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Surgical aspects of live kidney donation: an updated review

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1. ABSTRACT

In the early 1990s, live kidney donation regained popularity to meet the demand of kidney transplantation. Significant developments in the field of live kidney donation have established live donation as the prime source of kidney transplants. Nowadays, management is focused on logistic and immunological innovations, and improvements in care of the live donor. However, a flawless surgical procedure in both donor and recipient is a prerequisite for further expansion of live kidney donor transplantation. From a surgical perspective, the introduction of the laparoscopic approach has been a major breakthrough. Less invasive techniques to procure live donor kidneys have been held responsible for a steep increase in the number of live donors. In addition, less invasive imaging, improvements in perioperative care, and novel insights in the follow-up have all improved the care of the live donor. Live kidney donation is developing as the most promising source of renal organs since artificial kidneys, xenografts and stem cell therapy for restoring intrinsic kidney function will probably not find application on a large scale in the near future.

2. INTRODUCTION

The kidney is an essential organ, which plays a pivotal role in acid/base balance, sodium/potassium balance, calcium metabolism, regulation of blood pressure, red blood cell synthesis and excretion of metabolites. A variety of renal diseases finally results in renal insufficiency.

Kidney replacement therapy consists of dialysis and kidney transplantation. Haemodialysis and peritoneal dialysis bridge patients to kidney transplantation. However, dialysis is associated with a high mortality and morbidity rate, and a reduced quality of life. Especially, older age, male gender and duration of dialysis have an adverse effect on outcome. Kidney transplantation is considered the optimal renal replacement therapy for most patients with end-stage renal disease (1, 2).

In the early 1950s, Rene Kuss and Joseph Murray performed the first successful kidney transplantations using live donors in France and the United States, respectively (3, 4). The invention of adequate immunosuppressive therapy in the 1960s enabled deceased donor kidney transplantation, preventing risky operations performed on healthy individuals. As enough deceased donors were present at that time, live kidney donor transplantation was pushed into the background.

In the late 1980s and 1990s, a discrepancy between organ demand and supply occurred due to an increasing number of patients suffering from end-stage renal disease and a stagnating number of transplants. The average waiting time for a kidney from a deceased donor increased considerably and up to 20 percent of the patients had to be removed from the list annually, mainly because of mortality and worsening condition precluding transplantation (5). Alternatives to significantly increase the number of deceased donors have failed mainly due to relatives refusing donation (6). This prompted a new interest to revive live donor kidney transplantation as alternative.

In the last two decades, the number of transplants from live donors significantly increased in the Western World (7-11). The revival of live kidney donation is a result of the aforementioned gap between the demand and supply of organs. Live kidney donor transplantation has created opportunities including pre-emptive and ABO-incompatible kidney transplantation, and paired kidney exchange programs that contribute to the expanding success of live kidney donation. The expansion of live kidney donation is only possible by continuous innovations and research in screening of the donor, perioperative care and last but not least the surgical technique to maximize donor safety. These innovations have limited the discomfort of the donor and incited live donation. In this review we will focus on current surgical issues surrounding live kidney donation.

3. BENEFITS OF LIVE KIDNEY DONOR TRANSPLANTATION

Live kidney donor transplantation renders significant benefits over kidney transplantation from a deceased donor. First, the transplant usually starts functioning immediately following transplantation, as opposed to transplants derived from deceased donors due to shorter ischemic time by minimal ischemic damage of the allograft. This is important, as cold ischemic time is a well-known risk factor for delayed graft function (12). Second, transplant survival is significantly improved. Three-year survival rates are approximately 81 to 87 percent for living unrelated donors and 70 percent for cadaveric kidneys (6, 9, 13). Third, dialysis may be avoided by planning live donor kidney transplantation. This so-called pre-emptive kidney transplantation is gaining popularity. It reduces the costs of dialysis and the related operations needed to introduce a catheter or develop a shunt. Furthermore such an approach improves transplant function and patient survival (2). Current allocation guidelines impede pre-emptive kidney transplantation from a deceased donor. Fourth, live kidney donor transplantation turns emergent surgery into elective surgery and thereby improves surgical results. Candidates for donation can be carefully screened and the transplantation can be scheduled at a time when donor and recipient are well-prepared for surgery. Fifth, nowadays there are several incompatible donor-recipient pair programs: paired kidney exchange and unspecified donation enabling domino-paired kidney exchange (14). Sixth, ABO incompatible donors can donate by deriving the antibodies against the donor's blood from the recipients blood (15). Last, a higher degree of histo-incompatibility may be accepted in live kidney donor transplantation because the grafts are derived from healthy donors and do not sustain significant injury during the time awaiting explantation (6).

Nevertheless, live donor kidney transplantation is a surgical procedure with risks of mortality and morbidity for donor and recipient. Life-long immunosuppressive medication is required, harbouring the chance of opportunistic infections and malignancies. Still, most recipients prefer this treatment over dialysis as this treatment offers a better survival rate and quality of life. The surgical procedure of live kidney donation is performed on healthy individuals who will not benefit directly from this procedure. In addition, it may bring a risk of mortality and morbidity to the donor (16). Although the reported incidence of serious complications is small, it cannot be neglected.

3.1. Innovations in live kidney donation

Live kidney donation has been fostered by immunologic manoeuvres that can overcome biologic obstacles such as HLA disparity and ABO or cross-match incompatibility. In the classic, successful live kidney donor transplantations of the 1950s, the transplant was derived from a HLA identical individual, often a twin. Despite the rapid developments in immunosuppressive therapy, most transplants were derived from relatives until the early 1990s. Nowadays, transplants derived from genetically unrelated donors appear to provide excellent function and long-term survival comparable with the survival of a graft derived from related donors (6). Awareness of the success of grafts from unrelated donors resulted in a spectacular increase of unrelated donors, in particular from spouses (17). Among the genetically unrelated donors, the percentage of those without a direct relation to the recipient increases, including those participating in cross-over transplant programs, list-exchange programs and unspecified kidney donor programs (18-20).

