Laparoscopic versus open living donor nephrectomy

M.Y. Smits-Lind

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Laparoscopic Versus Open Living Donor Nephrectomy

Laparoscopische versus open nierdonatie bij leven

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To my mother, thank you for your unconditional love.
To Loet, thank you for being a part of our lives.
To Jeroen, thank you for your love, friendship and support.

Chapter 1

Introduction

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Open versus laparoscopic donor nephrectomy in renal transplantation.
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HISTORY

Donor nephrectomy

Renal transplantation was first performed in 1936 by Voronoy [1]. The kidney was harvested in a patient who had died from a head injury 6 hours earlier. The blood group of the donor was incompatible with that of the recipient. The renal graft did not function and the recipient died two days later. Subsequently, Voronoy performed kidney transplantations in five more patients under similar circumstances, however without success. After these early attempts, renal transplantations were not performed for over two decades.

Hemodialysis became possible by the invention of the first dialysis machine in 1943 by Kolff et al. [2]. In that same year, Medawar and colleagues found that loss of tissue allograft was induced by an unidentified antibody that resulted in an immune response [3].

Dr. Joseph Murray performed the first successful live donor kidney transplantation between identical twins, at the Peter Bent Brigham Hospital in Boston in 1954. Avoiding any risk of graft rejection by the use of a genetically identical donor, the recipient lived for over twenty years with a functioning graft until he died from coronary artery disease.

With time, new developments in transplant immunology such as immunosupressive therapy, histocompatibility and tissue typing resulted in better graft function and survival, opening the way to successful transplantation of organs from non-identical twins, related and non-related, living or cadaver donors. Also, improvements in the technique of organ procurement, preservation and implantation of the kidney resulted in better graft function.

Short- and longterm patient and graft survival rates are higher after living donation compared to cadaver donor transplants. Furthermore, Terasaki et al. showed comparable survival rates of parental- and living-unrelated donorgrafts [4].

At the 1960s and 1970s, most transplant candidates waited less than 18 months for a cadaver kidney. However, due to improvements in transplant outcome and expansion of criteria for acceptance as a transplant candidate, the waitinglist increased dramatically (Figures 1 and 2). Living (un)related donation represents a large potential supply of organs that may decrease the waiting time. Therefore, many centers have now implemented a living donation program, encouraging spouses and familymembers to donate their kidney (figure 3, 4). Currently, at the university hospital Rotterdam more than half of all renal transplants is from a living (un)related donor (figure 5).

Laparoscopic living donor nephrectomy

Laparoscopy made a final breakthrough with the invention of the television-chip camera in the early 80's. It offered advantages such as a binocular view, an enlarged image, easy observation of the procedure by the entire operating team and the possibility to operate with both hands. Semm, a gynaecologist, performed the first laparoscopic appendectomy in 1980 [5]. The first laparoscopic cholecystectomy was performed in 1985 by Muhe, for which he received the

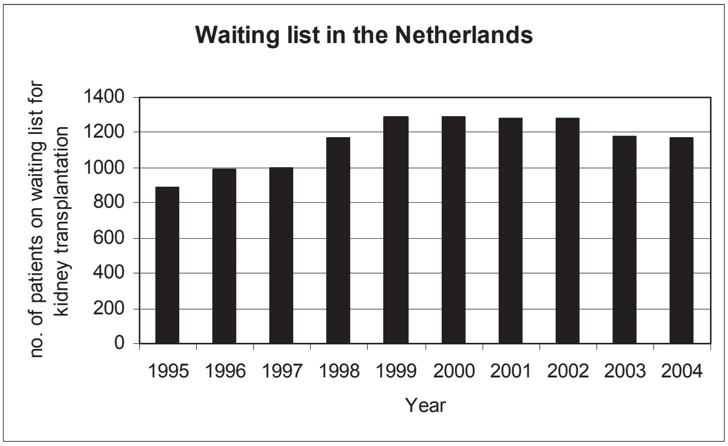

Figure 1. Number of patients on waiting list for renal transplantation in the Netherlands
(Data collected from Eurotransplant)

