line in 93.3%/88.9% of RAKTs, while venous anastomosis time was below the alarm/alert line in 88.9%/73.9%. The non-anastomotic RWT exceeded +3SD in 24.7% of procedures and +2SD in 37.1%. In only 46% of cases was the RWT below the alert line. The ureterocystoneostomy time was below +2 and +3SD in 87.9% and 90.2% of cases, respectively. The difference between preoperative eGFR and eGFR at POD 30 was at least 25 ml/min in 86.4%.

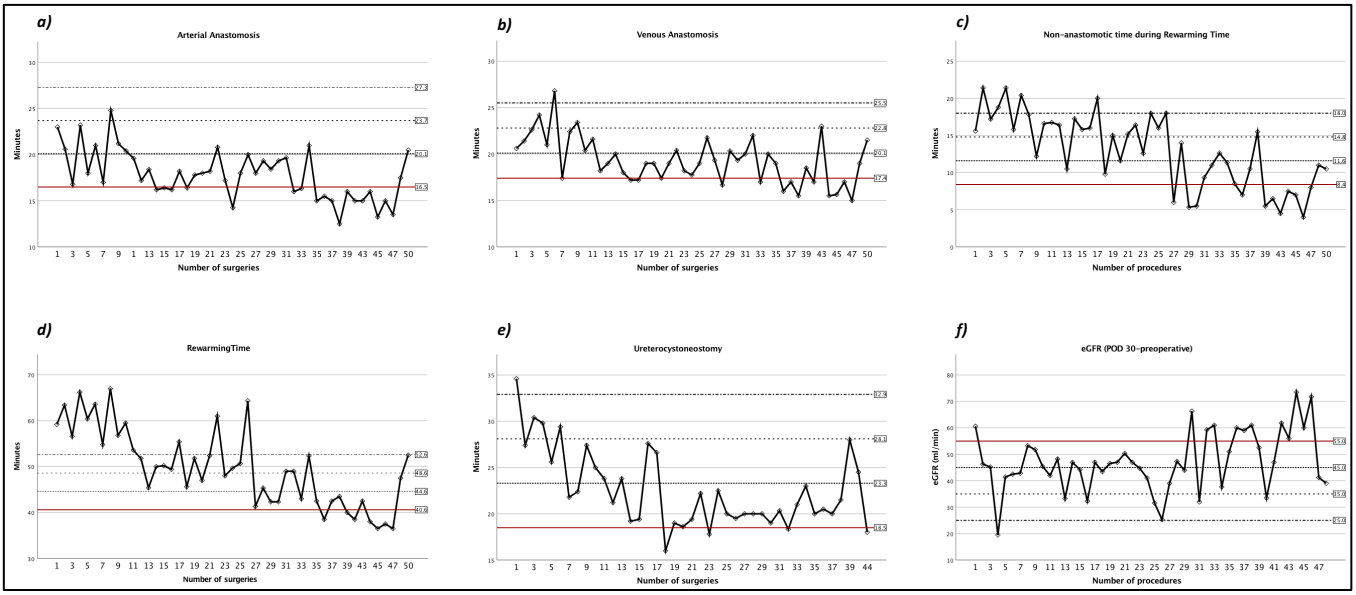


Figure 30. Shewhart control charts of vascular anastomosis (a-b), non-anastomotic time during RWT (c) and RWT (d), ureteroneocystostomy (e) and eGFR. Red line represents the target value, dashed lines +SD, +2SD (alert line) and +3SD (alarm line).

Cumulative summation analysis. Cumulative summation analysis showed that the learning curve for arterial anastomosis required up to 35 (mean=16) cases, with variation among the five centers (figure 31). A similar conclusion was reached for venous anastomosis, which may need more than 40 procedures (mean=24). The plateau in the ureterocystoneostomy curve was reached within 30 RAKTs in four of the centers, and within 40 RAKTs in the other one (mean=17).

The plateau for RWT was reached within 23 procedures at center 1, 44 at center 2, and 38 at center 3 (mean 35 cases); centers 4 and 5 did not reach it. Interestingly, the curves for non-anastomotic time during RWT resemble those for RWT. The learning curve in respect of kidney function was achieved after 20 cases in centers 1 and 5; in the other centers, no learning curve was observed as the slopes did not rise.

