Current status of live-donor renal transplantation

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Live kidney donation is assuming an increasingly prominent role in kidney transplantation programs. The traditional operative approach has been through an incision in the upper quadrant of the abdomen or in the loin, with potential postoperative complications associated with a large surgical wound. These problems may act as disincentives to prospective donors. The introduction of laparoscopic donor surgery in 1995 heralded a new era, offering reduced postoperative pain and improved cosmetic result. It is hoped that these benefits may counter some disincentives and thereby increase donation rates. Three minimal-access approaches, along with their advantages and disadvantages are described, including; classical laparoscopic, hand-assisted laparoscopic and retroperitoneoscopic surgery. All three approaches present specific challenges in the context of retrieving an organ that is fit for transplantation and safe for the donor. For minimal-access surgery to be accepted as the procedure of choice for live kidney donors, it must be demonstrated that morbidity is not transferred from donor to recipient when these techniques are used. Some concerns about these procedures are addressed. It appears that, with appropriate modifications, these techniques are safe for both the donor and the allograft. This review also covers other contemporary approaches to overcoming donor shortage by utilizing blood group-incompatible donor and recipient pairs.

Preoperative imaging
Preoperative imaging of live donors confirms the presence of two functioning kidneys, indicates pathology that would preclude donation and provides anatomical information necessary for planning the procedure. The ideal form of imaging is minimally invasive and provides accurate morphologic information on the renal parenchyma, collecting system and vascular anatomy [4,5]. Angiography combined with excretion urography is now obsolete and modern imaging for anatomical assessment of living renal donors comprises either computerized tomographic angiography (CTA) (Figure 1) or magnetic resonance angiography (MRA) [6,7]. Preoperative anatomical information assumes paramount importance before minimally invasive donor nephrectomy due to the reduced operative exposure and particular difficulties in the identification of complex renal vein tributaries. Thus, the location, size and number of renal veins and tributaries need to be accurately described preoperatively. Spiral CTA imaging compares favorably with conventional tomographic angiography (CTA) in the prediction of gross renal arterial and venous anatomy [8] and is a powerful tool for identification of renal vein tributary anatomy [9]. For a preoperative description of main renal artery and vein anatomy, MRA and CTA are comparable [10], but CTA may be more sensitive and specific for complex vascular anatomy [11] and small venous branches.

In Leicester UK, arterial and venous anatomy is evaluated using a CTA dual-phase protocol with venous injection of iodinated contrast
media (Iopamidol®). Arterial phase imaging is performed from the level of the celiac axis origin to include the lower renal pole. Venous phase imaging (60 s after contrast injection) includes the cephalocaudal extent of the left renal vein and the left renal sinus.

Development of minimal-access donor nephrectomy

The live donor nephrectomy operation has traditionally been performed through an open incision, necessitating a prolonged period of recovery and delay in returning to employment. This, and the cosmetic implications of a large flank wound [12], may represent discouragements to potential donors (Figure 2).

To reduce such disincentives there has been a move towards minimally invasive donor nephrectomy (DN), first performed as a classic transperitoneal laparoscopic procedure (LapDN) by Kavoussi and Ratner in 1995 [13]. Retrospective reports suggest that the LapDN is associated with decreased severity and duration of postoperative pain, shorter in-patient stay, quicker return to work and normal activities, and improved cosmetic result when compared with open donor nephrectomy [14,15] (Figure 3).

Furthermore, the overall societal cost of LapDN is lower and recipient quality of life (QoL) scores are higher [16].

Despite the current lack of published statistically powered randomized clinical trials, retrospective data suggests that minimal-access DN not only offers postoperative advantages to the donor, but also increases the number of transplants performed by reducing donor disincentives – estimates range from a 25% [17] to a 100% [18] increase in transplant activity. In the USA, 31% of live kidney donor procedures are performed laparoscopically and 65% of centers offer the procedure [19]. The UK is demonstrating year-on-year increases in live donor activity [20], and with accumulating evidence that high-quality grafts can be procured from laparoscopically obtained kidneys [3,21], more centers are adopting minimally invasive donor surgery.