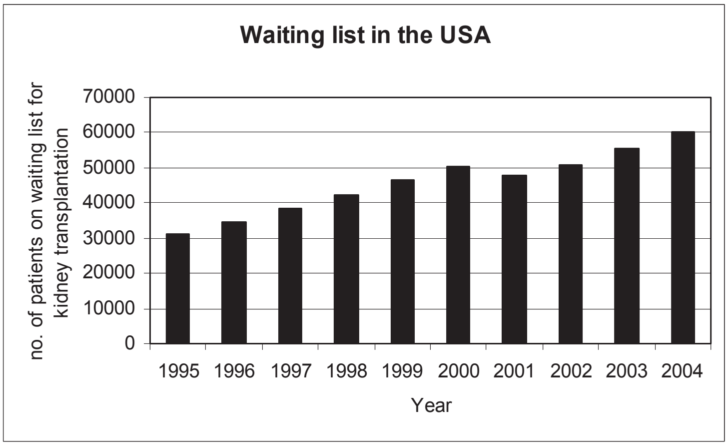

Figure 2. Number of patients on waiting list for renal transplantation in the United States of America
(Data collected from www.UNOS.org)

highest award of the German Surgical Society [6]. Laparoscopic cholecystectomy, associated with advantages such as lower morbidity, shorter hospitalisation, more rapid convalescence, and a better cosmetic result, has moved laparoscopy into generally accepted surgical practice for various disorders.

In urology, the laparoscope was initially used to diagnose the location of a cryptorchid testicle to plan a subsequent open operation [7]. Clayman et al. showed that laparoscopic nephrectomy was possible by the performance of the first successful laparoscopic nephrectomy for a renal mass in 1991 [8]. This entailed laparoscopic excision of a malignant tumor-bearing right kidney, which was morcellated and aspirated from within an impermeable bag in the abdomen. Laparoscopic living donor nephrectomy was described in an experimental porcine

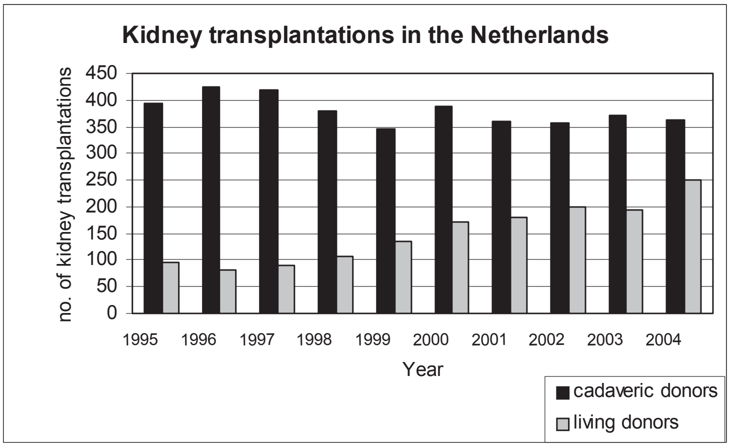

Figure 3. Number of kidney transplantations in the Netherlands.
(Data collected from Eurotransplant)

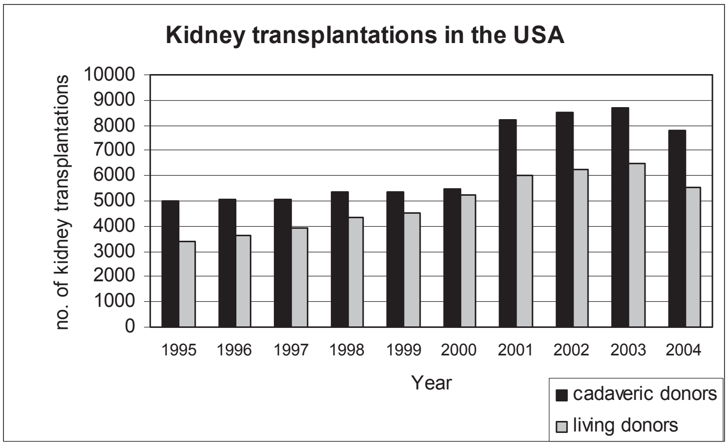

Figure 4. Number of kidney transplantations in the United States of America.
(Data collected from www.UNOS.org)

model in 1994 by Gill et al. [9]. Shortly hereafter, the first laparoscopic living donor nephrectomy in humans was performed by Ratner et al. in 1995 [10]. Since this initial report, the popularity of the procedure has increased and has been adopted by many centres, mainly in the USA. There are indications that the use of laparoscopic living donor nephrectomy has increased the supply of living kidney donors and the willingness to donate. Kuo et al. reported that 47% of donors donated solely because of the availability of the laparoscopic donor nephrectomy procedure and would not have otherwise donated their kidney [11].