Cross-over transplantation programs (paired exchange) intend to help recipients accompanied by a donor with a different, incompatible, blood group. This pair is coupled to one or two other pairs having the same problem of blood group incompatibility. Within this program a blood group compatible pair is combined, so the blood group of the donor of the first pair and the recipient of the second or third pair matches. Thus, donor A donates to recipient B, donor B donates to recipient C and donor C may donate to recipient A. Although the logistics are demanding and a sufficient pool is necessary to create combinations between pairs, these cross-over transplant programs or pair-wise donation are highly successful (21). Desensitization therapies have been developed to enable transplantation of highly pre-sensitized candidates by removing previous donor-specific antibodies from the blood. However, transplantation of highly pre-sensitized candidates is often complicated by the occurrence of acute and chronic antibody-mediated graft rejection leading to diminished graft function and survival. There is still a need to further develop desensitizing therapies to make transplantation of highly pre-sensitized candidates feasible (22).

Unspecified kidney donors are also denoted as truly altruistic donors who do not have any relation to a recipient (19). The transplants of these donors are usually intended for recipients awaiting deceased donor transplantation or to initiate a chain in domino-paired exchange (14) making a multiple cross-over transplantation possible (domino-paired exchange).

Via personal communication we have learned about an uncommon type of kidney donors: patients whose kidney are removed for medical indication (i.e. iatrogenic ureteral lesions that could not be repaired, kidney stones). These donors usually have another kidney that functions well and they do not require auto-transplantation (23). Unspecified donation may be an option. Another uncommon type of kidney donors are patients with a neurodegenerative disease who are dying from their disease with well-functioning kidneys, and who are willing to donate their kidney.

Integration of all aforementioned practices would help to reduce the number of transplant candidates waiting (24). Calculations estimate that up to 11 percent of the transplants are recruited from this pool of formerly uncommon donors (25).

Another innovative approach includes the transplantation of living donor renal allografts across blood group barriers (26, 27). This requires protocols to reduce and maintain anti-blood group antibodies at safe levels. Developments in immuno-absorption have resulted in good results for such transplantations (26).

4. CARE FOR THE LIVE DONOR

The most crucial aspect in live kidney donation is the potential harm to the donor. From an ethical perspective, live kidney donation is only justified if the harm to the donor is limited and the potential benefit to the recipient is significant. Therefore, it is very important to minimize the risks for immediate and long-term health consequences to the donor. To assess the medical suitability of the donor, the Amsterdam Forum developed an international standard of care on how live donors should be evaluated. The donors should have routine screening performed, according to the guidelines of the forum. They set forth a list of all the (relative) contra-indications to live kidney donation. The donors must have sufficient renal function (GFR more than 80 ml/min), no hypertension (less than 140/90), no obesity (BMI less than 35 kg/m²), negative urine analysis for protein (less than 300mg/24 hours), no diabetes, no kidney stone disease, no malignancy or recurrent urinary tract infections, a minor or no cardiovascular or pulmonary risk, smoking cessation and alcohol abstinence is obligatory (28). Despite these guidelines, policies vary significantly in Europe and the USA (7) and some (relative) contraindications are under current debate (29, 30).

A multidisciplinary approach is required to optimize quality of a live kidney donation program. Disciplines have to cooperate in the screening of donors and informing relatives without exerting pressure on potential donors. Each step in the multidisciplinary approach should be optimized. Imaging of the donor's kidneys and the surgical procedure should be performed without any complications. Furthermore, perioperative care should be optimally organized to minimize pain and discomfort to the donor. Advances in the surgical technique have improved the comfort of the donor considerably and the risks of morbidity and mortality have been minimized. Adequate follow-up may help donors from a social perspective by advising those who struggle with their recovery or experience problems resuming work. On the long-term it may identify donors in an early stage who are possibly at risk to develop end stage renal disease themselves, for example by developing hypertension (31). This risk is shown to generally be lower than in the general population, and estimated at 0.1-0.5. percent. The long term incidence of hypertension among donors after donation is 21-38 percent, independently correlated with the duration of the follow-up period (32, 33).

4.1. Improvements in imaging of the donor

In addition to providing detailed information on the donor's medical history, imaging is of utmost importance in selecting donors. The decision which kidney can safely be donated is largely dependent on imaging results. The guiding principle for this choice is that the donor should remain with the "best" kidney, i.e. the kidney with the lowest long-term risk for the donor. This requires state of the art diagnostic techniques to determine: kidney size, vascular anatomy, ureter anatomy, renal cysts or other abnormalities in both kidneys, and on indication renal split function. In laparoscopic donor nephrectomy (unless hand-assisted), the surgeon cannot rely on tactile feedback compared to open donor nephrectomy. Therefore, preoperative planning of these operations has become increasingly important. The anatomy of the renal arteries must be visualized, as multiple arteries are associated with increased complexity during nephrectomy and an increased rate of ureteral complications in the recipient (34).

In the past, the donor's renal anatomy was assessed by angiography with good results. However, it is considered an invasive technique, since it is associated with some risks for the donor, including exposure to a contrast agent enabling possible allergic reactions, radiation and a short hospital stay. Radiological examinations on the donor should be safe, minimally invasive and the time for these investigations should be limited. Therefore, magnetic resonance imaging (MRI) (35, 36) and computed tomography (CT) (37-41) have both been reported as feasible alternatives. In our hospital, MRI had gradually replaced angiography due to the associated risks. However, in our own study in which we compared both techniques with the perioperative anatomy, MRI was less accurate in predicting the arterial anatomy (42). Since, live kidney donors are healthy individuals who deserve the least invasive and the least time consuming imaging with the best predictive value, imaging with CT and MRI are good alternatives and less invasive than angiography. In addition, it does not require observation of the live donor in the hospital for several hours after the procedure. Nowadays, CT has replaced MRI and angiography as primary technique, because it visualises the anatomy of the kidney and associated vessels more accurate (43, 44). In addition, CT helps to determine renal split function (45). However, this is not routinely determined. In our center the renal split function by radioisotope renography (Tc99m-MAG3 scan) is determined on indication, i.e. when there are large benign kidney cysts or asymmetric kidney size of one cm or more. If the split function does not differ that much (less than five percent), we usually tend to procure the kidney with the easiest anatomy. However, the choice for which kidney to procure is usually determined by the longitudinal axis on CT during preoperative screening. Emamian *et al* studied both kidneys of 655 healthy volunteers. They found that above a three mm difference between kidney length, the volume difference can be up to ten percent (46). Determining the renal split function should be more liberally considered to contribute to donor's safety.

