A randomised controlled trial of conventional open versus laparoscopic-assisted live donor nephrectomy for renal transplantation.

Thesis submitted for the degree of

Doctor of Medicine

At the University of Leicester

By

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STATEMENT OF ORIGINALITY

This dissertation has been produced from my own individual work at the University of Leicester Department of Surgery from 2002-2003.

Mr Gareth R.R. Lewis
MBChB MRCS

Publications from data collected for this thesis

Papers

A Prospective Comparison of Traditional Open, Minimal incision, and Laparoscopic Donor Nephrectomy.
GRR Lewis, JR Waller, NR Brook, JC Bains, PS Veitch, ML Nicholson
Transplant International, October 2004, Vol 17(10): 589-595

A prospective study of the predictive power of spiral CT in delineating renal vascular anatomy for live donor nephrectomy.
GRR Lewis, K Mulcahy, NR Brook, PS Veitch, ML Nicholson.
BJU International, November 2004, Vol 94 (7): 1077-81

Published abstracts

A prospective comparison of open and laparoscopic live donor nephrectomy.
JR Waller, NR Brook, GRR Lewis, J. Thompson, PS Veitch, ML Nicholson.
Nephrology Dialysis Transplantation 2002; 17 (suppl 1) 38.

A prospective randomised controlled trial of laparoscopic and open donor nephrectomy: Effects on post-operative respiratory function.
JR Waller, NR Brook, GRR Lewis, J Thompson, PS Veitch, ML Nicholson.
Nephrology Dialysis Transplantation 2002; 17 (suppl 1) 185.

A prospective comparison of open and laparoscopic live donor nephrectomy.
GRR Lewis, JR Waller, JC Bains, R Elwell, SA white, PS Veitch, ML Nicholson.
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Laparoscopic live donor nephrectomy: The first forty cases from a single centre.
GRR Lewis, NR Brook, JR Waller, SA White, PS Veitch, ML Nicholson.
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A prospective study of the predictive power of spiral CT in delineating renal vascular anatomy for live donor nephrectomy.
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Laparoscopic donor nephrectomy yields kidneys that are structurally and functionally equivalent to those procured by open surgery: results of a randomised trial.
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Abstract

The use of live donors in renal transplantation is an area of rapidly expanding interest. This interest has been driven by the continuing fall in available cadaveric organs for transplantation. Live donor renal transplants accounting for twenty six percent of renal transplants in 2003, contrasting with an eight percent rate some ten years previously.

Traditionally kidneys have been harvested from donors via a loin incision with partial resection of the tip of the twelfth rib, which placed a considerable burden on the donors in terms of post-operative pain, absence from work, and morbidity. A new minimally invasive laparoscopic technique was developed in 1995, which promised to lessen this burden placed upon the donor. Several non-randomised comparative studies have shown this new technique to hold promise in terms of less pain, and faster inpatient and outpatient recovery, with no apparent loss in quality of the graft harvested.

Both pure laparoscopic and hand-assisted laparoscopic techniques are described, and two randomised trials have been published comparing a hand-assisted technique to the more traditional open technique. No study to date has compared a pure laparoscopic technique versus an open technique without resection of the twelfth rib.

Our study showed a significantly shorter hospitalisation following the laparoscopic technique, associated with less pain on day one after the procedure. There were other favourable trends demonstrated with the laparoscopic technique, but larger trial numbers

would be required to render these significant. No increase in donor morbidity, or difference in graft morphology, and graft function in the recipient was demonstrated.

In conclusion, we have demonstrated that in the correct hands, laparoscopic live donor nephrectomy is a potentially superior donor procedure, with provision of equivalent quality allograft when compared to the traditional open procedure.

1) Introductory Chapter

1.1 Introduction to living donor renal transplantation

Renal transplantation is still the most effective and cost efficient form of renal replacement therapy for patients with renal failure. The continuing decline in the number of cadaveric renal donors worldwide has led to a search for alternative sources of organs, to help bridge the widening gap between the numbers of patients on transplant waiting lists and the number of renal transplants being performed each year. Kidneys from non-heart beating donors (NHBD) in both a controlled and uncontrolled setting have shown promising results in some centres[1;2], and in 2004 accounted for 7.7% of all transplanted kidneys in the UK. This translated as a 31% increase in the number of non-heart beating kidneys from 2003-2004, and was secondary to the implementation of twelve new NHBD programmes in the UK (UK transplant figures). However, the effort and cost of creating and co-ordinating such a retrieval system is considerable[3].

The fastest growing source for alternative kidneys for transplantation at present is from live donors. The first successful renal transplantation from a live donor was performed in 1954 by Murray and colleagues at the Peter Bent Brigham Hospital, Boston, from one identical twin to another [4]. Despite ethical reservations of subjecting a perfectly healthy human being to a major operative procedure, and the subsequent long-term risks of surviving on a single kidney, this technique has enjoyed increasingly popularity. In 1993, the proportion of renal transplants from live donors in the UK was 8%, this has increased to 26% in 2003, and of these, 76% were from related donors, and 24% from unrelated donors (UK transplant figures).

The advantages of live renal transplantation are:

1) The procedure can be planned electively, avoiding the semi-emergency status associated with cadaveric and NHB kidney transplantation.
2) Most patients with pre or established renal failure have a potential source of a kidney from a compatibly matched relative or loved one
3) It has the highest 1, 3, and 5 year graft survival rate, and the lowest rate of primary graft non-function and delayed graft function
4) Recipients can be medically optimised, and it allows commencement of immunosuppressive therapy in advance of their transplant.

Its disadvantages are:

1) That a healthy individual has to undergo a major operative procedure, and is exposed to the associated mortality and morbidity of a donor nephrectomy.
2) Kidneys procured from live donors do not possess a Carrel aortic patch, which makes them technically more challenging to implant.
3) Financial loss to both the donor and their employer, from time off work
4) The ethical issues associated with donation, particularly from individuals without purely altruistic intentions.

1.2 Improved results with live donors

Renal transplantation using grafts from live donors give superior results when compared to cadaveric and non-heart beating grafts. The one, three and five year survival rates of live donor grafts are 94-97%, 87-95%, and 78-86%, compared to 88-97%, 75-76.5% and 64-75% for cadaveric grafts[1;5-8]. This compares with a five year survival of 46-79% for NHBD grafts[1;9]. Despite improved graft function, this does not confer improved patient survival[7]. Initial function graft function rates are highest in live donor grafts (93% vs 77% cadaveric vs 7% non-heart beating), and primary graft non function rates lowest (2% vs 3% cadaveric vs 7% non-heart beating)[1].

1.3 Mortality and morbidity

A perfectly healthy individual undergoing a unilateral nephrectomy is subject to risk. The overall mortality in series of 3000 to 10,000 donors in the USA has been quoted to be 0.03% -0.06%[10]. The most common causes of death were pulmonary embolus, myocardial infarction, and cardiac arrhythmia. Overall, at least 17 live donors in the states have died from causes relating to their nephrectomy. Severe complications occur with a frequency of 0.23%-4.4% (pulmonary embolus, re-operation secondary to bleeding, pneumothorax, splenic injury), and less severe complications in up to 15% (wound infection, chronic pain, incisional hernia)[11].

Long-term morbidity is more difficult to quantify due to the selected population of medically fit donors, and for this reason live renal donors have better long-term survival, and lower incidence of end-stage renal failure than the general population[12]. Unilateral nephrectomy has been shown to increase systolic and diastolic blood pressure marginally,

but, whether or not it increases the prevalence of hypertension in these groups is debated[13-16], but when compared against sibling controls, there is no increase.[16] It is also associated with non-progressive microscopic proteinuria[13;16], and an initial decrease in glomerular filtration rate (GFR). However, the GFR improves steadily after this expected initial fall, and progressive deterioration in renal function does not occur[13] .

Morbidity from flank incisions is also significant. In a follow up of 871 donors, there was an 8.2% overall post-operative complication rate. These consisted of pneumothorax (1.5%), wound infection (2.4%), pneumonia (1%), unexplained fever (1.3%), operative blood loss >750ml (0.9%), readmissions (0.3%), urinary tract infection (0.3%), atelectasis (0.3%), and a single uncomplicated enterotomy (0.1%). However, only two serious complications arose (retention of a swab, and a femoral nerve injury), and no donors were re-explored for bleeding or suffered deep wound infections[17]. Long term wound complications are common, with incisional hernia/bulge occurring in up to 7%[18], and significant bother related to wound pain in 25%. The same study reported patient dissatisfaction in scar location (11.5%), unsightliness of scar (9.6%), and length of scar (5.8%)[19].

Of donors undergoing flank incisions, 86% of donors state that the decision to donate was their own, and less than 1% of donors regretted their donation. However, 34% stated they took between 3 and 4 months to get over the procedure, 5% stating that they had never recovered fully[20].

The minimal incision open approach has recently emerged as a less invasive alternative to the traditional flank incision. This is performed either by a loin incision, or by a shorter, laterally placed sub-costal incision. A retroperitoneal approach is maintained, and rib resection is not required. This modified technique has been shown to have benefits in terms of reduced analgesic requirements, shorter incision length, and shorter inpatient stay compared to the traditional operation[21]. A reduction in wound morbidity is yet to be supported by evidence.

1.4 Laparoscopic live donor nephrectomy

The laparoscopic technique was introduced in 1995 by Ratner and colleagues at Johns Hopkins University School of medicine, Baltimore, in an effort to reduce the burden placed on live donors[22]. It potentially offers faster recuperation, with minimal disruption to family and work commitments. The first procedure was performed on a forty-year-old male, as a purely laparoscopic procedure. The graft was removed via a 90mm infra-umbilical incision, and functioned immediately in the recipient. The donor was discharged on the first post-operative day[22]. Since then, it has enjoyed increasing popularity, with 84% of the 31 largest US centres offering the procedure by 2000[23], and over 200 centres worldwide offering the procedure[24]. This approach has been embraced less enthusiastically in the UK, with only 21% of UK centres performing live renal transplants offering LDN in 2002[25]. This is, in part, due to lack of level one evidence of the benefits and safety of the procedure, and also the technical difficulty of performing this approach.

Two randomised trials of pure LDN versus the open procedure have been published to date[26;27]. The first of these was a study of eighty donors, and failed to show significant benefit, lacked detailed donor/recipient outcome, and had a high rate of splenic injury (5%) in the laparoscopic group. This is in stark contrast to several other studies with either historical control groups, or non-randomised series. These have consistently demonstrated shortened inpatient recovery, less analgesic use, shorter hospitalisation, better cosmetic outcome, reduced blood loss, and more rapid return to normal activities compared to the open technique[28-45]. This was supported by the recent publication of the second randomised trial, which compared 100 donors, and found that the laparoscopic procedure was associated with less post-operative pain, shorter hospitalisation, less blood loss, and yet with comparable complication rates. They also concluded less physical fatigue, and better physical function at one year post-nephrectomy. However, these benefits were at the expense of a longer procedure, and a significantly longer first warm ischaemic time[27].

Two additional randomised trials have compared a hand-assisted laparoscopic technique versus the open[46;47]. These concluded that donors undergoing hand-assisted LDN had a reduction in analgesia requirements, shorter hospitalisation, and shorter recovery. However, this was at the expense of a longer, more expensive procedure, shorter graft vessel length, and a prolonged first warm ischaemic time. More concerning was the 8% major complication rate of LDN in the Norwegian series. These donors all required re-operation, versus none in the open group.

The impact of LDN on live donor activity in the US has been marked. In one major US transplant centre, the implementation of a formal live donor education programme, and introduction of LRD has doubled the number of live donor transplants performed[48]. Up to 25% of donors 2 years after the introduction of the new technique stated that they would not have donated if the open procedure was the only option[49].

The operative cost of LDN is greater than ODN (+$1000), but when shortened hospitalisation and faster return to work are taken into consideration, overall costs are lower than ODN[50;51]. Additionally, when increased donation rates and a reduction in patients requiring dialysis are considered, then LDN begins to look an attractive option.

1.5 Disadvantages and concerns over laparoscopic approach

The most pressing concerns regarding LDN are its safety for the donor, and secondly, whether graft quality is compromised by the minimally invasive approach.

Major intra-operative complication rates are quoted at 2%, these consisted mainly of vascular injury (86%), the remainder bowel injury. This explains the transfusion rate of 1.6%. Minor injuries occurred in 6.8%, including uncomplicated splenic laceration, liver laceration, pneumothorax, diaphragmatic injury, conversion for obesity, stapler misfire, airway difficulties, difficult extractions, cardiac arrhythmia, and retained fragments of retrieval bag. Overall conversion rates are 1.6%, usually for haemorrhage[52].

Major post-operative complication rates are quoted as 2.3%. Complications include small bowel obstruction requiring re-operation, pancreatitis, retroperitoneal haematoma, atrial fibrillation, pneumonia, and sepsis/ARDS, in descending order of frequency. Minor complications occurred in 16%, including atelectasis, pulmonary oedema, urinary retention/infection, epididymitis, ileus, incisional hernia, thigh numbness, back pain, upper airway oedema, late depression, pleural/pericardial effusion, and abdominal pain.[52]

Comparisons of open and laparoscopic donor nephrectomy complication rates are difficult as each procedure has unique complications. A meta-analysis of comparative studies performed in 2003 commented that non-standardisation of reporting or grading of complications made comparison difficult. Quoted complication rates of 0-30% for LDN, and 0-35% for ODN illustrate this, however, none of the studies examined quoted statistically different complication rates between the two procedures[53].

Prolonged CO_2 pneumoperitoneum at 15mmHg or above has been shown in animal models to decrease renal blood flow by up to 70%, and potentiate renal dysfunction[54;55]. This decrease in renal perfusion can be corrected with intraoperative intra-venous fluid administration, but calculated creatinine clearance remains impaired despite these measures[55]. These effects are temporary in the donor, but there is concern whether this insult, combined with laparoscopic manipulation, injures the donor organ, or even predisposes it to increased risk of rejection[32;54;55]

It is accepted that the laparoscopic technique prolongs the first warm ischaemic time from an average of 2 to 4 minutes. This probably accounts for the slight compromise in immediate graft function with laparoscopically retrieved kidney grafts. This manifests itself as a higher serum creatinine at time of discharge (49.2% vs 44.9% with serum creatinine greater than 1.4mg/dL). However, this effect seems to be temporary, with graft function at one year identical to that of kidneys retrieved from open nephrectomy [56;57]. No difference in rejection rates between the two approaches has been observed[57]. Long term graft function and graft survival comparative data is yet to be produced.

There was initial concern over the significant increase in the incidence of ureteric complications in recipients of laparoscopically retrieved renal allografts[58;59]. This was thought to be secondary to denudation of the blood supply, following dissection and clip application prior to division. Fortunately this trend was reversed by a change in technique, involving a wider peri-ureteric dissection (including the gonadal vein), and use of an endovascular stapling device[58]. With the introduction of this modification, ureteral complication rates between LDN and ODN are now comparible[52;58-61]. Ratner et al also noted that the ureteric complication rate rose after introduction of the endocatch bag system for delivering the kidney from the abdominal cavity. This was thought to be secondary to closure of the drawstring around the incompletely contained ureter, resulting in a denuding crush injury. Once this was recognised, ureteric complication rates were comparable to the open procedure[61].

After initial reticence, right laparoscopic donor nephrectomy has emerged as an equivalent to the left sided procedure, and has the advantage of a shortened operative

time[62-64]. This is at the expense of renal vein and artery length (up to 1.5cm loss of vein if a linear stapler is used at the caval border), and hence a more technically challenging implantation[59;65]. However, no difference in rates of vascular complications in the recipients have been noted[62-64]. Techniques have been described to overcome both of these problems. The use of a laparoscopic modified Satinsky caval clamp, minimises renal vein length loss, but requires the cut border of the vena cava to be oversewn laparoscopically[65]. This is technically difficult, and has the potential for catastrophic blood loss if the clamp slips. Interaortocaval renal artery dissection has also been described for enhancing right renal artery length[66], but again carries potential risk of haemorrhage. Circumaortic left renal vein (9% of donors) does not preclude left laparoscopic donor nephrectomy[67], the posterior limb is commonly the smaller, and can be sacrificed without complication.

Recipient vascular and ureteric complication rates have been noted to be higher whilst the procedure was in its inception at those institutions[52;59;61]. This learning curve effect has been noted in other laparoscopic procedures, and is inversely related to the number of cases performed[68]. Operative exposure to the procedure has been shown to be the more important factor, with a clinically measurable improvement in trainees after as few as 13 cases as participant, or 6 as operative surgeon (hand-assisted laparoscopic donor nephrectomy)[68]. This effect was independent of trainee experience, which highlights the need for either a period of observation/assisitance in an experienced centre, or the presence of an experienced mentor. Ideally, LDN should be performed with two proficient laparoscopic surgeons present, as this has been shown to decrease both blood

loss and operative time[69]. The reduction in operative time is especially desirable in this setting because of the aforementioned concerns over prolonged pnuemoperitoneum[54;55].

1.6 Donor work-up

Selection of potential donors is dependant on the potential recipient's willingness to approach family members, or a spouse, with the idea of live donation. Potential donors should not be pressured, or feel obliged to donate, just because other family members are willing to donate themselves. Potential donors intentions should be strictly altruistic, and should not be motivated by personal gain, though this is difficult to quantify. If several potential donors come forward, then all are tested for blood group compatibility and briefly assessed as to their suitability as a donor. HLA matching is then performed to select the best-matched individual. Once matching has selected the first choice donor, they are subjected to a full medical and social history, and a thorough physical examination. Blood pressure measurements are taken on three separate occasions, and any borderline values are investigated with 24 hour monitoring. In our centre, controlled hypertension is not considered a contra-indication to donation. Blood samples are taken for laboratory analysis (U+E, LFT, bone, glucose, FBC, HIV, Hepatitis B & C, syphilis, toxoplasma, CMV, and EBV screening), and urine samples are tested for blood, glucose and protein.

A standard chest x-ray and 12 lead electro-cardiogram are also performed at this stage. Provided these tests and examination are normal, then detailed imaging of the kidneys, their vasculature and collecting system are obtained. This information is most commonly obtained with spiral computed tomographic angiography and a delayed abdominal scout

film, which confirms the presence of two kidneys, their position, absence of pathology, and details of the renal vascular anatomy. Left kidneys are harvested preferentially due to their longer renal vein. In the presence of multiple renal arteries or complex venous anatomy on the left side, the right kidney is harvested. If there is bilateral duplex arterial supply, or bilateral complex venous anatomy, then a DMSA split function nephrogram is obtained, and the kidney with least function is removed for transplantation. It is a rare occurrence that the vascular anatomy is so complex in both kidneys that it is technically unsafe or unwise to proceed to donation.

The most common reasons for not accepting a donor, in descending order, are ABO blood group incompatability, hypertension and/or renal disease, unwillingness of donor to proceed, heart/lung disease, obesity, latent diabetes, or death of the recipient during work up.[70]

Disincentives often cited by donors and potential donors are the risks of the surgery itself, post-operative pain, prolonged hospital stay and recovery, potential loss of earnings due to time off work, long term risks of unilateral nephrectomy, long term morbidity from the surgery, and concerns that they would not be able to donate to one of their children, should this be necessary at some point in the future[49].

1.7 Surgical Techniques

Traditional donor nephrectomy is performed via a muscle-splitting flank incision, with the patient in a lateral decubitus postion. A table bridge is implemented to open the space between the iliac crest and the sub-costal margin. The incision is made overlying the

twelfth rib and extended towards the umbilicus (approximately 150mm). Partial excision of the twelfth rib is performed to enhance exposure (see Figure 1.). On entering the retroperitoneal space, care is taken to preserve the integrity of the peritoneum, and it is swept forward to expose the kidney and its surrounding Gerota's fascia. This fascia can be removed with the kidney 'en-bloc' or can be incised, peeled away from the renal capsule, and left in-situ.