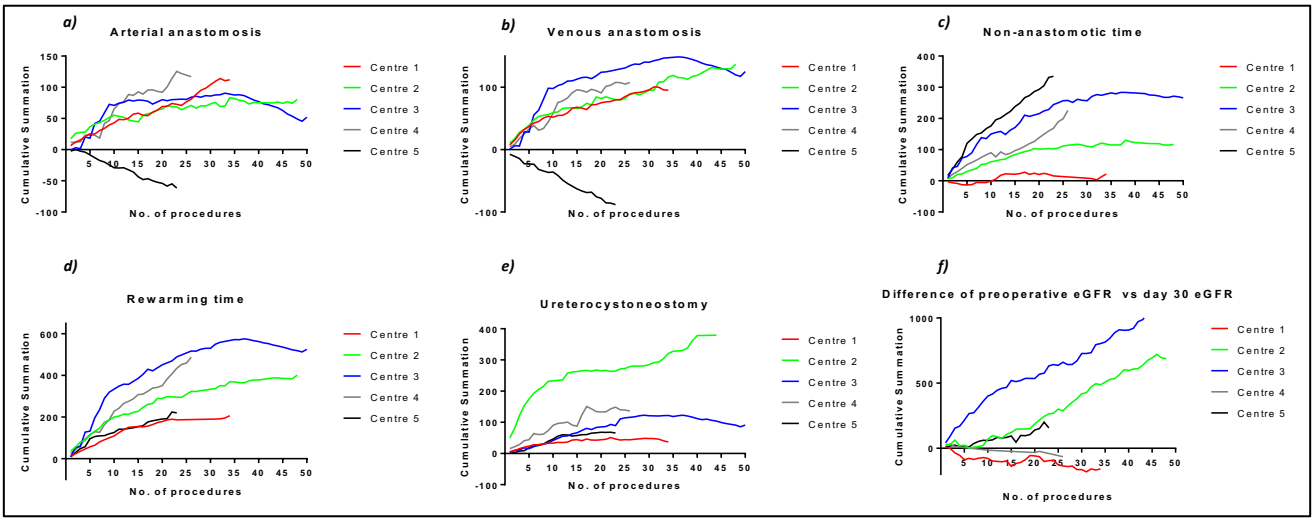


Figure 31. Cumulative summation analysis of vascular anastomosis (a-b), non-anastomotic time during RWT (c) and RWT (d), ureteroneocystostomy (e) and eGFR.

Reproducibility. On the linear regression model, all the anastomotic times were comparable (figure 32). The slopes in respect of non-anastomotic time during RWT were slightly different (p=0.0006), as was also true for RWT itself (p=0.007).

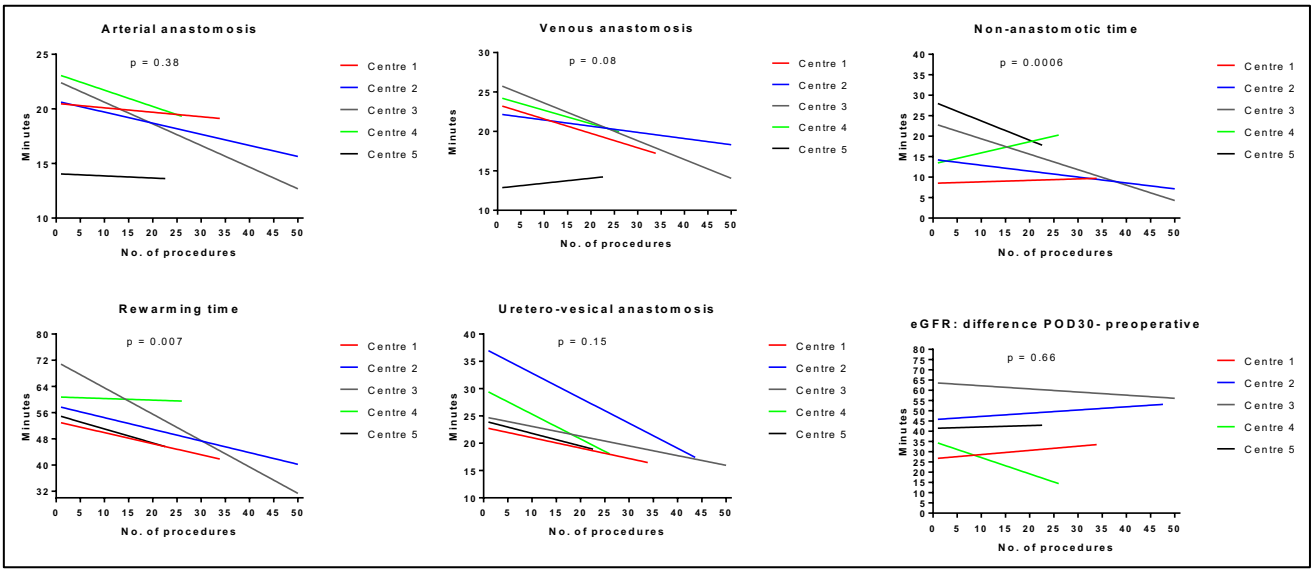


Figure 32. Linear regressions of vascular anastomosis (a-b), non-anastomotic time during RWT (c) and RWT (d), ureteroneocystostomy (e) and eGFR.

