Live Kidney Donation

A plea for the laparoscopic approach

Live Kidney Donation
A plea for the laparoscopic approach

Nierdonatie bij leven
Een pleidooi voor de laparoscopische benadering

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam,

op gezag van de
rector magnificus
Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor promoties.
De openbare verdediging zal plaatsvinden op
vrijdag 15 juni 2007 om 11.00 uur

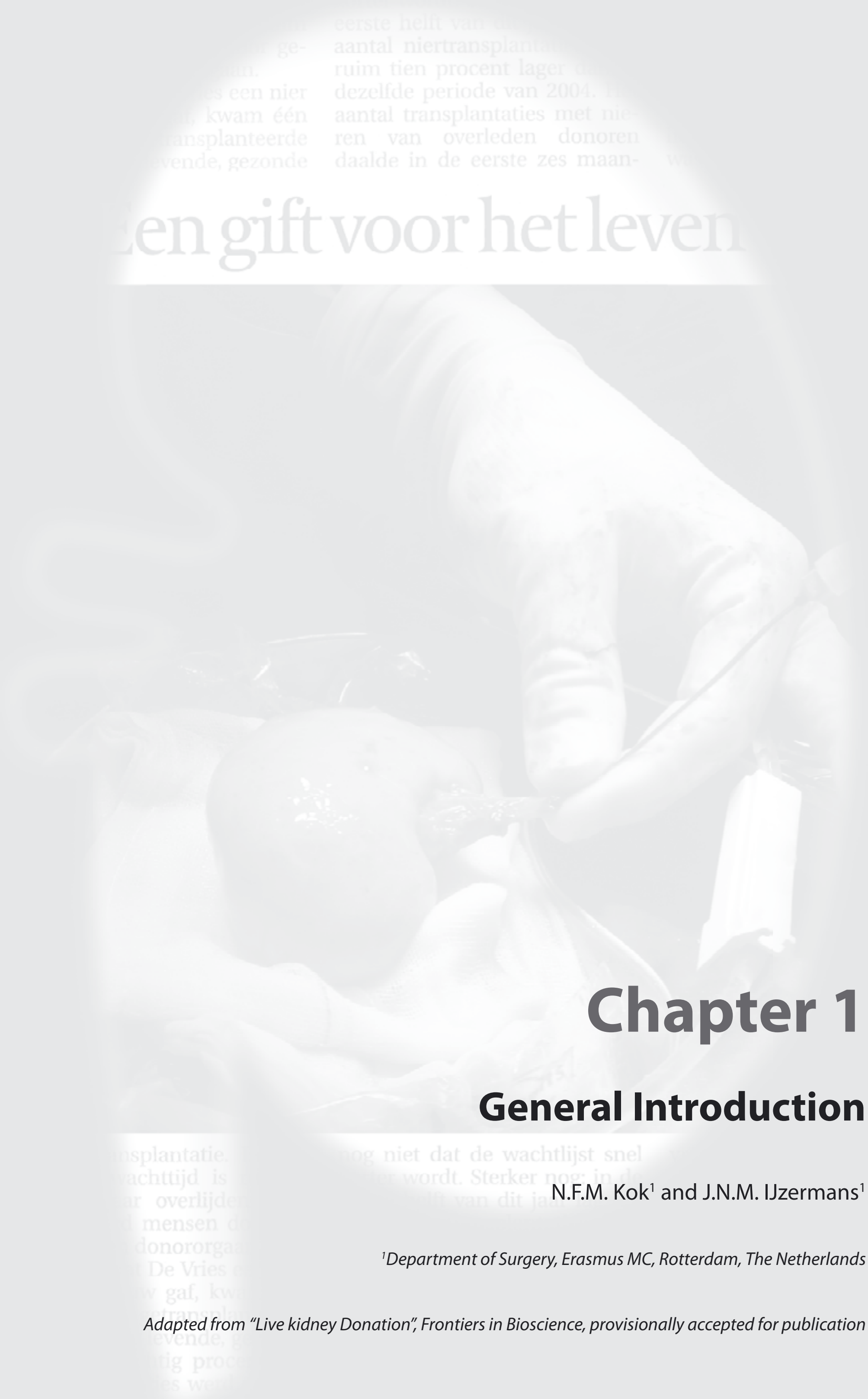
door

Niels Frederik Maarten Kok
geboren te Leiderdorp

PROMOTIECOMMISSIE:

Promotor:	Prof.dr. J.N.M. IJzermans
Overige leden:	Prof.dr. R.J. Ploeg
	Prof.dr. H. Obertop
	Prof.dr. W. Weimar
Copromotor:	Dr. I.P.J. Alwayn

CONTENTS



Chapter 1

General Introduction

N.F.M. Kok[1] and J.N.M. IJzermans[1]

[1]*Department of Surgery, Erasmus MC, Rotterdam, The Netherlands*

Adapted from "Live kidney Donation", Frontiers in Bioscience, provisionally accepted for publication

INTRODUCTION

The kidney is an essential organ that plays a pivotal role in acid/base balance, sodium/potassium balance, calcium metabolism, regulation of blood pressure, red blood cell synthesis and excretion of metabolites. A variety of renal diseases finally results in renal insufficiency.
Kidney replacement therapy consists of dialysis and kidney transplantation. Hemodialysis and peritoneal dialysis can lead to long-term survival and may bridge patients to kidney transplantation. However, the impact of dialysis on quality of life is enormous. Kidney transplantation is considered the optimal kidney replacement therapy for patients with end-stage renal disease.
In the early 1950s Rene Kuss and Joseph Murray performed the first successful kidney transplantations from live donors in France and the United States respectively (1, 2). The invention of adequate immunosuppressive therapy in the 1960s enabled deceased donor kidney transplantation, preventing risky operations performed on healthy individuals. As sufficient deceased donors were present at that time live kidney donor transplantation was pushed into the background.
In the late 1980s and 1990s an increasing number of patients suffering from renal insufficiency and a stagnating number of transplants resulted in a discrepancy between organ demand and supply. This prompted new interest in live donor kidney transplantation (Figure 1) amongst other alternatives. In the Netherlands, the number of patients awaiting kidney transplantation increased until 2004 despite a rising number of live donors. At that time the waiting list consisted of approximately 1200 patients. It is important to realize that only patients who started dialysis were considered for this list. The average waiting time for transplantation increased to five years. Meanwhile, approximately twenty percent of the patients waiting had to be removed of the list annually, because of mortality, worsening condition

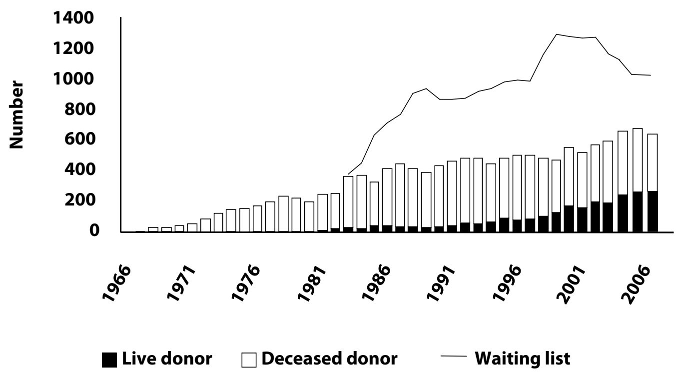


Figure 1. Kidney transplantation in the Netherlands 1966-2006

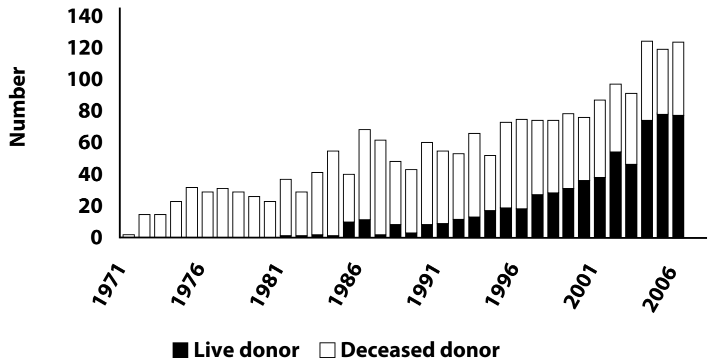


Figure 2. Kidney transplantation in Rotterdam (1971-2006).

precluding transplantation or unspecified reasons (3). Alternatives to significantly increase the number of deceased donors have failed mainly due to relatives refusing donation (3). The number of transplants from deceased donors decreased from 399 in 2005 to 360 in 2006 (3). Currently, the number of patients awaiting kidney transplantation has stabilized as a consequence of a significant rise in live kidney donation nation wide (3). In particular, the number of unrelated donors including spouses attributed to this increase. The results of transplantation of kidneys derived from unrelated donors are excellent (4).

The Erasmus MC is one of the largest transplant centers in Europe with regard to live kidney donor transplantation. Figure 2 displays the situation at the Erasmus MC, which has been a pioneer with regard to live kidney donation. As compared to other centers in the Netherlands and other countries in Western Europe the number of live kidney donors rose early and exponentially.

Live kidney donation appears the most realistic option to further reduce the persistent organ shortage.

Live kidney donor transplantations render some significant benefits. First, the transplant starts functioning immediately following transplantation as opposed to transplants derived from deceased donors. Second, transplant survival is significantly improved. Current analyses at our hospital show a median transplant survival after live kidney donor transplantation of more than twenty years as compared to ten to fifteen years after deceased donor kidney transplantation (unpublished data). Third, dialysis may be avoided by planning live donor kidney transplantation. This so-called pre-emptive kidney transplantation is increasingly performed at our center. Fourth, live kidney donor transplantation turns emergent surgery into elective surgery and therewith improves surgical results without any doubt. Both donors and recipients can be carefully selected and the transplantation can be scheduled when

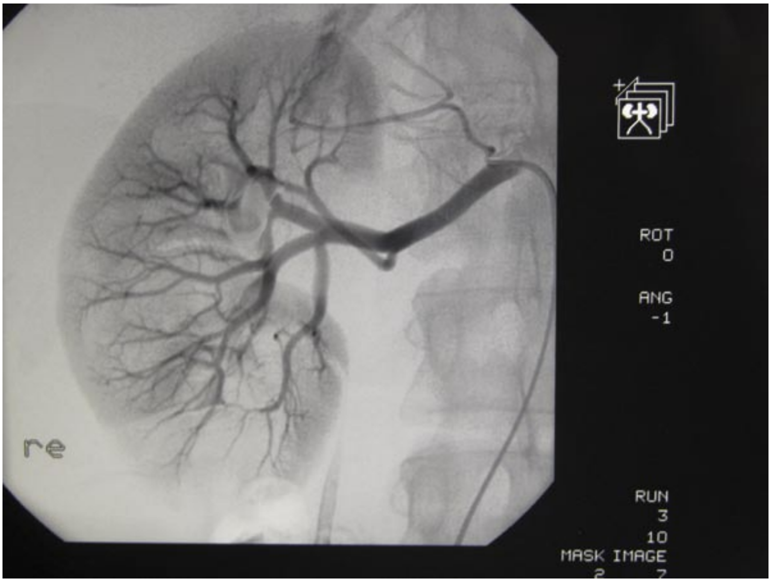


Figure 3. Imaging of the right kidney using digital subtraction angiography.

both the donor and recipient are fit for surgery. Although one should realize that kidney transplantation is a surgical procedure with risks of mortality and morbidity and that immunosuppressive medication may be required life long, harboring the chance of opportunistic infections and malignancies, most recipients prefer this therapy to dialysis. The crucial aspect of live kidney donor transplantation is the harm to the donor. From an ethical perspective live kidney donation is only justified if the harm to the donor is limited and the potential benefit to the recipient is significant. Advances in surgical technique have improved the comfort of the donor greatly and the risks of morbidity and mortality have been minimized. A multidisciplinary approach is required to optimize the quality of a live kidney donation program. All disciplines have to cooperate in screening of the donors and informing relatives without putting pressure to a potential donor. Imaging of the donor kidney (Figure 3) at the department of radiology should be performed without complications. The surgical procedure and peri-operative care should be optimally organized to minimize pain and discomfort to the donor. Adequate follow-up may early identify donors who develop hypertension (5) and may also aid donors from a social perspective, for example by advising those who struggle with their recovery or experience problems resuming work.

Traditionally, kidneys were harvested by a 15 to 25 cm flank incision that transsected three layers of abdominal muscles (Figure 4). Resection of ribs was frequently applied to allow sufficient access to the kidney. This procedure, also called classic lumbotomy, significantly injured the abdominal wall resulting in significant postoperative pain, an average hospital stay of a

Figure 4. Classic lumbotomy. All muscle layers are transsected.

week and prolonged sick leave. At long term, some donors suffered from chronic neuralgia and incisional hernias.

Fortunately, renewed interest in live kidney donation occurred in an era in which minimally invasive surgery gradually replaced conventional surgery. In 1995 Ratner and colleagues performed the first laparoscopic donor nephrectomy (6). Various alternatives to their laparoscopic approach have been presented since then including hand-assisted laparoscopic donor nephrectomy and retroperitoneoscopic donor nephrectomy. Meanwhile, the classic open approach was refined and minimally invasive principles were more often implied in open surgery. Currently applied minimally invasive techniques are as follows.

Laparoscopic donor nephrectomy

Ratner and colleagues described a complete laparoscopic technique (6). The position of the donor is a lateral decubitus position. The first trocar is inserted periumbilical. The abdomen is insufflated with CO_2, a 30° video-endoscope is introduced and three to four additional trocars are inserted (Figure 5A-C). The right or left hemicolon is dissected from the lateral abdominal wall and mobilized medially. Gravity aids this mobilization. The kidney is located behind the hepatic or splenic flexure. Gerota's fascia is openened and the kidney is dissected from the surrounding capsule. The renal vessels are dissected and encircled with vessel loops to facilitate identification from different directions. Venous branches of the renal vein are clipped and divided with scissors. The ureter is dissected until it crosses the gonadal vein. Then, a 5 to 8 cm horizontal suprapubic incision or pfannenstiel incision is made as extraction site while maintaining pneumoperitoneum. An endobag is introduced via a small incision in

Figure 5A. Laparoscopic donor nephrectomy. A camera is introduced periumbilically. Three to four trocars are inserted.

Figure 5B. Laparoscopic donor nephrectomy at a further stage. The endobag has been introduced in the suprapubic region (1). The cameraport with gas supply (2) has been made pararectal, which reduces the distance between the kidney and the abdominal wall. Two additional 10-mm trocars (3) have been inserted to the right of the first trocar and serve a working ports to dissect the kidney. A fourth trocar (4) has been inserted in the epigastric region and contains a babcock to retract the liver.

the peritoneum. Subsequently, the ureter is clipped and divided with scissors and the renal artery and vein are divided with an endostapler. The kidney is 'caught' with the endobag and extracted via the pfannenstiel incision. Then, the transplant is cooled down with perfusion of a preservation solution of 4° Celsius (cover photograph) and stored on ice (Figure 6. Vascular

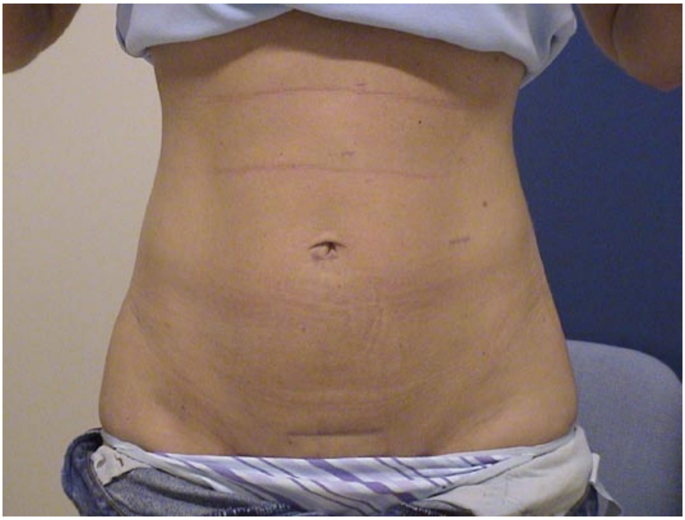


Figure 5C. Cosmetic result after Laparoscopic donor nephrectomy.

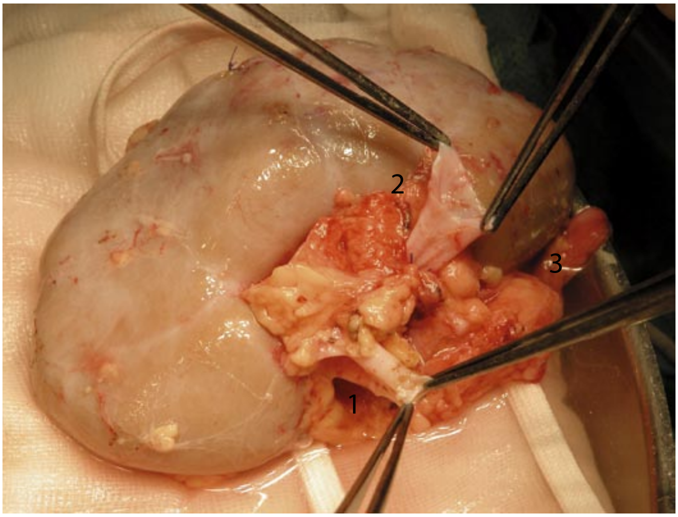


Figure 6. A kidney transplant just before transplantation into the iliac fossa of the recipient. The renal artery (1), the renal vein (2) and the ureter (3) are prepared for transplantation.

reconstructions can be performed if necessary either before or after storage). This step is similar in all techniques. The pfannenstiel incision is sutured and the pneumoperitoneum once restored. The peritoneal cavity is checked for bleeding, especially the remnants of the renal vessels and the adrenal gland. After haemostasis is ensured, the trocars are removed under vision and the incisions are sutured.

The introduction of this technique has caused a lot of discussions in the transplant society because the pneumoperitoneum, necessary to obtain vision, leads to an increased intra-abdominal pressure and therewith may affect renal perfusion with subsequent ischemia/reperfusion injury to the transplant. Recovery of transplant function would be delayed as indicated by slower declining recipient serum creatinine (7). Various studies have proven that short-term adverse effects of laparoscopic donor nehrectomy on transplant function do not exist (8-10). Adjusting the fluid regimen of the donor anticipates to potentially adverse effects of increased pressure and decreased perfusion (8). Several cohort studies from large volume centers in the United States have proven the feasibility and safety of the laparoscopic technique (11, 12).

Hand-assisted laparoscopic donor nephrectomy

Hand-assistance during laparoscopic donor nephrectomy requires an extraction incision that is little larger than the aforementioned extraction site for total laparoscopic donor nephrectomy to allow one hand of the surgeon to enter the peritoneal cavity via a hand-port. These hand-ports allow introduction of, manipulation by and removing of the surgeon's hand while maintaining pneumoperitoneum. Some surgeons make a midline incision to place their hand-port to facilitate an ergonomic position for themselves. The introduction of various trocars is similar as with the conventional laparoscopic approach. Benefits of this technique include maintaining tactile sensation, the possibility to present tissues and the creation of surgical planes with the hand. In case of bleeding it is easier to directly stop the bleeding with a finger and repair the injury. These advantages contribute to a steeper learning curve of the hand-assisted method as compared to the total laparoscopic approach (13). Potential disadvantages are higher costs because of the hand port, a worse ergonomic position of the surgeon during operation, a higher rate of wound infections and increased traumatic injury to the transplant as a consequence of manipulation. Literature with regard to the pros and cons of either technique is scarce and inconclusive (14).

Retroperitoneoscopic donor nephrectomy

Retroperitoneoscopic donor nephrectomy is a modification of the technique first described by Ratner. During this technique the peritoneal cavity is not opened. The technique has been described with and without hand-assistance (figure 7A and 7B)(15, 16). The retroperitoneal space is developed and insufflated with CO_2. Several trocars are introduced. The peritoneal sac containing the bowel is mobilized medially. The dissection of the kidney and the renal vessels looks like transperitoneal donor nephrectomy but the angle is different. The kidney is extracted via a muscle-splitting flank incision or a pfannenstiel incision (15-18). The discussion to use or not to use hand-assistance is similar to the discussion with regard to hand-assistance during the transperitoneal approach. Appropriate designed studies are lacking on this topic and the evidence is based on expert opinions. The potential advantage

Figure 7A. Hand-assisted retroperitoneoscopic donor nephrectomy. The surgeon creates the retroperitoneal space with his left hand. Thereafter, the trocars are introduced and the retroperitoneal cavity is insufflated.

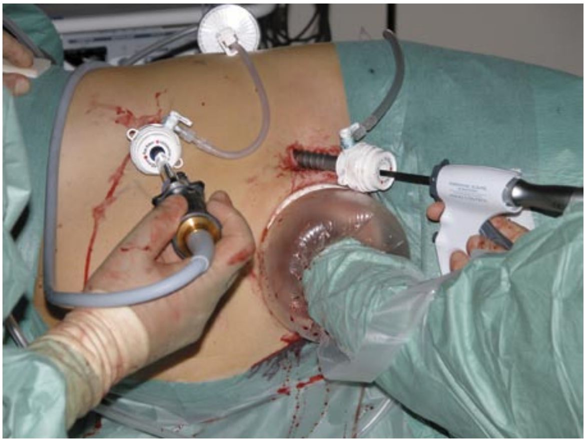


Figure 7B. Hand-assisted retroperitoneoscopic donor nephrectomy at a further stage.

of the retroperitoneoscopic technique is the opportunity to stay away from the contents of the peritoneal sac including the small bowel and the spleen, therewith avoiding injuries to these organs. Moreover, the angle to dissect the vessels may be preferable (15). Large case series or comparative cohort studies have not been published yet. In the future the value of retroperitoneoscopic donor nephrectomy alongside the transperitoneal approaches has to be assessed.

Minimally invasive open donor nephrectomy

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

A minimal flank incision most closely correlates to the conventional lumbotomy. With a smaller incision varying from 7 cm in lean donors to 15 cm in obese individuals the retoperitoneal cavity is accessed. The oblique and transverse abdominal muscles can be either divided or split. Mechanical retractors enable sufficient access with a minimal skin incision (Figure 8A). In addition, instruments also used in laparoscopic surgery, including endostaplers, may be used to maintain limited access in case of difficult anatomy i.e. multiple renal vessels. Most Dutch surgeons and urologists perform the muscle-split approach when open donor nephrectomy is performed. Because the surgical trauma is limited these operations result in shorter hospital stay and less pain as compared to conventional open surgery (9). Cosmetic outcome is excellent (Figure 8B).

A similar muscle-split approach can be performed even more anterior. This approach may me more difficult initially, because more organs are located between abdominal muscles and the

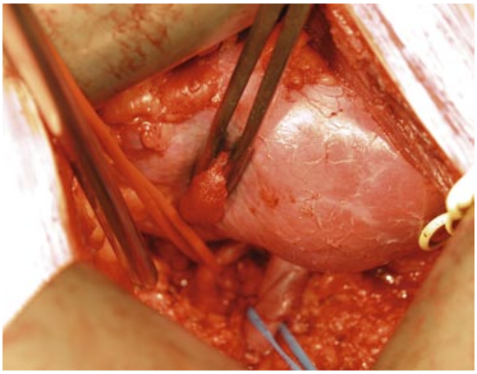


Figure 8A. Mini-incision open donor nephrectomy. The working space is limited. Long instruments are required to enable dissection of the kidney. The renal artery (red loop), the renal vein (blue loop) and the ureter (white loop) are dissected from the surrounding tissue.

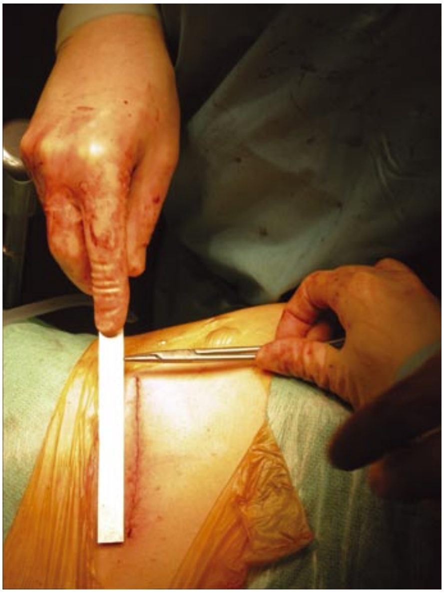


Figure 8B. Mini-incision open donor nephrectomy. The incision measures less than ten centimeters (indicated at the ruler) and the scar will be falling in the natural shade of the costal margin in erect position.

kidney, but the approach of the renal vessels is potentially easier. A concomitant advantage is that the intercostal nerves that innervate the oblique abdominal muscles are less likely to be injured and abdominal wall function may be superior.
A third option for minimally invasive open donor nephrectomy is a pararectal vertical skin-incision. This incision does not divide muscles but fascia only. As compared to conventional open approaches this technique leads to superior postoperative results (19).

Evidence for either surgical technique

Before the publication of this thesis only three randomized controlled trials comparing laparoscopic and open techniques had been published. All these studies compared left-sided hand-assisted laparoscopic donor nephrectomy with conventional open donor nephrectomy (20-22).
In the United States Wolf et al. randomized 50 donors to either hand-assisted laparoscopic donor nephrectomy or conventional lumbotomy (20). Inclusion criteria included normal weight and interest in the laparoscopic approach. The main conclusion of the authors was that the hand-assisted approach resulted in shorter hospital stay and earlier recovery. Simforoosh et al. performed a comparable study in Iran (21). Donors with overweight and complex renal anatomy were excluded. The donors in this study were relatively young. Again, the hand-assisted laparoscopic approach appeared favorable. The unacceptably high complication rate in the open group including 18 donors who sustained a pneumothorax was remarkable in this study. Øyen et al. from Norway randomized 122 live kidney donors (22). A relatively high complication rate in the laparoscopic group (including various re-operations) and minor differences with regard to postoperative pain resulted in the cautious conclusion that the laparoscopic approach confers advantages in some donors only, but should not be applied in all donors. The authors suggested to limit laparoscopy to donors having a normal weight or mild overweight only as complications mainly appeared in obese donors. Longer follow-up of the same Norwegian group confirmed a shorter recovery phase after laparoscopy (23). Various non-randomized studies have led to similar conclusions (24-34). Most of these studies were aimed at the safety and feasibility of the laparoscopic approach and rather presented laparoscopic donor nephrectomy as an alternative than as the technique to be advocated.
Presently, none of the aforementioned techniques is proven superior. Although evidence is mounting that laparoscopic and retroperitoneoscopic approaches are superior to conventional open surgery (35), evidence is lacking that these techniques also should be preferred to minimally invasive open donor nephrectomy. Moreover, in the published randomized trials various exclusion criteria have been handled hindering extrapolation of the results to the live kidney donor in general. Three European studies including one from Great-Britain and two from the Netherlands are about to be published or have recently been published (36). One of these studies is the backbone of this thesis. All three studies aimed to assess the superiority

of either the laparoscopic or the minimally invasive open approach. Furthermore, a Cochrane meta-analysis of laparoscopic versus open donor nephrectomy will be presented in 2007.

AIM OF THIS THESIS

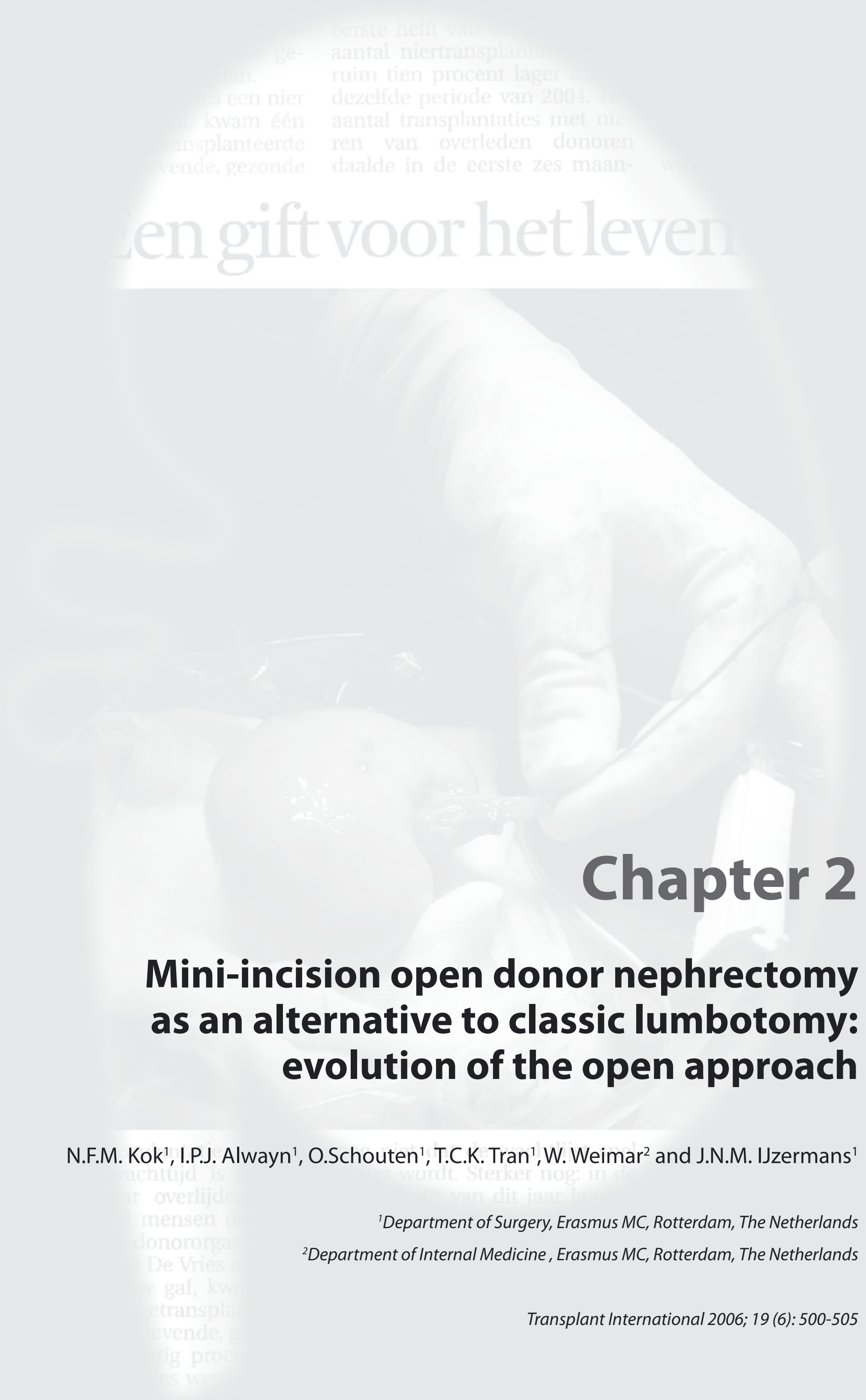
The aim of this thesis was to investigate whether laparoscopic donor nephrectomy was superior to mini-incision open donor nephrectomy. Most of this work is spent on the operative approach and the follow-up of the donor. In general, the introduction of a novel surgical technique can only be deemed acceptable if the technique offers an equal or better treatment to patients, if the technique is relatively easy to master and if the technique is cost-efficient. Other aspects are also important when evaluating novel techniques for live kidney donation. Recipient outcomes have to be considered, as the nephrectomy may influence transplantation of the kidney. Safety has to be investigated thoroughly, because, as opposed to all other operations, donor nephrectomy is carried out in humans that do not require an operation. Finally, resumption of daily activities, productivity losses, quality of life and experienced fatigue must be monitored and quantified in order to provide proper information to future donors. To date, little is known about these parameters.

To address the role of a minimally invasive approach in open kidney donation we first compared this technique to donor nephrectomy via a conventional flank incision **(Chapter 2)**. Then, we polled the opinion of transplant centers in Europe on the surgical technique of kidney donation **(Chapter 3)**. **Chapters 4** and **5** describe short and long-term outcomes of a comparative study between two concurrent cohorts of donors that underwent mini-incision and laparoscopic donor nephrectomy respectively. Results of a randomized trial comparing aforementioned techniques are presented in **Chapters 6** and **7**. In **Chapter 8 and 9** we report the results of two challenging situations in laparoscopic live kidney donation. **Chapter 8** describes preoperative imaging of renal vessels at our center and the consequences of multiple and undetected vessels respectively. In **Chapter 9** we report the data of a comparison between right-sided and left-sided laparoscopic donor nephrectomy. **Chapter 10** contains summaries in English and Dutch. In **Chapter 11** we converge the results of these studies to draw our conclusions and set some directions for future management of the live kidney donor.

REFERENCES

1. Kuss R, Teinturier J, Milliez P. Some attempts at kidney transplantation in man. Mem Acad Chir (Paris) 1951;77(22-23-24):755-64.
2. Guild WR, Harrison JH, Merrill JP, Murray J. Successful homotransplantation of the kidney in an identical twin. Trans Am Clin Climatol Assoc 1955;67:167-73.
3. http://www.transplantatiestichting.nl
4. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. N Engl J Med 1995;333(6):333-6.
5. Nguyen T, Vazquez M, Toto R. Living kidney donation and hypertension risk. Lancet 2007;369(9556):87-8.
6. Ratner LE, Ciseck LJ, Moore RG, Cigarroa FG, Kaufman HS, Kavoussi LR. Laparoscopic live donor nephrectomy. Transplantation 1995;60(9):1047-9.
7. Nogueira JM, Cangro CB, Fink JC, et al. A comparison of recipient renal outcomes with laparoscopic versus open live donor nephrectomy. Transplantation 1999;67(5):722-8.
8. Hazebroek EJ, Gommers D, Schreve MA, et al. Impact of intraoperative donor management on short-term renal function after laparoscopic donor nephrectomy. Ann Surg 2002;236(1):127-32.
9. Kok NF, Alwayn IP, Lind MY, Tran KT, Weimar W, IJzermans JN. Donor nephrectomy: mini-incision muscle-splitting open approach versus laparoscopy. Transplantation 2006;81(6):881-7.
10. Derweesh IH, Goldfarb DA, Abreu SC, et al. Laparoscopic live donor nephrectomy has equivalent early and late renal function outcomes compared with open donor nephrectomy. Urology 2005;65(5):862-6.
11. Leventhal JR, Kocak B, Salvalaggio PR, et al. Laparoscopic donor nephrectomy 1997 to 2003: lessons learned with 500 cases at a single institution. Surgery 2004;136(4):881-90.
12. Melcher ML, Carter JT, Posselt A, et al. More than 500 consecutive laparoscopic donor nephrectomies without conversion or repeated surgery. Arch Surg 2005;140(9):835-9; discussion 839-40.
13. Maartense S, Idu M, Bemelman FJ, Balm R, Surachno S, Bemelman WA. Hand-assisted laparoscopic live donor nephrectomy. Br J Surg 2004;91(3):344-8.
14. Bargman V, Sundaram CP, Bernie J, Goggins W. Randomized trial of laparoscopic donor nephrectomy with and without hand assistance. J Endourol 2006;20(10):717-22.
15. Tanabe K, Miyamoto N, Ishida H, et al. Retroperitoneoscopic live donor nephrectomy (RPLDN): establishment and initial experience of RPLDN at a single center. Am J Transplant 2005;5(4 Pt 1):739-45.
16. Wadstrom J. Hand-assisted retroperitoneoscopic live donor nephrectomy: experience from the first 75 consecutive cases. Transplantation 2005;80(8):1060-6.
17. Bachmann A, Wolff T, Ruszat R, et al. Retroperitoneoscopic donor nephrectomy: a retrospective, non-randomized comparison of early complications, donor and recipient outcome with the standard open approach. Eur Urol 2005;48(1):90-6; discussion 96.
18. Gjertsen H, Sandberg AK, Wadstrom J, Tyden G, Ericzon BG. Introduction of hand-assisted retroperitoneoscopic living donor nephrectomy at Karolinska University Hospital Huddinge. Transplant Proc 2006;38(8):2644-5.
19. Neipp M, Jackobs S, Becker T, et al. Living donor nephrectomy: flank incision versus anterior vertical mini-incision. Transplantation 2004;78(9):1356-61.
20. Wolf JS, Jr., Merion RM, Leichtman AB, Campbell DA, Jr., Magee JC, Punch JD, et al. Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation 2001;72(2):284-90.
21. Simforoosh N, Basiri A, Tabibi A, Shakhssalim N, Hosseini Moghaddam SM. Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial. BJU Int 2005;95(6):851-5.
22. Oyen O, Andersen M, Mathisen L, et al. Laparoscopic versus open living-donor nephrectomy: experiences from a prospective, randomized, single-center study focusing on donor safety. Transplantation 2005;79(9):1236-40.
23. Andersen MH, Mathisen L, Oyen O, et al. Postoperative pain and convalescence in living kidney donors-laparoscopic versus open donor nephrectomy: a randomized study. Am J Transplant 2006;6(6):1438-43.

24. Velidedeoglu E, Williams N, Brayman KL, et al. Comparison of open, laparoscopic, and hand-assisted approaches to live-donor nephrectomy. Transplantation 2002;74(2):169-72.
25. Flowers JL, Jacobs S, Cho E, et al. Comparison of open and laparoscopic live donor nephrectomy. Ann Surg 1997;226(4):483-9; discussion 489-90.
26. Lennerling A, Blohme I, Ostraat O, Lonroth H, Olausson M, Nyberg G. Laparoscopic or open surgery for living donor nephrectomy. Nephrol Dial Transplant 2001;16(2):383-6.
27. Hawasli A, Boutt A, Cousins G, Schervish E, Oh H. Laparoscopic versus conventional live donor nephrectomy: experience in a community transplant program. Am Surg 2001;67(4):342-5.
28. Kumar A, Dubey D, Gogoi S, Arvind NK. Laparoscopy-assisted live donor nephrectomy: a modified cost-effective approach for developing countries. J Endourol 2002;16(3):155-9.
29. Wolf JS, Jr., Marcovich R, Merion RM, Konnak JW. Prospective, case matched comparison of hand assisted laparoscopic and open surgical live donor nephrectomy. J Urol 2000;163(6):1650-3.
30. Rawlins MC, Hefty TL, Brown SL, Biehl TR. Learning laparoscopic donor nephrectomy safely: a report on 100 cases. Arch Surg 2002;137(5):531-4; discussion 534-5.
31. Leventhal JR, Deeik RK, Joehl RJ, et al. Laparoscopic live donor nephrectomy--is it safe? Transplantation 2000;70(4):602-6.
32. Stifelman MD, Hull D, Sosa RE et al. Hand assisted laparoscopic donor nephrectomy: a comparison with the open approach. J Urol 2001;166(2):444-8.
33. Simforoosh N, Bassiri A, Ziaee SA, et al. Laparoscopic versus open live donor nephrectomy: the first randomized clinical trial. Transplant Proc 2003;35(7):2553-4.
34. Buell JF, Hanaway MJ, Potter SR, et al. Hand-assisted laparoscopic living-donor nephrectomy as an alternative to traditional laparoscopic living-donor nephrectomy. Am J Transplant 2002;2(10):983-8.
35. Tooher RL, Rao MM, Scott DF, et al. A systematic review of laparoscopic live-donor nephrectomy. Transplantation 2004;78(3):404-14.
36. Kok NF, Lind MY, Hansson BM, et al. Comparison of laparoscopic and mini incision open donor nephrectomy: single blind, randomised controlled clinical trial. BMJ 2006;333(7561):221.
37. Handschin AE, Weber M, Demartines N, Clavien PA. Laparoscopic donor nephrectomy. Br J Surg 2003;90(11):1323-32.



Chapter 2

Mini-incision open donor nephrectomy as an alternative to classic lumbotomy: evolution of the open approach

N.F.M. Kok[1], I.P.J. Alwayn[1], O.Schouten[1], T.C.K. Tran[1], W. Weimar[2] and J.N.M. IJzermans[1]

[1]Department of Surgery, Erasmus MC, Rotterdam, The Netherlands

[2]Department of Internal Medicine , Erasmus MC, Rotterdam, The Netherlands

Transplant International 2006; 19 (6): 500-505

ABSTRACT

In Europe, the vast majority of transplant centers still performs open donor nephrectomy. This approach can therefore be considered the gold standard. At our institution, classic lumbotomy (CL) was replaced by a mini-incision anterior flank incision (MIDN) thereby preserving the integrity of the muscles. Data of sixty donors who underwent MIDN were compared with eighty-six historical controls who underwent CL without rib resection. Median incision length measured 10.5 and 20 cm (MIDN vs. CL, P <0.001). Median operation time was 158 minutes and 144 minutes (P=0.02). Blood loss was significantly less after MIDN (median 210 vs. 300 ml, P=0.01). Intra-operatively, 4 (7%) and 1 (1%) bleeding episodes occurred. Postoperatively, complications occurred in 12% in both groups (P=1.00). Hospital stay was 4 and 6 days (P <0.001). In 1 (2%) and 11 (13%) donors (P=0.02) late complications related to the incision occurred. After correction for baseline differences, recipient serum creatinine values were not significantly different during the first month following transplantation. In conclusion, MIDN is a safe approach, which reduces blood loss, hospital stay and the number of incision related complications as compared to CL with only a modest increase in operation time.

INTRODUCTION

Transplantation from living donors has successfully stabilised the number of end-stage renal disease patients awaiting renal transplantation in the Netherlands (1). In order to further reduce the number of patients on the waiting list and consequently the number of patients dying while waiting, live kidney donation programs have to be expanded. It is still a matter of debate which operation technique should be used for live donor nephrectomy. Europeans have been more reluctant towards laparoscopic donor nephrectomy than Americans (2). Recently a survey was sent from our department to transplant centers in twelve European countries. Of all centers the vast majority still performed open donor nephrectomy. Supported by the results of a recent clinical trial (3) open donor nephrectomy can truly be considered the gold standard in Europe.

Stimulated by the introduction of minimally invasive laparoscopic techniques, there have been refinements of the open technique. Omission of rib resection (4) and employment of smaller incisions (5) both contributed to decreased morbidity and faster recovery of the donor as compared to classic lumbotomy. A recent study showed that both laparoscopic and mini-incision open donor nephrectomy (MIDN) can improve donors' recovery (6). However, most of these modified open approaches damage the abdominal muscles and harm the integrity of the abdominal wall. Splitting in stead of transsecting the muscles could potentially leave the oblique and transverse muscles intact. At our institution classic lumbotomy (CL), performed without rib resection, was replaced by a mini-incision muscle-splitting anterior flank approach. The aim of this study was to describe the outcome of a smaller incision in terms of preservation of abdominal wall integrity of the donor.

PATIENTS AND METHODS

Patient characteristics

From January 1994 until December 2000 CL was performed in 86 donors at our institution. In 2001 mini-incision open donor nephrectomy (MIDN) was developed at our institution to offer donors a less invasive open approach. The operation technique is described in detail below. From September 2001 to May 2005 MIDN was performed in 60 donors. CL was not carried out anymore. As laparoscopic donor nephrectomy (LDN) was also performed during this period and evidence was lacking that LDN was better than MIDN, MIDN was presented to patients as a technique with results equivalent to laparoscopy. In these 60 patients MIDN was either the patient's or surgeon's preference. Patient's preferences for MIDN included shorter operation time and no conversion risk. Surgeon's preferences included the recipient's need for maximum vessel length, shorter operation times or lack of experience in LDN. Donors with complicated renovascular anatomy, obesity, donors with suitable right kidneys only, or

elderly donors were not restricted from LDN. An independent researcher intra-operatively and postoperatively recorded all data of donors who underwent MIDN.
All donors were preoperatively evaluated by nephrologists and cardiologists. Follow-up at the surgical outpatient clinic occurred at 3 weeks and 2 months after discharge and at the nephrology outpatient clinic at 3 months and 1 year.