The operative exposure is maintained with retractors, and the ureter is identified at the lower pole of the kidney, slung, and mobilised distally, ensuring that the ureteric blood supply is not disrupted. The renal vein is then identified as the most anterior structure at the renal hilum, slung, mobilised, and its tributaries controlled, ligated and divided. The superior mesenteric artery, passing anteriorly over the vein as it descends from its origin, limits mobilisation of the left renal vein medially.

The renal artery is situated directly posterior to the vein, and is mobilised in a similar fashion back to its origin at the aorta. Commonly there is a small adrenal branch that needs to be controlled at this point. It is important not to dissect the renal artery at the renal hilum, as the ureteric arterial branch may be damaged, rendering the ureter devoid of a blood supply.

Once the vessels have been isolated, the kidney is freed from its posterior retroperitoneal attachments, the ureter is ligated at the pelvic brim, divided, and then decompressed with a small incision in its side wall. The renal artery, followed by the vein, are double ligated,

and divided. Ties are placed as far proximally as possible on the renal vessels to try and preserve maximal length for the anastomoses in the recipient.

Once the kidney is removed, it is immediately perfused with hyperosmolar citrate preservation fluid at 4°C until the effluent runs clear (approx 500ml), and placed in a bath of iced preservation fluid. Typically one surgeon will perfuse the kidney whilst another inspects the renal bed and vascular pedicles for bleeding. The ligated vessel stumps are oversewn with a non-absorbable suture. A drain is placed in the renal bed if required, and the muscle layer is then closed with a non-absorbable synthetic suture, and an absorbable subcuticular suture is placed in the skin.

A variation of the traditional open approach is via a more lateral placed incision, without resection of the tip of the twelfth rib (see Figure 2.). This gives comparable operative exposure, but is associated with less post-operative pain, and less wound morbidity[21]. In our centre the traditional approach has been abandoned in favour of this modified open approach.

The laparoscopic technique was first introduced into practice in 1995[22]. Since its inception it has enjoyed increasing popularity in the US, and is now becoming embraced by European transplant surgeons. The left laparoscopic nephrectomy is performed via a transperitoneal approach, with the patient in a modified left lateral decubitus position, again with a table break to open the space between the iliac crest and the costal margin (see Figure 3). A pneumoperitoneum is established with a Veress needle, placed at the

Figure 1. A traditional rib-resecting loin approach for left live donor nephrectomy

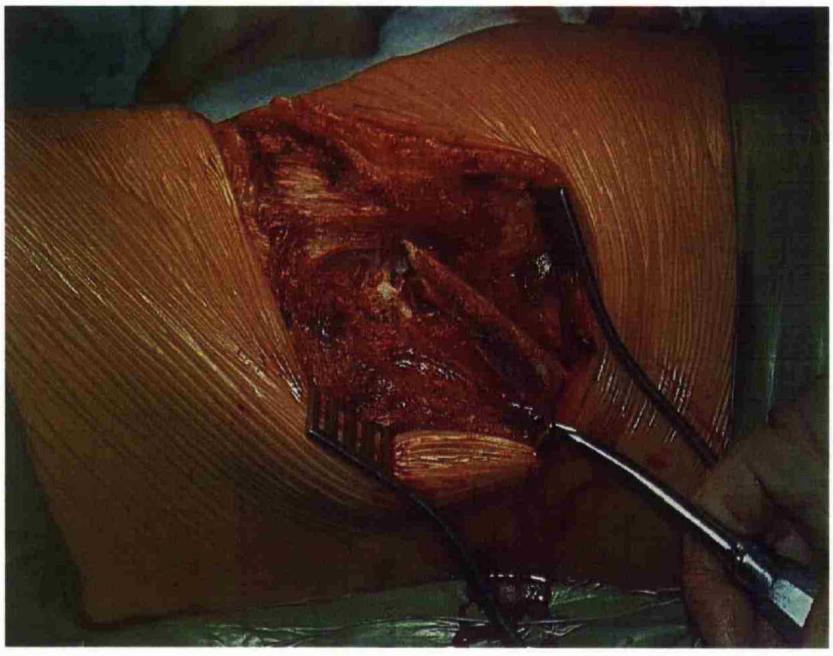
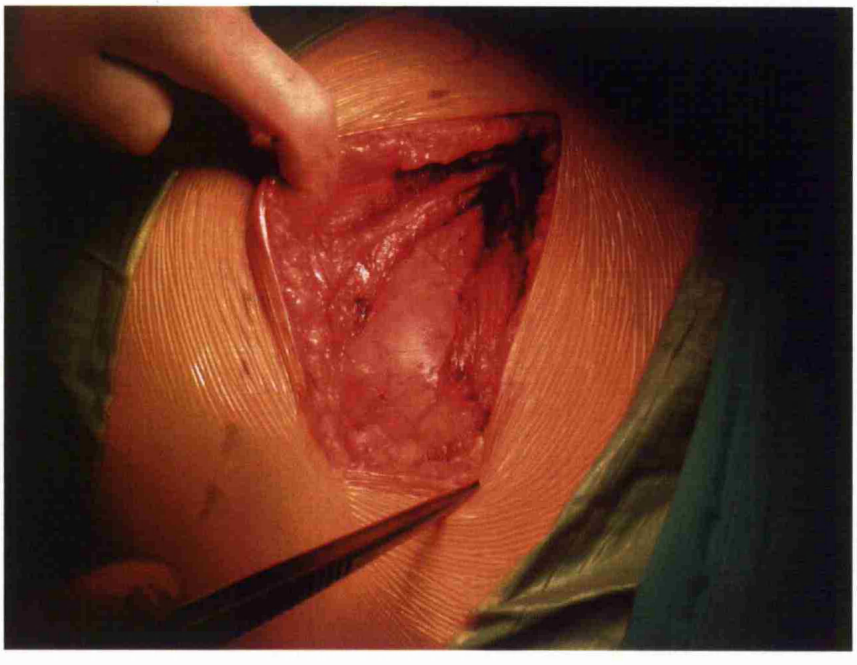


Figure 2. A non-rib resecting loin approach for left live donor nephrectomy



level of the umbilicus, at the edge of the rectus sheath (on the same side as the kidney being removed), and the peritoneal cavity insufflated to a pressure of 15mmHg. Four ports are inserted for dissection, 2x12mm ports in the midline (above/below the umbilicus and 2 fingerbreadths below the xiphisternum), 1x12mm port at the insufflation site, and a 5mm port iss inserted in the mid-axillary line, midway between the costal margin and the iliac crest. The umbilical port is used to house the video laparoscope, the epigastric and iliac ports are used for dissection instruments (see Figure 4.)

The colon is mobilised by dissection of the splenic/hepatic flexure, and division of the lateral peritoneal reflection. The colon is then medialised to expose Gerota's fascia, which is incised to expose the underlying kidney. The hilum is exposed to reveal the renal vein anteriorly, and more inferiorly, the upper ureter. Great care must be taken to preserve the ureteric branch of the renal artery at the renal hilum. The ureter is dissected first, taking care to include the gonadal vein during mobilisation in order to maintain a good margin of peri-ureteric tissue. The ureter is followed to the pelvic brim, where it is divided with an endovascular stapling device, and decompressed with a cut in the sidewall. The renal vein is then dissected free, and its gonadal, lumbar and adrenal tributaries secured with metal clips, and then divided. The renal artery is dissected back to its origin from the aorta and topical papaverine is applied to relieve any vasospasm. The remaining fascial attachments are divided to free the kidney.

The kidney is then manoeuvred into an endocatch retrieval bag (Tyco Healthcare Ltd, Gosport, UK), inserted via a short Pfannensteil incision. The pneumoperitoneum iss maintained with a pursestring suture in the peritoneum. The renal artery and vein are divided using an endovascular-stapling device, and the kidney removed via the Pfannensteil incision in the endocatch bag. The explanted kidney then has its staple lines excised, and is perfused in an identical manner to that for the open procedure.

The purse-string suture is then tied, and pneumoperitoneum re-established to inspect the renal bed. The Pfannenstiel incision is closed with a non-absorbable continuous suture to the rectus sheath, and a sub-cuticular absorbable suture to the skin. Port sites are closed with interrupted absorbable sutures to the muscle/fascia, and non-absorbable interrupted skin sutures.

Right laparoscopic donor nephrectomies required a modified approach to secure the renal vein. Port placement is a mirror image of that for the left side, and the technique for renal dissection remains unchanged. Once mobilised, a 6-10 cm transverse incision is made in the right upper quadrant instead of a Pfannensteil, and control of the vena cava is maintained with a partially occluding vascular clamp. This allows the full length of the relatively short right renal vein to be removed with the kidney. In these patients, the kidney is retrieved via the RUQ incision.

Figure 3. Picture showing lateral decubitus position for left laparoscopic live donor nephrectomy, port sites and Pfannensteil incision marked.

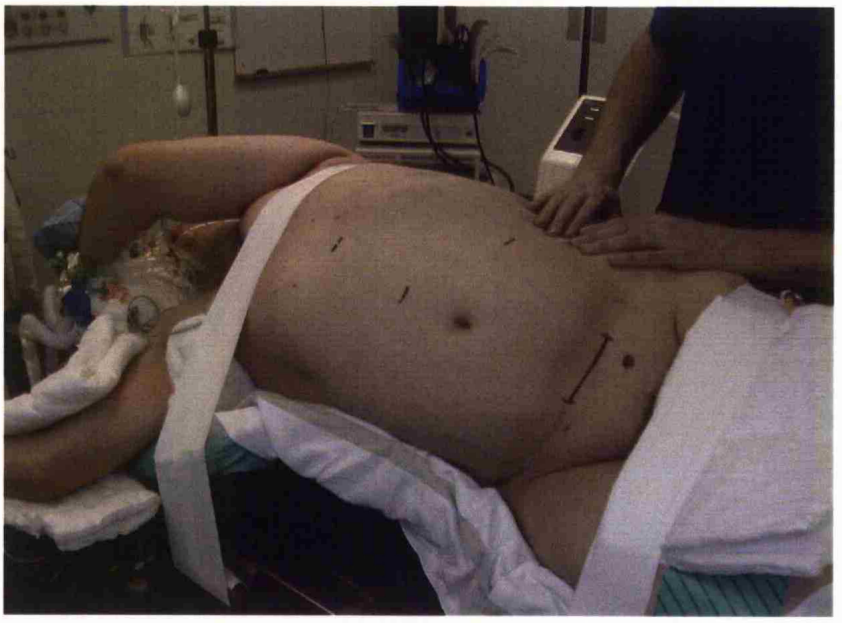
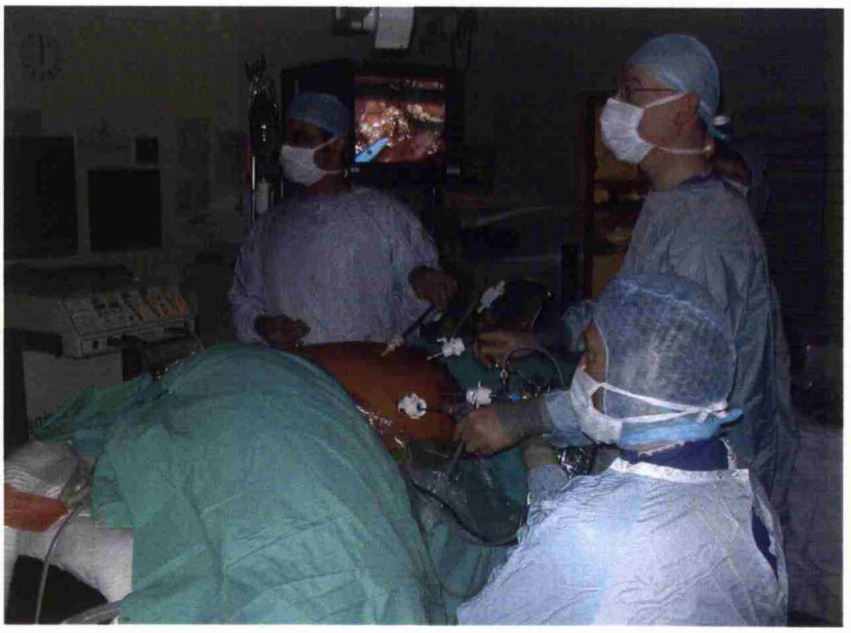


Figure 4. Picture showing port and surgeon placement during laparoscopic live donor nephrectomy



Kidneys are transplanted into the recipients via an extraperitoneal approach in the iliac fossa. The vein is anastomosed end-to-side to the external iliac vein, and the artery is anastomosed end-to-end (no Carrell patch) with the divided internal iliac artery. In those cases with multiple arteries, suitable branches of the internal iliac artery are utilised for anastomosis. The ureter is spatulated and anastomosed to the bladder as an extravesical onlay, over a double J stent.

1.8 Other new techniques

Hand-assisted laparoscopic donor nephrectomy is a variation of the pure laparoscopic procedure, where an airtight sleeve is utilised to allow one of the operator's hands direct access to the peritoneal cavity during dissection and retrieval. It has been shown to have the same advantages as the pure laparoscopic procedure compared to the open technique, but with the potential benefit of greater control over the vascular pedicle, shorter warm ischaemia, a shortened operative time when compared with the purely laparoscopic procedure[29;30;46;71;72]. It is also considered to be an easier procedure to learn, especially for those with limited laparoscopic experience[29]. Potential disadvantages are the less cosmetic, commonly used peri-umbilical midline incision, pneumoperitoneal CO_2 leakage from the sleeve, and forearm claudication in the surgeon. A randomised trial of these two popular minimally invasive procedures has yet to be published.

A retroperitoneoscopically-assisted technique has been described, which potentially allows donor nephrectomy to be performed via a shorter sub-costal incision. The largest

series reported by Yang et al, stated significantly shorter recovery, less analgesic requirements, and a shorter incision compared to the standard open donor nephrectomy[73].

1.9 Aims of the study

The aims of the study were to prove that these two minimally invasive procedures were superior to the traditional rib resecting technique. A three-way comparison of these techniques was undertaken (chapter two). This demonstrated clearly that the two minimally invasive techniques had better outcomes for the donors, but also showed that there was little difference between the minimal incision, and laparoscopic cohorts.

A further aim was to assess the accuracy of spiral computerised tomography in the assessment of donor renal anatomy, prior to donation. All donors were having dual phase scans, which allowed detailed arterial and venous assessment. In the laparoscopic setting, renal vein tributary anatomy is crucial to the procedure, as bleeding from these vessels can be very difficult to contain laparoscopically. We were keen to assess how accurate our specific donor reports were, when compared to the actual venous anatomy at the time of nephrectomy (chapter three).

The aim of the randomised study (chapter four) was to directly compare the two relatively new, minimally invasive techniques for donor nephrectomy. At the time of starting this project they had not been prospectively compared in a randomised trial.

The primary end points were proving the laparoscopic technique was safe, associated with less post-operative pain, faster donor recovery and recuperation compared to open minimum incision donor nephrectomy, and that graft function in the recipient was not deficient in the laparoscopic group. The secondary end points were to establish if there was any morphological difference in the grafts procured, or any demonstrable difference in physiological parameters between the two groups in the post-operative period.

2) A Comparison of Traditional Open, Minimal incision, and Laparoscopic Donor Nephrectomy

2.1 Introduction

Renal transplants from living donors have many advantages. The planned nature of the operation provides an opportunity to optimise both donor and recipient, and avoids a long waiting time. Live donor transplants also have the best allograft and patient survival rates[74]. A unique price has to be paid for these advantages as donor nephrectomy exposes an otherwise healthy individual to the mortality and morbidity of major abdominal surgery, entirely for the benefit of someone else.

Traditional open donor nephrectomy is performed via an extraperitoneal loin incision, with resection of part, or all, of the twelfth rib. A variation of this technique is to make a more lateral, subcostal incision, leaving the twelfth rib intact (minimal incision living donor nephrectomy). This approach has been associated with less post-operative pain, shorter incision length, and faster recovery when compared to the traditional open procedure[21].

Laparoscopically assisted donor nephrectomy was introduced into clinical practice in 1995[22], and this minimally invasive technique, along with the hand-assisted modification, have been associated with less post-operative pain, shorter hospitalisation, and faster return to normal activities when compared to the open technique via a loin incision[31;32;34-37;46;75]. The laparoscopic approach may remove some of the disincentives to donation and so increase donation rates[48;49]. The aim of this study was to compare donor recovery

rates and recipient allograft function after open donor nephrectomy with rib resection (ODN), minimal incision living donor nephrectomy (MILD), and laparoscopic donor nephrectomy (LDN).

2.2 Patients and methods

A consecutive series of 60 patients who underwent live donor nephrectomy, performed between 1995-2002 was studied. The study comprised of 20 patients in the ODN group, 20 in the MILD group, and 20 in the LDN group.

Between 1995-1998, all donor nephrectomies performed in Leicester were via the traditional open approach, with rib resection. The last 20 operations in this ODN series were compared to the first twenty MILD and LDN procedures performed in the period 1998-2002. The laparoscopic and minimal incision procedures were introduced at a similar time point. Donors were given informed consent on these two procedures, and allowed to choose.

The donor work up protocol included an isotope GFR measurement and either renal digital subtraction angiography (pre-1998) or spiral CT angiography to assess the renal vascular anatomy. The left kidney was removed preferentially, to provide longer vascular pedicles. In the presence of complicated vascular anatomy on the left, and normal anatomy on the right, the right kidney was removed.

All donors received 1 litre of crystalloid fluid intravenously in the twelve hours preceeding their nephrectomy, to improve renal perfusion during the procedure. Consultant surgeons carried out all donor nephrectomies, and consultant anaesthetists administered the general anaesthetics. Blood loss was assessed by measuring the content of the suction reservoir and by weighing swabs at the end of each operation but was not

recorded in the early part of the ODN series. Post-operatively, patients were managed using a patient controlled analgesia system (PCAS), delivering intravenous morphine in 1mg boluses with a five-minute lockout period. This was discontinued when it was felt that the patient could be maintained on oral analgesia alone. Patients were allowed to eat and drink when they felt able, and were discharged home when comfortable, ambulatory, and able to eat solid foods.

At the time of discharge donors were advised to return to normal activities as soon as they felt able. Donors were discharged with a simple diary sheet to record when they returned to the following activities: domestic tasks such as caring for the home and shopping; driving; exercising; feeling that they were able to return to work; actual return to work. The donors were reviewed in a dedicated follow up clinic six weeks after discharge from hospital.

2.3 The procedures

Two consultant surgeons working together performed all the nephrectomy operations in this series. Open nephrectomy with rib resection (ODN) was performed via a muscle cutting flank incision, with the patient in the lateral decubitus position and the operating table broken to open the angle between the iliac crest and the costal margin. The twelfth rib was exposed and partially or completely excised and Gerota's fascia was identified in the extraperitoneal space and dissected away from the kidney. The ureter was identified at the lower pole and dissected distally to the pelvic brim along with the gonadal vein in order to preserve the meso-ureter. The ureter was ligated with an absorbable tie and divided. The renal vein was then dissected free and its tributaries identified and divided.

The renal artery was dissected back to its origin from the aorta. The artery and vein were clamped and divided to remove the kidney. The renal artery stump was double ligated and oversewn with 5/0 polypropylene. The renal vein stump was oversewn with 5/0 polypropylene. The muscle layers were closed with a continuous 1 nylon suture and the skin was closed with a sub-cuticular absorbable suture. The incision was infiltrated with 0.25% Bupivacaine.