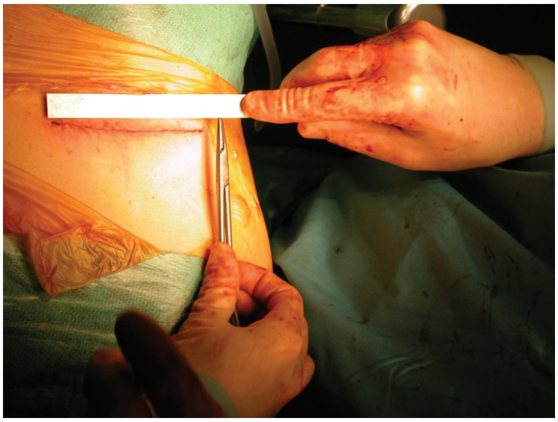

Figure 1. Mini-incision open donor nephrectomy. The incision measures less than ten centimeters (indicated by the ruler) and in erect position, the scar will lie in the natural shade of the costal margin. Reproduced with permission from (114).

4.2. Improvements in surgical technique

In the past, all live donor kidneys were procured by a 15 to 25 cm flank incision with transection of all abdominal wall muscles. Frequently, resection of the lower ribs had to be applied to allow sufficient access to the kidney. This procedure markedly injured the abdominal wall, resulting in significant postoperative pain, an average hospital stay of one week and prolonged recovery time. Not infrequently, donors suffered from chronic neuralgia and incisional hernias (47).

Fortunately, renewed interest in live kidney donation occurred in an era in which minimally invasive surgery was gradually replacing conventional surgery. In 1995, Ratner and colleagues performed the first laparoscopic donor nephrectomy (48). Various alternatives to this laparoscopic approach have been presented since, including hand-assisted laparoscopic donor nephrectomy, retroperitoneoscopic donor nephrectomy, robot-assisted donor nephrectomy, laparoendoscopic single-site and natural orifice transluminal endoscopic donor nephrectomy. Meanwhile, the conventional open approach has been refined and minimally invasive principles are more often applied in open surgery. An important trend towards more minimally-invasive live donor nephrectomy is observed (7, 10, 11).

4.2.1. Minimally invasive open donor nephrectomy

The introduction of minimal invasive techniques has encouraged refinement of the open techniques. Many centers have banned rib resections, replaced classic flank incisions by incisions at other, alternative sites, and currently apply principles of minimally invasive surgery, including minimal tissue damage and limited access. These incisions have in common that the incision is located anterior and more medial, compared with classic open flank incisions. In addition, the size of the incision is also much smaller (Figure 1).

A minimal flank incision most closely correlates to the conventional flank incision. The retroperitoneal cavity is accessed with a smaller incision, varying from 7 cm in lean donors to 15 cm in obese donors. The oblique and transverse abdominal muscles can be either divided or split. Mechanical retractors allow sufficient access with minimal skin incision. In addition, endoscopic instruments, such as endostaplers, may be used to maintain limited access in case of difficult anatomy i.e. multiple renal vessels. Most Dutch surgeons and urologists use the muscle-split approach when open donor nephrectomy is performed. Due to limited surgical trauma, these operations result in a shorter hospital stay, excellent cosmetic outcome and less postoperative pain compared with conventional open surgery (49). Most donor nephrectomies in our country are performed using laparoendoscopic techniques. In our center, 100 percent of donor nephrectomies are done robot-assisted or total laparoscopic, or hand-assisted retroperitoneoscopic.

4.2.2. Laparoscopic donor nephrectomy

As described above, Ratner and colleagues introduced a laparoscopic technique for live kidney donation in 1995. They used a midline incision to extract the donor kidney (31), as opposed to the Pfannenstiel incision we use nowadays (48). We will now give a general description of the operative steps. Many variations are clearly practised. First, the donor is positioned in right or left lateral decubitus position. Then, the first trocar is inserted periumbilically and a pneumoperitoneum is created by CO_2 insufflation, after which a 30° video-endoscope is introduced and depending on the side three to four additional trocars are inserted (Figure 2). Depending on a right or left-sided nephrectomy, the right or left hemicolon is dissected from the lateral abdominal wall and mobilized medially. Gravity aids the further mobilisation. The kidney is located behind the hepatic or splenic flexure. Gerota's fascia is opened and the kidney is exposed from a varying amount of surrounding perirenal fat. Next, the ureter is exposed until it crosses the gonadal vein. The renal vessels

Figure 2. Laparoscopic donor nephrectomy. A camera is introduced periumbilically (purple port). Three to four trocars are inserted. Reproduced with permission from (114).

are dissected and encircled with red or blue vessel loops to facilitate identification of the artery and vein from different directions, respectively. The vessel loops also enable safe manipulation of the vessels during the hilar dissection. The venous branches of the renal vein, especially in case of left sided donor nephrectomy, are clipped and divided with scissors. When the kidney, ureter, vein and artery are all fully dissected, a 5 to 8 cm horizontal suprapubic incision or Pfannenstiel incision is made as extraction site, while maintaining pneumoperitoneum. An endobag is introduced via a small incision in the peritoneum. Subsequently, the distal ureter is clipped and divided with scissors, secondly the renal artery is divided with an endostapler and last the renal vein is divided with an endostapler. The kidney is placed in the endobag and extracted via the incision. The donor kidney is immediately cooled by perfusion with preservation solution at 4° Celsius and put on ice. A thorough and detailed inspection of the donor kidney is now done, and further preparatory dissection on the donor vessels performed. If no vascular reconstruction or local excision is necessary, the kidney is packed and stored on ice. These steps are similar for all donor nephrectomy techniques. After the Pfannenstiel incision has been closed in layers, the peritoneal cavity is checked for bleeding, with special attention for the renal vessel stumps, clipped veins, ureter transection site and adrenal gland area. After haemostasis is ensured, the trocars are removed under vision, the larger fascia defects sutured, and the skin incisions sutured.

4.2.3. Hand-assisted laparoscopic donor nephrectomy (HALS)

Hand-assistance during transperitoneal laparoscopic donor nephrectomy requires an extraction incision that is generally larger than the aforementioned extraction site for conventional laparoscopic donor nephrectomy. This allows one hand of the surgeon to enter the peritoneal cavity via a hand port. These hand ports allow introduction of, manipulation by, and removal of the surgeon's hand while maintaining pneumoperitoneum. Some surgeons make a midline incision to place their hand port in a more ergonomic position. The introduction of various trocars is similar to the conventional laparoscopic approach. Advantages of this technique include maintaining tactile feedback, the possibility to present tissues and the creation of surgical planes with the hand. In case of bleeding, it is easier to directly stop the bleeding with a finger and repair the injury. These features contribute to a steeper learning curve for the hand-assisted method compared to the conventional laparoscopic approach (50). Most surgeons that use hand-assistance, also emphasize that they feel more safe with a hand in place. Potential disadvantages are higher costs due to the hand port, a challenging ergonomic position of the surgeon during operation, a higher rate of wound infections and increased traumatic injury to the transplant due to manipulation.