Surgical techniques

Classic Lumbotomy

With the donor placed in a lateral decubitus position, lumbotomy was performed in the eleventh intercostal space or below the twelfth rib. Rib resection was not performed. Muscles were transsected. A mechanical retractor (Omnitract surgical, St. Paul, USA) was installed. The retroperitoneal space was opened. The kidney was meticulously dissected and arterial and venous structures were identified. After dissection, the ureter was divided and sutured distally. After administration of 5,000 units of Heparin (Leopharma, Breda, The Netherlands) the renal artery and vein were clamped and divided distally. Thereafter, the kidney was extracted, flushed with 4º-Celsius Eurocollins (Fresenius, Bad Homburg, Germany) and stored on ice. Protamine sulphate (5,000 units, ICN Pharmaceuticals, Zoetermeer, The Netherlands) was administered. The renal artery and vein were controlled using Prolene 4/0 continuous sutures (Ethicon, Hamburg, Germany). The fascias of the abdominal muscles were closed using Vicryl 1/0 sutures (Ethicon, Hamburg, Germany). The subcutaneous fascia was approximated and the skin was sutured intracutaneously using Monocryl 3/0 sutures (Ethicon, Hamburg, Germany). Postoperatively, pain was controlled using an epidural catheter or a patient controlled analgesia device administrating intravenous morphine.

Mini-incision muscle-splitting anterior flank approach (MIDN)

With the patient placed in a lateral decubitus position and the operation table maximally flexed, a horizontal 10-15 cm skin incision was made anterior to the 11^{th} rib toward the umbilicus. The fascia and muscles of the abdominal wall were carefully split avoiding harm to the interostal nerves between the internal oblique and transvere abdominal muscles. A mechanical retractor (Omnitract surgical, St. Paul, USA) was installed. The peritoneum was displaced medially and Gerota's fascia was opened on the lateral side of the kidney. The working space was limited, given the fact that only the fingers of a medium sized hand could enter the wound. Therefore long instruments were used. Further dissection and preparation of the vascular structures was performed as described above. Following the administration of Heparin, the renal artery and vein were clamped and ligated using conventional clamps or an endostapler (EndoGia, US Surgical, Norwalk, USA). The endostapler was only used in case of multiple arteries and/or veins and if multiple clamps would hinder overview. Then, no additional Prolene sutures were required to secure the renal arteries and veins. Postoperatively, pain was controlled using a patient controlled analgesia device administrating intravenous morphine and oral administration of tablets acetaminophen.

Recipients

All recipients underwent renal transplantation using the standard technique of preperitoneal placement in the iliac fossa. Peroperatively, urine production of the transplanted kidney was recorded. A calcineurin inhibitor based immunosuppressive regimen was given to all recipients. For the first month postoperatively serum creatinine values were compared between recipients of a transplant procured by either MIDN or CL.

Definitions and Statistical analysis

CL was compared to MIDN concerning operative and postoperative characterisctics, early and late complications and recipient serum creatinine. Warm ischemia time was defined as time elapsing between occlusion of the first renal artery and flushing of the artery. Time until kidney removal was defined as the time elapsing between incision of the skin and extraction of the kidney. Operation time was defined as time elapsing between incision of the abdomen and tying the last suture. Intra-operative complications were defined as events unintentionally lengthening the operation and causing potential harm to the donor or the graft. Postoperative complications were defined as events requiring an intervention or causing unintentionally prolonged hospital stay of the donor. Intra-operative and postoperative complications were further categorized in major complications and minor complications. Late complications related to the chosen incision were defined as hernias, pseudo hernias (i.e. protrusion of the abdominal wall without presence of a hernia), intervention because of severe pain around the incision and not resolving sensibility loss of the skin surrounding the incision.

Categorical variables were compared with the Chi square test and displayed as number (percentage). Continuous variables were compared with the Mann Whitney U test and displayed as median (minimum-maximum). Recipient serum creatinine values were corrected for the donor's sex, age and relation to the recipient and calculated with repeated measurements ANOVA using mixed model analysis. All analyses were conducted using SPSS (version 11.5, SPSS Inc., Chicago, USA). A p-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Baseline characteristics

Baseline characteristics are shown in Table 1. All donors received the operation as planned. Rib resections were not performed in the CL group and incisions were not enlarged nor were muscles divided in the MIDN group. The MIDN group consisted of significantly more females.

Table 1. Baseline characteristics of the donors and recipients. Donors underwent either mini-incision donor nephrectomy (MIDN) or Classic lumbotomy (CL). Data are presented as number (%) unless stated otherwise.

	MIDN (N=60)	CL (N=86)	P-value
Donor			
Gender			
Male	16 (27%)	37 (43%)	0.05
Female	44 (73%)	49 (57%)	
Age in years			
median (range)	51 (22-90)	49.5 (20-77)	0.07
Kidney			
Left	27 (45%)	47(55%)	0.31
Right	33 (55%)	39 (45%)	
ASA Classification			
I	43 (72%)	68 (79%)	0.33
II	17 (28%)	18 (21%)	
Body Mass Index in kg/m^2			
median (range)	27.2 (19.9-41.0)	25.2 (16.2-36.0)	0.11
Renal Arteries			
1	50 (83%)	62 (72%)	0.16
≥ 2	10 (17%)	24 (28%)	
Renal Veins			
1	56 (93%)	76 (88%)	0.40
≥ 2	4 (7%)	10 (12%)	
Recipient			
Gender			
Male	31 (52%)	46 (53%)	0.87
Female	29 (48%)	40 (47%)	
Age in years			
median (range)	44.5 (8-77)	36 (18-67)	0.003
Relation between donor and acceptor			
Living related	37 (62%)	81 (94%)	<0.001
Living unrelated	23 (38%)	5 (6%)	

Other baseline characteristics of the donor did not significantly differ between MIDN and CL. Recipients were older in the MIDN group and more frequently unrelated to the donor. Figure 1 demonstrates the abdomen of a patient several weeks after MIDN. The scar is relatively small and is located subcostally in the natural shadow of the costal margin.

Surgery

Intra-operative data are shown in Table 2. MIDN was performed using an 8 to 15 cm incision. The length of the incision did significantly correlate with body mass index (BMI), indicating that incisions tend to be longer in patients with a higher BMI (Spearman correlation, r = 0.32, P=0.02). In the CL group incisions were significantly longer, reaching up to 30 cm (P < 0.001).

Figure 1. The scar of a male donor following mini-incision donor nephrectomy. In upright position, the scar is located just below the costal margin.

In this group no significant relation between incision length and BMI was assessed (spearman correlation, r = -0.10, P=0.50). Warm ischemia time did not significantly differ between both groups. However, warm ischemia time was only recorded in 15 of the 86 patient who underwent CL, because it was not considered relevant at that time as no alternatives to CL were available at our institution. Removal of the kidney took on average 25 minutes longer in the MIDN group (P < 0.001). Operation time was only 14 minutes longer (P=0.02) in the MIDN group indicating that closure of the renal vessels and approximating the fascias of the abdominal muscles are considerably faster in this group. Major intra-operative complications did not occur. Iatrogenic bleeding occurred in four patients during MIDN (maximum total blood loss 1285 ml). These included one donor in whom the vascular clamp slipped of the renal artery during extraction (total blood loss 900 ml). One bleeding occurred during CL (total blood loss 800 ml) due to bleeding from an aberration of the gonadal vein. None of these five patients required a blood transfusion. Some other patients lost up to 1400 and 1000 ml blood during MIDN and CL respectively. Blood loss was diffuse in these cases and there was no single bleeding. Over all, median blood loss was significantly reduced by MIDN (210 vs. 300 ml, P=0.01).

Postoperative data

Postoperative data and complications are depicted in Table 3. Major complications (i.e. requiring re-operation or re-admission) did not occur. Seven minor complications occurred in

Table 2. Intra-operative results of the donors undergoing mini-incision donor nephrectomy (MIDN) or Classic lumbotomy (CL). Data are presented as number (%) unless stated otherwise.

	MIDN (N=60)	CL (N=86)	P-value
Incision length in cm median (range)	10.5 (8-15)	20 (8-30)	< 0.001
Warm ischemia time in minutes median (range)	2.5 (1-9)	3 (1-7)*	0.22
Time until kidney removal in minutes median (range)	118 (60-196)	93.5 (55-195)	< 0.001
Skin-to-skin time in minutes median (range)	158 (84-251)	144 (76-310)	0.02
Intra-operative complications			
Major	-	-	1.00
Minor (Bleeds)	4 (7%)	1 (1%)	0.16
Blood loss in ml median (range)	210 (30-1400)	300 (50-1000)	0.01

* only recorded in 15 patients

Table 3. Postoperative results of the donors undergoing mini-incision donor nephrectomy (MIDN) or Classic lumbotomy (CL). Data are presented as number (%) unless stated otherwise.

Donor	MIDN (N=60)	CL (N=86)	P-value
Hospital stay in days median (range)	4 (2-9)	6 (3-14)	< 0.001
Postoperative complications			
Major	-	-	-
Minor	7 (12%)	10 (12%)	1.00
Blood transfusion	1	-	
Haematoma	1	1	
Pneumonia	-	1	
Ileus	-	1	
Prolonged nausea	1	-	
Urinary tract infection	1	2	
Fever	-	3	
Allergic reaction	-	1	
Pain necessitating intervention	1	-	
Infected left eye	1	-	
Psychosis	-	1	
Slowly declining serum creatinine	1	-	

seven patients following MIDN. These included delayed discharge in one patient. She had a slow decline in serum creatinine values to 150 μmol/l that led to prolonged hospital stay. In the CL group ten complications occurred in nine patients. Median postoperative hospital stay was four days in the MIDN group and 6 days in the CL group (P < 0.001).

Table 4. Late complications related to the incision of the donors undergoing mini-incision donor nephrectomy (MIDN) or Classic lumbotomy (CL). Data are presented as number (%) unless stated otherwise.

Donor	MIDN (N=60)	CL (N=86)	P-value
Incisional hernia	1 (2%)	4 (5%)	
Pseudo hernia	-	4 (5%)	
Pain necessitating intervention	-	2 (2%)	
Analgesia skin surrounding scar	-	1 (1%)	
In total	1 (2%)	11 (13%)	0.02

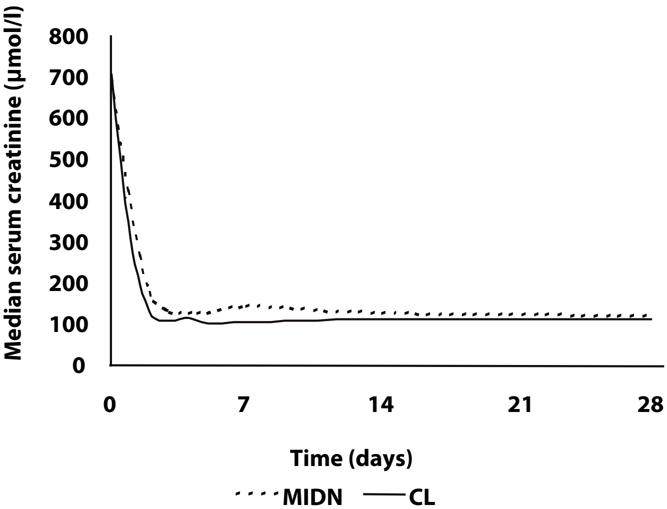


Figure 2. Median recipient serum creatinine following donor nephrectomy by either mini-incision donor nephrectomy (MIDN, interrupted line) or Classic lumbotomy (CL, continuous line).

Late complications

During follow-up (mean 19 vs. 113 months) late complications related to the incision occurred in one patient following MIDN and 11 following CL (P=0.02). The single patient in the MIDN group presented with an incisional hernia, which was treated laparoscopically. In the CL group four patients presented with incisional hernia. One of these patients needed three repair operations. Four others presented with pseudo hernias and two patients were referred to the outpatient pain clinic for treatment of unbearable pain. One patient had prolonged analgesia in the skin around the scar, which did not resolve at all.

Recipients

Of the transplanted kidneys 88% and 86% (MIDN vs. CL, P=0.80) produced urine within 1 hour following reperfusion. Recipient serum creatinine values declined fast and not statistically different between both groups (Figure 2). Serum creatinine values at day 1 to 7, 14, 21 and 28 did not differ. None of the recipients required dialysis in the postoperative phase.

DISCUSSION

The effort to use a smaller, muscle-splitting incision in MIDN is rewarding. MIDN results in similar donor safety, as reflected by the absence of major complications, a similar number of minor intra- and postoperative complications and equivalent graft function. With marginally longer operation time, donors benefit from reduced blood loss, shorter hospitalization and preservation of continuity of abdominal muscles. A small number of late, incision related complications occurred in the MIDN group. Except for the single incisional hernia that occurred in one of the first ten cases all later donors recovered uneventfully after MIDN.

Open donor nephrectomy is an evolving technique. In our opinion, muscle-splitting is the next step in the development of open surgical techniques. Previously, anterior extra-peritoneal incisions (7, 8), omission of rib resection (4), and smaller incisions (5) have improved open donor nephrectomy and reduced harm to the donor. The use of muscle-splitting incisions, which has been practiced for other surgical procedures to the kidney (9), is a logical next step. Similarly to muscle-splitting incisions for cholecystectomy (10), these types of incisions can probably reduce postoperative pain and facilitate sooner recovery.

The survey we recently sent to European centers has clarified that many European surgeons still prefer open approaches for donor nephrectomy (unpublished data). Moreover, in 40% of the centers the classic lumbotomy is still being performed and sometimes includes rib resection. Neipp et al. (11) presented excellent results with a small, vertical anterior approach. MIDN in our series adds preservation of the transverse abdominal muscle and provides a scar that usually disappears in the natural shade of the costal margin. As the incision we present is lateral to vertical and subcostal incisions, but medial to classic flank incisions, this incision combines traditional easy access to the retroperitoneal space and preservation of the integrity of the abdominal musculature. Under supervision of a transplant surgeon residents in the fifth and sixth year of their training carry out these procedure at our institution. This technique is easily learned and the advantage from the donor's perspective is clear. This might encourage transplant surgeons and urologists in the field to adopt less invasive open techniques.

Further prospective studies will classify the role of MIDN alongside laparoscopic donor nephrectomy. A recent trial (3) suggested that conventional open donor nephrectomy was superior to laparoscopic donor nephrectomy with regard to safety. Except for the omission of rib resection, none of the other mentioned improvements was applied. This study suggests that more refined, minimally invasive open approaches might be safer than laparoscopy, while providing quick recovery and good cosmetic outcomes. A non-randomized comparative study (6) using small muscle cutting incisions suggests that both MIDN and laparoscopic donor nephrectomy have good and probably equivalent outcomes. Therefore, in our view MIDN is not an inferior technique compared to the laparoscopic technique. This technique probably saves costs (12) and might be a good alternative for traditionally trained surgeons (13).

An ideal technique for donor nephrectomy is one that is applicable to all donors and all surgeons. The ongoing debate on selection for donor nephrectomy suggests that some donors will always require open approaches (3). MIDN can be used for obese donors, right kidneys and donors having multiple renal vessels, as demonstrated in this study. Despite the limited working space minimally invasive open techniques probably require little more experience than conventional open techniques.

Finally, for transplantation surgeons and urologists who prefer open surgery because of the potential hazardous effects of longer warm ischemia times, pneumoperitoneum and traumatic extraction applied in laparoscopic donor nephrectomy, MIDN is an acceptable alternative. For those favoring laparoscopic donor nephrectomy, MIDN is a feasible approach to convert to if necessary. Conversion has been reported to occur in up to 13% during laparoscopic donor nephrectomy (14). Conversion to MIDN does not necessarily threaten the donor's recovery and cosmetic outcome.

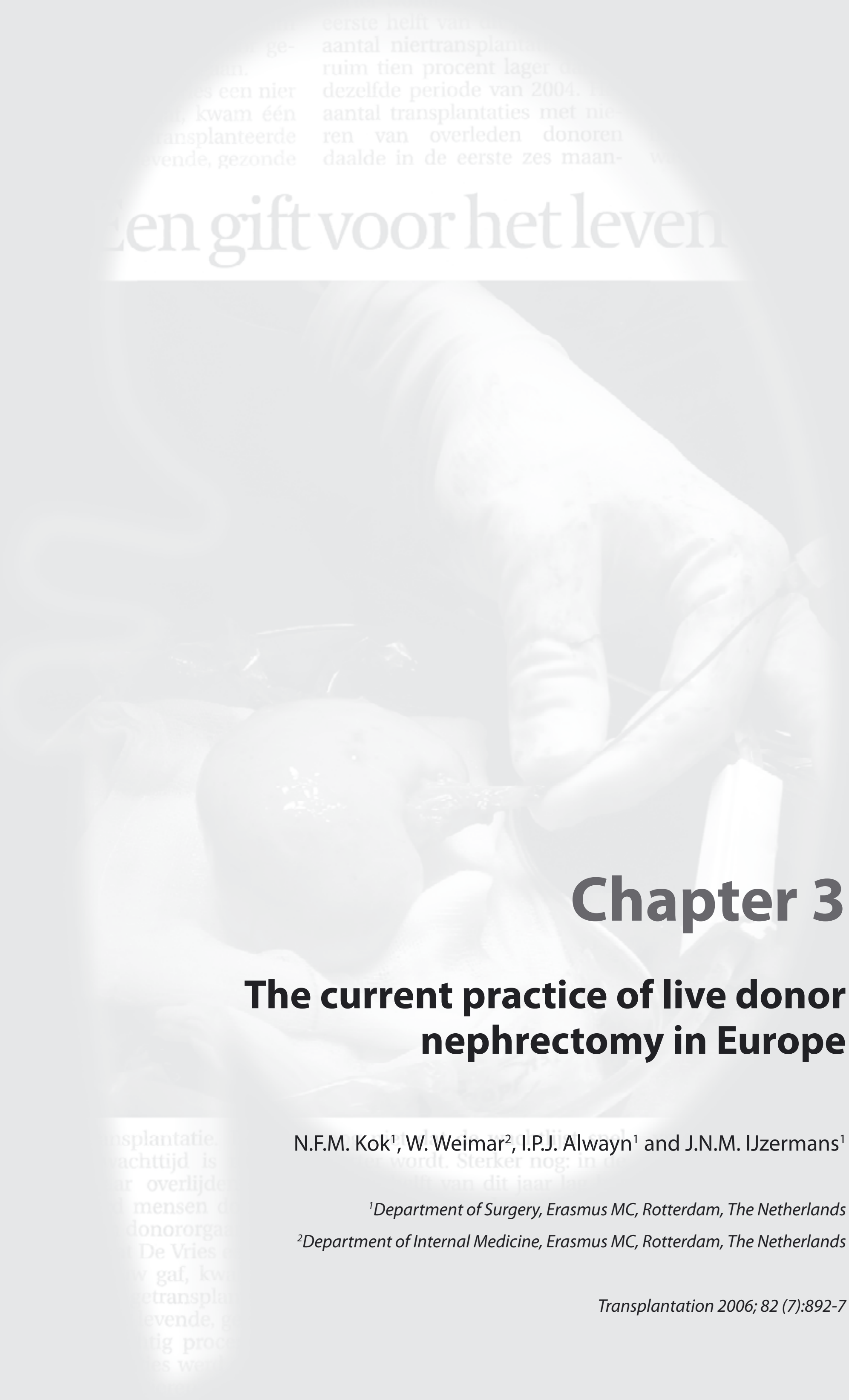
In conclusion, muscle-splitting MIDN is another step in improving open donor nephrectomy. Good outcomes with regard to safety of donor and graft and favorable recovery as compared to classic lumbotomy establish MIDN as the open approach of choice. We strongly encourage transplant surgeons and urologists who still practice conventional open donor nephrectomy to improve their results with smaller, muscle-splitting incisions. Prospective comparisons with laparoscopic donor nephrectomy are necessary to further explore the position of modern open donor nephrectomy in transplant surgery.

ACKNOWLEDGEMENTS

N.F.M. Kok is supported by an unrestricted grant of the Dutch Kidney Foundation.

REFERENCES

1. http://www.transplantatiestichting.nl/
2. Brook NR, Nicholson ML. An audit over 2 years' practice of open and laparoscopic live-donor nephrectomy at renal transplant centers in the UK and Ireland. BJU Int 2004;93(7):1027-31
3. Oyen O, Andersen M, Mathisen L, et al. Laparoscopic versus open living-donor nephrectomy: experiences from a prospective, randomized, single-center study focusing on donor safety. Transplantation 2005;79(9):1236-40
4. Srivastava A, Tripathi DM, Zaman W, Kumar A. Subcostal versus transcostal mini donor nephrectomy: is rib resection responsible for pain related donor morbidity. J Urol 2003;170(3):738-40
5. Yang SL, Harkaway R, Badosa F, Ginsberg P, Greenstein MA. Minimal incision living donor nephrectomy: improvement in patient outcome. Urology 2002;59(5):673-7
6. Lewis GR, Brook NR, Waller JR, Bains JC, Veitch PS, Nicholson ML. A comparison of traditional open, minimal-incision donor nephrectomy and laparoscopic donor nephrectomy. Transpl Int 2004;17(10):589-95
7. Jones KW, Peters TG, Walker GW. Anterior-retroperitoneal living donor nephrectomy: technique and outcomes. Am Surg 1999;65(3):197-204
8. Redman JF. An anterior extraperitoneal incision for donor nephrectomy that spares the rectus abdominis muscle and anterior abdominal wall nerves. J Urol 2000;164(6):1898-900
9. Giberti C, Martorana G, Carmignani G. The Giuliani muscle splitting and nerve-sparing anterolateral transabdominal approach to the kidney. Urology 1996;47(6):911-4
10. Baguley PE, de Gara CJ, Gagic N. Open cholecystectomy: muscle splitting versus muscle dividing incision: a randomized study. J R Coll Surg Edinb 1995;40(4):230-2
11. Neipp M, Jackobs S, Becker T, et al. Living donor nephrectomy: flank incision versus anterior vertical mini-incision. Transplantation 2004;78(9):1356-61
12. Kumar A, Tripathi DM, Srivastava A. Mini incision live donor nephrectomy: an optimal approach for the developing countries. Clin Transplant 2003;17(6):498-502
13. Greenstein MA, Harkaway R, Badosa F, Ginsberg P, Yang SL. Minimal incision living donor nephrectomy compared to the hand-assisted laparoscopic living donor nephrectomy. World J Urol 2003;20(6):356-9
14. Odland MD, Ney AL, Jacobs DM, et al. Initial experience with laparoscopic live donor nephrectomy. Surgery 1999;126(4):603-6; discussion 606-7



Chapter 3

The current practice of live donor nephrectomy in Europe

N.F.M. Kok[1], W. Weimar[2], I.P.J. Alwayn[1] and J.N.M. IJzermans[1]

[1]Department of Surgery, Erasmus MC, Rotterdam, The Netherlands

[2]Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

Transplantation 2006; 82 (7):892-7

ABSTRACT

The increasing number of live kidney donors in the last decade has stimulated interest in the surgical technique of donor nephrectomy. In this study we evaluated the current status of the surgical approach in European transplant centers. A questionnaire was sent to 131 centers in twelve European countries. Questions included the number of donors, the technique used, and the inclusion and exclusion criteria for a technique. Ninety-two replies (70%) were included in this audit. In the responding centers approximately 1450 live donor nephrectomies were performed in 2004 (more than 80% of all live kidney donations in these countries). The number of living donors ranged from 0 to 95 per center. Nineteen institutions (21%) removed kidneys using endoscopic techniques only. Twenty-two centers (24%) performed both open and laparoscopic donor nephrectomy. Vessel length, difficult anatomy and right-sided donor nephrectomy were common reasons to choose an open technique. Twelve centers had performed laparoscopic donor nephrectomy but quit their program for various reasons. In 51 centers (55%) only open donor nephrectomy was carried out. Lack of evidence that endoscopic techniques provide better results was the main reason for these centers to stick to an open approach. Incisional hernias occurred after all types of open surgery in up to 30% of the donors per center. Twenty-nine clinics still carry out the classic flank incision. In conclusion, the surgical technique of live donor nephrectomy varies greatly between transplant centers in European countries. To define the optimal surgical approach an European registration of donor nephrectomies would be helpful.

INTRODUCTION

Persistent organ shortage has led to renewed interest in live organ donation. The result is an ongoing increase in the number of transplantations from live kidney donors. These developments have inspired transplant surgeons and urologists to adopt less invasive surgical approaches in order to limit discomfort to the donor and encourage even more relatives of patients with end-stage renal disease to consider live donation. Since the introduction of laparoscopic donor nephrectomy by Ratner in 1995 various endoscopic alternatives have been presented to remove a kidney in a healthy individual, including hand-assisted laparoscopic donor nephrectomy and retroperitoneoscopic donor nephrectomy (1-4). Meanwhile open techniques have changed (5-9). Current alternatives to classic flank incisions include vertical and transverse anterior incisions and less invasive flank approaches.

A decade after the introduction of laparoscopy in live kidney donation the majority of transplant centers in the United States performs laparoscopic kidney donation. European centers have been more skeptical towards incorporating laparoscopic donor nephrectomy (10, 11). To investigate the status in Europe with respect to the implementation of less invasive techniques of donor nephrectomy, we sent out a questionnaire. In this article we evaluate which surgical techniques are performed in Western and Northern Europe and what rationale is behind these techniques.

METHODS

A questionnaire was sent to 131 transplant centers in Austria, Belgium, Denmark, France, Finland, Germany, Ireland, the Netherlands, Norway, Sweden, Switzerland and the United Kingdom. In each center either a surgeon, a nephrologist or an urologist in the field of transplantation was approached by mail or e-mail. Addresses were retrieved from the European Society of Organ Transplantation mailing list, the websites of the national transplant societies and online from the National Library of Medicine.

In May 2005 a first round of questionnaires was sent out, in September 2005 a second. The questionnaire consisted of questions about live kidney donation and transplantation. It was categorized in three parts (Table 1). Part A included questions on how many kidneys were transplanted from a deceased and a living donor respectively, Part B included questions on Laparoscopic donor nephrectomy (LDN) and Part C included questions on open donor nephrectomy (ODN). Answers were structured but space was provided for comments.

We mainly used descriptive statistics to present our data. Analyses were conducted using SPSS (version 11.5, SPSS Inc., Chicago, USA). Our aim was to evaluate which surgical techniques were applied in the twelve countries. Furthermore, we were interested to know whether a single technique was applied to all donors and whether a shift had been made towards laparoscopic surgery. If not we asked the participants why they preferred an open approach.

Table 1. Questions on live donor nephrectomy

A. Number of kidney transplantations
How many kidney transplantations from a deceased donor were performed in your center in 2004?
How many kidney transplantations from a living donor were performed in your center in 2004?
Did these numbers change over the past 5 years?
Do you have a registration of live donor nephrectomies?
B. Laparoscopic donor nephrectomy (LDN)
Is LDN currently performed in your center?
In which year was LDN introduced?
To your opinion, has the introduction of LDN contributed to increased live kidney donation in your center?
How many LDNs have been performed in your center in 2004 and in total?
How many percent of the LDNs in 2004 was converted to open?
Who does perform LDN in your center and how is your operation team composed?
Which extraction site is favored?
Which instrument is used to divide the renal vessels?
Is LDN restricted to left kidneys?
Do you use hand-assistance?
Do you operate all donors laparoscopically?
C. Open donor nephrectomy (ODN)
Did you ever try other techniques than ODN?
What kind of open technique do you perform?
Do you perform rib resection?
Do you divide or split the muscles of the abdominal wall?
Could you estimate you average incision length?
Do you see true incisional hernias postoperatively?

RESULTS

Ninety-four replies were received (72%). Two centers did not practice live donor nephrectomy anymore. Therefore these results are based on 92 replies from all twelve aforementioned countries. The specialists who responded and their affiliations are mentioned in the acknowledgements.

Number of transplantations

Figure 1 shows the case volume of the responding centers. In 2004 approximately 6800 transplantations were carried out in total. Seventy-nine percent of the transplants (about 5350 kidneys) was derived from a deceased donor and 21% (about 1450 kidneys) was derived from a live donor. The responding centers were responsible for approximately 80.6% of the live kidney donor transplantations in the twelve aforementioned countries and for approximately 62% of all European live kidney donor transplantations(12-17). In figure 2 the estimated numbers of live kidney donor transplantations of the responding centers, the remaining centers in the investigated countries and the rest of Europe respectively are shown. The number of

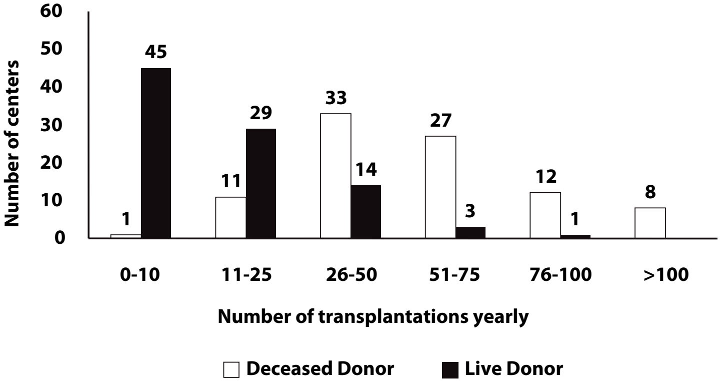


Figure 1. Centers categorized according to case volume.

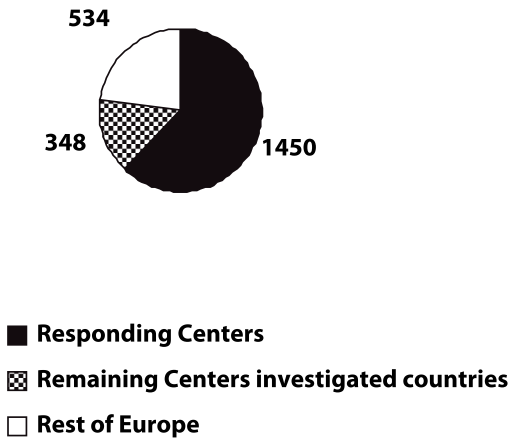


Figure 2. Estimated number of live kidney donors in Europe in 2004.

live donor nephrectomies in the investigated countries increased from 1279 in 2000 to 1798 in 2004 (41% increase) (12-17). The median number of live kidney donor transplantations was 16 per center (range 0-95). The ratio of live donors to deceased donors ranged from 0 to 3 among the centers. With regard to the annual number of transplantations from a deceased donor 23% of the centers reported a decrease in the last five years, 47% reported no changes and 30% reported an increase. With regard to the annual number of live kidney donor transplantations 7% of the centers reported a decrease, 30% no changes and 63% an increase. Eighty-four percent of the centers have a registration of live donor nephrectomies.

Laparoscopic donor nephrectomy (LDN)

Numbers, year of introduction and influence on live donation program

Forty-one centers reported to perform total LDN (n=19, including one center that uses a robot), hand-assisted LDN (n=20), either hand-assisted or total LDN (n=1), and retroperitoneoscopic donor nephrectomy (n=1). Three of them started their laparoscopic program in 2005. Therefore, data on numbers were available from 38 centers. In 2004 two centers did not perform any LDN. Thirty-six centers together performed 586 LDNs, which implies that 40% of the kidneys in all centers was laparoscopically procured. Altogether 848 live donor nephrectomies were performed in these 36 centers. So, in the centers performing open donor nephrectomy alongside LDN (in 2004 n=19) approximately 46% of the donors was still operated on using an open approach.

Fourteen centers (37%) had performed less than 25 laparoscopic procedures up to and including 2004. Eight centers had performed 25 to 50 procedures, eight centers had performed 50 to 100 procedures, six centers had performed 100 to 200 procedures and two centers had experience in more than 200 procedures. There was a positive association between performance of laparoscopic techniques and higher case volume (mean 22 versus 10 live donors in centers that do and do not perform LDN respectively, $P<0.001$, Mann Whitney U test). Eighteen centers (47%) introduced laparoscopic techniques to their transplantation programs within the last five years. Twenty centers think that laparoscopic techniques have contributed to an increasing number of live kidney donors presenting to their center. Centers that performed more LDNs in 2004 were more likely to answer that laparoscopy had led to more live donors (mean 20 versus 11 donors in centers that answered affirmative and negative respectively to this question, $P=0.002$, Mann Whitney U test).

Composition of the operation team

In 27 centers (66%) LDN is carried out by a general or a transplant surgeon, in 13 institutions (32%) by an urologist and in one clinic by either a surgeon or an urologist. In 19 clinics (46%) only one specialist has the expertise to perform laparoscopic kidney donation, in 16 clinics (39%) two specialists, in four clinics (10%) three specialists, and in two clinics (5%) four specialists. In total 71 specialists are trained to perform laparoscopic kidney donation in the responding centers. The operating team is composed of at least two consultants in 19 clinics (46%), and of one consultant and a registrar in the remaining centers.

Instruments, extraction site and conversion rate

In one center titanium clips alone are used to secure the renal vessels. Four clinics use self-locking clips and 23 clinics use a vascular endostapler (TA or GIA). The remaining centers use a combination of these three tools. As an extraction site most centers (61%) use a pfannenstiel incision. Other rather common incisions are sub- and supra-umbilical incisions.

Iliac incisions, subcostal incisions and hemi-pfannenstiel incisions are each practiced in one clinic. In 8 centers 14 out of 186 (7.5%) LDNs were converted to open. The conversion rate varied from 1% to 29%. Two of the centers that converted to open performed less than 10 procedures in 2004, two centers performed 11 to 20 LDNs, two centers performed 21 to 30 LDNs and two centers performed 41 to 50 LDNs. The total experience with LDN in these centers was less than 25 cases in one center, less than 50 cases in two centers, less than 100 in three centers, less than 200 in one center and more than 200 cases in one center. Three of the centers never used hand-assistance, three centers always and two sometimes. The center that reported a conversion rate of 29% stressed that LDN was being learned.

Right-sided LDN and Hand-assistance

In 12 centers (29%) LDN is restricted to the left side. Indications for right-sided LDN are summarized in Table 2. Other reasons to switch to the right side include urinary tract abnormalities and the statement that the best kidney should remain in the donor. Five centers perform right-sided LDN in 50% of the cases or more. Twenty-one centers (51%) use hand-assistance during donor nephrectomy. Reasons are stated in Table 2. Two centers use hand-assistance only in the terminal phase of the operation for quick extraction of the kidney. One center uses hand-assistance because of positive experiences with it during radical nephrectomy for cancer. The center that performs retroperitoneoscopic donor nephrectomy does not use hand-assistance.

Centers performing ODN alongside LDN

Nineteen centers (46%) only perform LDN or retroperitoneoscopic donor nephrectomy. The other 22 centers prefer an open approach in some cases. Reasons are stated in Table 3. Other reasons include the absence of the laparoscopic surgeon in two centers, multiple previous

Table 2. Indications for right-sided laparoscopic donor nephrectomy (LDN) and reasons for hand-assistance. Data are presented as the number of times a reason was mentioned (%).

Indications for right-sided LDN (27 institutions)	
Multiple vessels on the left side	21 (78%)
Stenosis right renal artery	10 (37%)
Smaller right kidney	10 (37%)
The right side is easier	7 (26%)
Other	3 (11%)
Reasons for hand-assisted LDN (22 institutions)	
Shorter warm ischemia time	8 (36%)
Shorter operation time	7 (32%)
Easier than traditional LDN	7 (32%)
Safety	6 (27%)
Learning setting	2 (9%)
Other	3 (14%)

abdominal operations in one center, conduction of a randomized controlled trial comparing ODN and LDN in one center and the statement of one center that LDN is an exception and ODN the standard.

Open donor nephrectomy (ODN)

Reasons to perform ODN

Seventy-three centers (79%) reported to perform ODN. Fifty-one centers (55%) use open approaches only. Thirty-nine clinics have never tried a laparoscopic technique for live donation for reasons summarized in Table 3. Lack of evidence that other techniques are better appears to be an important reason to stick to ODN. Other reasons than stated in the table include no trained people, too long operation times, no experience in laparoscopic surgery at all and the statement that good techniques should never be changed. The other 12 centers practiced endoscopic techniques in the past. One clinic performed complete laparoscopic LDN, hand-assisted LDN and retroperitoneoscopic donor nephrectomy but judged the results of a vertical pararectal open approach better. Three clinics performed both complete LDN and hand-assisted LDN but quit their laparoscopic programs because of temporary leave of the laparoscopic surgeon, results equivalent to open surgery and higher costs, or because other techniques were difficult to learn. Six clinics performed complete LDN but switched to ODN again because of too few cases in one clinic, results equivalent to open surgery in two clinics, a combination of equivalent results but higher costs in

Table 3. Reasons for centers also performing laparoscopic donor nephrectomy (LDN) to choose an open approach instead and reasons for centers that never tried LDN to stick to ODN. Data are presented as the number of times a reason was mentioned (%). BMI = body mass index

Reasons for centers also performing LDN to choose an open approach (22 institutions)	
Right-sided donor nephrectomy	12 (55%)
Vessel anatomy	8 (36%)
Difficult anatomy	6 (27%)
Patient's preference	5 (23%)
High BMI	2 (9%)
Safety	2 (9%)
Logistics	2 (9%)
Other	5 (23%)
Reasons for centers never to try LDN (39 institutions)	
Lack of evidence that LDN is better	22 (56%)
Other techniques hard to learn	8 (21%)
Evolution ODN	6 (15%)
Costs	6 (15%)
Too few cases	4 (10%)
Safety	3 (8%)
Other	4 (10%)

one clinic, a combination of equivalent results and difficulty with vascular variations in one institution and one clinic has LDN currently under evaluation. One clinic performed hand-assisted LDN but felt the results to be equivalent to open surgery. Retroperitoneoscopic donor nephrectomy was practiced in one clinic but the surgeons felt they had too few cases to perform this technique. In four of the aforementioned twelve clinics conventional open techniques are practiced (classic lumbotomy in three and median laparotomy in one).

Technique of ODN

The surgical techniques used for ODN are displayed in Table 4. Classic lumbotomy was defined as a classic 15 to 20 cm loin incision. Anterior horizontal incisions also include transverse subcostal incisions. One center performs both classic lumbotomy and minimal flank incision. Other techniques include a transverse anterior muscle-splitting incision in the upper part of the abdomen denoted as the "Groningen" muscle-splitting incision and an intercostal rib-tip incision. Two of the 28 centers performing classic lumbotomy always use a rib resection to explore the retroperitoneal space. Four additional centers sometimes perform a rib resection. Two of the centers performing a minimal incision flank approach standard carry out a rib resection. Sixteen of the centers performing classic lumbotomy divide the abdominal muscles, 11 centers split the muscles and one center either divides or splits the muscles. In the minimal flank approach group, 10 centers divide the muscles, 13 split the muscles and one center either divides or splits the muscles. The center that performs either classic lumbotomy or a minimal incision flank approach divides the muscles. Two centers performing vertical anterior incisions divide the muscles, three split the muscles and four make an incision in the aponeurosis. Seven centers that carry out horizontal incisions divide the muscles and one center splits the muscles. The centers performing a median laparotomy or a rib-tip incision both divide the muscles.

Incisional hernias and incision length

Incisional hernias are reported for all types of incisions except for the "Groningen" incision and the rib-tip incision. Nine centers (31%) in the lumbotomy group, 10 centers (40%) in the minimal incision flank group, three centers (33%) in the vertical anterior incision group and four centers (50%) in the horizontal anterior incision group encounter incisional hernias. Four centers report 1% incisional hernia rate, four centers report 2%, three centers report

Table 4. Open techniques practiced in the centers that perform open donor nephrectomy (n = 73)

Classic lumbotomy: 15-20 cm flank incision	28 (38%)
Minimal incision flank approach	24 (33%)
Anterior vertical, pararectal incision	9 (12%)
Anterior horizontal incision	8 (11%)
Median laparotomy	1 (1%)
Other	3 (4%)

3%, eight centers report 5%, seven centers report 10% and one center, which uses a minimal incision flank approach reported incisional hernias in up to 30% of the donors. Median average incision length for classic lumbotomy is 15 cm (range 10 to 22 cm). Median incision lengths for minimal flank, vertical and horizontal incisions are 12 cm (range 7 to 20 cm), 11 cm (range 7 to 17.5 cm) and 12.5 cm (range 10 to 20 cm) respectively. The "Groningen" incision is on average 8 cm, the median laparotomy 12 cm and the rib-tip incision 12.5 cm. A relation between incision length and occurrence of hernias was not observed. Median incision length in the group with and without hernias were 12 and 13 cm respectively (P=0.40). Eleven out of 29 centers (38%) reported hernias despite a muscle-splitting concept. This was not different from the 15 out of 37 (41%) centers that reported hernias after division of the abdominal muscles (P=1.00). Appliance of a muscle splitting concept did not correlate with higher case volume (P=0.43). Centers that performed more open procedures tended to have a higher chance to encounter hernias. In case of no hernias the annual number of ODNs was 7 and in case of hernias the annual rate was 15 ODNs (P=0.06).

DISCUSSION

This audit confirms the trend of increasing live kidney donor transplantations in the majority of Western European transplant centers. The number of centers performing LDN and its variants doubled in the last five years. However, the vast majority of centers still performs ODN, including classic lumbotomy, minimal flank approaches, vertical and horizontal anterior incisions. Forty percent of the live donor nephrectomies in Western-Europe is performed laparoscopically. This rate is smaller than in the USA. American surveys indicated that this percentage increased from approximately 48% in 2000 to approximately 67% in 2003 (18, 19). The most recent survey clarified that 36% of the surgeons involved in live kidney donation in the USA was trained in ODN only. An audit from Australia and New Zealand revealed that approximately 25% of the live donors was operated using laparoscopy in the period from February 1999 until June 2003 (20).

Transplant centers in the USA in general have higher case volumes than those in Europe and Australia. This partly explains the earlier expansion of LDN. LDN is a difficult procedure that requires extensive experience in endoscopy. Lack of fellowships in minimally invasive surgery may be another reason. Therefore, it is not only important to develop guidelines for LDN, but also for ODN. This survey is a first attempt to describe the practice of live donor nephrectomy in Europe.

All minimally invasive approaches, both laparoscopic and open, have been associated with shorter hospital stay and more rapid convalescence as compared to classic open approaches (2, 7-9, 21-23). Classic lumbotomy can still be considered the gold standard with regard to safety to the donor and the graft and can be advocated because of its universal suitability for live donor nephrectomy (24). A recent survey showed that life threatening bleeding episodes can occur during both open and laparoscopic approaches, and the case reports of living donors who died during LDN toned down the original enthusiasm towards laparoscopic kidney donation (18). There are other reasons mentioned by the responders to the questionnaire in favor of ODN. One important argument is that many responders are not convinced by current evidence suggesting that the endoscopic technique is better. Although a recent review stated that evidence has mounted that LDN is superior to an open technique (25), only three randomized controlled trials have been published to date (2, 24, 26). These studies have shown that there is, at least in some donors, a benefit for (hand-assisted) LDN over classic ODN. The conclusion of the most recent study by Oyen et al. (24) that ODN is a secure technique that is superior with regard to safety, may support centers to maintain ODN. This study was performed in one of the largest transplant centers in Europe where nearly one hundred live donor nephrectomies are performed yearly. Other arguments to maintain an open approach are, first, that a not well-defined learning curve exists for LDN, and, second, that an open approach will remain necessary for certain cases, such as right kidneys. This has become clear from the present study and from the randomized trials that only included left-sided laparoscopic donor nephrectomies. Low volume centers in particular may interpret these data as evidence for a conventional approach and therewith justify their approach.