Minimal incision living donor nephrectomy (MILD) was performed through a muscle cutting flank incision running from the tip of the twelfth rib towards the umbilicus. The rest of the operation was carried out in the same way as the ODN procedure including the use of wound infiltration with 0.25%. A fixed retraction system (Omnitract, www. meddis.co.uk) was used during MILD nephrectomy.

Laparoscopic nephrectomy was performed via a transperitoneal approach, with the patient in a modified lateral decubitus position and a table break to open the space between the iliac crest and the costal margin. A pneumoperitoneum was established by placing a Veress needle through the incision for the ilac fossa port and insufflating the peritoneal cavity with carbon dioxide to a pressure of 15 mmHg. Three 12mm ports were placed in the midline above the umbilicus, two fingerbreadths below the xiphisternum and in the left iliac fossa at the edge of the rectus sheath at the level of the iliac crest. A fourth 5mm port was inserted in the mid-axillary line, midway between the costal margin and the iliac crest. The umbilical port was used to house the video laparoscope, the epigastric and iliac ports were used for dissection instruments and the 5mm port was used

for retraction. The colon was mobilised by dissection of the splenic flexure and division of the lateral peritoneal reflection. The left colon was then medialised to expose Gerota's fascia, which was incised to expose the underlying kidney. The ureter was dissected first, taking care to include the gonadal vein during mobilisation in order to maintain a good margin of peri-ureteric tissue. The ureter was followed to the pelvic brim, where it was divided with an endovascular stapling device. The renal vein was then dissected free, and its gonadal, lumbar and adrenal tributaries secured with metal clips, and then divided. The renal artery was dissected back to its origin from the aorta and topical papaverine was applied to relieve any vasospasm. The remaining fascial attachments were divided to free the kidney. The renal artery and vein were divided using an endovascular stapling device and the kidney was removed using an endocatch retrieval bag (Tyco Healthcare Ltd, Gosport, UK) introduced through a short supra-pubic Pfannensteil incision. This incision was closed with a non-absorbable continuous suture to the rectus sheath, and a sub-cuticular absorbable suture to the skin. Port sites were closed with interrupted absorbable sutures to the muscle/fascia, and non-absorbable interrupted skin sutures. The Pfannensteil and port site incisions were infiltrated with 0.25% Bupivacaine at the end of the procedure.

Right laparoscopic donor nephrectomies required a modified approach to secure the renal vein. In these patients (n=3), a 6-8 cm transverse incision was made in the right upper quadrant, and the vena cava was controlled using a Satinsky side-biting vascular clamp. This allowed the full length of the relatively short right renal vein to be removed with a thin cuff of vena cava. The caval defect was closed with a double layer of continuous 5/0

polypropylene sutures. In these patients, the kidney was retrieved directly through the right upper quadrant incision without using the endocatch system.

After removal, the kidney was placed in a bowl of iced hyperosmolar citrate solution and then perfused with 500ml of the same solution cooled to 4°C. The first warm time was recorded as the time between clamping the renal artery and the commencement of flushing with cold preservation solution.

The same consultant surgeon performed all the kidney transplants. The iliac vessels were approached extraperitoneally through a muscle cutting incision in the iliac fossa. The renal vein was anastomosed end-to-side to the external iliac vein using continuous 5/0 polypropylene sutures, and the artery was anastomosed end-to-end to the divided internal iliac artery using interrupted 6/0 polypropylene. In those cases with multiple arteries, suitable branches of the internal iliac artery were utilised for anastomosis. The spatulated end of the ureter was anastomosed to the bladder as an extravesical onlay, over a double J stent.

2.4 Data analysis

Data are presented as raw numbers or as a group mean ± SD. Continuous data were analysed by one-way analysis of variance (ANOVA). Where significant differences were demonstrated between the three groups, post-tests were performed using the Tukey-Kramer multiple comparisons test. Categorical data was analysed using χ^2 or Fisher's exact test. A P-value of <0.05 was taken as a significant result.

2.5 Results

Donor characteristics (table 1)

There were no significant differences in donor age, sex, weight or side of nephrectomy between the three groups.

Intra-operative variables (table 2)

The operative time for the laparoscopic approach was significantly longer than the other two groups. The first warm ischaemic time was significantly longer in the laparoscopic group but was limited to a mean of only 4 minutes compared to 2 minutes in both open groups. Intraoperative blood loss was numerically higher for ODN but this did not reach statistical significance.

Hospital recovery and analgesia (table 3)

There was no significant difference between groups in time taken to oral fluids but the time taken to recommence solid food was significantly longer in the ODN group. In-patient stay was significantly shorter in the LDN group (4.4±1.8 days), compared to both ODN (6.6±1.6 days) and MILD (6±1.1 days). Postoperative intravenous morphine requirements were twice as high as following ODN compared to both MILD and LDN. The duration of use of the PCA system was significantly shorter in the LDN group, when compared to both the open groups.

Table1. Demographic distribution of donors in the three groups studied

Characteristic	ODN	MILD	LDN	P Value
Age (years)	45 ±10	43±10	43±13	0.798
Female/Male	14/6	12/8	11/9	0.610
Weight (Kg)	68 ±10	73 ±11	71 ±13	0.488
Left/Right kidney	17/3	15/5	17/3	0.641

(Values are mean ± SD)

Table 2. Comparison of Intra-operative variables between the three groups

Variable	ODN	MILD	LDN
Operative Time (min)	121 ±24	147 ±27	232 ±35*
First warm ischaemic time (min)	2 ±2	2 ±1	4 ±1*
Blood loss (ml)	150# ±1439	200# ±195	300# ±185

(Values are means ± SD. # is a median value. * P<0.001 vs ODN and MILD)

= Traditional open donor nephrectomy with rib resection
= Minimal incision living donor nephrectomy
= Laparoscopic donor nephrectomy

Outpatient recovery (Table 4)

Twelve patients were not employed, and therefore did not give values for actual return to work. 7 did not drive, and 6 did not participate in any regular exercise. Two male donors did not participate in domestic tasks at home. LDN was associated with a quicker return to normal activities compared to ODN. Donors in the laparoscopic group returned to work and started driving, performing domestic tasks in the home and exercising earlier than donors in the ODN group. When compared to the MILD group, LDN patients started driving and exercising and returned to work more quickly.

Donor complications

There were no significant differences in the overall rate of donor complications following the three different operations. Eight complications occurred in the LDN group: unilateral pulmonary oedema in the dependant lung (n=2); chest infection (n=2); post-operative ileus; renal bed collection (treated conservatively); adhesional pain; and urinary retention. None of the laparoscopic procedures required conversion to an open operation. There were a total of 7 complications in the ODN group: haemorrhage from the ovarian vein requiring emergency laparotomy and blood transfusion; wound pain secondary to a suture granuloma; hypertension; persistently raised serum creatinine; proteinurea; and wound 'bulge'. Seven complications occurred in the MILD group: post-operative anaemia requiring blood transfusion; chest infection (n=2); persistently raised serum creatinine (n=2); prolonged wound pain; and wound 'bulge'.

Table 3. Comparative donor inpatient recovery following donor nephrectomy

Variable	ODN	MILD	LDN
Time to oral fluids (days)	1 ±0.4	1 ±0	1 ±0.2
Time to food (days)	3.5 ±1.5*	2.3 ±1	2.4 ±0.8
Inpatient stay (days)	6.6 ±1.6	6 ±1.1‡	4.4 ±1.8#
Total Morphine (mg)	182 ±113	86 ±48†	71 ±45#
Duration of PCA (hours)	55 ±18	53 ±14	41 ±12+

Values are means ± SD.* P<0.05 compared to MILD and LDN

† P <0.01 compared to ODN

‡ P <0.01 compared to LDN

# P <0.001 compared to ODN

Table 4. Comparative donor outpatient recovery following donor nephrectomy

Activity (weeks)	ODN	MILD	LDN
Felt able to return to work	12 ±8	7 ±6	5 ± 2*
Actual return to work	11 ±5	10 ±7	6 ±2
Driving	5 ±4	4 ±1	2 ±1*
Domestic tasks	4 ±3	2 ±1†	2 ±1
Exercise	13 ±14	5 ±2	4 ±1†

Values shown are means ± SD. * P <0.01 compared to ODN

† P <0.05 compared with ODN

= Traditional open donor nephrectomy with rib resection
) = Minimal incision living donor nephrectomy
= Laparoscopic donor nephrectomy

Recipient complications

There were no significant differences in the overall recipient complication rate. One transplant from the LDN group was poorly perfused on clamp release due to a dissection of the transplant artery. The kidney was explanted and flushed with cold hyperosmolar citrate solution. The dissected segment of renal artery was then excised and reconstructed using a saphenous vein graft. The transplant functioned immediately and the serum creatinine fell to the normal range on the fourth postoperative day. There were no other early vascular complications in the series. Two patients have subsequently developed transplant renal artery stenosis and required percutaneous transluminal angioplasty with stenting. These were both short peri-anastomotic stenoses that occurred after MILD and LDN.

To date, three ureteric stenoses have occurred (5%), two following LDN and one following MILD. The first case after LDN was thought to be secondary to an episode of vascular rejection treated by ATG. The whole length of the ureter was found to be markedly strictured 9 weeks after this early rejection episode. This was initially treated by anastomosing the ipsilateral native ureter to the donor renal pelvis but this anastomosis leaked due to necrosis of the renal pelvis and attempted Boari flap reconstruction was then performed, but there was insufficient renal pelvis to anastomose onto, therefore this was abandoned. The patient was subsequently managed with a percutaneous nephrostomy for a total of 44 months. The second case after LDN developed 4 weeks post-transplant in a patient with an ileal conduit. The stenosis developed at the ureter-conduit anastomosis and was very localised. This was successfully treated by balloon

ureteroplasty. The two cases that occurred in the LDN series led to a change in the laparoscopic technique for harvesting the ureter. This entailed a wider excision margin, with the gonadal vein being taken en-bloc. Since this modification, no further ureteric complications have occurred in our centres LDN recipients.

The third case, a long distal ureteric stricture, occurred three months post-transplant of a kidney removed by MILD nephrectomy. This was treated by performing a uretero-ureretostomy between the native and transplant ureters.

Early graft function

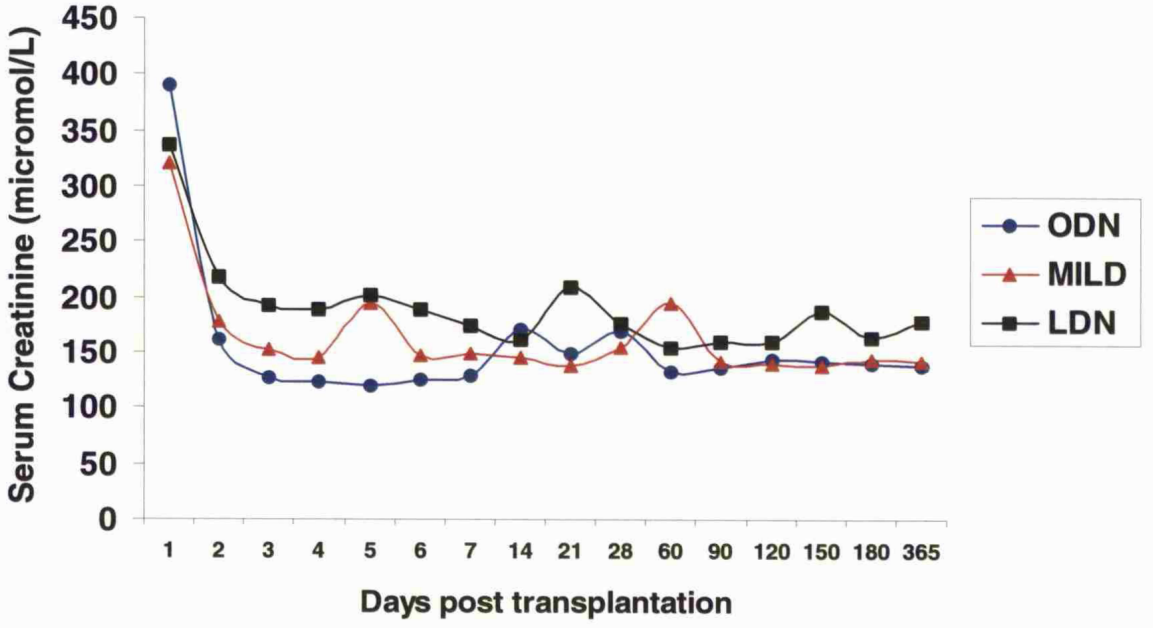
There were no episodes of primary non-function or delayed graft function in this series. Recipient serum creatinine values were numerically higher following LDN compared to both MILD and ODN, but there were no statistically significant differences between the three groups at any time point up to one-year post-transplant (Figure 1). We also assessed graft function by calculating the estimated glomerular filtration rate (eGFR = 186 x $(\text{Creat} / 88.4)^{-1.154}$ x $(\text{Age})^{-0.203}$ x (0.742 if female) x (1.210 if black). This again showed a non-significant trend in favour of the two open approaches. There was no significant difference in the incidence of graft rejection between groups.

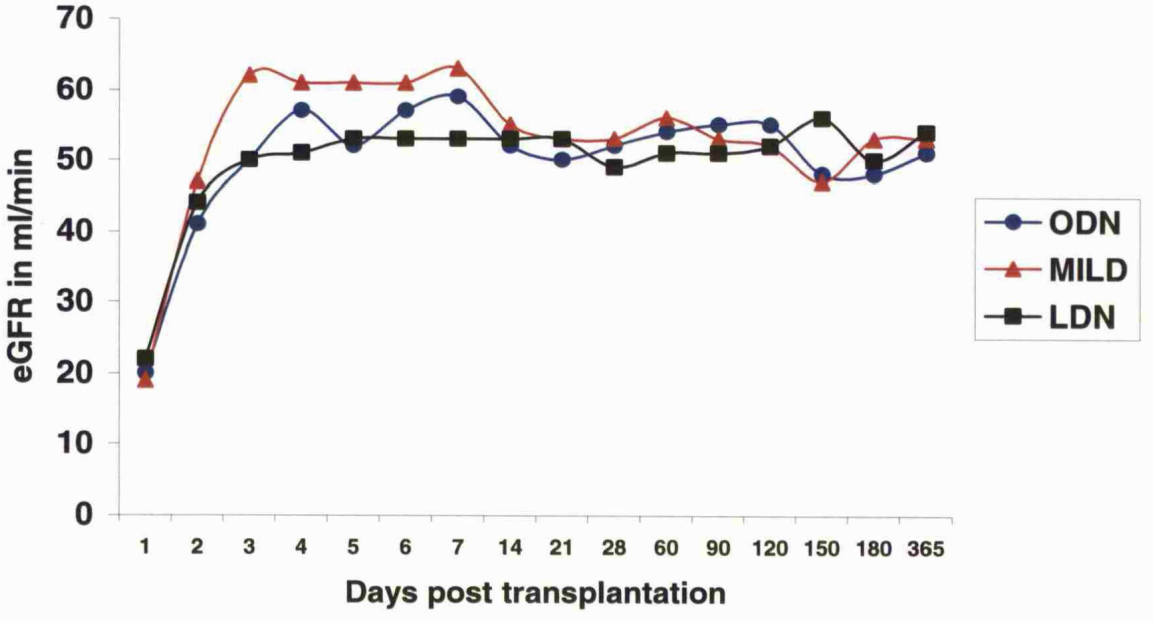
Graft losses

One recipient in the laparoscopic group underwent a laparotomy for small bowel perforation 5 days post-transplant. This was secondary to a loop of bowel being sutured into the wound closure, and was followed by a period of anuria secondary to severe acute tubular necrosis and the transplant developed accelerated chronic allograft nephropathy

(CAN) leading to graft loss 6 months later. Five further graft losses have now occurred (2 after LDN, 2 after MILD, 1 after ODN). The earliest of these was at 21 months secondary to recurrent focal segmental glomerulosclerosis, the latest was at 68 months secondary to CAN. The other causes of graft failure were: recurrent IgA nephropathy; accelerated CAN secondary to polyoma virus; and CAN following an early acute rejection episode treated with ATG and OKT3.

Figure 1. Comparison of allograft function between the three groups over first 12 months following transplantation. Function was estimated by serial serum creatinine measurement of the recipients at clinic visits, this was then used to calculate estimated glomerular filtration rates (eGFR).





Traditional open donor nephrectomy with rib resection
Minimal incision living donor nephrectomy
Laparoscopic donor nephrectomy

Table 5. Rejection rates in recipients

	ODN	MILD	LDN	P Value
Rejection Y/N	11/9 (55%)	12/8 (60%)	13/7 (65%)	0.81
Steroid resistant Y/N	9/2 (81%)	1/10 (10%)	6/7 (46%)	0.09

= Traditional open donor nephrectomy with rib resection
= Minimal incision living donor nephrectomy
= Laparoscopic donor nephrectomy

2.6 Discussion

This is the first study to compare donor recovery and recipient outcome after LDN and two different open nephrectomy procedures. Laparoscopic donor nephrectomy has several advantages when compared to traditional open nephrectomy with rib resection. LDN patients required less postoperative analgesia, were discharged from hospital earlier and returned to normal activities, including employment, more quickly. The laparoscopic approach also had advantages over minimal incision donor nephrectomy, including earlier discharge from hospital and quicker return to work. Donors undergoing MILD required less postoperative analgesia and a shorter in-patient stay compared to the ODN group.

The laparoscopic procedure had a number of disadvantages. The mean operation time for LDN was nearly 4 hours, compared to less than two and a half hours for both ODN and MILD. The first warm ischaemic time was also longer for LDN when compared to the open operations, although this did not have any adverse consequences in terms of early allograft function. The laparoscopic cohort being the first 20 cases performed (the 'learning curve'), probably confounded these disadvantages. This technique is technically more challenging to learn than the minimal incision group, which explains the large disparity in operating time.

The overall complication rates of the three types of nephrectomy were not significantly different but there were differences in the types of complication occurring. There were no conversions in the LDN series and no requirement for blood transfusion. The two

cases of unilateral pulmonary oedema may have been related to the per-operative administration of several litres of intravenous crystalloid fluid. This initial protocol was developed in an attempt to maintain adequate renal perfusion in the face of a prolonged pneumoperitoneum held at 15 mmHg, but has now been abandoned in favour of a less aggressive fluid regimen. One patient in each group suffered a postoperative haemorrhage. The episode following LDN was a small collection in the renal bed, which was treated conservatively. In the ODN and MILD groups the single episodes of bleeding were more serious requiring an emergency laparotomy with blood transfusion, and a blood transfusion alone respectively. After both of the open operations one patient developed evidence of wound herniation manifested as significant bulging of the wound. Whilst this complication was not seen following LDN, one patient in this group was admitted with abdominal pain ascribed to adhesions.

An important advantage of this study is that all the data, including information relating to recovery, was collected prospectively. The series describes the natural development of the local live donor programme and there was no selection of donors for LDN according to such criteria as weight and body habitus. The main limitation of this study is that it was non-randomised. In addition, the indices of donor recovery used were subjective and were difficult to interpret as so many factors, including the attitudes of the donors themselves and their hospital and family doctors, affect them. The time taken to return to work showed considerable variability and is likely to be influenced by the type of work done (sedentary or manual; self employed or not) as well as the personality type of the donor and the attitudes and policies of their employers. Donors were asked to record

when they felt able to return to full time work, as well as their actual return to work, in attempt to take account of some of these influences. After LDN donors returned to full-time employment in a mean time of 6 weeks and it is striking that this is comparable to the recovery from laparoscopic cholecystectomy[76].