4.2.4. Retroperitoneoscopic donor nephrectomy

Retroperitoneoscopic donor nephrectomy is a modification of the technique first described by Ratner. Using this technique, the peritoneal cavity is not opened. It has been described with and without hand-assistance (51, 52). The retroperitoneal space is entered and insufflated with CO_2. Several trocars are introduced (Figure 3). The peritoneal sac containing the bowels is mobilized medially. The exposure of the kidney and the renal vessels is similar to transperitoneal laparoscopic donor nephrectomy, however, the angle is different. The kidney is extracted via a muscle-splitting flank incision or a Pfannenstiel incision (51-54).

4.2.5. Hand-assisted retroperitoneoscopic donor nephrectomy (HARP)

The first series of hand-assisted retroperitoneoscopic donor nephrectomy was published by Wadstrom *et al* in 2002 (55). In HARP a 7-10 cm Pfannenstiel incision is made, in which after blunt dissection to create a retroperitoneal space,

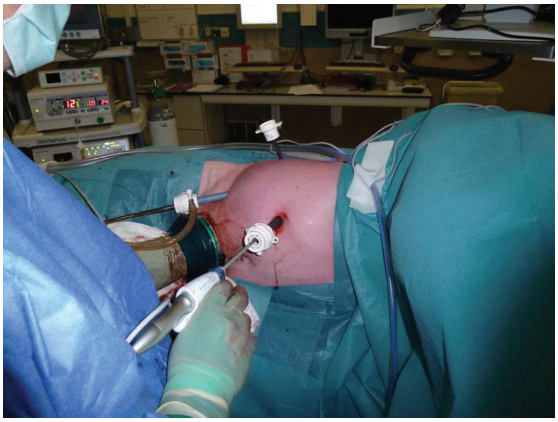

Figure 3. Hand-assisted retroperitoneoscopic donor nephrectomy. The surgeon creates the retroperitoneal space with his left hand. Thereafter, the trocars are introduced and the retroperitoneal cavity is insufflated.

Figure 4. Full robot-assisted laparoscopic donor nephrectomy.

the hand port is inserted. Blunt introduction of the first trocar between the iliac crest and the hand port is guided by the operator's hand inside the abdomen. CO_2 is insufflated retroperitoneally to 12 cm H_2O pressure. Two other 10-12 mm trocars, respectively just outside the midline inferior to the costal margin and in the flank, were inserted to create a triangular shape. Dissection of the kidney and renal vessels is similar to transperitoneal donor nephrectomy but with hand-assistance and from a slightly different angle. The kidney is removed manually. Two advantages of this technique are avoiding the peritoneal cavity and hand-assistance while operating.

4.2.6. Full robot-assisted laparoscopic donor nephrectomy

With the rapid development of minimal invasive techniques and the acceptation of laparoscopy as good or even better alternative to open surgery, a new system has been implemented to the surgical armamentarium: The DaVinci Surgical System, a robot-assisted surgery device. Laparoscopy has proven to reduce donor discomfort, has a faster recovery and excellent cosmetic results compared with open surgery. In addition, the DaVinci Surgical System recreates hand-eye coordination, enables 360° range of motion in the three articulated arms of the robot, a three-dimensional magnified view, and elimination of tremor. It received US Food and Drug Administration (FDA) approval in 2000 for general surgery use. The operating surgeon sits behind the console operating with 3-4 robot-arms while the operating assistant stands beside the patient. The position of the trocars and extraction site of the kidney is similar to conventional laparoscopic donor nephrectomy (Figure 4).

The first published article on robot-assisted donor nephrectomy is by Horgan *et al.* in 2002 on ten consecutive left-sided procedures. They performed their first robot-assisted donor nephrectomy in 2000 using the DaVinci Surgical System and a hand port to facilitate intraoperative exposure and safe removal of the graft. The mean operative time was 166 minutes compared with 110 minutes during laparoscopy. The warm ischemia time was an average of 85 seconds. There were no intraoperative complications and no open conversions. All grafts became functional upon implantation. There were two postoperative complications in this group: one donor developed C. difficile colitis, and a second developed a superficial wound infection at the site of the hand port incision, which required opening of the wound. The mean hospital stay was 2.2. days. The authors concluded that robot-assisted donor nephrectomy can be performed with the same degree of safety as the more conventional laparoscopic approach. In addition, the benefits of the DaVinci Surgical System allows surgeons to operate with greater precision, confidence, and comfort (56). The largest series published so far, is by Galvani *et al*. in 2005 on 145 donor nephrectomies. The results showed no significant differences in operative time, warm ischaemia time, blood loss, conversions, hospital stay, and donor and recipient outcomes compared with laparoscopy. They concluded that robot-assisted donor nephrectomy is a safe and effective method, and a good alternative to laparoscopy (57). No randomised controlled trials comparing robot-assisted donor nephrectomy with laparoscopy have been published so far.

4.2.7. Laparoendoscopic single-site donor nephrectomy (LESS)

Laparoendoscopic single-site surgery has been developed in an attempt to further reduce the morbidity and scarring associated with surgical intervention. This innovative technique accesses the abdominal cavity using a single small-length incision through which different laparoscopic tools pass simultaneously to perform a complete surgical procedure. The most widespread approach is the transumbilical, in which the navel is used as a natural embryonic orifice to hide the access scar to the peritoneal cavity. However, in donor nephrectomy a larger incision is needed to safely extract the kidney without causing (organ) damage.

In 2012, Fan *et al*. published a systematic review and meta-analysis comparing laparoendoscopic single-site nephrectomy (for all indications) with conventional laparoscopy. A subgroup analysis on donor nephrectomy showed no significant differences in postoperative pain scores, warm ischemic time, operative time, length of hospital stay, serum creatinine of graft recipients, analgesic requirement or perioperative complication rates. The overall results for LESS nephrectomy (for all indications) compared with conventional laparoscopy showed statistically significant differences in favour of laparoendoscopic single-site surgery in cosmetic satisfaction scores, postoperative pain scores and length of hospital stay. However, laparoendoscopic single-site surgery showed a significant longer operative time and higher conversion rate. The authors indicate that laparoendoscopic single-site surgery may be a good alternative without compromising surgical safety. Nevertheless, the inherent limitations of included studies prevent them from reaching definitive conclusions (58). Future large-volume, well-designed randomized controlled trials with extensive follow-up are awaited to reach to a definitive conclusion regarding superiority of laparoendoscopic single-site donor nephrectomy.