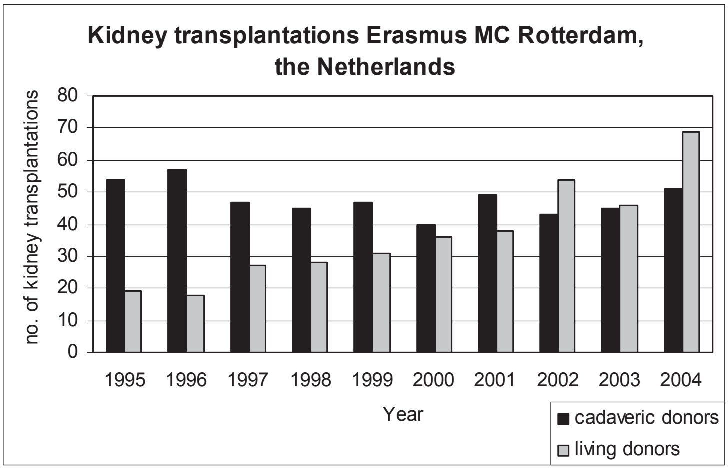

Figure 5. Number of kidney transplantations at the University Hospital Rotterdam, the Netherlands

LIVING DONOR NEPHRECTOMY: OPERATING TECHNIQUE

Open donor nephrectomy

Conventional lumbotomy

The patient is placed in a full lateral decubitus position by flexing the operating table to gain maximum access between the iliac crest and the ribs.

The classical method for live donor nephrectomy consists of an extra-peritoneal approach, with a flank incision just above or below the twelfth rib, without resection of the rib. Gerota's fascia is opened and the kidney is mobilised to get access to the renal vessels. After clamping of the renal vessels as close to the aorta and caval vein as possible, these structures and the ureter are cut. By the use of a Satinsky clamp the vessels can be transected very close to the aorta and caval vein. The organ is removed through the incision and is placed in a basin filled with ice and saline solution. A needle is placed in the artery, and the kidney is flushed with a 4 °C preservation solution (Eurocollins) until the venous effluent is clear and the kidney is discoloured.

Open nephrectomy is a safe procedure for harvesting a kidney in a living donor, with reported mortality rates of 0.03% [12]. Warm ischemia time is approximately 2 minutes. However, the morbidity of open donor nephrectomy of 4.4 ± 3.5%, may deter potential living donors from volunteering [13]. Morbidity involves acute and chronic wound pain, incisional hernia, wound infection up to 4%, pneumothorax up to 7% and prolonged convalescence.

Mini-incision (The Erasmus MC technique)

The patient is positioned in a full lateral decubitus position and the operation table is maximally flexed. A 8-12 cm skin incision is made anterior to the 11th rib. The fascia and muscles of the abdominal wall are carefully divided in the longitudinal direction ('muscle split'). A mechanical retractor (Omnitract surgical, St. Paul, USA) is installed. The peritoneum is displaced medially and the perinephric fascia (Gerota's fascia) is opened on the lateral side of the kidney. Meticulous dissection of the kidney is performed, especially at the upper pole of the kidney to avoid damage to the adrenal gland and at the vascular pedicle. Ureter, renal vein and artery are identified and encircled with vessel loops. Gonadal, lumbar and adrenal vasular branches are divided if necessary. Thereafter, the ureter will be clipped and divided. Before clamping and ligating renal artery and vein successively, 5,000 units of heparin are administered intravenously. The kidney is removed. Perfusion as aforementioned for the lumbotomy. Prothrombine is given, and haemostasis is applied. The fascia of the abdominal muscles are closed using vicryl 1/0 (Ethicon Inc., Cincinnati, USA). The subcutaneous fascia is approximated and the skin is sutured intracutaneously.

In order to reduce morbidity associated with lumbotomy, the muscle split mini-incision was introduced. Several studies show a reduction in hospital stay and postoperative pain in the mini-incision donor group compared to the classical open donor nephrectomy group [14-16].

Till this time no prospective randomized trials has been published comparing laparoscopic and muscle-split donor nephrectomy. This is why we conducted a randomized, blinded, multicenter trial comparing these two techniques regarding operative variables, quality of life, graft function and costs. The short term results are described in **Chapter 8**.