Complications. Intraoperative complications occurred in 3/50 (6%) patients in group 1, 1/50 (2%) in group 2, and 3/83 (3.6%) of group 3 (p=0.6). In group 1, postoperative Clavien-Dindo grade III/IV complications were reported in 7/50 (14%) cases, while in groups 2 and 3 they occurred in 1/50 (2%) and 3/83 (3.6%) cases, respectively (p=0.02). Three graft losses occurred in group 1, all because of arterial thrombosis; none were reported in the other groups (3/183; 1.6%; p=0.02).

Graft function. Mean eGFR on POD 7 and 30 and at 1 year was comparable between groups 1 and 2, and was better for group 3 vs 2 (all p<0.05; table 16). DGF was observed in 4.4% (2/45), 2.4% (1/42), and 1.3% (1/80) of cases in groups 1, 2, and 3, respectively (p=0.5).

11.4 Discussion

This study demonstrated that a minimum of 35 cases is necessary to reach reproducibility in the surgical time, complications, and functional results [53].

The anastomotic time and RWT can potentially affect the functional outcomes of KT [102][103]. For this reason, we studied a target population represented by cases with <48 min of RWT and evaluated 183 consecutive patients (the largest series in the literature) who underwent RAKT in a multicenter prospective setting. The results showed that the learning curve in vascular anastomosis ranged between 0 and 40 cases, with procedures being under control (below the alert line) in 73.9%–88.9% of RAKTs. Similar results could be observed for the ureterocystoneostomy (90.2% below the alert line), with a learning curve comprising 30 surgeries in four of the five centers. Furthermore, the curves were reproducible.

The RWT and the non-anastomotic time curves were the most variable, with similar learning curves and the highest percentage of procedures out of control (46.9% and 24.7%, respectively). The non-anastomotic time spent during RWT is mainly represented by positioning of the graft and by the synergic work with the assistant. It depends on the surgical teamwork, which renders it more variable, and this highlights the importance of having an established surgical team for this demanding intervention. It appears to be as important as the vascular anastomosis time and to be the most improvable time.

Although Sood et al. [104] reported that there was no learning curve for experienced surgeons, it must be underlined that the SD values were significantly wider (45+15, +30, +45) for RWT, with the consequence that RWT was suggested to be under control in all surgeries. This may be questionable, as maintenance of low graft temperatures within the peritoneal cavity represents one of the main challenges of RAKT. More recently, Ahlawat et al. [105] reported a short learning curve in RAKT for experienced surgeons, with continuing improvements in skill up to 20–25 cases.

The functional results do not seem to be affected by RWT (86.3% cases were under control), possibly due to regional hypothermia. DGF was reported in less than 2% of cases. Intraoperative complications occurred in 4.4% of patients in group 1 and in 3% in groups 2 and 3. The rate of Clavien-Dindo grade III/IV complications was 14% during the first ten RAKTs, but only 3% after this threshold.

Graft loss occurred during the first ten RAKTs due to arterial thrombosis. However, the rate of arterial graft thrombosis (1.6%) in our population is comparable to the OKT experience (0.5%–3.5%) [106].

The present study is not devoid of limitations. First, it relates to very skilled surgeons treating a population mainly represented by pre-emptive patients. Second, the evaluation of the learning curve analyzing the timing is open to some debate.

The surgical technique, including tips and tricks described above, was acquired during the learning phase by each surgeon, and robot training has been proven to be significantly associated with improved task completion times. With the twin aim of improving general robotic skills and providing specific hands-on training using porcine models, ORSI Academy courses were organized, providing a good opportunity to reduce the risk of the first RAKTs. In view of the surgical complexity of the procedure, proctorship should be considered mandatory.

In conclusion, when performing RAKT, experienced surgeons require 35 cases to achieve positive technical results in terms of RWT. Synergy between the surgeon and the assistant must be created in order to reduce time between vascular anastomoses, the learning curves for which are safe and reproducible among different operators. In order to reduce the risk of complications during the early RAKTs, hands-on training and proctorship are highly recommended.

12. CONCLUSIONS

Although most RAKTs have been performed in a few high-volume institutions by highly experienced robotic surgeons in a wide range of elective clinical scenarios, available data confirm the safety of RAKT regarding surgical complication rate, DGF, graft loss, and recipient survival at mid-term follow-up, providing distinct advantages from both the surgeon's and the patient's perspective.