The findings of the present study are in broad agreement with other published studies comparing LDN with open nephrectomy [27;31;32;34-37;46;47;47;75]. . These all show that LDN led to significantly reduced postoperative pain and quicker donor recovery rates. The main weakness of several of these studies is that the comparative open nephrectomy control groups were historical and some of the donor recovery data was collected in retrospect. The findings relating to the comparison of MILD and ODN are also in agreement with the paper by Yang et al[21] who demonstrated no difference in operative time or in-patient stay but a shorter duration of narcotic use in the MILD group.

LDN requires advanced laparoscopic skills and has not yet been introduced widely into surgical practice in the UK[77]. Modification of the technique to include a device that allows a hand to be introduced into the abdomen (hand-assisted or handoscopy) may widen the applicability of LDN. The hand-assisted approach is associated with less post-operative pain, shorter in-patient stay and a quicker recovery time when compared to open donor nephrectomy without rib resection[46;47]. This procedure is a distinct entity from the laparoscopic assisted approach, and further studies are required to compare laparoscopic nephrectomy, minimal incision donor nephrectomy, and hand-assisted

laparoscopic nephrectomy, as all three appear to have advantages over the standard open donor nephrectomy with rib resection [21;31;32;34-37;46;75].

There has been some concern that LDN leads to a higher urological complication rate in the subsequent recipient transplant [58;61]. The transplant ureter is particularly susceptible to ischaemic injury as its sole blood supply is the ureteric branch of the renal artery, which can easily be damaged during the donor operation. This may be particularly the case in the laparoscopic procedure and it has been suggested that the risk of vascular injury to the ureter is reduced if the gonadal vein and the ureter are mobilised together to provide a generous margin of peri-ureteric tissue[58;61].

LDN will not prove to be an advance if it simply transfers morbidity from the donor to the recipient. Its success must therefore also be gauged by the results of the subsequent transplant. Some studies have shown that LDN leads to a slower fall in recipient serum creatinine compared to ODN transplants[56;78]. This has been attributed to a longer first warm time and a fall in donor intraoperative renal blood flow and urine output secondary to a prolonged pneumoperitoneum[79]. All 60 live donor renal transplants in this series demonstrated initial graft function and there were no statistically significant differences in post-transplant renal function following the three nephrectomy techniques used in this series. However, the laparoscopic group did have a trend towards a lower eGFR, especially during the first week post transplant. This may be secondary to the prolonged pneumoperitoneum in this group, resulting in a more pronounced ischaemic insult to the graft.

This study suggests that laparoscopic donor nephrectomy is safe for the donor and does not significantly increase morbidity in the recipient. The benefits of LDN include reduced post-operative pain and shorter in-patient stay and recovery times. Open donor nephrectomy performed through a limited incison and without rib resection (MILD) also confers significant advantages on the donor when compared to open nephrectomy with rib resection and merits further investigation alongside the developing laparoscopic procedures.

3) A prospective study of the predictive power of spiral CT angiography for defining renal vascular anatomy before live donor nephrectomy

3.1 Introduction

Kidneys from live donors are increasingly used in renal transplantation in an attempt to address the shortfall in organs available from other sources. Pre-operative imaging of live donors is mandatory for a number of reasons; it provides confirmation of the presence of two functioning kidneys, identifies their position, indicates absence of pathology and provides anatomical information necessary for planning the procedure. The ideal form of imaging would be minimally invasive and acceptable to patients whilst providing accurate morphological information on the renal parenchyma, collecting system and vascular anatomy. It should also confirm the absence of pathology that would preclude donation[80;81]. Traditionally, imaging has been performed using a combination of angiography and excretion urography[80;82], but there are inherent risks in this invasive procedure[83]. Prolonged post-procedural observation is required for angiography, which is an inconvenience to potential donors and incurs additional costs to the transplant programme[84]. Furthermore, venous imaging is limited with arterial contrast injection[84], and separate excretion urographic studies are necessary to visualise the collecting system[81]. These disadvantages have been the driving force behind the introduction of spiral computed tomographic angiography (CTA) for anatomical assessment of living renal donors. CTA is relatively, non-invasive nature (with greater acceptability for patients), demonstrates improved resolution of both arterial and venous anatomy of the

kidney (including renal vein triburaries)[85-88], and is cheaper than other imaging techniques[84;85;89]. Pre-operative anatomical information is of course necessary for open donor nephrectomy, but assumes paramount importance in the laparoscopic procedure because of reduced exposure and field-of-view, and particular difficulties in the identification of complex renal vein tributaries (see figure 1). Therefore, the location, size and number of renal veins and tributaries need to be described pre-operatively.

Spiral CTA imaging compares favourably with conventional angiography in the prediction of renal arterial anatomy[89;90]. A number of studies have examined the accuracy of CTA for delineating gross venous anatomy, in terms of presence and position of multiple renal veins and/or adrenal veins[87;89;91-93]. This is the first study to describe the predictive power of spiral CT angiography for identification of renal vein tributary anatomy by comparing preoperative imaging with post-procurement findings in the setting of open and laparoscopic live renal donors. In particular, we investigated the prediction of lumbar tributaries, as these display the greatest intra-individual variation[94].

3.2 Methods

Forty live kidney donors underwent spiral CT renal angiography between March 1999 and October 2002, and were issued with reports detailing the venous tributary anatomy. Only one of the consultant radiologists issued such detailed reports, and was responsible for examining the majority of the live donor scans. All patients were assessed by physical examination and had completed blood group and HLA matching, and isotope GFR measurement prior to imaging. Computed tomographic angiography (CTA) was performed on a single spiral CT scanner (GE Prospeed SX power). The protocol (Collimation = 3mm; Table feed = 4-5mm; Rotation time = 1second) allowed assessment of both arterial and venous anatomy using a dual phase protocol. Arterial phase imaging was performed from the level of the coeliac axis origin to include the lower renal pole. Venous phase imaging was performed to include the cephalo-caudal extent of the left renal vein and the left renal sinus. The arterial phase scan was optimised to peak arterial enhancement by use of a test injection of 25mls iodinated contrast media (Iopamidol, 300mg/ml; Rate = 4mls/s.) and intermittent measurement of attenuation within the aortic lumen at the level of the renal arterial origin. The data acquisition scan was performed following an injection of 100mls of the same contrast media, and rate of injection and an inter-scan delay was calculated to allow initiation of the venous phase scan at 60 seconds.

The axial images were reconstructed to an interval of 1mm and the data transferred to a diagnostic workstation for analysis (GE Advantage Windows 1.2; Sun Sparc 20). The aforementioned consultant radiologist recorded data during review of both the axial images and 3D MIP reconstructed images. The reports were issued prior to the

commencement of this study, and therefore the reporting protocol was not amended to accommodate this study. The number of renal arteries and veins, and presence and diameter of renal vein tributaries were reported. Anomalies of the collecting system and ureter were analysed by a follow- through plain abdominal film 20 minutes after administration of intra-venous contrast for the CT.

Two consultant surgeons performed donor nephrectomies. Left kidneys were preferentially harvested (n=33) if vascular anatomy was uncomplicated. Indications for right nephrectomy were multiple left renal arteries in the presence of a single right renal artery (n=4), multiple renal veins on the left side (n=1), three renal arteries on the left in the presence of two on the right (n=1), and bilateral single accessory renal arteries with a subsequent DMSA nephrogram showing the right kidney had least function (n=1). After back-table perfusion of the harvested graft, the number of arteries and veins was recorded, along with the presence and diameter of renal vein tributaries. For analysis, back-table measurements were taken as the 'actual' measurements and pre-operative image data were taken as those 'predicted' by the CTA. Tributaries of 1mm or less were not included in the analysis as they were considered to be of less clinical significance than larger tributaries, and the 3mm collimation of the CTA made their prediction unreliable.

The data were used to calculate sensitivity, specificity, positive and negative predictive values, and overall accuracy of spiral CT in evaluating donor vascular anatomy. In addition predicted venous tributary diameter was compared against actual tributary

diameter, and a correlation coefficient calculated, expressed as a Kappa value. The closer this value was to 1.0, the better the correlation. Actual measured diameter of renal vein tributaries at nephrectomy was calculated as half the circumference of the vein, as measurements were taken with the vein collapsed, whilst measurement on CT interpretation involved examining the vessel in circular cross-section. Therefore, the formula *measured diameter of collapsed vessel/π X 2* was used to calculate the true diameter.

3.3 Results

Mean donor age was 46 years (SD ±11), and the majority (65%) were female. Twenty-five donors underwent the laparoscopic procedure (of which three were right sided), and 15 underwent an open procedure (four right sided). At nephrectomy, all forty kidneys selected for retrieval were found to be suitable for transplantation. There were no conversions to open operation in the laparoscopic group.

(i) Renal arteries and veins

From the total of 40 kidneys harvested, 48 renal arteries and 41 renal veins were demonstrated at donor nephrectomy. Of these, 47 arteries (98%), and 40 veins (98%) were predicted by pre-operative imaging. Eight accessory renal arteries were identified in seven kidneys at nephrectomy, seven of which were correctly predicted. Importantly, none of the kidneys with multiple arteries were predicted as having single vessels. One right kidney was predicted to have two arteries, when actually three were present. This was the only accessory artery not predicted in this series, and 2mm in diameter. The only accessory renal vein encountered in this series was in the same patient, and this was not predicted. On retrospective analysis of the images, the second vein was visible, but the third artery was not. None of the patients in this series were predicted as having, or subsequently found to have, a retro-aortic, or circumflex aortic renal vein.

(ii) Renal vein tributaries

The total number of renal vein tributaries found at donor nephrectomy was 88 of which 80 were predicted. However, nine of these were false positive predictions. Therefore, a total of 17 false negatives for renal vein tributaries were found in forty patients. Seventeen of the 40 CTA reports (42%) exactly matched operative findings for arterial, venous and venous tributary anatomy. Five scans had greater than one false positive or negative finding. A summary of the prediction of renal vein tributaries is shown in Table 1.

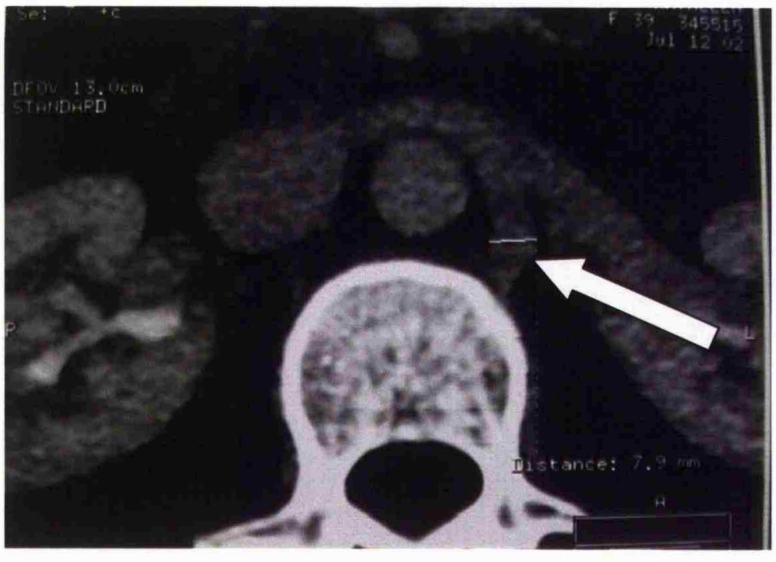
Gonadal veins

Thirty seven gonadal tributaries (all associated with left kidneys) were demonstrated after nephrectomy, of which 33 (91%) were correctly predicted. Four left kidneys had double gonadal tributaries. Two of these were correctly identified by CTA, the remaining two kidneys were predicted as having one, and no gonadal vein respectively. All 4 gonadal veins missed on CTA were 4mm or less in diameter. On retrospective review of the images, 2 were visualised (having previously been mistaken as mesenteric vessels), and two were not. CTA imaging predicted 4 second gonadal veins that were not actually present. On retrospective review of these four images, one may have been a misinterpreted lymph node on a single phase scan, another two may have been secondary to an unidentified common lumbo-gonadal trunk at surgery, and the fourth still looked convincing.

Table 1: Values for sensitivity, specificity, predictive value and accuracy of spiral CT angiography for the detection of tributaries of the renal vein in live renal donors

	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)	Kappa value
Gonadal veins	89	64	89	64	83	0.65
Adrenal Veins	82	88	96	57	83	0.59
Lumbar veins	65	81	76	71	75	0.47

Figure 1. A large posterior lumbar tributary of the left renal vein (arrowed)



Overall, CTA prediction of presence or absence of gonadal veins matched actual findings in 33 (83%) donors. All right kidneys (n=7) were correctly predicted as having no gonadal tributary of the renal vein.

Adrenal Veins

Thirty-three adrenal veins were demonstrated at nephrectomy (all in left kidneys), with 27 (82%) of these being correctly predicted. There were 6 false negative adrenal veins on CTA. Of these, two were second adrenal veins, the remaining four were single adrenal veins. Two kidneys had dual adrenal veins demonstrated at nephrectomy, both of which were predicted. Overall, 33 CTA scans (83%) matched actual findings for adrenal vein anatomy. Again, all right kidneys were correctly predicted as having no adrenal tributary of their renal vein. All 6 false negative adrenal veins were less than 5 mm in diameter, as measured after nephrectomy with the vein collapsed (1/2 circumference). On retrospective review of these images, one vein was difficult to discern due to the close proximity of the adrenal gland to the renal vein, and the other five veins were not visualised.

Lumbar veins

CT correctly predicted 13/20 lumbar vein tributaries (65%). The seven false negative lumbar veins ranged from 2-13mm in diameter. The largest of these was a lumbar tributary in a right kidney. This was the only right renal vein tributary demonstrated in the series, and on retrospective review of the images, was not visible. Of the remaining 6 (2-7 mm) false negatives, 5 were left single lumbar veins and one was a second lumbar

tributary. A total of four false positive lumbar tributaries were predicted, all of which were convincing on retrospective review of the images.

Retrospective analysis of the seven scans on which no lumbar tributaries were demonstrated, revealed five veins. Failure to identify these tributaries at initial reporting was due to oblique path/tortuosity of the vein (n=3), and a vein being mistaken as an arterial branch due premature venous phase contrast enhancement (n=2).

Eight patients were predicted as having a common lumbo-gonadal trunk; none of these were confirmed at nephrectomy. However, in five of these patients, false positive lumbar (n=1), 2nd lumbar (n=1), gonadal (n=1), and 2nd gonadal (n=2) veins were predicted.

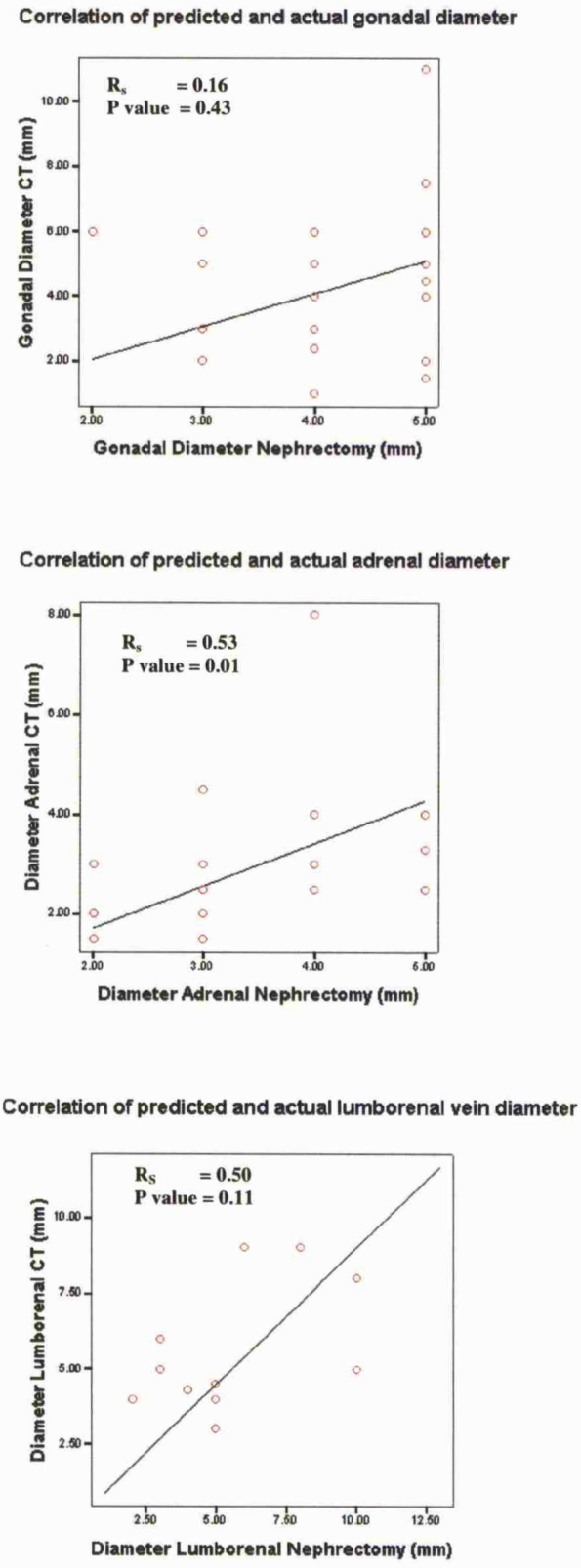
(iii) Vein diameter

For the gonadal veins (n=30), there was a weak correlation between actual and predicted diameter (Spearman's correlation coefficient (R_s) = 0.16, P=0.43). Correlation of predicted and actual adrenal vein (n=23) diameter was better (R_s= 0.53, P=0.01), with a similar (but non-significant) correlation for lumbar vein (n=11) diameter (R_s= 0.50, P=0.11). (see Figure 2).

(iv) Collecting system

All of the retrieved kidneys in this series were correctly predicted to have single ureters.

Figure 2. Graphs showing correlation analysis for tributary vein diameter measured pre-operatively by spiral CT angiography, and after kidney harvesting.



earman's correlation coefficient

3.4 Discussion

By examining renal vessel and tributary anatomy after donor nephrectomy, and comparing this to findings on pre-operative imaging, this study has examined the predictive power of spiral CT angiography in the setting of live donor nephrectomy.

This operation is increasingly employed for donor pool expansion in renal transplant programs, and a recent development has been the introduction of laparoscopic donor nephrectomy in an attempt to reduce disincentives for donation. This technique demands advanced laparoscopic skills and presents unique challenges, especially in the area of upper renal pole dissection and adequate visualisation of the superio-posterior and inferior aspects of the renal vein. It is at these points that variable venous tributaries, which need control and division, are found; prior information on the anatomy of these tributaries is therefore important for the surgeon. Donor imaging using spiral CT angiography is a powerful tool not only for detection of renal tract and parenchymal abnormalities and large vessel anatomy, but also for detection of smaller venous tributaries. Recognised venous variants include multiple veins (28% of right renal veins), right sided gonadal and adrenal veins entering the renal vein (rare), posterior lumbar tributaries entering the renal vein (right 3%, left 60-80%), left retro-aortic (3%) and circumaortic (17%) renal veins[80;94].

In terms of renal artery anatomy, 98% of the retrieved kidneys showed exact concordance with pre-operative prediction. Of the eight accessory arteries in this series, one was missed on CT evaluation and was not identifiable on retrospective examination.