Endoscopy

Transperitoneal approach

The patient is positioned on the operating table similar to the open approach allowing a conversion to lumbotomy, if necessary. Orogastric tube and urinary catheter are placed routinely. After a subumbilical open introduction of a 10 mm Hasson-trocar, pneumoperitoneum is established by insufflation of carbon dioxide with an abdominal pressure of 12 mmHg. A 10 mm 30˚ video endoscope is inserted and the abdomen is inspected. Under direct vision a 10 mm trocar and three to four 5 mm trocars are placed and instruments can be introduced (figure 6). A 5 mm endo-babcock clamp is used for retraction of the liver or spleen. Retraction is secured by grasping the lateral abdominal wall. The hepatic or splenic flexure of the colon is mobilised using a 5 mm curved ultrasonic device (Ultracision®, Ethicon, Sommersville, NJ) and retracted medially, exposing the kidney. Gerota's fascia is opened and the renal vein and ureter are identified and dissected. The anterior and posterior aspects of the kidney are both freed as well as the upper pole from adjacent attachments and structures. At this point, the kidney is

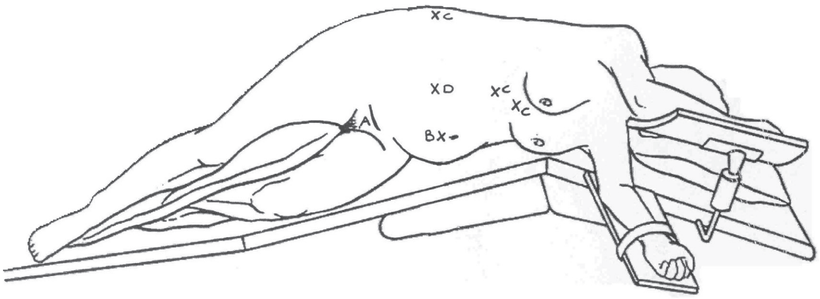

Figure 6. Positioning of the patient and location of trocar ports for right donor nephrectomy.

allowed to fall medially and the renal artery, which is identified behind the renal vein, is dissected towards the aorta. The vessels are encircled with a rubber vessel loop to enable gentle traction and correct positioning of the stapling device. Dissection of the ureter, including the peri-ureteral tissue and the ureteral arterial branch, is carried on to the crossing with the iliac artery. The left gonadal, lumbar and adrenal veins are clipped and divided. The adrenal gland is released from the medial superior aspect of the renal capsule using the ultrasonic device. Preparations are then being made for extraction of the kidney by making a suprapubic or periumbilical incision of about 5 cm. Through this incision, an extraction device (Endocatch, US Surgical, Norwalk, CT) is inserted. After administration of 5000 U of heparin the ureter is clipped and divided. The renal vein and artery are divided using a linear vascular stapler (EndoGIA 30®, US Surgical, Norwalk, CT). Anticoagulation is then reversed with protamine. The kidney is placed in a specimen bag and brought out through the 5 cm incision.

After closure of the incision, pneumoperitoneum is re-established and the abdomen is inspected. After complete hemostasis, the trocars are removed and the incisions are closed.

Several retrospective studies comparing open to laparoscopic donor nephrectomy have shown significant advantages in favour of the laparoscopic technique (Table 1). In summary, blood loss, analgesic requirements, hospital stay and return to work are reduced in the laparoscopic donor nephrectomy group compared to open donor nephrectomy. Disadvantages of laparoscopic donor nephrectomy are longer operating- and warm ischemia times. Also, this laparoscopic procedure is associated with higher cost of 900 USD due to the use of disposable laparoscopic instruments [17].

Studies comparing return to work after laparoscopic and open donor neprectomy have all been conducted in the United states were health care structures differ significantly from that in the Netherlands. Therefore, a study was conducted to investigate the period of sick-leave after laparoscopic, hand-assisted and open donor nephrecomy in the Netherlands, as described in **Chapter 4**. No studies have been published comparing the laparoscopic and open kidney donation objectively with regard to the cosmetic result. In **Chapter 3** the body image of donors was determined after open (lumbotomy) and laparoscopic kidney donation.

