

## Surgical techniques in living donor nephrectomy

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Author: Norma Gibbons, David Nicol

### GUIDELINES

- a. Recipient outcomes are equivalent with laparoscopic and open live donor nephrectomy (Level II evidence)
- b. No recommendations possible with respect to donor mortality and major complications based on Level I or II evidence

### SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- Donor mortality and major complications appear equivalent with laparoscopic and open donor nephrectomy. In open surgery, the risks appear related to perioperative complications including pulmonary emboli, pneumonia and ischaemic events. With laparoscopic surgery, complications are largely due to catastrophic intraoperative events related to securing of the vascular pedicle. Measures to reduce these specific problems should be undertaken and tailored to the technique used by individual transplant units.
- Use of a non-transfixing mechanism for securing the renal artery is not recommended, particularly with laparoscopic donor nephrectomy.
- Laparoscopic donor nephrectomy is more resource-intensive, but may offer advantages to many donors:
  - Increased operative time but equivalent hospitalization (based on hospital stay in five out of six randomized controlled trials) with laparoscopic compared with open donor nephrectomy
  - Reduced analgesic requirements and return to normal activities with laparoscopic donor nephrectomy compared with open surgery.
- Death and major complications occur infrequently following donor nephrectomy. This limits the feasibility of randomized controlled trials comparing donor surgical techniques. The best available evidence will evolve over time with comprehensive registry data.

### IMPLEMENTATION AND AUDIT

The use of a multi-institutional registry database is potentially the only means of resolving safety issues in live kidney donation. Compulsory prospective contribution to an independent central database would ensure accurate reporting of all cases of live kidney donation and any adverse perioperative or postoperative events therein. This would ensure that

important operative events that may influence future management practice are not excluded.

### BACKGROUND

The rising incidence of end-stage kidney disease (ESKD), together with static or reduced deceased donors, have led to an increased reliance on live donors for renal transplantation in Australia and other developed nations. Over the past decade, live donor transplantation has increased from 22% (in 1995) to 41% (in 2005) of all renal transplants.<sup>1</sup> This period has also been associated with the introduction of laparoscopic donor nephrectomy.

To date, a total of 4354 live donor transplants have been performed in Australia ( $n = 2907$ ) and New Zealand ( $n = 1645$ ).<sup>1</sup> The precise number of laparoscopic live donor operations is unknown, although almost certainly over 600 of the donor procedures have used this technique. Two donors are known to have died as an operative or postoperative complication; one of these occurred during an open procedure and was related to bleeding from the renal artery. In this case, clips similar to those used in many cases of laparoscopic nephrectomy were used to secure the renal artery; these became dislodged in the early postoperative period. This local operative mortality risk is consistent with the internationally reported rate with donor nephrectomy.<sup>2,3</sup>

The first living donor transplant was performed in 1954 between identical twins by Joseph Murray and colleagues at Peter Brent Brigham Hospital in Boston.<sup>4</sup> During the ensuing 40 years, live donor nephrectomy was performed predominantly via a large open flank incision, usually with a retroperitoneal approach to the kidney. Alternative techniques involve a transperitoneal approach via either a midline or subcostal abdominal incision. The disadvantages of open surgery include pain, a long convalescence, potential pneumothorax, and long-term wound complications.<sup>5–7</sup>

Laparoscopic ablative nephrectomy was first reported in 1991<sup>8</sup> and subsequently applied to donor nephrectomy in

1995.<sup>9</sup> As with open nephrectomy, a number of techniques have evolved with laparoscopy and include transperitoneal and retroperitoneal approaches. Hand-assisted variations of both of these have also been described.<sup>10–16</sup> The technique used appears to be based on the individual surgeon's or institution's preference.