4.2.8. Natural orifice transluminal endoscopic surgery (NOTES)

NOTES is a surgical technique to perform scar less abdominal operations with an endoscope passed through a natural orifice and an internal incision in stomach, vagina, bladder or colon. Thus, avoiding any external incisions or scars and making it technically more challenging. During NOTES donor nephrectomy, trocars are placed in the umbilicus site, the left iliac fossa, next to the ribs and through the vagina perforating cavum Douglasi. The procedure is comparable with regular laparoscopic transabdominal nephrectomy, except for the use of a trocar through the vagina and the extraction of the kidney from this side.

In 2011, Alcaraz *et al*. published the largest case serie of 20 transvaginal-NOTES donor nephrectomies so far. Except for warm ischemia time, there were no other statistically significant differences in favour of conventional laparoscopy, with comparable recipient creatinine after one month. One reported complication is an uterine artery injury during transvaginal trocar insertion that had not been noticed during surgery, requiring immediate reoperation. Thirteen out of the 20 women were evaluated on postoperative sexual dysfunction and all stated not to experience any change in their sexual function. Transvaginal-NOTES donor nephrectomy appears to be a feasible and reproducible surgical technique. It may be considered a good alternative procedure that might increase living donor rate in the female population (59). It is still questionable whether transvaginal-NOTES donor nephrectomy will be permanently implemented as a procedure to procure kidneys. Olakkengil *et al*. conducted a survey among 49 women, who had already undergone conventional laparoscopic donor nephrectomy, on their opinion on transvaginal-NOTES. A majority of the women had no aversion towards scars after surgery, however when asked whether they would prefer an alternative, visibly scar less method, a majority answered yes. These women felt that an alternative procedure would induce less pain. When questioned about the use of their vagina as an entry point for abdominal surgery, a small minority felt unhappy of the idea. A third of patients expressed concern with any potential negative impact on their sexual function. When asked for their preference between transvaginal-NOTES and conventional laparoscopy, almost two-third preferred conventional laparoscopy over transvaginal-NOTES (60). Future studies are needed to establish its future role in live kidney donation.

4.3. Evidence-based approach in surgical management

Evidence has mounted that laparoscopic and retroperitoneoscopic approaches are superior to conventional open surgery. Even for donor nephrectomy, laparoscopy has significantly more advantages over the open approach (61-63). During the past decennia there has been an increase in live donor nephrectomies. Laparoscopy has become the preferred technique, however the open approach is still being performed as well. The discussion on the different operation techniques, with or without hand-assistance and choosing an appropriate donor, is depicted below based on the current literature.

4.3.1. Open versus laparoscopic donor nephrectomy

The introduction of the laparoscopic technique has given rise to much discussion in the transplant society regarding the need for pneumoperitoneum to create an operation field, leading to an increased intra-abdominal pressure and thereby may affect renal perfusion intra-operatively, with subsequent ischemia-reperfusion injury to the transplant. Recovery of transplant function would be delayed, however there is no significant difference in long-term renal function between laparoscopic and open donor nephrectomy (64). In our center, a randomized controlled trial between laparoscopic versus open live donor nephrectomy was performed by Kok *et al*. They concluded that laparoscopic donor nephrectomy results in a better quality of life compared with mini incision open donor nephrectomy but equal safety and graft function (62). Nanidis *et al* meta-analysed studies comparing the open versus laparoscopic approach in which they found similar results (65).

This is confirmed in 2011, by a Cochrane review on laparoscopic versus open live donor nephrectomy. Laparoscopy is associated with reduced analgesia use, shorter hospital stay, and faster return to normal physical function. However, extracted kidneys were exposed to longer warm ischaemia times (2 to 17 minutes) with no associated short-term consequences. We think that generally, the warm ischemia times were influenced by learning curves. The conversion rate from laparoscopy to an open procedure ranged from 1 percent to 1.8. percent. The open technique was associated with shorter operative time. For those outcomes that could be meta-analysed there were no significant differences between laparoscopy or open procedure for perioperative complications, re-operations, early graft loss, delayed graft function, acute rejection, ureteric complications, kidney function at one year or graft loss at one year. The authors concluded that laparoscopy has significantly more advantages, however it is more expensive and has longer warm ischaemia time compared with open techniques (63). Laparoscopic live donor nephrectomy is technically more demanding than the open approach, with a prolonged learning curve (66, 67). Therefore, the introduction of the laparoscopic method in small centers can be challenging (68), and European training programs, proctoring programs and fellowships are highly recommended.

4.3.2. Retroperitoneoscopic versus transperitoneal laparoscopic donor nephrectomy

In 2004, Ng *et al*. published their comparison of donor and recipient early outcomes of right retroperitonescopic donor nephrectomy versus left transperitoneal laparoscopic donor nephrectomy. All 143 patients underwent endoscopic donor nephrectomy successfully without conversion. Right retroperitonescopic donor nephrectomy was performed in 29 patients. There were statistical significantly differences in warm ischemia time, vein and ureteral length in favour of the transperitoneal laparoscopic approach. However, operative time and estimated blood loss were statistical significantly different in favour of the retroperitoneal approach. The recipient serum creatinine levels after transplantation were similar after transperitoneal and retroperitoneoscopic donor nephrectomy on day 5 and day 30. Four donors undergoing transperitoneal laparoscopic left donor nephrectomy had an intraoperative complication due to a splenic capsular tear by a trocar, renal arterial/aortic bleeding due to clip malfunction, dislodged adrenal vein clip and faulty video equipment. Two donors undergoing right retroperitoneoscopic donor nephrectomy had an intraoperative complication, including a renal parenchymal tear injury with subcapsular hematoma and a renal capsular tear. Both were repaired on the bench table and successfully transplanted. The authors concluded that the retroperitoneoscopic approach to transperitoneal laparoscopic right donor nephrectomy provides similar donor and recipient outcomes compared with the transperitoneal laparoscopic approach for the left kidney (69).