Table 1. Comparison of laparoscopic (LDN) and open (ODN) donor nephrectomy

	No. of patients		Operative time (min)			Warm ischemia (min)			Blood loss (ml)		
	LDN	ODN	LDN	ODN	p	LDN	ODN	p	LDN	ODN	p
Ratner et al. [32]	10	20	227	183	<0.012	4.2			137	393	0.004
Flowers et al. [38]	70	65	226	212	0.166	3.0			122	408	0.0001
Rawlins et al. [39]	100	50	231	209	0.002	2.3			102	193	<0.001
Berends et al.[40]	57	27	240	145	0.001	7.8	4.8	<0.001	298	316	NS
Kumar et al. [41]	49	50	181	102	0.001				86	220	<0.001
Brown et al. [42]	50	50	234	208	0.007	2.8			114	193	0.0001
Leventhal et al.[43]	80	50	276	186	<0.05	3.8			165	174	NS
Odland et al. [44]	30	30	183	148	<0.05	5.0	1.7	<0.05	116	192	NS

	Hospital stay (days)			Resumption of work (days)			Narcotic use		
	LDN	ODN	p	LDN	ODN	p	LDN	ODN	p
Ratner et al.	2.7	5.7	< 0.001	27.3	44.8	0.024	24.4 mg*	123.6 mg*	<0.001
Flowers et al.	2.2	4.5	0.0001	15.9	51.5	0.0001	28.6 hours	60.1 hours	0.0001
Rawlins et al.	3.3	4.7	<0.001						
Berends et al.	3.9	6.0	<0.001						
Brown et al.	3.5	4.7	0.0001						
Kumar et al.	3.14	5.7	<0.001				155 mg**	252 mg	<0.001
Leventhal et al.	2.1	3.2	<0.05				17.2 hours	38.3 hours	<0.05
Odland et al.	2.7	3.8	< 0.05	19	37	< 0.05	24 hours	60 hours	< 0.05

* = Morfine Sulfate
** = Tramadol

Retroperitoneal approach

Gill et al. reported their technique for a retroperitoneal donor nephrectomy [18, 19]. Access is gained through a 1.5 to 2 cm horizontal skin incision just below the tip of the 12th rib. Flank muscle fibers are bluntly separated and the retroperitoneum is entered by piercing the anterior thoracolumbar fascia with a finger or hemostat. Dissection of the retroperitoneum is performed with the finger positioned anterior to the psoas fascia, remaining posterior and outside Gerota's fascia.

A balloon-dilatator (Origin Medsystems®, Menlo park, California, USA) is inserted and positioned at this location and inflated with 800 mL of air. The balloon displaces the kidney anteromedially and exposes the primary anatomic landmark, the psoas muscle. The balloon dilatator is removed and a 12-mm Blunttip cannula (Origin Medsystems) is secured. Retropneumoperitoneum is established to 15 mm Hg and a 30° laparoscope is inserted. Additional retroperitoneal ports (one 12 mm port, 2 or 3 fingers above anterior superior iliac spine and one 5-mm port lateral to paraspinal muscles) are placed and a longitudinal incision is made in

Gerota's fascia, identifying the renal hilum. The renal artery is circumferentially mobilized from the renal hilum up to its retrocaval location. The renal vein and a portion of the caval vein are similarly mobilized. The ureter is dissected into the pelvis and clipped.

Before division of the vessels, a muscle splitting Gibson incision is made over the right iliac fossa and the transversalis fascia is left intact. After administration of 5000 units of heparin, the vessels are divided using a vascular endo-stapler. The fascial layer at the Gibson incision is divided and the kidney is extracted manually and perfused with a cold preservation fluid to achieve hypothermia. After confirming hemostasis, the port sites and Gibson incision are closed in a standard fashion.

Gill et al. reported an operating time for retroperitoneal donor nephrectomy of 186 minutes, with a warm ischemia time of 4 minutes. This is comparable to the transperitoneal laparoscopic method. The visualization of the structures, however, is diminished because of the small retroperitoneal space. Also, organs separated only by the peritoneal layer are susceptible to injury because they are not clearly visible. Retroperitoneal donor nephrectomy is, because of the minimal operating space, more complicated in obese donors with abundant perinephric fat or donors with renovascular and ureteral anomalies.

Hand assisted endoscopy

The procedure is performed with the patient in full lateral decubitus position. The abdominal cavity is insufflated with carbon dioxide and two or three 12 mm ports are placed. A hand-assisted device (Pneumosleeve®, Dexterity, Atlanta, GA) is applied onto the abdomen in the midline, above or below the umbilicus. An 8-cm incision is made within the ring, which is placed on the abdominal skin. An occlusive sleeve is fitted over the surgeon's non-dominant hand and is placed through the handsize abdominal incision. Once the ring of the sleeve is locked onto the ring to prevent gas leakage, pneumoperitoneum is re-established [20]. The operation is conducted in the same order as with the laparoscopic procedure. After dissecting and dividing of the ureter and the vessels, the kidney is removed with the aid of the hand-assisted device and perfused with cold preservation fluid.