On inspection of venous anatomy of the 40 kidneys, one right kidney had double renal veins, which was missed on initial scanning. Retrospective examination of the scans identified this accessory vein. Interestingly, in this series, one patient was identified with two left renal veins on imaging (which led directly to a right nephrectomy in this patient, so was unconfirmed). With the exception of circumaortic left renal vein, duplex renal veins on the left side are rare[94], and it was surprising to see this anomaly in a small series. Left kidneys with circumaortic or retroaortic renal veins were not encountered in this series. Indeed these abnormalities have not been encountered in our potential donors since the introduction of spiral CT angiography in our department in 1999, despite the quoted incidences of 17 and 3% respectively. Use of left kidneys with these venous anomalies for live renal transplantation has recently been reported, with no detriment to donor morbidity, or graft function[67]. In experienced hands, therefore, these anomalies cannot be considered contraindications to left laparoscopic live donor nephrectomy.

Overall, the findings of this study in terms of the predictive power of spiral CT angiography in detection of multiple renal vessels concur with other similar studies[84-86;89;91;93;95-97]. Left kidneys are procured preferentially due to their longer renal vein. It is primarily the presence of multiple arteries on the left side that leads to procurement of a right kidney with a single artery. This is due to the inferior results of transplantation of kidneys with multiple arteries[98]. Left renal vein anomalies alone are unlikely to lead to procurement of the right kidney, but the additional venous anatomical information gleaned by spiral CTA is still of considerable value to the operating surgeon. The posterior aspect of the left renal vein is particularly difficult to expose, and it is here that

avulsion injuries (and subsequent bleeding) to large venous tributaries can be difficult to control laparoscopically. Prior knowledge of such tributaries may lead to a more cautious approach, and indeed large tributaries of 10mm in diameter or greater, may need securing with endovascular stapling devices.

Because of the technical difficulties encountered when dealing with renal vein tributaries, especially in the setting of laparoscopic donor nephrectomy, this study has concentrated on the power of spiral CTA imaging for prediction of tributary anatomy. We report overall accuracies ranging from 83% (gonadal veins and adrenal veins) to 75% (lumbar veins). The relatively low accuracy for detection of lumbar tributaries of the renal vein, and the relatively poor correlation of actual to predicted diameter for this vein, are surprising given that it is generally the largest renal vein tributary (figure 5). Furthermore, owing to its position, it is perhaps the most difficult to control and divide, and failure to adequately control it results in bleeding that is particularly challenging to arrest.

It is well recognised that single spiral CT techniques offer lower spatial resolution in the cephalo-caudal axis than in the transaxial plane. Where the spiral is extended to reduce radiation dose, or where tube capacity of the scanner is limited, the effective slice width and partial volume averaging is increased. This could result in impaired demonstration of veins orientated in the axial plane, particularly if they are collapsed or poorly enhanced at the time of the examination. Multi-slice CT offers much higher resolution in this axis, and therefore might be expected to overcome this limitation.

Because we have included only those scans of patients who underwent donor nephrectomy, we have only been able to report the ability of spiral CTA to predict renal vein anatomy in kidneys that were subsequently retrieved. All imaging reports included details of both left and right kidneys, but only those removed could be compared directly with operative findings. Likewise, we were not able to report on the ability of CTA angiography for detection of renovascular abnormalities such as renal artery aneurysm or stenosis. Other studies examining CTA in potential live donors have shown it to be accurate at detecting aneurysms of the renal artery, but less reliable for the detection of stenotic lesions, particularly those secondary to fibromuscular dysplasia, when compared to conventional angiography[80;84;89;91;95;97;99;100].

The information required prior to donor nephrectomy encompases morphology of the renal parenchyma, outflow tract and vessels. In laparoscopic donor nephrectomy, limited operative visualisation, especially in the areas where small tributaries may be encountered, necessitates accurate pre-operative imaging. The accuracy of spiral CTA for prediction of these small tributaries ranges from 75 to 83% in this series; vessel diameter prediction correlates poorly with actual findings. These results suggest that although CTA is important and helpful in pre-operative planning, full operative dissection and complete visualisation of vessels is necessary, as the discovery of venous tributaries that have escaped detection by imaging is a common occurrence.

4) A randomised controlled trial of donor recovery and allograft outcome following laparoscopic and minimal incision open donor nephrectomy

4.1 Introduction

Laparoscopic live donor nephrectomy was introduced into practice in an attempt to reduce the burden on donors, reduce disincentives, and ultimately to increase the number of live donors coming forward. This seems to have been achieved in some of the larger US centres, but to date only four randomised trials have been published comparing a laparoscopic technique to the proven traditional method[26;27;46;47]. The first of these published was a comparison of a hand-assisted technique versus a subcostal incision without rib resection, consisting of fifty (23 laparoscopic and 27 open) donors[46]. The hand-assisted group had significantly less analgesic consumption, shorter hospitalisation, faster recovery, and less long-term residual effects. The second publication was a pure laparoscopic technique versus flank incision with rib resection, and consisted of eighty donors, which claimed a more modest benefit for the minimally invasive technique, but suffered two deaths in the laparoscopic group (pulmonary embolus, and myocardial infarct), and demonstrated a high splenic injury rate (5%)[26]. The third randomised trial was a mixture of pure and hand-assisted laparoscopic donor nephrectomy (pure laparoscopic n=17, hand-assisted n=46) versus an open non-rib resecting approach (n=59)[47]. This concluded similar benefits to Wolf et al[46], but had a high re-operation rate in the laparoscopic cohort (8%), with no major complications in the open group. They concluded that a perfect LDN is a superior procedure in terms of donor recovery, but inferior in terms of donor safety, especially in obese donors. Their own experience, and the deaths of five donors shortly after surgery in the USA[101] (not confirmed LDN)

highlighted the importance of caution in introducing this new technique, but maintaining its status as an evolving technique[47]. The fourth trial published recently, compared 100 donors randomised to either a pure laparoscopic approach, or a minimal incision open procedure. This concluded shorter hospitalisation, less pain, less blood loss, comparable complication rates, and improved physical recovery of donors at one year post-nephrectomy[27]. This is perhaps the most compelling evidence to date, but the relative lack of randomised trial data has led to a somewhat reluctant acceptance of this new procedure, whose track record has primarily been in the private medical centres in the US.

Randomised trials have not materialised from the States due to the demand for this minimally invasive technique, with donors travelling to recognised laparoscopic centres specifically for the new procedure. In this scenario, it is difficult to persuade a donor to be randomised and potentially then have a procedure they could have had closer to home.

The majority of the large US transplant centres were offering the new technique by 2000[23], and a number of studies with non-randomised or historical control groups have supported the potential benefit of this new technique[28-44]. Concerns still remain over the safety of the procedure, and the quality of the procured graft, despite evidence to the contrary[53;56;57], and this has been discussed in depth in the introductory chapter.

The purpose of this study was to perform a randomised trial of pure laparoscopic versus the modified minimal incision open procedure. Both techniques are described in detail in

chapter one. We feel that both these procedures carry significant benefit over the traditional technique of flank incision with partial excision of the twelfth rib, as shown in chapter two. At the commencement of this study, no randomised trials had emerged comparing both a purely laparoscopic technique with a minimal incision open donor nephrectomy.

4.2 Patients and methods

Forty consecutive renal donors were randomised to either laparoscopic or modified open donor nephrectomy, in a two to one ratio. This was a deliberate manoeuvre to keep the number of laparoscopic donor nephrectomies being performed in the department at a high level. Randomisation was via sealed envelopes, the list having been generated from the Instat software statistics programme (GraphPad Software, San Diego California USA, Copyright 1992-1998 GraphPad Software Inc.). Randomisation was performed the day prior to surgery, in order to allow theatre preparation. All potential donors who came forward for work up were considered for, and informed of the trial. Patients were excluded if they refused consent, or would only consider one of the two approaches. There was no blinding of randomisation results.

Following randomisation, and prior to theatre, patients underwent a physical examination, baseline spirometry, serum biochemical analysis, and overnight pulse oximetry. In addition, all donors received 1 litre of intravenous crystalloid fluid in the twelve hours before surgery, to maximise renal perfusion at the time of nephrectomy.

Donor nephrectomies and transplants were performed in a consecutive manner. The surgical techniques have previously been discussed in the introductory chapter. A consultant in all cases administered anaesthetics, and intra-operative analgesic administration was recorded. Duration of surgery, blood loss, and graft morphology were

recorded prospectively, as well as 1st warm ischaemic time (from application of renal artery clamp to cold perfusion of organ), and duration of cold ischaemia. All retrieved kidneys were perfused immediately with hyperosmolar citrate preservation fluid at 4°C until the effluent ran clear (approx 500ml), and placed in a bath of iced preservation fluid. Donor arterial blood gas analysis was performed at induction, muscle cutting/insufflation, pre-, and post-clamp of the renal artery.

Post-operatively, patients were managed using a patient controlled analgesia system (PCAS), delivering intravenous morphine in 1mg boluses with a five-minute lockout period. This was discontinued when the patient felt they could be maintained on oral analgesia alone. Intraoperative opiate analgesic administration was added to the total analgesic requirements. The number of days to resumption of oral fluids and eating were recorded.

Linear visual analogue pain score charts were recorded for all patients on days 1 and 3 post-op. These consisted of a 100mm horzontal line (no pain at the left extreme, worst possible pain at the other) marked vertically by the patient at the point they felt represented their current pain level. Scores were given from 0 to a maximum of 100 (worst possible pain) based on the intersection of the horizontal line from 0.

Peri-operative respiratory function was assessed by spirometry (Enhanced VM1 Mini Spirometer 3239285, Clement Clarke) and overnight pulse oximetry (Edentrace II software, and Edentec II pulse oximeter, Tyco Healthcare). Spirometry was repeated on

post-op days 1 and 3, the highest FVC of three efforts being recorded. Overnight pulse oximetry was repeated on the night of day 1, and the night of day 3 (if still hospitalised). Patients were administered oxygen at the discretion of the nursing staff, based on routine O_2 saturation observations, and this was documented on the traces obtained. Daily serum creatinine, C-reactive protein, and urinary albumin/creatinine ratio were recorded for all patients from admission, up to discharge. All donors were given a diary to document recovery of physical activities (commencement of routine household chores, driving a car, normal level of exercise, feeling able to return to work, and actual return to work).

All donors were reviewed at six weeks post-op in the day services department. Isotope glomerular filtration rate, serum creatinine, C-reactive protein, and linear analogue wound cosmetic scores were recorded. Blood pressure and a urine dipstick test were also recorded. Activity diaries were collected at this time, and those not yet back to full activity were followed up with telephone interviews. Any complications or ongoing pain were documented at this juncture. Annual blood pressure, serum creatinine, and urine dipstick monitoring was arranged for all donors with their general practioners.

4.3 Protocol Violations

Three donors agreed to enter the trial, but withdrew having been randomised to have the open procedure. They subsequently went on to have a laparoscopic procedure, but were excluded from the trial. Data was still collected for these three donors, and retrospective inclusion of them in the open group did not significantly alter any result in the analysis of

data. Randomisation of donors continued until 40 patients had been recruited for data collection.

4.4 Data analysis

The study was powered to show that a difference in one standard deviation in mean inpatient stay between groups would be significant (P=<0.05). At a power of 80%, 34 patients (N) were required to demonstrate this difference. Due to the unequal sample groups, the modified sample size (N') was calculated with the formula $N' = N(1+k)^2/4k$. N equals the sample size based on the nomogram power calculation with equal groups, and k equals the ratio between the numbers in the two groups (in this case 2:1). Therefore, N'=9N/8, which equated to 38. We decided that 40 patients would allow margin for error.

Data are presented as raw numbers or as a group mean ± SD, unless otherwise stated. Analysis was performed with Instat software statistics programme (GraphPad Software, San Diego California USA, Copyright 1992-1998 GraphPad Software Inc.). Continuous data were analysed by Unpaired T-test if there was normal Gausian distribution of data and equal standard deviation between groups, Unpaired T-test with Welch correction if normal Gausian distribution but unequal standard deviation, and Mann-Whitney test if non-Gausian distribution of data. Categorical data was analysed using χ^2 or Fisher's exact test. A two tailed P-value of <0.05 was taken as a significant result.

4.5 Results

(i)Patient demographics

There were no significant differences in donor demographics between the two sexes or operative techniques. See table 1 and 2.

(ii)Intra-operative variables

A single laparoscopic procedure was converted to open (3.7%) due to bleeding from a slipped arterial metallic clip. Subsequently all arterial ligation was achieved with an endovascular stapling device. The patient required blood transfusion, but was discharged 5 days following her procedure without further complication.

Duration of the procedure was significantly longer in the laparoscopic group by a mean of 54 minutes. There was no difference in intra-operative blood loss, and the length of the incision utilised to remove the graft was significantly shorter in the laparoscopic group (not unexpectedly). See Table 3.

Table 1. Sex demographics of all donors in the trial

	Age*	BMI*	Lap/open	Right/left
Male (n=19)	44 ± 9.9	26.8 ± 3.9	12/7	3/16
Female (n=21)	48 ± 10.7	26.6 ± 4.1	15/6	3/18
P value	0.27	0.84	0.74	1.0

*Values shown are mean ± standard deviation

Table2. Comparison of demographic distribution of donors for each procedure

	Right (♂/♀)	Left (♂/♀)	Age*	BMI*
Lap (n=27)	4 (3/1)	23 (9/14)	47.5 ± 9.7	27.0± 3.9
Open (n=13)	2 (0/2)	11 (7/4)	43.4 ± 11.5	25.7 ± 4.0
P Value	1.0	1.0	0.24	0.33

*Values shown are mean ± standard deviation

Table 3. Comparison of intraoperative variables between the two procedures

	Duration of procedure (min)	Blood loss (ml)	Incision length (mm)
Laparoscopic	192 ± 32	327 ± 377	110 ± 47
Open	138 ± 27	233 ± 181	155 ± 36
P value	<0.0001*	0.328	0.0007*

Values shown are mean ± standard deviation. * Denotes statistically significant result

Morphological features of grafts were recorded after cold perfusion. There was no significant difference in weight, vessel length, or ureter length between the two groups. There were no instances of graft damage during nephrectomy in either group. See table 4.

Right donor nephrectomy yielded grafts with a significantly shorter renal vein, but no other morphological differences. See table 5.

The first warm ischaemic time (WIT) was measured as the time taken from cross clamping of the renal artery to commencement of cold perfusion. The first WIT was significantly longer in the laparoscopic group, taking an extra 2 minutes to ligate the vessels, and remove the graft from the shorter incision. Cold ischaemic time (CIT) was measured from commencement of cold perfusion to removal of the graft from its ice bath, and commencement of the vascular anastomosis in recipient. This was prolonged in the laparoscopic group, (possibly due to the additional time taken to inspect the renal bed, and close the multiple incisions), but didn't reach statistical significance. The second WIT (commencement of vascular anastomosis to release of arterial clamps/perfusion of graft in recipient) was inexplicably longer in the open group. See table 6.

Donor arterial blood gas analysis was performed at induction, muscle cutting/insufflation, pre-, and post-clamp of the renal artery. There was a significantly higher $PaCO_2$ in the laparoscopic group at pre, and post clamp blood gas samples. PaO2 levels were not significantly different. See Graph 1 and 2.

Table 4. Comparison of graft morphology between the procedures

	Weight (g)	Renal artery (mm)	Renal vein (mm)	Ureter (mm)
Laparoscopic	177 ± 39	32 ± 7	37 ± 12	116 ± 23
Open	185 ± 32	32 ± 9	32 ± 11	104 ± 19
P value	0.541	0.966	0.206	0.105

Values shown are mean ± standard deviation.

Table 5. Graft morphology variation compared with donor site.

	Weight (g)	Renal artery (mm)	Renal vein (mm)	Ureter (mm)
Left	175 ± 36	33 ± 8	38 ± 10	112 ± 22
Right	208 ± 27	28 ± 8	18 ± 8	110 ± 23
P value	0.058	0.222	0.0001*	0.805

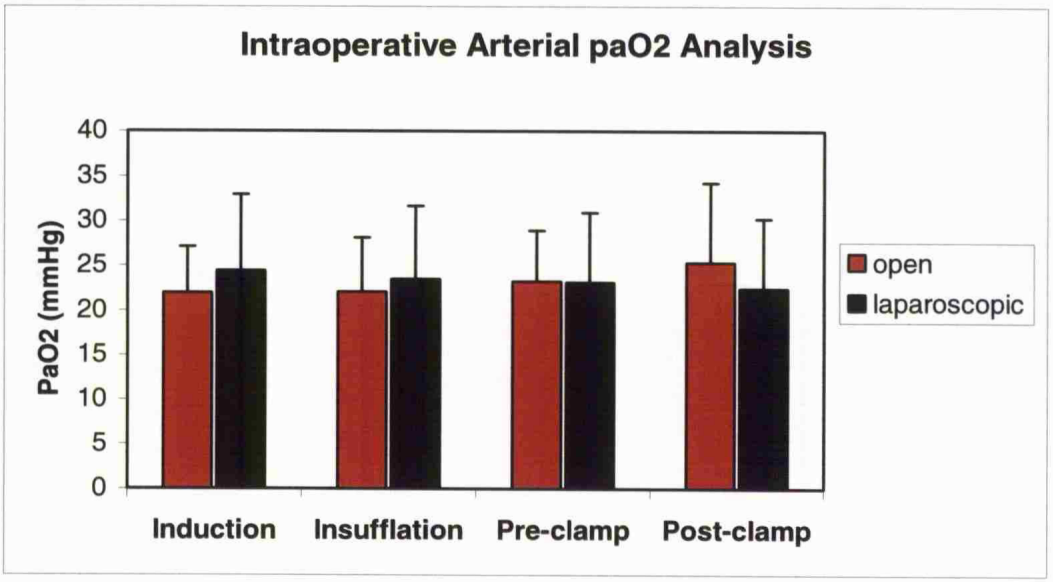
Values shown are mean ± standard deviation. * Denotes statistically significant result

Table 6. Comparison of graft ischaemic times between procedures

	1st WIT (min)	2nd WIT (min)	Total WIT (min)	CIT (min)
Laparoscopic	3.5 ± 1	28 ± 5	32 ± 5	193 ± 31
Open	2.2 ± 1	33 ± 7	35 ± 7	175 ± 54
P value	0.0004*	0.031*	0.166	0.207

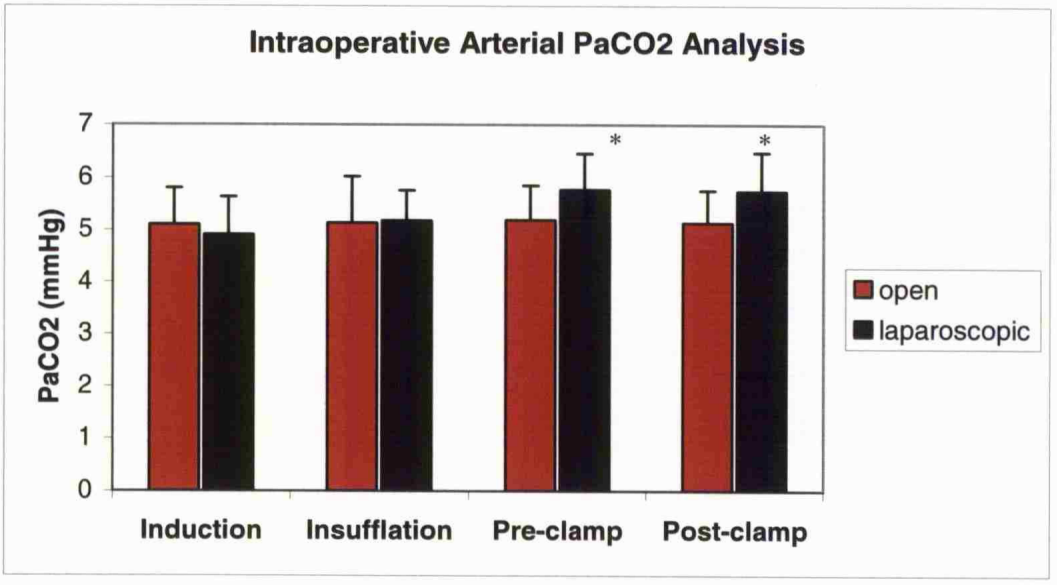
Values shown are mean ± standard deviation. * Denotes statistically significant result

Graph 1. Comparison of intra-operative measurement of arterial oxygen partial pressure



Values shown are mean. Error bars show standard deviation.