However, a low case volume alone is not a reason to stick to open methods for all centers. Eleven centers have a laparoscopic kidney donation program with an annual number of living donors up to ten. One center even performs LDN with the Da Vinci Robot while the annual number of living donors is 15 only.

Twelve centers have practiced laparoscopic techniques, but felt that these techniques had results equivalent to open surgery. Nevertheless, the number of centers incorporating (hand-assisted) LDN or retroperitoneoscopic donor nephrectomy in their programs is still rising. These techniques are performed with good results. An estimated total number of 14 conversions in 586 procedures in 2004 indicates an adequate expertise in these techniques. It should be noted that we did not collect data on complications and re-operations. To set standards for donor nephrectomy in Europe we need to collect the data from smaller and larger centers in an international registry.

Half of the centers use hand-assistance and the other half do not. This is comparable with the experience in the USA (19). Only two centers reported to use hand-assistance because they were in a learning phase. This rebuts the prejudice some may have that hand-assistance should be used during a learning phase only and confirms that hand-assisted LDN has become a true alternative to traditional transperitoneal laparoscopy (27). As high level evidence to support either technique is not available, the choice to use hand-assistance at some stage during the operation should be left to the center. Only one center performs retroperitoneoscopic donor nephrectomy. Some good early results have been reported with this technique (3, 4) and several centers state that they will further explore this technique in the future.

It might encourage other centers considering initiating a laparoscopic live kidney donation program that the operation team consists of one consultant only in about half of the centers. It is conceivable that the continuous presence of two consultants during live kidney donation is not feasible in smaller transplantation centers.

This audit shows that about half of the centers that perform LDN also perform ODN, mainly for right-sided donor nephrectomy. Half of all centers manages to operate all donors laparoscopically. Several reports demonstrate that right-sided LDN is feasible (28, 29). Transfer of knowledge between transplant centers may help to overcome difficulties in laparoscopic kidney donation.

In the present survey we did not study changes in the open technique. There is evidence in the literature that minimal incisions (7, 9), omission of rib resection(30) and anterior incisions (5, 31) improve the results of ODN. Currently, 40% of the centers maintain classic loin incisions. We believe that muscle-splitting incisions are important in open surgery to preserve abdominal wall integrity. It would be valuable to start studies that compare muscle division and muscle-splitting to see if muscle-splitting incisions can further improve the surgical technique of ODN. In the Netherlands and the United Kingdom three clinical trials comparing modern open approaches and (hand-assisted) LDN are in a final stage. These studies will determine the position of less invasive, modified open approaches alongside LDN and will probably set new standards for the future.

In conclusion, with an increasing annual number of living donors, the preferred operation technique varies between and within European countries. Although the number of centers that perform LDN increases, most centers still practice ODN. Open techniques will probably remain their place in the surgical armamentarium in Europe because the majority of transplant centers perform a small number of live donor nephrectomies only. In the Eurotransplant countries several characteristics of the live donor including age, gender, side and warm ischemia time are already being registered. By adding other parameters such as complications, re-operations, and length of stay a useful registry may be developed that will help to set new standards and guidelines to optimize the surgical approach in live kidney donation programs.

ACKNOWLEDGEMENTS

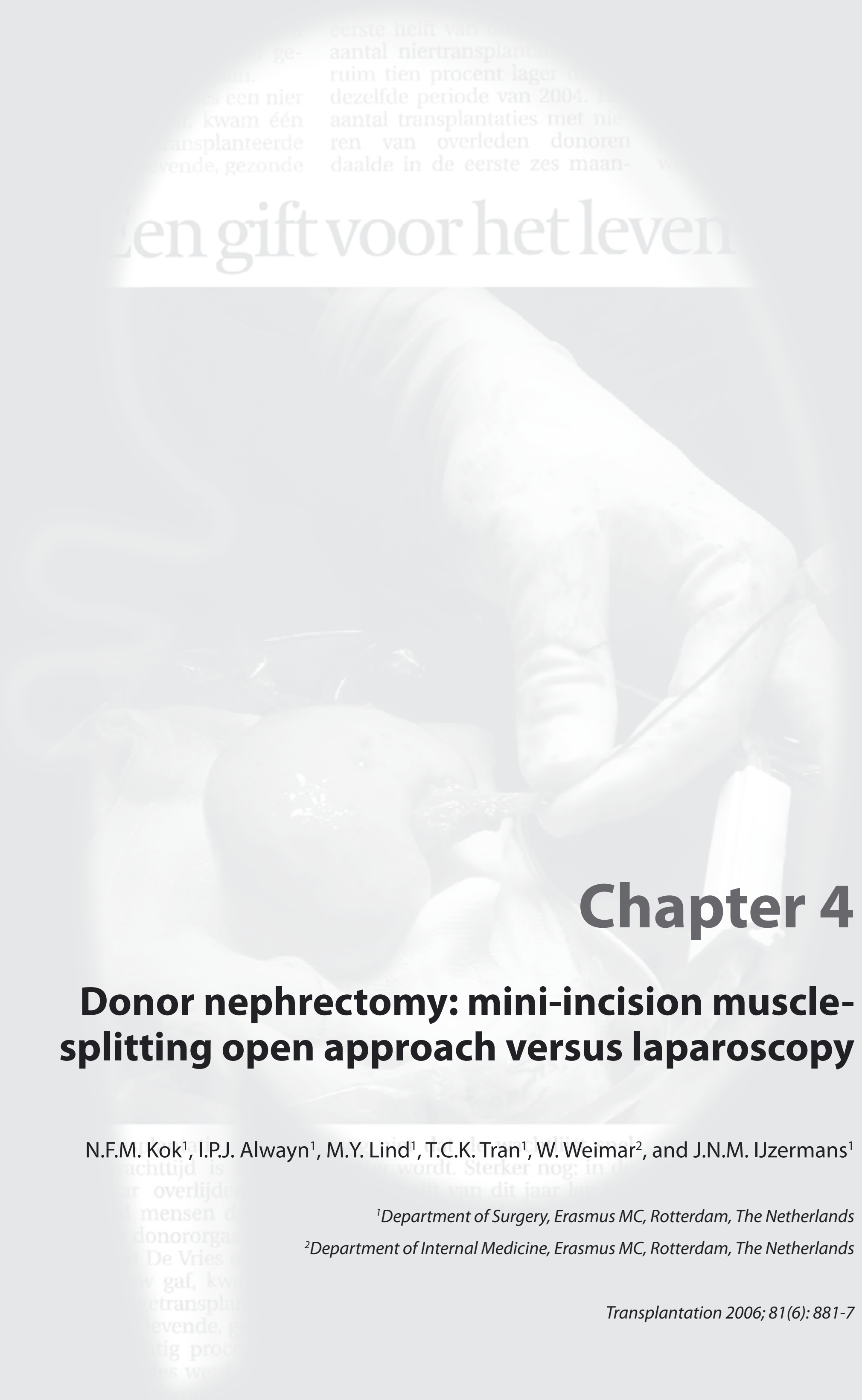
Niels F.M. Kok is partly funded by the Dutch Kidney Foundation. The authors would like to thank the following persons for their contributions to this study: K. Rigg, Nottingham, N.R. Brook, Leicester, L.J. Buist, Glasgow, J.L. Forsythe, Edinburgh, D. Hickey, Dublin, P.A. Rowe, Plymouth, N. Mamode, London, N. West, Coventry, A.T. Raftery, Sheffield, R.W. Chang, London, A. Asderakis, Cardiff, P.A. Lear, Bristol, R. Praseedom, Cambridge, N. Ahmad, Leeds, A. Obed, Regensburg, C.E. Broelsch, Essen, M. Karaorman, Mannheim, J. Schmidt, Heidelberg,

M. Neipp, Hannover, T. Kälbe, Fulda, G. Offermann, Berlin, A. Homburg, Aachen, M. Giessing, Berlin, D. Abendroth, Ulm, H. Riedmiller, Würzburg, E. Domínguez, Marburg, M. Stöckle, W. Steurer, Tübingen, K.M. Schrott, Erlangen, B. Grabensee, Düsseldorf, N. Senninger, Münster, H. Seiter, Rostock, M. Stangl, München, J.W. Thüroff, Mainz, L. Mirow, Lübeck, F. Fändrich, Kiel, P. Fornara, Halle, P. Pisarski, Freiburg, S. Leike, Dresden, K. Dreikorn, Bremen, Th. Steiner, Jena, Ph.E. Nagel, Augsburg, H.U. Klehr, Bonn, R. Viehbahn, Bochum, P. Merkle, Stuttgart, R. Függer, Linz, C. Groß, Linz, R. Margreiter, Innsbruck, F. Mühlbacher, Vienna, H. Müller, Graz, C.C. Abbou, Creteil, J. Hubert, Nancy, M. Devonec, Lyon, B. Hurault de Ligny, Caen, F. Iborra, Montpellier, Y. Lebranchu, Tours, B. Bourbigot, Brest, F. Berthoux, Saint Etienne, F. Kleinclauss, Besançon, Y. Chretien, Paris, B. Dore, Poitiers, G. Karam, Nantes, J.F. Subra, Angers, B. Bourgeon, St Denis, P. Wolf, Strasbourg, J. Chanard, Reims, P. Grise, Rouen, B. Barrou, Paris, G. Benoît, Le Kremlin Bicêtre, M. Mouzin, Toulouse, E. Lechevallier, Marseille, Ø. Øyen, Oslo, J.M. Hansen, Herlev, Ø. Østraat, Århus, N. Rohr, Odense, S.S. Sørensen, Copenhagen, K. Salmela, Helsinki, M. Idu, Amsterdam, R.J. Ploeg, Groningen, J. Ringers, Leiden, L.W.E. van Heurn, Maastricht, J.A. van der Vliet, Nijmegen, R.W.H. van Reedt Dortland, Utrecht, M. Matter, Lausanne, M. Weber, Zürich, D. Candinas, Bern, P. Morel, Geneva, L. Gürke, Basel, G. Tufveson, Uppsala, L. Mjörnstedt, Göteborg, N.H. Persson, Malmö, D. Ysebaert, Antwerpen.

REFERENCES

1. Ratner LE, Ciseck LJ, Moore RG, Cigarroa FG, Kaufman HS, Kavoussi LR. Laparoscopic live donor nephrectomy. Transplantation 1995; 60 (9): 1047-9.
2. Wolf JS, Jr., Merion RM, Leichtman AB, et al. Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation 2001; 72 (2): 284-90.
3. Bachmann A, Wolff T, Ruszat R, et al. Retroperitoneoscopic donor nephrectomy: a retrospective, non-randomized comparison of early complications, donor and recipient outcome with the standard open approach. Eur Urol 2005; 48 (1): 90-6.
4. Wadstrom J. Hand-assisted retroperitoneoscopic live donor nephrectomy: experience from the first 75 consecutive cases. Transplantation 2005; 80 (8): 1060-6.
5. Redman JF. An anterior extraperitoneal incision for donor nephrectomy that spares the rectus abdominis muscle and anterior abdominal wall nerves. J Urol 2000; 164 (6): 1898-1900.
6. Greenstein MA, Harkaway R, Badosa F, Ginsberg P, Yang SL. Minimal incision living donor nephrectomy compared to the hand-assisted laparoscopic living donor nephrectomy. World J Urol 2003; 20 (6): 356-9.
7. Yang SL, Harkaway R, Badosa F, Ginsberg P, Greenstein MA. Minimal incision living donor nephrectomy: improvement in patient outcome. Urology 2002; 59 (5): 673-7.
8. Neipp M, Jackobs S, Becker T, et al. Living donor nephrectomy: flank incision versus anterior vertical mini-incision. Transplantation 2004; 78 (9): 1356-61.
9. Lewis GR, Brook NR, Waller JR, Bains JC, Veitch PS, Nicholson ML. A comparison of traditional open, minimal-incision donor nephrectomy and laparoscopic donor nephrectomy. Transpl Int 2004; 17 (10): 589-95.
10. Brook NR, Nicholson ML. An audit over 2 years' practice of open and laparoscopic live-donor nephrectomy at renal transplant centers in the UK and Ireland. BJU Int 2004; 93 (7): 1027-31.
11. Pietrabissa A, Boggi U, Vistoli F, Moretto C, Ghilli M, Mosca F. Laparoscopic living donor nephrectomy in Italy: a national profile. Transplant Proc 2004; 36 (3): 460-3.
12. http://www.eurotransplant.nl.
13. http://www.uktransplant.org.
14. http://www.efg.sante.fr.
15. http://www.etco.org.
16. http://www.scandiatransplant.org.
17. http://www.swisstransplant.org.
18. Friedman AL, Peters TG, Jones KW, Boulware LE, Ratner LE. Fatal and Nonfatal Hemorrhagic Complications of Living Kidney Donation. Ann Surg 2006; 243 (1): 126-30.
19. Matas AJ, Bartlett ST, Leichtman AB, Delmonico FL. Morbidity and mortality after living kidney donation, 1999-2001: survey of United States transplant centers. Am J Transplant 2003; 3 (7): 830-34.
20. Tooher R, Boult M, Maddern GJ, Rao MM. Final report from the ASERNIP-S audit of laparoscopic live-donor nephrectomy. ANZ J Surg 2004; 74 (11): 961-3.
21. Perry KT, Freedland SJ, Hu JC, et al. Quality of life, pain and return to normal activities following laparoscopic donor nephrectomy versus open mini-incision donor nephrectomy. J Urol 2003; 169 (6): 2018-21.
22. Flowers JL, Jacobs S, Cho E, et al. Comparison of open and laparoscopic live donor nephrectomy. Ann Surg 1997; 226 (4): 483-9.
23. Ratner LE, Kavoussi LR, Sroka M, et al. Laparoscopic assisted live donor nephrectomy--a comparison with the open approach. Transplantation 1997; 63 (2): 229-33.
24. Oyen O, Andersen M, Mathisen L, et al. Laparoscopic versus open living-donor nephrectomy: experiences from a prospective, randomized, single-center study focusing on donor safety. Transplantation 2005; 79 (9): 1236-40.
25. Tooher RL, Rao MM, Scott DF, et al. A systematic review of laparoscopic live-donor nephrectomy. Transplantation 2004; 78 (3): 404-14.
26. Simforoosh N, Basiri A, Tabibi A, Shakhssalim N, Hosseini Moghaddam SM. Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial. BJU Int 2005; 95 (6): 851-55.

27. Ruiz-Deya G, Cheng S, Palmer E, Thomas R, Slakey D. Open donor, laparoscopic donor and hand assisted laparoscopic donor nephrectomy: a comparison of outcomes. J Urol 2001; 166 (4): 1270-3.
28. Lind MY, Hazebroek EJ, Hop WC, Weimar W, Bonjer HJ, IJzermans JN. Right-sided laparoscopic live-donor nephrectomy: is reluctance still justified? Transplantation 2002; 74 (7): 1045-8.
29. Posselt AM, Mahanty H, Kang SM, et al. Laparoscopic right donor nephrectomy: a large single-center experience. Transplantation 2004; 78 (11): 1665-9.
30. Srivastava A, Tripathi DM, Zaman W, Kumar A. Subcostal versus transcostal mini donor nephrectomy: is rib resection responsible for pain related donor morbidity. J Urol 2003; 170 (3): 738-40.
31. Jones KW, Peters TG, Walker GW. Anterior-retroperitoneal living donor nephrectomy: technique and outcomes. Am Surg 1999; 65 (3): 197-204.



Chapter 4

Donor nephrectomy: mini-incision muscle-splitting open approach versus laparoscopy

N.F.M. Kok[1], I.P.J. Alwayn[1], M.Y. Lind[1], T.C.K. Tran[1], W. Weimar[2], and J.N.M. IJzermans[1]

[1]Department of Surgery, Erasmus MC, Rotterdam, The Netherlands

[2]Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

Transplantation 2006; 81(6): 881-7

ABSTRACT

The introduction of laparoscopic donor nephrectomy (LDN) has encouraged the development of less invasive open techniques. Aim of the present study was to compare short-term outcomes between contemporary cohorts of donors who underwent either mini-incision open or laparoscopic kidney donation. From May 2001 to September 2004 data of all living kidney donations and transplantations were prospectively collected. Fifty-one donors underwent mini-incision, muscle-splitting open donor nephrectomy (MIDN) and 49 donors underwent LDN. Baseline characteristics of donors and recipients in the study groups were comparable except for donors' gender. Median incision length in MIDN was 10.5 cm. In two patients LDN was converted to open. MIDN resulted in significantly shorter warm ischemia and operation time (2.5 vs. 6.5 minutes and 157 vs. 240 minutes respectively). During MIDN, donors had more blood loss (200 vs. 120 ml, P=0.02). Disposables used for MIDN were cheaper (328 vs. 1784 Euros). In the LDN group 4 (8%) major intra-operative and 2 (4%) major postoperative complications occurred versus no major complications in the MIDN group. Morphine requirement, pain and nausea perception, and time to dietary intake did not significantly differ between the groups. Following MIDN, donors were discharged later (4 vs. 3 days, P=0.02). Transplantation of kidneys procured by either approach led to a similar decline in serum creatinine throughout the first year. One-year graft survival was 100% following MIDN and 86% following LDN (P=0.005). In conclusion, MIDN and LDN both lead to satisfactory results. Both techniques can be used to expand living donor programs.

INTRODUCTION

Living kidney donation has become an established alternative to organ transplantation from a deceased donor. Minimally invasive techniques are being developed to cause minimal harm to the living donor. Laparoscopic donor nephrectomy (LDN) revolutionary changed short-term results of the donor and gained wide acceptance among surgeons and donors. Early comparative reports (1, 2) between LDN and classic techniques for open donor nephrectomy described less blood loss, less pain and faster recovery after LDN. By now, evidence has mounted that short term results in donors following LDN are superior to results of classic open donor nephrectomy (3).
The introduction of LDN has also encouraged the development of less invasive techniques in open donor nephrectomy. Classic incisions that often included rib resections have been replaced by smaller incisions, thereby fuelling further comparisons between LDN and less invasive open techniques (4, 5). In this article we describe a prospective comparison between LDN and a mini-incision incision, muscle-splitting open approach (MIDN).

PATIENTS AND METHODS

Patients

Between May 2001 and September 2004 51 donors underwent MIDN and 49 LDN at the Erasmus MC Rotterdam. All donors were preoperatively screened by nephrologists and cardiologists. Donors were admitted to the surgical ward one day before operation. The surgeon presented MIDN and LDN as operations with comparable outcome with regard to in-hospital stay and cosmetic outcome. Unless contra-indicated, the patient was able to decide which type of nephrectomy was performed. If the patient did not prefer a technique, MIDN was performed. If the donor had a previous history of renal or adrenal surgery or if the recipient had a condition that required maximum vessel length, an open approach was often used. Selection of the right or left kidney was based on renovascular anatomy and size. If no differences in anatomy were present, the right kidney was removed (6). Obese donors, donors with complicated renovascular anatomy or older donors were not restricted from either technique. The evening before the operation infusion of crystalloids was started in every donor to prehydrate the kidneys (7). Intra-operatively, data were prospectively recorded by an independent researcher in the operation room. The same researcher prospectively collected all postoperative data. Postoperative pain was managed by a patient controlled analgesia device, which administrated morphine intravenously after pressing a button. Visual analogue scales of pain and nausea (0 to 10 scale) were filled out by 82 donors who could read Dutch at 1, 3, 7 and 14 days. Donors were discharged only if they had resumed their normal diet and were able to walk a flight of stairs. Postoperative hospital stay was calculated with and without correction for time spent in the hospital because of social aspects (i.e. donors, who desired to stay another day to be close to the recipient or donors who could not be discharged because of lack of care at home). Follow-up at the nephrology and surgery outpatient clinics were at three weeks, three months and one year postoperatively.

Surgical Procedures

LDN has been performed in our institution since 1997. MIDN has been performed since 2000. Both techniques (LDN and MIDN) were carried out by a team of either two general surgeons or a surgeon and a surgical resident ranging from first to sixth year of training. Prophylactic antibiotics were not administrated during either procedure.

Laparoscopic donor nephrectomy (LDN)

With the patient placed in a lateral decubitus position and the operation table maximally flexed, a 10-mm trocar was introduced subumbillically under direct vision. The abdomen was insufflated to 12-cm H_2O carbon dioxide pressure. A 30º video endoscope and 3 to 4 additional trocars were introduced. The colon was mobilized and displaced medially. Opening of the renal capsule and division of the perirenal fat was facilitated using an ultrasonic device (Ultracision, Ethicon, Cincinnati, USA). The ureter was identified and dissected ensuring sufficient periureteral tissue. The renal vessels were identified, encircled with vessel loops. Branches of the adrenal, gonadal and lumbar veins were clipped with titanium clips (Ligaclip, Ethicon, Cincinnati, USA) and divided. Then, a Pfannenstiel incision was made. An endobag (Endocatch, US surgical, Norwalk, USA) was introduced into the abdomen. The ureter was clipped distally and divided. After the administration of 5,000 units of heparin, the renal artery and vein were divided using an endoscopic stapler (EndoGia, US Surgical, Norwalk, USA). The kidney was extracted through the suprapubic incision, flushed with 4º-Celsius Eurocollins (Fresenius, Bad Homburg, Germany) and stored on ice. Meanwhile, 5,000 units of protamine were administered and the Pfannenstiel incision was closed in two layers. Again, the abdomen was insufflated. Hemostasis was ensured and the trocars were removed. The fascia of keyholes measuring 10 mm was closed. Skin incisions were sutured intracutaneously.

Mini-incision, muscle-splitting open donor nehrectomy (MIDN)

With the patient placed in a lateral decubitus position and the operation table maximally flexed a horizontal 10-12 cm skin incision was made anterior to the 11^{th} rib towards the umbilicus. Subsequently, the fascia of the external abdominal oblique muscle was divided with scissors and prepared from the underlying muscle. The fibers of the muscle were split in the longitudinal direction of the muscle using spreading movements of the scissors. Likewise, the fascias of the internal oblique abdominal muscle and the transverse abdominal muscle were prepared from the underlying muscles, allowing easy approximation at the end of the operation. These muscles were longitudinally split as well. A mechanical retractor (Omnitract surgical, St. Paul, USA) was installed. The peritoneum was displaced medially and the perinephric fascia (Gerota's fascia) was opened on the lateral side of the kidney. After meticulous dissection of the kidney, ureter, renal vein and artery were identified and encircled with vessel loops. Gonadal, lumbar and adrenal vascular branches were divided if necessary. Thereafter, the ureter was clipped and divided. Five thousand units of heparin (Leopharma, Breda, The Netherlands) were administered intravenously. The renal artery and vein were successively clamped and ligated. The kidney was extracted. Perfusion and storage were as aforementioned for laparoscopy. Five thousand units of protamine (ICN Pharmaceuticals, Zoetermeer, The Netherlands) were administered. Haemostasis was applied. The fascias of the three abdominal muscles were closed using 1/0 vicryl (Ethicon, Hamburg, Germany) sutures. The subcutaneous fascia was approximated and the skin was sutured intracutaneously.

Recipients

All recipients underwent renal transplantation using the standard technique of preperitoneal placement in the iliac fossa. The presence or absence of urine production following kidney reperfusion was recorded in the operation room. A calcineurin inhibitor based immunosuppressive regimen was given to all recipients. The nephrologist prospectively collected data of the recipients. Data included ureteral complications as defined as the need for a percutaneous nephrostomy, ureter reconstructions, acute rejection rates (histologically proven), one-year patient- and graft suvival rates, and serum creatinine values during the first year postoperatively.

Definitions and Statistical analysis

Warm ischemia time was defined as time elapsing between occlusion of the first renal artery and flushing of the artery. Time until kidney removal was defined as the time elapsing between incision of the skin and extraction of the kidney. Operation time was defined as time elapsing between incision of the abdomen and tying the last suture at closure of the abdominal wall. Intra-operative complications were defined as events unintentionally lengthening the operation or causing potential harm to donor or graft. These complications were further characterized as 'minor' complications i.e. requiring no repair or conversion and 'major' complications i.e. damage to adjacent organs or conversion prompted by bleeds. Postoperative complications were defined as events requiring an intervention or causing unintentionally prolonged hospital stay of the donor. These complications were further characterized as 'minor' complications i.e. requiring no re-intervention and 'major' complications i.e. re-intervention or lasting complications. Data were analyzed according to the intention to treat principle. Categorical data were displayed as number (percentage). Continuous data were displayed as median (minimum-maximum) unless specified otherwise. Categorical variables were compared with the Chi square test, continuous variables were compared with the Mann Whitney U test and repetitive variables were compared with repeated measurement ANOVA using correction for baseline values, donors' gender and age. Analyses were conducted using SPSS (version 12.0, SPSS Inc., Chicago, USA). A P-value < 0.05 (two-sided) was considered statistically significant.

RESULTS

In Table 1 baseline characteristics of donors and recipients are displayed. The MIDN group consisted of more female donors. Other characteristics did not differ between MIDN and LDN.

In Table 2 intra-operative outcomes of MIDN and LDN are demonstrated. Median incision length in the MIDN group was 10.5 cm. None of the incisions was enlarged. Two laparoscopies were converted to open of which one was converted to a muscle-splitting open approach immediately after introduction of the camera due to the presence of massive intra-abdominal adhesions. The other conversion was necessitated by bleeding from the renal vein after clipping and dividing a lumbar branch. Due to significant and rapid blood loss a lumbotomy with dissection of the abdominal muscles was performed. Median time until kidney removal and operation

Table 1. Baseline characteristics of donors and recipients

	MIDN (N=51)	LDN (N=49)	P-value
Donor			
Gender – No. (%)			0.004
Male	12 (24%)	26 (53%)	
Female	39 (76%)	23 (47%)	
Age – years	48 (22-72)	50 (20-74)	0.72
Kidney – No. (%)			0.84
Left	24 (47%)	25 (51%)	
Right	27 (53%)	24 (49%)	
ASA Classification – No. (%)			0.82
I	38 (75%)	38 (78%)	
II	13 (25%)	11 (22%)	
Body mass index – kg/m^2	26.8 (19.9-41.0)	26.0 (17.7-32.4)	0.44
Renal Arteries – No. (%)			0.59
1	44 (86%)	40 (82%)	
≥ 2	7 (14%)	9 (18%)	
Renal veins – No. (%)			1.0
1	48 (94%)	47 (96%)	
≥ 2	3 (6%)	2 (4%)	
Preoperative Serum Creatinine – µmol/l	71 (43-105)	72 (55-110)	0.22
Recipient			
Sex – No. (%)			0.69
Male	27 (53%)	28 (57%)	
Female	24 (47%)	21 (43%)	
Age – years	44 (8-77)	47 (16-73)	0.22
Relation between donor and recipient – No. (%)			1.0
Living related	33(65%)	32 (65%)	
Living unrelated	18 (35%)	17 (35%)	
Pre-emptive transplantation	9 (18%)	11 (22%)	0.62

Table 2. Intra-operative outcomes of MIDN versus LDN

	MIDN (N=51)	LDN (N=49)	P-value
Incision length – cm	10.5 (8-15)	–	
Conversion to open – No. (%)	–	2 (4%)	
Warm ischemia time – minutes	2.5 (1-8.5)	6.5 (2-16.5)	<0.001
Time until kidney removal – minutes	111 (60-196)	191 (104-339)	<0.001
Operation time – minutes	157 (84-251)	240 (136-390)	<0.001
Blood loss – ml	200 (30-1400)	120 (30-1400)	0.03
Costs of disposable instruments – Euros	328 (236-1245)	1784 (1077-2454)	<0.001
Complications – No. (%)	2 (4%)	6 (12%)	0.15
Minor complications – No. (%)	2 (4%)	2 (4%)	
Major complications – No. (%)	0	4 (8%)	

Table 3. Postoperative outcomes of MIDN versus LDN

	MIDN (N=51)	LDN (N=49)	P-value
Donor			
Return to regular diet – hours	21 (3-99)	19 (3-63)	0.16
Morphine requirement – mg			
First 24 hours	15 (0-145)	13 (0-82)	0.90
In total	18 (0-145)	14 (0-98)	0.69
Complications – No. (%)	7 (14%)	5 (10%)	0.76
Minor complications – No. (%)	7 (14%)	3 (6%)	
Major complications – No. (%)	0	2 (4%)	
Postoperative hospital stay – days			
Uncorrected	4 (2-9)	3 (1-10)	0.02
Corrected	3 (1-9)	3 (1-10)	0.07
Incisional hernia – No. (%)	1 (2%)	2 (4%)	
Recipient			
Immediate urine production – No. (%)	44 (86%)	48 (98%)	0.06
Dialysis in the first week – No. (%)	-	-	
Percutaneous nephrostomy – No. (%)	13 (26%)	10 (20%)	0.64
Re-operation due to ureteral stenosis – No. (%)	3 (6%)	4 (8%)	0.71
Thrombosis – No. (%)	-	-	
Acute Rejection – No. (%)	17 (33%)	11 (22%)	0.27
One-year graft survival – No. (%)	51 (100%)	42 (86%)	0.005*
One-year patient survival – No. (%)	51 (100%)	43 (88%)	0.01*

* Early graft function in all patients was satisfactory. Six recipients of a laparoscopically procured kidney died of causes not related to the operation of the donor.

time were approximately 80 minutes shorter for MIDN. Blood loss was significantly more after MIDN (200 vs. 180 ml). The costs of disposable instruments were considerably lower in MIDN. The median difference of 1460 Euros was mainly caused by the use of the ultrasonic device and the endostapler. However, sometimes an endostapler was also used in MIDN because of the relatively small working space. Therefore, costs in MIDN range from 236 Euros to 1245 Euros.

Minor complications involved bleeding and occurred in two open procedures (total blood loss 800 and 1250 ml) and two laparoscopic procedures (total blood loss 200 and 600 ml.) Major complications occurred in 4 laparoscopies including a small bowel lesion which was sutured laparoscopically, a bladder lesion during the introduction of the endobag, which could be sutured without enlarging the pfannenstiel incision, a tear of splenic capsule, which could be managed conservatively by direct pressure with a gauze and the aforementioned conversion due to bleeding (total blood loss 2700 ml).

Postoperative data are summarized in Table 3. Donors generally resumed their regular diet on the first postoperative day regardless of surgical technique. Morphine requirement on the first day and for the total hospital stay did not differ between MIDN and LDN. Perception of nausea and pain in 82 Dutch-speaking patients did not differ (Figure 1).

Minor complications occurred in 7 patients following MIDN. These included retroperitoneal bleeding which required a single blood transfusion in one patient, a patient who presented with an urinary tract infection shortly after discharge, a patient with a haematoma delaying discharge for three days, a patient who had so much pain on the first postoperative day that she required an additional locoregional nerve block applied by the anesthesiologist, a patient with an infected left eye, possibly related to the tape applied during anesthesia in order to keep the eyes shut, a patient with prolonged nausea, but with present bowel sounds. She resumed her regular diet after four days. Finally, one patient had a slow decline in serum creatinine values to 150 µmol/l, which led to prolonged hospital stay. Three minor complications occurred following LDN including two wound infections, which were treated with oral antibiotics and temporarily sensibility loss in the area supplied by the cutaneous lateral

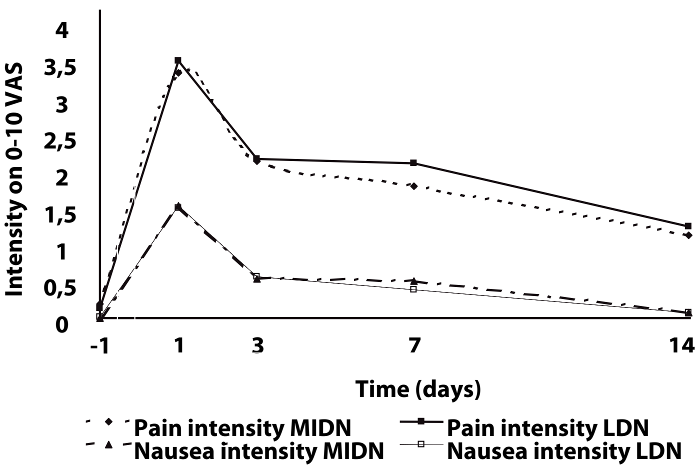


Figure 1. Pain and nausea intensity of donors following Mini-incision donor nephrectomy (MIDN, pain, interrupted line, diamond, nausea continuous line, triangle) and Laparoscopic donor nephrectomy (LDN, pain, continuous line, open square, nausea, interrupted line, filled square) measured on a Visual Analogue Scale (VAS).

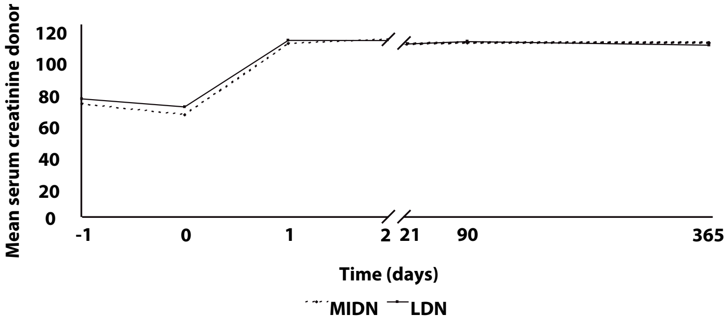


Figure 2. Donor serum creatinine values (μmol/l) following Mini-incision donor nephrectomy (MIDN, diamond, interrupted line) and Laparoscopic donor nephrectomy (LDN, filled square, continuous line).

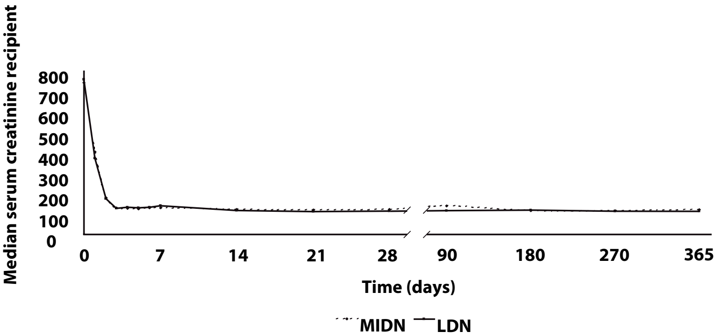


Figure 3. Recipient serum creatinine values (μmol/l) following Mini-incision donor nephrectomy (MIDN, diamond, interrupted line) and Laparoscopic donor nephrectomy (LDN, filled square, continuous line).

femoral nerve. Major complications occurred in two patients following LDN. One patient was suspected of bleeding and underwent a laparoscopy. No bleeding was found and postoperative course was uneventful. Another patient was readmitted because of a subcapsular splenic haematoma one week after kidney donation. This complication was treated by open splenectomy. Donor serum creatinine values did not differ during one-year follow-up (Figure 2).
In the majority of recipients (Table 3) the transplant produced urine while the recipient was still in the operation room. None of the recipients required dialysis in the first week following transplantation. After MIDN and LDN a comparable number of recipients required placement of a percutaneous nephrostomy because of obstruction of the urinary outflow. Three (6%) and four (8%) recipients respectively required additional surgery due to stenosis of the ureter. Thrombosis of the renal vein did not occur. The number of recipients with one or more episodes of acute rejection did not differ. One patient in the LDN group lost her graft 10 months after transplantation because of a gynaecologic infection, which had spread to the transplant. Six other recipients in the LDN died in the first year due to causes not related to the operation in the donor. Two recipients died due to myocardial infarction respectively

10 days and 6 months after transplantation. Two recipients died due to therapy resistant infections at 3 weeks and 11 months postoperatively. One patient died due to a cerebral lymphoma at 5 months and one patient died because of a sclerosing peritonitis complicated by therapy resistant sepsis 10 weeks postoperatively. Graft loss was not observed following MIDN. During one-year follow-up serum creatinine values did not significantly differ between recipients of transplants procured by MIDN and LDN (Figure 3).

DISCUSSION

Various techniques have been proposed which are less invasive than classic lumbotomy. We compared mini-incision muscle-splitting open donor nephrectomy and complete laparoscopic donor nephrectomy, which we believe are respectively the least invasive open and laparoscopic technique for living kidney donation. MIDN can compete with LDN as demonstrated by minimal pain and fast recovery of donors following MIDN. More strongly, the absence of major surgical complications favors MIDN as safety of the donor is of paramount importance in live kidney donation. Hospital stay was shorter after LDN. However, this significant difference diminished after correction for social stay.

On the other hand increased experience with LDN has removed some of the outstanding issues attributed to this technique. Prompt conversion using a muscle intersecting lumbotomy was necessary in one patient only. Although three other major intra-operative complications occurred in the LDN group, these complications could be managed without causing significant postoperative morbidity.

The effect of laparoscopic procurement on the graft has been subject of discussion for a decade. An increased incidence of urological complications (8, 9), thrombosis of the renal vein (10) and delayed graft function (9) as measured by initial higher values of serum creatinine (9) have been reported in the literature. However, in the present study, complications in the recipient were comparable. This is in conjunction with recent reports. A large case summary (11) showed decreasing numbers of urological complications as experience increased. A randomized study of hand-assisted LDN and classic open donor nephrectomy (12) revealed no significant differences in graft function. The six recipients who died in our series are worrisome and demand an alert attitude towards long-term results of recipients of laparoscopically procured kidneys. However, the good early function of all these grafts and the causes of death do not support a direct relation to LDN.

Three randomized trials (12-14) comparing hand-assisted LDN and classic open donor nephrectomy have investigated peri-operative complications and short term recovery of the donor. Wolf et al. (13) compared hand-assisted and conventional open donor nephrectomy. After strict selection of donors the main conclusion of the authors was the association of LDN with a briefer, less intense, and more complete convalescence. Simforoosh et al. (12) also applied strict exclusion criteria. They concluded that hand-assisted LDN resulted in similar hospital stay, but greater satisfaction, less pain and faster recovery than classic MIDN. Øyen et al. (14) determined that donors following hand-assisted LDN perceived less pain than those following classic open donor nephrectomy. However, major complications occurred in 8% of the patients in the LDN group versus no major complications in the open surgery group. They emphasized the superior safety of conventional open donor nephrectomy as compared to laparoscopy. As LDN is still evolving, uncomplicated LDN might appear to be superior in the future. Therefore, they suggested selecting donors according to body mass index.

As opposed to these studies, we did not compare laparoscopy and classic lumbotomy and we did not handle strict selection criteria. It has been shown previously that minimal incisions can improve short-term outcome (4, 5, 15). We added splitting of the muscles, which leads to even less surgical damage. With the placement of the incision used as extraction-site as major difference, outcome is likely to be similar to LDN. The attitude towards laparoscopic donor nephrectomy might well have attributed to these results. It is remarkable that so many donors either chose MIDN or did not mind which technique would be used. A study comparing laparoscopic and small incision cholecystectomy (16) which used blinding supports the idea that removal of prejudices towards an operation might influence outcome.

MIDN has major advantages. First, major complications associated with this technique did not occur in our institution, whereas one conversion and two re-operations were clearly associated with LDN. This is in line with the report of Øyen et al. (14). As a center gains experience in LDN, major complications will probably occur rarely, but even high-volume centers can not avoid complications (17). Our series illustrated that surgeons performing LDN should be vigilant to avoid and notice injuries to other abdominal organs.

Second, MIDN is easier learned as demonstrated by residents, who perform some of the MIDNs in our hospital. MIDN is applicable to all donors including obese donors, donors with more suitable right-sided kidneys or donors with complicated renovascular anatomy. Third, costs are significantly lower for this approach. If hospital stay is not significantly shorter as demonstrated in the most recent randomized trial (14) and suggested by our data on corrected hospital stay, health care related costs will always remain higher for LDN given costs related to imaging equipment and longer operation times. With diminishing advantages and disadvantages of LDN, further high quality studies, which assess cost-efficiency and long-term outcome, will determine the position of minimal invasive open techniques among LDN. It seems likely that transplant centers with only a few kidney donations annually, will stick to open approaches based on these data. Finally, the debate on graft function and graft survival still continues. Despite similar decline of creatinine values of recipients of transplants procured with either technique throughout the first year, the recipients in the LDN group not surviving one year might have biased these figures. Although these deaths were not directly related to surgical technique in the donor, the conclusion that LDN does not affect survival remains premature. Longer follow-up and a larger number of recipients should lead to definitive conclusions.

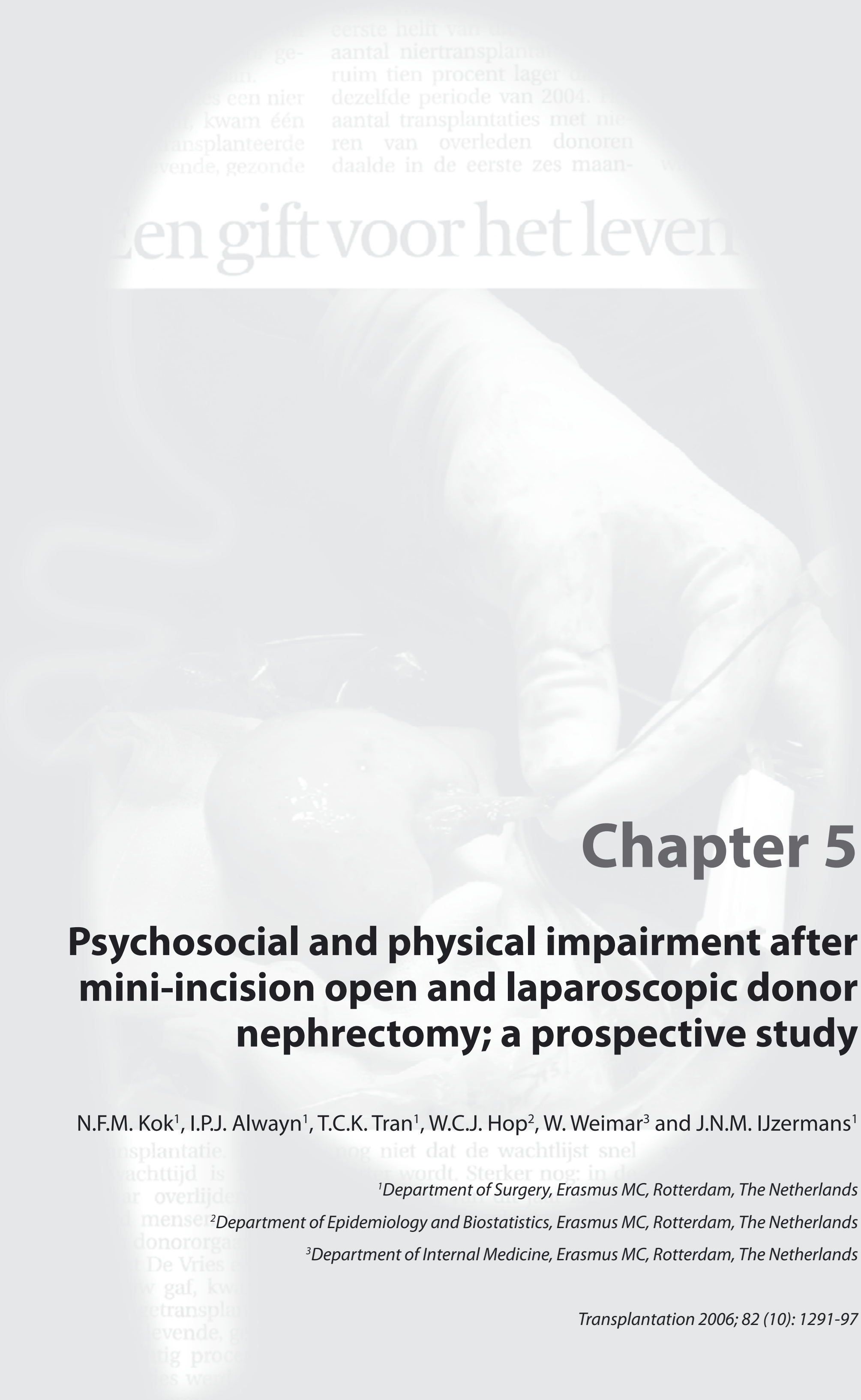
In conclusion, similar short-term results were found after MIDN and LDN, which makes both techniques attractive to expand living kidney transplantation programs. Which technique is applied will probably be determined by the experience of the surgeon, the frequency of living kidney donations in a center and the amount of money hospitals and insurance companies are willing to pay for living donor nephrectomy.