One of the most compelling challenges in the field of KT is to delineate the added value of robotic technology for KT from both these perspectives. This is a key unmet need as this information will soon become crucial for guideline developers in order to codify appropriate, cost-effective indications for RAKT, thereby increasing the pool of patients who may benefit from a minimally invasive approach. Unfortunately, providing proper evidence supporting the use of RAKT is demanding and may require long time frames. Indeed, the introduction of RAKT in the community of KT surgeons remains one of the most pressing current challenges, given that to date it has taken hold in only a slow, stepwise fashion. Moreover, while major improvements in outcomes for transplant patients will likely be driven by advances in the field of immunology, it is difficult to measure the incremental clinical improvement provided by a new technology with limited data. Another important aspect to consider is that it is crucial for success that the surgery (i.e., RAKT) is always performed by the same dedicated team. However, this will at times be very difficult to achieve in deceased donor transplantation (owing to night shifts and the difficulty of using the robot at night).
Lastly, despite RAKT is a great innovation in the minimally invasive transplantation field, the costs still represent a barrier to its spread, and some centers have a limited number of procedures accepted per year.

A further issue that needs to be addressed is how the number of RAKTs worldwide from both living and deceased donors can be increased. My perspective, which is grounded in the currently available evidence as well as in the increasing experience with RAKT, is that structured robotic transplant programs should be implemented in clinical practice in order to increase the pool of patients who may benefit from a minimally invasive approach. This vision is based on three cornerstones: a) robotic surgery may allow minimization of the surgical morbidity of KT; b) the robotic platform may equalize the learning curve for KT; and c) RAKT has the potential to make KT easier in particular challenging clinical scenarios, with important implications for living donor nephrectomy practices and KT techniques. It is important to emphasize that a high level of expertise is required in kidney transplantation (i.e., open surgery) and robotic surgery (i.e., urological procedure including a reconstructive phase such as partial nephrectomy, prostatectomy, or intracorporeal ileal conduit/neobladder) before starting the RAKT program. As far as the learning curve is concerned, according to the previously reported data, experienced surgeons require 35 cases to achieve positive technical results in terms of RWT. However, the safety of the procedure and graft outcome should be guaranteed even during the learning curve. Therefore, proctoring and careful patient selection (e.g., suitable BMI and no previous abdominal surgery) are important during the learning phase. With the twin aim of improving general robotic skills and providing specific hands-on training using porcine models, ORSI Academy courses are available; these provide a good opportunity to reduce the risk of the first RAKTs. In addition, in view of the surgical complexity of the procedure, proctorship should be considered mandatory during the first cases.

Finally, the best study design to prove the non-inferiority (or even superiority) of RAKT as compared with OKT would be a large multicenter randomized trial with long-term follow-up; yet, the need for and feasibility of such a trial are questionable. In the prospective study comparing OKT with RAKT in pre-emptive living donor renal transplantation, no significant differences were noted in the kinetics or magnitude of postoperative SIRS according to the surgical approach. In addition, the functional outcomes were similar and no major complications occurred. Therefore, in selected patients and when performed by skilled surgeons, the robotic approach does not compromise the outcome of living donor KT.

Despite the benefits of RAKT, there are multiple clinical concerns relating to the applicability of robotic surgery in KT, which is the reason why open surgery is still the gold standard in KT [22]. In particular, there is a need for: (1) improvement in tactile feedback to enhance the performance of vascular anastomosis and (2) more effective standardized methodology for hypothermal preservation of the kidney, avoiding the risk of local and/or systemic hypothermia.

The lack of tactile feedback in robotic surgery may be considered an important limitation for this emerging approach. Since the recipients, especially when in hemodialysis, have a high incidence of arterial atherosclerosis and since most of them have severe and multiple arterial calcified plaques, the absence of tactile feedback can potentially compromise arterial clamping and/or vascular anastomosis, with consequent further risk of distal embolism and/or thrombosis.

As regards the second issue, the cooling device currently used (gauze jacket filled with ice slush) entails the gradual intra-abdominal melting of ice, which might result in renal allograft impairment when there is an extended vascular anastomosis time. Even though this technique has been confirmed to be safe and effective, many concerns remain about the local and possibly systemic hypothermia related to the use of intraperitoneal cooling to maintain a constant low temperature of the graft. In order to try to solve this potential inconvenience, a new cold ischemia device (described in Chapter 9) has been designed and developed, though to date it has been tested only in a preclinical model.

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