In 2010, Troppmann *et al*. published a matched pair pilot study on retroperitoneoscopic versus transperitoneal laparoscopic donor nephrectomy. After ten years of performing live donor nephrectomy transperitoneal, they implemented the retroperitoneoscopic approach at once. They describe their first 52 cases performed by three surgeons. Seven cases were switched to hand-assisted transperitoneal laparoscopic donor nephrectomy. Analysis showed no difference between these cases compared with the other 45 retroperitoneoscopic cases in patient characteristics, median warm ischemia time, median estimated blood loss, median operating time, median length of hospital stay, complications, graft function and graft survival. However, analysis showed that all intraoperative conversions from pure endoscopic to hand-assistance were made during the first ten retroperitoneoscopic donor nephrectomies of two surgeons. In their matched-pair analysis and comparison of the 45 hand-assisted retroperitoneoscopic with 45 hand-assisted transperitoneal laparoscopic donor nephrectomies, they observed a significantly longer warm ischemia time for retroperitoneoscopic grafts but no statistically significantly differences in delayed graft function and recipient serum creatinine levels at one week. Graft and patient survival at 90 days was 100 percent. Furthermore, there were no statistically significant differences for all other intraoperative and postoperative donor outcomes (70).

Appropriately designed studies on this topic are lacking and the evidence is based on expert opinions and small case series. The potential advantage of the retroperitoneoscopic technique is that the intraperitoneal organs are not within the operation field, and there is no mobilisation of the descending colon and the splenocolic ligament, thereby avoiding injuries to these organs. Moreover, the angle at which the vessels are dissected may be preferable (51). The hand-assisted technique is claimed to offer advantages in the management of severe bleeding (50, 71, 72). No large case series or comparative cohort studies have been published to date. In our center, the value of retroperitoneoscopic donor nephrectomy alongside the transperitoneal approaches is assessed. The primary endpoint is the quality of life, with operative time and complications as secondary endpoints (73, 74).

4.3.3. Total endoscopic versus hand-assisted donor nephrectomy

In 2011, Wadstrom *et al*. published a systematic review and meta-analysis on hand-assisted laparoscopic techniques versus open and laparoscopic techniques. A total of 30 donor nephrectomy studies were included withholding 3102 donors. Blood loss was statistically significant less in the hand-assisted group when compared with both the open and laparoscopic group, probably due to tactile feedback and the ability to apply direct pressure on the vessel. Operative time and warm-ischemia time were statistically significant in favour of open procedures when compared with hand-assisted procedures. However, when compared with the laparoscopic group, there was a statistically significant difference favoring the hand-assisted group. There were significantly more conversions in the laparoscopic group compared with the hand-assisted group. The length of hospital stay was shorter in the hand-assisted group compared with both other groups. Meta-analytic results of mortality, perioperative, and long-term complications were not statistically different. The authors stated that the hand-assisted technique offers significantly clinically relevant advantages (75). However, more evidence is needed to prove the superiority of the hand-assisted approach, and whether the side of nephrectomy show different results.

After publishing an initial study comparing 20 left-sided hand-assisted retroperoneoscopic donor nephrectomies versus 40 left-sided transperitoneal donor nephrectomies in which the hand-assisted donor nephrectomy provided to be equally safe with shorter warm ischemia time and mean operation time (74); Dols *et al.* published a randomized controlled trial in 2014. The hand-assisted group consisted of 95 patients and the laparoscopy group consisted of 95 patients. Warm ischemia time and median skin-to-skin time were significantly shorter in favour of the hand-assisted group. Intraoperative complications were significantly higher in the laparoscopic group, confirmed previously by Wadstrom *et al*. Postoperative complication rates did not significantly differ between groups, as well as total morphine requirement, and length of hospital stay. During follow-up, estimated glomerular filtration rates in donors and corresponding recipients, quality of life, and graft and recipient survival did not differ between both groups. The authors stated that the hand-assisted approach may be a valuable alternative for left-sided donor nephrectomy (76). Subsequently, in 2014 Klop *et al* from the same center published a randomized controlled trial comparing 20 right-sided hand-assisted retroperoneoscopic donor nephrectomies versus 20 right-sided transperitoneal donor nephrectomies. Warm ischemia time was significantly shorter in the hand-assisted group, and blood loss was significantly less in the laparoscopic group. Intraoperative and postoperative complications showed no difference between both groups, and also recipient and graft survival were similar. Quality of life showed no statistical difference between both procedures (77).

Overall, these randomized controlled trials on left and right-sided hand-assisted versus laparoscopic donor nephrectomy show that hand-assisted donor nephrectomy is feasible and at least equally safe.

4.3.4. Left-sided versus right-sided donor nephrectomy

The principle should always be to let the good kidney remain with the donor. Nonetheless, there is no consensus on which technique is superior for the left or right sided donor nephrectomy when both kidneys are equal. Due to longer renal vessel lengths, left sided donor nephrectomy is the preferred technique, especially if the recipient has an increased BMI (10). However, right-sided donor nephrectomy is easily to perform and has decreased risk of splenic laceration.

In 2008, Minnee *et al*. published a randomized controlled trial comparing left-sided versus right-sided hand-assisted donor nephrectomy for patients with equal kidneys. The left-sided group consisted of 29 donors and the right-sided group of 31 donors. The results showed a statistical significant median operating time in favour of the right-sided group. There were no conversions in both groups. Intraoperative complications occurred in three patients (10 percent) during the left-sided approach: bleeding in two and one lesion of a polar artery. Four intraoperative complications (13 percent) occurred during the right-sided approach: two serosal lesions of the colon, bleeding in one, and one lesion of a polar artery. All with successful recoveries. No minor postoperative complications occurred in the right-sided group compared with two in the left-sided group. No major postoperative complications occurred in either group. All patients had a similar quality of life after surgery, equal to the situation before surgery. There were also no significant differences between both groups in pain visual analogue score (VAS) scores. The authors concluded, that the operating time of the right kidney is significantly shorter than of the left kidney. With no differences in morbidity of donor and recipient, hospital stay, and donor quality of life (78).

Until now no prospective randomized controlled trial has been published regarding left-sided versus right-sided transperitoneal donor nephrectomy. But all published reports show that there is no evidence excluding either the left or right kidney for donation (79, 80). It is surgically possible to procure and implant both kidneys. Some recipients of live donor kidney transplants may have had several previous transplantations and therefore may have special requirements, including longer length of the renal vessels. In such cases, the left-sided kidney is preferred to achieve longer vessel lengths. The application of vessel clamps in open surgery results in considerably less loss of vessel length than the application of the endostapler in laparoscopic surgery. The application of self-locking clips in laparoscopic surgery may save some length, but is considered less safe for the donor due to postoperative haemorrhagic complications associated with clips (81).