ACKNOWLEDGEMENTS

Niels F.M. Kok was financially supported by the Dutch Kidney Foundation. The authors thank Mrs. J. van Duuren, data manager, for her contributions to this study.

REFERENCES

1. Flowers JL, Jacobs S, Cho E, et al. Comparison of open and laparoscopic live donor nephrectomy. Ann Surg 1997; 226 (4): 483-89.
2. Ratner LE, Kavoussi LR, Sroka M, et al. Laparoscopic assisted live donor nephrectomy--a comparison with the open approach. Transplantation 1997; 63 (2): 229-33.
3. Tooher RL, Rao MM, Scott DF, et al. A systematic review of laparoscopic live-donor nephrectomy. Transplantation 2004; 78 (3): 404-14.
4. Neipp M, Jackobs S, Becker T, et al. Living donor nephrectomy: flank incision versus anterior vertical mini-incision. Transplantation 2004; 78 (9): 1356-61.
5. Lewis GR, Brook NR, Waller JR, Bains JC, Veitch PS, Nicholson ML. A comparison of traditional open, minimal-incision donor nephrectomy and laparoscopic donor nephrectomy. Transpl Int 2004; 17 (10): 589-95.
6. Lind MY, Hazebroek EJ, Hop WC, Weimar W, Bonjer HJ, IJzermans JN. Right-sided laparoscopic live-donor nephrectomy: is reluctance still justified? Transplantation 2002; 74 (7): 1045-8.
7. Hazebroek EJ, Gommers D, Schreve MA, et al. Impact of intraoperative donor management on short-term renal function after laparoscopic donor nephrectomy. Ann Surg 2002; 236 (1): 127-32.
8. Philosophe B, Kuo PC, Schweitzer EJ, et al. Laparoscopic versus open donor nephrectomy: comparing ureteral complications in the recipients and improving the laparoscopic technique. Transplantation 1999; 68 (4): 497-502.
9. Nogueira JM, Cangro CB, Fink JC, et al. A comparison of recipient renal outcomes with laparoscopic versus open live donor nephrectomy. Transplantation 1999; 67 (5): 722-8.
10. Mandal AK, Cohen C, Montgomery RA, Kavoussi LR, Ratner LE. Should the indications for laparascopic live donor nephrectomy of the right kidney be the same as for the open procedure? Anomalous left renal vasculature is not a contraindiction to laparoscopic left donor nephrectomy. Transplantation 2001; 71 (5): 660-4.
11. Su LM, Ratner LE, Montgomery RA, et al. Laparoscopic live donor nephrectomy: trends in donor and recipient morbidity following 381 consecutive cases. Ann Surg 2004; 240 (2): 358-63.
12. Simforoosh N, Basiri A, Tabibi A, Shakhssalim N, Hosseini Moghaddam SM. Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial. BJU Int 2005; 95 (6): 851-55.
13. Wolf JS, Jr., Merion RM, Leichtman AB, et al. Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation 2001; 72 (2): 284-90.
14. Oyen O, Andersen M, Mathisen L, et al. Laparoscopic versus open living-donor nephrectomy: experiences from a prospective, randomized, single-center study focusing on donor safety. Transplantation 2005; 79 (9): 1236-40.
15. Greenstein MA, Harkaway R, Badosa F, Ginsberg P, Yang SL. Minimal incision living donor nephrectomy compared to the hand-assisted laparoscopic living donor nephrectomy. World J Urol 2003; 20 (6): 356-9.
16. Majeed AW, Troy G, Nicholl JP, et al. Randomised, prospective, single-blind comparison of laparoscopic versus small-incision cholecystectomy. Lancet 1996; 347 (9007): 989-94.
17. Melcher ML, Carter JT, Posselt A, et al. More than 500 consecutive laparoscopic donor nephrectomies without conversion or repeated surgery. Arch Surg 2005; 140 (9): 835-9.



Chapter 5

Psychosocial and physical impairment after mini-incision open and laparoscopic donor nephrectomy; a prospective study

N.F.M. Kok[1], I.P.J. Alwayn[1], T.C.K. Tran[1], W.C.J. Hop[2], W. Weimar[3] and J.N.M. IJzermans[1]

[1]*Department of Surgery, Erasmus MC, Rotterdam, The Netherlands*

[2]*Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, The Netherlands*

[3]*Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands*

Transplantation 2006; 82 (10): 1291-97

ABSTRACT

The aim of the present study was to prospectively investigate how mini-incision donor nephrectomy (MIDN) and laparoscopic donor nephrectomy (LDN) affected the donor's quality of life and fatigue. Forty-five donors underwent MIDN and 55 donors underwent LDN. Quality of life and fatigue were recorded preoperatively and four times during one year follow-up on the Short-form 36 (SF-36) and Multidimensional fatigue inventory-20 (MFI-20) respectively. One-year response rates were 89% and 95% following MIDN and LDN respectively. After MIDN all dimensions of the SF-36 significantly declined. Most dimensions returned to preoperative values at 3 months except for "vitality" (6 months) and "bodily pain" (12 months). After LDN the scores of the SF-36 dimensions returned to preoperative values at three months except for "vitality" and "role physical" (both six months). Between groups analysis revealed significantly better scores of the SF-36 dimensions "physical function" (P=0.03) and "bodily pain" (P=0.04) following LDN at one month postoperatively. Fatigue scores did not significantly differ between the groups at any point in time. General and physical fatigue (MFI-20) remained affected up to one year after either type of surgery. After MIDN 4% of the donors had returned to work at 4 weeks postoperatively versus 28% after LDN (P=0.04). Return to preoperative activity level was not significantly different between groups. In conclusion, both procedures clearly impact quality of life and fatigue. The beneficial effect on the quality of life and the earlier return to work encourage us to advocate LDN as the surgical approach to be preferred.

INTRODUCTION

In many countries live kidney donor transplantation has become a well-recognized alternative to transplantation from a deceased donor. It is of utmost importance that live donors return to the preoperative physical and mental level as soon as possible. However, long-term physical and psychosocial effects of donor nephrectomy have been reported (1, 2) and, during follow-up at our outpatient clinic, fatigue is a common complaint reported up to one year after live kidney donation. Validated instruments have been developed to allow patients to describe the changes in quality of life (QOL) and the fatigue experienced after an intervention (3,4).

The surgical procedure in live donor nephrectomy may affect the physical and psychosocial condition of the donor. When compared to classic open lumbotomy, mini-incision donor nephrectomy (MIDN) and laparoscopic donor nephrectomy (LDN) have both improved short-term surgical outcome, including shorter length of stay and earlier return to work, without detrimental effects on graft survival (5-10). To investigate the impact of each surgical technique on the short and long term postoperative course of donors we used the Short Form-36 (SF-36) and the Multidimensional Fatigue Inventory-20 (MFI-20) in a prospective controlled study.

PATIENTS AND METHODS

Patients

Eligible for participation in this study were 125 patients who were scheduled for donor nephrectomy between May 2001 and January 2005. All donors were preoperatively screened by a nephrologist and a medical psychologist. Radiological evaluation of their kidneys was performed by ultrasound and magnetic resonance imaging or subtraction angiography. Donors who underwent a classic lumbotomy, donors with insufficient knowledge of the Dutch language and donors living outside North-Western Europe were not approached to fill out the required forms. Donors who completed at least one-month follow-up were included in this analysis, as this was the first postoperative point in time at which QOL and fatigue were evaluated.

We previously reported the similarity in in-hospital stay and cosmetic outcome between MIDN and LDN (8, 11). Briefly, the donor could decide which technique would be performed as long as there were no complicating factors (i.e. previous adrenal surgery, or requirement of maximum vessel length in the recipients). Obese donors, donors with complicated renovascular anatomy or older donors were not restricted from either technique. In this study we focus on QOL fatigue, activity level and return to work. Previously we reported on the surgical outcome of both techniques (8).

Donors were admitted the day before transplantation and case record forms were completed. Postoperatively, follow-up visits were scheduled at three weeks, two and three months and one year at the outpatient clinic of the departments of surgery and nephrology. Case record forms were sent to the donors at 1,2,4 and 6 weeks to record the daily activity level (as compared to preoperative activity level) and whether the donors had returned to work or not. In a retrospective study conducted by our department donors reported to have resumed work at 6 weeks postoperatively (12). We assumed that donors who could perform 90% or more of their preoperative daily activities would also have been able to resume work, if applicable. The Medical Ethics Committee of the Erasmus MC approved the study protocol.

Surgical techniques

Five surgeons, who also performed the transplantation in the recipient, performed both techniques, which are described previously (10). Briefly, MIDN was performed using an 8 to 15 cm (depending on BMI) skin incision anterior to the eleventh intercostal space towards the umbilicus. The three muscle layers of the abdominal wall were subsequently split ensuring preservation of underlying branches of the thoracic nerves. Thereafter, the kidney was carefully dissected using long instruments. After division of the ureter and the vessels, the kidney was extracted.

During laparoscopic donor nephrectomy (LDN) a camera and 3 to 4 additional trocars were introduced into the abdomen. The colon was mobilized and displaced medially. An ultrasonic device (Ultracision, Ethicon, Cincinnati, USA) was used to dissect the kidney, the ureter and the renal artery and vein. A pfannenstiel incision was made. An endobag (Endocatch, US surgical, Norwalk, USA) was introduced into the abdomen. After division of the ureter, renal artery and vein the kidney was extracted through the pfannenstiel incision.

Instruments to measure quality of life (QOL) and fatigue

The Short Form-36 (SF-36) is a validated and commonly used multi-item scale measuring each of eight dimensions associated with health-related quality of life (3). These include physical functioning, role limitations due to physical health problems (“role physical”), bodily pain, general health, vitality, social functioning, role limitations due to emotional problems (“role emotional”), and mental health. The dimensions physical function, role physical, bodily pain and general health are most sensitive to differences in physical functioning and well being, whereas vitality, social function, role emotional and mental health mainly attribute to mental function and well-being.

The responses were scored in standardized fashion. This led to scores up to 100. Higher scores indicated a better quality of life. A 5 point difference between the two techniques on one of the subscales of the SF-36 is generally considered the minimal clinically relevant difference (1). A 10 point difference on one of the subscales can be considered moderate (1). The SF-36 was administered one day preoperatively and 1,3,6 and 12 months postoperatively.

The Multidimensional Fatigue Inventory-20 (MFI-20) is 20-item scale measuring fatigue in five dimensions validated in healthy subjects in the Dutch population (4). These dimensions include general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. Each dimension is represented by 4 statements. Scores per statement range from 1 to 5 (ranging from completely affirmative to completely incorrect). Accordingly, the total score per scale ranged from 4 (no fatigue) to 20 (exhausted). The MFI-20 was administered one day preoperatively and 1, 3, 6 and 12 months postoperatively.
The Euroqol-5 dimensional survey (EQ-5D) is a validated scale, which describes health according to five attributes: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D represents the easiest scale in our study. Each attribute had three levels, i.e. "no problems", "some problems" or "severe problems" (13). Standardized weighting of each attribute leads to EQ-5D utility scores that range from –0.5 ("health status worse than death") to 1.0 ("excellent health") (13). In addition, a 0 to 100 visual analogue score measures general health. On this scale, 0 represents the worst health status and 100 the best health status. The EQ-5D was administered one day preoperatively and 3, 7 and 14 days, and 1,3, 6 and 12 months postoperatively.

Statistical analysis

Donors whose laparoscopic procedure was converted to open were analyzed in the LDN group. Categorical variables were compared with the Chi square test, continuous variables were compared with the Mann Whitney U test, and repeated measurements were compared by repeated measurement ANOVA using SPSS mixed models, which allowed adjustment for baseline values, donor's gender and donor's age. Age and gender have been described to influence quality of life in the Dutch population (14). Differences between the groups on the dimensions of the SF-36, MFI-20 and EQ-5D were studied both per point in time and for the whole follow-up. Continuous data were displayed as median (minimum-maximum). Differences from the baseline per group were tested for statistical significance using Wilcoxon's signed rank sum test. All analyses were conducted using SPSS (version 11.5, SPSS Inc., Chicago, USA). A P-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Of the 125 donors eligible for inclusion 100 donors were included in this study. Among the 25 donors not participating in this study, 13 patients did not have adequate knowledge of the Dutch language, three lived abroad, four did not want to participate and two were operated using a classic lumbotomy because of lack of experience of the operating surgeon with MIDN. Finally, three donors who originally gave written permission to participate in this study withdrew from the study within two weeks. Therefore, this analysis is based on 100 donors.

Forty-five patients underwent MIDN and fifty-five underwent LDN. Baseline characteristics are shown in Table 1. The MIDN group consisted of significantly more female donors than the LDN group (76% vs. 49%, P=0.008). Other baseline characteristics did not differ.

Surgical Outcome

Table 2 demonstrates surgical outcome, complications, graft survival and patient survival. In the LDN group five procedures were converted to open approaches. These included four muscle-splitting incisions. One of these conversions was performed immediately after the introduction of the video-endoscope in the abdomen because of massive adhesions. In two obese donors abundant intra-abdominal fat hindered a laparoscopic approach and a MIDN was preferred. In two donors persistent bleeding was reason for conversion: in one donor continuous oozing from the peri-aortic tissue necessitated a small muscle splitting approach after extraction of the kidney (total blood loss 425 ml) and in a second donor bleeding from a lumbar branch necessitated a classic flank incision (total blood loss 2700 ml).

Skin-to-skin time was significantly shorter for MIDN (171 vs. 237 minutes, P<0.001) and blood loss significantly higher (230 vs. 120 ml, P=0.02). In the MIDN group intra-operative complications included bleeding in three patients (blood loss 900, 1250, and 1285 ml, no blood transfusions). Postoperative complications in this group did not include re-interventions or re-admissions and were considered minor. Except for two complications requiring conversion all complications in the LDN group were recognized immediately and treated accordingly without conversion. Postoperative complications included one re-operation because of bleeding. No bleeding was found. One patient was re-admitted because of a wound infection requiring intra-venous antibiotics. All other complications were minor and did not require intervention. Length of stay was longer after MIDN (4 vs. 3 days, P=0.01). Median donor serum creatinine values at 3 and 12 months were 113 and 107 µmol/l in the MIDN group and 111 and 107 µmol/l in the LDN group (P=0.84 and P=0.50 at 3 and 12 months respectively).

During follow-up, one recipient of the kidney of a donor in the MIDN group died of a myocardial infarction. Seven recipients died in the LDN group either because of myocardial in-

Table 1. Baseline characteristics of donors. MIDN versus LDN.

Donor	MIDN (n=45)	LDN (n=55)	P- Value
Male Gender – No. (%)	11 (24%)	28 (51%)	0.008
Age – years	51 (22-90)	53 (20-74)	0.76
ASA Classification >1 – No. (%)	13 (29%)	12 (22%)	0.49
Left Kidney – No. (%)	18 (40%)	28 (51%)	0.32
Body mass index – kg/m^2	26.2 (19.9-35.5)	26.0 (18.1-32.4)	0.57
Relation between donor and recipient – No. (%)			0.34
Living related	24 (53%)	28 (51%)	
Living unrelated	19 (42%)	20 (36%)	
Anonymous / Cross over	2 (4%)	7 (13%)	

farction (n=2), untreatable sepsis (n=4) and intracerebral lymphoma (n=1). In addition one graft was lost in either group. In the MIDN group one recipient developed sepsis and her immunosuppressive medication was stopped. In the LDN group one graft was lost because of venous thrombosis after left-sided LDN.

Return to Work and Activity Level

In Table 2 is shown that the number of LDN donors that returned to work was significantly higher at four weeks. At six weeks postoperatively only 29% and 42% of the donors who preoperatively performed labor returned to work in the MIDN and LDN group, respectively. The number of donors that resumed 90% of their daily activities did not differ between groups.

Quality of Life

During follow-up response rates ranged from 100% to 89% and from 100% to 95% in the MIDN group and LDN group, respectively. Within group analysis of the SF-36 showed that

Table 2. Surgical outcome, return to work and activity level following MIDN versus LDN.

	MIDN (n=45)	LDN (n=55)	P- Value
Incision length – cm	10 (8-15)	-	
Conversion to open – No. (%)	-	5 (9%)	
Skin-to-skin time – minutes	171 (100-251)	237 (136-395)	<0.001
Blood loss – ml	230 (30-1285)	120 (20-2700)	0.02
Complications – No. (%)			
Intra-operative	3 (7%)	9 (16%)	0.22
Postoperative	7 (16%)	7 (13%)	0.78
Late	1 (2%)	2 (4%)	n.a.[1]
Length of stay – days	4 (2-9)	3 (1-10)	0.01
One-year recipient survival– No. (%)[2]	44 (98%)	49 (89%)	0.13
One-year graft survival censored for death– No. (%)[2]	43 (98%)	48 (98%)	1.00
Number of donors returned to work– No. (%)[3]			
1 week postoperatively	-	-	
2 weeks postoperatively	-	2 (6%)	0.51
4 weeks postoperatively	1 (4%)	10 (28%)	0.04
6 weeks postoperatively	7 (29%)	15 (42%)	0.42
Activity level (as compared to preoperatively) – No. (%)			
1 week postoperatively ≥90%	2 (4%)	5 (9%)	0.44
≥100%	-	2(4%)	0.50
2 weeks postoperatively ≥90%	4 (9%)	7 (13%)	0.75
≥100%	-	2 (4%)	0.50
4 weeks postoperatively ≥90%	7 (16%)	15 (27%)	0.23
≥100%	3 (7%)	4 (7%)	1.0
6 weeks postoperatively ≥90%	20 (44%)	29 (53%)	0.41
≥100%	8 (18%)	13 (24%)	0.47

[1]Numbers too small to test

[2]One recipient in the MIDN group and 6 recipients in the LDN group died of non-graft related causes

[3]Preoperatively, 24 donors performed paid labour in the MIDN group and 36 in the LDN group

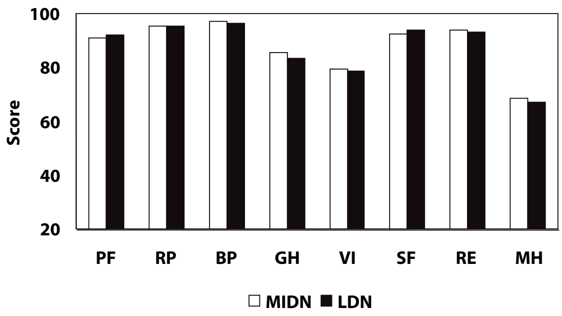


Figure 1A. SF-36 score per dimension preoperatively. White bars: Mini-incision Donor Nephrectomy (MIDN). Black bars: Laparoscopic Donor Nephrectomy (LDN). Abbreviations: PF physical functioning, RP role physical, BP bodily pain, GH general health, VI vitality, SF social functioning, RE role emotional, MH mental health.

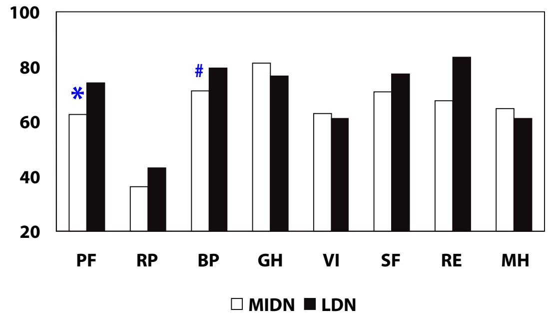


Figure 1B. SF-36 score per dimension one month postoperatively. White bars: Mini-incision Donor Nephrectomy (MIDN). Black bars: Laparoscopic Donor Nephrectomy (LDN). Abbreviations: PF physical functioning, RP role physical, BP bodily pain, GH general health, VI vitality, SF social functioning, RE role emotional, MH mental health. * significant higher score in LDN group (P=0.03). # significant higher score in LDN group (P=0.04).

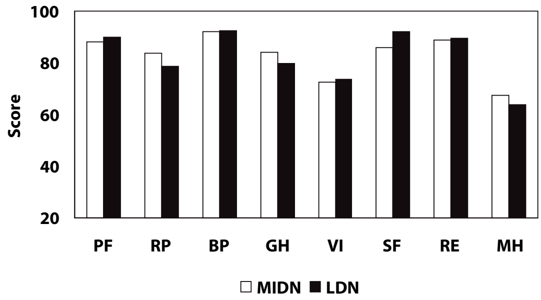


Figure 1C. SF-36 score per dimension three months postoperatively. White bars: Mini-incision Donor Nephrectomy (MIDN). Black bars: Laparoscopic Donor Nephrectomy (LDN). Abbreviations: PF physical functioning, RP role physical, BP bodily pain, GH general health, VI vitality, SF social functioning, RE role emotional, MH mental health.

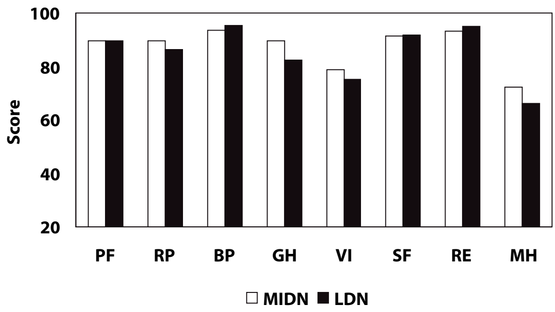


Figure 1D. SF-36 score per dimension six months postoperatively. White bars: Mini-incision Donor Nephrectomy (MIDN). Black bars: Laparoscopic Donor Nephrectomy (LDN). Abbreviations: PF physical functioning, RP role physical, BP bodily pain, GH general health, VI vitality, SF social functioning, RE role emotional, MH mental health.

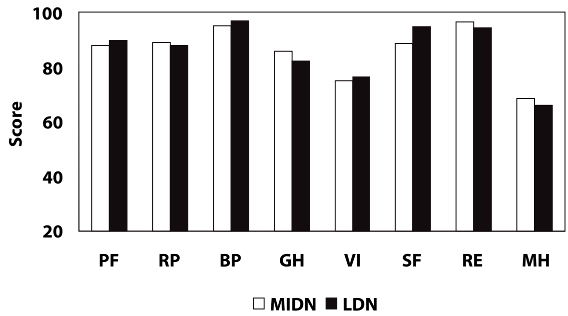


Figure 1E. SF-36 score per dimension twelve months postoperatively. White bars: Mini-incision Donor Nephrectomy (MIDN). Black bars: Laparoscopic Donor Nephrectomy (LDN). Abbreviations: PF physical functioning, RP role physical, BP bodily pain, GH general health, VI vitality, SF social functioning, RE role emotional, MH mental health.

MIDN donors scored significantly lower at one month as compared to baseline at all dimensions (P values ranged from < 0.001 to 0.03). At three months bodily pain and vitality (both P=0.02) were still significantly lower than baseline values. At 6 months vitality had returned to baseline values, whereas bodily pain had not (P=0.03). At twelve months bodily pain had returned to preoperative values. Following LDN, donors scored significantly lower as compared to baseline at one month at all dimensions (all significant differences had P values <0.002) except for role emotional, which did not significantly deviate from baseline. At three months, only role physical (P=0.005) and vitality (P=0.04) were significantly lower than baseline values. At 6 months, all dimensions had normalized to preoperative levels.

Between groups analysis of the SF-36 (Figure 1A to 1E) showed significant differences in the dimensions physical functioning (P=0.03, estimated difference -9.4, 95% confidence interval -18.0 to -0.9) and bodily pain (P=0.04, estimated difference -9.0, 95% confidence interval -17.8 to -0.1) at one month postoperatively in favor of LDN (i.e. nine points in both cases in favor of LDN). All other dimensions did not differ at any point in time. Between groups analysis comparing the SF-36 dimensions for the whole follow-up duration in total did not show any differences (data not shown).

At baseline, general fatigue scores were significantly lower in the MIDN group as compared to the LDN group, indicating less fatigue. Within group analysis showed that donors in the MIDN group scored significantly lower ($P < 0.001$) at one month at all dimensions except for mental fatigue as compared to baseline. Reduced motivation normalized in this group at three months, reduced activities normalized at six months whereas general fatigue and physical fatigue did not normalize at all throughout the first year (P-values 0.03 and 0.02 respectively at twelve months). One month after LDN donors scored significantly lower as compared to baseline at all dimensions (P-values ranging from <0.001 to 0.05). Mental fatigue, reduced activities and reduced motivation normalized at three months whereas general fatigue ($P=0.02$) and physical fatigue ($P=0.002$) still differed at twelve months postoperatively. Between groups analysis of the MFI-20 did not reveal any significant differences between open and laparoscopic surgery. Neither at the separate points in time (figure 2A to 2E) nor for the whole follow-up duration (data not shown) significant differences were found.

Within group analysis of the EQ-5D sum score and the score on the 0-100 VAS scale showed that both scores returned to preoperative levels at three months in both groups. Between groups analysis did not show any significant differences regarding sum score (Figure 3A) or score on the VAS (Figure 3B).

All analyses were repeated after exclusion of the donors whose kidney was lost during one-year follow up due to death of the recipient or graft loss due to other causes. No statistically significant differences other than outlined above were observed.

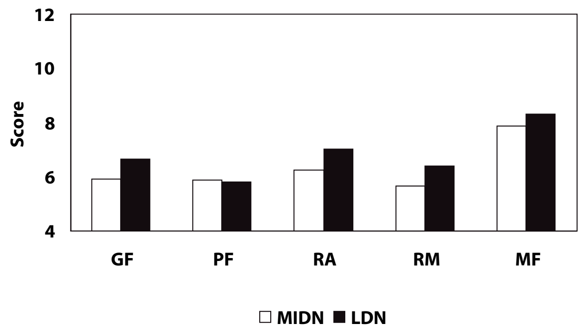


Figure 2A. MFI-20 score per dimension preoperatively. White bars: Mini-incision Donor Nephrectomy (MIDN). Black bars: Laparoscopic Donor Nephrectomy (LDN). Abbreviations: GF general fatigue, PF physical fatigue, RA reduced activities, RM reduced motivation, MF mental fatigue.

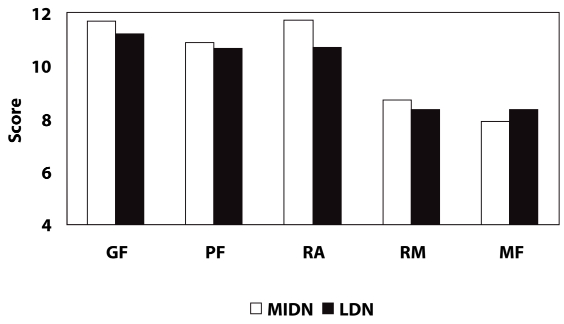


Figure 2B. MFI-20 score per dimension one month postoperatively. White bars: Mini-incision Donor Nephrectomy (MIDN). Black bars: Laparoscopic Donor Nephrectomy (LDN). Abbreviations: GF general fatigue, PF physical fatigue, RA reduced activities, RM reduced motivation, MF mental fatigue.

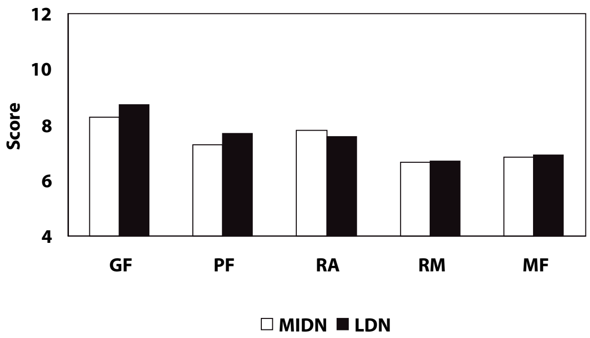


Figure 2C. MFI-20 score per dimension three months postoperatively. White bars: Mini-incision Donor Nephrectomy (MIDN). Black bars: Laparoscopic Donor Nephrectomy (LDN). Abbreviations: GF general fatigue, PF physical fatigue, RA reduced activities, RM reduced motivation, MF mental fatigue.

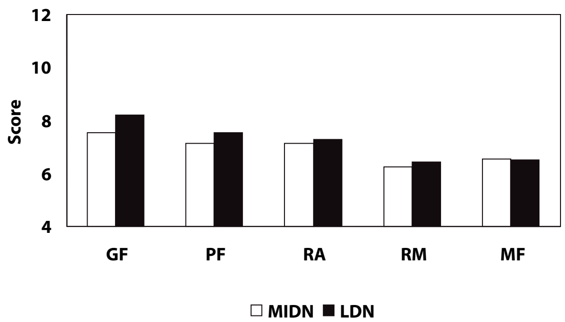


Figure 2D. MFI-20 score per dimension six months postoperatively. White bars: Mini-incision Donor Nephrectomy (MIDN). Black bars: Laparoscopic Donor Nephrectomy (LDN). Abbreviations: GF general fatigue, PF physical fatigue, RA reduced activities, RM reduced motivation, MF mental fatigue.

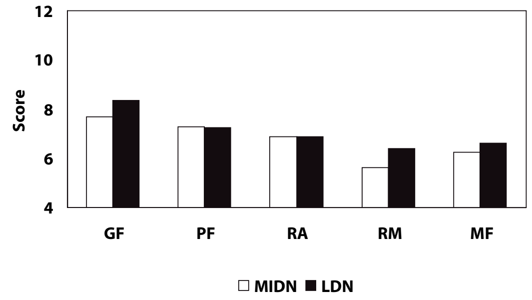


Figure 2E. MFI-20 score per dimension twelve months postoperatively. White bars: Mini-incision Donor Nephrectomy (MIDN). Black bars: Laparoscopic Donor Nephrectomy (LDN). Abbreviations: GF general fatigue, PF physical fatigue, RA reduced activities, RM reduced motivation, MF mental fatigue.

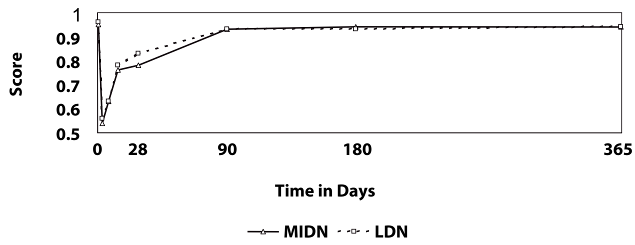


Figure 3A. Euroqol 5-dimension (EQ-5D) sum score during follow up. Continuous line with triangles: Mini-incision Donor Nephrectomy (MIDN). Interrupted line with squares: Laparoscopic Donor Nephrectomy (LDN).

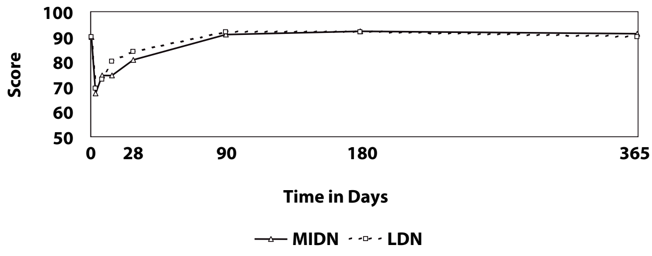


Figure 3B. 0-100 Visual Analogue Scale (VAS) during follow up. Continuous line with triangles: Mini-incision Donor Nephrectomy (MIDN). Interrupted line with squares: Laparoscopic Donor Nephrectomy (LDN).

The surgical approach to live donor nephrectomy is a prominent factor influencing the donor's recovery phase. Unlike traditional measures of recovery like postoperative hospital stay and return to work, quality of life and fatigue scores measure what donors experience themselves (1). Previous data reported by us suggest that the moment that the donors return to work is determined by several factors and not only by recovery from the operation (12). The present study clearly shows an effect of both surgical procedures on quality of life. The repeatedly measured decreased quality of life scores correspond with the self-reported data on activity level and return to work. The impact of live kidney donation on the donor might be greater and more pronounced than commonly thought. This impression is in accordance with a report by Smith et al. (2), who focused attention on the risks of psychosocial and physical impairment of live donor nephrectomy.

In the present study we evaluated the effect of the surgical technique of live donor nephrectomy on physical and psychosocial outcome. The between groups analysis showed only modest differences between donors who underwent muscle-splitting MIDN and LDN. LDN resulted in significantly better scores for bodily pain and physical functioning at one month postoperative only and more donors had returned to work in this group by 4 weeks. The type of incision can probably explain differences in bodily pain and physical functioning at one month. The abdominal muscles are stretched during muscle-splitting MIDN, which results in bruised muscles. Although muscle continuity is preserved, the stretching of the external and internal oblique abdominal muscles might result in contusions and it will take several weeks to recover. When performing LDN, stretching of the rectus abdominis muscles during extraction of the kidney only lasts for several seconds. This can result in muscular pain during the first few days, but will not take weeks to recover.

Most studies addressing the donor's quality of life have been designed retrospectively (15-20). Those studies had several limitations. First, comparison to baseline is impossible. Therefore, the conclusion that quality of life is not affected by donor nephrectomy is unfounded (17). Second, it is impossible to adjust for time effects if some donors receive quality of life questionnaires after one year and others after five years (19). Third, studies might be biased by low response (16) or different response rates for both treatment arms (18). To date other studies did not investigate the effect of the surgical approach on the outcome of the donation procedure: either only one surgical technique was studied, or an analysis of quality of life as a factor of the surgical intervention was not performed (20). Prospectively designed studies (2, 7, 21) focused on open surgical techniques (7), cost-effectiveness (21), or did not include the effect of surgical technique (3) as such. From the study by Pace et al. (21) it was concluded that LDN resulted in improved QOL at lower costs as compared to conventional open donor nephrectomy. The EQ-5D is a questionnaire, which can be used to calculate quality adjusted life years (QALYs) and subsequently assess cost-effectiveness. In the present study it was found that scores on the EQ-5D questionnaire were comparable between MIDN and LDN and that hospital stay only differed one day in favor of LDN. This indicates that MIDN is probably a more cost-effective procedure.

The present analysis allowed for adjustment of baseline values, donor's gender and age. Moreover, quality of life and fatigue were assessed at various points in time following living kidney donation, which allows additional and more reliable information (20).

Although the effect of surgical technique on quality of life and fatigue scores is clear and a difference in quality of life between techniques seems to be limited to the first few weeks, these results should be carefully interpreted. It is not known whether gender, age, relation between donor and recipient, conversion to another technique, surgical complications and postoperative course of the recipient influence the donor's quality of life following living kidney donation (22). The relatively high number of conversions and the higher number of deceased recipients in the LDN group could have influenced scores in this group. Subgroup analyses revealed great variability within donors who were related to a recipient that died or lost the graft. Further studies should address the effect of aforementioned variables on quality of life.

This study stresses the success of novel open approaches to live donor nephrectomy. We already reported good short-term results and excellent graft survival (8). Now, we add long-term results on physical and psychosocial outcome that are comparable between the minimal invasive muscle splitting and laparoscopic approach. This finding legitimates the open approach for centers that do not have the capacity or expertise to offer LDN to every living kidney donor. MIDN is a relatively easy and valuable alternative. LDN has several short-term benefits, including a shorter hospital stay and a better quality of life at one month postoperatively and may be advocated for these reasons. Future studies should include a cost-utility analysis to weigh the value of a temporarily higher quality of life.

ACKNOWLEDGEMENTS

Niels F.M. Kok was partly funded by the Dutch Kidney Foundation. The authors like to thank Mrs. J. van Duuren, datamanager, for her contribution to this study.

REFERENCES

1. Bergman S, Feldman LS, Mayo NE, et al. Measuring surgical recovery: the study of laparoscopic live donor nephrectomy. Am J Transplant 2005; 5 (10): 2489-95.
2. Smith GC, Trauer T, Kerr PG, Chadban SJ. Prospective psychosocial monitoring of living kidney donors using the Short Form-36 health survey: results at 12 months. Transplantation 2004; 78 (9): 1384-9.
3. Ware JE KM, Gandek B. SF-36 Health Survey. Manual and Interpretation Guide: Lincoln, 1993, 2000.
4. Smets EM, Garssen B, Cull A, de Haes JC. Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. Br J Cancer 1996; 73 (2): 241-5.
5. Ratner LE, Kavoussi LR, Sroka M, et al. Laparoscopic assisted live donor nephrectomy--a comparison with the open approach. Transplantation 1997; 63 (2): 229-33.
6. Flowers JL, Jacobs S, Cho E, et al. Comparison of open and laparoscopic live donor nephrectomy. Ann Surg 1997; 226 (4): 483-9.
7. Wolf JS, Jr., Merion RM, Leichtman AB, et al. Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation 2001; 72 (2): 284-90.
8. Kok NF, Alwayn IP, Lind MY, Tran KT, Weimar W, IJzermans JN. Donor nephrectomy: mini-incision muscle-splitting open approach versus laparoscopy. Transplantation 2006; 81 (6): 881-7.
9. Neipp M, Jackobs S, Becker T, et al. Living donor nephrectomy: flank incision versus anterior vertical mini-incision. Transplantation 2004; 78 (9): 1356-61.
10. Lewis GR, Brook NR, Waller JR, Bains JC, Veitch PS, Nicholson ML. A comparison of traditional open, minimal-incision donor nephrectomy and laparoscopic donor nephrectomy. Transpl Int 2004; 17 (10): 589-95.
11. Lind MY, Hop WC, Weimar W, IJzermans JN. Body image after laparoscopic or open donor nephrectomy. Surg Endosc 2004; 18 (8): 1276-9.
12. Lind MY, Liem YS, Bemelman WA, et al. Live donor nephrectomy and return to work: does the operative technique matter? Surg Endosc 2003; 17 (4): 591-5.
13. Brooks R. EuroQol: the current state of play. Health Policy 1996; 37 (1): 53-72.
14. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51 (11): 1055-68.
15. Giessing M, Reuter S, Schonberger B, et al. Quality of life of living kidney donors in Germany: a survey with the Validated Short Form-36 and Giessen Subjective Complaints List-24 questionnaires. Transplantation 2004; 78 (6): 864-72.
16. Buell JF, Lee L, Martin JE, et al. Laparoscopic donor nephrectomy vs. open live donor nephrectomy: a quality of life and functional study. Clin Transplant 2005; 19 (1): 102-9.
17. Isotani S, Fujisawa M, Ichikawa Y, et al. Quality of life of living kidney donors: the short-form 36-item health questionnaire survey. Urology 2002; 60 (4): 588-92.
18. Perry KT, Freedland SJ, Hu JC, et al. Quality of life, pain and return to normal activities following laparoscopic donor nephrectomy versus open mini-incision donor nephrectomy. J Urol 2003; 169 (6): 2018-21.
19. Giessing M, Reuter S, Deger S, et al. Laparoscopic versus Open Donor Nephrectomy in Germany: Impact on Donor Health-Related Quality of Life and Willingness to Donate. Transplant Proc 2005; 37 (5): 2011-5.
20. Reimer J, Rensing A, Haasen C, Philipp T, Pietruck F, Franke GH. The Impact of Living-Related Kidney Transplantation on the Donor's Life. Transplantation 2006; 81 (9): 1268-73.
21. Pace KT, Dyer SJ, Phan V, et al. Laparoscopic versus open donor nephrectomy. Surg Endosc 2003; 17 (1): 134-42.
22. Ku JH. Health-related quality of life of living kidney donors: review of the short form 36-health questionnaire survey. Transpl Int 2005; 18 (12): 1309-17.

Chapter 6

Comparison of laparoscopic and mini-incision open donor nephrectomy; A blinded, randomized controlled clinical trial

N.F.M. Kok[1], M.Y. Lind[1], B.M.E. Hansson[2], D. Pilzecker[3], I.R.A.M. Mertens zur Borg[4], B.C. Knipscheer[5], E.J. Hazebroek[1], I.M. Dooper[3], W. Weimar[6], W.C.J. Hop [7], E.M.M. Adang[8], G.J. van der Wilt[8], H.J. Bonjer[1], J.A. van der Vliet[2] and J.N.M. IJzermans[1]

[1]Department of Surgery, Erasmus MC, Rotterdam, The Netherlands

[2]Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands

[3]Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands

[4]Department of Anaesthesiology, Erasmus MC, Rotterdam, The Netherlands

[5]Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands

[6]Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

[7]Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, The Netherlands

[8]Department of Medical Technology Assessment, Radboud University Medical Center, Nijmegen, The Netherlands

British Medical Journal 2006; 333 (7561): 221

Nederlands Tijdschrift voor Geneeskunde in press

ABSTRACT

To determine the best approach for live donor nephrectomy that minimises discomfort to the donor and provides good graft function we set up a single-blind randomized controlled trial in two university medical centers. Using a well-defined multidisciplinary protocol for the management of 100 living kidney donors participants were randomly assigned to either laparoscopic donor nephrectomy (LDN) or mini-incision muscle-splitting open donor nephrectomy (ODN).

Primary outcome was physical fatigue (MFI-20). Primary secondary outcome was physical function (SF-36). Other secondary outcomes were postoperative hospital stay, pain, operating times, recipient graft function and graft survival. Conversions did not occur. As compared to ODN, LDN resulted in longer skin-to-skin time (median 221 vs. 164 minutes, $P<0.001$), longer warm ischemia time (6 vs. 3 minutes, $P<0.001$), less blood loss (100 vs. 240 ml, $P<0.001$) and a comparable number of complications (intra-operatively 12% vs. 6%, P=0.49, postoperatively both 6%). After LDN, donors required less morphine (16 vs. 25 mg, P=0.005), hospitalisation was shorter (3 vs. 4 days, P=0.003). Following LDN mean physical fatigue was less (mean difference -1.3, 95% CI -2.4 to -0.1, P=0.03) and physical function was better (mean difference 6.2, 95% CI 2.0 to 10.3, P=0.004) during one-year follow-up. Recipient renal function and one-year graft survival rate censored for death (100% after LDN and 98% after ODN) did not differ. In conclusion, LDN results in a better quality of life with equal safety as compared to ODN. Therefore, LDN is the technique of choice for living kidney donation programs.