Three approaches have been described comprising transperitoneal [22], extraperitoneal [23,24] and hand-assisted [25] live DN (LDN). Ratner’s original description was of a classical transperitoneal operation that requires a considerable level of laparoscopic expertise [13]. The hand-assisted operation is said to be easier to learn [25] and can be safely and efficiently performed by surgeons with less laparoscopic experience [26]. The retroperitoneal approach avoids breaching the peritoneum and may also have a particular application in right DN [27].

Minimally invasive donor nephrectomy techniques

Transperitoneal laparoscopic donor nephrectomy (left)

The patient is placed in a modified lateral decubitus position and a CO2 pneumoperitoneum is established using a Veress® needle. In general, four laparoscopic ports are required. The video-laparoscope is introduced through a 12 mm umbilical port and two further 12 mm ports are placed in the epigastrium and left iliac fossa for the main dissecting instruments (Figure 4).

A retractor for the colon can be passed through a 5 mm port placed in the mid-axillary line. The procedure starts with scissor diathermy of the lateral peritoneal reflection of the splenic flexure and descending colon to the level of the pelvic brim; this enables the colon to be reflected medially, demonstrating the kidney within Gerota’s fascia. The ureter and gonadal vessels are identified at the pelvic brim, anterior to the psoas muscle. The gonadal vein...
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procedure is technically demanding and there is potential for damage to the renal vessels and ureter during dissection. It takes longer than open nephrectomy and exposes the allograft to a short period of warm ischemic damage. There is also the potential for reduced graft perfusion before extraction in the presence of a pneumoperitoneum. The technique will only gain acceptance if morbidity is not transferred from the donor to the recipient.

Contraindications
There are no absolute contraindications to minimal-access DN other than those applying to the open operation. The relative contraindications are dictated by donor factors and the experience of the surgeon and center. The donor must be anesthetically fit, with special consideration given to the physiologic stress of pneumoperitoneum or pneumoretroperitoneum. Obesity is a relative contraindication for both open and laparoscopic surgery, but the hand-assisted approach may be better suited in such patients [35]. Previous abdominal surgery is a further relative contraindication because of the potential for adhesions. Multiplicity of renal vessels should not hinder LapDN – if the left kidney has multiple vessels it can still be taken unless there is a clear advantage to the donor to leave it [36], or recipient if implantation would be technically difficult.

Effect of pneumoperitoneum
Transient intraoperative oliguria secondary to decreased renal blood flow is a frequent occurrence during laparoscopic procedures. Proposed mechanisms include decreased cardiac output, renal vein compression, ureteral obstruction, renal parenchymal compression and systemic hormonal effects [37]. Intracranial pressure rises during pneumoperitoneum, with release of vasoconstrictor agents that may decrease renal blood flow [38]. Use of a lower pressure reverses decreases in renal blood flow and urine output, it did not attenuate the changes in creatinine clearance induced by the pneumoperitoneum. The pioneers of LapDN report using 8 to 10 l of crystalloid pre- and intraoperatively to maintain renal perfusion at satisfactory levels in the presence of pneumoperitoneum [3]. At the Leicester (UK) unit, two episodes of marked unilateral pulmonary edema in the dependent lung have led to a change in practice (now volume-loading the donor with 2 l of crystalloid the night before surgery and using replacement fluids only during surgery) with no apparent detriment to renal function. The retroperitoneal technique avoids pneumoperitoneum and low pressures (7 mmHg) can be used [43].

Recipient serum creatinine
In a comparison of open, laparoscopic and hand-assisted DN, recipient serum creatinine was statistically equal in all three groups up to 1 year [44]. Wolf and colleagues’ randomized trial of OpenDN versus hand-assisted DN demonstrated equal graft function up to three months post-transplant [31]. In a retrospective study of recipients of kidneys from LapDN (n = 132) versus OpenDN (n = 99), mean serum creatinine was statistically higher in the LapDN group at 1 week and 1 month after transplant [41]. By 6 months there were no differences and by 1 year, the LapDN group had lower serum creatinine. The rate of delayed graft function was higher in the LapDN group than the OpenDN group (7.6 vs. 2%). In a more recent study by Ratner and colleagues of LapDN (n = 110) and OpenDN recipients (n = 48), the rate of decline of serum creatinine was faster in the open group for the first 4 days but there were no significant differences thereafter [18].