The safety of a donor nephrectomy also depends on the multiplicity of the vessels, especially the arteries. Which is subsequently associated with the outcome of the recipient. The vascular anatomy also influences the side that is chosen for donor nephrectomy. Paragi *et al.* published the largest case serie in 2011 on their experience with single versus multiple arteries during donor nephrectomy. Seven hundred and ninety-nine cases of single arteries were compared with 177 cases of multiple arteries. Comparison of perioperative parameters between single and multiple artery kidney patients revealed no significant difference for mean donor age, mean preoperative creatinine, mean postoperative creatinine, mean estimated blood loss, or mean length of hospital stay. The only parameter that was statistically different between the two groups was operative time. Twenty-seven patients (3.4. percent) with a single artery kidney had at least one complication compared to six patients (3.4. percent) with a multiple artery kidney. The estimated overall mean graft survival was significantly higher in favour of the single artery group. The authors concluded that multiple artery kidneys are no contraindication for live donor nephrectomy in regard to perioperative outcomes for the donor and complication rates. However, preoperative counselling is important regarding the inferior graft survival rates following live donor nephrectomy of multiple arteries compared to single arteries (82).

4.3.5. Choosing an appropriate donor

Some donor characteristics are considered relative contraindications for donation, such as high BMI, renal arterial stenosis, pre-malignant cysts and parenchymal tumors. BMI above 35 is considered a relative contraindication, which is in accordance with the Amsterdam forum guidelines (28). A systematic review and meta-analysis of the relation between BMI and short-term donor outcome of laparoscopic donor nephrectomy by Lafranca *et al.*, found statistically significant differences in operation time, conversion rate and rise in serum creatinine favoring low BMI (29.9. or less). However, these small differences were not considered to be clinical relevant. Furthermore, no higher complication rates were found in the high BMI group. The authors concluded that high BMI alone is no contraindication for live kidney donation regarding short-term outcome (29). In our center donors with high BMI can donate if there are no other relative contraindications. Renal arterial stenosis is usually caused by arteriosclerosis followed by fibromuscular dysplasia and is usually expressed by hypertension. Reports on single sided renal arterial sclerosis show that after donating this kidney, the donor sometimes becomes normotensive and the recipient has a good graft function (83, 84). Donors with bilateral renal arterial stenosis can be considered for donation, in case the donor will be left with a mild stenosis, in which the hypertension can be controlled with one or two hypertensive agents (84). Renal cysts with Bosniak class IIF or higher are considered premalignant. Bosniak class IIF and III can become malignant in 25 percent and 54 percent, respectively (85). When diagnosed, these cysts are followed up with ultrasonography yearly. These kidneys can be taken into consideration for donation. Clearly, the risks are then being transferred from the donor to the recipient, which should be discussed in a multidisciplinary team and with the patient, as follow up is needed. However, nowadays kidneys containing small renal carcinomas are procured for live donation. These malignancies are excised on the bench and implanted in the recipient. Nicol *et al.*, reported on 43 patients who had less than 3 cm small tumors, chose to have a radical nephrectomy and who were willing to donate this kidney. The tumors were excised on the bench and successfully implanted in elderly donors and donors with significant comorbities who might not survive the waiting period if they are dependent on a deceased donor graft. Over ten years, graft survival was more than 80 percent. In one of the transplanted kidneys, a possible recurrence of the tumor had occurred after nine years, after which the recipient declined further treatment (86). All relative contraindications as described above should be taken into consideration to potentially expand the live donor pool (30).

4.4. Improvements in perioperative care

Two factors in live kidney donation can be influenced by improvements in perioperative care. First postoperative pain and nausea, and second perioperative fluid management.

4.4.1. Postoperative pain and nausea

In our center, the combination of local infiltration of ropivacaine, patient controlled opiod analgesia (PCA) with morphine or dipidolor, and paracetamol is being used for postoperative pain management of the donor resulting in a mean hospital stay of 2-4 days. In 2012, a Cochrane review was published on PCA versus conventional opioid analgesia for postoperative pain. Fifty-five studies were included with 2023 patients receiving PCA and 1838 patients assigned to a control group. PCA provided better pain control and greater patient satisfaction than conventional parenteral analgesia. Patients using PCA consumed larger amounts of opioids than controls and had a higher incidence of pruritus, however PCA had a similar incidence of other adverse effects. There was no difference in the length of hospital stay. The authors concluded that PCA is an efficacious alternative to conventional systemic analgesia for postoperative pain control (87). In that same year, Thiyagarajan *et al.* published a review on pain management in laparoscopic donor nephrectomy in which they evaluate PCA, epidural, systemic and local analgesia. They reported the same benefits of PCA as the Cochrane review, although some disadvantages of PCA were highlighted, such as not providing optimal dynamic pain relief after major surgery and that postoperative morbidity is not reduced by PCA compared to intermittent morphine opioids. In addition, a high incidence of postoperative nausea and vomiting, respiratory depression and sedation were noted during morphine use when compared to epidural analgesia. Also, obstipation can be a problem for which profylactic laxantia is prescribed. Therefore, the use of opioids are far from the ideal postoperative analgesics of choice following laparoscopic donor nephrectomy. Epidural analgesia has disadvantages as well, such as urinary retention and risk of infection at the catheter site. Long-acting local anaesthetic agents such as ropivacaine are used to locally infiltrate before or after surgery with good results within the first 48 hours (88). For other surgical procedures, epidural analgesia has been reported to significantly reduce perioperative morbidity including ileus, acute renal failure (approximately 30 percent) and blood loss (approximately 30 percent), and not only improve analgesic efficacy but also reduce opioid demand and side-effects such as nausea, vomiting and sedation (89-92). The use of thoracic epidural analgesia (TEA) for laparoscopic procedures is becoming more common, especially with colon surgery, where TEA significantly improved early analgesia and had a significant, favorable impact on dietary tolerance and length of stay (93). To date, reports describing the effect of epidural analgesia or PCA during laparoscopic donor nephrectomy on postoperative pain and nausea have not been published to our knowledge.