INTRODUCTION

Kidney transplantation is the best treatment for patients suffering from end-stage renal disease. As the number of patients requiring kidney-replacement therapy steeply increases, it is important to recruit more kidney donors. Living donation is the most realistic option to expand organ donation (1). From an ethical point of view, living kidney donation becomes more acceptable if harm to the donor and the graft is limited. Therefore, optimising the management of the living donor including screening, surgical and anaesthesiological management is of utmost importance.

Traditionally the kidney was removed through a flank incision often including rib resection to allow sufficient access and resulting in significant postoperative pain, incisional hernias and chronic neuralgia. Employment of small incisions has improved postoperative comfort of the donor greatly. In less than a decade, laparoscopic surgery has been adopted by the majority of centers. Laparoscopic donor nephrectomy was first performed by Ratner in 1995 (2). Concurrently the open technique of donor nephrectomy has been refined to a muscle sparing mini-incision without resection of the ribs which has improved convalescence of the donors (3-5). To date the best surgical technique within the multidisciplinary management of living donors is not defined.

A prospective randomized trial comparing laparoscopic donor nephrectomy (LDN) and mini-incision donor nephrectomy (ODN) was designed. The donors were blinded to the surgical approach. We report fatigue scores, quality of life and clinical outcomes from this trial.

PATIENTS AND METHODS

Patients

Live kidney donors at the UMC's in Rotterdam and Nijmegen were considered for randomization.

The Medical Ethics Committees of both centers approved the study protocol. Screening of the donors included preoperative examination by a nephrologist, renal ultrasonography and magnetic resonance angiography or CT-angiography to evaluate arterial and venous anatomy of the kidneys. If both kidneys were suitable for transplantation the right kidney was preferred for removal (6). Exclusion criteria were bilateral abnormalities of the renal arteries (i.e. origin stenosis), previous operations of the kidney or adrenal gland, radiological abnormalities necessitating a modified approach (i.e. solid tumours requiring frozen sections) and the inability to read Dutch. Multiple arteries, obesity, abdominal surgery other than adrenal or renal surgery or age did not preclude participation in this trial. Informed consent was affirmed the day before surgery by the operating surgeon. The surgeon called the study coordinator to open the next numbered sealed opaque envelope provided by the trial statistician.

The series of envelopes was prepared according to a computer generated randomization list using a (hidden) block size of four. There was no stratification by center. All patients were randomized less than 12 hours prior to surgery. All involved health care professionals except for the members of the surgical team were unaware of the allocated procedure. At the end of the operation the abdomen of all donors was covered with a standard pattern of blood stained dressings that were not removed until discharge. A sealed envelope with information about the performed procedure was left in the chart for emergencies.

Anaesthesia and Analgesia

Donors were prehydrated using intravenous crystalloids. Anti-thrombotic stockings were used routinely. After endotracheal intubation anaesthetic procedures were performed according to a strict protocol for medication, ventilation and fluid regimen. One hour after the start of surgery 20 mg Mannitol was administered. Except for one patient who required endocarditis prophylaxis no antibiotics were given. At the end of operation patients received Patient Controlled Analgesia (PCA) using intravenous morphine. Furthermore, two 500-milligram acetaminophen tablets were offered four times daily until discharge. The PCA-device was removed when morphine had not been required for at least six hours.

Surgical Procedures

All procedures were performed according to the randomization by one of four referent surgeons who were skilled in both procedures. The trial coordinator in each center attended all operations to document blood loss, operation time, use of instruments and complications. Complications were defined as events necessitating intra-operative or postoperative interventions or causing prolonged admission.

Both techniques were performed as described previously (5) with the donor in a lateral decubitus position. Briefly, during LDN the camera and three to four additional trocars were introduced under vision. After meticulous dissection of the kidney, the ureter and the vascular structures, an endobag (Endocatch, US Surgical, Norwalk, CT, USA) was introduced. The renal artery and vein were divided with linear stapling devices (Endo GIA, US Surgical, Norwalk, CT, USA) and the kidney was extracted through a pfannenstiel incision. The skin wounds were sutured intracutaneously.

To enable ODN a horizontal 10-12 cm skin incision was made anterior to the 11th rib. The fascia and muscles of the abdominal wall were carefully split using a mechanical retractor (Omnitract surgical, St. Paul, USA). Gerota's fascia was opened on the lateral side of the kidney. After meticulous dissection of the kidney, the ureter, the renal artery and vein were successively clamped, cut and ligated. The kidney was extracted. The fascias of the abdominal muscles were closed, the subcutaneous fascia was approximated and the skin was sutured intracutaneously.

Postoperative data and QOL

The donor determined the moment of discharge from the hospital given tolerance of a normal diet and ability to walk the stairs. Postoperative hospital stay was calculated with and without correction for time spent in hospital because of non-medical reasons (i.e. because of lack of homecare). After discharge, donors were seen at the outpatient clinic at three weeks, three months and one year postoperatively. Donors were asked to complete forms related to pain, nausea, body image, fatigue and QOL. Pain and nausea were scored on a 0-10 visual analogue scale (VAS, 0 represents no complaints, 10 represents severe complaints) preoperatively and at days 1,3,7 and 14.

The body image questionnaire (7) (BIQ) consisted of two scales and was assessed at 1 year postoperatively. The body image scale (BIS) consisted of five questions regarding the attitude of the patient towards bodily appearance and results in a score ranging from 5 to 20. The cosmetic scale (CS) consisted of 3 questions measuring the degree of satisfaction with respect to the appearance of the scar, which results in a score ranging from 3 to 24. On both scales higher scores indicated greater satisfaction.

To assess whether LDN and ODN differentially impacted on health related QOL and fatigue, the Short Form-36 (SF-36) and the Multidimensional Fatigue Inventory-20 (MFI-20) were administered preoperatively and 1, 3, 6, and 12 months postoperatively. The SF-36 includes one multi-item scale measuring each of eight health concepts: physical function, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health (8). Scores per dimension of the SF-36 ranged from 0 to 100 with higher scores indicating better QOL. A 5-point difference between LDN and ODN on a dimension was considered the minimal clinically relevant difference (8).

The MFI-20 (9) determined the level of fatigue and consisted of 20 items divided into five scales: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. Scores per item ranged from 1 to 5. Accordingly, the total score per scale ranged from 4 (no fatigue) to 20 (exhausted).

Recipients

Recipients were admitted to another surgical ward separated from the donor to minimize influence on the donor's recovery. They underwent renal transplantation using the standard technique of preperitoneal placement in the iliac fossa. Immunosuppressive regimen included mycofenolate mofetil, tacrolimus and prednisone. One-year patient- and graft survival rates, acute rejection rates (histologically proven), venous thrombosis, ureteral complications as defined as the need for a percutaneous nephrostomy, ureter reconstructions, and renal function during the first year postoperatively were recorded.

Statistical considerations

Fatigue and quality of life are closely related. However, fatigue as an outcome of the intervention might be more suitable to indicate the effect of a surgical approach than the quality of life test. The latter may be influenced by other factors, such as satisfaction after donor nephrectomy. Therefore, primary outcome was physical fatigue on the MFI-20 and secondary outcome was physical function at the SF-36. Other secondary endpoints were postoperative hospital stay, pain, operating times, recipient graft function and graft survival. Power calculations were based on physical fatigue. Fifty donors had to be included in each arm to establish a moderate significant difference of 0.6 standard deviations in physical fatigue with a power of 80% and an alpha of 0.05. Categorical variables were compared with the Chi square test. Continuous variables were compared with the Mann Whitney U test. Repeated continuous variables were compared with repeated measurement ANOVA. Repeated measures were adjusted for baseline values, donor's sex and age. Analyses were conducted using SPSS (version 11.0, SPSS Inc., Chicago, USA). Data were analysed according to the intention to treat principle. A p-value <0.05 (two-sided) was considered statistically significant.

Funding

This study was financially supported by unrestricted grants of the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) and the Dutch Kidney Foundation.

RESULTS

From November 2001 until February 2004 105 of 163 live kidney donors were included (Figure 1). Among not included patients were two donors who participated in a Cross-over program (10). After randomization one operation was cancelled and four other operations were postponed because of clinical or radiological findings at the night before surgery. In Rotterdam 34 LDNs and 38 ODNs were performed. In Nijmegen 16 LDNs and 12 ODNs were performed. The number of patients included in this study in Nijmegen was smaller because inclusion started later due to delayed approval of the Medical Ethics Committee. Patient Characteristics are shown in Table 1.

Surgery (Table 2)

All procedures were executed as planned without conversion to open or formal lumbotomy. In the LDN group skin-to-skin time and warm ischemia time were significantly longer and blood loss was less. Intra-operative complications occurred in six patients (12%) during LDN and included bleeding (n=3, total blood loss ranging from 400-860 ml), one serosal lesion of the colon, one bladder lesion and one small capsular tear of the spleen. All lesions were recognized immediately and adequately treated without conversion. Re-interventions were

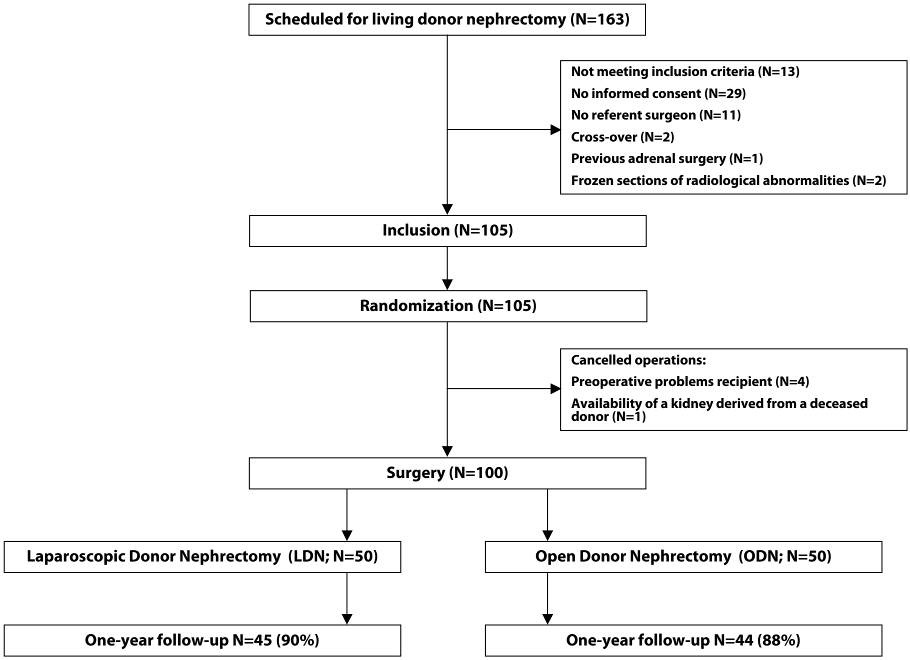


Figure 1. Flowchart of 163 patients eligible during the study period.

not indicated. All 3 (6%) complications during ODN involved bleeding (range total blood loss 1000-1800 ml) controlled during the operation.

Postoperative outcomes (Table 2)

LDN resulted in faster recovery as reflected by earlier resumption of solid diet, less intravenous morphine requirement and earlier discharge. During the first weeks patients experienced significantly less pain following laparoscopy. Postoperative complications following LDN included a single blood transfusion and two wound infections at the extraction site which were treated with oral antibiotics. Complications following ODN included a urinary tract infection, a minor pulmonary infiltrate both not requiring administration of antibiotics, and an infected retroperitoneal haematoma, which required readmission for intravenous administration of antibiotics. Other complications, including incisional hernias, did not occur. Donor serum creatinine levels were similar between the groups. Scores on the Body Image Scale did not significantly differ between groups.

Recipients (Table 2)

One recipient (LDN) died on the first postoperative day due to myocardial infarction. Two others (LDN and ODN) died in the first year due to progressive infections related to their

Table 1. Baseline characteristics of donors and recipients. Categorical data are given as No. (%) and continuous variables as median (range).

	LDN (N=50)	ODN (N=50)
Donor		
Sex – No. (%)		
Male	29 (58%)	24 (48%)
Female	21 (42%)	26 (52%)
Age – years	49 (20-77)	48.5 (21-75)
Kidney – No. (%)		
Left	30 (60%)	31(62%)
Right	20 (40%)	19 (38%)
ASA Classification – No. (%)		
I	38 (76.0%)	34 (68%)
II	12 (24.0%)	15 (30%)
III		1 (2%)
Body mass index – kg/m^2	25.9 (16.5-36.6)	26.0 (17.7-33.2)
Renal Arteries – No. (%)		
1	37 (74%)	40 (80%)
≥ 2	13 (26%)	10 (20%)
Renal Veins – No. (%)		
1	42 (84%)	46 (92%)
≥ 2	8 (16%)	4 (8%)
Preoperative Serum Creatinine – µmol/l	76 (49-105)	79 (54-99)
Physical function (SF-36)	95 (35-100)	100 (45-100)
Physical fatigue (MFI-20)	4 (4-10)	4.0 (4-20)
Recipient		
Sex – No. (%)		
Male	32 (64%)	23 (46%)
Female	18 (36%)	27 (54%)
Age – years	48 (13-68)	44 (11-72)
Relation between donor and acceptor – No. (%)		
Living Related	39 (78%)	35 (70%)
Living Unrelated	11 (22%)	15 (30%)
Preoperative Serum Creatinine – µmol/l	799 (299-1793)	783 (300-1777)

immune-compromised state. Additionally, one recipient (ODN) lost her graft due to vascular rejection. She is alive and undergoes haemodialysis. Renal vein thrombosis did not occur in either group. Ureteral complications including ureteral stenosis and leaking led to three ureteral reconstructions following ODN. Serum creatinine values decreased parallel wise to comparable levels without any significant differences over time between recipients, who received a kidney after either laparoscopic or open procurement of the kidney.

QOL and Fatigue (Table 3)

Response ranged from 97% at one month to 89% at twelve months with an equal distribution between LDN and ODN at all times. At baseline both groups had an excellent health status (8).

Table 2. Surgical outcomes of the donor and postoperative outcomes of donor and recipient. Categorical data are given as No. (%) and continuous variables as median (range).

	LDN (N=50)	ODN (N=50)	P- Value
Donor			
Conversion to open – No.	0	–	–
Operation times – minutes			
Time until kidney removal	181(107-307)	118(61-201)	<0.001
Skin-to-skin time	221(135-354)	164(92-298)	<0.001
Time in the operation room	289.5(180-420)	226 (157-365)	<0.001
Warm ischemia time – minutes	6 (2-14)	3 (1-6)	<0.001
Blood loss – ml	100 (10-860)	240 (20-1800)	<0.001
Complications – No. (%)			
Intra-operative	6 (12%)	3 (6%)	0.23
Postoperative	3 (6%)	3 (6%)	1.00
Return to diet – hours	19.5 (3-48)	24 (16-72)	0.01
Morphine requirement – mg	16 (0-93)	25 (1-107)	0.005
Length of stay – days			
Uncorrected	3 (1-6)	4 (2-8)	0.003
Corrected	3 (1-6)	3 (2-8)	0.002
Serum Creatinine donor – μmol/l			
Day 1	112 (75-158)	112.5 (68-183)	0.81
Day 2	118 (76-167)	117.5 (74-222)	0.99
Month 3	107 (76-157)	117 (79-191)	0.31
Year 1	107 (72-153)	114 (75-169)	0.17
Nausea – 0-10 VAS scale			
Day 1	0 (0-9.2)	0 (0-7.7)	0.52
Day 3	0 (0-4.6)	0 (0-5.2)	0.24
Day 7	0 (0-3.2)	0 (0-8.0)	0.31
Day 14	0 (0-2.2)	0 (0-8.0)	0.14
Pain – 0-10 VAS scale			
Day 1	2.7 (0-6.2)	3.5 (0-7.7)	0.04
Day 3	1.4 (0-6.6)	1.8 (0-7.8)	0.12
Day 7	0.4 (0-6.1)	1.7 (0-8.0)	0.03
Day 14	0 (0-4.8)	0.4 (0-8.0)	0.008
Body Image Questionnaire			
Body Image Scale (BIS)	20 (13-20)	20 (14-20)	0.40
Cosmetic Scale (CS)	20 (7-24)	18 (12-24)	0.14
Recipient			
Acute Rejection – No. (%)	9 (18%)	15 (30%)	0.24
Ureteral Complications – No. (%)	6 (12%)	10 (20%)	0.41
1-year Graft Survival* – No. (%)	48 (100%)	48 (98%)	1.00
1-year Patient survival – No. (%)	48 (96%)	49 (98%)	1.00

* censored for death

Scores on the domains role physical and bodily pain were comparable at all time points. All other dimensions differed over time in favor of LDN (Table 3). In Figure 2a physical function is shown over time. Patients in the LDN group had higher mean scores for physical function

Table 3. Quality of Life of Laparoscopic Donor Nephrectomy (LDN) versus Open Donor Nephrectomy (ODN). Estimated adjusted differences of means , 95% confidence intervals and P-values for the dimensions of the SF-36 and MFI-20 scales during follow-up. Positive differences regarding SF-36 dimensions indicate a better Quality of life following LDN. Negative differences regarding the MFI-20 dimensions indicate less fatigue following LDN.

Dimension	Estimated difference (LDN minus ODN)	95% Confidence Interval	P-Value
SF-36			
physical function	6.2	2.0 to 10.3	0.004
role physical	7.7	-2.1 to 17.5	0.12
bodily pain	4.1	-0.3 to 8.5	0.07
general health	7.2	2.2 to 12.1	0.005
vitality	6.7	1.1 to 12.2	0.02
social functioning	5.9	0.5 to 11.4	0.03
role emotional	11.8	4.1 to 19.5	0.003
mental health	5.6	1.8 to 9.4	0.005
MFI-20			
general fatigue	-0.7	-2.0 to 0.6	0.31
physical fatigue	-1.3	-2.4 to -0.1	0.03
reduced activities	-0.8	-2.0 to 0.3	0.16
reduced motivation	-1.0	-2.1 to 0.1	0.07
mental fatigue	-0.2	-1.7 to 0.3	0.70

during follow-up indicating better QOL (difference 6.2 points, 95% confidence interval 2.0 to 10.3 P=0.004). For the other dimensions similar patterns were found (data shown in Table 4). Physical fatigue scores (MFI-20) were significantly lower for donors in the LDN group indicating less physical fatigue (Figure 2b, difference during one year follow-up -1.3, 95% CI -2.4 to -0.1, P=0.03). Other dimensions of fatigue did not differ between LDN and ODN over time (data shown in Table 4).

DISCUSSION

This trial compares the least traumatic version of ODN to complete LDN without any conversions. This allows a true assessment of both techniques.

Complete or hand-assisted LDN has been compared with conventional ODN. Most studies investigated perioperative complications and recovery shortly after operation. Three randomized trials compared hand-assisted LDN and ODN without blinding (11-13). Mini-incision donor nephrectomy has been proposed as an acceptable alternative to laparoscopic surgery (14), certainly if complicating conditions can be expected.

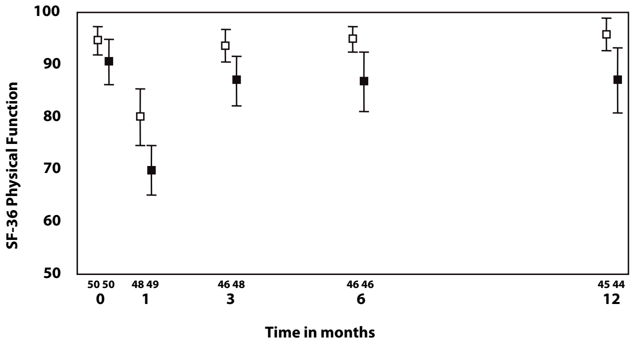


Figure 2a. Physical function during follow-up displayed as means and corresponding confidence intervals. Laparoscopic Donor Nephrectomy (LDN, open squares) versus Open Donor Nephrectomy (ODN, filled squares). Numbers underneath the x axis represent the numbers of donors evaluated at each point in time; on the left the LDN donors, on the right the ODN donors.

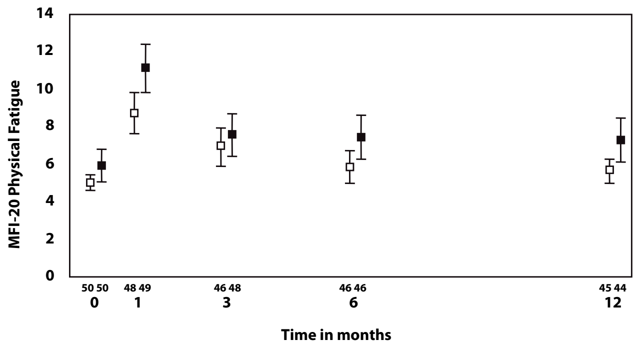


Figure 2b. Physical fatigue during follow-up displayed as means and corresponding confidence intervals. Laparoscopic Donor Nephrectomy (LDN, open squares) versus Open Donor Nephrectomy (ODN, filled squares). Numbers underneath the x axis represent the numbers of donors evaluated at each point in time; on the left the LDN donors, on the right the ODN donors.

In the present study common exlusion criteria for LDN such as high body mass index and right kidneys did not restrict donors from participation. Unlike traditional lumbotomy, the applied open approach used a small incision and preserved continuity of abdominal wall muscles resulting in few complications, fast recovery (15,16) and cosmetic outcome equivalent to LDN. Despite modification of the open technique, LDN proved to be superior with regard to recovery and, more important, fatigue and QOL during follow up. The use of blood stained wound dressings blinded donors and medical staff in the direct post-operative phase. In previous reports on laparoscopic versus open cholecystectomy this strategy avoided bias caused by medical staff (17,18). Although bias could have been present after discharge, this is the best possible blinding. The difference in parameters measured shortly after the operation such as pain scores and length of stay was significantly in favor of LDN despite blinding.

In our view, restoration of QOL is of utmost importance following living kidney donation. Other retrospective studies showed an improved QOL after laparoscopic surgery as compared to conventional open surgery (11,19,20). The present analysis demonstrated that the laparoscopic approach leads to an advantageous postoperative course with a better QOL of donors. In laparoscopic versus open studies for benign or malignant causes, QOL is at best considered secondary outcome. Removal and permanent correction of the abnormality is the primary outcome and influences feelings of patients postoperatively. Conversions from laparoscopic to open often blur the effect of the operation on QOL. As donors are healthy individuals their profit from laparoscopic surgery resembles the actual advantage of laparoscopic operations for other patients.

Although the benefits of LDN were obvious in this study it remains important to realize that extensive experience in laparoscopic surgery is necessary to implement a laparoscopic kidney donation program. Complications were rare in our study, but still some minors occurred. Furthermore, the operation time in our study was about an hour longer for LDN. Both the complete laparoscopic set-up of LDN and the inclusion of donors with more difficult anatomy attributed to this. Other alternatives closely related to LDN may be explored to address these issues. Retroperitoneoscopic donor nephrectomy may combine the advantage of a shorter operation time and a lower chance of complications from lesions of intra-peritoneal organs (21).

In conclusion LDN results in faster recovery, less fatigue and better QOL of the donor and equal safety and function for donor and graft as compared to mini-incision ODN. Therefore, LDN may be advocated as the technique of choice for live kidney donation programs.

ACKNOWLEDGEMENTS

The authors also thank Mrs. J.G. van Duuren-van Pelt, datamanager, and Dr. I.P.J. Alwayn, surgeon for their contributions to this study.

REFERENCES

1. Ingelfinger JR. Risks and benefits to the living donor. N Engl J Med 2005;353(5):447-9.
2. Ratner LE, Ciseck LJ, Moore RG, Cigarroa FG, Kaufman HS, Kavoussi LR. Laparoscopic live donor nephrectomy. Transplantation 1995;60(9):1047-9.
3. Srivastava A, Tripathi DM, Zaman W, Kumar A. Subcostal versus transcostal mini donor nephrectomy: is rib resection responsible for pain related donor morbidity. J Urol 2003;170(3):738-40.
4. Yang SL, Harkaway R, Badosa F, Ginsberg P, Greenstein MA. Minimal incision living donor nephrectomy: improvement in patient outcome. Urology 2002;59(5):673-7.
5. Kok NF, Alwayn IP, Lind MY, Tran KT, Weimar W, IJzermans JN. Donor nephrectomy: mini-incision muscle-splitting open approach versus laparoscopy. Transplantation 2006;81(6):881-7.
6. Lind MY, Hazebroek EJ, Hop WC, Weimar W, Jaap Bonjer H, IJzermans JN. Right-sided laparoscopic live-donor nephrectomy: is reluctance still justified? Transplantation 2002;74(7):1045-8.
7. Dunker MS, Bemelman WA, Slors JF, van Duijvendijk P, Gouma DJ. Functional outcome, quality of life, body image, and cosmesis in patients after laparoscopic-assisted and conventional restorative proctocolectomy: a comparative study. Dis Colon Rectum 2001;44(12):1800-7.
8. Ware JE KM, Gandek B. SF-36 Health Survey. Manual and Interpretation Guide: Lincoln, 1993,2000.
9. Smets EM, Garssen B, Cull A, de Haes JC. Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. Br J Cancer 1996;73(2):241-5.
10. de Klerk M, Keizer KM, Claas FH, Witvliet M, Haase-Kromwijk BJ, Weimar W. The Dutch national living donor kidney exchange program. Am J Transplant 2005;5(9):2302-5.
11. Wolf JS, Jr., Merion RM, Leichtman AB, et al. Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation 2001;72(2):284-90.
12. Simforoosh N, Basiri A, Tabibi A, Shakhssalim N, Hosseini Moghaddam SM. Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial. BJU Int 2005;95(6):851-5.
13. Oyen O, Andersen M, Mathisen L, et al. Laparoscopic versus open living-donor nephrectomy: experiences from a prospective, randomized, single-center study focusing on donor safety. Transplantation 2005;79(9):1236-40.
14. Lewis GR, Brook NR, Waller JR, Bains JC, Veitch PS, Nicholson ML. A comparison of traditional open, minimal-incision donor nephrectomy and laparoscopic donor nephrectomy. Transpl Int 2004;17(10):589-95.
15. Berends FJ, den Hoed PT, Bonjer HJ, et al. Technical considerations and pitfalls in laparoscopic live donornephrectomy. Surg Endosc 2002;16(6):893-8.
16. Lind MY, Liem YS, Bemelman WA, et al. Live donor nephrectomy and return to work: does the operative technique matter? Surg Endosc 2003;17(4):591-5.
17. Majeed AW, Troy G, Nicholl JP, et al. Randomised, prospective, single-blind comparison of laparoscopic versus small-incision cholecystectomy. Lancet 1996;347(9007):989-94.
18. Johansson M, Thune A, Nelvin L, Stiernstam M, Westman B, Lundell L. Randomized clinical trial of open versus laparoscopic cholecystectomy in the treatment of acute cholecystitis. Br J Surg 2005;92(1):44-9.
19. Perry KT, Freedland SJ, Hu JC, et al. Quality of life, pain and return to normal activities following laparoscopic donor nephrectomy versus open mini-incision donor nephrectomy. J Urol 2003;169(6):2018-21.
20. Buell JF, Lee L, Martin JE, et al. Laparoscopic donor nephrectomy vs. open live donor nephrectomy: a quality of life and functional study. Clin Transplant 2005;19(1):102-9.
21. Wadstrom J. Hand-assisted retroperitoneoscopic live donor nephrectomy: experience from the first 75 consecutive cases. Transplantation 2005;80(8):1060-6.

Chapter 7

Cost-effectiveness of laparoscopic versus mini-incision open donor nephrectomy: a randomized study

N.F.M. Kok[1], E.M.M. Adang[2], B.M.E. Hansson[3], I.M. Dooper[4], W. Weimar[5], G.J. van der Wilt[2] and J.N.M. IJzermans[1]

[1] Department of Surgery, Erasmus MC, Rotterdam, The Netherlands

[2] Department of Medical Technology Assessment, Radboud University Medical Center, Nijmegen, The Netherlands

[3] Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands

[4] Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands

[5] Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

Transplantation in press

ABSTRACT

Cost-effectiveness remains an issue surrounding the introduction of laparoscopic donor nephrectomy (LDN). In a randomized controlled trial the cost-effectiveness of LDN versus mini-incision open donor nephrectomy (ODN) was determined. Fifty donors were included in each group. All in-hospital costs were documented. Postoperatively, case record forms were sent to the donors during one-year follow-up to record return to work and societal costs. To offset costs against quality of life the Euroqol-5D questionnaire was administered pre-operatively and 3,7,14,28,90,180 and 365 days postoperatively. Mean total costs were 6,090 Euros ($7308) following LDN and 4,818 Euros ($5782) following ODN ($P<0.001$). Disposables influenced the cost difference most. Mean productivity loss was 68 and 75 days after LDN and ODN respectively, corresponding to 783 ($940) gained Euros per donor after LDN. The main gain in Quality of Life in the LDN group was realized within 4 weeks postoperatively. LDN resulted in a mean gain of 0.03 quality adjusted life year at mean costs of 1271($1525) and 488 ($586) Euros from respectively a healthcare perspective and a societal perspective. This implies that one additional QALY after LDN costs about 16,000 Euros ($19,200) from a societal point of view and about 41,000 Euros ($49,200) from a health-care perspective. Activities other than work were significantly earlier resumed after LDN (66 vs. 91 days, $P=0.01$). In conclusion, in addition to a clinically relevant donor-experienced benefit from LDN, this technique appeared, given a societal perspective, a cost-efficient procedure mainly due to less productivity losses.

INTRODUCTION

Live kidney donor transplantation has become the most realistic option to expand kidney transplantation and has several benefits over transplantation of kidneys from deceased donors including shorter waiting lists, better initial graft function and longer graft survival (1). From the perspective of the donor laparoscopic donor nephrectomy (LDN) has become the preferred technique to procure the kidney (2-5).

In general, the widespread introduction of a novel surgical technique is only acceptable if the technique offers an equal or better treatment to patients, if the technique can be mastered relatively easily and if the technique is cost-efficient. With regard to the first aspect, evidence has mounted that LDN provides clinically relevant benefits to the donor including less pain, earlier convalescence and superior quality of life (2-7). After early concern with regard to graft function following LDN recent reports showed similar graft function after laparoscopic and open donor nephrectomy (4, 8). With regard to the second aspect, in the USA more than 60% of the live donor kidneys is procured laparoscopically with acceptably low mortality and morbidity rates (9). In Western Europe LDN has been introduced by more than 40% of the transplant centers (10).

The missing keystone impeding wide-spread acceptance of laparoscopic surgery for live kidney donation is the cost-efficiency issue. The assumption that LDN is associated with higher costs and the idea that the additional time and money spent on LDN are not rewarding are common reasons to stick to open techniques (10). We evaluated the cost-effectiveness of LDN versus mini-incision open donor nephrectomy (ODN) alongside a randomized, blinded clinical trial.

PATIENTS AND METHODS

Patients

Live kidney donors at the University Medical Centers in Rotterdam and Nijmegen in the Netherlands were considered eligible for participation in the Living Donors trial. The medical ethics committees of both hospitals approved the study protocol. In this study a complete laparoscopic approach for live kidney donation was applied to 50 donors whereas 50 others underwent a mini-incision muscle-splitting open approach. Four experienced surgeons supervised all procedures. Details of donors, recipients, screening, surgical procedures and perioperative analgesia have been published elsewhere (3).

Briefly, all donors scheduled for donor nephrectomy on the following day were randomized using sealed opaque envelopes. To further guarantee opacity, the papers that contained the procedure to be performed and the trial number were double-folded twice. The trial statistician had created a computer-generated randomization list. There was no stratification per center. Donors had to have adequate knowledge of the Dutch language and had to give informed consent. All personnel outside the operation team was kept unaware of the surgical approach using a standard pattern of blood stained dressings. These dressings were removed at discharge only. Donors were only discharged from the hospital if they resumed a normal diet and were able to walk stairs.

To harvest the kidney during LDN an endobag was inserted via a pfannenstiel incision. To harvest the kidney in ODN a 10-12 cm skin incision was made anterior to the 11th rib with subsequent splitting of the oblique and transverse abdominal muscles. A mechanical retractor (Omnitract surgical, St. Paul, USA) provided the required working space.

Data collection

Direct treatment costs

Costs prior to admission to the hospital including charges of screening and imaging were not taken into account as these were similar for both techniques. Direct treatment costs constituted of personnel, material and capital costs like: total operating time, hospital days (prime and recurrent), capital costs associated with the operating theatre for both procedures (monitors, endoscopic tower etc.), personnel costs such as surgical costs (surgeon, assistant), anesthetics costs (anesthesiologist, assistant), operating nurses and material costs (disposables). Furthermore outpatient visits, GP consultations and homecare related costs were included. Hospital overhead costs were added as a fixed percentage (35%) to the costs of the personnel in the operation room. Unit resource prices were based on guideline prices according to the Dutch Insurance Board to improve generalization of the results and limit dependence on local negotiations between healthcare instances and the insurance companies (i.e. standard prices were available for the rate of a day in an university hospital, the rate for a visit to the general practitioner) (11). If these prices were not available real costs prices were determined (i.e. the costs of the endobag to retrieve the kidney). The trial coordinator in either center attended all operations from the arrival of the donor until leave to the recovery room. Together with the scrub nurse use of all instruments and other items such as the sheets to cover the operation field were documented. Costs of sterilization of re-usable instruments were calculated. Depreciation of hardware used during the procedures such as monitors, the endoscopic tower and the mechanical retractor was included. Salaries of anesthesiologist, surgeons, nurses and supporting personnel in the operation room were all included and expressed as a function of the time spent in the operation room.

At the surgical ward, a standard price was counted for every day spent in (an academic) hospital according to the national guideline (11). All costs related to the re-admission of single donor including administration of intravenous antibiotics were added to the total in-hospital costs.

Use of health care resources during follow-up were registered using case record forms that were administered preoperatively, 1,2,4 and 6 weeks postoperatively and every two weeks thereafter until complete return to preoperative activity. Donors were asked whether or not they had housekeeping or homecare, whether or not they visited their general practitioner or a doctor in the hospital, or the first aid department. Participants were also asked to quantify these items. For these resources guideline prices were available. These data were cross-checked with data from the electronic patient files from the hospital. If donors did not reply to the case record forms, we sent a reminder. If they did not respond to the reminder, we called them on the phone. We did not attempt to incorporate charges related to the recipient including dialysis, the renal transplantation and the immunosuppressive therapy of recipients.

Societal costs

Additional burden to society was quantified by calculating productivity losses for donors who performed paid labor preoperatively using the friction costs method. The friction costs method assumes that an employee on sick leave is replaced if this sick leave takes too long. The friction costs period was set at 154 days on average based on 2003 figures. This implies that an employee on sick leave for more than 154 days would have been replaced. Productivity loss was fixed at an average of 80% of 40 euros ($48) per hour. With the aforementioned case-record forms data were gathered on preoperative occupation, including whether this occupation was physically demanding or not and whether the job was part-time or not. Up to every lost hour, productivity losses were documented, therewith also addressing those donors who started working part-time first and resumed regular working hours later. Because the donor's physical condition is known not be the only factor determining return to work in a previous study the day that patients resumed 90% and 100% of daily activities was also determined (12). We did not give any advice to the donors when to resume work.

Cost-utility analysis

Quality of life (QOL) during follow-up, measured on the Euroqol-5D was defined as utility (13). QOL of both surgical modalities was evaluated preoperatively and 3, 7, 14, 28 days and 3, 6, 12 months postoperatively. Health status was described according to five attributes: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each attribute had three levels, i.e. "no problems", "some problems" or "severe problems". From these EQ-5D scores Quality Adjusted Life Years (QALYs) were derived using the trapezium rule. One QALY means one year in good health. The trapezium rule is a way to approximately calculate the definite integral over a function f(x). The trapezium rule applied to QALYs is conducted by approximating the region under the function QALY=f(QALY*t) by a trapezium and calculating its area. In this equation t expresses the aforementioned Euroqol-5D measurement points at baseline. A 0-100 VAS scale measuring health (with 0 indicating very poor health and 100 indicating superior health) was also included to document health, but did not attribute to the cost-utility analysis.

The cost-effectiveness analysis was conducted from a health care perspective as well as a societal perspective, the latter including lost productivity. Patient costs and QALYs were combined and subjected to bootstrap analysis (14). Bootstrap analysis is a method to deal with non-normality of two combined variables. By re-sampling with replacement from the original sample the chance that outliers significantly influence the cost-utility analysis becomes smaller (i.e. the re-admission in the open group led to significant additional costs and may be considered an outlier). One thousand incremental cost-effectiveness ratio's (ICERs) were generated. These ICERs were plotted in a cost-effectiveness plane from which an ICER acceptability curve was derived. In general, insurance companies and governmental organizations are willing to pay up to 50,000 euros per QALY (15). The maximum amount of money people are willing to pay per QALY is called the ceiling ratio or threshold.

Data analysis and statistical considerations

Physical fatigue and physical function have been the primary and primary secondary endpoint of this trial (3). These endpoints were chosen to quantify surgical recovery and to focus on the physical burden on the donor after live kidney donation. Power calculations led to 50 donors in either group to establish a moderate significant difference in physical fatigue with a power of 80% and an alpha of 0.05. Return to work, return to daily activity and cost-effectiveness were in the original protocol defined as important secondary outcomes. To express costs in American dollars ($) we applied a currency exchange ratio of 1.2$ per euro. Categorical variables were compared with the Chi square test. Continuous variables were compared with the Mann Whitney U test. Repeated continuous variables were compared with repeated measurement ANOVA. Repeated measures were adjusted for baseline values, donor's sex and age. Analyses were conducted using SPSS (version 11.5, SPSS Inc., Chicago, USA). Data were analyzed according to the intention to treat principle. A p-value <0.05 (two-sided) was considered statistically significant.

Funding

This study was financially supported by unrestricted grants of the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) and the Dutch Kidney Foundation.

RESULTS

Between November 2001 and February 2004 100 donors underwent surgery according to the randomization. Conversions or crossovers did not occur. During one-year follow-up response rates for quality of life ranged from 97% to 88%. Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics. Categorical data are displayed as No. (%) and continuous variables as mean (range).

	LDN (N=50)	ODN (N=50)
Gender (male)	29 (58%)	24 (48%)
Age (years)	50 (20-77)	48 (21-75)
Kidney (right)	20 (40%)	19 (38%)
ASA Classification (I)	38 (76%)	34 (68%)
Body mass index (kg/m^2)	26 (17-37)	26 (18-33)
Renal Arteries (>1)	13 (26%)	10 (20%)
Relation (Living related)	39 (78%)	35 (70%)
Employed	34 (68%)	34 (68%)
Physically demanding work	18 (36%)	18 (36%)

Thirty-four donors in either group were employed preoperatively. Eighteen donors in either group performed physically demanding work. Donors worked 34 hours on average in either group.

Intra- and direct postoperative outcomes

Most of these outcomes have been published elsewhere (3). Presence of the donor in the operation room (induction of anesthesia, operation, extraction and perfusion of the transplant, and extubation of the donor) lasted 293 minutes on average during LDN and 234 minutes during ODN (P<0.001). Mean postoperative hospital stay was 3 days (range 1-6 days) in the LDN group and 4 days (range 2-8 days) in the ODN group (P=0.003). Three postoperative complications occurred in either group. The influence of five of these complications was limited (a transfusion with two packed red blood cells and two oral antibiotic cycles to treat wound infections, an untreated pulmonary infiltrate and an untreated urinary tract infection). However, one donor experienced an infected haematoma requiring re-admission to the hospital and administration of intravenous antibiotics for 14 days.

Direct treatment costs

Direct treatment costs are categorized in Table 2. Higher costs in the operation room are the main reason why total charges for LDN are significantly higher. Fixed costs are higher in the LDN group because of significant higher charges for maintenance (50 vs. 10 Euros, $60 vs. $12) and depreciation of the endoscopic tower and the monitors (126 and 47 Euros respectively per laparoscopic operation, $151 vs. $56). Personnel costs were higher for laparoscopy, which is mainly caused by longer operation times. Disposables were significantly more expensive in the LDN group. In particular the use of ultrasonic shears, the endobag and endostapler were cost-drivers.

Charges for hospitalization were lower in the LDN group, because the average hospital stay was about one day shorter. In addition, expenses after discharge were lower as a consequence

Table 2. Costs, return to work and activity level. Categorical data are displayed as No. (%), continuous data are displayed as mean (range)

	LDN (N=50)	ODN (N=50)	P- Value
Direct treatment costs (Euros$)	6090 (4983-7635)*	4818 (3179-12417)*	<0.001
Intra-operative	4074 (2851-6162)*	2244 (1605-3393)*	<0.001
Fixed material costs	420	222	<0.001
Disposables	1871 (1164-2902)	533 (241-1178)	<0.001
Other material costs	63 (59-98)	107 (67-173)	<0.001
Personnel costs	1719 (979-2775)	1381 (851-2388)	<0.001
Postoperative	2016 (1080-3600)*	2575 (1414-10470)*	0.001
Hospitalization	1495 (476-2856)	1923 (952-8092)	<0.001
After hospitalization	521 (100-853)	652 (100-1101)	<0.001
Mean calculated productivity losses (days)**	68	75	
Additional productivity losses (working hours)	-	36	
Additional indirect treatment costs (euros)			
Per employed donor	-	1152	
Per donor operated***	-	783	
Return to work (%)			
After 1 week	1 (3%)	0 (0%)	1.00
After 2 weeks	2 (6%)	2 (6%)	1.00
After 4 weeks	3 (9%)	5 (15%)	0.71
After 6 weeks	16 (47%)	12 (35%)	0.46
After 8 weeks	22 (65%)	19 (56%)	0.62
After 10 weeks	27 (79%)	25 (74%)	0.78
After 12 weeks	28 (82%)	28 (82%)	1.00
At day number (range)	55 (6-154)	58 (10-154)	0.42
Activity level (at day)			
Resumption of 90% of daily activities (range)	49 (7-154)	68 (14-154)	0.06
Resumption of 100% of daily activities (range)	66 (7-154)	91 (15-154)	0.01

$ a currency exchange rate of $1.2 per euro was anticipated

* standard deviations for direct treatment costs, intraoperative costs and postoperative costs respectively (LDN and ODN): 667 Euros and 1332 Euros, 695 Euros and 351Euros, 580 Euros and 1349 Euros

** weighted for % full time equivalent

*** 34 out of 50 donors were employed preoperatively. Therefore the additional indirect treatment costs per donor were the additional costs per employed donor multiplied by 34/50.

of less visits to the outpatient clinic on average and the aforementioned re-admission in the ODN group.