The technical difficulty of standard laparoscopic living donor nephrectomy appears to limit its application. Manual assistance, which exploits the incision necessary for intact organ removal, might encourage more surgeons to offer laparoscopic donor nephrectomy. Various occlusion methods enable the introduction of a hand into the abdomen while maintaining pneumoperitoneum. Identification of structures by palpation and the use of the hand for retraction and dissection instead of an instrument, are notable advantages of hand-assisted over standard laparoscopic techniques. Also, hemostasis is obtained easier in case of a bleeding by compressing the vessel with the fingers.

Hand-assisted laparoscopic technique compared to the "pure" laparoscopic technique showed reduction of operative time (2.02 vs. 3.12 hours, p = < 0.05) and warm ischemic time (1.23 vs. 3.91 minutes, p = < 0.05) [21]. Length of stay and recovery time to normal activities were not different between the hand-assisted laparoscopy and the "pure" laparoscopy, but significantly shorter than after open surgery.

The hand-assisted laparoscopy seems to shorten the learning curve of a laparoscopic procedure, an advantage which will allow more transplant centers to perform the procedure, thereby making it available to more patients, and as a consequence, further increasing the number of living kidney donors [22].

Disadvantages of the hand-assisted laparoscopic donor nephrectomy consist of discomfort for the surgeon due to the tight sleeve and stooped posture. The visibility in the abdomen can be impaired because of the relatively large intra-abdominal hand. An other disadvantage is the incision that is usually larger than the incision made in the "pure" laparoscopic procedure. Also, a second incision is needed when conversion is necessary. A final obstacle in the implementation of the hand-assisted laparoscopy is the cost. The hand-assisted device accounts for 11% of the operating room cost [22]. The cost of the device is approximately $ 400 [23].

Alternative methods

Modification of right laparoscopic donor nephrectomy

Mandal et al. suggested modifications for laparoscopic live donor nephrectomy on the right side, due to a high incidence of venous thrombosis [24]. The right vein is shorter than the left one, and the use of the laparoscopic vascular stapling device results in a loss of 1 - 1.5 cm of the length of the renal vein. One modification to preserve as much venous length as possible was to pass the stapler through a right lower quadrant port at the lateral border of the rectus abdominis muscle parallel to the inferior vena cava.

The second modification consisted of relocation of the incision for extraction of the kidney. A right 5-6 cm subcostal skin incision was made, the rectus abdominal muscle was split and reflected but not incised. Prior to extraction, instead of using a stapler, a Satinsky clamp was placed on the inferior vena cava at the origin of the right renal vein. This provided maximal renal vein length. After the kidney was removed, the caval venotomy was closed with a nonabsorbable, monofilament suture in an open fashion. In case of insufficient length of the renal vein a third modification was made. The recipients greater sapheneous vein was used to extent the renal vein.

Because of the relatively short right renal vein, modifications that provide maximum length are very useful. However, these modifications as suggested by Mandal are associated with an increase of morbidity due to the localization of the incision and the use of the greater sapheneous vein.

Laparoscopic donor nephrectomy in combination with minilaparotomy

Mourad et al. have reported their technique, combining laparoscopy with a minilaparotomy [25]. Positioning of the patient and trocars is similar as in the standard laparoscopic procedure. Dissection, on the right side, is started by cutting the triangular ligament of the liver. The parietal peritoneal reflection is cut at the border of the liver in the direction of the inferior caval vein, exposing the adrenal gland and the superior edge of the right kidney. The duodenopancreatic block is displaced medially in order to expose the anterior aspect of the caval vein. After opening of Gerota's fascia the vessels and ureter are dissected.

On the left side, the splenic flexure and the descending colon are mobilized by opening the peritoneal reflection. Dissection of the ureter and the renal vessels is performed. Gonadal and adrenal veins are clipped and divided. Accordingly, the operation is performed identical to the right side.

When the kidney is only attached with its vessels, a minilaparotomy is performed by a transverse incision beginning at the level of the midaxillary port in the direction of the anterior axillary line port. Through this incision, ureter and renal vessels are divided with sufficient length and the kidney is extracted manually.