4.4.2. Perioperative fluid management

Proposed mechanisms resulting in slower recovery of graft function after laparoscopic donor nephrectomy include mechanical injury to the graft, longer operative time until nephrectomy, longer first warm ischemia time and increased abdominal pressure due to the pneumoperitoneum leading to decreased cardiac output and decreased renal blood flow (94, 95). The predictive value of these findings on graft survival remains unclear as the mean half life of a graft procured from a live donor is much longer than the time elapsed since the first laparoscopic donor nephrectomy by Ratner *et al.* in 1995 (48). Retrospective studies at our institution showed that higher recipient serum creatinine values remained present in spite of administration of a sufficient amount of intraoperative fluids (94, 96). Therefore, we hypothesized that not only intraoperative fluid management is important, but also prehydration. An adequate prehydration regimen may indeed improve donor and recipient creatinine clearance. At our center we analysed the role of preoperative infusion of fluids to maintain adequate perfusion of the donor's kidneys during laparoscopic donor nephrectomy. Twenty-one patients undergoing laparoscopic donor nephrectomy were randomized into three groups: group 1 received overnight infusion and received a bolus of colloid before induction of anaesthesia, followed by a bolus just before pneumoperitoneum; group 2 received overnight infusion and a colloid bolus before anaesthesia; group 3 served as controls and received only infusion during operation. All three groups received the same total amount of crystalloids and colloids until nephrectomy. Urine output was measured from the start of operation until the moment of kidney extraction. In controls, the urine production was significantly lower compared to group 1. Creatinine clearance decreased in the control group directly after pneumoperitoneum, but not in the other groups. From two days postoperative, creatinine clearance was comparable between the three study groups. While under-hydration may contribute to renal dysfunction, perioperative fluid excess can also cause problems, such as pulmonary oedema, ileus and increased risk of cardiopulmonary and wound healing complications, which might result in longer hospital stay. In our center a preoperative fluid regimen is used comparable with group 1, optimizing perioperative perfusion (97). Aiding to a well-functioning kidney during the entire operation.

4.4.3. Improvements in follow-up

With the implementation of laparoscopic donor nephrectomy, the quality of life of donors has improved significantly. The health related quality of life is usually measured with the short-form 36 (SF-36), multidimensional fatigue inventory 20 (MFI-20) or EuroQol (EQ-5D) questionnaires. Especially short-term physical functioning and bodily pain score (SF-36) significantly favours laparoscopy compared with open surgery. Fatigue and diminished quality of life may be present until one year after donation in both groups (62, 98, 99). Most donors demonstrate a better quality of life compared to the general population both in short and long term post donation (100, 101). Part of the donors nevertheless, experience a reduced mental component score (SF-36) compared to baseline which is associated with reduced quality of life, a higher level of fatigue, a lower level of societal participation, and show a trend towards less often contact or joint activities with the recipient after donation. A reduced physical component state (SF-36) after donation is associated with a higher BMI and smoking prior to donation, and higher expectations regarding health consequences prior to donation. No association of reduced quality of life with kidney function prior to or post donation is found (101). Studies has been done among donors on cosmetic results after live donor nephrectomy by conducting a body image questionnaire. Results show no significant difference in body image scores between donors who underwent a laparoscopic donor nephrectomy versus donors who underwent open donor nephrectomy (102). Another study by Klop *et al*. showed excellent body image scores among donors who underwent a laparoscopic and mini-incision donor nephrectomy. In which elderly donors had significantly higher scores when compared with young donors (103).

Expansion of unspecified donation may increase the number of disappointed live donors, as the personal advantages for the donor are usually smaller with these types of donation. Recently, Timmerman *et al.*, presented their study on psychological functioning of unspecified living kidney donors before and after donation. Forty-nine donors were asked to fill out a psychological symptom checklist (SCL-90) pre and post donation. On a group level, they found an increase in overall psychological symptoms, such as anxiety, depressive symptoms, somatization, hostility, and sleep problems between predonation and postdonation. However, the means of these scales remained within the average range compared with norm scores after donation, with the exception of sleep problems. On an individual level, most of all 33 donors showed no statistically significant change, whereas 3 donors showed a statistically significant decrease and 13 donors showed an increase in psychological symptoms. According to the authors, these results highlight the importance of long-term psychological follow-up of unspecified living kidney donors and psychosocial support upon indication. A subsequent question is whether the fluctuations found are attributable to the donation process, warranting further research (104).

With regard to medical follow-up, donors may be monitored cautiously for hypertension and proteinuria as an expression of renal disease. Individuals with one kidney have a reduced functional reserve. Although most kidney diseases will affect both kidneys, early recognition of deteriorating kidney function may be beneficial in preventing end-stage renal disease (105-107). When in the Netherlands a live kidney donor develops end-stage renal disease and needs a kidney transplant, the donor is placed on top of the postmortal transplant waiting list. Follow up of the donors is also needed in order to gather more data regarding the long-term consequences of kidney donation. Previous studies on large cohorts confirm that kidney donors have a normal life span, good health status and an excellent quality of life (32, 108-111). Most of these studies are retrospective, lacking a good control group and do not include donors with comorbidities. Recent long-term follow-up of live kidney donors show contradictive results in the development of end-stage renal disease (112) and increased mortality risk (113). An accurate study on baseline renal function is needed with a large cohort including all donors, who will be matched with a representative, prospective control group on age, sex, ethnicity, BMI and pre-existing comorbidity for all study parameters. Currently, such a study is being performed in our center to present potential donors with all available information regarding the potential short- and long-term risks and benefits of donation. At our institution we schedule follow-up visits at the nephrology and surgery outpatient clinics at one, three and twelve months and annually thereafter.

5. CONCLUSION AND FUTURE PERSPECTIVES

Live kidney donor transplantation has rapidly been developed as the most important life-saving procedure and the treatment that offers the best quality of life for patients with end stage renal failure.

Further expansion of unspecified kidney donation, paired kidney exchange, and renal transplantation across blood group barriers will help those recipients with an incompatible blood group. An increase in pre-emptive transplantation improves results of renal transplantation and reduces the costs of dialysis. Laparoscopic donor nephrectomy may be applied in the majority of donors and offers a better outcome to the donor with regard to quality of life. Future directions include development of minimal invasive surgical techniques and proving their superiority to conventional laparoscopy, long term outcomes of live kidney donors, in particular older and obese donors, and donors with pre-existing comorbidity, and increasing the number of live kidney donors by a tailor made approach without compromising safety to the donor or the graft.

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