Return to work and resumption of daily activities

In Table 2 data are presented on return to work and daily activities. After 55 and 58 days on average donors in the LDN and ODN group respectively returned to work. Remarkably, 18% of the donors in either group had not resumed work by 3 months. The operative approach, gender, nor the relation to the recipient influenced return to work. Donors who performed physically demanding work returned to work later than those who did not have a physically demanding job (67 vs. 45 days, P=0.006). The mean number of days of productivity loss was

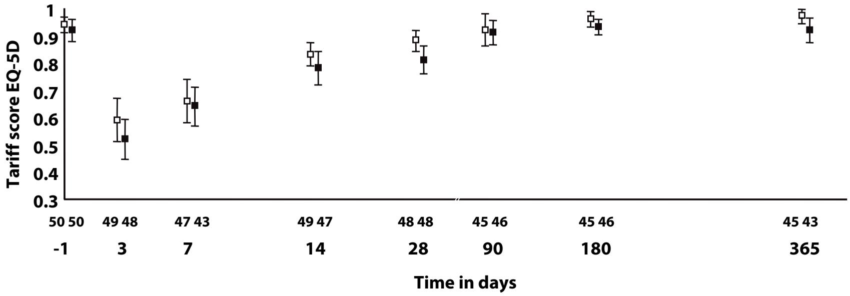


Figure 1. Tariff score of the Euroqol 5-D. Data are non-adjusted and displayed as mean ± 95% CI. Open squares LDN, filled squares ODN. Numbers underneath the x-axis represent the number of replies (left LDN, right ODN). Mean difference during one-year one-follow-up 0.035, P=0.047, 95% CI 0.00 to 0.07.

also calculated. This number is a summary measure for the total number of days lost. On average, productivity losses were 68 days in the LDN group and 75 days in the ODN group. This corresponded with 36 hours of additional lost productivity in the ODN group.

The difference regarding the mean day at which 90% of daily activities other than work were resumed approached statistical significance in favor of LDN. Complete resumption of activities occurred significantly earlier following LDN.

Quality of life (QOL) and Health score

QOL as measured on the Euroqol 5-D is displayed in Figure 1. During one-year follow-up the QOL score or so called Tariff score was significantly higher following LDN (mean difference 0.035, P=0.047, 95% CI 0.00 to 0.07) indicating better QOL. Converted to QALYs, LDN provided an additional 0.03 QALY, mainly generated within the first four weeks. In Figure 2 the results of the 0-100 VAS regarding health are presented. This graph is rather similar to Figure 1. During one-year follow-up the health score has a tendency to be statistically superior following

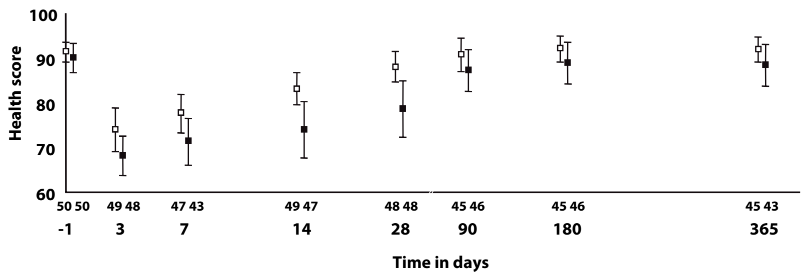


Figure 2. Health score of the 0-100 VAS. Data are non-adjusted and displayed as mean + 95% CI. Open squares LDN, filled squares ODN. Numbers underneath the x-axis represent the number of replies (left LDN, right ODN). Mean difference during one-year follow-up 3.3 in favor of LDN, P=0.054, 95% CI –0.6 to 6.7

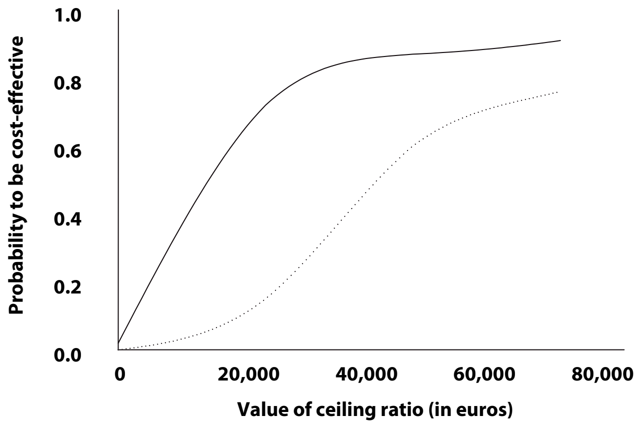


Figure 3. Acceptability curves for Laparoscopic Donor Nephrectomy (LDN) versus Open Donor Nephrectomy (ODN) calculated from a societal perspective (continuous line) and from a health care perspective (interrupted line). The ceiling ratio is the maximum amount of money governmental organizations or insurance companies are willing to pay per QALY. The probability represents the chance that LDN is cost-effective at a certain ceiling ratio. For example, if one is willing to pay up to 40,000 Euros ($48,000) for one QALY, the probability that LDN is cost-effective can be determined by drawing a vertical line that crosses the x-axis at 40,000. The associated probabilities are the crossings between the vertical line and the two plotted lines; the probability that LDN is cost-effective is 0.43 from a health care perspective and 0.85 from a societal perspective.

LDN (mean difference 3.3, P=0.054, 95% CI –0.6 to 6.7) after adjusting for baseline differences, gender and age. Again the main difference is generated within the first four weeks.

Cost-utility analysis

Thirty-six additional working hours were lost per working donor in the ODN group. Thirty-six hours cost 1152 Euros ($1382; Table 2, 36 hours x 80% x 40 Euros or $48 per hour). Therefore, additional productivity losses per donor were 783 Euros ($940) following ODN (34/50 x 1152 Euros or $1382). Bootstrap analysis resulted in a mean gain of 0.03 QALY (95% confidence interval 0.00 to 0.07 QALY) at mean costs of 1271 Euros ($1525; 95% confidence interval 853 Euros to 1690 Euros) and 488 Euros $586; 95% confidence interval 70 Euros to 906 Euros) from a healthcare perspective and a societal perspective respectively. Consequently the mean ICER was 41,278 and 15,844 Euros (about $50,000 and $19,000 respectively) per QALY. Acceptability curves are displayed in Figure 3. Given a societal perspective, there is an 80% probability that the ICER falls in a range [3,000 Euros; 50,000 Euros] or [$3,600; $60,000] per QALY.

DISCUSSION

This is the first paper that addresses cost-effectiveness of laparoscopic versus mini-incision open donor nephrectomy alongside a randomized controlled clinical trial. The collection of data regarding costs was rather detailed and even included depreciation of hardware, homecare and visits to the general practitioner. As reported earlier the majority of costs were generated within the first 24 hours (16). We collected data on return to work prospectively, which is more reliable than telephone interviews at one-year postoperatively as applied by investigators in a prominent previous study (2). Although we did not assess a difference in return to work in general, LDN resulted in less hours of lost productivity. This is in contrast with previous studies in which return to work differed significantly between laparoscopic and conventional open surgery (2, 12). The disappearing difference between (partial) resumption of work may reflect improvement of the open technique. However, LDN rewards both employer and employee, because total productivity losses are lower and the donors experience better health and QOL. As described earlier by Andersen et al. sick leave is much longer in Europe than generally accepted in the Northern America (2, 17, 18). This reflects both the social system in Europe, as well as the attitude towards work. Although we did not advice donors when to resume work, many donors got six weeks off for donation. Return to work contrasts with resumption of non-work related activities. We assume that donors in the laparoscopic group would have been able to start working earlier.

The finding of favorable health scores and QOL in the LDN group is concordant with earlier published data of this trial (3). The Euroqol 5-D is a less sensitive instrument to measure QOL than the SF-36, but is primarily developed to express QOL in QALYs. This explains why the difference in QOL appears smaller than the differences between the groups with regard to the SF-36. The conversion of QOL in QALYs has been debated, but current guidelines in the Netherlands advise quantification of QOL in QALYs (20). The main advantage of this conversion into QALYs is that the gain of a therapy allows comparison to the gain of other therapies (i.e. heart transplantation or dialysis). Rapidly expanding costs of healthcare in Western countries force policy makers to draw decisions whether or not to allow new treatments. Cost-effectiveness may be decisive. The difference of 0.03 QALYs is smaller than the 0.06 QALYs found by Pace et al. (19), which may reflect improvements of the open technique, but confirms the superiority of LDN from the perspective of the donor.

We applied rather conservative methods in the cost-utility analysis. An average salary of 40 Euros ($48) per hour is moderate. Higher salaries would further offset the initial financial disadvantages of LDN. Furthermore, an advisory organ of the Dutch Ministry of Finance recently reported that treatments costing up to 80,000 Euros (about $96,000) per QALY may be acceptable (20). In the United Kingdom the acceptable threshold equals about 50,000 Euros (15). For governmental organizations and policy makers the societal perspective of cost-effectiveness is the most interesting perspective because it offers the most detailed reflection of the treatment effect, including besides plane costs also the savings due to limited productivity losses. Regardless of a threshold chosen at 50,000 or 80,000 Euros, the incremental costs of laparoscopy are most likely justified.

Regardless this conservative perspective, more frequent use of endoscopic equipment, use of re-usable material instead of the disposables and cheaper disposables as well as less productivity losses will make LDN more attractive. Hand-assistance during laparosopy or retroperitoneoscopy may be cost-saving as the operation times may be reduced. However, studies providing a detailed cost-effectiveness analysis of laparoscopic kidney donation with and without hand-assistance are lacking.

In this study some aspects were not investigated. First, we did not combine data of donor and recipient. There has been some concern about slower graft-function of laparoscopically harvested grafts (21). With an increased number of graft-related complications and lower graft survival an initial benefit of LDN would vanish with a significant effect on cost-effectiveness. Current data do not support earlier raised concerns (8). In our own study we found a similar rate of graft-related complications after LDN and ODN and a similar one-year graft survival. We focused on the donation procedure assuming that costs related to the preoperative work-up of the donor and the recipient, preoperative dialysis and transplantation were independent of the costs of the donation procedure. Inclusion of these costs in our analysis would have revealed that the costs of the live donor nephrectomy on its own and the incremental costs of laparoscopy were only a small fraction of the expenses for live kidney donor transplantation. Transplantation is cost saving (22). This would be an argument to implement laparoscopic donor nephrectomy regardless of the value of the ceiling ratio provided that the donor experiences significant benefit and the safety to the recipient is comparable.

Second, we did not include data on the learning curve of LDN. It is well known that it takes several procedures to learn this technique. This probably implies longer operation times, more complications and re-operations at the beginning of the learning curve. The number of significant postoperative complications was very small in the present study. Re-operations for bleeds, perforations or later presenting incisional hernias did not occur. Less experience would probably adversely affect the benefit of LDN and increase its costs. Finally, we did not investigate whether LDN led to more live kidney donors in Europe. Live kidney transplantation is the most cost-efficient treatment of end stage renal disease (22). In a recent survey about half of the surgeons thought that LDN resulted in increased live kidney donation rates and the other half did not (10). If it were true that LDN leads to more donors, LDN would become a true dominant strategy, because the financial benefits realized with more kidney donors easily outweigh slightly higher costs of the operative procedure.

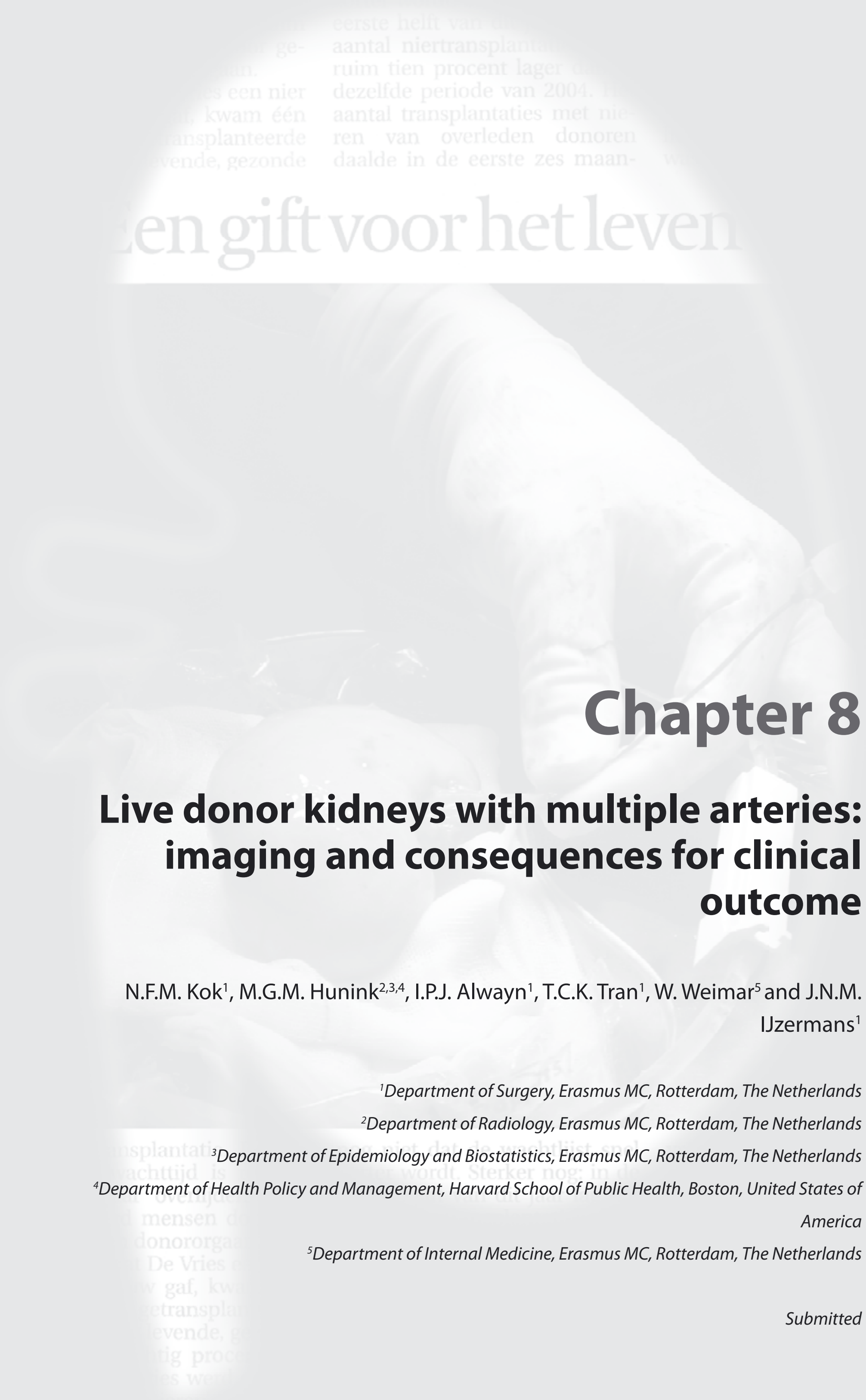
In conclusion, these data confirm the donor-experienced benefit of laparoscopic surgery. Because LDN is also cost-efficient, at least given a societal perspective, LDN has truly become the standard of care for live kidney donation.

ACKNOWLEDGEMENTS

The authors are very grateful to Dr. W. Hop, Msc PhD for statistical advice and Mrs. J. van Duuren-van Pelt for data management.

REFERENCES

1. www.unos.org
2. Andersen MH, Mathisen L, Oyen O et al. Postoperative pain and convalescence in living kidney donors-laparoscopic versus open donor nephrectomy: a randomized study. Am J Transplant 2006;6(6):1438-43.
3. Kok NF, Lind MY, Hansson BM et al. Comparison of laparoscopic and mini incision open donor nephrectomy: single blind, randomised controlled clinical trial. BMJ 2006;333(7561):221.
4. Simforoosh N, Basiri A, Tabibi A, Shakhssalim N, Hosseini Moghaddam SM. Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial. BJU Int 2005;95(6):851-5.
5. Wolf JS, Jr., Merion RM, Leichtman AB et al. Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation 2001;72(2):284-90.
6. Flowers JL, Jacobs S, Cho E et al. Comparison of open and laparoscopic live donor nephrectomy. Ann Surg 1997;226(4):483-9; discussion 489-90.
7. Ratner LE, Kavoussi LR, Sroka M et al. Laparoscopic assisted live donor nephrectomy--a comparison with the open approach. Transplantation 1997;63(2):229-33.
8. Derweesh IH, Goldfarb DA, Abreu SC et al. Laparoscopic live donor nephrectomy has equivalent early and late renal function outcomes compared with open donor nephrectomy. Urology 2005;65(5):862-6.
9. Friedman AL, Peters TG, Jones KW, Boulware LE, Ratner LE. Fatal and Nonfatal Hemorrhagic Complications of Living Kidney Donation. Ann Surg 2006;243(1):126-130.
10. Kok NF, Weimar W, Alwayn IP, IJzermans JN. The current practice of live donor nephrectomy in europe. Transplantation 2006;82(7):892-7.
11. http://www.cvz.nl/resources/handleiding_kostenonderzoek2004_tcm13-10217.pdf. In.
12. Lind MY, Liem YS, Bemelman WA et al. Live donor nephrectomy and return to work: does the operative technique matter? Surg Endosc 2003;17(4):591-5.
13. Brooks R. EuroQol: the current state of play. Health Policy 1996;37(1):53-72.
14. Efron B. Bootstrap Methods: Another look at the jackknife. Ann stat 1979; 7(1) 1-26
15. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35(11):1095-108.
16. Buell JF, Lee L, Martin JE et al. Laparoscopic donor nephrectomy vs. open live donor nephrectomy: a quality of life and functional study. Clin Transplant 2005;19(1):102-9.
17. Kuo PC, Johnson LB, Sitzmann JV. Laparoscopic donor nephrectomy with a 23-hour stay: a new standard for transplantation surgery. Ann Surg 2000;231(5):772-9.
18. Bergman S, Feldman LS, Mayo NE et al. Measuring surgical recovery: the study of laparoscopic live donor nephrectomy. Am J Transplant 2005;5(10):2489-95.
19. Pace KT, Dyer SJ, Phan V et al. Laparoscopic versus open donor nephrectomy. Surg Endosc 2003;17(1):134-42.
20. http://www.rvz.net.nl.
21. Nogueira JM, Cangro CB, Fink JC et al. A comparison of recipient renal outcomes with laparoscopic versus open live donor nephrectomy. Transplantation 1999;67(5):722-8.
22. Mullins CD, Thomas SK, Pradel FG, Bartlett ST. The economic impact of laparoscopic living-donor nephrectomy on kidney transplantation. Transplantation 2003;75(9):1505-12.



Chapter 8

Live donor kidneys with multiple arteries: imaging and consequences for clinical outcome

N.F.M. Kok[1], M.G.M. Hunink[2,3,4], I.P.J. Alwayn[1], T.C.K. Tran[1], W. Weimar[5] and J.N.M. IJzermans[1]

[1]Department of Surgery, Erasmus MC, Rotterdam, The Netherlands

[2]Department of Radiology, Erasmus MC, Rotterdam, The Netherlands

[3]Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, The Netherlands

[4]Department of Health Policy and Management, Harvard School of Public Health, Boston, United States of America

[5]Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

Submitted

ABSTRACT

Live donor kidneys with multiple arteries have been associated with increased complexity for removal and an increased rate of ureteral complications in the recipient. We evaluated the outcome of vascular imaging and the clinical consequences of multiple arteries and veins. From 2001 to 2005 data of 288 live kidney donations and transplantations were prospectively collected. Vascular anatomy at operation was compared to vascular anatomy as imaged by MRI or subtraction angiography and clinical consequences of multiple arteries were investigated.

Simple renal anatomy with a solitary artery and vein was present in 208 (72%) of the kidneys. Sixty (21%) transplants had multiple arteries. Thirty (10%) transplants had multiple veins. MRI failed to predict arterial anatomy in 23 of 220 donors (10%) as compared to 3 of 101 (3%) failures with angiography (P=0.047). For outcomes after both open and laparoscopic donor nephrectomy (ODN and LDN respectively) the presence of multiple veins was inconsequential. Multiple arteries did not affect clinical outcomes in ODN (N=103). In LDN (N=185) multiple arteries were associated with longer operation time (245 vs. 221 minutes (P=0.023) and more blood loss (150 vs. 100 ml, P=0.029) as compared to a single artery. In general, neither multiple arteries nor vascular reconstructions affected recipient creatinine clearance or ureteral complications. However, accessory arteries to the lower pole correlated with an increased rate of ureteral complications (47% vs. 14%, P=0.01). In conclusion, multiple arteries may increase operation time and accessory lower pole arteries are associated with a higher rate of recipient ureteral complications indicating the importance of arterial imaging. Currently, both MRI and angiography provide suboptimal information on renal vascular anatomy.

INTRODUCTION

Minimally invasive donor nephrectomy has become the standard of care for live kidney donation (1-4). Minimally invasive approaches include modified open and laparosopic or retroperitoneoscopic approaches. These approaches have in common that the perception of renal anatomy is compromised as compared to conventional flank incisions due to loss of tactile sensation and/or impeded view. Complex vascular anatomy may influence surgical outcome (5). Therefore, preoperative planning of these operations has become increasingly important.
Live kidney donors are healthy individuals that deserve the least invasive and the least time consuming imaging with the best predictive value. Traditionally, the donor's renal anatomy was assessed by angiography with good results but significant consequences for the donor including radiation and a short stay in the hospital. Magnetic resonance imaging (6, 7) and computed tomography (8-13) have both been reported feasible alternatives. In our hospital angiography was gradually replaced by MRI as this technique does not cause radiation and, in addition, provides information on the venous anatomy (14).
In this study we evaluated the diagnostic performance of our imaging to predict arterial anatomy during a 5-year period. Furthermore, we investigated the consequences of multiple arteries on clinical outcome therewith addressing the potential harm due to vessels missed on preoperative imaging.

PATIENTS AND METHODS

Patients

From January 1st 2001 to December 31st 2005 data of all laparoscopic and mini-incision open live kidney donations and corresponding transplantations were prospectively collected. Two-hundred-eighty-eight donor nephrectomies were performed. During this period three studies were performed after approval by the medical ethics committee. These included a radiological study comparing MRI and digital subtraction angiography (DSA) in an effort to image renal anatomy of live kidney donors, a prospective study addressing laparoscopic versus open donor nephrectomy, and a randomized controlled trial comparing laparoscopic versus open donor nephrectomy. The main outcomes of these studies have been published previously (2, 15, 16). Internal board review was obtained.
All donors were preoperatively screened by a nephrologist and subsequently by a medical psychologist, an anaesthesiologist, and cardiologist if indicated. Imaging consisted of ultrasound and either DSA or MRI except for donors included in the aforementioned radiological study who underwent both DSA and MRI. Obese donors, donors with complicated renovascular anatomy or older donors were not restricted from either surgical technique. Right-sided

kidney donation was not avoided. The results of the aforementioned studies led to the preferential use of MRI and laparoscopic donor nephrectomy since the second half of 2004.

Digital subtraction angiography (DSA) and Magnetic resonance imaging (MRI)

High-quality DSA images were made using a 38-cm field of view and an image matrix of 1,024 x 1,024 pixels (Integris V3000, Philips medical systems). A 4-French catheter was introduced transfemorally and positioned above the renal arteries. First, an aortogram was performed using non-ionic contrast. Subsequently, selective catheterization of all (accessory) renal arteries was performed. Finally, a urogram was obtained 7 minutes after catheterization of the arteries.

A 1.5-T MR scanner (Signa CV/i, GE Healthcare) was used for MR images. Various coronal, sagital and axial sequences with and without contrast (gadopentetate dimeglumine; Magnevist, Schering) were performed to obtain images of the renal arteries, veins and collecting systems. Arterial reconstructions were made allowing a 360° view of the arterial anatomy.

Surgical techniques

The operative technique has been described previously (16). Briefly, in LDN we applied an open technique to access the peritoneal cavity with the first trocar. A 30º-video-endoscope was used. Four additional ports were used on the right-side including a 5mm-trocar in the epigastric region to retract the liver. On the left side three additional ports were created. Ultrasonic scissors (Ultracision, Ethicon, Cincinnati, USA) were used throughout the procedure. A pfannenstiel incision was made at the extraction site. The renal vessels were stapled and the kidney was harvested with an endobag (Endocatch, US surgical, Norwalk, USA). Open donor nephrectomy was carried out using a muscle-splitting approach with an 8 to 15 cm incision (depending on BMI) running from the tip of the eleventh rib towards the umbilicus.

The operation team that operated the live donor reconstructed the renal vessels if necessary and also performed the kidney transplantation.

Data collection and statistical analysis

A radiologist and a transplant surgeon both evaluated the images preoperatively and recorded their data. They discussed difficult cases if necessary. A research fellow attended all procedures to record the data including arterial and venous anatomy, warm ischemia time, time until kidney extraction, operation time and blood loss. The nephrologist prospectively collected postoperative data of the recipients. Follow-up visits at the nephrology and surgery outpatient clinics were scheduled at three weeks, three months and one year postoperatively.

The true vascular anatomy as assessed during the operation and perfusion was considered as gold standard and compared to the vascular anatomy imaged by MRI or DSA. Therefore, sensitivity and specificity were calculated. Then, we analyzed the effect of additional arteries on

clinical outcome, including the effect of misinterpreted accessory arteries. In all recipients a nuclear scan (MAG 3) of the transplant was performed one or two days after surgery. We were especially interested in the consequences of (missed) accessory arteries to the lower pole of the kidney. Previous studies concluded that vascular reconstructions of multiple arteries may lead to an increased rate of ureteral complications (5).
Categorical variables were compared with the Chi square test and continuous variables were compared with the Mann Whitney U test. All analyses were conducted using SPSS (version 11.5, SPSS Inc., Chicago, USA). A P-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Preoperative imaging was performed in 278 of 288 donors in the Erasmus MC. CT or DSA of ten donors was performed elsewhere, including 4 donors participating in the cross-over program of the Dutch transplant centers. Baseline characteristics of the donors are outlined in Table 1.
Based on preoperative findings the right kidney was selected for removal in 156 (54%) donors. In 78% of the donors who underwent right-sided donor nephrectomy significant advantages in anatomy of the right kidney (arterial or venous) as compared to the left kidney, or ipsilateral stenosis of the artery and/or smaller size demanded procurement of the right kidney.

Table 1. Baseline characteristics of donors and recipients. Categorical data are presented as number (percentage). Continuous data are presented as mean (standard deviation).

	Live donors and recipients (N=288)
Donor	
Gender (male; female)	114 (40%)/174 (60%)
Age (years)	50 (14)
Kidney (left; right)	132 (46%)/156 (54%)
ASA Classification (I:II:III)	220 (76%)/66 (23%)/2 (1%)
Body mass index (kg/m^2)	26.2 (4.1)
Preoperative serum creatinine (µmol/l)	73 (13)
Recipient	
Relation (Living related; living unrelated; cross-over or anonymous)	173 (60%)/ 102 (35%)/13 (5%)
Gender (male; female; child)	173 (60%)/111 (39%)/4 (1%)
Age (years)	46 (15)
Preemptive transplantation (yes; no)	66 (23%)/222 (77%)
Preoperative serum creatinine (µmol/l)	793 (315)

Table 2A. The number of renal arteries found at surgery versus the number of arteries as assessed by the MRA. Data presented as number (%).

		Surgery		
		1 artery	**2 arteries**	**> 3 arteries**
MRA	1 artery	166 (75%)	16 (7%)	0 (0%)
	2 arteries	3 (1%)	29 (13%)	4 (2%)
	≥ 3 arteries	0 (0%)	0 (0%)	2 (1%)

Table 2B. The number of renal arteries found at surgery versus the number of arteries as assessed by the DSA. Data presented as number (%).

		Surgery		
		1 artery	**2 arteries**	**> 3 arteries**
DSA	1 artery	85 (84%)	2 (2%)	0 (0%)
	2 arteries	0 (0%)	12 (12%)	1 (1%)
	≥ 3 arteries	0 (0%)	0 (0%)	1 (1%)

To image arterial and venous anatomy 220 MRIs were performed, of which 177 as only diagnostic test and 43 followed by DSA. Thirty of the latter were performed within the MRI vs. DSA study, in which both MRI and DSA were performed. A DSA was advised after 19 of the aforementioned 220 MRIs to rule out stenosis of the artery.

DSA was performed in 101 donors. In 51 donors DSA was the primary diagnostic test, 30 donors participated in the MRI vs. DSA study and 13 additional DSAs were performed to rule out stenosis. In addition, MRI failed in 7 donors because of claustrophobia (n=5) or inability to communicate breath-holding instructions due to a foreign language (n=2).

Comparison of surgical anatomy and preoperatively imaged anatomy

The majority of the transplants had a single artery and a single vein (Figure 1). Three transplants had a single artery and three veins, five transplants had three arteries and a single vein,

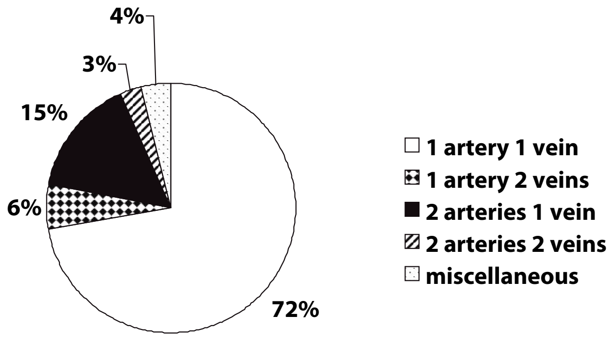


Figure 1. Variation in arterial and venous anatomy.

Table 3. Discordant findings at surgery as compared to preoperative assessment of anatomy by MRI or DSA. Data presented as numbers.

	Live donors (N=288)
MRI	**220**
Only one artery present at surgery (two predicted)	2
Common trunk instead of separate arteries	1
No common trunk but separate arteries	1
Accessory lower pole artery	6
Accessory upper pole artery	9
Accessory middle pole artery	1
Additional renal vein(s)	11
Additional vein after incorrect imaging of the venous phase	2
Additional renal vein and accessory upper pole artery	1
Additional renal vein and accessory lower pole artery	1
MRA with artefacts. Accessory artery missed with MRA but seen preoperatively with additional DSA	1
DSA	**101**
Accessory lower pole artery	1
Accessory upper pole artery	2
Multiple renal veins*	11

*Renal veins are not visible with DSA. However we included this parameter to illustrate how often multiple veins were encountered without preoperative imaging of the venous system.

one transplant had three arteries and two veins and one transplant had four arteries and a single vein.

Twenty-three MRIs (10%) were discordant with regard to arterial anatomy assessed intraoperatively as compared to 3 (3%) DSAs. (Table 2A and B). The sensitivity of MRI and DSA was 0.61 and 0.81 respectively (Table 2A and B). The specificity of MRI and DSA was 0.98 and 1.00 respectively. The positive predictive value was 0.91 and 1.00 respectively. The negative predictive value was 0.89 and 0.97 respectively. Thirteen MRIs (6%) were discordant with regard to venous anatomy. Two other donors presented with multiple veins while the venous phase was imaged with an incorrect protocol allowing no judgment. In 11 donors (11%) with a DSA multiple veins were discovered at surgery. All discordant findings are presented in Table 3. In cases in which DSA and MRI were both performed DSA revealed an additional accessory artery in one donor and doubt about the arterial anatomy in another donor. Accessory arteries were present in both donors.

None of the baseline characteristics had a significant association with arterial discordance. The only factor associated with discordant venous anatomy was side. Right-sided donor nephrectomy was associated with an increased rate of undetected accessory veins as compared to left-sided donor nephrectomy (9% vs. 3%, P=0.038).

Table 4A. Outcomes of procurement of kidneys with single versus multiple arteries by open donor nephrectomy. Categorical data are displayed as No. (%) and continuous variables as mean (SD).

	Single artery (n=84)	Multiple arteries (n=19)	P-value
Warm ischemia time (minutes)	2.9 (1.7)	4.5 (2.3)	0.001
Time until kidney extraction (minutes)	117 (31)	125 (31)	0.409
Skin-to-skin time (minutes)	161 (38)	174 (50)	0.244
Blood loss (ml)	301 (288)	357 (323)	0.949
Intra-operative complications	2 (2%)	2 (10%)	0.097
Postoperative complications	8 (10%)	2 (11%)	0.894

Table 4B. Outcomes of procurement of kidneys with single versus multiple arteries by laparoscopic donor nephrectomy. Categorical data are displayed as No. (%) and continuous variables as mean (SD).

	Single artery (n=47)	Multiple arteries (n=138)	P-value
Warm ischemia time (minutes)	6.0 (2.8)	7.3 (3.1)	0.009
Time until kidney extraction (minutes)	182 (48)	204 (55)	0.023
Skin-to-skin time (minutes)	225 (51)	247 (57)	0.023
Blood loss (ml)	220 (456)	225 (204)	0.029
Intra-operative complications	22 (16%)	7 (15%)	0.864
Postoperative complications	11 (8%)	6 (13%)	0.326

Consequences of multiple arteries

Intra-operatively, 66 kidneys had more than one artery including 6 right kidneys with earlier branching than expected preoperatively. These six cases were not classified as discordant cases, because at preoperative imaging the renal artery clearly did not branch in the renal hilum. Fifteen accessory arteries ran to the lower pole of the kidney.

In ODN warm ischemia time was significantly shorter in the single artery group. Other parameters did not significantly differ between a single artery and multiple arteries (Table 4A). In LDN, multiple arteries resulted in significantly longer warm ischemia and operation times and increased blood loss (Table 4B). Multiple arteries in general did not lead to an increased rate of ureteral complications or higher postoperative recipient serum creatinine values (Table 5).

Nine smaller accessory arteries to the upper pole, one artery to the middle pole and one capsular artery were ligated. Postoperative nuclear imaging (MAG 3) showed a defect that was smaller than 10% of the nephron mass in two transplants only. The other postoperative scans did not reveal loss of renal parenchyma at all, implying that sacrificing these branches was inconsequential. Arterial reconstruction after harvest of the transplant was performed in 40 cases (61%). Two or more arterial anastamoses were created in 15 transplants.

Arterial reconstructions were not associated with ureteral complications. Accesory arteries to the lower pole however resulted significantly more often in ureteral complications (47% vs.

Table 5. Graft outcome. Categorical data are displayed as No. (%) and continuous variables as mean (SD).

	Single artery (n=222)	Multiple arteries (n=66)	P-value
Second warm ischemia time (minutes)	29 (16)	32 (12)	0.008
Urine production within one hour of reperfusion	201 (91%)	61 (92%)	0.639
Ureteral complications	30 (14%)	14 (21%)	0.127
Ureteral complications leading to reoperation	11 (5%)	7 (11%)	0.096
Acute rejection	48 (22%)	16 (24%)	0.653
Recipient serum creatinine at postoperative day 1(μmol/l)	408 (223)	462 (268)	0.201
Recipient serum creatinine at postoperative day 2 (μmol/l)	224 (164)	291 (247)	0.120
Recipient serum creatinine at postoperative day 7 (μmol/l)	183 (145)	246 (224)	0.101
Recipient serum creatinine at postoperative month 1(μmol/l)	137 (74)	156 (118)	0.156
Recipient serum creatinine at postoperative year 1 (μmol/l)	128 (48)	124 (38)	0.630

14% in the donors with multiple arteries but without an accessory artery to the lower pole, P=0.011) and ureteral reconstructions (27% vs. 6%, P=0.042).

Consequences of arteries undetected at imaging

Three non-detected accessory arteries were ligated during kidney donation, one because of the small caliber (upper pole), one because of bleeding (lower pole) and one because it was not recognized at operation but at cold perfusion (lower pole). Discordant arterial anatomy did not adversely affect clinical outcomes of either ODN or LDN including complications, blood loss, operation time and ureteral complications in the recipient.

Consequences of multiple veins

Seven donors (7%) who underwent ODN and 23 donors (12%) who underwent LDN had multiple renal veins. Neither in open surgery, nor in laparoscopic surgery multiple veins were associated with adverse outcomes during and after donor surgery or worse graft outcomes in the recipient. Undetected renal veins were inconsequential in terms of blood loss, complications and prolonged operation time.

DISCUSSION

This study presents a detailed analysis of prospectively collected data on imaging renal anatomy and subsequent surgical complications at one of the largest European transplant centers with regard to live kidney donor transplantations during a five year period. We recently advocated laparoscopic kidney donation as the technique of choice (2). In the current study multiple arteries were associated with prolonged operation time and warm ischemia time and increased blood loss in laparoscopic donor nephrectomy. However, despite a statistically significant association the clinical impact is limited. Our data confirm the feasibility of laparoscopic kidney donation in donors with multiple arteries as demonstrated by others (5, 17-20). We add that arterial reconstructions do not necessarily result in detriment to the graft. However, lower pole accessory arteries often result in ureteral complications probably because of an impaired ureteral blood flow.

As opposed to other radiological studies that focused on the accuracy of imaging we were more interested in the consequences for daily practice. Therefore the clinician and the radiologist both evaluated the radiological images and both MRI and DSA were included, because sometimes it was easier and faster to plan DSA and sometimes the other way around. The first step of imaging in potential live kidney donors is excluding disorders in the renal parenchyma and stenosis. The second step is planning the operation including which kidney best to harvest and what vascular anatomy to expect. The third step is quality control by comparing findings at surgery with the images. We focused on the latter aspects as MRI has already proven its value in detecting parenchymal abnormalities(15). Observation during the operation, in particular during cold perfusion after nephrectomy, was considered the gold standard. Therefore we did not include data of DSAs and MRIs of the contralateral side remaining in the donor.

Because we know from our daily practice that the anatomy of branches of the renal vein including the gonadal vein, the adrenal vein and lumbar branches is highly variable and sometimes poorly visualized by our MRI scan, we did not attempt to incorporate these data. We acknowledge that these branches may be better visualized with CT (21). The highly variable presence of these vessels always requires attention of the surgeon during donor nephrectomy. Although these branches can cause significant trouble including bleeds and difficulties to position the vascular endostapler, they do not affect postoperative transplant function. In right-sided kidney donation preoperative assessment of these branches may be helpful as these are usually absent. The same holds for accessory renal veins; these can be troublesome but can usually be sacrificed without any further consequence. Therefore, imaging should be primarily directed at detection of parenchymal abnormalities, arterial stenosis and accessory arteries.

MRI appeared less accurate in predicting arterial anatomy than DSA failing in ten percent and three percent respectively. Although an important number of right kidneys was harvested the percentage of discordant findings related to arterial anatomy was not different from the 12% assessed by Ames et al (6). They reported an increased rate of arterial discordance in right kidney donation. Of all discordant arterial findings 78 per cent is possibly visible on the images on review stressing the necessity of special attention while and experience in observing these images.

The presence of multiple veins remained undetected in about 11% of the donors if DSA was the sole imaging modality of the renal vessels, which is concordant with previous studies (22). In our series the number of discordant scans was comparable to percentages in the current literature on imaging renal anatomy by either CT or MRI with rates of discordant scans ranging from 2 to 14 percent (6-13). Interpretation of the accuracy in all these studies includes realizing that a single artery and single vein is present in the vast majority of cases, which influences the predictive value of any diagnostic tool.

Although discordant findings do not necessarily result in worse outcomes, it is clear that preoperative imaging of the donor can be improved. This could be accomplished by improved communication between radiologist and clinician (12), tailored use of current techniques and further development of both MRI and CT. With regard to the second aspect we would like to draw attention to the 26 donors in our series that needed an additional DSA to rule out stenosis, because of claustrophobia or inability to comprehend breath-holding instructions. The sensitivity of CT to rule out stenosis may be higher as compared to the sensitivity of MRI. However, in hypertensive patients both modalities are inadequate to rule out stenosis (23). Perhaps, hypertensive donors should undergo DSA primarily. The motion artefacts of the current MRI imply that donors who do not understand instructions should be primarily imaged with CT or DSA. We acknowledge the increased risk of radiation, contrast allergy and contrast nephropathy if CT is used. Therefore we would suggest to image younger individuals in the fertile age using MRI. In older individuals the adverse effects of ionizing radiation are relatively less hazardous. Currently a single 'one-stop shop' modality for preoperative evaluation of potential live kidney donors simply does not exist. Future developments including stronger magnetic fields of MRI scans and more detailed CT scans will undoubtedly improve imaging of the live donor and change the spectrum of imaging.

In conclusion, we have shown the drawbacks and consequences of current preoperative imaging of live kidney donors. Preoperative assessment of accessory arteries running to the lower pole is crucial. At present no single imaging modality is universally applicable. Tailored imaging and cooperation between radiologists and clinicians may improve outcomes.

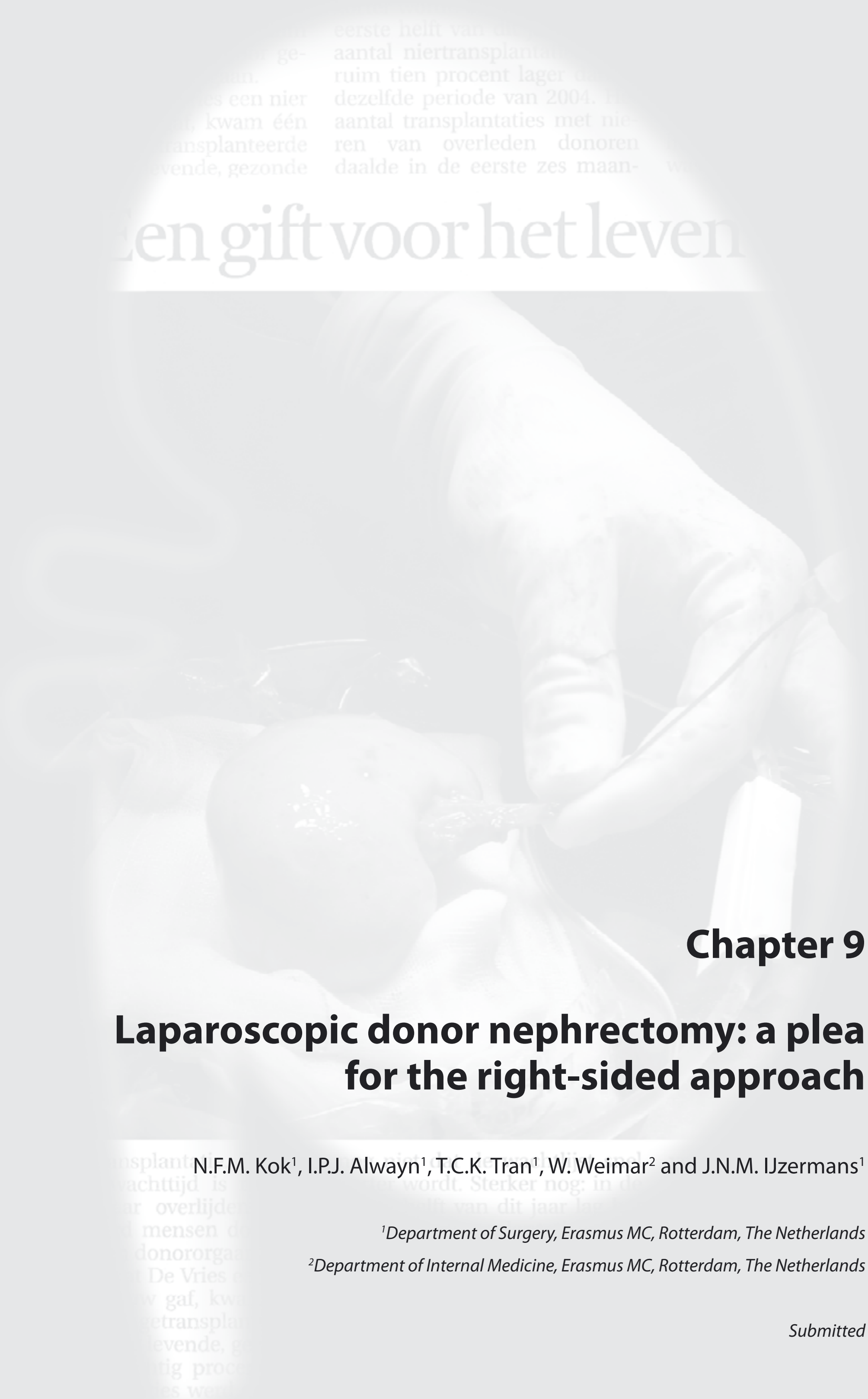
ACKNOWLEDGEMENTS

Niels F.M. Kok was financially supported by the Dutch Kidney Foundation. The authors thank Mrs. J. van Duuren, datamanager, for her contributions to this study.