The combination of laparoscopy with minilaparotomy provides a safe control of vessels and sufficient length of vessels and ureter after division. Horizontal laparotomy allows opening by retraction without muscular transection. However, this subcostal incision is often associated with neuralgia because of the severance of multiple cutaneous nerves.

LAPAROSCOPIC LIVING DONOR NEPHRECTOMY

Left versus right nephrectomy

Left laparoscopic donor nephrectomy is by most surgeons preferred for renal transplantation because of its longer renal vein. Especially after stapling of the right renal vein with a GIA instrument (GIA®, US Surgical, Norwalk, CT) with two triple staple lines, further shortening of the vein occurs. The TA instrument (TA®, US Surgical, Norwalk, CT) applies one triple staple line, thus leaving more length of the vessel.

Mandal et al. reported an incidence of venous thrombosis in three of the eight (37,5%) right allografts [24]. Based on these initial results, the laparoscopic technique was modified as discussed previously. These modifications, together with the mobilisation of the iliac vein at implantation of the kidney to provide a tension-free venous anastomosis, resulted in no subsequent vascular complications. In contrast, Buell et al. found an incidence of venous thrombosis in right-sided laparoscopic donor nephrectomy of 2%, without these modifications [26].

The authors of this review prefer right-sided donor nephrectomy. We consider the right-sided technique to be easier due to the lack of venous branches of the renal vein. As a consequence, in our experience right donor nephrectomy operating time is almost one hour shorter than left donor nephrectomy. Also, right-sided donor nephrectomy avoids a serious complication such as a splenic laceration, which is often the cause for conversion. Retraction of the liver is effectuated by the use of an endo-babcock and no serious liver lacerations have occurred in our hospital.

Studies comparing right and left donor nephrectomy consist mainly of small right-sided kidney groups. In the Erasmus MC, a significant large group of 70 right-sided donor nephrectomies were performed. In **Chapter 2** the incidence of venous thrombosis was investigated comparing left and right sided laparoscopic donor nephrectomy.

Obesity

A retrospective study on obese living kidney donors and open nephrectomy showed that the obese group experienced more minor complications, usually wound related, and slightly longer operation time [27]. In contrast, Kuo et al. concluded that obesity is not associated with increased morbidity and mortality after a laparoscopic donor nephrectomy [28]. Our advice is not to attempt laparoscopic donor nephrectomy in patients with a body mass index over 35 until there is sufficient experience.

Recipient

Laparoscopic live donor nephrectomy for renal transplant demands not only an operation that is safe for the donor but must also deliver a functionally intact kidney that is technically transplantable and provides graft survival comparable to open donor nephrectomy. One concern is that elevated intra-abdominal pressure, associated with pneumoperitoneum, might result in renal ischemia, acute tubular necrosis, delayed graft function and increased allogenicity. In a porcine model, London et al. have demonstrated that pneumoperitoneum resulted in decreased renal blood flow and urinary output [29]. However, intravascular volume expansion may alleviate the effects of CO_2 pneumoperitoneum on renal hemodynamics. McDougall et al. concluded that the decreased urinary output during prolonged intra-abdominal pressure greater than or equal to 15 mm Hg in the animal model was associated with a corresponding decrease in renal vein flow, but did not appear to be associated with any permanent renal derangement nor any histological changes [30].

Recipient creatinine levels reported in three clinical studies were compared between laparoscopic and open nephrectomy groups. One of these studies showed that early creatinine levels were significantly higher for recipients of laparoscopic donor nephrectomy grafts compared to open donor nephrectomy grafts [31]. Mean serum creatinine levels were higher at 1 week and 1 month after transplantation. However, at 3 and 6 months, serum creatinine were similar in both groups. Two other studies reported no statistically significant differences in longer term recipient creatinine levels [32, 33]. In our experience, mean serum creatinine levels in the recipient are higher the fist week postoperatively, after implantation of a laparoscopically donated kidney.

Van Roijen et al. reported urological complications in 6% of the recipients after kidney transplantation [34]. Others have reported urological complication in 7.1 and 7.7% [35, 36]. When comparing the incidence of urological complications for laparoscopic or open donor nephrectomy, Philosophe et al. found the number of ureteral complications requiring operative repair to be significantly higher for the laparoscopic group, 7.7% versus 0.6% [33]. There was however, a learning curve. The number of complications decreased with time. In contrast, Ratner et al. described a similar incidence of ureteral complications between the two groups, with similar survival rates for recipient and graft [37].