Acute rejection, early & late graft loss
Pretransplant ischemia may render the donor kidney more immunogenic by inducing major histocompatibility complex (MHC) Class II expression [45,46]. However, acute rejection rates and the severity of rejection do not seem to be higher in laparoscopic than in open live-donor
kidneys (despite the longer warm time) [18,36,47,48]. In Wolf’s randomized trial of open and hand-assisted procedures, the number of treated rejection episodes in the first 3 months was similar in the two groups [31]. Allograft survival was statistically equal in the two groups, although it should be stated that allograft loss in the hand-assisted group was three in 23 (13%) and one in 27 (3%) in the open group. One graft loss was due to medically supervised withdrawal of immunosuppression and the other two to pathologically proven ischemic necrosis not due to renal vein thrombosis or acute rejection. Herein lies the importance in the modification of the technique – with topical papaverine applied to the artery, desufflation of the abdomen and cessation of manipulation of the kidney for at least 5 min before transection of the artery to maximize blood flow. Since the introduction of the above triad of adaptations, no allograft losses have occurred.

**Pediatric recipients of laparoscopically derived kidneys**

Troppmann and colleagues have recently published an important retrospective study reporting 995 open and laparoscopic live adult-donor transplants into pediatric recipients [49]. Children receiving LDN kidneys had significantly higher rates of delayed graft function and acute rejection than those transplanted with open-donor organs. This effect was more marked in the 0 to 5 year-old than the 6 to 18 year-old group. These findings highlight two points. First, there may be subclinical functional or immunologic alterations in laparoscopically derived kidneys that are unmasked only when additional stresses are placed on the organ (not seen in most adult recipients). The hemodynamic strain of placing a large kidney in a small recipient and the more vigorous immune response of children may be such stresses. Second, care must be taken in planning the donor operative approach for a pediatric recipient, in view of the impact of acute rejection and delayed graft function on graft survival.

**Ureteric complications**

Post-transplant complications associated with ureteric ischemia were more common in some groups’ initial experience of LDN [50–52]. Philosophers and colleagues describe a ureteric complication rate (necessitating operative repair) of 7.7% in LapDN compared with 0.6% for OpenDN [53] – for the Maryland group the figures were 11.2 and 3.4%, respectively [52] (although this figure included simple placement of a ureteric stent as an operative procedure). The problem is related to stripping of the delicate ureteric blood supply originating from the renal artery and traveling parallel to the ureter. Modifications of technique, such as ensuring sufficient periureteral tissue is taken and that the dissection does not occur too close to the renal pelvis [3] (dissect no further laterally than the medial border of the gonadal vein [51]) have reduced the complication rate [52]. A further technique is to take the gonadal vein and ureter together in a clip or stapling device [50]. Similar rates of ureteric complications were observed in open versus hand-assisted donation (1 out of 27 and 2 out of 23, respectively) [31]. The group performing this study have stapled the ureter and gonadal vein together since the inception of the hand-assisted technique. Tanabe and colleagues reported two ureteric complications in 135 retroperitoneal laparoscopic procedures [43]. Treatment required only temporary placement of a ureteric stent.

**Multiple renal vessels**

The presence of multiple arteries is not a barrier to successful use of grafts from laparoscopic donors. In a series of 320 LapDN procedures, multiple renal arteries were demonstrated in 64 cases (20%), with bench arterial reconstruction in 14 and multiple arterial implantation in the other 50 (16%) [54]. An early report of 124 LDN indicated that the presence of multiple renal arteries did not alter graft or patient survival, or prevalence of immunological events [52]. Likewise, Brown and colleagues reported multiple renal arteries in 26% of their 50 laparoscopic donors, with no effect on subsequent graft function or survival [14]. Hsu and colleagues reviewed their experience of 353 LapDN, finding one renal artery in 277 cases (78.5%), two arteries in 71 cases (20.1%) and three in five cases (1.4%) [55]. Despite increased warm ischemic time in the presence of multiple renal arteries, there was no association with intraoperative blood loss, postoperative hospital stay, graft function or complication rate for the donor.