REFERENCES

1. Andersen MH, Mathisen L, Oyen O, et al. Postoperative pain and convalescence in living kidney donors-laparoscopic versus open donor nephrectomy: a randomized study. Am J Transplant 2006; 6 (6): 1438-43.
2. Kok NF, Lind MY, Hansson BM, et al. Comparison of laparoscopic and mini incision open donor nephrectomy: single blind, randomised controlled clinical trial. BMJ 2006; 333 (7561): 221.
3. Simforoosh N, Basiri A, Tabibi A, Shakhssalim N, Hosseini Moghaddam SM. Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial. BJU Int 2005; 95 (6): 851-5.
4. Wolf JS, Jr., Merion RM, Leichtman AB, et al. Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation 2001; 72 (2): 284-90.
5. Carter JT, Freise CE, McTaggart RA, et al. Laparoscopic procurement of kidneys with multiple renal arteries is associated with increased ureteral complications in the recipient. Am J Transplant 2005; 5 (6): 1312-8.
6. Ames SA, Krol M, Nettar K, et al. Pre-donation assessment of kidneys by magnetic resonance angiography and venography: accuracy and impact on outcomes. Am J Transplant 2005; 5 (6): 1518-28.
7. Hodgson DJ, Jan W, Rankin S, Koffman G, Khan MS. Magnetic resonance renal angiography and venography: an analysis of 111 consecutive scans before donor nephrectomy. BJU Int 2006; 97 (3): 584-6.
8. El Fettouh HA, Herts BR, Nimeh T, et al. Prospective comparison of 3-dimensional volume rendered computerized tomography and conventional renal arteriography for surgical planning in patients undergoing laparoscopic donor nephrectomy. J Urol 2003; 170 (1): 57-60.
9. el-Diasty TA, Shokeir AA, el-Ghar ME, Gad HM, Refaie AF, el-Din AB. Contrast enhanced spiral computerized tomography in live kidney donors: a single session for anatomical and functional assessment. J Urol 2004; 171 (1): 31-4.
10. Feifer AH, Fong BC, Feldman L, et al. Preoperative evaluation of laparoscopic living renal donors with computerized tomography and its effect on donor morbidity and graft function. Can J Urol 2005; 12 (3): 2713-21.
11. Janoff DM, Davol P, Hazzard J, Lemmers MJ, Paduch DA, Barry JM. Computerized tomography with 3-dimensional reconstruction for the evaluation of renal size and arterial anatomy in the living kidney donor. J Urol 2004; 171 (1): 27-30.
12. Johnson JE, Loveday EJ, Archer LJ, Lear P, Thornton MJ. Preoperative evaluation of live renal donors using multislice CT angiography. Clin Radiol 2005; 60 (7): 771-77.
13. Sahani DV, Rastogi N, Greenfield AC, et al. Multi-detector row CT in evaluation of 94 living renal donors by readers with varied experience. Radiology 2005; 235 (3): 905-10.
14. Hussain SM, Kock MC, IJzermans JN, Pattynama PM, Hunink MG, Krestin GP. MR imaging: a "one-stop shop" modality for preoperative evaluation of potential living kidney donors. Radiographics 2003; 23 (2): 505-20.
15. Kock MC, IJzermans JN, Visser K, et al. Contrast-enhanced MR angiography and digital subtraction angiography in living renal donors: diagnostic agreement, impact on decision making, and costs. AJR Am J Roentgenol 2005; 185 (2): 448-56.
16. Kok NF, Alwayn IP, Lind MY, Tran KT, Weimar W, IJzermans JN. Donor nephrectomy: mini-incision muscle-splitting open approach versus laparoscopy. Transplantation 2006; 81 (6): 881-87.
17. Oh HK, Hawasli A, Cousins G. Management of renal allografts with multiple renal arteries resulting from laparoscopic living donor nephrectomy. Clin Transplant 2003; 17 (4): 353-7.
18. Husted TL, Hanaway MJ, Thomas MJ, Woodle ES, Buell JF. Laparoscopic living donor nephrectomy for kidneys with multiple arteries. Transplant Proc 2005; 37 (2): 629-30.
19. Kuo PC, Cho ES, Flowers JL, Jacobs S, Bartlett ST, Johnson LB. Laparoscopic living donor nephrectomy and multiple renal arteries. Am J Surg 1998; 176 (6): 559-63.
20. Troppmann C, Wiesmann K, McVicar JP, Wolfe BM, Perez RV. Increased transplantation of kidneys with multiple renal arteries in the laparoscopic live donor nephrectomy era: surgical technique and surgical and nonsurgical donor and recipient outcomes. Arch Surg 2001; 136 (8): 897-907.
21. Schlunt LB, Harper JD, Broome DR, et al. Multidetector computerized tomography angiography to predict lumbar venous anatomy before donor nephrectomy. J Urol 2006; 176 (6 Pt 1): 2576-81.

22. Giessing M, Kroencke TJ, Taupitz M, et al. Gadolinium-enhanced three-dimensional magnetic resonance angiography versus conventional digital subtraction angiography: which modality is superior in evaluating living kidney donors? Transplantation 2003; 76 (6): 1000-2.
23. Vasbinder GB, Nelemans PJ, Kessels AG, et al. Accuracy of computed tomographic angiography and magnetic resonance angiography for diagnosing renal artery stenosis. Ann Intern Med 2004; 141 (9): 674-82.



Chapter 9

Laparoscopic donor nephrectomy: a plea for the right-sided approach

N.F.M. Kok[1], I.P.J. Alwayn[1], T.C.K. Tran[1], W. Weimar[2] and J.N.M. IJzermans[1]

[1]Department of Surgery, Erasmus MC, Rotterdam, The Netherlands

[2]Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

Submitted

ABSTRACT

Laparoscopic donor nephrectomy (LDN) has become the preferred procedure for live donor nephrectomy. Most transplant surgeons are reluctant towards right-sided LDN (R-LDN) fearing short vessels and renal vein thrombosis. In the last five years our decision to procure either kidney was similar to conventional decision-making for open donor nephrectomy. All intra- and postoperative data were prospectively recorded. Ninety-four R-LDNs (53 per cent) and 83 left-sided LDNs (L-LDN, 47 per cent) were performed. Baseline characteristics were not significantly different. Side-related complications occurred in one versus 14 procedures (R-LDN vs. L-LDN, $P<0.001$) resulting in 0 and 5 conversions respectively. R-LDN was associated with shorter operation time (mean 208 vs. 257 minutes, $P<0.001$) and less blood loss (132 vs. 340 ml, $P<0.001$). Hospital stay was similar in both groups (3 days). With regard to the recipients, the second warm ischemia time was similar (29 vs. 28 minutes, $P=0.587$). Renal vein thrombosis occurred in one recipient of a left kidney. In conclusion, R-LDN is faster and safer than L-LDN and does not adversely effect graft function. R-LDN may be advocated to allow donors to benefit from the advantages of laparoscopic surgery.

INTRODUCTION

Laparoscopic donor nephrectomy (LDN) has increasingly gained popularity since its introduction by Ratner in 1995 (1). Although the techniques for open donor nephrectomy changed concurrently, evidence has mounted that LDN either with or without hand-assistance is the preferred technique (2). As compared to mini-incision open donor nephrectomy LDN results in faster recovery and superior quality of life (3,4). However, an important number of live donor kidneys is still procured using an open approach. Approximately one third of the American surgeons involved in donor nephrectomy is trained in open donor nephrectomy only (5). Approximately eighty per cent of 92 polled centers in Northern and Western Europe still performed open donor nephrectomy in 2004 (6).

Right-sided LDN (R-LDN) has been associated with short vessel lengths and renal vein thrombosis in the recipient (7). For this reason, many centers refrain from laparoscopically procuring right kidneys for transplantation even if multiple arteries are present on the left side (6). The vascular anatomy of left-sided kidneys is more complicated and transplants with multiple arteries may lead to more ureteral complications (8). Furthermore when the left kidney is unsuitable for donation or subsequent transplantation, an open technique is often chosen to procure the right kidney.

We have reported the feasibility of R-LDN previously (9). Other centers affirmed the conclusions (8,10). The aim of this study was to further investigate the role R-LDN in live kidney donation. In absence of contra-indications for right-kidney donation R-LDN was chosen. We compared R-LDN to left-sided LDN (L-LDN).

METHODS

Study population and data collection

In this study we included all donors who underwent LDN at our centre between May 2001 and January 2006. In this time we had a prospective study and a prospective randomized trial running at our hospital to determine whether LDN was to be preferred over mini-incision open donor nephrectomy (4,11). Upon completion of these studies we offered all donors LDN. A nephrologist screened all donors preoperatively. Renal anatomy was imaged using either digital subtraction angiography or magnetic resonance angiography (MRA). Obese donors, older donors and donors with multiple arteries on both sides were not restricted from LDN.

A research fellow collected all intra-operative data on location. Postoperative data at the ward and during follow-up were also prospectively recorded. Visits to the outpatient surgical clinic were scheduled three weeks and two months following donor nephrectomy.

The Institutional Review Board of the Erasmus MC approved this study.

Decision-making

The decision to perform R-LDN or L-LDN was prospectively recorded. If imaging revealed unilateral anatomical abnormalities i.e. ipsilateral arterial stenosis that side was chosen. If there was an obvious difference in size the smallest kidney was harvested. If possible the kidney with simplest vascular anatomy was removed i.e. we reviewed the number of renal arteries and the possibility of early branching. In case of a unilateral duplicated ureteral system the kidney with a single ureter was removed. If arterial and ureteral anatomy were similar, we tried to avoid venous anomalies including retro-aortic veins and circum-aortic veins. Finally, if none of the previous examinations revealed any difference, we usually selected the right kidney since branches (gonadal, adrenal and lumbal veins) to the right renal vein are uncommon (7).

Surgery

Since 1997 LDN has been performed at our institute without hand-assistance. We started with L-LDN. After five cases the first R-LDN was performed because of multiple arteries on the left. Before the present study was initiated 100 LDNs had been performed with approximately 30% L-LDNs. The operative technique has been described previously (11). Briefly, we applied an open technique to access the peritoneal cavity with the first trocar. A 30º-video-endoscope was used.

Four additional ports were used on the right-side including a 5mm-trocar in the epigastric region to retract the liver. On the left side three additional ports were created. Ultrasonic scissors (Ultracision, Ethicon, Cincinnati, USA) were used throughout the procedure. A pfannenstiel incision was made as extraction site. The renal vessels were stapled en the kidney was harvested with an endobag (Endocatch, US surgical, Norwalk, USA).

The operation team that operated the live donor reconstructed the renal vessels if necessary and also performed the kidney transplantation.

Statistical analysis

Categorical variables were compared with the Chi square test, continuous variables were compared with the Mann Whitney U test. All analyses were conducted using SPSS (version 11.5, SPSS Inc., Chicago, USA). A P-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Kidney selection (Table 1)

Ninety-four R-LDNs and 83 L-LDNs were performed. In accordance to our protocol the right kidney was removed in 42 donors. There were no reasons to favor one of the kidneys in 52

Table 1. Reasons to choose either the right or the left kidney for removal. Data are presented as number (percent).

R-LDN (n=94)	Number (%)
Fibromuscular dysplasia right artery	2 (2%)
Stenosis right artery	5 (5%)
Multiple arteries and retrocaval vein on the left side	2 (2%)
Multiple arteries on the left side	18 (19%)
Very early branching left artery	2 (2%)
Double ureteral system on the left side	2 (2%)
Multiple veins on the left	3 (3%)
Retro-aortic vein on the left side	3 (3%)
Circumaortic vein on the left side	2 (2%)
Miscellaneous	3 (3%)
Facultative	52 (55%)
L-LDN (n=83)	**Number (%)**
Stenosis left artery	7 (8%)
Multiple arteries on the right side	32 (39%)
Branching right artery behind vena cava	28 (34%)
Double ureteral system on the right side	2 (2%)
Multiple veins on the right side	10 (12%)
Desire for maximum vessel length	2 (2%)
Miscellaneous	2 (2%)

donors. In these donors the right kidney was selected. Miscellaneous reasons to remove the right kidney included one donor with a previous history of renal stones in the right kidney, one donor with a cyst at the outer border of the left kidney and a significantly smaller right kidney in one donor. Miscellaneous reasons to select the left kidney included cortical tissue loss in one donor and early branching of the right renal vein in another donor.

Demography (Table 2)

Baseline characteristics between donors of right and left kidneys were not significantly different. Baseline characteristics between recipients of kidneys procured on the left side or the right side were not different either.

Intra-operative outcomes (Table 3)

The complication rate was lower for R-LDN. Complications in this group included two serosal lesions of the colon, sutured laparoscopically, a small bowel perforation and a bladder lesion. Only one serosal injury occurred during mobilization of the right kidney and was caused by a thermal injury to the right hemicolon.

Fourteen of sixteen complications on the left side were site-specific and included 7 bleeds (blood loss 425 ml, 600 ml, 860 ml, 2000 ml, 2300 ml, 2700 ml, and 3500 ml, six times from the

Table 2. Baseline characteristics of R-LDN vs. L-LDN. Categorical data are presented as number (percent). Continuous data are presented as mean (SD).

	Right (N=94)	Left (N=83)	*P-value*
Donor			
Male Gender	38 (40%)	40 (48%)	0.363
Age (years)	48 (16)	47 (17)	0.973
ASA Classification>1	21 (22%)	17 (21%)	0.855
Body mass index (kg/m^2)	26.3 (4.1)	25.4 (3.8)	0.239
>1 Renal Artery	26 (28%)	18 (22%)	0.388
>1 Renal Vein	15 (16%)	9 (11%)	0.382
Recipient			
Male Gender	61 (65%)	51 (61%)	0.643
Age (years)	46 (17)	44 (17)	0.341
Pre-emptive transplantation	27 (29%)	19 (23%)	0.396

Table 3. Intra-operative outcomes of R-LDN vs. L-LDN. Categorical data are presented as number (percent). Continuous data are presented as mean (SD).

	Right (N=94)	Left (N=83)	P-value
Complications	4 (4%)	16 (19%)	0.002
Complications related to side	1 (1%)	14 (17%)	<0.001
Conversion to open	-	10 (12%)	<0.001
Conversions related to side	-	5 (6%)	0.021
First warm ischemia time (minutes)	5.7 (2.1)	6.7 (3.4)	0.099
Time until kidney removal (minutes)	166 (45)	213 (49)	<0.001
Operation time (minutes)	208 (46)	257 (51)	<0.001
Blood loss (ml)	132 (152)	340 (575)	<0.001
Second warm ischemia time (minutes)	28 (10)	29 (12)	0.587

renal vein or its tributaries and once from peri-aortic lymph nodes). Five superficial splenic injuries and one splenic haematoma were treated conservatively. In one donor procedure an accessory lower pole artery was unintentionally cut. No impact on the graft function in the recipient was noted. Five conversions were necessary to treat complications that occurred during the donor procedure. Five other L-LDNs were converted because of massive adhesions, lack of an adequate view due to abundant adipose tissue (n=3) and firm attachments of the splenic flexure. In nine of ten conversions the kidney was extracted by a muscle-splitting incision. An emergent conversion was performed in one donor only. Complications on the left side without a relation to the kidney chosen were a haematoma of the renal capsule and a serosal lesion of the small bowel. Operation time and blood loss were favorable in R-LDN. Warm ischemia time was comparable between groups.

Postoperative outcomes (Table 4)

Return to diet, morphine requirement, post-operative complication rate and hospital stay did not significantly differ between groups. Complications after R-LDN included one major complication; the small bowel perforation described previously was undetected until two days after donor nephrectomy and required a subumbilical midline laparotomy. Minor complications included migraine (n=1), postoperative fever (n=2), wound infections treated with oral antibiotics (n=2) and a small pneumothorax which was not treated at all.

Major complications following L-LDN included re-laparoscopy (presumed continuous bleeding), re-laparotomy (splenectomy after iatrogenous splenic injury), re-admission to intravenously treat a wound infection, which was followed by an exploration of the lumbotomy wound (no hernia) several months later, and two incisional hernias requiring laparoscopic correction. Minor complications included one pneumonia and two wound infections all treated with oral antibiotics. One donor had temporarily sensibility loss of the lateral skin of the thigh. Three received a blood transfusion.

One recipient of a left kidney may have suffered from renal vein thrombosis. He lost his graft on the first day for an unclear reason. Renal vein thrombosis did not occur in recipients of right kidneys. One recipient of a right kidney developed renal artery thrombosis and lost the graft at the first postoperative day due to what turned out to be a factor V Leiden clotting disorder. Other outcomes of the recipients were similar (Table 4). Most kidneys in either group immediately functioned after reperfusion. Glomerular filtration rates of recipients of right versus left kidneys did not differ (data not shown). During follow-up (range 5 months

Table 4. Postoperative outcomes of R-LDN vs. L-LDN. Categorical data are presented as number (percent). Continuous data are presented as mean (SD).

	Right (N=94)	Left (N=83)	P-value
Donor			
Return to regular diet (hours)	27 (16)	24 (15)	0.554
Morphine requirement (mg)			
First 24 hours	17 (13)	21 (24)	0.887
In total	20 (18)	24 (28)	0.861
Complications	7 (7%)	12 (14%)	0.151
Minor complications	6 (6%))	7 (8%)	
Major complications	1 (1%	5 (6%)	
Postoperative hospital stay (days)	3.3 (1.2)	3.5 (1.5)	0.324
Recipient			
Immediate urine production	88 (94%)	77 (93%)	1.000
Ureteral complications	15 (16%)	10 (12%)	0.521
Re-operation due to ureteral complications	4 (4%)	6 (7%)	0.519
Lymfocele	3 (4%)	6 (7%)	0.519
Venous thrombosis	-	1 (1%)	-
Acute Rejection	13 (14%)	17 (21%)	0.316

to 5 years) six recipients died in the R-LDN group and three in the L-LDN group. Causes of death in recipients in the R-LDN group were myocardial infarction (n=4), varicella zoster virus infection and sclerosing peritonitis. Causes of death in recipients in the L-LDN group were untreatable urosepsis (n=2) and cerebral lymphoma. In addition to the aforementioned losses due to thrombosis, 4 grafts were lost. One graft was lost in the R-LDN group due to chronic allograft nephropathy. In the L-LDN group three transplants were lost due to a spreading gynaecological infection, chronic allograft nephropathy, and reactivation of the hemolytical uremic syndrome.

DISCUSSION

R-LDN should be implemented in live kidney donation programs to offer all donors the benefits from LDN and to procure optimal grafts. Moreover, we believe that right-sided laparoscopic donor nephrectomy may be advocated. In three out of four recent randomized trials addressing laparoscopic versus open live kidney donation, LDN was restricted to left kidneys with a single artery (3,12,13). Our data show that selection of the right kidney was inevitable in eight donors due to a certain degree of stenosis of the renal artery at the right side. Furthermore, 20 right kidneys with single arteries could be procured instead of left kidneys with multiple-arteries. This facilitated both the nephrectomy and the implantation and may have avoided ureteral complications (14).

It is not surprising that R-LDN is faster and safer. The anatomic position, which is more caudal in the abdomen, and the overlying right flexure of the colon which is easier mobilised than the left flexure attribute to shorter operation times for R-LDN. The venous anatomy is more simple at the right side where there is no need to dissect branches of the renal vein. The liver, which is easily retracted from the surgical site and, as opposed to the spleen on the left side, is unlikely to cause bleeds. Dissection of the right artery and vein is further away from the peri-aortic lymph nodes and vessels.

Two common reasons influence many surgeons not to perform R-LDN. First, a positive association of laparoscopically procured right kidneys and renal vein thrombosis has been reported (7). However, the absolute number of renal vein thrombosis has been very low and did not allow firm inferences. Data may be biased by selection of right kidneys. Most transplant centers have started with L-LDN and R-LDN is often performed as an exception only. In various reports by high volume centers the percentage of right kidneys procured is lower than 5% (15-17). Second, in many centers a laparoscopic surgeon performs the nephrectomy and another surgeon transplants the kidney. The second surgeon (i.e. the transplant surgeon) has to be satisfied with vessel lengths and vessel quality. In our experience shorter and presumed weaker right renal veins do never cause problems during implantation. We believe that the prejudices of transplant surgeons against the short vessels of R-LDN are a more likely reason that the laparoscopic procurement of right kidneys is limited, rather than incidental thrombosis.

Absence of right renal vein thrombosis in the current study rebuts the issue of higher rates of renal vein thrombosis. In addition, despite inevitable shorter renal vein lengths (10), right kidney procurement did not result in more difficult transplantation or worse initial graft function.

The intra-operative complication and conversion rates for L-LDN in our study appear notably high. The prospective registration with a research fellow recording all events in the operation room certainly attributes to these relatively high rates. Retrospective single-center reports mainly performed L-LDN and report low conversion rates and low intra-operative complication rates (15-17). We would like to stress that most reported complications required brief, conservative treatment only and are likely to be underscored in retrospective studies. Safety of the donor and the graft is of utmost importance during live donor nephrectomy. As a result, in our opinion it is necessary to document any adverse event lengthening operation time or hospital stay or causing potential danger to donor or graft. We realize that this approach may sometimes blur the true detriment a kidney donor may have from some reported complications (i.e. a small splenic injury without any consequence). Furthermore, good results with mini-incision open donor nephrectomy at our center have led to a low threshold for elective conversion to a muscle splitting open approach when nephrectomy appears not easy (11).

Ideally, a randomized trial would assess the superiority of R-LDN over L-LDN. However, as indicated there is a good reason to procure one of the kidneys in approximately 70% of the donors. The remainder could be randomized, but accrual of participants would be slow. This is the first report that includes a relatively high number of R-LDNs. To avoid the learning curve of LDN as a potential confounder in this study (L-LDN was learned first in our institute), we decided to test the selection protocol only after enough experience had been gained with both techniques.

We have previously reported the feasibility of R-LDN and also showed good results, at least partly because of the later introduction of R-LDN (8). Many American and European centers still prefer not to perform R-LDN (4). As our data do not only indicate the feasibility but also show the superiority of R-LDN, the current study may remove prejudices against laparoscopic procurement of right kidneys. Adopting R-LDN is for the benefit of the surgeon, the donor and the recipient.

REFERENCES

1. Ratner LE, Ciseck LJ, Moore RG, Cigarroa FG, Kaufman HS, Kavoussi LR. Laparoscopic live donor nephrectomy. Transplantation 1995; 60(9):1047-1049.
2. Tooher RL, Rao MM, Scott DF, et al. A systematic review of laparoscopic live-donor nephrectomy. Transplantation 2004; 78(3):404-414.
3. Andersen MH, Mathisen L, Oyen O, Edwin B et al. Postoperative pain and convalescence in living kidney donors-laparoscopic versus open donor nephrectomy: a randomized study. Am J Transplant 2006; 6(6):1438-1443.
4. Kok NF, Lind MY, Hansson BM, et al. Comparison of laparoscopic and mini incision open donor nephrectomy: single blind, randomised controlled clinical trial. BMJ 2006; 333(7561):221.
5. Friedman AL, Peters TG, Jones KW, Boulware LE, Ratner LE. Fatal and Nonfatal Hemorrhagic Complications of Living Kidney Donation. Ann Surg 2006; 243(1):126-130.
6. Kok NF, Weimar W, Alwayn IP, IJzermans JN. The current practice of live donor nephrectomy in Europe. Transplantation 2006;82(7):892-897.
7. Mandal AK, Cohen C, Montgomery RA, Kavoussi LR, Ratner LE. Should the indications for laparascopic live donor nephrectomy of the right kidney be the same as for the open procedure? Anomalous left renal vasculature is not a contraindication to laparoscopic left donor nephrectomy. Transplantation 2001; 71(5):660-664.
8. Lind MY, Hazebroek EJ, Hop WC, Weimar W, Jaap Bonjer H, IJzermans JN. Right-sided laparoscopic live-donor nephrectomy: is reluctance still justified? Transplantation 2002; 74(7):1045-1048.
9. Posselt AM, Mahanty H, Kang SM, et al. Laparoscopic right donor nephrectomy: a large single-center experience. Transplantation 2004; 78(11):1665-1669.
10. Kay MD, Brook N, Kaushik M, Harper SJ, Bagul A, Nicholson ML. Comparison of right and left laparoscopic live donor nephrectomy. BJU Int 2006;98: 843-844.
11. Kok NF, Alwayn IP, Lind MY, Tran TC, Weimar W, IJzermans JN. Donor nephrectomy: mini-incision muscle-splitting open approach versus laparoscopy. Transplantation 2006; 81(6):881-887.
12. Simforoosh N, Basiri A, Tabibi A, Shakhssalim N, Hosseini Moghaddam SM. Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial. BJU Int 2005; 95(6):851-855.
13. Wolf JS, Jr., Merion RM, Leichtman AB, et al. Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation 2001; 72(2):284-290.
14. Carter JT, Freise CE, McTaggart RA, Mahanty et al. Laparoscopic procurement of kidneys with multiple renal arteries is associated with increased ureteral complications in the recipient. Am J Transplant 2005; 5(6):1312-1318.
15. Jacobs SC, Cho E, Foster C, Liao P, Bartlett ST. Laparoscopic donor nephrectomy: the University of Maryland 6-year experience. J Urol 2004; 171(1):47-51.
16. Leventhal JR, Kocak B, Salvalaggio PR, et al. Laparoscopic donor nephrectomy 1997 to 2003: lessons learned with 500 cases at a single institution. Surgery 2004; 136(4):881-890.
17. Su LM, Ratner LE, Montgomery RA, et al. Laparoscopic live donor nephrectomy: trends in donor and recipient morbidity following 381 consecutive cases. Ann Surg 2004; 240(2):358-363.

Chapter 10

Summaries in English and Dutch

N.F.M. Kok

SUMMARY IN ENGLISH

In **Chapter One** we described the development of live kidney donation. Currently, live donor kidney transplantation is the best solution to attack the persistent organ shortage in the Western World. Because of this shortage live kidney donation is still interesting over fifty years after Joseph Murray and Rene Kuss performed the first live kidney donor transplantations. The revival of live kidney donation in the 1990s still continues. Developments in immunosuppressive therapy, crossing the blood barrier, intelligent logistic solutions, improvements of peri-operative care and last but not least less invasive surgical techniques all attribute to the successes of live kidney donor transplantations. In this thesis we focused on the latter aspect, but one have to keep in mind that improvements in surgical and peri-operative care of the donor can only exist within a solid system providing screening of potential donors, selection of transplant candidates and accurate medical treatment of the recipients.
In the United States Ratner and colleagues introduced laparoscopic donor nephrectomy in 1995. This technique has greatly revolutionized live kidney donation. Presently the majority of live kidney donors is operated on using a (modified) laparoscopic approach. However, the introduction of minimally invasive surgery has also encouraged refinement of open techniques. Most studies up to now aimed to prove the feasibility of a new surgical technique for live kidney donation. In this thesis, we compared these novel techniques, therewith addressing short term surgical outcomes, quality of life, costs and transplant outcome.

Chapter two outlines the changes in the open technique in the last decade. As compared to a classic lumbotomy or flank incision, mini-incision open donor nephrectomy provides excellent results including reduced blood loss, shorter hospital stay and less incision related complications with only a modest increase in operation time. These features look like the earlier reports addressing laparoscopic donor nephrectomy versus conventional open donor nephrectomy.

A survey among transplant centers in Western European countries **(Chapter three)** revealed that approximately 80% of the polled centers still performed open approaches in 2004. Moreover, the majority of the centers practiced only open approaches. Of the centers carrying out open techniques, an important number applies a classic flank incision with transsection of the muscles and sometimes even rib resection. Incisional hernias occurred in up to 30% of the donors after open surgery.

In a prospective study we compared concurrent data of mini-incision open donor nephrectomy versus laparoscopic donor nephrectomy **(Chapters four and five)** at the Erasmus MC. **Chapter four** clarifies the safe nature of the novel open technique, which did not result in major complications or more pain as compared to the laparoscopic approach. Operation times were shorter, but median hospital stay was one day longer. Although most donors leave the hospital within four days after the operation, their quality of life remains affected up to months after surgery **(Chapter five)**. General fatigue remained affected up to one year following donor nephrectomy in general. Donors who underwent the laparoscopic approach performed better with regard to the quality of life dimensions "physical function" and "bodily pain". Together with a somewhat earlier return to work and short-term beneficial benefits such as shorter hospital stay, we decided to offer our donors laparoscopic donor nephrectomy as the preferred technique. However, the mini-incicion muscle-splitting technique is a very safe and widely applicable technique that generates good results and may therefore be advocated in low-volume centers that do not have the capacity to run a laparoscopic live kidney donation program.

Together with the departments of surgery, nephrology and urology of the Radboud University Medical Center in Nijmegen we conducted a randomized controlled trial to assess whether the laparoscopic approach was truly superior to the mini-incision open technique **(Chapter six and seven)**. One hundred donors were blinded to the surgical approach during hospital stay. Laparoscopic donor nephrectomy proved favorable with regard to fatigue, quality of life and postoperative pain **(Chapter six)**. Both techniques provided comparable safety to the donor and the graft up to two years after surgery.

During the operation the costs of the laparoscopic approach were considerably higher mainly due to the use of disposables and other laparoscopic equipment including the monitors and the endoscopic tower **(Chapter seven)**. In open donor nephrectomy mainly reusable instruments are used. This difference in costs is never compensated despite shorter hospital stay after laparoscopic donor nephrectomy, lower costs after discharge and less productivity losses. However, quality of life is superior and the difference between donors, who were operated on laparoscopically and open can be expressed as 0.03 quality adjusted life years (QALY). This implies that one additional year in good health after laparoscopic donor nephrectomy costs approximately € 16,000. For those who determine health care policy at the government or at insurance companies this is easily acceptable as the upper border is recently set at € 80,000 per QALY.

Chapter eight is about radiological screening of the live donor. We evaluated imaging over a five-year period. In the past the kidneys of live donors were imaged with conventional angiography. Computed tomography (CT) and Magnetic resonance imaging (MRI) have gradually replaced this technique because of a less invasive nature. In this chapter we argue a tailored approach for screening of the donor because MRI has its drawbacks too and underscores the vascular anatomy of the kidney. In particular preoperative assessment of accessory arteries running to the lower pole appears important as these branches adversely affect graft outcome. One radiological diagnostic applicable to all live donors is a dream for the future.

Chapter nine is a plea for right-sided laparoscopic donor nephrectomy. Many hospitals do not perform this approach. However, as compared to left-sided laparoscopic donor nephrectomy, right-sided laparoscopic donor nephrectomy results in fewer complications and conversions, shorter operation time and less blood loss without compromising graft function. Stronger, by limiting the number of grafts with lower pole arteries the right-sided nephrectomy may even improve graft outcome.

SAMENVATTING IN HET NEDERLANDS

In **Hoofdstuk één** is de ontwikkeling van nierdonatie bij leven beschreven. Op dit moment is niertransplantatie van levende donoren de beste oplossing om het orgaantekort in het Westen te bestrijden. Ruim vijftig jaar nadat Kuss en Murray de eerste succesvolle niertransplantaties verrichtten met nieren afkomstig van levende donoren staat deze vorm van niertransplantatie weer volop in de belangstelling door de schaarste aan organen.
Ontwikkelingen in de behandeling van afstoting met immunosuppressieve medicatie, het doorkruisen van de bloedbarrière, intelligente logistieke oplossingen, verbeteringen in de zorg rondom de operatie en bovenal minimaal invasieve chirurgische technieken hebben allen bijgedragen aan het succes van levende donor niertransplantatie. In dit proefschrift hebben wij de nadruk gelegd op de chirurgische techniek. Verbeteringen in chirugische en perioperatieve zorg zijn alleen mogelijk binnen een solide systeem waarin donoren accuraat worden gescreend en geselecteerd en waarin ontvangers adequaat medicamenteus worden behandeld.
Ratner et al. hebben de laparoscopische techniek om een nier bij een levende donor te verwijderen in 1995 geïntroduceerd in de Verenigde Staten. Deze techniek betekende een doorbraak voor nierdonatie bij leven programma's. Op dit moment wordt het merendeel van de levende nierdonoren in de Westerse Wereld geopereerd met een (gemodificeerde) laparoscopische techniek. De introductie van de laparoscopische techniek leidde ook tot verfijning van de "open", traditionele methode om een nier te verwijderen. De meeste studies tot nu toe die dit onderwerp aansneden waren gericht op de geschiktheid van de nieuwe chirurgische techniek voor nierdonatie bij leven. In dit proefschrift vergeleken wij de laparoscopische techniek met een nieuwe open techniek. De belangrijkste parameters waren chirurgische uitkomsten, kwaliteit van leven, kosten en transplantaat gerelateerde uitkomsten.

Hoofdstuk twee laat de veranderingen zien die de open operatietechniek heeft ondergaan in het afgelopen decennium. In vergelijking tot een klassieke lumbotomie of flank incisie biedt de nieuwe mini-incisie, waarbij de spieren gespleten worden in plaats van doorgenomen, uitstekende resultaten. De operatieduur bij deze nieuwe methode is weliswaar iets langer, maar het minder invasieve karakter van de ingreep leidt tot minder bloedverlies, minder complicaties die gerelateerd zijn aan de gekozen incisie en een kortere opnameduur. Deze conclusies lijken veel op conclusies uit eerdere publicaties die een vergelijking van de lumbotomie met de laparoscopische techniek beschreven.

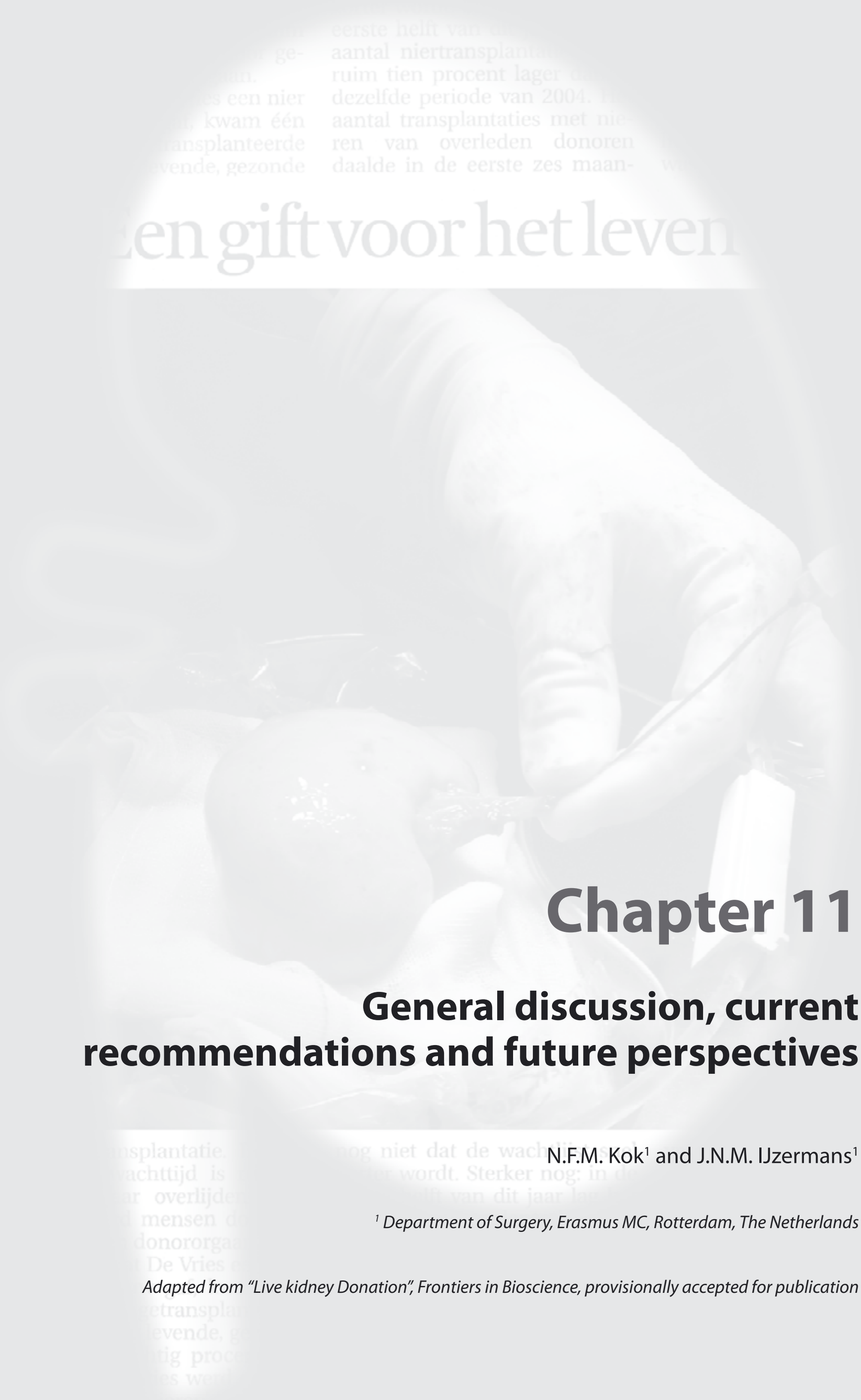
Een enquête onder transplantatiecentra in West-Europese landen **(Hoofdstuk drie)** toonde aan dat open technieken in 2004 nog werden gebruikt in ongeveer 80% van de ondervraagde centra en dat het merendeel van de centra alleen maar open operaties verrichtte. Vele centra antwoordden dat zij een met een klassieke flank incisie -en soms zelfs een resectie van een rib- toegang verkregen tot de nierloge. Littekenbreuken werden frequent gerapporteerd. In het uiterste geval kwam bij 30% van de donoren geopereerd in een van de centra een littekenbreuk voor.

In een prospectieve studie vergeleken wij mini-incisie open donornefrectomie en laparoscopische donornefrectomie. In **Hoofdstuk vier** verduidelijken wij de veilige opzet van de open methode. Deze methode leidde niet tot ernstige complicaties of meer pijn dan de laparoscopische methode. Operatietijden waren korter bij de open benadering, maar de gemiddelde opnameduur was langer. Hoewel de meeste donoren binnen vier dagen het ziekenhuis verlieten, was hun kwaliteit van leven aangedaan tot maanden na de ingreep **(Hoofdstuk vijf)**. Algemene vermoeidheid was zelfs gedurende een jaar aantoonbaar onafhankelijk van de chirurgische techniek. Donoren die met de laparoscopische methode waren geopereerd, scoorden beter op de kwaliteit van leven dimensies "fysiek functioneren" en "pijn". Ook gingen zij iets eerder aan het werk. Deze resultaten leidden samen met voordelen op korte termijn zoals een korter verblijf in het ziekenhuis tot onze beslissing om potentiële donoren primair de laparoscopische benadering aan te bieden. Echter, de nieuwe open methode was een zeer veilige en gemakkelijk toepasbare chirurgische benadering met uitstekende resultaten. Deze techniek zou in transplantatie centra met een lager aantal donornefrectomieën op jaarbasis een goed alternatief kunnen zijn voor de laparoscopische methode.

Samen met de afdelingen heelkunde, nefrologie en urologie van het Universitair Medisch Centrum Nijmegen voerden wij een gerandomiseerde studie uit om te bewijzen dat de laparoscopische donornefrectomie daadwerkelijk superieur was aan de gemodificeerde open methode **(Hoofdstuk zes en zeven)**. Honderd donoren kregen tijdens hun opname niet te horen hoe zij waren geopereerd. Laparoscopische donornefrectomie verdient de voorkeur boven open nierdonatie vanwege minder vermoeidheid, een betere kwaliteit van leven en minder postoperatieve pijn **(Hoofdstuk zes)**. De veiligheid voor de donor en de ontvanger was vergelijkbaar tot tenminste twee jaar na de operatie. Door het gebruik van wegwerp instrumenten en de afschrijving op dure endoscopische apparatuur zoals de monitor waren de kosten van de laparoscopische benadering tijdens de operatie aanzienlijk hoger **(Hoofdstuk zeven)**. Veel instrumenten die werden gebruikt tijdens open donornefrectomie konden worden gesteriliseerd en opnieuw worden gebruikt. Een kortere opname duur, minder kosten na de operatie en minder arbeidsverzuim na laparoscopisch donornefrectomie maakten het tijdens de operatie ontstane verschil in kosten tussen beide technieken nooit goed. Kwaliteit van leven uitgedrukt in QALYs (een eenheid voor tijd in een goede gezondheid) was wel beter na laparoscopische nierdonatie. Omgerekend kostte een jaar in goede gezondheid na laparoscopische nierdonatie €16.000. Voor verzekerings- en overheidsinstanties is dit een zeer acceptabel bedrag.

Hoofdstuk acht gaat over de radiologische work-up van de donor. Wij evalueerden de beeldvorming in ons ziekenhuis over een periode van vijf jaar. In het verleden werden de nieren in beeld gebracht met een conventionele angiografie. Deze techniek heeft geleidelijk plaats gemaakt voor CT- en MR-scans, omdat deze methoden minder invasief zijn. In dit hoofdstuk pleiten wij voor een radiologische work-up die aangepast is op het individu, omdat het gebruik van MR-scans ook nadelen had en de anatomie van de niervaten soms niet goed in beeld werd gebracht. In het bijzonder is het belangrijk om accessoire nierarteriën, die naar de onderpool van de nier lopen, af te beelden, omdat juist deze vaten de functie van het transplantaat kunnen beïnvloeden. Eén radiologisch diagnosticum voor alle donoren is op dit moment een toekomstdroom.

Hoofdstuk negen vormt een pleidooi voor het laparoscopisch verwijderen van de rechter nier. Veel ziekenhuizen mijden rechtszijdige donornefrectomie. Echter, in vergelijking tot het laparoscopisch weghalen van de linker nier resulteert de "laparoscopische donornefrectomie rechts" in minder complicaties, minder bloedverlies, kortere operatietijden en minder conversies naar een open benadering zonder daarbij transplantaatfunctie negatief te beïnvloeden. Het toepassen van zowel rechts- als linkszijdige laparoscopische donornefrectomie kan het aantal getransplanteerde nieren met onderpoolsarteriën verkleinen en zo de gemiddelde transplantaatfunctie zelfs verbeteren.



Chapter 11

General discussion, current recommendations and future perspectives

N.F.M. Kok[1] and J.N.M. IJzermans[1]

[1] Department of Surgery, Erasmus MC, Rotterdam, The Netherlands

Adapted from "Live kidney Donation", Frontiers in Bioscience, provisionally accepted for publication

In the last few years, several developments in the field of live kidney donor transplantation have accelerated the need for an optimal, multidisciplinary approach to live kidney donation. The live kidney donor is a healthy individual who voluntarily donates one of his/her kidneys. The word 'donor' is derived from the Latin verb 'donare' that means 'to give'. Traditionally donors also receive. Kidney donation is considered a benefaction and donation to a relative causes intense feelings of well-being, much more intense than for example donating money for charity. Furthermore, the closer the relationship between donor and recipient is, the more likely the quality of life of the donor is positively influenced by the success of the transplantation to the recipient. This is most clearly illustrated in some cases of spousal live kidney donor transplantation. Some donors report their benefit of successful transplantation because the recipient regains the role he/she had prior to the end-stage of the kidney disease including return to work, picking up sports and regaining sexual activity.