Graph 2. Comparison of intra-operative measurement of arterial carbon dioxide partial pressure



Values shown are mean. Error bars show standard deviation. * Denotes statistically significant result

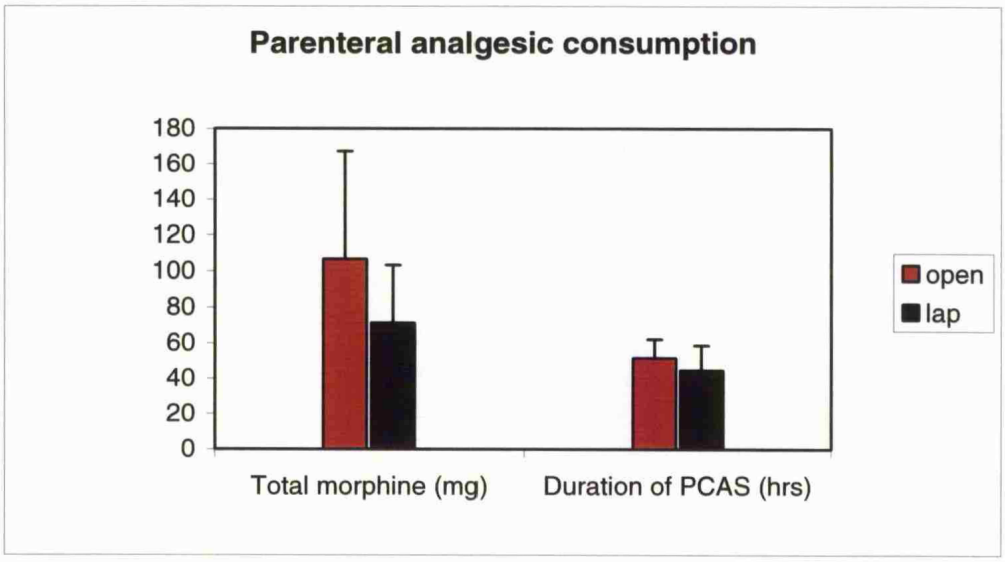
(iii) Inpatient recovery

A significant difference in post-operative hospital stay was demonstrated. Commencement of oral fluids was within 24 hours for all patients, there was no difference in the time from surgery to commencement of solid nutrition. See table 7.

Post-operative analgesic requirement was estimated by documenting the volume of intravenous morphine that had been administered post-operatively by the PCAS system. Opiate analgesics administered intra-operatively (and in theatre recovery) were also documented and added to the total parenteral analgesic requirements. The duration of dependence on the PCAS system for analgesia was also recorded. Oral analgesic requirements were not recorded. The laparoscopic group used less morphine, and were able to be maintained on oral analgesia alone earlier. However neither of these reached statistical significance (see graph 3). Linear analogue pain scores were recorded as described above. These were performed on post-operative days one and three, both at rest and on maximal inspiration. Again, at all 4 measurements, the laparoscopic group had lower scores, but only on day 1 (on inspiration) was there a significant statistical difference demonstrated (see graph 4).

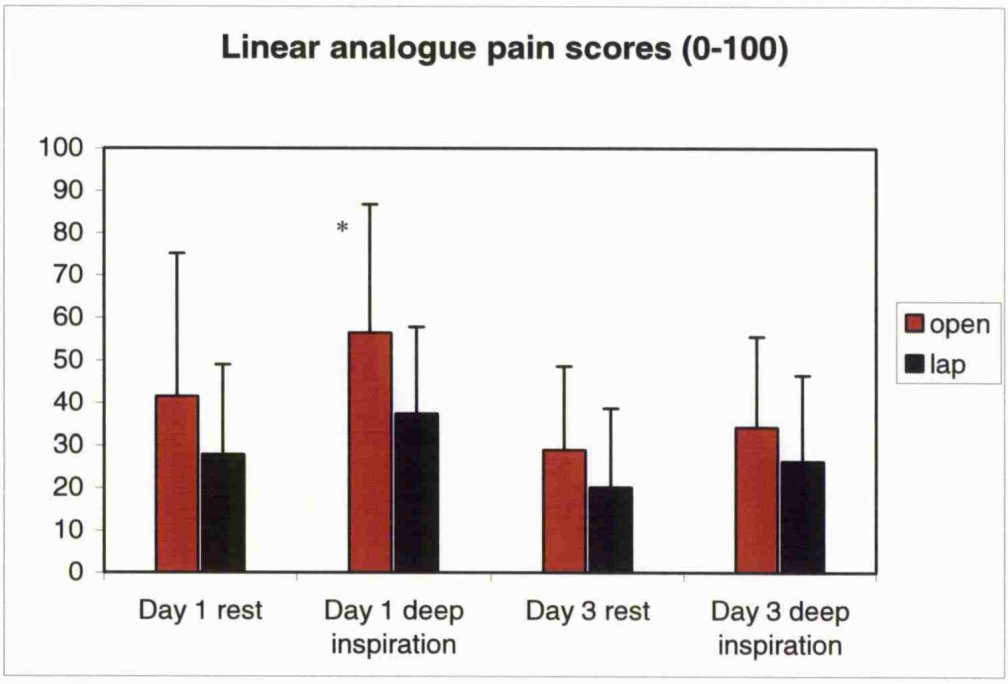
When post–operative donor serum creatinine levels were compared, there was no significant difference between groups on any of the days. The percentage increase in serum creatinine was also no different (see graphs 5 and 6). Serum C reactive protein values were also not significantly different between groups (see Graph 7).

Graph 3. Comparison of parenteral analgesic requirements during, and after live renal donation



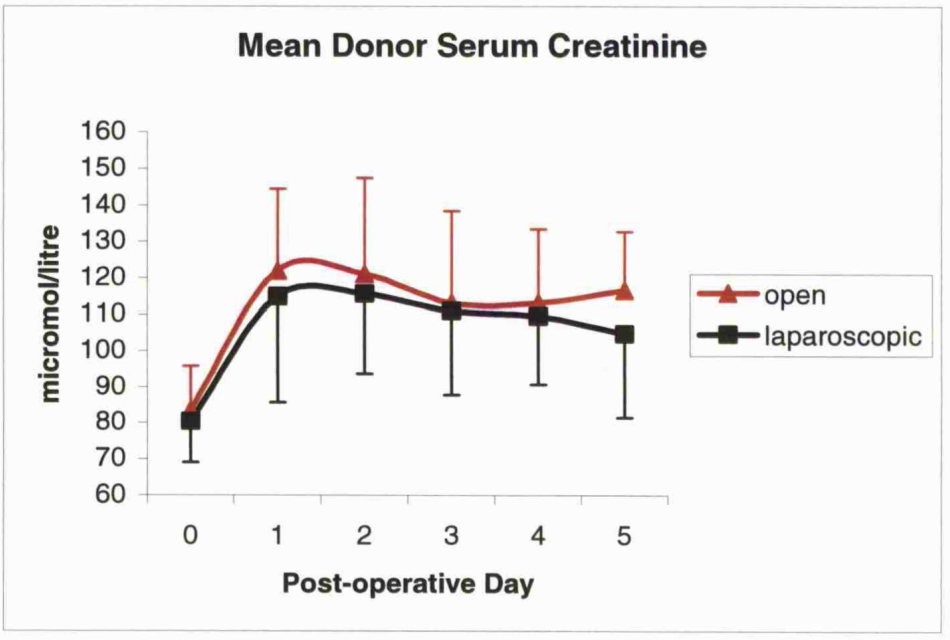
Values shown are mean. Error bars show standard deviation.

Graph 4. Comparison of visual analogue pain scoring between groups, performed on the first and third post-operative day.



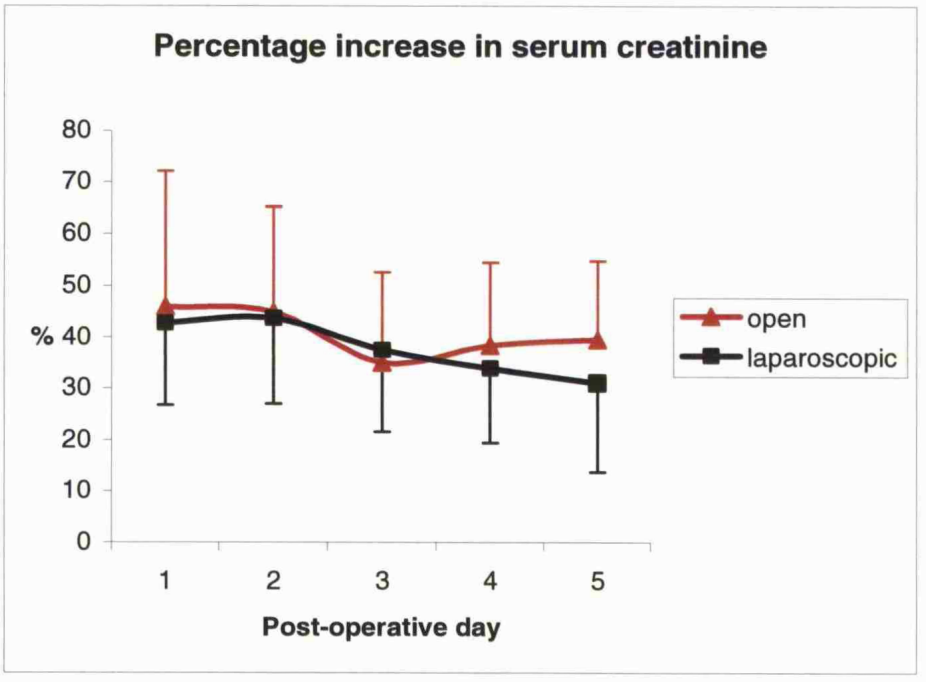
Values shown are mean. Error bars show standard deviation. * Denotes statistically significant result

Graph 5. Comparison of donor serum creatinine in post-operative period



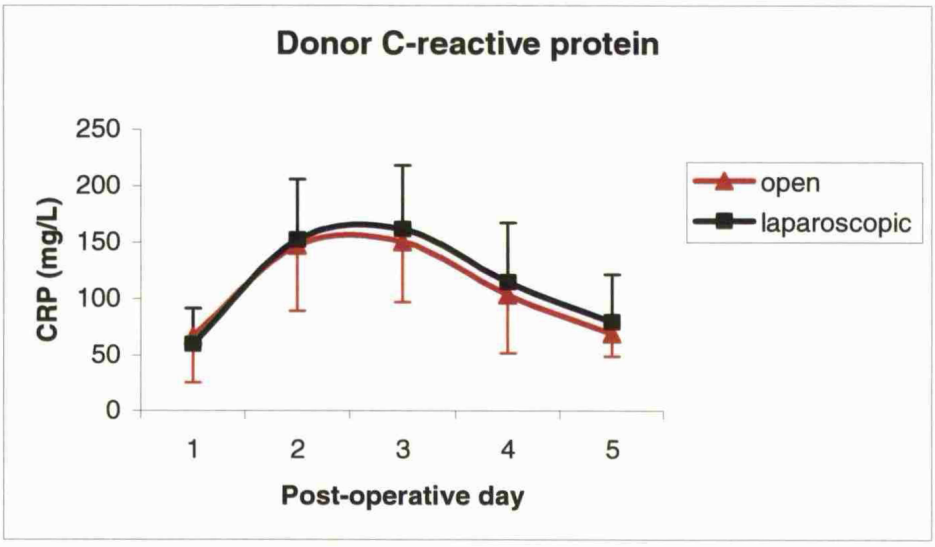
Values shown are mean. Error bars show standard deviation.

Graph 6. Percentage increase in serum creatinine in donors following nephrectomy



Values shown are mean. Error bars show standard deviation.

Graph 7. Comparison of post-operative serum C-reactive protein measurement between groups



Values shown are mean. Error bars show standard deviation.

Table 7. Summary of donor inpatient recovery

	Inpatient stay (days)	Oral fluid (days)	Solid nutrition (days)
Laparoscopic	4 ± 1	1	2
Open	5 ± 1	1	2
P value	0.036*	1.0	0.870

Values shown are mean ± standard deviation. * Denotes statistically significant result

Urinary albumin/creatinine ratio (10ml sample) was performed on all donors, both pre-operatively, and daily prior to discharge. This was to assess glomerular permeability in the immediate post-operative period. There were no significant differences in the absolute urinary albumin content (μg/ml), although the laparoscopic group had a higher trend in the first four days.

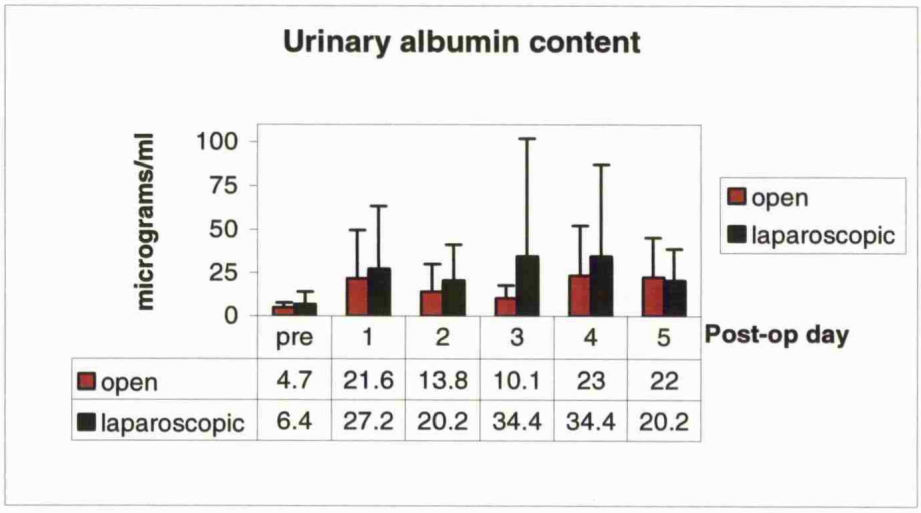
Only the pre-operative specimen showed a significant difference in albumin/creatinine ratio between the two groups. This remains unexplained, but levels were very low for both groups. Again, the laparoscopic group had a higher trend over the first four days. See Graph 8 and 9.

(iv) Perioperative respiratory function

Only one donor had mild asthma (treated with a salbutamol inhaler), was a smoker, and was in the open group. The distribution of smokers is shown below and was not statistically significant (table 8).

Spirometry was performed the day prior to surgery, and again on post-operative days one, and three. Patients were asked to give three traces at each recording, and the best of these (highest FVC) was documented. There were no significant differences in the absolute mean values for FVC, or PEFR at any of the three time points. There was also no significant difference in the mean percentage decrease of the two. See graphs 10-13.

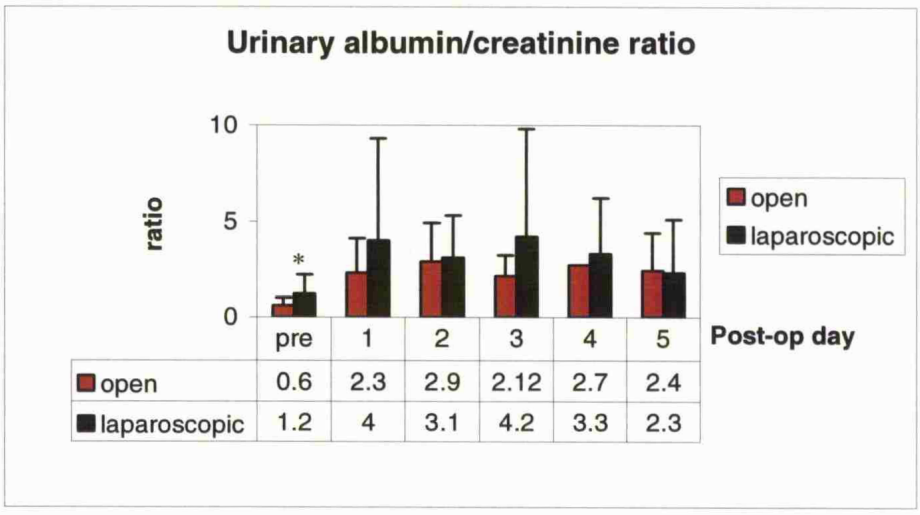
Graph 8. Comparison of post-operative urinary total albumin content



	pre	1	2	3	4	5
open	4.7	21.6	13.8	10.1	23	22
laparoscopic	6.4	27.2	20.2	34.4	34.4	20.2

Values shown are mean. Error bars show standard deviation. * Denotes statistically significant result

Graph 9. Comparison of post-operative urinary albumin/creatinine ratio



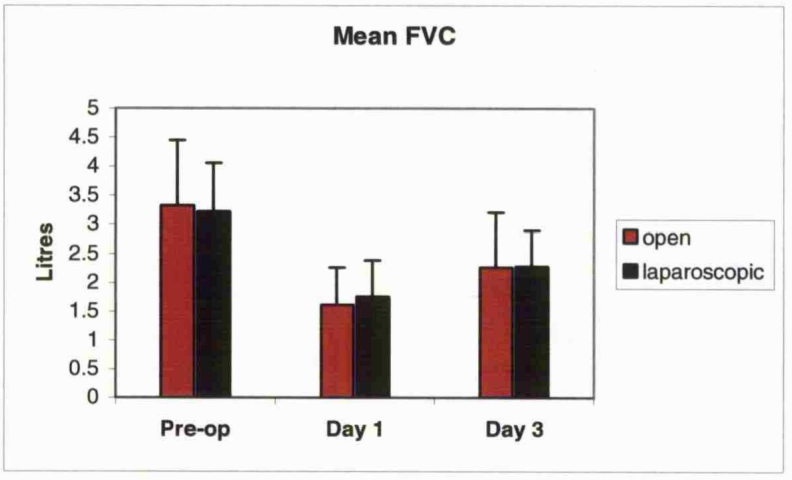
	pre	1	2	3	4	5
open	0.6	2.3	2.9	2.12	2.7	2.4
laparoscopic	1.2	4	3.1	4.2	3.3	2.3

Values shown are mean. Error bars show standard deviation. * Denotes statistically significant result

Table 8. Distribution of tobacco smoking between groups

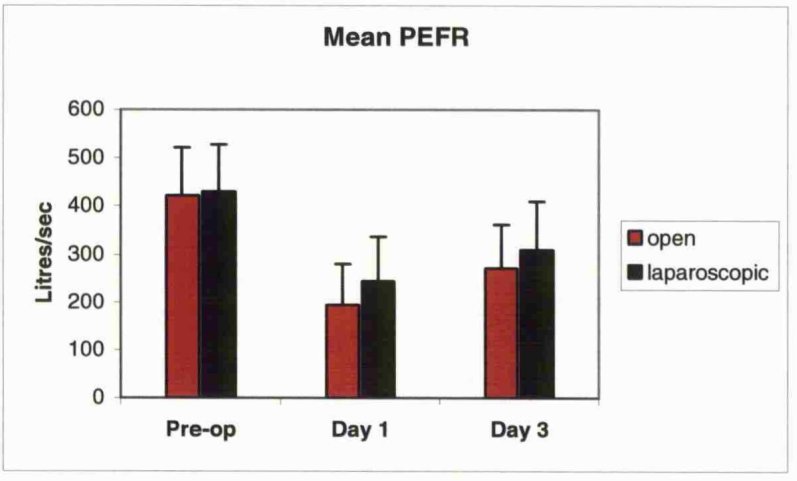
	Open (n=13)	Laparoscopic (n=27)
Non smokers	7	17
Smokers/Ex-smokers	3/3	8/2
P-value (Fisher's Exact)	0.733	0.733

Graph 10. Mean peri-operative Forced Vital Capacity



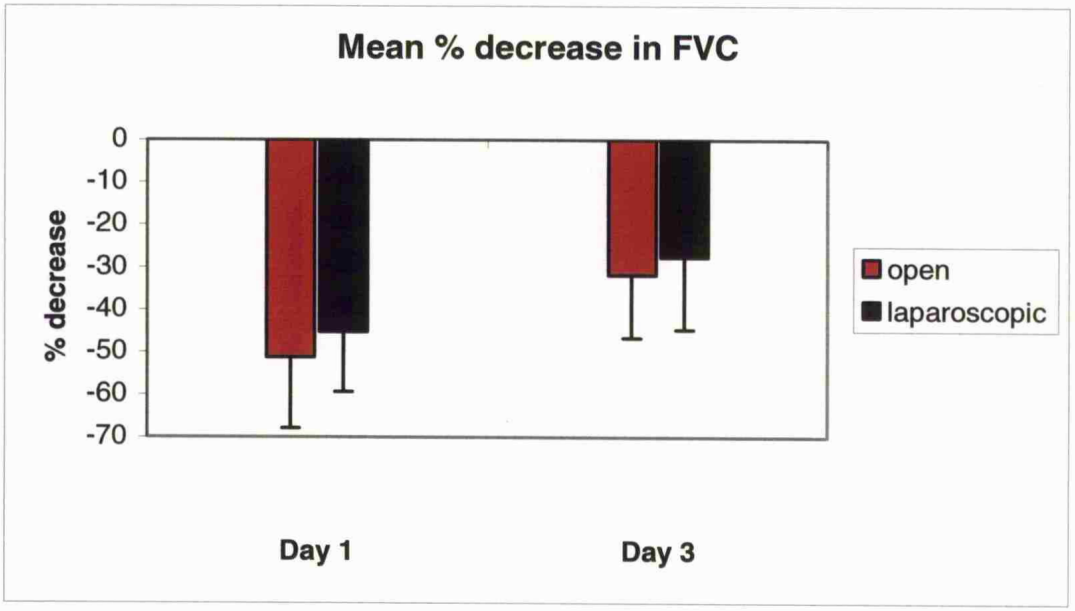
Values shown are mean. Error bars show standard deviation.