The introduction of laparoscopic donor nephrectomy resulted in the dissemination of the technique without clear evidence of the true merit of this compared with open surgery.<sup>17</sup> The potential for reduced morbidity, consumer enthusiasm and what may be interpreted as commercial promotion of individual transplant programmes drove the rapid escalation of this technique, despite unresolved concerns regarding donor safety as well as technical complications (vascular thrombosis, ureteric ischaemia) and functional outcome in recipients.<sup>6</sup>

Living donor nephrectomy is a unique and very demanding procedure. The reason for the high level of difficulty is related to the nature of the surgery, in which the removed organ has to function normally in the recipient. In addition, the donor is a healthy individual who is being subjected to major surgery for the benefit of another person without direct advantage, and possibly harm, to their own health. Consequently, it is of utmost importance that no harm is inflicted on the donor.

Given this, the major issues with live donor surgery in order of priority are to:

- maximize safety for the healthy donor,
- minimize donor morbidity, and
- minimize any technical or functional compromise to the graft that may affect recipient outcome.

Further issues to be considered in the technique of live donor surgery include:

- hospital resource implications,
- training and expertise of surgeons,
- transfusion devices, and
- patient factors.

The purpose of this guideline is to review the available evidence and formulate recommendations on surgical technique for live donor nephrectomy, particularly in relation to laparoscopic and open surgery, as a reference for renal transplant units in Australia and New Zealand.

## SEARCH STRATEGY

**Databases searched:** MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for living donor and combined with MeSH terms and text words for open and laparoscopic nephrectomy. The search was carried out in Medline (1966 – September Week 1, 2006). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of searches:** 15 September 2006.

**Update search:**

**Databases searched:** MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for living donor and combined with MeSH terms and text words for open and laparoscopic nephrectomy. The

search was carried out in Medline (1966 – March Week 1, 2009). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of searches:** 9 March 2009.

## WHAT IS THE EVIDENCE?

One meta-analysis has been performed by Nanidis *et al.*, which included 73 studies with a total of 6594 patients, of which 3741 had undergone laparoscopic surgery and 2843 open nephrectomy.<sup>18</sup> The authors evaluated operative and warm ischaemia times, blood loss, donor complications, length of hospital stay, time to return to work, and delayed graft function. The open nephrectomy group had shorter operative and warm ischaemia times by 52 min and 102 s (both  $P < 0.001$ ) but this did not translate into higher delayed graft function or graft loss rates between the two groups. The laparoscopic group had a shorter hospital stay and shorter return to work time. A significantly higher rate of overall donor complications was found in the open nephrectomy group. The authors concluded that laparoscopic nephrectomy is a safe alternative, and patients may benefit from a shorter hospital stay and return to work time without compromising graft function.

By 2007, five randomized controlled trials<sup>19–23</sup> had been reported with a total of 754 patients. Several of these series have been the subject of more than one publication.<sup>21–26</sup> The features and findings of these studies are summarized in Table 1 (Appendix) with one series including an initial report<sup>24</sup> with subsequent updating of numbers.<sup>22</sup>

In these studies, there was no reported donor mortality and no difference between open and laparoscopic nephrectomy with respect to major complications. The types of complications were different in the two groups. In the laparoscopic group, bleeding from the port site, splenic capsular tear, stapler injury, bowel injury, bladder perforation and wound infection were reported. In the open group, complications included hypoxia, pulmonary embolism, thrombophlebitis, deep vein thrombosis (DVT) and wound infection. Recipient outcomes were comparable with respect to technical complications and functional outcome. These studies showed no difference in the incidence of ureteric complications and vascular thrombosis, which had been a concern with early series reports with laparoscopic donor nephrectomy (at which time the technique was at a developmental stage and experience limited). There were a number of shortcomings with these trials, both individually and collectively. All were inadequately powered to detect clinically significant differences in many of the outcome measures. Given the reported frequency of major complications and perioperative mortality (0.03%),<sup>2–3</sup> randomized controlled trials do not appear feasible in resolving these major safety issues due to the large number of subjects required.

A further shortcoming of these trials was the fact that in three out of the five series,<sup>19,21,24</sup> right kidneys (which are more technically challenging) were excluded, thus reducing the potential relevance of the studies to routine clinical

practice in which up to 25% of live donor transplants involve the right kidney.<sup>27</sup> Moreover, only one of four studies reported a reduction in duration of hospitalization with laparoscopic nephrectomy.<sup>19</sup> The remaining series reported no difference compared with open surgery.<sup>21,23,24</sup> Overall, the series indicate that laparoscopic nephrectomy is associated with reduced analgesic requirements, increased warm ischaemia times (although without impact on graft function) and longer operative times. The relevance of the latter finding is uncertain as differences between series with the same operative technique were greater than those seen within series comparing the two techniques. No data were provided with regards to re-admission rates in any of the studies and in three studies, details were scant regarding intraoperative and postoperative complications.

Cost comparison was an outcome measure in one randomized controlled trial.<sup>19</sup> Mean operating room costs for the laparoscopic group were 161% greater than for the open surgical group, relating to increased operative times and additional equipment expenses. The latter accounted for only 24% of the operative costs for open surgery compared with 61% for laparoscopy. This series reported a shorter hospital stay in the laparoscopic group, which offset some of the increased operative costs such that mean hospital cost was 24% greater in the laparoscopic group. The loss of occupational income for laparoscopic donors during their convalescence was 75% that of the open surgical donors. As a result, the global cost of the nephrectomy, which included the total hospital costs and loss of occupational income, was not significantly different between the two groups (2% greater in the laparoscopic group.)

Several techniques have been described for laparoscopic donor nephrectomy – as a purely laparoscopic approach either transperitoneally or extraperitoneally or as a hand-assisted transperitoneal approach. In the USA, both pure laparoscopic and hand-assisted approaches appear to be used equally.<sup>2</sup> One randomized controlled trial of hand-assisted and pure laparoscopic donor nephrectomy has been reported.<sup>28</sup> Forty patients were randomized; no differences were apparent in terms of outcomes or analgesic requirements. There are no trials comparing transperitoneal and retroperitoneal approaches.

The remaining evidence relating to surgical technique for donor nephrectomy relies on incomplete registry data, multi-institutional surveys or series reports from individual transplant centres with contemporaneous (non-randomized) or historical open nephrectomies as comparators.

Donor mortality is a catastrophic event with living donor transplantation. Registry data and multi-institutional surveys suggest that risk of donor death is approximately 3 in 10 000.<sup>2</sup> The true number of donor deaths is unknown. Isolated reports of laparoscopic donor deaths relate this to intraoperative events, particularly in relation to securing the hilar vessels, resulting in exsanguinating haemorrhage, air embolism and visceral injury.<sup>2,3,29,30</sup> Analysis of the available case reports suggest that delayed conversion to an open procedure may have contributed to the consequences of the initial event.<sup>3,29,30</sup>

A multi-institutional survey of members of the American Society of Transplant Surgeons has identified that the risk of significant bleeding with both open and laparoscopic donor nephrectomy is associated with the use of non-transfixion methods for securing the renal artery.<sup>3</sup> Locking and standard clips applied to the renal artery appeared associated with the greatest risk. One device (Autosuture – Endo-Clip disposable clip applier – United States Surgical Corporation) includes a Food and Drug Administration (FDA) approved package insert with the device that specifically recommends against the use of disposable clips on the renal artery.<sup>2,3,31–34</sup>

Donor mortality with open nephrectomy relates to ischaemic events (cerebral and cardiac), postoperative infection, principally pulmonary and venous thromboembolism.<sup>2</sup> Although there is no specific evidence in donor nephrectomy in relation to strategies to prevent or minimize these complications, the general principles applicable to other types of major abdominal surgery should apply. These include aggressive cardiovascular screening to identify patients at risk, which may preclude some donors from consideration. Adequate analgesia, incentive spirometry and chest physiotherapy are particularly recommended with open surgery.<sup>35</sup> All patients should receive standard DVT prophylaxis with heparin, graduated stockings and pneumatic compression devices.<sup>36</sup>

Numerous series report major complications following laparoscopic and open donor nephrectomy with rates between 3% and 38%. This enormous variability relates to both definition of complication and accuracy of reporting. This limitation prevents any conclusion or comparison from the available reports. Similar variability is noted with respect to transfusion rates.

For anatomical reasons, the left kidney is used in preference to the right for living donor transplantation. Where multiple vessels are present on the left, the right kidney may be preferred and has been used in up to 25% of cases in historical series. Many series of laparoscopic donor nephrectomy have specifically excluded the right kidney largely due to concerns about the length of the renal vein. In eight series with a total of 722 cases (unrandomized – 448 left kidneys, 274 right kidneys), no difference was observed in recipient outcome with respect to side.<sup>14,27,37–42</sup> Case selection was not apparent in these reports, but nevertheless could still remain as a source of outcome bias.<sup>14,27,37–42</sup> Similar considerations apply to the issue of multiple renal vessels. In three series with a total of 558 donor nephrectomies (unrandomized – 418 with single vessels, 133 with multiple vessels) operative and warm ischaemia time was increased with multiple arteries, but the increases were not statistically significant. There was also no significant difference noted with respect to the complication rate.<sup>43–45</sup>

Training, experience and operative case load have not been defined for many major surgical procedures. Concerns are frequently raised on this issue, particularly with the introduction of new surgical techniques including donor nephrectomy. Minimal data exists in relation to these points with donor nephrectomy. Institutional reports that, in many cases, incorporate patients from the era of technical evolution of laparoscopic nephrectomy have suggested a much

higher risk of complications, and conversion to an open operation as a consequence of technical problems during the initial 30 cases.<sup>46</sup> It has been suggested that the progression of inexperienced individual surgeons through the learning curve in institutions performing laparoscopic nephrectomy may obscure the real effect of the learning curve.<sup>47</sup>

## SUMMARY OF THE EVIDENCE

When performed in experienced high-volume transplant centres, equivalent outcomes (donor and recipient) occur with open living donor nephrectomy and laparoscopic donor nephrectomy performed by surgeons with significant previous laparoscopic experience.

Major complications and donor mortality occur infrequently and limit the feasibility of randomized controlled trials in comparing these occasional but extremely important events. Use of multi-institutional registry data is potentially the only means of resolving these safety issues. Compulsory prospective contribution to an independent central database will guarantee accurate reporting and ensure that important events that may influence conclusions are not excluded.

Laparoscopic donor nephrectomy is associated with reduced analgesic requirements and more rapid return to normal activities compared with open surgery. Longer operative times and institutional costs occur, which are only partly offset by reduced loss of income by the donor in terms of overall costs to the community.

## WHAT DO THE OTHER GUIDELINES SAY?

**Kidney Disease Outcomes Quality Initiative:** No recommendation.

**UK Renal Association:** No recommendation.

**British Transplant Society:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** No recommendation.

**Amsterdam Forum: Care of the live kidney donor**

There are no guidelines available for surgical technique in living donor nephrectomy.

In relation to DVT prophylaxis, factor v-leiden, a variant of the coagulation protein factor v, is associated with venous thrombosis, especially in oral contraceptive users. It is the most common hereditary blood coagulation disorder and is present in 3–8% of the healthy white population. Factor v-leiden mutant genes have been detected in 2% of living donors. The odds ratio of a venous thrombo-embolic event is 11 times greater in women taking oral contraceptives who have factor v-leiden mutation than those who do not. It is recommended that a history of venous thromboembolism be ascertained prior to an in-depth coagulation work-up. Unless the medical history reveals a medical concern that would necessitate a comprehensive coagulation profile, tests are considered not likely to yield information. Such tests include PT, PTT, antithrombin 3, protein S, Protein C, Activated protein C resistance (APC), PT- Prothrombin mutation, cardiolipin antibodies and lupus anticoagulants.

It is recommended that oral contraceptives and hormone replacement therapy be withheld for 3 months prior to donation.

## SUGGESTIONS FOR FUTURE RESEARCH

Transplant units performing live donor nephrectomy should be required to submit prospective audit data to a centralized, independently-maintained registry as the most feasible means of identifying differences in major outcome measures of donor safety.

## CONFLICT OF INTEREST

Norma Gibbons and David Nicol have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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## APPENDICES

**Table 1** Characteristics of included studies

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)
Anderson <i>et al.</i> 2006 <sup>25</sup>	122	Randomized controlled clinical trial	University hospital, Norway	122 living kidney donors	Laparoscopic nephrectomy	Open nephrectomy	1 month
Kok <i>et al.</i> 2006 <sup>23</sup>	100	Randomized controlled clinical trial	University hospitals, Netherlands	100 living kidney donors	Laparoscopic nephrectomy	Open nephrectomy	12 months
Oyen <i>et al.</i> 2005 <sup>21</sup>	122	Randomized controlled clinical trial	University hospital, Norway	122 living kidney donors	Laparoscopic nephrectomy	Open nephrectomy	<3 months
Simforoosh <i>et al.</i> 2005 <sup>24</sup>	200	Randomized controlled clinical trial	University hospital, Iran	200 living kidney donors	Laparoscopic nephrectomy	Open nephrectomy	12 months
Simforoosh <i>et al.</i> 2003 <sup>22</sup>	80	Randomized controlled clinical trial	University hospital, Iran	80 living kidney donors	Laparoscopic nephrectomy	Open nephrectomy	10 months
Wolf <i>et al.</i> 2001 <sup>19</sup>	70	Randomized controlled clinical trial	Single centre, USA	70 living kidney donors	Laparoscopic nephrectomy	Open nephrectomy	12 months

**Table 2** Quality of randomized trials

Study ID (author, year)	Method of allocation concealment†	Blinding			Intention-to-treat analysis‡	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Anderson <i>et al.</i> 2006 <sup>25</sup>	Block randomization	No	No	No	Yes	1.6
Kok <i>et al.</i> 2006 <sup>23</sup>	Sequentially labelled opaque sealed envelopes	No	Yes	No	No	15.2
Oyen <i>et al.</i> 2005 <sup>21</sup>	Not specified	No	No	No	Yes	0.0
Simforoosh <i>et al.</i> 2005 <sup>24</sup>	Not specified	No	No	No	Unclear	0.0
Simforoosh <i>et al.</i> 2003 <sup>22</sup>	Not specified	No	No	No	Unclear	0.0
Wolf <i>et al.</i> 2001 <sup>19</sup>	Sequentially labelled opaque sealed envelopes	No	No	No	No	44.0

†Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.

‡Choose between: yes; no; unclear.

**Table 3** Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) (95% CI)	Risk difference (RD) (95% CI)
Anderson <i>et al.</i> 2006 <sup>25</sup>	Mortality	0/63	0/59	Not estimable	0.00 (95% CI: 0.03, 0.03)
	No pain	40/63	24/59	1.56 (95% CI: 1.09, 2.24)	0.23 (95% CI: 0.06, 0.401)
Kok <i>et al.</i> 2006 <sup>23</sup>	Mortality	2/50	1/50	2.00 (95% CI: 0.19, 21.36)	0.02 (95% CI: 0.05, 0.09)
	Renal vein thrombosis	0/50	0/50	Not estimable	0.00 (95% CI: 0.04, 0.04)
	Acute rejection	9/50	15/50	0.60 (95% CI: 0.29, 1.24)	-0.12 (95% CI: 0.29, 0.05)
	Ureteral complications	6/50	10/50	0.60 (95% CI: 0.24, 1.53)	-0.08 (95% CI: 0.22, 0.06)
	Graft survival at 1 year	48/50	48/49	0.98 (95% CI: 0.91, 1.05)	-0.02 (95% CI: 0.09, 0.05)
Oyen <i>et al.</i> 2005 <sup>21</sup>	Perioperative incidents	4/63	1/59	3.75 (95% CI: 0.43, 32.56)	0.05 (95% CI: 0.02, 0.12)
	Reoperations	5/63	0/59	10.31 (95% CI: 0.58, 182.53)	0.08 (95% CI: 0.01, 0.15)
	Other/late complications	5/63	3/59	1.56 (95% CI: 0.39, 6.25)	0.03 (95% CI: 0.06, 0.12)
Simforoosh <i>et al.</i> 2005 <sup>24</sup>	Discharged within 48 h of surgery	83/100	85/100	0.98 (95% CI: 0.87, 1.10)	-0.02 (95% CI: 0.12, 0.08)
	Intraoperative complications	4/100	18/100	0.22 (95% CI: 0.08, 0.63)	-0.14 (95% CI: 0.22, -0.06)
	Postoperative complications	19/100	9/100	2.11 (95% CI: 0.08, 0.63)	0.10 (95% CI: 0.00, 0.20)
Simforoosh <i>et al.</i> 2003 <sup>22</sup>	Reoperation	1/40	0/40	3.00 (95% CI: 0.13, 71.51)	0.03 (95% CI: 0.04, 0.09)
	Pneumothorax	0/40	4/40	0.11 (95% CI: 0.01, 2.00)	-0.10 (95% CI: 0.20, 0.00)
	Bleeding	1/40	0/40	3.00 (95% CI: 0.13, 71.51)	0.03 (95% CI: 0.04, 0.09)
	Retention	1/40	0/40	3.00 (95% CI: 0.13, 71.51)	0.03 (95% CI: 0.04, 0.09)
	Ileus	1/40	2/40	0.50 (95% CI: 0.05, 5.30)	-0.03 (95% CI: 0.11, 0.06)
	UTI	1/40	0/40	3.00 (95% CI: 0.13, 71.51)	0.03 (95% CI: 0.04, 0.09)
	Scrotal swelling	1/40	0/40	3.00 (95% CI: 0.13, 71.51)	0.03 (95% CI: 0.04, 0.09)
	Small spleen injuries	2/40	0/40	5.00 (95% CI: 0.25, 100.97)	0.05 (95% CI: 0.03, 0.13)
Wolf <i>et al.</i> 2001 <sup>19</sup>	Minor postoperative complications	4/23	4/27	1.17 (95% CI: 0.33, 4.18)	0.03 (95% CI: 0.18, 0.23)

UTI, urinary tract infection.

**Table 4** Summary of randomized controlled trials comparing open laparoscopic donor nephrectomy

Study	Case no.	Mean donor age (years)	Kidney R/L	Mean operation time (min)	Mean WIT (min)	Vascular control	Kidney retrieval	Conversion	Mortality	Mean hospital stay (days)	Creatinine day 3 mmol/L	Creatinine 3 months
1. Simforoosh <i>et al.</i> 2003 <sup>22</sup>	Laparoscopic	40	27.3	All left	251.4	6.6	Metal clips	1	0	2.21	1.91	1.32
	Open	40	29.2	All left	135	2.09	Metal clips	0	0	2.13	1.46	1.37
2. Simforoosh <i>et al.</i> 2005 <sup>24</sup>	Laparoscopic	100	27.8	All left	270.8	8.7	Metal clips	0	0	2.26	2.01	1.47
	Open	100	29.2	All left	152.2	1.87	Metal clips	0	0	2.2	1.85	1.41
3. Oyen <i>et al.</i> 2005 <sup>21</sup>	Laparoscopic	63	46	All left	180	4.3	Metal clips Endovascular stapler	1	0	6.2	–	–
	Open	59	45	All left	140	1.4	Metal clip Endovascular stapler	0	0	6.7	–	–
4. Wolf <i>et al.</i> 2001 <sup>19</sup>	Laparoscopic	23	38	All left	206	3.3	Endoscopic staple device	0	0	1.7	1.7	1.2
	Open	27	41	All left	125	1.36	–	0	0	2.6	2.1	1.5
5. Kok <i>et al.</i> 2006 <sup>23</sup>	Laparoscopic	50	49	L-30 R-20	289	6	Endovascular stapler	0	0	3	1.18	1.07
	Open	50	48.5	L-31 R-19	226	3	–	0	0	3	1.17	1.17
6. Andersen <i>et al.</i> 2006 <sup>25</sup>	Laparoscopic	63	46	All left	180	NA	NA	0	0	6.2	NA	NA
	Open	59	45	All left	140	NA	NA	0	0	6.7	NA	NA

WIT, warm ischemia time.