In cases of complex arterial and/or venous anatomy, skilled ‘back-table’ vessel surgery may be required by the recipient surgeon before transplantation. When three donor arteries are present, this may necessitate harvesting of recipient iliac artery [56], or saphenous vein (for formation of a Carrel patch) to facilitate reconstruction [52].
Right-donor nephrectomy

Historic reviews of OpenDN indicate use of right donor kidneys in 20 to 30% of cases, but the literature regarding LapDN suggests the right side is used in less than 10% of cases [51,57,58]. This relative paucity of experience relates to concerns over the operative safety of the right-sided laparoscopic operation, primarily the difficulties involved in obtaining the full length of the right renal artery and an adequate length of the short right renal vein.

Most centers initiating LapDN programs therefore limit their initial procedures to left-sided kidneys. Some surgeons have raised concerns that this practice has led to compromise of the maxim that the better kidney remains with the donor [59]. Pregnancy-associated pyelonephritis and hydronephrosis are more common in the right kidney [60,61] and some centers consider age and gender (female) a specific indication for right-sided donation in individuals with two normal kidneys [59].

In a multicenter review of 97 right tran-peritoneal LapDN, Buell and colleagues describe the most common reasons for using the right kidney as having: multiple vessels on the left side (59%), small right kidney (8%) and right renal cyst(s) (5%) [58]. A 14% complication rate comprised three open conversions, two liver lacerations, one vena cava bleed, two recipient graft losses from renal vein thrombosis and three upper pole arterial injuries.

Lind and colleagues report a historical review of 73 right and 28 left laparoscopic procedures, with no significant differences in any donor or recipient parameter [62]. This lack of difference was confirmed by Posselt and colleagues in 54 right and 333 left LapDN [63]. In both studies, operating time was significantly less for right DN, as also found in Leicester. This may be due to the splenic flexure dissection can be difficult and time consuming, and less colon mobilization is required to adequately visualize the ureter. Furthermore, the venous anatomy tends be less complex on the right.

Johnson and colleagues describe 15 right DN with hand-assisted laparoscopy, and despite two cases of delayed graft function, final graft function was equal to historic left sided grafts [64]. Use of stapling devices on the renal vein leaves a line of staples on both the graft and patient side of the vessels. When staples are trimmed, approximately 5 mm of vessel length is lost. Additional length can be safely acquired by using a single Hem-o-lok® (Teleflex Medical) on the renal artery, a single Endo-TA® (US Surgical) stapler (which has only one line of staples) on the renal vein, dividing the vessels with scissors and leaving the graft-side of the vessel unsecured [65]. Other techniques include the use of inter-aortocaval renal artery dissection to maximize the right renal artery length [29,66]. Mobilization of the right lateral and posterior aspects of the vena cava through division of short lumbar veins and medial retraction of the cava to expose the right lateral aortic surface exposes the right aortorenal junction and facilitates harvesting of maximum artery length (Figure 6).

This maneuver also allows the vein to be placed on slight traction, permitting division on the renocaval junction. In 20 consecutive right sided hand-assisted procedures, this technique gave a mean renal vein length of 2.5 cm (compared with 2.7 cm by right-open operation) and renal artery length of 3.6 cm (compared with 3.7 cm by right-open operation) [29].

These adaptations in right LapDN mean that many centers have reverted to a Pfannenstiel incision for organ extraction. The upper quadrant muscle cutting incision (Figure 7) is generally not now required to allow harvesting of adequate vessel length.
Economic considerations

In two US studies, laparoscopic donation was marginally more expensive than open surgery (US$10,310 vs. $9850 [16] and $11,072 vs. $10840 [67]), but the QoL for the donor was higher. Mackey and colleagues estimated productivity loss was US$4600 less in laparoscopic compared with open donors [68]. Moreover, by potentially increasing organ donor rates, LapDN is likely to offer an overall cost saving by reducing the number of patients on dialysis [16]. For the hand-assisted technique, theater costs are greater than with the open operation [31]. This is accounted for by the pneumosleeve and endovascular stapling devices, but is countered to some extent by a shorter hospital stay. Furthermore, loss of occupational income in the hand-assisted donors was 75% of that in the open-donor group. With all these factors taken into consideration, there are no significant differences in the overall cost of the hand-assisted and open procedure.

Training

Training issues in minimal-access DN are likely to arise as patient demand increases. We have recently surveyed all renal transplant centers in the UK and Ireland and, whilst half of the units offer trainees the opportunity to undertake supervised training in open nephrectomy, only a small number of units perform LapDN, with consultants undertaking all of the work [69]. The widespread use of animal laboratories for training may account for the greater prevalence of the laparoscopic donation in the USA – there is no scope for this kind of training in the UK. Indeed, studies in swine demonstrated the safety and efficacy of the laparoscopic procedure before its introduction in humans. The technical difficulties of transperitoneal LapDN confer a particularly steep learning curve and the fact that lead clinicians themselves need to learn the technique precludes, at least initially, the involvement of trainees. It may be that the hand-assisted technique has a place not just as an alternative, but also as a technical stepping stone to the full laparoscopic technique.

Development of blood group-incompatible transplant programs

Until recently, it was felt that ABO blood group compatibility was a prerequisite for successful transplantation because of the risk of hyper acute antibody mediated graft rejection in noncompatible recipients and donors. A proportion of otherwise suitable live donor–recipient pairs will be blood group incompatible – such patients had not been transplanted but rather went onto, or remained on, the cadaveric transplant waiting list. Recently, the use of incompatible donor–recipient pairs has shown promise. This is particularly the case with A2 blood group donors (20% of blood group A Caucasians) transplanted into B or O recipients. A2 is expressed in a different form and at lower levels than the A1 subtype [1,70] and A2 kidneys are less likely to undergo antibody-mediated rejection at a given level of anti-A antibody [1]. If the recipient's anti-A antibody titer is low, the transplant can be performed without other interventions. If the titer is high, pretransplant recipient plasmapheresis to reduce antibody levels can result in safe transplantation. Alkhunazi and colleagues report 14 group O or B recipients of living or cadaveric A2 kidneys that received plasmapheresis and demonstrated a 1-year graft survival of 93% [71]. The use of non-A2 donors (mainly A1 or B), has been also explored [1,72]. In this setting, antibody titers are high. As well as pretransplant plasmapheresis, recipients require splenectomy (at the time of transplant) and post-transplant monitoring of antibody titers. Winters and colleagues [73] report their experience of 26 ABO-incompatible transplants at
the Mayo Clinic, USA. Conditioning consisted of plasma exchanges, intravenous immunoglobulin and splenectomy. Post-transplant immunosuppression comprised anti-T lymphocyte antibody, tacrolimus, mycophenolate mofetil and prednisone. No hyper-acute rejection occurred, and patient and graft survivals at last follow-up were 92 and 85%, respectively (mean follow-up: 400 days). Antibody-mediated rejection occurred in 46% of recipients, but was reversed in 83% by plasma exchange and increased immunosuppression. The authors suggest that controlled clinical trials are needed to identify the optimum conditioning for ABO-incompatible renal transplants. Although the majority of the antibody-mediated rejections were reversible, there may be an element of irreversible damage caused by such episodes. Furthermore, the graft survival rates are slightly lower than that expected for ABO-compatible transplants [74].

Tanabe and colleagues described 141 ABO-incompatible living kidney transplants performed between 1989 and 2001 [72]. Plasmapheresis was used to remove anti-A and/or anti-B antibodies before transplantation and splenectomy was undertaken at the time of kidney transplantation. Patient survival rates were similar between groups. Acute rejection episodes occurred significantly more frequently among recipients of ABO-incompatible grafts (85 of 141, 60%) compared with ABO-compatible recipients (377 of 777, 49%). The 1-, 5- and 10-year graft survival rates among ABO-incompatible recipients were 82, 76 and 56%, respectively. The graft survival rates among ABO-compatible recipients were 96, 85 and 67% at the same time points. There was a significant difference in the short-term graft survival rates between ABO incompatible compatible renal transplants but no difference in long-term graft survival. With the introduction of newer immunosuppressants, graft survival since 1998 has markedly improved – the 5-year graft survival rate is now more than 90% and is not significantly different from that of ABO-compatible cases. Almost all of the graft losses occur during the first year post-transplant. Thereafter, very few grafts are lost. Thus, the allograft seems to tolerate anti-ABO antibodies well over time (graft accommodation), despite the recurrence of serum ant-blood group antibodies and the persistence of blood group antigens in the graft [1].