Graph 11. Mean peri-operative Peak Expiratory Flow Rate



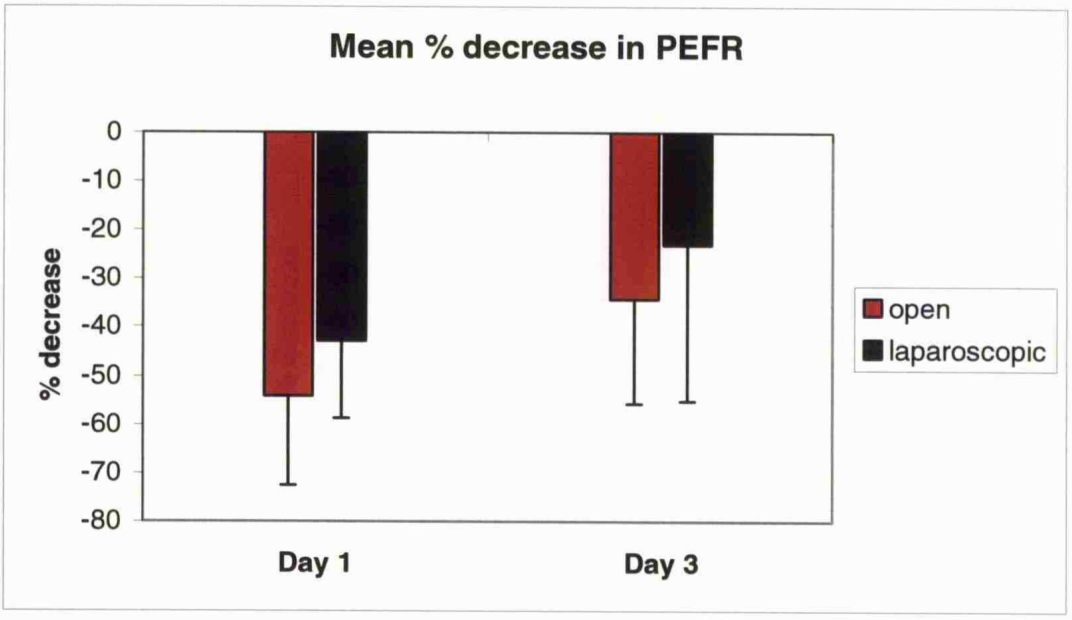
Values shown are mean. Error bars show standard deviation.

Graph 12. Mean percentage decrease in Forced Vital Capacity post-op



Values shown are mean. Error bars show standard deviation.

Graph 13. Mean percentage decrease in Peak Expiratory Flow Rate post-op



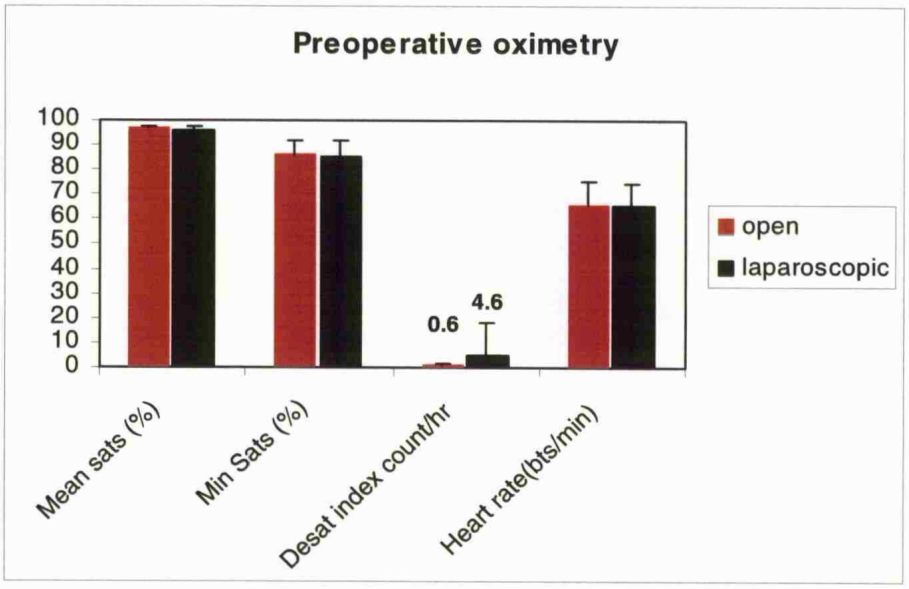
Values shown are mean. Error bars show standard deviation.

Pulse oximetry was performed on the night prior to theatre, and again on the night of post-op day 1 and 3. The oximeter recorded mean capillary oxygen saturation (via a finger probe) throughout the recorded period, the minimum recorded saturation value, average heart rate, and also the number of desaturation episodes, defined as a drop of 4% or greater for more than 10 seconds. The desaturation index was the average number of episodes per hour. The trace was applied at 22:00 and removed at 07:00 the following morning.

Oxygen administration via a facemask (4L/min via nasal specs) was encouraged in all donors on their first post-operative night. However, continued use of oxygen thereafter was at the discretion of the nursing staff, and was generally continued if oxygen saturation on room air was less than 95%. This was difficult to control for, but all donors who were using oxygen at the time of their oximetry were recorded as doing so. This needs to be taken into consideration when interpreting the results, but there was no significant difference in oxygen usage between the two groups.

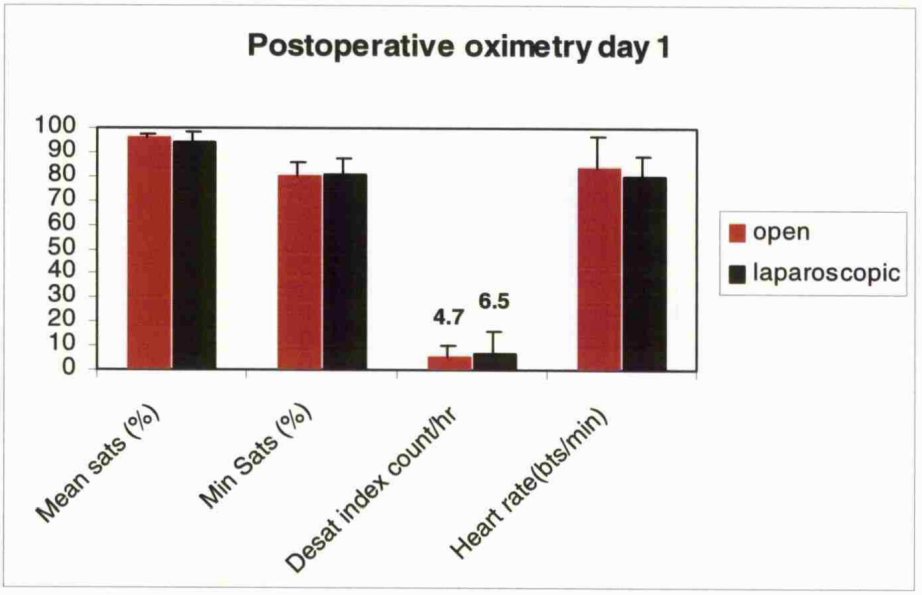
There was no significant difference in any of the measured parameters. See graphs 14-16.

Graph 14. Oximetry results for the pre-operative night



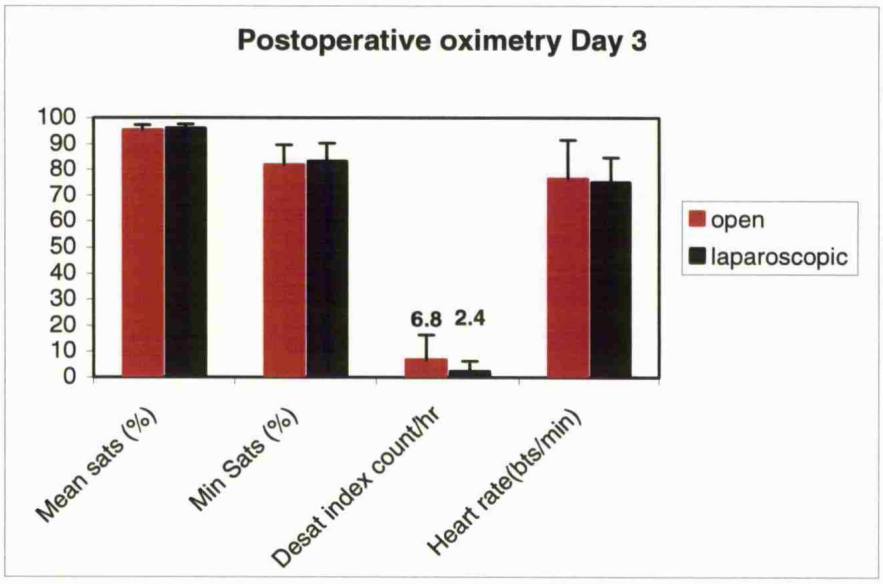
Values shown are mean. Error bars show standard deviation.

Graph 15. Oximetry results for the night of the first post-operative day



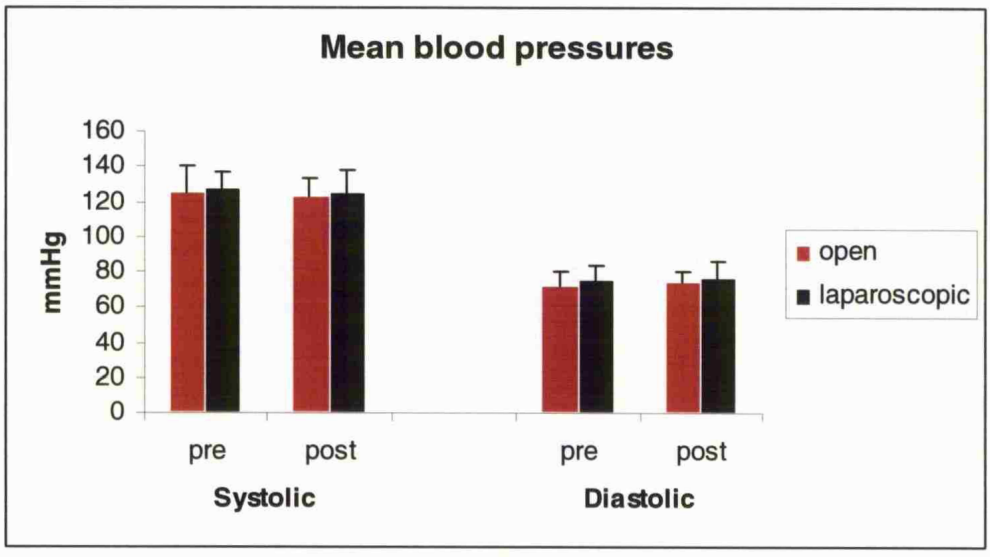
Values shown are mean. Error bars show standard deviation.

Graph 16. Oximetry results for the night of the third post-operative day



Values shown are mean. Error bars show standard deviation.

Graph 17. Comparison of change in systolic and diastolic blood pressure after donor nephrectomy



Values shown are mean. Error bars show standard deviation.

(v) Outpatient recovery

At six weeks post-op, at the outpatient check, there were no significant differences in the absolute donor creatinine, percentage creatinine increase, or fall in glomerular filtration rate. Percentage increase in serum creatinine correlated well with percentage decrease in GFR in both groups (see table 8).

There were no significant differences in systolic or diastolic blood pressures pre-, or post-operatively between groups. Nephrectomy did not significantly alter either systolic, or diastolic blood pressure in either group (see graph 17).

All donors were examined for microscopic proteinuria at six-week follow up. There was no significant difference in the distribution of donors with persistent microscopic proteinuria between groups, 44% in the open group, 42% in the laparoscopic group (P=1.0).

Wound cosmetic scores were not significantly different between cohorts, the laparoscopic group scoring 66/100, versus 62/100 for the open group (P=0.7).

All donors were asked to complete an outpatient diary to document the elapsed time (number of weeks) from surgery to resumption of activities. All were asked to document when they were able to help with housework/shopping, able to drive, and able to return to

their normal level of pre-operative exercise. In addition they were asked to document when they returned to work. Not all donors were in full time employment, or were retired (two in the open group, three in the laparoscopic group). Therefore all donors were asked to document when they **felt able** to return to work, in addition to the **actual** date of return to work. This also helped to overcome bias caused by patients taking fixed amounts of leave (up to three months in some cases). Five donors did not drive, and one donor did not drive, exercise, work, or help with the housework. Three donors were followed up elsewhere and did not provide completed diaries.

There was a general trend showing faster recovery in the laparoscopic group, but none of the results reached statistical significance.

The result of the analysis is shown in table 9.

(vi) Donor complications

Major complications

There was no donor mortality in either group. The most serious complication was haemorrhage in one of the laparoscopic group, leading to open conversion. The cause of the bleeding was slippage of all three metallic surgical clips from the divided renal artery stump, during stapling of the renal vein. Subsequently, all renal arteries were divided

using the endo-vascular stapling device, as for the vein. This was the only patient who required blood transfusion in either group.

A single donor in the open group (8%), and three in the laparoscopic group (11%) developed signs of unilateral pulmonary oedema in the dependant lung immediately following nephrectomy. All of these were young donors (29-58), and responded promptly to diuretic treatment. All cases were thought to be secondary to per operative administration of intravenous fluid.

There was no significant difference in serious complication rates between groups (P=1.0).

Minor complications

A total of twenty-three patients had twenty-seven minor complications (58%). Of these, 6 were unique to the laparoscopic group. Three of these were temporary paraesthesia of the L1 nerve root distribution, and in two, abdominal pain requiring laparoscopic adhesiolysis. One of the donors in the open group suffered with significant long term wound pain, requiring referral to a chronic pain clinic.

A summary of these minor complications is shown in table 10.

Table 8. Renal function in the donor six weeks after nephrectomy

	Creatinine (μmol/litre)	% increase creatinine	Pre-op GFR	Post-op GFR	% GFR loss
Laparoscopic	111 ± 22	39 ± 16	108 ± 16	65 ± 14	39 ± 10
Open	112 ± 13	36 ± 14	117 ± 20	67 ± 11	43 ± 9
P value	0.859	0.642	0.142	0.648	0.262

Values shown are mean ± standard deviation.

Table 9. Outpatient recovery of normal activities

	Shopping/ Housework	Driving	Exercise	Felt able to work	Actually able to work
Laparoscopic	2.5 ± 1	3.8 ± 2	3.5 ± 2	5.6 ± 3	7.6 ± 5
Open	3 ± 3	4.2 ± 1	8.2 ± 10	7.1 ± 3	9.4 ± 6
P value	0.567	0.638	0.177	0.218	0.371

Values shown are mean ± standard deviation.

Three of the four donors found to be hypertensive at follow up required only temporary anti-hypertensive treatment (the other required no treatment and spontaneously returned to normal range). In none of the donors found to have serum creatinine higher than normal range at follow up, was a progressive increase demonstrated. There was no significant difference in minor complication rates between groups (P=1.0).

(vii) Graft function in the recipient

Three grafts failed perioperatively. All of these were in the laparoscopic group, and were secondary to recurrent primary disease in the grafts (Henoch-Schönlein purpura in one at three months post-transplant, and focal segmental glomerulosclerosis in two immediately post-transplant).

There was no significant difference in graft function, measured by serum creatinine, between groups at any of the measured intervals. See graphs 18 and 19.

(viii) Complications in the recipient

Three vascular complications were seen in grafts from the laparoscopic group, one immediate, one early, and one late. There were no vascular complications in grafts from the open group, but this was not statistically significant (P=0.54).