However, recent changes in live kidney donor transplantation may disturb this balance between giving and receiving. In the last few years the live donor pool has been expanded with unrelated donors with less close emotional ties to the recipient, including neighbors for example, but also donors who intend their kidney for an unknown recipient, also denoted as 'good Samaritan kidney donation' (1). For these donors donation is still a benefaction, but the rest of 'the reward' is less clear. A high standard of care of the donor is necessary to make these donations ethically acceptable.

Another alternative to "direct donation" (i.e. the donor and recipient are related someway) is cross-over donation. The Dutch cross-over program has been started with excellent results (2). In this program two or three donor-recipient combinations with incompatible blood-groups exchange their donor kidneys i.e. the recipient of pair A receives a transplant of the donor of pair B and the recipient of pair B receives the donor kidney from pair A (or C). Although these donations are indirect, the donor still benefits from a functioning transplant. The donors usually move to the other center, if applicable, while the recipients stay in the transplant center that performed the work-up for transplantation. This implies that in the Dutch situation where all seven transplant centers participate in the cross-over program the quality of live kidney donation should be excellent and that there should not be significant differences between the centers with regard to quality.

Third, one more solution has been proposed to help blood-group incompatible donor/recipient pairs, especially those pairs that are not being helped by the aforementioned cross-over transplantations. Plasmapheresis or immunoabsorption can remove circulating antibodies directed against the transplant (3, 4). These transplantations are higher risk transplantations that even deserve a higher degree of attention during the donor operation to secure optimal graft function.

These three aspects on top of the rapid expansion of live kidney donor transplantations demand a new standard of care for live kidney donation including donor screening, surgery, peri-operative care and follow-up.

SCREENING

Optimal radiological screening is indispensable in the work-up of the live kidney donor. Imaging should reveal parenchymal and vascular abnormalities. In an era in which many imaging modalities including ultrasound (US), magnetic resonance imaging (MRI), computer tomography (CT) and digital subtraction angiography (DSA), are available and various protocols per modality are used, the right modality and protocol must me chosen. We described imaging at the Erasmus MC during a five-year period (**Chapter 8**). Neither MRI nor DSA resulted in procedure related complications (i.e. bleeding, allergies to the contrast agent). However, both MRI and DSA did not accurately project renal vascular anatomy because minor vessels were not visualized and venous anatomy was not projected respectively. Undetected vessels did not result in complications and did not affect graft function either. However, we suggest tailoring imaging to the donor. Possibly, CT is more accurate in some of the donors. More detailed imaging of the renal vessels with CT may aid laparoscopic donor nephrectomy in more difficult cases such as the obese male. Donors who suffer from claustrophobia or donors who do not understand the breath holding instructions due to hearing loss or foreign language should not be imaged with MRI but primarily undergo CT or angiography. Finally, in hypertensive donors we suggest to perform DSA as primary diagnostic, because that is the only investigation that can accurately rule out arterial stenosis or fibromuscular dysplasia (5). All other donors may undergo MRI as primary investigation with satisfactory results. Flaws in imaging can be reduced by proper cooperation between clinician and radiologist (6). Optimal imaging will never replace surgical suspicion of aberrant renal anatomy and accurate dissection of the renal artery and vein.

SURGICAL TECHNIQUE

The eminent question of this thesis is whether laparoscopic donor nephrectomy is superior to minimally invasive open donor nephrectomy. We clearly demonstrated the benefits of the mini-incision muscle-splitting approach over the flank incision used in the past in **Chapter 2** (7). By now we believe that sufficient evidence has been provided that both minimally invasive open approaches and laparoscopic alternatives are superior to classic flank incisions in terms of pain, recovery and incision related complications (7-15). We should remark that studies comparing a novel surgical approach and classic flank incision never had complications as primary endpoint, but in most studies the number of complications during and after the novel technique favorably compares to the complication rate after classic lumbotomy. Therefore we suggest abandoning classic flank incisions for donor nephrectomy in the interest of the recovery of the live donor.

In **Chapters 4 and 5** we compared prospectively collected data of two cohorts of live donors that concurrently underwent mini-incision open donor nephrectomy and laparoscopic donor nephrectomy at our institute. In these studies there were no statistically significant differences with regard to postoperative pain. Donors who underwent the laparoscopic approach stayed shorter in the hospital and returned to work earlier. Some advantages with regard to quality of life were present after laparoscopy. Interestingly, mean general fatigue scores did not normalize in either group within the first year following kidney donation. Some advantages were present in the group of donors who underwent an open approach including shorter operation times, lower costs of disposables and absence of major intra-operative complications. Furthermore, an unexplained difference in recipient survival was present in favor of the open method. Based on these figures we concluded that mini-incision open donor nephrectomy is a very safe and viable alternative, but that we preferred the laparoscopic approach because of some short-term benefits for the donor.

When we randomized and blinded the donors, the benefits of laparoscopic surgery over minimally invasive open surgery became evident **(Chapters 6 and 7)**. In the introduction we stated that the success of the novel technique, in this case laparoscopic kidney donation, depended on completion of various goals that included provision of superior results, proven cost-effectiveness, similar graft survival, safety and wide applicability. Donors in the laparoscopic group experienced less pain, were discharged earlier and experienced less fatigue. Quality of life was significantly better in this group throughout the first year postoperatively. The additional costs of the laparoscopic approach were deemed acceptable and graft survival was similar. With regard to safety we must state that in all the studies described in this thesis we precisely scored intra-operative and postoperative complications. Due to definition and prospective registration, the presented complication rates may overestimate the burden to the donor. One may argue that the double amount of intra-operative complications occurred during laparoscopic donor nephrectomy. However, the clinical relevance was limited. To set up a study with complications as primary endpoint with an alpha of 0.05 and a beta of 0.20, 280 donors are required to assess a ten-percent difference. Since the difference between complicationrates of open and laparoscopic donor nephrectomy is most likely smaller than ten percent, multiple donors would be required. Therefore, it is unlikely that a statistical significant difference in complications with a similar study design is confirmed or denied. Other study designs like large prospective databases may further address this issue. In our view, most of the requirements to incorporate laparoscopic donor nephrectomy in donation programs are fulfilled.

Although it is generally accepted that a randomized controlled trial confers better evidence than prospectively designed comparative cohort studies, the difference in outcomes between these studies in this thesis demands a closer look. Several aspects may explain the assessed differences. First, baseline characteristics were perfectly balanced in the randomized study. In the non-randomized study these characteristics may have shown more variation including more females in the open group. By now, we know that in obese male donors in particular the laparoscopic approach appears more difficult (unpublished data).

Then, the randomized study was conducted in two centers and the non-randomized study in Rotterdam alone. There may always be slight variations between surgeons and between centers. In a test phase before the start of the trial in Nijmegen, the focus was on the performance of the laparoscopic approach. Maybe that explains the somewhat greater difference between laparoscopic and open surgery in the Nijmegen center accounting for the somewhat conflicting results of the studies. In the randomized study we did not stratify by center. However, for the most important outcomes the trial statistician performed analyses per center, which led to similar conclusions i.e. laparoscopic surgery led to superior outcomes in either center.

Next, one may argue that the blinding of the donors and staff only lasted a couple of days in the randomized study and therefore may have positively influenced outcomes of laparoscopic surgery. Donors may have been glad to be operated on by the fanciest approach. There are several arguments to rebut this proposition. Preoperatively, we presented both techniques to the donors as elegant techniques with similar outcomes. Of all donors who did not want to participate in this study, a comparable number demanded the open and laparoscopic approach respectively. Furthermore, just before discharge we polled forty participating donors whether we had performed open or laparoscopic surgery. A quarter of the donors gave the wrong answer. Finally, the effect of blinding was present at the time of assessment of some outcomes including hospital stay, pain at days one and three postoperatively.

Sufficient experience by presence of one of the referent surgeons was one of the principle requirements to allow participation in the randomized study. As opposed to the non-randomized study, conversions to open surgery did not occur during the randomized study.

Finally, in the randomized study graft and recipient survival was similar between groups. A different survival as assessed in the non-randomized study, may affect postoperative recovery and the donor's quality of life, although the number of donors of whom the corresponding recipient died is too small to perform appropriate statistical analyses. In case of recipient mortality, the earlier mentioned benefaction of donation may in fact turn into a notion that without transplantation the recipient might still have been alive. However, some donors who participated in our studies stated after the death of the recipient that they were glad that they had taken the opportunity to provide chances for long-term, high-quality survival and were very satisfied with the procedure.

In conclusion we believe that we have conferred high quality evidence that total laparoscopic donor nephrectomy is superior to mini-incision muscle-splitting open donor nephrectomy in the hands of a trained surgeon. The open approach is a viable alternative providing excellent results. This implies that if a surgeon does not have the experience in laparoscopic donor nephrectomy and can not train sufficiently because of a limited number of donor nephrectomies annually, open approaches may be advocated. This conclusion also means that if a laparoscopic procedure turns out to be more difficult than expected and the surgeon is not capable to continue safely, immediate elective conversion to a muscle-splitting open approach is warranted. We foresee potential difficulties for centers solely practicing laparoscopic approaches. The ability to convert to open surgery fast, safely and with good results will be needed if all donors will be operated on laparoscopically. Training in open renal surgery is advisable.

When reviewing the literature from transplant centers in North America, it almost seems ridiculous to still practice open approaches for live kidney donation, because in every single article, that usually is written by authors from large volume centers, the benefits (shorter hospital stay and shorter recovery phase) are stressed. Consumers in the United States desire a laparoscopic approach and laparoscopic donor nephectomy has become a marketing tool that is said to have increased live donation (16). Nevertheless, when surgeons were polled about the surgical approach to donor nephrectomy a third of participants was only trained in open donor nephrectomy (17). At the recent World Transplant Congress during the session 'live donor nephrectomy; surgical issues' the chairman polled the audience on who practiced open donor nephrectomy. One third to half of the audience rose their hands. This indicates that open donor nephrectomy is still performed on a daily basis in the United States. This rather corresponds to the situation in Western European countries, where open approaches to donor nephrectomy are common **(Chapter three)**. The transplant community must stay alert to prevent laparoscopic donor nephrectomy from becoming a marketing tool. The technique should be reserved for experienced surgeons only. We believe that sufficient expertise can only be gained in high volume centers.

Other prime surgical issues in live kidney donation are whether all live kidney donors should undergo laparoscopic donor nephrectomy and whether or not hand-assistance should be applied during surgery. The answer to the former question is clearly negative given the aforementioned argument that experience is necessary. At present, in many European centers less than ten live donor nephrectomies are annually performed (18). Energy spent on persuading surgeons to adopt any minimally invasive approach is rather effective in bringing live donor nephrectomy to a higher level of quality than attempts to centralize live donor nephrectomy or forcing surgeons to adopt laparoscopic approaches.

Currently, the literature does not provide evidence whether or not to use hand-assistance at some stage during laparoscopic donor nephrectomy. As in all centers laparoscopic kidney donation is started either with or without hand-assistance, it is almost impossible to properly investigate the role of hand-assistance in the learning phase of laparoscopic donor nephrectomy and all reports can be considered expert opinions (i.e. the lowest level of evidence). About half of the surgeons performs hand-assisted laparoscopic donor nephrectomy. We compared open surgery with total laparoscopic surgery, because we did not experience the benefits of hand-assistance previously. Other authors clearly have this experience (18). A total laparoscopic approach may be even less invasive, but hand-assisted donor nephrectomy may confer other benefits such as shorter operation times (19). A comparison of hand-assisted and total laparoscopic donor nephrectomy is difficult to organize. To assess potential interesting differences such as the rate of conversion and wound infections, hundreds of donors must be enrolled in such a study, because the absolute number of events is so small.

Except for tailoring the surgical approach to the experience of the surgeon and the center, the type of donor and the requirements of the recipient must be taken into account. Previous surgery, multiple arteries (**Chapter 8**) and obese donors (20,21) may lead to challenging situations in laparoscopic kidney donation. Especially when a combination of these features is present sufficient expertise is warranted. Right-sided donor nephrectomy usually results in a shorter renal vein. Experience with the right-sided approach will eventually not reveal struggle with short vessels, but significant benefits to the donor and the surgeon (**Chapter 9**). When straightforward laparoscopic donor nephrectomy is not expected, donors are probably better of in experienced centers. A single surgeon requires many procedures to gain sufficient expertise in all aforementioned scenarios.

Presently, we investigate hand-assisted retroperitoneoscopic left-sided kidney donation. This technique may combine the benefits of the minimally invasive open approach and the transperitoneal laparoscopic approach. Because right-sided laparoscopic kidney donation is fast and safe (**Chapter 9**), we currently test the retroperitoneoscopic approach only when left-sided nephrectomy is indicated. Comparative studies assessing the role of retroperitoneoscopic kidney donation alongside laparoscopic kidney donation are warranted. To date, good initial results of some cohort studies have been published (22-25).

Some recipients of live kidney donor transplants may have had several previous transplantations and therefore may have special requirements including maximum length of the renal vessels. In those cases, mini-incision open donor nephrectomy may be preferred. The application of vessel clamps in open surgery results in considerably less loss of vessel length than application of the endostapler in laparoscopic surgery. The application of self-locking clips in laparoscopic surgery may save some length but is presently considered less safe to the donor (17).

PERI-OPERATIVE CARE

At our center we currently analyze the role of preoperative infusion of fluids to maintain adequate perfusion of the donor's kidneys during laparoscopic donor nephrectomy. Also, the additional benefits of epidural anesthesia and analgesia to laparoscopic surgery are investigated. Preliminary results suggest that cooperation between surgeon and anesthesiologist in fluid and pain management will certainly aid the donor and the recipient in the immediate postoperative phase.

FOLLOW-UP OF THE DONOR

Three to four control visits are currently scheduled at our department. Thereafter, we offer donors an annual screening. Follow-up of the donor should be aimed at detecting social and medical problems.

We have clearly shown in **Chapters 5 and 6** that fatigue may be present until one year after the donation and that quality of life may be impaired. There is a subgroup of donors that does not return to preoperative values. Further studies to characterize these donors are warranted.

Regular follow-up may help donors who do not recover fast and donors who have conflicts with their employers with regard to resumption of work. Incidentally, we encounter disturbed relationships between donor and recipient that are recognized early. Professional aid can be offered if necessary. In our opinion, the transplant community and governmental organizations are obliged to provide help to struggling donors, because they have significantly helped society.

With regard to medical follow-up, donors may be monitored cautiously for hypertension and renal disease (26). Although individuals with one kidney do not appear to have an increased chance to develop renal insufficiency (27), they have a reduced functional reserve. Although most kidney diseases will affect both kidneys, early recognition of deteriorating kidney function may be beneficial in preventing end stage renal disease and may also be considered a minimal service of the society to our kidney donors.

CONCLUSION AND FUTURE PERSPECTIVES

Laparoscopic donor nephrectomy may be applied in the majority of donors and offers the best outcome to the donor with regard to quality of life. Future directions include addressing the position of the retroperitoneocopic approach, long term outcomes of live kidney donors, in particular hypertensive, older and obese donors and increasing the number of life kidney donors without compromising safety to the donor or the graft. Until an artificial kidney, a xenograft or stemcell therapy restoring intrinsic kidney function are clinically applicable, live kidney donor transplantation will remain an important live-saving procedure.

REFERENCES

1. Morrissey PE, Dube C, Gohh R, Yango A, Gautam A, Monaco AP. Good samaritan kidney donation. Transplantation 2005;80(10):1369-73.
2. de Klerk M, Keizer KM, Claas FH, Witvliet M, Haase-Kromwijk BJ, Weimar W. The Dutch national living donor kidney exchange program. Am J Transplant 2005;5(9):2302-5.
3. Kayler LK, Colombe B, Farber JL, et al. Successful living donor renal transplantation despite ABO incompatibility and a positive crossmatch. Clin Transplant 2004;18(6):737-42.
4. Norden G, Briggs D, Cockwell P, et al. ABO-incompatible live donor renal transplantation using blood group A/B carbohydrate antigen immunoadsorption and anti-CD20 antibody treatment. Xenotransplantation 2006;13(2):148-53.
5. Vasbinder GB, Nelemans PJ, Kessels AG, et al. Accuracy of computed tomographic angiography and magnetic resonance angiography for diagnosing renal artery stenosis. Ann Intern Med 2004;141(9):674-82; discussion 682.
6. Johnson JE, Loveday EJ, Archer LJ, Lear P, Thornton MJ. Preoperative evaluation of live renal donors using multislice CT angiography. Clin Radiol 2005;60(7):771-7.
7. Kok NF, Alwayn IP, Schouten O, Tran KT, Weimar W, IJzermans JN. Mini-incision open donor nephrectomy as an alternative to classic lumbotomy: evolution of the open approach. Transpl Int 2006;19(6):500-5.
8. Andersen MH, Mathisen L, Oyen O, et al. Postoperative pain and convalescence in living kidney donors-laparoscopic versus open donor nephrectomy: a randomized study. Am J Transplant 2006;6(6):1438-43.
9. Flowers JL, Jacobs S, Cho E, et al. Comparison of open and laparoscopic live donor nephrectomy. Ann Surg 1997;226(4):483-9; discussion 489-90.
10. Lewis GR, Brook NR, Waller JR, Bains JC, Veitch PS, Nicholson ML. A comparison of traditional open, minimal-incision donor nephrectomy and laparoscopic donor nephrectomy. Transpl Int 2004;17(10):589-95.
11. Neipp M, Jackobs S, Becker T, et al. Living donor nephrectomy: flank incision versus anterior vertical mini-incision. Transplantation 2004;78(9):1356-61.
12. Oyen O, Andersen M, Mathisen L, et al. Laparoscopic versus open living-donor nephrectomy: experiences from a prospective, randomized, single-center study focusing on donor safety. Transplantation 2005;79(9):1236-40.
13. Ratner LE, Kavoussi LR, Sroka M, et al. Laparoscopic assisted live donor nephrectomy--a comparison with the open approach. Transplantation 1997;63(2):229-33.
14. Simforoosh N, Basiri A, Tabibi A, Shakhssalim N, Hosseini Moghaddam SM. Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial. BJU Int 2005;95(6):851-5.
15. Wolf JS, Jr., Merion RM, Leichtman AB, et al. Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation 2001;72(2):284-90.
16. Barry JM, Conlin M, Golconda M, Norman D. Strategies to increase living donor kidney transplants. Urology 2005;66(5 Suppl):43-6.
17. Friedman AL, Peters TG, Jones KW, Boulware LE, Ratner LE. Fatal and Nonfatal Hemorrhagic Complications of Living Kidney Donation. Ann Surg 2006;243(1):126-30.
18. Kok NF, Weimar W, Alwayn IP, IJzermans JN. The current practice of live donor nephrectomy in europe. Transplantation 2006;82(7):892-7.
19. Kokkinos C, Nanidis T, Antcliffe D, Darzi AW, Tekkis P, Papalois V. Comparison of laparoscopic versus hand-assisted live donor nephrectomy. Transplantation 2007; 83 (1): 41-7.
20. Heimbach JK, Taler SJ, Prieto M, et al. Obesity in living kidney donors: clinical characteristics and outcomes in the era of laparoscopic donor nephrectomy. Am J Transplant 2005; 5 (5): 1057-64.
21. Jacobs SC, Cho E, Dunkin BJ, Bartlett ST, Flowers JL, Jarrell B. Laparoscopic nephrectomy in the markedly obese living renal donor. Urology 2000;56 (6): 926-9.
22. Bachmann A, Wolff T, Ruszat R, Giannini O, Dickenmann M, Gurke L, et al. Retroperitoneoscopic donor nephrectomy: a retrospective, non-randomized comparison of early complications, donor and recipient outcome with the standard open approach. Eur Urol 2005;48(1):90-6; discussion 96.

23. Tanabe K, Miyamoto N, Ishida H, et al. Retroperitoneoscopic live donor nephrectomy (RPLDN): establishment and initial experience of RPLDN at a single center. Am J Transplant 2005;5(4 Pt 1):739-45.
24. Wadstrom J. Hand-assisted retroperitoneoscopic live donor nephrectomy: experience from the first 75 consecutive cases. Transplantation 2005;80(8):1060-6.
25. Gjertsen H, Sandberg AK, Wadstrom J, Tyden G, Ericzon BG. Introduction of hand-assisted retroperitoneoscopic living donor nephrectomy at Karolinska University Hospital Huddinge. Transplant Proc. 2006;38(8):2644-5.
26. Nguyen T, Vazquez M, Toto R. Living kidney donation and hypertension risk. Lancet 2007;369(9556):87-8.
27. Fehrman-Ekholm I, Norden G, Lennerling A et al. Incidence of end-stage renal disease among live kidney donors. Transplantation 2006; 82(12):1646-8.

ABBREVIATIONS

BMI	Body mass index
CL	Classic lumbotomy
CT	Computer tomography
DSA	Digital subtraction angiography
EQ-5D	Euroqol-5 dimensional survey
ICER	Incremental cost effectiveness ratio
LDN	Laparoscopic donor nephrectomy
L-LDN	Left-sided laparoscopic donor nephrectomy
MFI-20	Multidimensional Fatigue Inventory-20
MIDN	Mini-incision donor nephrectomy
MRI	Magnetic resonance imaging
ODN	Open donor nephrectomy
QALY	Quality adjusted life year
QOL	Quality of Life
R-LDN	Right-sided laparoscopic donor nephrectomy
SF-36	Short Form-36
USA	United States of America
$	US dollar

CONTRIBUTING AUTHORS

Dr. I.P.J. Alwayn
Department of Surgery
Erasmus MC
Rotterdam

Dr. E.M.M. Adang
Department of Medical Technology Assessment
Radboud University Medical Center Nijmegen
Nijmegen

Prof.Dr. H.J. Bonjer
Department of Surgery
Dalhousie University
Halifax, Canada

Dr. I.M. Dooper
Department of Nephrology
Radboud University Medical Center Nijmegen
Nijmegen

Ms. B.M.E. Hansson
Department of Surgery
Canisius Wilhelmina Hospital
Nijmegen

Dr. E.J. Hazebroek
Department of Surgery
Erasmus MC
Rotterdam

Dr. W.C.J. Hop
Department of Epidemiology and Biostatistics
Erasmus MC
Rotterdam

Prof.Dr. M.G.M. Hunink
Department of Radiology
Erasmus MC
Rotterdam

Prof.Dr. J.N.M. IJzermans
Department of Surgery
Erasmus MC
Rotterdam

Mr. B.C. Knipscheer
Department of Urology
Radboud University Medical Center Nijmegen
Nijmegen

Mrs. I.R.A.M. Mertens zur Borg
Department of Anesthesiology
Erasmus MC
Rotterdam

Mrs. D. Pilzecker
Department of Nephrology
Radboud University Medical Center Nijmegen
Nijmegen

Mr. O. Schouten
Department of Surgery
Erasmus MC
Rotterdam

Dr. M.Y. Smits-Lind
Department of Surgery
Erasmus MC
Rotterdam

Ms. T.C.K. Tran
Department of Surgery
Erasmus MC
Rotterdam

Dr. J.A. van der Vliet
Department of Surgery
Radboud University Medical Center Nijmegen
Nijmegen

Prof.Dr. W. Weimar
Department of Internal Medicine
Erasmus MC
Rotterdam

Prof.Dr. G.J. van der Wilt
Department of Medical Technology Assessment
Radboud University Medical Center Nijmegen
Nijmegen

ACKNOWLEDGEMENTS/DANKWOORD

Hoewel alleen mijn naam op de voorkant van dit proefschrift staat vermeld, is het beschreven werk door vele handen verricht en ondersteund. Een aantal mensen wil ik in het bijzonder danken.

Bovenal wil ik alle nierdonoren bedanken die belangeloos deelnamen aan dit onderzoek. Uw bereidheid om mee te werken aan een betere procedure voor toekomstige donoren was overweldigend. Ik heb veel respect voor u omdat u een ander met een nierziekte onder het mes ging en vooral ook vanwege de manier waarop. U bent daarbij een voorbeeld voor velen.

Graag wil ik de Nierstichting Nederland, het Revolving fund van het Erasmus MC en SAGES bedanken voor de financiële ondersteuning van dit project.

Mijn promotor, Prof. Dr. J.N.M. IJzermans, beste Jan, jij bent degene die aan de basis stond van dit onderzoek, de financiering regelde, en een belangrijk deel van de operaties zelf uitvoerde. Ik heb het werk onder jouw leiding af mogen maken. Ik ben je zeer dankbaar voor de ruimte die ik daarvoor heb gekregen. Ik vind het heel bijzonder hoe jij onderzoek, opleiding, academische topzorg en niet te vergeten gezinsleven weet te combineren. Ik hoop de komende jaren nog veel van je te leren en jou ondertussen te overtuigen dat golf toch echt beter bij je past dan tennis.

Mijn co-promotor, Dr. I.P.J. Alwayn, beste Ian, dank voor je hulp in het schrijven van de artikelen. Een enkele correctie van jou kan een passage soms zoveel leesbaarder maken. Ik vind het leuk dat jij je na ons werkbezoek aan Uppsala inmiddels de retroperitoneale benadering eigen hebt gemaakt en verder bouwt aan de verbetering van de behandeling van de levende donor.

Prof. Dr. W. Weimar, Mr. ‘live donor én cross-over’, beste Willem, jij staat aan de wieg van een zeer succesvol niertransplantatie programma. Hoewel jij mij tijdens de voorlichtingsavonden de bloederige plaatjes liet presenteren, heb jij het voor elkaar gekregen dat patiënten denken door jou te worden geopereerd. Dank voor de discussie, het opbouwende commentaar en je interesse in mijn werk in de afgelopen jaren.

Prof. Dr. R.J. Ploeg, het is voor mij een eer dat de snelste hoogleraar op ski’s deel uit maakt van mijn commissie. Ik weet zeker dat wij nog lang kunnen discussiëren over vermoeidheidsscores en anterieure benaderingen.

Prof. Dr. H. Obertop, dank dat u dit onderzoek een warm hart toedraagt en dat u in de nadagen van uw imposante carrière plaats heeft willen nemen in de leescommissie. Ik vind het onvoorstelbaar dat een chirurg van zoveel onderwerpen op de hoogte kan zijn.

Prof. Dr. J.W. de Fijter, dank voor de Leidse input in mijn promotie.

Prof.Dr. D. Poldermans, beste Don, fantastisch dat jij vandaag aan de andere kant van tafel plaats wilt nemen. Ik waardeer jouw spitsvondigheid, kritische houding en energie. Het zal je tegenvallen vandaag over ‘zachte eindpunten’ te moeten spreken. Over die harde eindpunten moeten wij het nog maar eens hebben. Pillen en chirurgie is een combinatie die ook mij bekend in de oren klinkt.

Dr. C.H.J. van Eijck, beste Casper, zonder jou had ik niet hier in Rotterdam gestaan. Ik ben je zeer dankbaar. Je bent een groot clinicus met hart voor je patiënten. Als ik wat verder in mijn opleiding ben hoop ik nog veel van je te leren.

Prof.dr. G.W.A.M. Padberg, beste George, jij bent degene die mij als klein jochie al enthousiast heeft gemaakt voor het vak. Ook daarna heb jij mij geholpen belangrijke stappen te nemen in mijn professionele leven en daar ben ik je zeer dankbaar voor.

Dr. Ir. W.C.J. Hop, beste Wim, wat heb ik ontzettend veel van jou geleerd uit de correspondentie met de statisticus van de BMJ! Hartelijk dank voor de plezierige samenwerking.

De Nijmegen connection, Desiree Pilzecker, Bibi Hansson en Dr. Ine Dooper, dank voor jullie bereidheid te participeren in het onderzoek en op ongewenste momenten toch weer informatie te verzamelen of handtekeningen te zetten. Onze samenwerking heeft met twee mooie artikelen en een derde in de maak zeker zijn vruchten afgeworpen.

MTA Nijmegen, Dr. E.M.M. Adang en Prof.Dr. G.J. van der Wilt, beste Eddy en Gert-Jan, een modern onderzoek kan mijns inziens niet meer zonder kosteneffectiviteitanalyse. Ik ben jullie zeer dankbaar voor jullie inzet voor het onderzoek en vooral ook de bereidheid de ingewikkelde berekeningen uit te leggen.

Khe Tran, dank voor je hulp bij het schrijven van artikelen en voorbereiden van presentaties, de gezelligheid bij congressen en buitenschoolse activiteiten (chirurgencup rules!), en je persoonlijke betrokkenheid. Met jou in de zaal kon het niet verkeerd gaan. Ik kijk uit naar de toekomstige colleges waarbij jij je ‘rood op rood, wit op wit en blauw op blauw’ principe doceert.

Eric Hazebroek en May Smits-Lind, dank jullie wel voor het grondige voorwerk. Na jullie boekjes is dit proefschrift is het derde op een rij en er zijn nog heel veel data beschikbaar. Noor, veel succes met de analyses daarvan!

Anneke van Duuren en Conny Vollebregt, dankzij jullie kunnen de meeste klinische onderzoekers daadwerkelijk wat presteren. Ik vind dat jullie aandeel vaak onderschat wordt. Daarnaast hebben jullie altijd een luisterend oor voor ons. Anneke, ik heb het meest met jou samen mogen werken en ben jou erg dankbaar voor je bijdrage aan dit proefschrift.

Majoor Mertens zur Borg, beste Ingrid, jij hebt enorm veel werk verzet om met je team (anesthesisten, anesthesisten i.o, en anesthesie-assistenten, dank!) een gestandaardiseerd anesthesie- en pijnbeleid neer te zetten. Daardoor was ons chirurgisch onderzoek veel makkelijker te organiseren en te interpreteren. Daarnaast hebben Diederik en jij er met jullie vochtbeleid voor gezorgd dat de postoperatieve verschillen in kreatinine klaring na respectievelijk laparoscopische en open nierdonatie verdwenen zijn. Heel veel dank en succes met je eigen promotie.

Verpleegkundigen van 9 Zuid, afdeling vaat- en transplantatiechirurgie, ik ben jullie allen veel dank verschuldigd voor jullie tomeloze inzet bij het onderzoek. Zonder jullie waren veel gegevens verloren gegaan. In het bijzonder wil ik Margareth, Nathalie en Betsy danken voor hum coördinerende rol.

OK-assistenten van 11 Noord, jullie zijn geweldig! Wat een rotklus om elk instrument dat op tafel gaat in te vullen op een formulier en om elke keer te zorgen dat biopten op de juiste tijdstippen worden afgenomen en opgeslagen en dat allemaal voor een halve zak drop! Hoewel het moeilijk is om wetenschappelijk aan te tonen, zijn jullie een belangrijke spil in het succes van de Rotterdamse aanpak van de donornefrectomie.

Marry, Anne-Marie en Willij, dank voor de plezierige samenwerking. Jullie deelden de interesse in de levende donor en maakten daardoor de communicatie tussen chirurgie en nefrologie een stuk makkelijker.

Jolanda, Monica, Lieneke, Conny, en Julia, hartelijk dank voor jullie flexibiliteit en dank voor jullie luisterend oor.

Mijn collega onderzoekers in het Z-gebouw en experimenteel laboratorium: Armagan, Akkie, Robert, Yuri, Esther, Jeroen, Marc, Martin, Gabriëlle, Ruth, Fabian, Berthold, Miranda, Gerhard, Ruben, Joost, Hester, Niels, Jens, Pim, Sander, Arthur, Denis, Kim en Barend dank voor de gezelligheid en samenwerking. Veel succes met jullie eigen promoties.

Arts-assistenten en stafleden van de Afdeling Heelkunde van het Erasmus MC, dank voor jullie ondersteuning van en interesse in het onderzoek, en tevens dank voor wat ik in de kliniek van jullie mag leren!

Ron de Bruin, Fred Bonthuis en Sandra van den Engel, dank voor jullie steun in het labonderzoek. Hoewel niets van al ons werk in dit boek staat beschreven, hoop ik dat het levermodel zijn vruchten binnenkort gaat afwerpen.

Dirk en Hanne-Lise, het is echt gaaf om met zulke slimme en enthousiaste leeftijdgenoten aan iets te mogen werken! Fantastisch dat jullie uitwaaieren naar Pittsburgh en Parijs voor jullie carrière. Heel veel succes allebei!

Jorg, Sander en Gabe, tijdens en na de co-schappen hebben wij bijzonder veel lol met elkaar gehad. Ondanks dat wij zijn uitgewaaierd over Nederland is jullie vriendschap voor mij erg belangrijk. Veel succes met jullie eigen onderzoek en carrière en dat we nog maar een hoop plezier mogen maken.

Niels Kock en Robert Schuurman, ook voor jullie geldt dat jullie de uithoeken van ons land op hebben gezocht. Nu wij alledrie onze opleidingsplek hebben en (bijna) een huis hebben waar we kunnen blijven logeren, wordt het toch echt weer tijd om elkaar vaker te zien.

Vliet, Ruud, Kampie, Sturm, Neel, Drenth, Guido, A-J, Daamen, Huug, Klink, en Beije: dank voor alle mooie avondjes, diepgaande discussies en bovenal alle gekkigheid. Dank voor jullie begrip als ik omwille van de zieke medemens moe(s)t afhaken. Als tegenprestatie zal ik dit jaar 3 feestjes voor jullie organiseren.

Sanne, Menno, Albertien en Evelien (& partners) dank voor jullie vriendschap en begrip.

Dirk, Thijs en Oliver, snaecken! Jullie zorgen telkens weer voor een hoop pret in mijn leven.

Lieve Antje, beste Frits en Boudewijn, mede dankzij jullie heb ik in de afgelopen jaren toch nog af en toe tijd gevonden even ultiem te genieten aan boord van de Noordster of de Windekind. King of the Picksea word je niet elke dag!

Bonetta en Cees, dank voor alle belangstelling voor het wetenschappelijke werk van Linet en mij, de geanimeerde discussies over het vak en bovenal de warmte van jullie gezin. Sabine (& Pim) en Mar (& Han) dank voor de momenten die we samen hebben gehad en die nog komen gaan. Wanneer gaan we weer koehandelen?

Lieve Bam en Aad, jullie staan van jongs af aan altijd voor mij klaar! Echt amazing… Ik ben jullie daar heel erg dankbaar voor!

Olaf, speciaal voor jou een Duitse stelling om voor te lezen. Dank voor de afgelopen jaren waarin jij mij ter zijde hebt gestaan en dank dat je dat ook vandaag wil doen. Ik hoop dat je geen Delfts bruine brogues aan hebt onder je rok.

Roelof, van jongste broertje ben jij verworden tot zeer dierbare vriend van Diederik en mij. Jij bent een zondagskind dat zijn leven nu al, zo jong als je bent, erg goed voor elkaar heeft. Het is voor mij een eer dat jij bij alle mooie gelegenheden dit jaar zo dicht bij mij staat. Ik hoop dat we na mijn promotie weer vaker uren gaan maken in de J en de boog samen met Died en Pap.

Eline en Diederik en…? Wat heerlijk om te kunnen genieten van elkaars geluk! Died, ik vind het zo bijzonder dat wij elkaar zoveel kunnen zeggen zonder veel te zeggen. Daarnaast is het heerlijk om samen onze energie kwijt te raken. Hoewel jij met zwemmen toch altijd net wat sneller bent gebleven, hoop ik dat wij nog veel samen genieten op, in of onder water.

Lieve Pap en Mam, het is met geen pen te beschrijven wat jullie voor ons drieën over hebben (gehad). Alles kan en mag altijd; geen plan is te gek. Jullie steun in ons leven, en nu ook weer bij mijn promotie, onze bruiloft en ons huis is overweldigend. Mam, ik vind het uniek dat jij je hele leven hebt gewerkt en ons tegelijk het gevoel hebt weten te geven dat je altijd thuis was. Ik weet zeker dat je nu gaat genieten van een wel verdiend pensioen, alhoewel stil zitten niet bij je past. Pap, jij hebt altijd aan het roer gestaan van ons gezin en ik hoop dat je nog lang blijft zitten op je bankje in de boog. Ik wens jullie heel veel geluk samen!

Lieve Linet, er kan er maar een de laatste en toch de eerste zijn. Jij kunt mij juist dat tikkie in de goede richting geven, en dat geldt zeker ook voor het schrijven van dit proefschrift. Het is uniek om iemand gevonden te hebben die zo vaak hetzelfde denkt en die dezelfde interesses heeft. Toeval? Wij denken allebei van niet. Jij bent veel te bescheiden, maar ook dat maakt jou zo mooi. Jij bent mijn alles. Ik houd van jou!

LIST OF PUBLICATIONS

Kok NF, Lind MY, Hansson BM, Pilzecker D, Mertens zur Borg IR, Knipscheer BC, Hazebroek EJ, Dooper IM, Weimar W, Hop WC, Adang EM, van der Wilt GJ, Bonjer HJ, van der Vliet JA, IJzermans JN.
Comparison of laparoscopic and mini incision open donor nephrectomy: single blind, randomised controlled clinical trial.
BMJ. 2006: 333(7561):221

Kok NF, Alwayn IP, Lind MY, Tran KT, Weimar W, IJzermans JN.
Donor nephrectomy: mini-incision muscle-splitting open approach versus laparoscopy.
Transplantation. 2006: 81(6):881-7

Kok NF, Alwayn IP, Schouten O, Tran KT, Weimar W, IJzermans JN.
Mini-incision open donor nephrectomy as an alternative to classic lumbotomy: evolution of the open approach.
Transpl Int. 2006: 19(6):500-5

Kok NF, Weimar W, Alwayn IP, IJzermans JN.
The current practice of live donor nephrectomy in Europe.
Transplantation. 2006: 82(7):892-7

Kok NF, Alwayn IP, Tran KT, Hop WC, Weimar W, IJzermans JN.
Psychosocial and physical impairment after mini-incision open and laparoscopic donor nephrectomy: A prospective study.
Transplantation. 2006: 82(10):1291-7

FS Doekhie, WE Mesker, JH van Krieken, NFM Kok, HH Hartgrink, EK Kranenbarg, H Putter, PJ Kuppen, HJ Tanke, RA Tollenaar, CJ van de Velde. Clinical relevance of occult tumor cells in lymph nodes from gastric cancer patients.
Am J Surg Pathol. 2005: 29(9):1135-44

Schouten O, Dunkelgrun M, Feringa HH, Kok NF, Vidakovic R, Bax JJ, Poldermans D.
Myocardial Damage in High-risk Patients Undergoing Elective Endovascular or Open Infrarenal Abdominal Aortic Aneurysm Repair.
Eur J Vasc Endovasc Surg. 2007: 33(5):544-9

Kok NF, Alwayn IP, IJzermans JN.
Laparoscopic versus open donor nephrectomy.

Transplantation. 2006: 82(9):1243-4

van der Windt DJ, Kok NF, Hussain SM, Zondervan PE, Alwayn IP, de Man RA, IJzermans JN.
Case-orientated approach to the management of hepatocellular adenoma.
Br J Surg. 2006: 93(12):1495-502

Schouten O, Kok NF, Hoedt MT, van Laanen JH, Poldermans D.
The influence of aneurysm size on perioperative cardiac outcome in elective open infrarenal aortic aneurysm repair.
J Vasc Surg. 2006: 44(3):435-41

Kok NF, Alwayn IP, IJzermans JN.
The first 100 hand-assisted laparoscopic donor nephrectomies at the Academic Medical Center in Amsterdam.
Nederlands Tijdschrift voor Geneeskunde. 2006: 150(25):1427-8

Schouten O, Kok NF, Boersma E, Bax JJ, Feringa HH, Vidakovic R, Statius van Eps RG, van Sambeek MR, Poldermans D.
Effects of statins on renal function after aortic cross clamping during major vascular surgery.
Am J Cardiol. 2006: 97(9):1383-5

Kok NF, Koppert LB.
Regarding "3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors reduce the risk of perioperative stroke and mortality after carotid endarterectomy".
J Vasc Surg. 2006: 43(3):643-4

Schouten O, Shaw LJ, Boersma E, Bax JJ, Kertai MD, Feringa HH, Biagini E, Kok NF, Urk H, Elhendy A, Poldermans D.
A meta-analysis of safety and effectiveness of perioperative beta-blocker use for the prevention of cardiac events in different types of noncardiac surgery.
Coron Artery Dis. 2006: 17(2):173-9

Kok NFM, de Jong SC, Hendriks JM.
Een man met een aneurysma van de arteria carotis interna.
Nederlands Tijdschrift voor Heelkunde. 2006: 15 (8):242-245

Kok NFM, IJzermans JNM.
Laparoscopische donornefrectomie.
Transplantatie actueel. 2006: Mei nummer

van der Windt DJ, Kok NFM, de Man RA, IJzermans JNM.
Diagnostiek en behandeling van het levercel adenoom in Nederland.
Nederlands Tijdschrift voor Geneeskunde, In press

Kok NFM, Adang EMM, Hansson BME, Dooper IM, Weimar W, van der Wilt GJ, IJzermans JNM.
Cost-effectiveness of laparoscopic versus mini-incision open donor nephrectomy: a randomized study.
Transplantation, In press

Han-Geurts IJM, Hop WCJ, Kok NFM, Lim A, Brouwer KJ, Lont H, Tilanus HW and Jeekel J
The impact of early enteral feeding on postoperative ileus duration and postoperative recovery: a prospective randomized multicentre trial.
Br J Surg. 2007: 94(5):555-561

CURRICULUM VITAE

Niels Frederik Maarten Kok was born on July 25th 1978 in Leiderdorp, the Netherlands. In 1996 he graduated from secondary school at the "Stedelijk Gymnasium" in Leiden. Thereafter, he started his study 'Medicine' at the University of Leiden. During his study he worked as a student assistant at the Department of Human Anatomy and Embryology. He enjoyed electives in the anatomy of the head and neck (Prof.Dr. A.C. Gittenberger-de Groot) and "UV-light and skin cancer" (Dr. S. Pavel). As a student he was involved in a research project investigating the clinical significance of micrometastases from gastric cancer at the Department of Surgical Oncology (Prof.Dr. C.J.H. van de Velde).

In 2002, he went to Capetown for an elective in General Surgery at the Tygerberg Hospital (University of Stellenbosch, Prof.Dr. B.L. Warren). After returning to the Netherlands he graduated from Medical School cum laude and started working as a PhD student at the Department of Surgery of the Erasmus MC in Rotterdam. He mainly investigated the best surgical technique for live kidney donation under auspices of Prof.Dr. J.N.M. IJzermans and Dr. I.P.J. Alwayn. The Dutch Kidney Fundation supported a randomized, blinded clinical trial, in which laparoscopic and mini-incision open donor nephrectomy were compared. This study forms the backbone of this thesis. In July 2006 Niels started his surgical residency at the Department of Surgery of the Erasmus MC (Prof.Dr. J.N.M. IJzermans). He will continue his training at the Department of Surgery of the IJsselland Hospital in Capelle aan de IJssel (Dr. I. Dawson).

Niels enjoys playing golf and sailing regattas with his brothers and father. Recently, he proposed to Linetta Koppert. They will marry in December 2007.