**Development of donor exchange programs**

Despite the encouraging data from ABO-incompatible kidneys, there remains an element of risk from early graft loss and severe antibody-mediated rejection. Although not yet utilized in the UK, other countries have developed donor exchange programs as an alternative system. These enable simultaneous direct exchange between live donors (a paired exchange such that the two recipients are transplanted with ABO-compatible kidneys), or a live donor–deceased donor indirect exchange [75]. These arrangements yield an additional donor source for patients awaiting a deceased donor kidney. Every paired exchange transplant removes two patients from the waiting list and thereby increases access to deceased donor kidneys for the remaining candidates on the list [75].

**Direct exchange**

With direct live donor exchange relative inequalities are still possible. For example one donor may be older than the other, but as the exchange is direct there is no negative impact on the cadaveric waiting list, apart from allowing two recipients the possibility of not entering the list and thus reducing pressures.

**Indirect exchange**

If an intended recipient has a potential but ABO incompatible live donor, the donor can donate to a patient at the top of the cadaveric waiting list. The recipient originally paired with the live donor assumes a priority position on the cadaveric waiting list, but still remains behind zero HLA mismatched and sensitized donors, and children. The potential inequality is the swap of a live-donor kidney for a cadaveric one. Further, if the living donor’s intended paired recipient is blood group O, they are placed ahead of other group O recipients who already wait longer than those with other blood groups do. This kind of exchange is a rare occurrence.

**Nondirected donation**

The consensus in western democracies has been that live organ donation should be between genetically or emotionally related individuals. However, with the increasing shortage of organs for transplantation some transplant programs have both considered and developed nondirected donation programs whereby individuals donate kidneys for financial gain or a more complex emotional reward. Iran has virtually eliminated a kidney transplant waiting list by...
offering a compensated, state-regulated system of unrelated donation [76], whilst some centers now offer healthy individuals the opportunity of ‘altruistic’ donation [77–79]. Proponents of these schemes argue that state-regulated unrelated donation, in the current climate of supply and demand, is the only way to stem the tide of unscrupulous ‘black market’ organ traders exploiting donors and recipients [80]. Opponents suggest that the difficult ethical questions raised by nondirected donation are insurmountable.

**Expert commentary & outlook**

Live kidney donation is assuming an increasingly prominent role in renal transplant programs in response to the persistent rise in the number of patients requiring definitive treatment for end-stage renal failure. Minimally invasive DN was introduced to reduce the donor disincentives associated with the traditional open operation. A number of concerns have surrounded the introduction of this technique, but with attention to certain points of technique, graft outcomes equivalent to the open operation are achieved. Many potential donor–recipient pairs are blood group incompatible, which has precluded transplantation in the past. New approaches to circumvent the blood group barrier include organ exchange programs and ABO incompatible transplantation, possibly with preconditioning of the donor using plasmapheresis and splenectomy where appropriate. The risk of antibody-mediated rejection is high and it is still not clear from the literature whether graft survival is equivalent to ABO-compatible transplantation.

**Highlights**

- Laparoscopic donor nephrectomy is widespread in the USA, but few centers in the UK offer the procedure. Training issues are likely to arise as demand for minimal access surgery increases.
- The most common minimal access technique is a classical transperitoneal laparoscopic operation. The hand-assisted laparoscopic and retroperitoneal approaches may have advantages in certain settings.
- Concerns over allograft damage during minimal access donation do not seem to be founded, as long as certain operative principles are adhered to.
- ABO incompatible transplantation is possible using A2 blood group donors, and B or O recipients. A1 recipient into a B or O donor requires recipient pre-conditioning with plasmapheresis (to remove anti-blood group antibodies) and splenectomy.
- In some countries, recipients with a potential but ABO-incompatible live donor can enter donor exchange programmes. Kidneys are swapped between donor/recipient pairs so that each receives a compatible kidney, or a kidney is donated in exchange for a priority position on the waiting list.

**Bibliography**


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