Table 10. Comparison of minor complications between donor groups

Complication	Open	Laparoscopic
Chest infection	3	2
Raised serum creatinine	4	4
Wound related	2	2
Hypertension	1	3
L1 paraesthesia	0	3
Abdominal pain	0	2
Testicular pain	0	1

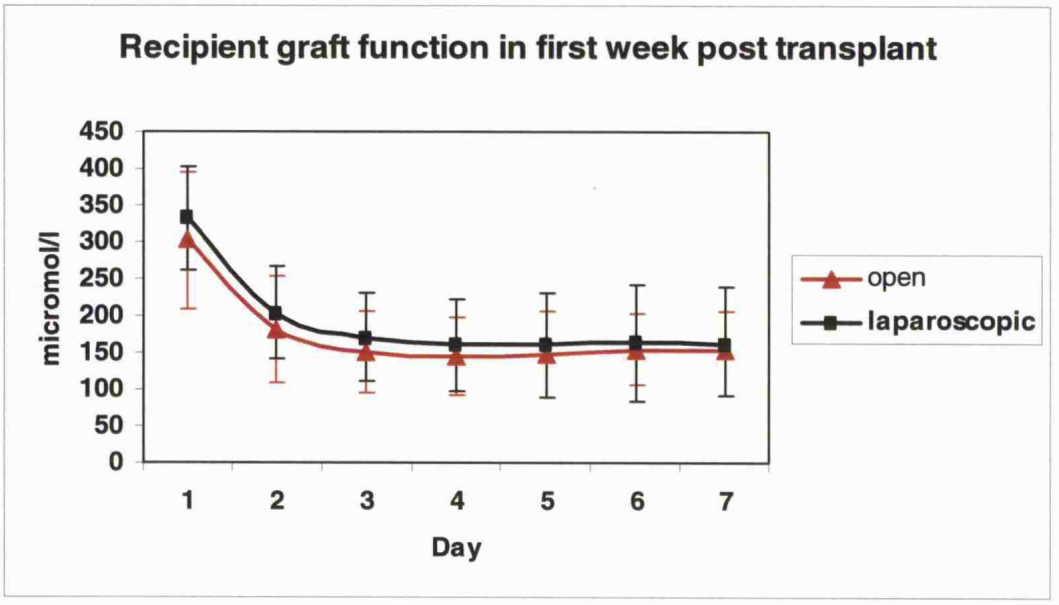
The first of these grafts was explanted and re-anastomosed intra-operatively. This was performed because of poor perfusion, and this was found to be secondary to an intimal flap. The second of these grafts was oliguric postoperatively, and ultrasound doppler examination indicated poor vascular perfusion. However, exploration of the graft in theatre revealed excellent perfusion, and no further action was required. Both these grafts had serum creatinine values of less than 120 μmol/l at twelve months. The third complication was in a graft that developed dysfunction 6 months post transplantation, along with resistant hypertension in the recipient. This graft was demonstrated to have a distal renal artery stenosis on arteriography. This was treated successfully with an intra-luminal arterial stenting, and serum creatinine at 12 months post-transplantation was 168 μmol/l.

Two recipients developed post transplant lymphoproliferative disorder (PTLD), one from each group. One responded simply to dose reduction of their immunosuppression, the other required additional treatment with rituximab.

A single ureteric complication was observed in a graft from an open donor nephrectomy. This was an ischaemic stricture of the distal half of the ureter, and was treated with a transplant to native uretero-ureterostomy.

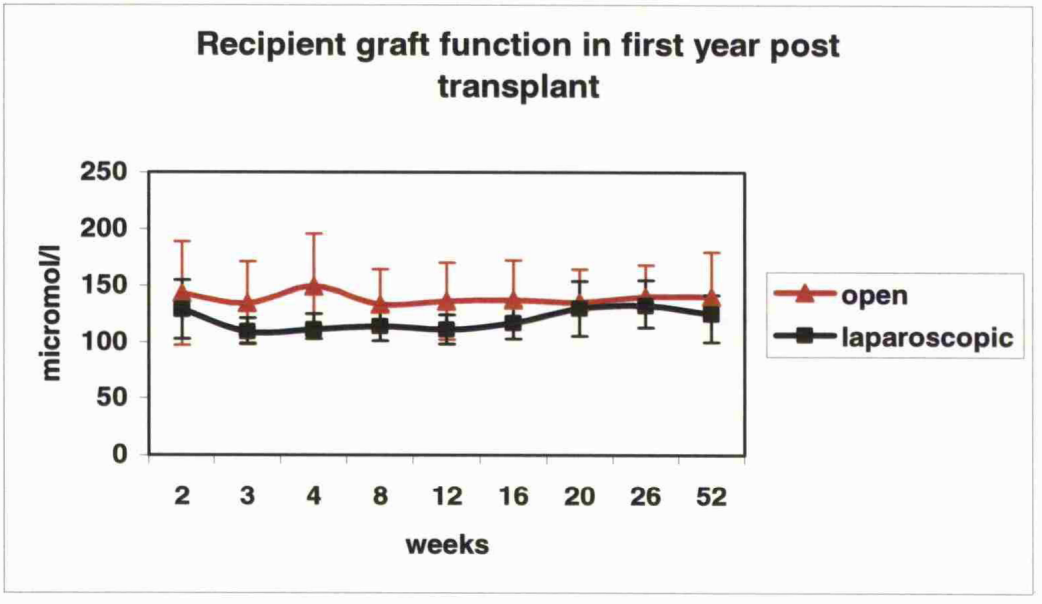
A single recipient from the open group developed a postoperative pelvic lymphocoele, requiring marsupialisation.

Graph 18. Allograft function in the first week following transplantation



Values shown are mean. Error bars show 95% confidence intervals.

Graph 19. Allograft function in the first year following transplantation



Values shown are mean. Error bars show 95% confidence intervals.

A single graft from the open group developed marked nephrocalcinosis and graft dysfunction within 12 months of transplantation. Recipient complications are summarised in table 11.

Overall rejection rates were 27%. This was numerically higher in the open group, and this did reach statistical significance. This was despite there being no difference in HLA matching between the two groups. However, 2 of the recipients in the laparoscopic group required treatment with anti-thymocyte globulin, as they did not respond to steroid treatment. All cases of rejection were treated successfully, and no grafts were lost. Two of the rejection episodes seen in the laparoscopic group, and one in the open group, were secondary to a reduction of immunosuppression for PTLD, or calcineurin inhibitor toxicity. See table 12.

Table 11. Recipient complications following transplantation

Complication	Open	Laparoscopic
Vascular	0	2
Ureteric	1	0
PTLD	1	1
Pelvic lymphocoele	1	0
Nephrocalcinosis	1	0

Table 12. Rejection rates in recipient

	Rejection rate	Steroid resistance
Laparoscopic (n=27)	15% (n=4)	50% (n=2)
Open (n=13)	54% (n=7)	0%
P Value	0.0204*	0.1091

*Denotes significant result

4.6 Discussion

This study has shown these two donor procedures to be safe, with rapid recovery time, minimal morbidity, and a yield of excellent quality grafts for renal transplantation.

In particular it has revealed laparoscopic donor nephrectomy is associated with a faster inpatient recovery, may be associated with less pain, and may be associated with faster outpatient recovery when compared directly to minimal incision open donor nephrectomy. These benefits appear to be gained without increased donor morbidity, or a compromise in graft function in the short and medium term. The cost of these benefits is a significantly prolonged operative procedure, and a prolonged warm ischaemic injury to the retrieved allograft. These findings are consistent with those of a comprehensive review published in 2004, examining all available comparative data for laparoscopic live donor nephrectomy and the open procedure[45]. It also concurs with the findings of the Kok et al[27].

However, there are a number of questions and concerns that were raised by this study. The greatest concern was the high incidence of post-operative pulmonary oedema in 10% of donors. None of these cases were life threatening, but caused significant distress to the donors and their family. The incidence of this complication was similar with both nephrectomy techniques, therefore is not a problem isolated to the laparoscopic technique, rather donor nephrectomy itself. A change to per operative donor fluid administration had been implemented two years prior to commencement of the trial,

because of unilateral pulmonary oedema of the dependant lung in a number of donors. We now give 1 litre of normal saline the night prior to nephrectomy, and give less intra-operative fluid. Despite this less aggressive fluid regimen, a number of trial donors developed problems. We do not implement central venous monitoring in live donors in our centre, because of the potential complications of central line insertion. However, if this complication is demonstrated to continue to occur this regularly without invasive monitoring, then this intervention may have to be considered in order to ensure maintenance of the central venous pressure in the desirable range (8-12cm/water). The occurrence of post-operative pulmonary oedema has been reported in other studies, but more commonly in the open nephrectomy group[27;45].

Only 5 major complications occurred in our forty donors, 4 of which were the patients who developed pulmonary oedema, and have been discussed already. The other was a laparoscopic procedure that was converted to open due to bleeding from the renal artery stump. This patient required blood transfusion, but made an otherwise uneventful recovery. The laparoscopic to open conversion rate was 3.7%, which compares favourably with that in the reported literature, 0-13%[45;47]. The randomised study from Norway reported a high re-operation rate in both laparoscopic and hand-assisted approaches (8%)[47], for bleeding (n=2), retained swab, and bowel injury (n=2) in the per operative period. In addition 2 donors required re-operation for port-site herniation (more than 1 year after donation), another developed chronic abdominal pain. Two donors in our laparoscopic group required a second laparoscopy and division of adhesions (presented with abdominal pain) several months following donation due to abdominal

pain (5.4%), but none required re-operation in the immediate per operative period. There were fewer complications reported in the Dutch study[27], and none of the donors required re-operation. However, there were three visceral injuries noted during laparoscopic procedures, each of which could potentially have been catastrophic if unnoticed. The remaining intra-operative complications in both groups were haemorrhagic, but none of the three laparoscopic cases required conversion to an open procedure[27].

The prolonged operative duration of the laparoscopic procedure was not associated with impaired postoperative respiratory function, or respiratory complications. However, three donors in the laparoscopic group had altered sensation in the L1 dermatome on the side of the donated graft, for several weeks after nephrectomy. All three donors had complete resolution of their symptoms. This complication was not seen in the minimal incision group at all, and may be secondary to prolonged positioning in a laterally flexed, 'broken' position. Less marked lateral flexion of the lower thoracic and lumbar vertebrae when positioning donors may eliminate this complication.

The increased $PaCO_2$ in the laparoscopic group on blood gas analysis both pre and post clamping of the renal artery reached statistical significance. This had no demonstrable effects on donor or graft outcome. Certainly this phenomenon has been noted in laparoscopic cholecystectomy previously, and is thought to be independent of duration of pneumoperitoneum. Hypoperfusion induced metabolic acidosis caused by increased abdominal pressure in may contribute to the effect, in addition to CO_2 absorption[102]. No

difference in per operative spirometry or pulse oximetry was demonstrated between groups.

LDN demonstrated a clear trend in lower pain scores and analgesia use, but only pain scoring on maximal inspiration on postoperative day one reached significance. With larger numbers in this trial, we are confident that these trends would have proven conclusive. This is supported by 13 studies that reported significantly lower parenteral narcotic use in LDN, and 11 others that showed a favourable trend when compared to the open approach[27;45;47].

C-reactive protein levels in the serum post-operatively are proportional to the level of tissue injury[103]. Previous studies have shown a less marked inflammatory response in laparoscopic cholecystectomy[104;105], appendicectomy[106] and colonic resections[107;108], when compared to the equivalent open procedure. This observation is not repeatable between laparoscopic and open radical nephrectomy[109]. Our results confirm these observations with donor nephrectomy, suggesting that the degree of tissue injury sustained with both approaches is comparable. This may be because the intra-abdominal/retroperitoneal area of dissection is of comparable size, and that the total length of port site incisions, when added to the Pfannenstiel incision, is equal to that of the open procedure. Similarly, microproteinuria and microalbuminaemia are proportional to extent of surgical injury[110], and no demonstrable difference was shown in this study.

Interestingly, there was no difference in subjective scoring of long-term scar satisfaction between these two groups. We expected the laparoscopic group to have much higher scores than the open cohort.

This study was powered to demonstrate a statistically significant difference in inpatient stay. This study has demonstrated a significantly shorter hospitalisation following LDN. Unfortunately this number of donors has proved inadequate to fully demonstrate other potential advantages of LDN compared to minimal incision donor nephrectomy. In particular, pain scoring, analgesic consumption, outpatient recovery, and return to work all demonstrated clear trends in favour of the laparoscopic technique, but small numbers prevented this from reaching significance. The trial is ongoing; having been continued beyond the initial recruitment of forty donors in order to try and demonstrate what we believe is the potential superiority of the laparoscopic technique.

An omission of this study was an attempt to quantify quality of life both before, and following live donor nephrectomy. Validated forms are available for this purpose (eg. SF36), and in retrospect, this would have provided valuable information for this study.

This study has shown that the potential benefits of LDN are not at the expense of the provision of excellent quality graft. There were no morphological differences in grafts procured laparoscopically, or via the open approach. There were significant differences in renal vein length in right-sided kidneys, but this was independent of the nephrectomy technique used, and resulted in no recipient complications. There were also no significant differences in graft loss, delayed graft function, or graft function at 1 year. Interestingly,

there was a significantly lower incidence of acute allograft rejection in the laparoscopic group, despite comparable HLA matching. This remains unexplained, but may have been influenced by a concurrent living donor recipient immunosuppression trial being run at our centre during the same period.

An increase in the first warm ischaemic time of two minutes was again demonstrated in the laparoscopic group. This did not lead to any demonstrable difference in delayed graft function, function over the first year, or incidence of rejection events. A slower fall of recipient serum creatinine in the first week following transplantation in the laparoscopic group was demonstrated, however, this did not reach statistical significance. This trend was also noted in chapter two, but appeared more marked in the first 20 laparoscopic donors. This is probably explained by the longer mean operative time in this 'learning curve' group (232 minutes in the first 20 LDN, versus 192 minutes in the randomised LDN group). Indeed, the prolonged duration of the laparoscopic technique itself, in addition to the prolonged first warm ischaemic time, is likely to explain this observed trend. In both studies, graft function at one year was equivalent. The slight delay in initial graft function has been well documented previously, but remains of unknown significance[57]. Prolonged first warm ischaemic time is a recognised disadvantage of the laparoscopic approach[27;45]. In 2002, laparoscopic donor nephrectomy accounted for more than half of living donor nephrectomies reported to UNOS. There was no difference in 3-year graft survival or in early graft function associated with the type of donor surgery for 19,223 living-donor transplants between 1998-2001[57;111]. This increase in warm

ischaemic time is definitely an undesirable aspect of LDN, and a solution to this problem remains a challenge, its long-term sequelae are yet to be ascertained[45].

An increased incidence of vascular graft complications was noted in the LDN group, this did not reach statistical significance, but was nevertheless worrying. One of the three grafts was found to have excellent perfusion on re-exploration, so does not represent a genuine complication, however the recipient had to undergo a second procedure to confirm this after an ultrasound scan demonstrated poor perfusion. Nevertheless, this still leaves two genuine vascular graft complications in the laparoscopic, and none in the open group. Certainly an endocatch bag induced traction injury to the endothelium, sustained during stapling of the renal vessels could explain the two events that required intervention, but this is conjecture. Long-term function of the grafts requiring vascular stenting, and re-implantation is yet to be determined, but it is difficult to imagine these complications will not be deleterious in some way. Whether LDN pre-disposes to this complication will have to be studied with a greater number of donors.

Comparisons of the hand-assisted and pure laparoscopic techniques have shown comparable donor recovery and graft outcome, but also have demonstrated shorter duration of the operative procedure, and shorter first warm ischaemic time in the hand-assisted group[29;30;38;71]. It is proposed that the hand-assisted technique may allow faster acquisition of laparoscopic skills, and also afford an element of safety over the pure laparoscopic technique[68], but randomised trials directly comparing the two techniques, or their learning curves have yet to materialise.

4.7 Conclusion

The role of LDN in current live donor transplant programmes is increasing[23-25], and it is likely that it is here to stay, despite concerns about donor safety and graft quality. We conclude that LDN is safe for the donor, is associated with a shorter hospitalisation, it yields morphologically equivalent grafts to open procedure, graft function for the first twelve months is identical, and it may demonstrate other significant advantages to the donor, namely less postoperative pain, and faster return to normal activities with extension of the trial. Questions that remain unanswered are the long-term outcome of laparoscopically retrieved grafts, and whether LDN can increase the number of potential live donors coming forward, in the face of a continuing decline in the numbers of cadaveric donor organs.

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Appendix

Please see attached CD-ROM for raw data and statistical analysis

PATIENT CONSENT FORM

A prospective randomized comparison of donor and recipient outcomes following open and laparoscopic live donor nephrectomy

Principle Investigator *Professor M L Nicholson*

This form should be read in conjunction with the Patient Information Leaflet, Version No 2 dated 19/06/2000

I agree to take part in the above study as described in the Patient Information Sheet.

I understand that I may withdraw from the study at any time without justifying my decision and without affecting my normal care and medical management.

I understand that members of the research team may wish to view relevant sections of my medical records, but that all the information will be treated as confidential.

For drug studies if appropriate: At the termination of this trial I understand that there is no guarantee that the drug treatment received during this trial will continue.

I understand medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

I have read the patient information leaflet on the above study and have had the opportunity to discuss the details with Professor M L Nicholson and ask any questions. The nature and the purpose of the tests to be undertaken have been explained to me and I understand what will be required if I take part in the study.

Signature of patient .... Date.....
(Name in BLOCK LETTERS) .....

I confirm I have explained the nature of the Trial, as detailed in the Patient Information Sheet, in terms which in my judgement are suited to the understanding of the patient.

Signature of Investigator ..... Date.....
(Name in BLOCK LETTERS) .....

For studies involving children and patients unable to give written consent (e.g. unconscious patients) please refer to the guidelines for consent for these groups.

PATIENT INFORMATION LEAFLET

A prospective randomized comparison of donor and recipient outcomes following open and laparoscopic live donor nephrectomy

Principle Investigator *Professor M L Nicholson*

You may contact *Professor M L Nicholson*

What is the purpose of the study ?

The operation to remove a kidney for living donor transplantation (nephrectomy) is performed in Leicester in one of two ways. The first is an open operation and the second is a laparoscopically assisted operation (keyhole surgery). In the open operation the kidney is removed through a 10-12 cm incision made over the kidney in the region of the flank. In the laparoscopic operation three or four 12 mm stab incisions are made in the abdomen and after the kidney has been separated from the surround tissues it is removed through a 8-10 cm cut made low down in the abdomen. Although both of these operations are carried out through relaltively small incisions, we are not sure whether the open or the laparoscopic procedures have any advantages over each other. The aim of this study is therefore to compare the recovery rate in donors operated on either by the open or the laparoscopic procedure. We also want to compare the outcome of the kidney transplant in the recipient for kidneys removed using these two different techniques. The only scientific way to compare two operations like this is to randomly allocate donors to one operation or the other (on the toss of a coin).

What will be involved if I take part in the study ?

If you take part in this study, the work-up for the kidney donation operation and the postoperative management will not differ from that currently used in the Leicester Transplant Unit. Once you have consented to donation you will be randomly allocated to either the open or the laparoscopic procedure and told which operation you are to undergo. Postoperatively we will record the level of any wound discomfort that you have and the amount of painkillers you need. Fluids and diet will be introduced normally on the first and second postoperative days and you will be allowed to go home when you feel well enough, which is usually between the third and sixth postoperative day. In the postoperative period we would like to assess how your heart, lungs and kidneys respond to surgery. The function of the lungs will be measured by asking you to blow into an instrument called a spirometer and we will also measure the oxygen saturation in the blood, by a non-invasive probe worn on the finger for the first two to three days after

surgery. The response of the heart circulation and kidneys to surgery will be measured by taking blood and urine samples both during the surgery and on each postoperative day up to the fifth day after surgery. As blood is normally taken at these times you will not require any more blood taking procedures but on each occasion an extra 20 ml blood will be taken for various tests. When you are discharged we will give you a diary which will contain a list of events and we would like you to record the date on which each of these occur. The events to be recorded will be as follows: returning to driving, returning to housework, returning to shopping, returning to exercise and returning to full-time employment. You will be reviewed in the clinic six and twelve weeks after your operation, which is the normal practice for this Unit.

Will information obtained in the study be confidential ?

Yes. All the features of your progress postoperatively and the outcome of the various tests will be recorded in your medical records and in a special trials folder. The information will then be placed on a computer database for subsequent analysis. Any information collected about you during the study will be held in complete confidence by the doctors on the Transplant Unit. The information on computer will not identify you by name as you will be given a trial number. Only authorized hospital staff will be given the opportunity to see the original medial records or the computerized information about your kidney donation. Finally, your GP will be informed of your participation in this study.

What if I am harmed by the study ?

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS, ie compensation is only available if negligence occurs.

What happens if I do not wish to participate in this study or wish to withdraw from the study ?

If you do not wish to participate in this study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected.