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**Australian Safety
and Efficacy
Register of New
Interventional
Procedures-Surgical**

Systematic Review of Laparoscopic Live Donor Nephrectomy

ASERNIP-S REPORT NO. 3

**Australian Safety & Efficacy Register of
New Interventional Procedures – Surgical**

The Royal Australasian College of Surgeons

Systematic review of laparoscopic live donor nephrectomy

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Safety and Efficacy Classification for Laparoscopic Live Donor Nephrectomy

The ASERNIP-S Procedure Classifications were revised in August 1999 by the ASERNIP-S Management Committee. As such, each of the four procedures already assessed by ASERNIP-S was allocated a new classification from the following list;

1. Safety and efficacy is established. Procedure is equal to, or better than the nominated gold standard. Procedure may be introduced into practice.
2. The safety and efficacy of the procedure cannot be determined due to an incomplete and/or poor quality evidence-base. One of the following recommendations is made:
 - 2.1 An audit is required.
 - 2.2 A Controlled Clinical Trial, preferably prospective with concurrent controls, is required.
 - 2.3 A Randomised Controlled Clinical Trial is required.
3. Safety and efficacy of procedure is shown to be unsatisfactory. Procedure should not be used.

The new classification for Laparoscopic Live Donor Nephrectomy is 2.2. A *Controlled clinical trial is required to assess both safety and efficacy.*

References to previous classifications remain unchanged in the document.

Important Note: The information contained in this report is a distillation of the best available evidence located at the time the searches were completed as stated in the protocol. Please consult with your medical practitioner if you have further questions relating to the information provided, as the clinical context may vary from patient to patient.

The Systematic Review of Laparoscopic Live Donor Nephrectomy,
Recommendations and Safety and Efficacy Classification were
ratified by the:

ASERNIP-S Management Committee
May 8th 1999
Auckland, New Zealand.

Council of the Royal Australasian College of Surgeons in
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**Australian Safety
and Efficacy
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Review Protocol

Laparoscopic Live Donor Nephrectomy

January 1999

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1. Objective

To make recommendations on the safety and efficacy of laparoscopic live donor nephrectomy; in comparison to the standard open nephrectomy for live donors, based on a thorough and systematic review of the peer-reviewed literature.

2. Background

The first live donor renal transplant was performed in 1956¹. Currently, though, the majority of transplants (excepting those in Japan)² are performed using cadaveric kidneys. For example, in 1995 in the United States, live donor renal transplants accounted for only 29% of kidney transplants reported to the United Network for Organ Sharing³.

Potential donors are often reluctant to undergo nephrectomy as it is a major operation performed with no direct health benefit to the individual^{4,5}. The “open” nephrectomy is most commonly undertaken via a retroperitoneal or transperitoneal approach. It involves a large skin incision, wide muscle division, and in some instances, rib resection in a healthy individual. It is associated with significant postoperative pain and extended convalescence³.

A retrospective review of the peri operative morbidity associated with 681 open donor nephrectomies found no mortality, and low – although not inconsequential – morbidity⁶. Complications were as follows: 7% required a chest tube due to pneumothoraces, 5% developed a urinary tract infection, 4% a wound infection, 0.3% needed blood replacement, and 0.003% developed pulmonary emboli. Long-term complications of open donor nephrectomy have been variously cited to include incisional hernia (3.6%), small bowel obstruction (2.0%), scarring and suture granuloma (4.4%)⁷.

Other research has indicated an operative mortality rate of between 0.03% and 0.07% for open live donor nephrectomy and an incidence of major complications of between 1-8%⁵. Donors operated on using the flank approach, which is associated with lower morbidity than the transperitoneal approach, have developed wound complications including infection and hernia formation (9%), and pneumothoraces requiring drainage of the pleural space (8%). Long-term morbidity has been thought to be more substantial, ranging from and possibly exceeding 15-20%. Up to 25% of donors have reported chronic incisional pain or wound diastasis (bulging). After open nephrectomy, the donor may not be able to return to normal activity for another 6-8 weeks^{7,8}. Hospitalisation and the subsequent extended convalescence associated with live kidney donation ensures that it is often a proposition that is logistically and financially unfeasible for the potential donor⁵. Postoperative pain and cosmetic concerns are also inhibitory^{4,5}.

Clayman and associates performed the first clinically successful laparoscopic nephrectomy in a patient with benign renal disease in 1990⁹. The laparoscopic removal of a large solid organ like the kidney had previously not been possible due to a lack of proper control over the larger vascular structures, and an inability to remove the organ through the small laparoscopic port incision¹⁰.

Laparoscopic nephrectomy is now commonly offered at a number of institutions for appropriate patients suffering from benign or malignant renal disease. In terms of mortality and morbidity, laparoscopic nephrectomy for benign disease has been associated with a 15% incidence of complications in patients, including retroperitoneal haematoma, congestive heart failure and pulmonary emboli¹¹. Gill *et al* undertook a multi-institutional review of complications associated with laparoscopic nephrectomy for benign and malignant disease¹². They found no mortality and a 16% incidence of complications, primarily during early experience with the procedure. This compares favourably with the 6-25% incidence of complications associated with undergoing open nephrectomy for benign or malignant disease⁴.

Comparisons of laparoscopic and open nephrectomy for benign disease have found that the laparoscopic approach results in significantly less postoperative pain, shorter hospitalisation and convalescence, and improved cosmesis^{10,11}. The potential advantage of the laparoscopic approach in the live donor situation is that the spectre of major surgery, pain and convalescence is removed. There is a likelihood that as a consequence there would be increased acceptance of the donor operation and, thus, an increase in potential kidney donors³.

In laparoscopic nephrectomy for benign or malignant disease the kidney is often morcellated before removal. However, the donor operation requires that the integrity of the kidney is not insulted. It must be removed intact to ensure a successful transplantation to the recipient. The kidney must therefore have adequate lengths of ureter and renal vasculature, and there must be an acceptably short warm ischaemic time in order to minimise renal tubular damage^{2,5}.

Ratner and colleagues undertook the first clinically successful laparoscopic live donor nephrectomy in February 1995¹³. This followed the pioneering work of Gill *et al* in the porcine model¹⁴. Since that time, several centres have begun performing laparoscopic live donor nephrectomies. Variations on two approaches are used. The common approach is intra- or transperitoneal with gas insufflation (although this has also been done without insufflation^{2,15}). This approach ensures a wider visual field and facilitates access to adequate lengths of ureter and renal vasculature. Experience with the second approach, an extra- or retroperitoneal approach without gas insufflation, is limited and it has not yet gained wider acceptance^{16,17}.

Variations occur within the “standard” transperitoneal laparoscopic live donor nephrectomy technique *i.e.* number of ports used, operative sequencing etc. An example of the technique used for transperitoneal laparoscopic left nephrectomy in a donor is as follows³; the donor receives a general endotracheal anaesthesia and is placed in the right decubitus position. A 15mmHg carbon dioxide pneumoperitoneum is created using a closed technique with Verres needle insertion in the left subcostal region. A total of four operating ports are used for dissection – one for the video endoscope, two dissection ports, and a retraction port. A fifth operating port is placed later during the procedure, through a 6-10cm midline incision to assist in the extraction of the kidney. The operative procedure includes: mobilisation of the left colon and spleen, dissection of the renal vein and renal artery, dissection of the ureter, mobilisation of the kidney (opening of the renal fascia and division of perinephric fat), creation of the extraction incision, insertion and deployment of a large plastic sac over the liver, the placement of the kidney into the extraction sac, and delivery through the midline wound.

With the increasing utilisation of this technique internationally, it is the purpose of this review to determine whether laparoscopic live donor nephrectomy is as safe and efficacious as the traditional, open live donor nephrectomy.

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3. Inclusion Criteria

Papers were selected for inclusion in this literature review on laparoscopic live donor nephrectomy on the basis of the following criteria.

□ **Participants:**

Human and animal studies were included in this review. Specifically, studies on any of the following types of participants were included:

- live kidney donors
- live-donor kidney recipients
- individuals with benign or malignant renal disease undergoing laparoscopic nephrectomy.

□ **New Intervention:**

If the paper included concerned the new intervention, it related to -

Laparoscopic live donor nephrectomy

- extra/retroperitoneal or intra/transperitoneal approaches
- with or without gas insufflation.

□ **Comparative Intervention(s):**

If the paper included concerned a comparative intervention, it related to one or more of the following:

1. Retroperitoneal open donor nephrectomy
2. Transperitoneal open donor nephrectomy
3. Laparoscopic nephrectomy for benign or malignant renal disease.

□ **Outcomes:**

The paper included must have contained information on at least one of the following outcomes of the new or comparative interventions:

1. Peri- and postoperative mortality of patients/donors
2. Peri- and postoperative morbidity of patients/ donors, which may include:
 - pneumothorax
 - haemorrhage
 - fever
 - chronic incisional pain
 - ileus/vomiting
 - wound infection
 - wound hernia/seroma

- urinary retention
 - pneumonia
 - dyspnoea
 - thigh paraesthesia
3. Intraoperative and early postoperative factors for patients/donors, including but not limited to:
 - operative time
 - estimated blood loss
 - blood transfusion
 - conversion from laparoscopic to open procedure
 - parenteral analgesic requirements
 - resumption of oral intake
 4. Graft function and survival, including but not limited to:
 - allograft renal artery, renal vein and ureter lengths
 - warm ischaemic time
 - production of urine intraoperatively, after transplantation
 - length of time to graft function
 - creatinine levels/creatinine clearance in graft recipients
 - graft survival
 5. Convalescence of patients/donors, including but not limited to:
 - ambulation
 - length of hospitalisation
 - time until resumption of normal activities
 - creatinine levels/creatinine clearance
 6. Rates of consent/compliance by potential donors for laparoscopic vs. open nephrectomy.

□ **Types of studies:**

Papers included in the review were in one of the following forms:

- Randomised controlled trials, controlled clinical trials (historical, non-randomised), case-series and case-reports.
- Additional published material in the form of letters, conference material, commentary and discussions, was included in the submissions to the Review Surgeon as background information.
- Study types other than those mentioned above could have been included if they were felt to be relevant and if valid reasons were given in the protocol.

4. Exclusions:

- The ASERNIP-S Researcher and the Protocol Surgeon excluded references that clearly did not meet the inclusion criteria.
- Reasons were documented for excluding particular references that did meet the inclusion criteria.
- Exclusions were documented in Appendix A.

5. Additional Information:

- Guidelines on assessing the published material in terms of methodological design and validity (*i.e.* hierarchy of study designs, bias, confounding, sample size, statistical power) were sent to the Review Surgeon. Supplementary material on the review process was attached, including excerpts from The Cochrane Collaboration Handbook, and the NH&MRC 1995 guidelines for assessing research evidence.
- As this review was an exclusively narrative systematic review, data is summarised in the Independent Methodological Assessment in table format, rather than through meta-analysis.

6. Literature Search Strategies:

□ Databases searched:

- SilverPlatter Medline (WinSpirs)
- Ovid Current Contents
- The Cochrane Collection (The Cochrane Library CD - 1998, Issue 2)
- Lexis-Nexis Embase

Search Terms: - Three search strategies were devised by the ASERNIP-S Researcher and Protocol Surgeon for the Medline, Current Contents and Embase databases.

1. Base search -

This search was performed to enable the retrieval of papers dealing with laparoscopic live donor nephrectomy. The search terms entered were:

((nephrectom* or nephrectomy) and (living donors or liv* donor*) and (laparoscop* or endoscop* or retroperitoneoscop*))

NB:

- 'nephrectomy' and 'living donors' are MeSH headings
- * is a truncation symbol, which retrieves variations of the indicated text, *e.g.* laparoscop* retrieves laparoscope, laparoscopy, laparoscopic. In Medline the truncations symbol is *; in Current Contents it is \$; in Embase it is !.

For example, the search strategy was recognised by the Medline database as:

```
((nephrectom*[All Fields] OR ("Nephrectomy"[MeSH Terms] OR nephrectomy[Text Word]))
AND
(("Living Donors[MeSH Terms] OR living donors[Text Word]) OR (liv*[All Fields]
AND
donor*[All Fields]))
AND
((laparoscop*[All Fields] OR endoscop*[All Fields]) OR retroperitoneoscop*[All Fields]))
```

The same search terms were utilised for the other databases, for the sake of consistency. Current Contents and Embase do not utilise MeSH headings, so the MeSH headings and other terms were simply searched, by default, as free text in all fields.

2. *Search on authors* -

This search was performed on authors known to publish in the field of laparoscopic nephrectomy. The search terms entered were:

((Clayman or Peters or Bartlett) in au) and (nephrectom* or nephrectomy))

3. *Search on general live donor nephrectomy* -

This search was performed to retrieve the most recent research (within the last five years) on open live donor nephrectomy - to be used for comparative purposes. It would also retrieve papers on laparoscopic live donor nephrectomy that were potentially missed by the Base search.

The search terms entered were:

((nephrectom* or nephrectomy) and (living donors or liv* donor*) and (py=1993-1998))

NB: - 'py=1993-1998' limits the references by publication year to between, and including, 1993 and 1998.

4. The ASERNIP-S Researcher used a different, broad strategy for The Cochrane Collection database because the restricted searches turned up very few references.

The simple search term entered was:

'nephrectomy'

□ **Search Time Frame:**

1. SilverPlatter Medline (WinSpirs)

Base search

- Searched the database on 10/8/98
- Year range searched = 1966 - 8/98
- 15 references found

Search on authors

- Searched the database on 10/8/98
- Year range searched = 1984 - 8/98
- 71 references found

Search on general live donor nephrectomy

- Searched the database on 24/8/98
- Year range searched = 1993 - 1998
- 64 references found

2. Ovid Current Contents

- Base search*
- Searched the database on 10/8/98
 - Year range searched = 1993 - 1998 Week 31
 - 24 references found

- Search on authors*
- Searched the database on 10/8/98
 - Year range searched = 1993 - 1998 Week 31
 - 1 reference found

- Search on general live donor nephrectomy*
- Searched the database on 24/8/98
 - Year range searched = 1993 -1998 Week 33
 - 51 references found

3. Lexis-Nexis Embase

- Base search*
- Searched the database on 14/8/98
 - Year range searched = all years
 - 16 references found

- Search on authors*
- Searched the database on 14/8/98
 - Year range searched = all years
 - 71 references found

- Search on general live donor nephrectomy*
- Searched the database on 24/8/98
 - Year range searched = 1993 -1998
 - 53 references found

4. The Cochrane Collection (The Cochrane Library CD - 1998, Issue 2)

- Search on nephrectomy*
- Searched the database on 30/6/98
 - Year range searched = 1966 -1998
 - 80 references found
 - Only 4 references met the inclusion criteria

7. Literature Database:

□ Exclusions by ASERNIP-S Researcher:

- 370 references formed the Reference Manager database.
- 173 references were duplicates.
- 64 references were excluded because they did not meet the inclusion criteria (see Appendix A).

- 6 references concerning the comparative surgical procedures were excluded because the full papers would require translation into English. This could not be justified as these references did not significantly add to the body of knowledge concerning the safety and efficacy of these procedures (see Appendix A).
- 1 reference concerning the new surgical procedure was excluded because the full paper would require translation into English. This could not be justified because the two cases reported in this paper were included in a case series reported in English by the same authors elsewhere.
- 126 references were deemed appropriate for the review.

□ **Inclusions by ASERNIP-S Researcher:**

- 1 reference was included which did not turn up in the search of databases (see Appendix B). It was found in the reference lists of key papers. It fitted the inclusion criteria and so was added to the literature review database.
- Therefore, a total of 127 references were deemed appropriate for the review.
- Abstracts from the International Workshop on Living Donor Kidney Transplantation (held on September 10-12, 1998 in Uppsala, Sweden) were included as background material for the Review Surgeon, where they met the inclusion criteria.

□ **Exclusions by Protocol Surgeon:**

- No further exclusions were thought necessary.

□ **Inclusions by Protocol Surgeon:**

- Abstracts from the Transplantation Society XVII World Congress (held on July 12-17, 1998 in Montreal, Canada) were included as background material for the Review Surgeon, where they met the inclusion criteria.

8. Draft Review:

□ **Exclusions by Review Surgeon:**

- Only clinical studies/papers were included in the Draft Review. This numbered 13 articles.
- In some instances, several papers written by the same group of authors included cases that were documented in previous papers. Therefore, only the most recent paper, reflecting all of the previous material was cited in the Draft Review. As such, 3 articles by Ratner *et al.*, and one paper by Yang *et al.* were excluded from discussion in the Review (see Appendix C).

Appendix A

Exclusions

□ Papers that did not meet the inclusion criteria:

1. Ahsan N, Manning EC, Dabbs DJ, Gifford RR, Yang HC. Recurrent type 1 membranoproliferative glomerulonephritis after renal transplantation and protective role of cyclosporine in acute crescentic transformation. *Clin Transplant*. 1997;**11**(1):9-14.
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Appendix B

This paper was retrieved outside of the database searches and was included because it met the inclusion criteria.

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Appendix C

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**The Safety and Efficacy of Laparoscopic Live
Donor Nephrectomy - A Review of the
Literature**

By

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LAPAROSCOPIC LIVE DONOR NEPHRECTOMY

In a review of the safety and efficacy of Laparoscopic Live Donor Nephrectomy for renal transplantation the case does not need to be argued for the benefits of renal transplantation using cadaver kidneys. They have been transplanted successfully since 1963 when Calne first used Imuran and steroids. Progressively from that time to the present the results of kidney transplantation, as measured by one year primary graft survival, has improved from 50% to 90%¹. This improvement is due in part to more effective immunosuppressive drugs, better management of the organ donor and the use of preservation techniques to minimise damage to the kidney.

Despite the success of cadaveric transplantation, unfortunately the number of cadaveric kidneys available falls short of the number required by transplant patients on waiting lists. In Australia, there are approximately 1500 patients requiring renal transplants and they have to wait one to eight years¹. Families have the option to consider live donation - either related, usually a first order relative (sibling or parent), or a living unrelated donor, almost always a spouse¹. In Australia the number of live donors was 13% of the total renal transplants in 1990 increasing to 29% in 1997¹. In the U.S.A. where there is an active cadaveric and living donor program the live donor rate was similar in 1994 at 25%². In Asian countries where cadaveric donation is rare because of cultural issues many active transplant centres can only offer living donor transplants. The one year graft survival following living donation is 95%^{1,3} - marginally better than cadaveric grafts. At ten years post transplant cadaveric renal transplant survival is half that of living related renal allografts^{3,4}.

The decision to proceed with a nephrectomy on a living donor and use the kidney for transplantation requires that the surgical team should be able to complete the surgery with low morbidity and near zero mortality.

Unfortunately in moderately major surgery such as nephrectomy, which is done in considerable volume, zero mortality is not achieved in the long term. The published risks of mortality for open live donor nephrectomy is 0.03 – 0.07% and significant morbidity is 1-8%². Death can occur following major surgery due to anaesthetic complications, acute myocardial infarction, pulmonary emboli, and haemorrhage. Morbidity may include wound infections, pulmonary complications and urinary tract infection. Longer-term problems include wound pain and incisional hernia development.

The new procedure of laparoscopic live donor nephrectomy or laparoscopically assisted live donor nephrectomy is a refinement of the traditional open nephrectomy used for live donors. The procedure of laparoscopic nephrectomy was first described by Clayman⁵ in 1990 and is practiced for both benign and malignant disease by a few surgeons who have developed expertise with laparoscopic techniques^{6,7}. The demands on the surgeon in laparoscopic assisted living donor nephrectomy is somewhat greater in that he must remove the kidney with careful dissection of the renal vessels and ureter so that it is suitable for immediate transplantation into the recipient.

In 1994, in an experimental study, Gill⁸ reported on a left nephrectomy and autotransplantation in the pig. Similar renal function was observed in surviving animals after the left nephrectomy was done by either the open or laparoscopic technique.

The attraction of laparoscopic live donor nephrectomy is the potential for more rapid recovery by the donor from the surgical insult. This could result in shorter length of hospital stay, less post operative pain, less post operative morbidity and an earlier return to normal activities, whether to home duties or paid work. These advantages would need to be achieved without further risk to the live donor or the immediate and long-term function of the kidney in the recipient.

The technique of laparoscopic live donor nephrectomy has some inherent limitations. Certainly initially, and likely even after a considerable experience, the length of time to complete the laparoscopic procedure will be longer than an open operation⁹. There are difficulties in the laparoscopic technique to obtain as long a length of the renal vein, particularly on the right side compared to the open technique. Unexpected arterial or venous anomalies are potentially a more difficult problem with the laparoscopic technique. If this is done transabdominally, it may cause some patients to develop intra-abdominal adhesions. The long-term risk to the donor of a small bowel obstruction is estimated to be a 2% life time risk¹⁰. It will take another decade or more to be confident of the risk following laparoscopic transperitoneal nephrectomy.

A period of pneumoperitoneum at a pressure of 20 mm Hg causes a reduction in renal blood flow and glomerular filtration rate to 25% of normal¹¹. During prolonged dissection and therefore prolonged pneumoperitoneum it would be expected to compromise immediate renal function. Finally the warm ischaemia time will be longer with the laparoscopic technique. This is unlikely to be critically longer unless difficulties are encountered in removing the kidney from a too small laparotomy incision.

With these potential advantages to the patient and the potential hazards inherent in the technique of laparoscopic live donor nephrectomy what is the evidence to date? Unfortunately the technique was only introduced in 1995 by Ratner and the reported techniques, by this and other authors, have included a trans-abdominal approach, both with CO₂ insufflation (Ratner⁹, Schulam¹², Flowers¹³,) and without CO₂ insufflation (Suzuki¹⁴, Ishikawa¹⁵); and a retroperitoneal approach without CO₂ insufflation (Suzuki¹⁶, Yang¹⁷).

In reviewing these studies evidence is gained from a review of historical open live donor nephrectomy patients compared to selected patients judged suitable for the laparoscopic technique. In each paper reviewed the authors are enthusiastic advocates of this new technique, but can only provide evidence of the short-term morbidity of the laparoscopic approach.

In the paper by Flowers¹³ 70 patients were selected for laparoscopic live donor nephrectomy compared to 65 patients treated by open nephrectomy. Of the 70 patients selected for laparoscopic nephrectomy, the operation was successfully completed in 66. One kidney was discarded when a small renal cell cancer was identified. Four patients were converted to an open procedure. Two significant vascular injuries – one renal artery and one external iliac artery required immediate open repair. A third vascular injury was due to avulsion of a branch of the renal vein. The final conversion was due to an inability to maintain a pneumoperitoneum. One patient in the laparoscopic group required re-operation for a bleed from the spleen requiring a splenectomy. In the laparoscopic group 14% of patients had in-hospital postoperative morbidity – similar to the proportion of morbidity in the open group. Flowers' comparison of data collected prospectively in the laparoscopic group with retrospective analysis of records in the open group showed a reduction in the in-hospital stay

of 2.3 days between the laparoscopic nephrectomy and open nephrectomy groups. Similarly there was a significant reduction in analgesic use, earlier return to a normal diet and significant shorter return to normal activities for the laparoscopic group.

Similar results are reported from the John Hopkins group in papers by Hiller¹⁸ and Ratner⁹. Again their studies of smaller groups of patients reported a current laparoscopic nephrectomy group and a retrospectively analysed open nephrectomy group. Again there has been a clear benefit to the donor as shown by the length of hospital stay, analgesic use and return to normal activities. As has been noted in similar studies with inguinal hernia repair, patients treated by laparoscopic means may return to normal activities more quickly than patients treated by the open technique nevertheless they tend to use their full leave entitlements before returning to work.

Articles describing the retroperitoneal approach by Suzuki¹⁶ and Yang¹⁷ describe two to three patients and indicate only that the technique is possible.

Conclusion

In analysing this topic of laparoscopic live donor nephrectomy this review is being carried out just four years after the procedure was first described. The technique is still evolving - with advocates of both a transperitoneal approach using a pneumoperitoneum or retraction, and a retroperitoneal approach using retraction and a combination of laparoscopic and open instrumentation.

There are no papers to review that give the results of the morbidity and the recovery following the various laparoscopic techniques compared to a contemporaneous series of cases of open live donor nephrectomy. All papers reviewed are from centres with a special interest, expertise, and enthusiasm for laparoscopic surgery.

These observations I think indicate the way ahead and I would make the following recommendations:

1. Laparoscopic live donor nephrectomy should only be done in Units where there are surgeons with considerable expertise in open live donor nephrectomy.
2. The live donor nephrectomy surgical team planning to start laparoscopic live donor nephrectomies should include a surgeon with established experience in a range of laparoscopic procedures.
3. Laparoscopic live donor nephrectomy should be done initially in either a large animal or the technique used in a patient requiring a nephrectomy for benign disease.
4. Renal Transplant Units planning to undertake laparoscopic live donor nephrectomy should plan to do a series of these cases and maintain detailed records of the theatre costs, hospital costs, morbidity and outcome in both open and laparoscopic cases.
5. Surgeons should be alert to the literature on evolving techniques of laparoscopic nephrectomy. Of particular interest is the option to use an extraperitoneal approach compared to a transperitoneal approach.

Unfortunately at this early stage in the evolution of laparoscopic live donor nephrectomy, I do not believe from the literature that there is evidence that this technique has advantages that would require Transplant Units to change from the established technique of an open live donor nephrectomy to the laparoscopic technique. Nevertheless, the evidence is that in surgical teams with considerable skills in both laparoscopic surgery and renal transplantation this procedure can be done with an acceptable low morbidity, near zero mortality, and that the removed kidneys function well in the recipients. I think a recommendation can be made for its cautious introduction where the above skills exist and where there is a commitment to do 10-20 of these cases per year in order to gain the necessary experience and report the results.

In the ASERNIP-S safety and efficacy categories I would recommend Category 3.

1. Safety and efficacy is established. Procedure may be used.
2. The procedure is sufficiently close to a procedure of established safety and efficacy to give no reasonable grounds for questioning safety and efficacy. Procedure may be used subject to continuing audit.
- 3. Safety and efficacy of the procedure is not yet established. Procedure requires further evaluation and may be used only as part of systematic research; comprising either an observational study or a controlled clinical trial.**
4. Safety and efficacy of the procedure is shown to be unsatisfactory. Procedure should not be used.

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ASERNIP/S



**Australian Safety
and Efficacy
Register of New
Interventional
Procedures-Surgical**

**Independent Methodological
Assessment:
Laparoscopic Live-Donor Nephrectomy
Literature**

**Mrs Tracy Merlin
Research Assistant
Australian Safety and Efficacy Register
Of New Interventional Procedures - Surgical
Royal Australasian College of Surgeons**

Summary

Laparoscopic live donor nephrectomy is a comparatively new procedure that is being evaluated by a nominated ASERNIP-S Review Group. ASERNIP-S is primarily concerned with comparing the safety and efficacy of laparoscopic live donor nephrectomy with the “gold standard” of open live donor nephrectomy.

As expected, there is a lack of published literature on laparoscopic live donor nephrectomy. It has only been five years since the procedure was first developed in the animal model¹ and only four years since it was first conducted on humans².

After extensive searches of the medical electronic databases, only seventeen articles on laparoscopic live donor nephrectomy were identified and disseminated for review to the ASERNIP-S Review Group.

Of these seventeen articles, one was a brief communication describing a technique for managing multiple renal arteries during laparoscopic live donor nephrectomy³, two were letters relating to this communication^{4,5}, and one was a news report⁶.

The thirteen remaining papers were clinical studies that are described and critiqued in the attached Review Table Summary. These papers ranged from Level II to Level IV evidence (see Appendix I, Hierarchy of Evidence [National Health and Medical Research Council]). Level I evidence - a systematic review of all relevant randomised controlled trials - was not available.

One randomised controlled trial (Level II evidence) was conducted to initially determine the feasibility of laparoscopic live donor nephrectomy in pigs¹. The internal validity of the study was average, hindered by possible observation bias and a small sample size. The external validity, however, was poor. Results regarding the safety and efficacy of the procedure in pigs could not be generalised to potential human donors.

Two controlled clinical trials with concurrent controls (Level III-2 evidence) were undertaken^{7,8}. The internal validity of the studies was average due to possible selection and observation bias. Both studies found that donors undergoing the laparoscopic technique had a significantly lower duration of hospitalisation, of post-discharge pain medication usage, and a faster convalescence or return to usual activities than donors that received the standard open live donor nephrectomy. The external validity of the results was, again, of poor to average quality. Differences in the selection criteria applied to donors that were eligible for both types of surgery and a lack of information regarding these criteria meant that the safety and efficacy results of the two studies could not be generalised with confidence to the potential human donor population.

One study used a combination of concurrent and historic controls (Level III-2/III-3 evidence)⁹. The safety and efficacy findings had average internal validity - the main problems being possible selection and observation bias. Donors undergoing the laparoscopic technique had significantly lower blood loss, faster convalescence and return to usual activities, and less pain medication than donors receiving the open live donor nephrectomy do. Eligibility and selection criteria were well delineated in the paper so the external validity of the study was good. Results could be generalised to most potential kidney donors, excluding those with the conditions outlined in the paper.

Five papers were controlled clinical trials with historic controls (Level III-3 evidence). Two of these studies had average internal and external validity^{10,11} - hampered, once again, by possible observation and selection bias. Both papers reflected the findings of studies with a better study design - the laparoscopic group had significantly lower blood loss and use of pain medication, and a faster convalescence and return to usual activities. Two of the three remaining historically controlled studies, variously comparing laparoscopy-assisted live donor nephrectomy with retroperitoneoscopy-assisted live donor nephrectomy and open live donor nephrectomy, had poor internal and external validity^{12,13}. Possible observation and selection bias, as well as chance variation (due to the very small sample size), influenced the results of these studies.

The last of these historically controlled clinical trials compared retroperitoneoscopy-assisted live donor nephrectomy with open live donor nephrectomy and was purely descriptive¹⁴. The sample size was too small to produce meaningful inferential statistics.

Level IV evidence was represented by three case-series papers, on two to three cases each, that described the laparoscopic live donor nephrectomy procedure¹⁵ and a slightly different retroperitoneoscopy-assisted live donor nephrectomy procedure^{16,17}. The remaining paper was the initial case report by Ratner (1995) of laparoscopic live donor nephrectomy when it was first conducted on a human².

Conclusion

High level evidence comparing the safety and efficacy of laparoscopic live donor nephrectomy and open live donor nephrectomy is non-existent. Limited level III-2 evidence would suggest that laparoscopic live donor nephrectomy may have advantages over open live donor nephrectomy with regard to the donor's hospital stay, convalescence, pain, and return to usual activities. No statistically significant differences in donor mortality or morbidity were found in any of the papers comparing the laparoscopic technique with the open technique. However, the small sample sizes in these papers indicate that statistically significant differences would have been very difficult to detect. Further, statistical significance should not be equated with clinical significance.

Studies of better quality and design, with larger sample sizes, are required before the safety and efficacy of laparoscopic live donor nephrectomy, in comparison to open live donor nephrectomy, can be properly assessed. Indications so far are that the possible benefits of laparoscopic live donor nephrectomy should be further investigated but under highly controlled conditions and using quality scientific methodology. Randomised controlled trials, as a first choice, may be difficult to implement because of ethical reasons. The next best option would be several multi-centre, prospective studies of large sample size and with concurrent controls. Attention should also be given to the control of observation and selection bias and possible confounders in the study design.

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REVIEW TABLE SUMMARY

REVIEW TABLE SUMMARY

Lap LD Nx = laparoscopic live donor nephrectomy

Open LD Nx = open live donor nephrectomy

Authors	Yr.	Location	Description of Evidence				
			Intervention	Design	Level of Evidence	Study Population	Main Results
Gill Carbone Clayman Fadden <i>et al.</i>	1994	Division of Urology, University of Kentucky Albert Chandler Medical Centre, Lexington, Kentucky Division of Urology & Division of Radiology, Washington University School of Medicine, St Louis, Missouri.	<i>Study</i> - Lap LD Nx. (left k) Transperitoneal Pneumoperitoneum. <i>Control</i> - Open LD Nx. (left k). Technique?	Randomised controlled trial. Allocated randomly to study and control groups.	II (animal)	<i>Sample size:</i> control: n=5 study: n=10 <i>Study period: ?</i> Female farm pigs weighing 70 - 90 pounds (all laparoscopically, right-kidney nephrectom- ised 3 weeks previously).	Left kidney removed in both groups of pigs and autotransplanted. <i>1. Safety of Lap LD Nx:</i> Mortality - Lap LD Nx = 4/10 = 40%; Open LD Nx = 3/5 = 50%. Reasons: Lap LD Nx - pneumonitis (1); wound dehiscence leading to intestinal gangrene (1); haemorrhage from disruption of the renal vein anastomosis (1); primary non-function of the kidney (1). Open LD Nx - pneumonitis (1); primary non-function of the kidney (1); graft thrombosis (1). Morbidity/complications - Intra-operative complications = 0 in both groups; Postoperative complications: Lap LD Nx - vascular (1), Open LD Nx - vascular (1). <i>2. Efficacy of Lap LD Nx:</i> Mean serum creatinine levels (mg/dL) Days 1 -30 - Lap LD Nx (n=6): peaked on day 2 (5.9); Open LD Nx (n=2): peaked on day 1 (3.5). By day 7 - similar levels in both groups. At 7 and 30 days post-op N.S. difference between lap and open groups, p=0.4. Mean creatinine clearance (mg/min) Days 0 -30 - Creatinine clearance slightly higher in open group than lap group but not significantly different. Lap LD Nx (n=6); Open LD Nx (n=2). Mean length of R.A. (cm) - Lap LD Nx = 2.6 +/- 0.9; Open LD Nx = 2.4 +/- 0.6. N.S. p=0.69 Mean length of R.V. (cm) - Lap LD Nx = 3.1 +/- 0.6; Open LD Nx = 2.9 +/- 1.1. N.S. p=0.79 Mean length of ureter (cm) - Lap LD Nx = 13.6 +/- 2.8; Open LD Nx = 11.6 +/- 1.5. N.S. p=0.18 Mean width of mesoureter (cm) - Lap LD Nx = 3.3 +/- 1.8; Open LD Nx = 1.9 +/- 0.3. Signif. P=0.031 Mean length of skin incision (cm) - Lap LD Nx = 5.8 +/- 1.0; Open LD Nx = 33.5 +/- 1.0. Signif. P=0.0001 Mean operative time (min) - Lap LD Nx = 175.4 +/- 60.6; Open LD Nx = 75.2 +/- 19.1. Signif. P=0.0005 Mean warm ischaemia time (min) - Lap LD Nx = 9.8 +/- 7.2; Open LD Nx = 1.9 +/- 0.6. Signif. P=0.0075 Mean cold ischaemia time (min) - Lap LD Nx = 131.9 +/- 18.2; Open LD Nx = 159.2 +/- 18.9 Signif. P=0.018 (all study kidneys underwent laparoscopic in situ hypothermic perfusion) Mean revascularisation time (min) - Lap LD Nx = 52.0 +/- 29.3; Open LD Nx = 53.0 +/- 3.7. N.S. p=0.92 Renal core temps - N.S difference between groups. P=0.067. Histologic comparisons - N.S. difference between groups re glomerular, tubular or interstitial damage in biopsies. Renal functional status at molecular level. Renal parenchymal concentrations. ATP (adenosine triphosphate) (mMKw) - significantly lower in Lap LD group (0.37) than Open group (0.75); PCr (phosphocreatinine) (mMKw) - significantly lower in Lap LD group (0.06) than Open group (0.13); Lactate (mMKw) - significantly higher in Lap LD group (12.6) than Open group (4.55). Results consistent with longer ischaemia in lap group but do not appear to be clinically significant as there was normal histologic appearance and similar post-transplant renal function in both groups.

REVIEW TABLE SUMMARY (cont)

Authors	Summary of Internal Validity		Summary of External Validity
<p>Gill Carbone Clayman Fadden <i>et al.</i></p>	<p><i>1. Bias</i> a. Possibility of observation bias - no single blinding; and unclear as to whether all outcome measures for both groups were measured the same way. However, outcome measures were mainly objective. b. Misclassification bias unlikely. d. Selection bias unlikely - randomised allocation to groups.</p> <p><i>2. Confounding</i> Randomisation will have minimised problem of confounders, although sample size was so small that non-equivalence of groups cannot be ruled out completely. Age and weight of pigs are possible confounders.</p> <p><i>3. Chance</i> a. Unclear as to whether inferential statistics have been used appropriately (details of all tests used have not been provided). b. Very small numbers in study and control groups so there is an increased likelihood that significant results were actually due to chance variation. c. Power of test inadequate.</p> <p>Chance variation, therefore, was possible explanation for the significant results.</p>	<p><i>4. Time and Strength</i> Intervention design - therefore, outcomes followed exposure.</p> <p>Lap LD Nx had a 33% protective effect from mortality, compared to Open Nx. The relative risk calculated at ASERNIP -S was 0.67. 95% confidence intervals [0.24, 1.96] - so the effect was non-significant. The study had not nearly enough power to detect significant differences.</p> <p><i>5. Overview</i> Effects of selection bias, misclassification bias and confounding appear to have been largely nullified through a prospective, randomised design. There is a small possibility that there was observation bias, as the design did not include blinding. The greatest test to the internal validity, however, is the possibility that the observed differences between Lap LD Nx and Open Nx are due to chance variation. The likelihood that the observed differences between the groups were the unequivocal effect of the different types of surgery cannot be assured.</p> <p>Internal validity: average.</p>	<p>Results cannot be applied to potential human donors. The animal model is sufficient to suggest that Lap LD Nx may be technically possible in humans but the safety and efficacy cannot be generalised.</p> <p>External validity: poor.</p>

Authors	Yr.	Location	Description of Evidence				
			Intervention	Design	Level of Evidence	Study Population	Main Results
Hiller Sroka Holocek Morrison Kavoussi Ratner	1997	Departments of Surgery & Urology, Johns Hopkins University School of Medicine and Johns Hopkins Bayview Medical Centre, Baltimore, Maryland, USA.	<p><i>Study</i> - Lap LD Nx. Transperitoneal. Pneumoperitoneum.</p> <p><i>Control</i> - Open LD Nx. Flank/extraperitoneal?</p>	<p>Controlled clinical trial. Concurrent controls. Non-randomised.</p> <p>[not, as described in the paper, a descriptive survey - otherwise the sampling would not be based on a defined exposure]</p>	<p>III-2</p>	<p><i>Sample size:</i> control: n=27 study: n=9 (n=10 for some outcomes)</p> <p><i>Study period:</i> control - 1/95 - 4/96 study - 1/95 - 4/96</p> <p>Non-randomised - patients in Lap LD Nx self-selected i.e. chose lap over open. Eligibility for Lap LD Nx possibly also determined by surgeon (info not given). Patients in Open Nx group attended a different transplant centre. Same surgeons? Were not offered Lap LD Nx.</p>	<p>No information regarding which kidney was removed.</p> <p><i>1. Safety of Lap LD Nx:</i> Conversion rate - 0% Mortality - Lap LD Nx = 0; Open LD Nx = 0. Morbidity/complications - Lap LD Nx = 1/9 (11%); Open LD Nx = 4/27 (15%). R.R. = 0.75, 95% C.I. [0.1, 5.7]. N.S. Lap LD Nx - incisional hernia in infra-umbilical incision following surgery = 1/9 (11%) Open LD Nx - pulmonary embolus = 1/27 (4%); wound dehiscence = 2/27 (7%); wound infection = 1/27 fever (4%);</p> <p><i>2. Efficacy of Lap LD Nx:</i> Post-discharge pain medication (prescription) (days) - Lap LD Nx = 3.3 +/- 4.4; Open LD Nx = 8.8 +/- 6.5. Signif. P=0.02 Post-discharge pain medication (over-counter) (usage) - Lap LD Nx = 2/9 (22%); Open LD Nx = 15/27 (56%). R.R. = 0.4, 95% C.I. [0.1, 1.1]. N.S. Post-discharge pain medication (over-counter) (days) - Lap LD Nx = 1.1 +/- 2.4; Open LD Nx = 20.1 +/- 30.1. Signif. P=0.03 Mean length of stay (days) - Lap LD Nx = 2.6 +/- 1.0; Open LD Nx = 5.5 +/- 1.0. Signif. P<0.001 Mean resumption of employment (weeks) - Lap LD Nx = 3.8 +/- 2.2; Open LD Nx = 6.4 +/- 3.4. Signif. P=0.035. [Many Lap LD Nx donors felt able to return to work sooner but decided to make full use of their disability benefits] Mean resumption of exercise (days) - Lap LD Nx = 22.4 +/- 17.7; Open LD Nx = 61.4 +/- 55.7. Signif. P=0.03. Mean resumption of housework (days) - Lap LD Nx = 17.5 +/- 15.5; Open LD Nx = 34.0 +/- 36.7. N.S. Mean resumption of driving (days) - Lap LD Nx = 14.8 +/- 13.1; Open LD Nx = 22.2 +/- 18.4. N.S. Required post-discharge care (usage) - Lap LD Nx = 3/9 (33%); Open LD Nx = 15/27 (55%). R.R. = 0.6, 95% C.I. [0.25, 1.43]. N.S. Required post-discharge care (days) - Lap LD Nx = 1.8 +/- 1.0; Open LD Nx = 11.9 +/- 7.7. Signif. P=0.04. Mean resumption of grocery shopping (days) - Lap LD Nx = 17.8 +/- 14.4; Open LD Nx = 23.2 +/- 20.7. N.S. Mean resumption of caring for family members (days) - Lap LD Nx = 16.5 +/- 17.6; Open LD Nx = 20.7 +/- 20.4. N.S.</p> <p>Descriptive statistics are given of the subjective donor experience re the decision to donate, whether the option of a Lap LD Nx influenced decision-making, and the donation experience as a whole.</p>

Authors	Summary of Internal Validity		Summary of External Validity
Hiller Sroka Holochek Morrison Kavoussi Ratner	<p><i>1. Bias</i></p> <p>a. Possible observation bias - no single/doubling blinding; interviewers were transplant coordinators. However, instrument was standardised to some degree.</p> <p>b. Misclassification bias unlikely - concurrent controls and follow-up time were non-differential. Misclassification error a possibility due to reliance on recall.</p> <p>c. Selection bias likely - self-selection of Lap LD Nx donors and probable differential eligibility criteria for both groups.</p> <p><i>2. Confounding</i></p> <p>Non-differential distribution of several potential confounders (i.e. age, gender, occupation) determined in analyses. However, not all potential confounders (e.g. obesity, SES, comorbidity) addressed.</p> <p><i>3. Chance</i></p> <p>a. Descriptive and inferential statistics used appropriately.</p> <p>Chance variation cannot be ruled out as an explanation for the significant results, given the small sample size.</p>	<p><i>4. Time, Strength and Consistency</i></p> <p>Intervention design - therefore, outcomes followed exposure.</p> <p>Strong associations and wide, non-significant, confidence intervals (determined by ASERNIP-S) for morbidity, medication usage, and the need for post-discharge care. It, therefore, cannot be concluded that there was no appreciable difference between the groups for these variables - larger sample size is needed.</p> <p>Relationship consistent for one sub-group analysis re those with physically demanding work.</p> <p><i>5. Overview</i></p> <p>Results are unlikely to be explained by misclassification bias. It is possible that the findings could be attributed to a confounder (like obesity) or due to chance variation (small sample size). Selection bias and, to a lesser extent, observation bias are the major concern. The likelihood that the observed differences between the groups were the unequivocal effect of the different types of surgery cannot be assured.</p> <p>Internal validity: average.</p>	<p>Results cannot be applied fully to the potential human donor population. Differences within the eligible and source populations and the lack of information concerning absolute/relative contraindications means that the safety and efficacy results cannot be generalised with confidence.</p> <p>External validity: poor-average.</p>

Authors	Yr.	Location	Description of Evidence				
			Intervention	Design	Level of Evidence	Study Population	Main Results
Ratner Hiller Sroka Weber Sikorsky Montgomery Kavoussi	1997	Departments of Surgery & Urology, Johns Hopkins University School of Medicine and Johns Hopkins Medical Institutions, Baltimore Maryland, USA.	<p><i>Study</i> - Lap LD Nx. Transperitoneal? Pneumoperitoneum?</p> <p><i>Control</i> - Open LD Nx. Flank/extraperitoneal</p>	Controlled clinical trial. Concurrent controls. Non-randomised.	III-2	<p><i>Sample size:</i> control: n=37 study: n=25</p> <p><i>Study period:</i> control - 12/1/95 - 1/12/96 study - 12/1/95 - 1/12/96</p> <p>Non-randomised. No information re selection criteria (presume it was similar to that in their other papers).</p> <p>Lap LD Nx donors from Johns Hopkins Bayview Medical Centre and Johns Hopkins Hospital. Open LD Nx donors from Johns Hopkins Hospital.</p>	<p><i>1. Efficacy of Lap LD NX:</i> ?Mean post-discharge pain medication (prescription) (days) - Lap LD Nx = 4.2 +/- 3.5; Open LD Nx = 11.8 +/- 13.4. Signif. P=0.004 ?Mean post-discharge pain medication (over-counter) (days) - Lap LD Nx = 2.9 +/- 6.5; Open LD Nx = 16.9 +/- 27.3. Signif. P=0.028 ?Mean length of stay (days) - Lap LD Nx = 2.9 +/- 1.0; Open LD Nx = 5.5 +/- 1.2. Signif. P<0.001 ?Mean 'felt able' to return to work (weeks) - Lap LD Nx = 3.2 +/- 2.1; Open LD Nx = 6.2 +/- 3.2. Signif. P<0.001 ?Mean actual return to work (weeks) - Lap LD Nx = 4.4 +/- 2.7; Open LD Nx = 6.3 +/- 3.3. Signif. P=0.020. ?Mean resumption of driving (days) - Lap LD Nx = 13.5 +/- 10.8; Open LD Nx = 22.2 +/- 17.0. Signif. P=0.01 ?Mean resumption of exercise (days) - Lap LD Nx = 25.2 +/- 27.0; Open LD Nx = 65.8 +/- 58.2. Signif. P=0.003. ?Mean caring for the home (days) - Lap LD Nx = 12.7 +/- 10.7; Open LD Nx = 31.7 +/- 3.3. Signif. P<0.001 ?Mean recommencing caring for others (days) - Lap LD Nx = 13.0 +/- 11.8; Open LD Nx = 21.8 +/- 20.8. N.S. ?Mean resumption of grocery shopping (days) - Lap LD Nx = 15.3 +/- 9.6; Open LD Nx = 23.6 +/- 19.4. N.S.</p>

Authors	Summary of Internal Validity		Summary of External Validity
Ratner Hiller Sroka Weber Sikorsky Montgomery Kavoussi	<p><i>1. Bias</i></p> <p>a. Observation bias a possibility - no single/doubling blinding; record review and telephone surveying by investigators; no standardised instrument; most outcome measures were subjective.</p> <p>b. Misclassification error a possibility due to lack of <i>a priori</i> definition/categorisation - retrospective review. Misclassification bias possible as more care and attention may have been used for records relating to the new procedure, in comparison to the standard procedure.</p> <p>c. Selection bias a possibility. No information in the paper on donor selection criteria or whether it was differentially applied to the two groups. Other studies/papers by Ratner's group indicate selection bias.</p> <p><i>2. Confounding</i></p> <p>Both groups analysed with respect to age, gender, race, and the proportion caring for home, caring for others, or with physically demanding employment. All of these variables were possible confounders but were not significantly distributed differentially across the two groups. Other possible confounders were not addressed addressed i.e. weight, comorbidity and SES.</p> <p><i>3. Chance</i></p> <p>a. Assumption was that the data were in the form of means and standard deviations, although this was not explicitly stated.</p> <p>b. Statistical tests were appropriate for the type of data and analysis.</p> <p>c. Sample size was on the small-side but not inadequate.</p> <p>d. Chance variation an unlikely explanation for the observed differences between the two groups.</p>	<p><i>4. Time and Strength</i></p> <p>Intervention design - therefore, outcomes followed exposure.</p> <p>Measures of association were not calculated in this paper, or by ASERNIP-S, because the data was not in the form of counts.</p> <p><i>5. Overview</i></p> <p>Effects of confounding and chance appear to have been largely nullified. Bias, though, was an issue. Observation bias was possible given the lack of blinding, the use of retrospective record review and investigator surveying. There was no mention of a standardised instrument. Misclassification error and bias were possible given the retrospective nature of the study, lack of <i>a priori</i> definition/categorisation, and likelihood that outcomes of the new laparoscopic procedure would be more carefully documented. Selection bias was a possibility although no information was presented in the study on eligibility criteria or whether it was differentially applied.</p> <p>The likelihood that the observed differences between the groups were the unequivocal effect of the different types of surgery cannot be completely assured.</p> <p>Internal validity: average.</p>	<p>There was no information in the paper regarding the eligibility criteria for potential donors for each type of surgery. There was no information on the participation rate. Whether participant results can be applied to the eligible population cannot be assessed.</p> <p>Some of the source population came from a different transplant centre (Johns Hopkins Bayview Medical Centre).</p> <p>Results cannot be generalised fully to the potential human donor population until there is more information on the selection criteria used and actual participation rate.</p> <p>External validity: poor.</p>

Authors	Yr.	Location	Description of Evidence				
			Intervention	Design	Level of Evidence	Study Population	Main Results
Flowers Jacobs Cho Morton <i>et al.</i>	1997	University of Maryland School of Medicine Baltimore, Maryland	<i>Study</i> - Lap LD Nx. Transperitoneal. Pneumoperitoneum. <i>Control</i> - Open LD Nx. Flank/extraperitoneal.	Controlled clinical trial. Mixed historic/ concurrent controls. Non-randomised.	III-2/ III -3	<i>Sample size:</i> control: n=65 study: n=70 <i>Study period:</i> control - 1/94 - 3/97 study - 3/96 - 3/97 Control & study groups matched for age, gender, race & comorbidity.	Left kidney removed in all Lap LD Nx patients; Open LD Nx ? <i>1. Safety of Lap LD Nx:</i> Conversion rate - 4/70 (5.7%). Reasons: vascular injury (3), morbid obesity/inability to sustain peritoneum (1). Mortality - Lap LD Nx = 0; Open LD Nx = 0. Morbidity/complications - Lap LD Nx = 10/70 (14%), incl conversions; Open LD Nx = 35% (sev. patients had more than 1 complication - not sure how they arrived at this figure, i.e. have data on no. of complications rather than no. of cases). O.R. = 4.1. N.S. Lap LD NX - haemorrhage/blood transfusion (6%) - 1 of these patients required re-operation for a splenic injury; hypoxia (3%); renal artery injury (1.4%); external iliac artery injury (1.4%); urinary retention (1.4%); congestive heart failure (1.4%). Open LD Nx - pneumothorax (22%); haemorrhage (11%); fever (9%); persistent incisional pain (8%); ileus/vomiting (6%); wound hernia/seroma (6%); urinary retention (6%); dyspnoea (3%). Mean estimated blood loss (ml) - Lap LD Nx = 122.3 (30% of Open); Open LD Nx = 408.0. Signif. P=0.0001 <i>2. Efficacy of Lap LD NX:</i> Graft survival - Lap LD Nx (n=69) = 97%; Open LD Nx (n=65) = 98%. N.S. p=0.6191. (follow-up 2-12 months, ave. 7 months) Delayed graft function - Lap LD Nx (n=69) = 3%; Open LD Nx (n=65) = 2%. N.S. p=0.4961. Mean operating room time (min) - Lap LD Nx = 226.3; Open LD Nx = 212.8. N.S. p=0.1658 Mean resumption of diet/liquids (hr) - Lap LD Nx = 16.3 (30% of Open); Open LD Nx = 51.0. Signif. P=0.0001 Mean resumption of diet/solids (hr) - Lap LD Nx = 40.0; Open LD Nx = 77.7. Signif. P=0.0001 Mean duration of parenteral narcotics (hr) - Lap LD Nx = 28.6 (48% of Open); Open LD Nx = 60.1. Signif. P=0.0001 Mean length of stay (days) - Lap LD Nx = 2.2 (49% of Open); Open LD Nx = 4.5. Signif. P=0.001 Mean resumption of housework (days) - Lap LD Nx = 8.8 (33% of Open); Open LD Nx = 26.9. Signif. P=0.0001 Mean resumption of driving (days) - Lap LD Nx = 11.1 (35% of Open); Open LD Nx = 31.6. Signif. P=0.0001 Mean resumption of employment (days) - Lap LD Nx = 15.9 (31% of Open); Open LD Nx = 51.5. Signif. P=0.0001. Open LD Nx results skewed by 3 patients with prolonged recovery due to chronic incisional pain. Minus these outliers, it would be 45.5 days.

Authors	Summary of Internal Validity		Summary of External Validity
Flowers Jacobs Cho Morton <i>et al.</i>	<p><i>1. Bias</i></p> <p>a. Possible observation bias - no single/doubling blinding; and likely differentials in data collection method. Outcome measures are mainly objective.</p> <p>b. Possible misclassification bias due to retrospective data collection.</p> <p>c. Strong possibility of selection bias - different eligibility criteria/relative contraindications for Lap LD Nx compared to Open Nx.</p> <p><i>2. Confounding</i> Data matched on age, gender, race and comorbidity. Confounders appear to have been adequately addressed, although a randomised design would have been ideal.</p> <p><i>3. Chance</i></p> <p>a. Descriptive and inferential statistics used appropriately.</p> <p>b. More information should have been given regarding the use of 1 or 2-tailed tests, how the covariates/matching variables were addressed, and confidence intervals.</p> <p>c. Power level strong enough to detect significant differences were they to exist.</p> <p>Chance variation, therefore, was an unlikely explanation for the significant results.</p>	<p><i>4. Time and Strength</i> Intervention design - therefore, outcomes followed exposure.</p> <p>Strong relationship between morbidity and exposure. Open Nx donors had 4 times the risk of complications than Lap LD Nx donors. The relationship could be a consequence of chance variation, however, as it was not statistically significant. Also, selection bias - 'fitter' donors in the Lap LD Nx group - may explain the result.</p> <p><i>5. Overview</i> Effects of confounding and chance appear to have been nullified. The effect of misclassification bias would be only to reduce the observed differences between the groups.</p> <p>However, the possibility of observed differences between Lap LD Nx and Open Nx being due to selection bias or systematic observation bias cannot be dismissed. The likelihood that the observed differences between the groups were the unequivocal effect of the different types of surgery cannot be assured.</p> <p>Internal validity: average.</p>	<p>Participation rate was very high (92%) and there was no missing data.</p> <p>Results can be applied to an adult population who are healthy enough for selection as a potential kidney donor (see # below) and who are not morbidly obese.</p> <p># Excluding those without 2 healthy kidneys, with ABO incompatibility, pregnant donors, those with certain infectious diseases, renal arterial occlusive disease, renal parenchymal diseases, uncorrectable coagulopathy, and horseshoe kidney.</p> <p>6 of the 76 donors eligible for Lap LD Nx were excluded. Therefore, from a safety perspective it would be inadvisable to generalise the results to donors with morbid obesity, renal artery aneurysm or a pelvic mass.</p> <p>External validity: average-good.</p>

Authors	Yr.	Location	Description of Evidence				
			Intervention	Design	Level of Evidence	Study Population	Main Results
Ratner Kavoussi Schulam Bender Magnuson Montgomery	1997	Departments of Surgery & Urology, Johns Hopkins University School of Medicine and Johns Hopkins Bayview Medical Centre, Baltimore, Maryland, USA.	<p><i>Study</i> - Lap LD Nx. Transperitoneal. Pneumoperitoneum.</p> <p><i>Control</i> - Open LD Nx. Flank/extraperitoneal</p>	Controlled clinical trial. Historic controls. Non-randomised.	III-3	<p><i>Sample size:</i> control: n=20 study: n=19</p> <p><i>Study period:</i> control - 1/91 - 1/95 study - 2/95 - 9/96</p> <p>People selected as donors according to clinical practice guidelines. No information as to whether selection process differed between two groups. Allocation non-random. Historic Open LD Nx donors selected from the Johns Hopkins Bayview Medical Centre. Lap LD Nx donors selected from those operated on at Johns Hopkins Bayview Medical Centre and Johns Hopkins Hospital.</p>	<p><i>1. Safety of Lap LD Nx:</i> Conversion rate - nil Mortality - Lap LD Nx = 0; Open LD Nx = 0. Morbidity/complications - Lap LD Nx = 1/19 (5%); Open LD Nx = 0/20 (0%). O.R.=1.1, 95% C.I. [0.92, 1.32]. N.S. Lap LD NX - haemorrhage/blood transfusion Mean estimated blood loss (ml) - Lap LD Nx = 222 +/- 157 (56% of Open); Open LD Nx = 393 +/- 335. Signif. P<0.05</p> <p><i>2. Efficacy of Lap LD NX:</i> Mean operative time (min) - Lap LD Nx = 224 +/- 29; Open LD Nx = 183 +/- 48 (82% of Lap) Signif. p=0.003 Mean resumption of oral intake (days) - Lap LD Nx = 0.8 +/- 0.4 (32% of Open); Open LD Nx = 2.5 +/- 1.0. Signif. P<0.001 Mean parenteral analgesia (mgMS) - Lap LD Nx = 34 +/- 34 (27% of Open); Open LD Nx = 124 +/- 88. Signif. P<0.001 Mean length of stay (days) - Lap LD Nx = 3.1 +/- 1.2 (54% of Open); Open LD Nx = 5.7 +/- 1.7. Signif. P<0.001 Mean full activity resumed (week) - Lap LD Nx = 2.2 +/- 0.8 (52% of Open); Open LD Nx = 4.2 +/- 2.4. Signif. P=0.008. Mean resumption of employment (week) - Lap LD Nx = 3.9 +/- 1.8 (61% of Open); Open LD Nx = 6.4 +/- 3.1. Signif. P=0.01. Graft function (intra-op) - Lap LD Nx = 19/19 (100%); Open LD Nx = 20/20 (100%). Graft function (post-op) - Lap LD Nx = 3/19 (16%); Open LD Nx = 0/20 (0%). Lap LD NX - cholesterol emboli & acute rejection (1); graft thrombosis - lost day 3 post-op (1); recurrent acute rejection & haemolytic uraemic syndrome - lost 2 months post-op (1). Mean recipient creatinine clearance levels [3 months/longest follow-up on functioning allografts] (mL/min) - Lap LD Nx = 63.1 +/- 14.3; Open LD Nx = 64.8 +/- 21.4. N.S.</p> <p>Descriptive statistics are given re warm ischaemic time, lengths of renal artery, vein and ureter in Lap LD Nx patients - all were adequate. 6 of the 19 Lap LD Nx donors (32%) would not have donated if the laparoscopic approach had not been available.</p>

Authors	Summary of Internal Validity		Summary of External Validity
Ratner Kavoussi Schulam Bender Magnuson Montgomery	<p><i>1. Bias</i></p> <p>a. Observation bias a possibility - no single/doubling blinding; no standardised instrument; data collection through record review by investigators.</p> <p>b. Misclassification bias and error also possible due to the use of retrospective review and historic controls.</p> <p>c. Selection bias probable given the use of donors from different transplant centres; and the likely differential application of eligibility criteria to the two groups.</p> <p><i>2. Confounding</i></p> <p>Two of the major confounders (age and weight) were equivalently distributed in the two groups. Other possible, although less likely, confounders were not addressed i.e. SES, comorbidity, gender.</p> <p><i>3. Chance</i></p> <p>a. Descriptive and inferential statistics used appropriately.</p> <p>b. Sample size small but not completely inadequate.</p> <p>Chance variation was an unlikely explanation for the observed differences between the two groups.</p>	<p><i>4. Time and Strength</i></p> <p>Intervention design - therefore, outcomes followed exposure.</p> <p>The relationship between exposure (Lap LD Nx) and morbidity was negligible (O.R.=1.1, 95% C.I. [0.92, 1.32]) and non-significant. Despite the small sample size, the confidence interval was narrow so it is likely that we can accept the non-significant result.</p> <p><i>5. Overview</i></p> <p>Effects of confounding and chance appear to have been largely nullified. Bias, however, is an issue. Observation bias was possible given the lack of blinding and the retrospective review of records - no standardised measuring instrument. Misclassification error and bias were also possible given the use of retrospective record review and use of historic controls. Selection bias was likely given the use of donors from different transplant centres, and the probability that the surgeons' selection of eligible donors for Lap LD Nx differed from that of Open LD Nx donors.</p> <p>The likelihood that the observed differences between the groups were the unequivocal effect of the different types of surgery cannot be assured.</p> <p>Internal validity: average.</p>	<p>Results cannot be applied fully to the potential human donor population. Differences within the eligible and source populations - i.e. likely different selection criteria for both groups, and two different transplant centres providing source populations - would suggest that the safety and efficacy results from the study cannot be generalised with confidence to the target population.</p> <p>External validity: poor-average.</p>

Authors	Yr.	Location	Description of Evidence				
			Intervention	Design	Level of Evidence	Study Population	Main Results
Ratner Kavoussi Sroka Hiller Weber Schulam Montgomery	1997	Departments of Surgery & Urology, Johns Hopkins University School of Medicine and Johns Hopkins Bayview Medical Centre, Baltimore, Maryland, USA.	<i>Study</i> - Lap LD Nx. Transperitoneal. Pneumoperitoneum. (9 left kidney; 1 right kidney) <i>Control</i> - Open LD Nx. Flank/extraperitoneal	Controlled clinical trial. Historic controls. Non-randomised.	III-3	<i>Sample size:</i> control: n=20 study: n=10 <i>Study period:</i> control - 1/91 - 1/95 study - 2/95 - 4/96 Selection process differed for Lap LD Nx and Open LD Nx groups. All had the standard medical evaluation, however donors were only eligible for the laparoscopic operation if they possessed at least one kidney with normal renal anatomy. Eligibles were then self-selected for either the Lap LD Nx or Open LD Nx operation - all chose Lap LD Nx.	<i>1. Safety of Lap LD Nx:</i> Conversion rate - nil Mortality - Lap LD Nx = 0; Open LD Nx = 0. Morbidity/complications (post-op) - Lap LD Nx = 1/10 (10%); Open LD Nx = 1/20 (5%). R.R.=2, 95% C.I. [0.14, 27.6]. N.S. Lap LD Nx - incisional hernia in the infraumbilical incision (1) Open LD Nx - incisional hernia (1). Blood transfusions - nil Mean estimated blood loss (ml) - Lap LD Nx = 137 +/- 79 (35% of Open); Open LD Nx = 393 +/- 335. Signif. P=0.004. <i>2. Efficacy of Lap LD Nx:</i> Mean operative time (min) - Lap LD Nx = 227 +/- 27; Open LD Nx = 183 +/- 48 (81% of Lap). Signif. P=0.012 Mean resumption of oral intake (days) - Lap LD Nx = 0.7 +/- 0.5 (28% of Open); Open LD Nx = 2.5 +/- 1.0. Signif. P<0.001 Mean parenteral analgesia (mgMS) - Lap LD Nx = 24.4 +/- 14.8 (20% of Open); Open LD Nx = 123.6 +/- 88.0. Signif. P<0.001 Mean length of stay (days) - Lap LD Nx = 2.7 +/- 1.0 (47% of Open); Open LD Nx = 5.7 +/- 1.7. Signif. P<0.001 Mean full activity resumed (weeks) - Lap LD Nx = 2.3 +/- 1.1 (55% of Open); Open LD Nx = 4.2 +/- 2.4. Signif. P=0.028. Mean resumption of employment (weeks) - Lap LD Nx = 3.9 +/- 1.6 (61% of Open); Open LD Nx = 6.4 +/- 3.1. Signif. P=0.024. Graft function - Lap LD Nx = 1/10 (10%); Open LD Nx = ? Mean recipient creatinine clearances [3 months post-transplant] (ml/min) - Lap LD Nx = 67.0 +/- 11.5; Open LD Nx = 64.8 +/- 21.4. N.S. Descriptive statistics are given re warm ischaemic time, lengths of renal artery, vein and ureter in Lap LD Nx patients - all were adequate. 4 of the 10 Lap LD Nx donors (40%) would not have donated their kidneys if the laparoscopic approach had not been available.

Authors	Summary of Internal Validity		Summary of External Validity
Ratner Kavoussi Sroka Hiller Weber Schulam Montgomery	<p><i>1. Bias</i></p> <p>a. Observation bias a possibility - no single/doubling blinding; data collection through record review and survey by investigators; no standardised instrument.</p> <p>b. Misclassification bias probable due to retrospective review and use of historic controls.</p> <p>c. Selection bias probable due to the differential application of eligibility criteria to the two groups.</p> <p><i>2. Confounding</i></p> <p>The major confounders (age, weight, race and gender) were equivalently distributed in the two groups. Other possible, although less likely, confounders were not addressed i.e. SES, comorbidity.</p> <p><i>3. Chance</i></p> <p>a. Descriptive and inferential statistics used appropriately.</p> <p>b. Sample size for each group was small, therefore chance variation as an explanation for the observed differences between the groups cannot be ignored.</p>	<p><i>4. Time and Strength</i></p> <p>Intervention design - therefore, outcomes followed exposure.</p> <p>The relationship between exposure (Lap LD Nx) and morbidity was strong (R.R.=2, 95% C.I. [0.14, 27.6]) although non-significant. The sample size was small and the confidence interval was very wide so it cannot be concluded that there was no appreciable difference between the groups.</p> <p><i>5. Overview</i></p> <p>Effects of confounding and chance appear to have been addressed properly, although the small sample size needs to be taken into account. Bias, however, is an issue. Observation bias was possible given the lack of blinding, the use of retrospective record review and investigator-surveying. There was no mention of a standardised instrument. Misclassification bias probable given the use of retrospective record review and the use of historic controls. Selection bias probable given the differential eligibility criteria for the two groups.</p> <p>The likelihood that the observed differences between the two groups were the unequivocal effect of the different types of surgery cannot be assured.</p> <p>Internal validity: poor-average.</p>	<p>Participation rate was high (100% for Lap LD Nx; 95% for Open LD Nx).</p> <p>The source population was approximately the same for both groups.</p> <p>Results can be applied to an adult human population who are healthy enough for selection as potential kidney donors and who have at least one kidney with normal renal anatomy.</p> <p>External validity: average-good.</p>

Authors	Yr.	Location	Description of Evidence				
			Intervention	Design	Level of Evidence	Study Population	Main Results
Ishikawa Suzuki Saisu Kageyama Ushiyama Fujita	1998	Department of Urology, Hamamatsu University School of Medicine, Hamamatsu, Japan.	<p><i>Study</i> - Lap-assist LD Nx. 'Laparoscopy- Assisted' Transperitoneal Lifting Retractors</p> <p><i>Control 1</i> - Retro-assist LD Nx 'Retroperitoneoscopy- Assisted' Retroperitoneal Lifting Retractors</p> <p><i>Control 2</i> - Open LD Nx. Flank/extraperitoneal?</p>	Controlled clinical trial. Historic/non-concurrent controls. Non-randomised.	III-3	<p><i>Sample size:</i> study: n=4 (3 left k, 1 right) control 1: n=4 (4 left k) control 2: n=8 (which k?)</p> <p><i>Study period:</i> study - 3/95 - 12/95 control 1 - 1/96 - 12/96 control 2 - ? (in another paper by this group - Suzuki, '97 - the same 8 controls were used and were described as historic controls).</p> <p>Non-randomised. No information re selection criteria or whether it differed for each group. No clear information as to whether all donors came from the same centre - assume that this was the case (see Suzuki, '97). Lap-assist LD Nx and Retro-assist LD Nx not done concurrently. Assume Open LD Nx done historically to both new procedures (see Suzuki, '97).</p>	<p><i>1. Safety of Lap-assist LD Nx:</i> Mortality - nil. Morbidity/complications - Lap-assist LD Nx = 1/4 (25%); Retro-assist LD Nx = 2/4 (50%); Open LD Nx = 0/8 (0%). Lap-assist LD Nx - pneumonia (1). Retro-assist LD Nx - wound infection (2). Mean blood loss (ml) - Lap-assist LD Nx = 207.5 +/- 232.9; Retro-assist LD Nx = 159.8 +/- 151.5; Open LD Nx = 126.6 +/- 81.8. Lap-assist LD Nx vs Open LD Nx = N.S. Lap-assist LD Nx vs Retro-assist LD Nx = N.S.</p> <p><i>2. Efficacy of Lap-assist LD Nx:</i> Mean operating time (min) - Lap-assist LD Nx = 307.0 +/- 35.9; Retro-assist LD Nx = 220.8 +/- 24.7; Open LD Nx = 206.1 +/- 26.9 Lap-assist LD Nx vs Open LD Nx = Signif. P<0.001. Lap-assist LD Nx vs Retro-assist LD Nx = Signif. P<0.008. Mean ambulation (days) - Lap-assist LD Nx = 2 +/- ?; Retro-assist LD Nx = 1.0 +/- ?; Open LD Nx = 2.3 +/- 0.4. Mean resumption of oral intake (days) - Lap-assist LD Nx = 2.5 +/- 0.6; Retro-assist LD Nx = 1.5 +/- 0.6; Open LD Nx = 2.1 +/- 0.3. Lap-assist LD Nx vs Open LD Nx = N.S. Lap-assist LD Nx vs Retro-assist LD Nx = Signif. P<0.05. Mean full recuperation (days) - Lap-assist LD Nx = 6.8 +/- 1.7; Retro-assist LD Nx = 5.5 +/- 1.3; Open LD Nx = 11.9 +/- 0.9. Lap-assist LD Nx vs Open LD Nx = Signif. P<0.001. Lap-assist LD Nx vs Retro-assist LD Nx = N.S. Mean warm ischaemic time (min) - Lap-assist LD Nx = 5.5 +/- 1.7; Retro-assist LD Nx = 3.5 +/- 0.6; Open LD Nx = 2.8 +/- 1.0. Lap-assist LD Nx vs Open LD Nx = Signif. P<0.01 (biopsy, however, revealed no remarkable pathologic changes in all cases). Lap-assist LD Nx vs Retro-assist LD Nx = N.S. Mean time of 1st urine output (after graft revascularisation) (min) - Lap-assist LD Nx = 4.5 +/- 2.1; Retro-assist LD Nx = 4.3 +/- 3.2; Open LD Nx = 3.0 +/- 1.7. Lap-assist LD Nx vs Open LD Nx = N.S. Lap-assist LD Nx vs Retro-assist LD Nx = N.S. Mean serum creatinine of recipient (post-op day 3) (mg/dl) - Lap-assist LD Nx = 1.0 +/- 0.4; Retro-assist LD Nx = 1.9 +/- 0.7; Open LD Nx = 1.5 +/- 0.7. Lap-assist LD Nx vs Open LD Nx = N.S. Lap-assist LD Nx vs Retro-assist LD Nx = N.S.</p>

Authors	Summary of Internal Validity		Summary of External Validity
Ishikawa Suzuki Saisu Kageyama Ushiyama Fujita	<p><i>1. Bias</i></p> <p>a. Observation bias was a possibility - no single/doubling blinding; no information as to whether standardised measuring instruments were used to collect data. Most outcome measures were objective.</p> <p>b. Misclassification error and bias were possibilities. However, as it was unclear whether data was collected prospectively or retrospectively, or whether the controls were historic or concurrent, then the bias cannot be ascertained definitively.</p> <p>c. Selection bias was also a possibility. However, again there was no information in the paper on the eligibility criteria used to select donors for surgery, or whether the criteria differed for the different types of surgery.</p> <p><i>2. Confounding</i></p> <p>All groups were analysed with respect to two possible confounders - age and gender. When the Lap-assist LD Nx and Open LD Nx groups were compared with respect to age and gender, and the Lap-assist LD Nx and Retro-assist LD Nx were compared, there were no significant differences. Other possible confounders (e.g. weight/obesity, SES and comorbidity) were not addressed.</p> <p><i>3. Chance</i></p> <p>a. Data in the form of means and standard deviations.</p> <p>b. Chi-square test used appropriately for count data.</p> <p>c. Student t test used for continuous data. Would perhaps have been more appropriate to use the non-parametric Mann-Whitney U test as the distribution was likely to be non-normal (very small sample size).</p> <p>Chance variation was a likely explanation for the observed differences between the groups.</p>	<p><i>4. Time and Strength</i></p> <p>Intervention design - therefore, outcomes followed exposure.</p> <p>Measures of association were not calculated in this paper. Attempt was made (by ASERNIP-S) to calculate the relative risk for morbidity count data. However, unable to divide 'Risk in exposed' by 'Risk in non-exposed', as it equalled zero.</p> <p><i>5. Overview</i></p> <p>It was likely that the data were collected retrospectively and that both control groups were non-concurrent, suggesting that misclassification error and bias were possible. Similarly, it is possible that there was selection bias as eligibility or selection criteria for donors undergoing the different types of surgery were not mentioned, nor whether the selection criteria differed for each group.</p> <p>Observation bias was a possibility as there was no investigator or donor-blinding, and no mention of standardised data collection or measuring instruments.</p> <p>There were no significant differences in the distribution of age and gender (two of the likely confounders) across these groups. Other possible confounders (e.g. weight/obesity, SES and comorbidity) were not addressed.</p> <p>Chance variation was a likely explanation for the observed differences between the groups because the sample size was very small. Further, a parametric test was used to test differences on the continuous data, when a non-parametric test would perhaps have been more appropriate.</p> <p>The likelihood that the observed differences between the groups were the unequivocal effect of the different types of surgery cannot be assured.</p> <p>Internal validity: poor.</p>	<p>Results cannot be applied to the potential human donor population. The lack of information provided on the participation rate, eligible population and source populations means that the results cannot be generalised with confidence to the target population. Further detailed information is required.</p> <p>External validity: poor.</p>

Authors	Yr.	Location	Description of Evidence				
			Intervention	Design	Level of Evidence	Study Population	Main Results
Suzuki Ushiyama Kageyama Ishikawa Mugiya Fujita	1997	Department of Urology, Hamamatsu University School of Medicine, Hamamatsu, Japan	<p><i>Study</i> - Lap-assist LD Nx (4) "GLAN" - Gasless Laparoscopy-assisted Live-donor Nephrectomy Transperitoneal Lifting Retractors</p> <p>Retro-assist LD Nx (1) "GLAN" Extra/Retroperitoneal Lifting Retractors</p> <p><i>Control</i> - Open LD Nx. Flank/extraperitoneal?</p>	Controlled clinical trial. Historic controls. Non-randomised.	III-3	<p><i>Sample size:</i> study: n=5 [1 retro, 4 transp; 4 left kidney, 1 right kidney] control: n=8 [which kidney?]</p> <p><i>Study period:</i> study - 3/95 - 1/96 control - ? (in another paper by this group - Suzuki, '97 - the same 8 controls were used and were described as historic controls).</p> <p>Non-randomised. No information re selection criteria or whether they differed for both groups. No information as to whether all donors came from the same centre - assume that this was the case (see Suzuki, '97). Study group includes operations by both transperitoneal and retroperitoneal approach. Assume Open LD Nx donors were historic (see Suzuki, '97).</p>	<p><i>1. Safety of Lap-assist/Retro-assist LD Nx:</i> Mortality - nil. Morbidity/complications - Lap-assist/Retro-assist LD Nx = 1/5 (20%); Open LD Nx = 0/8 (0%). Lap-assist/Retro-assist LD Nx - pneumonia (1) Mean blood loss (ml) - Lap-assist/Retro-assist LD Nx = 185.2 +/- 185.8; Open LD Nx = 126.6 +/- 81.8. N.S.</p> <p><i>2. Efficacy of Lap-assist/Retro-assist LD NX:</i> Mean operating time (min) - Lap-assist/Retro-assist LD Nx = 292.8 +/- 39.8; Open LD Nx = 206.1 +/- 26.9. Signif. P<0.001. Mean ambulation (days) - Lap-assist/Retro-assist LD Nx = 1.8 +/- 0.4; Open LD Nx = 2.3 +/- 0.43. N.S. Mean resumption of oral intake (days) - Lap-assist/Retro-assist LD Nx = 2.2 +/- 0.7; Open LD Nx = 2.1 +/- 0.3. N.S. Mean full recuperation (days) - Lap-assist/Retro-assist LD Nx = 6.4 +/- 1.5; Open LD Nx = 11.9 +/- 0.9. Signif. P<0.001. Mean warm ischaemic time (min) - Lap-assist/Retro-assist LD Nx = 5.2 +/- 1.5; Open LD Nx = 2.75 +/- 0.97. Signif. P<0.01. Mean cold ischaemic time (min) - Lap-assist/Retro-assist LD Nx = 40.8 +/- 4.7; Open LD Nx = 42.25 +/- 6.34. N.S. Mean time of 1st urine output (after graft revascularisation) (min) - Lap-assist/Retro-assist LD Nx = 4.2 +/- 1.7; Open LD Nx = 3.0 +/- 1.66. N.S. Mean serum creatinine of recipient (post-op day 3) (mg/dl) - Lap-assist/Retro-assist LD Nx = 1.07 +/- 0.34; Open LD Nx = 1.49 +/- 0.69. N.S.</p>

Authors	Summary of Internal Validity		Summary of External Validity
Suzuki Ushiyama Kageyama Ishikawa Mugiya Fujita	<p><i>1. Bias</i></p> <p>a. Observation bias was a possibility - no single/doubling blinding; no information as to whether standardised measuring instruments were used to collect data. Most outcome measures were objective.</p> <p>b. Results from two different types of surgery were combined in the study group which was likely to have contributed to misclassification error. It was likely that the data were collected retrospectively and that the control group was historic, further suggesting that misclassification error and bias were possible.</p> <p>c. Selection bias was also a possibility. However, there was no information in the paper on the eligibility criteria used to select donors for surgery, or whether the criteria differed for the different types of surgery.</p> <p><i>2. Confounding</i></p> <p>Both groups were analysed with respect to two possible confounders - age and gender - and there was no significant difference in their distribution. Weight was another possible confounder. Descriptive information was supplied regarding one obese donor in the Lap-assist/Retro-assist LD Nx group, with which there were intra-operative difficulties. Weight was not looked at systematically across both groups - neither were two other possible confounders i.e. SES, comorbidity.</p> <p><i>3. Chance</i></p> <p>a. Data in the form of means and standard deviations.</p> <p>b. Chi-square test used appropriately for count data. Student t test used for continuous data. Would perhaps have been more appropriate to use the non-parametric Mann-Whitney U test as the distribution was likely to be non-normal (very small sample size).</p>	<p><i>4. Time and Strength</i></p> <p>Intervention design - therefore, outcomes followed exposure.</p> <p>Measures of association were not calculated in this paper. Attempt was made (by ASERNIP-S) to calculate the relative risk for morbidity count data. However, unable to divide 'Risk in exposed' by 'Risk in non-exposed', as it equalled zero.</p> <p><i>5. Overview</i></p> <p>It was likely that the data were collected retrospectively and that the control group was historic, suggesting that misclassification error and bias were possible. Results from two different types of surgery were combined in the study group which was also likely to have contributed to misclassification error. Similarly, it is possible that there was selection bias, as selection criteria for donors undergoing the different types of surgery was not mentioned, nor whether eligibility differed for each group. Observation bias was a possibility as there was no investigator or donor-blinding, and no mention of standardised data collection/measuring instruments.</p> <p>There was no significant difference in the distribution of age and gender (two of the likely confounders) between the groups. Other possible confounders (e.g. weight, SES and comorbidity) were not addressed.</p> <p>Chance variation was a likely explanation for the observed differences between the groups because the sample size was very small. Further, a parametric test was used to test differences on the continuous data, when a non-parametric test would perhaps have been more appropriate.</p> <p>The likelihood that the observed differences between the groups were the unequivocal effect of the different types of surgery cannot be assured.</p> <p>Internal validity: poor.</p>	<p>Results cannot be applied to the potential human donor population. The lack of information provided on the participation rate, eligible population and source populations means that the results cannot be generalised with confidence to the target population. Further detailed information is required.</p> <p>External validity: poor.</p>

Authors	Yr.	Location	Description of Evidence				
			Intervention	Design	Level of Evidence	Study Population	Main Results
Suzuki Ushiyama Ishikawa Mugiya Fujita	1997	Department of Urology, Hamamatsu University School of Medicine, Hamamatsu, Japan	<p><i>Study</i> - Retro-assist LD Nx 'Retroperitoneoscopy - assisted live donor Nephrectomy' Retroperitoneal Lifting Retractors</p> <p><i>Control 1</i> - Lap-assist LD Nx 'Laparoscopy - assisted live-donor Nephrectomy' Transperitoneal Lifting Retractors</p> <p><i>Control 2</i> - Open LD Nx. Flank/extraperitoneal?</p>	Controlled clinical trial. Historic controls. Non-randomised.	III-3	<p><i>Sample size:</i> study: n=2 control 1: n=4 control 2: n=8</p> <p><i>Study period:</i> study - 1/96 - ? control 1 - 3/95 - 12/95 (see Ishikawa '98) control 2 - 4/92 - ?12/95 or ?2/95</p> <p>Non-randomised. No information re selection criteria or whether they differed for each group. All donors came from the same centre. Control groups were historic.</p>	<p>1. <i>Safety of Retro-assist LD Nx:</i> Mortality - nil. Morbidity/complications - Retro-assist LD Nx = nil; controls = ? Mean blood loss (ml) - Retro-assist LD Nx = 102.0 +/- 6.0; Lap-assist LD Nx = 207.5 +/- 232.9; Open LD Nx = 126.6 +/- 81.8.</p> <p>2. <i>Efficacy of Retro-assist LD NX:</i> Mean full recuperation (days) - Retro-assist LD Nx = 4.5 +/- 0.5; Lap-assist LD Nx = 6.8 +/- 1.7; Open LD Nx = 11.9 +/- 0.9. Mean warm ischaemic time (min) - Retro-assist LD Nx = 3.5 +/- 0.5; Lap-assist LD Nx = 5.5 +/- 1.7; Open LD Nx = 2.8 +/- 1.0. Mean recipient serum creatinine concentration (mg/dl) - Retro-assist LD Nx = 2.1 +/- 0.7; Lap-assist LD Nx = 1.0 +/- 0.4; Open LD Nx = 1.5 +/- 0.7.</p> <p>Comparisons are descriptive only. No statistical testing was conducted - rightly, as the sample size was too small to get meaningful results or exclude chance variation. Without the use of inferential statistics/comparisons, it is not relevant to look at internal or external validity.</p>
Schulam Kavoussi Cheriff Averch Montgomery Moore Ratner	1996	Departments of Urology and Surgery, Johns Hopkins Bayview Medical Centre, Baltimore, Maryland, USA.	<p><i>Study</i> - Lap LD Nx. Transperitoneal Pneumoperitoneum</p>	Case series (3 cases)	IV	<p><i>Sample size:</i> n=3</p> <p><i>Study period:</i> 2/95 - 6/95</p>	<p>Descriptive (uncontrolled study): No intra-operative or postoperative complications. Donors discharged within 3 postoperative days. Normal preoperative activities resumed within 2 weeks. All 3 donated kidneys transplanted successfully. Recipient serum creatinine levels decreased after the operation, with normal renal function by the 2nd postoperative day.</p>
Yang Park Lee Lee Park	1995	Departments of Urology and Surgery, Yonsei University College of Medicine, Seoul, Korea.	<p><i>Study</i> - Retro-assist LD Nx. 'Retroperitoneal endoscopy-assisted live-donor Nephrectomy' Retractor</p>	Case series (3 cases)	IV	<p><i>Sample size:</i> n=3</p> <p><i>Study period:</i> ?</p>	<p>Descriptive (uncontrolled study): Operating time was 2 - 3.5 hours. 2 of the 3 cases received a vascular tear which was repaired uneventfully. Apparently, graft survival was excellent and donor recovery was rapid.</p>

Authors	Summary of Internal Validity		Summary of External Validity
Suzuki Ushiyama Ishikawa Mugiya Fujita	n/a	n/a	n/a
Schulam Kavoussi Cheriff Averch Montgomery Moore Ratner	n/a	<i>Overview</i> Not relevant - uncontrolled study. Results are descriptive only. No conclusions regarding safety and efficacy can be drawn from the results. Merely showcases the feasibility of the technique; and raises issues that should be properly investigated.	n/a
Yang Park Lee Lee Park	n/a	<i>Overview</i> Not relevant - uncontrolled study. Results are descriptive only. No conclusions regarding safety and efficacy can be drawn from the results. Merely showcases the feasibility of the technique; and raises issues that should be properly investigated.	n/a

Authors	Yr.	Location	Description of Evidence				
			Intervention	Design	Level of Evidence	Study Population	Main Results
Yang Lee Rha Park	1994	Departments of Urology and Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.	<i>Study</i> - Retro-assist LD Nx. 'Retroperitoneal endoscopy-assisted live-donor Nephrectomy' Retractor	Case series (2 cases)	IV	<i>Sample size:</i> n=2 <i>Study period:</i> ?	Descriptive (uncontrolled study): The operative time was approximately 2 hours. One of the donors received a vascular tear which was repaired uneventfully. Apparently graft survival was excellent and postoperative patient discomfort was minimal.
Ratner Ciseck Moore Cigarroa Kaufman Kavoussi	1995	Departments of Surgery and Urology, Johns Hopkins University School of Medicine and Johns Hopkins Bayview Medical Centre, Baltimore, Maryland, USA.	<i>Study</i> - Lap LD Nx. Transperitoneal Pneumoperitoneum	Case report	IV	<i>Sample size:</i> n=1 <i>Study time:</i> 8/2/95	Descriptive (uncontrolled study): Operative time was 3.5 hours. There were no intra-operative complications. Blood loss was minimal. Warm ischaemic time was under five minutes. Oral intake was tolerated on the evening of surgery. Donor discharged on post-op day 1. Apparently, the donor experienced minimal postoperative pain. Total parenteral analgesia included morphine sulphate (20 mg) in the recovery room and meperidine (100 mg) on post-op day 1. No pain felt within 7 days of surgery. Resumption of work within 2 weeks. Urine production immediate once graft revascularised. Recipient serum creatinine level had decreased by post-op day 2.

Authors	Summary of Internal Validity		Summary of External Validity
Yang Lee Rha Park	n/a	<p><i>Overview</i> Not relevant - uncontrolled study. Results are descriptive only. No conclusions regarding safety and efficacy can be drawn from the results. Merely showcases the feasibility of the technique; and raises issues that should be properly investigated.</p>	n/a
Ratner Ciseck Moore Cigarroa Kaufman Kavoussi	n/a	<p><i>Overview</i> Not relevant - uncontrolled study. Results are descriptive only. No conclusions regarding safety and efficacy can be drawn from the results. Merely showcases the feasibility of the technique; and raises issues that should be properly investigated.</p>	n/a

APPENDIX I

Hierarchy of Evidence

[National Health and Medical Research Council 1999]

- I. Evidence obtained from a systematic review of all relevant randomised controlled trials.
- II. Evidence obtained from at least one properly designed randomised controlled trial.
- III-1. Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
- III-2. Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time-series with control group.
- III-3. Evidence obtained from comparative studies with historical control, two or more single arm studies or interrupted time series without a parallel control group.
- IV. Evidence obtained from case-series, either post-test or pre-test and post-test.

COMMENTARY ON DRAFT REVIEW

Review Group Commentary on Draft Review

Oral and written commentary is summarised. The Review Group teleconference took place on Thursday, April 29th 1999 at 4:00pm CST.

Group Consensus:

- ❑ All Review Group members felt that the Draft Review accurately reflected the available literature and appropriately covered the safety and efficacy issues of Laparoscopic Live Donor Nephrectomy.
- ❑ All Review Group members agreed with the Recommendations outlined in the Draft Review, as well as the Safety and Efficacy Classification 3 which was allocated to Laparoscopic Live Donor Nephrectomy.

Additional Comments

Mr Frank Bridgewater (Other Specialty Surgeon):

- ❑ It is clear from the Independent Methodological Assessment that the number of donors upon which the literature is based is quite small. The work by Ratner and co-workers in three sequential reports is really quite deceptive as each report is founded upon donor numbers discussed in preceding reports.
- ❑ The Draft Review highlights in Recommendation 4 the matter of hospital costs. A cost-benefit analysis is not available.
[Ed. Cost-benefit analysis is not part of the ASERNIP-S brief. The safety and efficacy of Laparoscopic Live Donor Nephrectomy is the only concern.]
- ❑ The variety of techniques for Laparoscopic Live Donor Nephrectomy will compound the difficulty in assessing the value of this particular procedure.

Associate Professor David Francis (Nominated Surgeon):

- ❑ The Draft Review does not give detailed consideration to the significantly longer operating time required for Laparoscopic Live Donor Nephrectomy compared to Open Live Donor Nephrectomy. This factor has implications for the safety of the donor and the functionality of the renal graft due to, respectively, the prolonged exposure to anaesthesia and pneumoperitoneum. Also, the longer operating time may have practical implications for the smaller Transplant Units.

Mr Daryl Wall (Nominated Surgeon):

- ❑ The Draft review reflects the published literature up until the end of 1998. There is more published information that has become available recently *i.e.* early 1999.
- ❑ Perhaps the Draft Review could have more thoroughly pursued the effects of pneumoperitoneum.

- ❑ The support expressed for the retroperitoneal approach in the Draft Review should be pursued by a recommendation for a prospective trial.
- ❑ The data presented should encourage those involved to compare kidney removal by the retroperitoneal approach with the intraperitoneal approach (with low pressure).

Mr Mohan Rao (Protocol Surgeon):

- ❑ Published literature does not accurately reflect the current state of experience for Laparoscopic Live Donor Nephrectomy because of the delays in publication. Recently one of the leading teams in this field, University of Maryland, Baltimore, presented their experience with 250 laparoscopic donor nephrectomies at the Society of American GI Endoscopists in March. With modifications in the operative techniques, the perioperative complications decreased from 20% in the earlier group to 6% in the recent group. So far there has been no death or life threatening complication reported.
- ❑ The laparoscopic procedure can be converted to an Open procedure in a matter of minutes as the patient is in the same position for both procedures, and instruments for the Open procedure are laid out on the table at the start of the operation.
- ❑ The effect of intra-abdominal pressure on the renal blood flow has been well documented and most teams keep it well below 14 mmHg. Many teams do not attempt right nephrectomy because of the nature of the right renal vein, and the higher incidence of complications.
- ❑ The retroperitoneal approach has not gained popularity and only a few cases have been reported. However, it will avoid the possible effects of intra-abdominal pressure on the renal blood flow, and the abdominal adhesions could be avoided.