Pneumoperitoneum and warm ischemia may have a negative effect on renal function in donor and recipient. In **Chapter 5**, long term serum creatinine levels of donors and recipients were compared after laparoscopic and open donor nephrectomy. In **Chapter 6**, the effect of warm ischemia with- or without pneumoperitoneum on the long term graft function was investigated in a syngeneic rat transplant model. Contradictory reports on ureteral complications resulted in a study comparing ureteral complications after laparoscopic and open donor nephrectomy in the Erasmus MC, as described in **Chapter 7**.

OBJECTIVES OF THIS THESIS

This thesis presents clinical studies and an experimental study, determining the effect of laparoscopic and open donor nephrectomy on donor and recipient. The objectives of this thesis can be summarized as follows:

Chapter 2. To compare right- and left sided laparoscopic donor nephrectomy, focussing on the incidence of venous thrombosis.

Chapter 3. To compare the cosmetic impact of laparoscopic and open donor nephrectomy using the Body Image Questionnaire.

Chapter 4. To compare the duration of sick leave after laparoscopic, open and hand-assisted donor nephrectomy in the Netherlands.

Chapter 5. To compare long-term serum creatinine in donor and recipient after laparoscopic and open donor nephrectomy.

Chapter 6. To determine the effect of prolonged warm ischemia and pneumoperitoneum on the long-term renal function in a syngeneic rat transplantation model.

Chapter 7. To compare the number of ureteral complications in the recipient after laparoscopic and open donor nephrectomy.

Chapter 8. To compare laparoscopic and open donor nephrectomy in a randomized, single blind, multi-center study.

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Chapter 2

Right-sided laparoscopic live donor nephrectomy. Is reluctance still justified?

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ABSTRACT

Background: Laparoscopic donor nephrectomy (LDN) of the right kidney is performed with great reluctance because of the shorter renal vein and possible increased incidence of venous thrombosis.

Methods: In this retrospective, clinical study, right LDN and left LDN were compared.

Between December 1997 and May 2001, 101 LDN were performed. 73 (72%) Right LDN were compared to 28 (28%) left LDN for clinical characteristics, operative data and graft function.

Results: There were no significant differences between the two groups regarding conversion rate, complications, hospital stay, thrombosis, graft function and graft survival. Operating time was significantly shorter in the right LDN group (218 vs. 280 minutes).

Conclusion: In this study, right LDN was not associated with a higher number of complications, conversions or incidence of venous thrombosis compared to the left side. Thus, reluctance toward right LDN is not justified and should therefore not be avoided.

INTRODUCTION

With considerably decreased morbidity and favourable graft function, LDN is progressively accepted [1]. However, controversy persists whether procurement of the right kidney can be done successfully by laparoscopic approach. Most surgeons performing laparoscopic live donor nephrectomy prefer the left kidney due to a longer renal vein. Mandal et al. observed that right kidneys are at risk for allograft thrombosis, presumably due to the short renal vein [2]. Exclusion of donors with arterial or venous anomalies on the left side, due to a reluctance towards the right LDN, would deprive a significant proportion of donors a laparoscopic procedure and its benefits.

We prefer right-sided donor nephrectomy and find right LDN to be less complicated due to the lack of side branches of the renal vein. In this article, we compare left laparoscopic donor nephrectomy (LLDN) and right laparoscopic donor nephrectomy (RLDN) performed at our hospital.

PATIENTS AND METHODS

Patient selection

LDN was performed in 101 patients from December 1997 through May 2001. Patient data were retrospectively collected from medical records. Operative and postoperative data included blood loss, warm ischemia time, operating time and postoperative complications (influencing the postoperative course) and length of postoperative hospitalisation (starting the first day after operation). Per-operative urine production (directly after declamping of the renal vessels), mean serum creatinine levels and graft survival were compared for all recipients. All potential donors were subjected to routine examination, renography, Seldinger angiography, percutaneous utrasonography and MRI-angiography. In case of normal function of both kidneys and assessment of one vein and artery on both sides, the right kidney was preferred for LDN. All renal transplantations were performed by the same transplant surgeon (JNM IJ.).

Operative technique

In eight cases, a pneumatic sleeve was used to allow performance of hand-assisted nephrectomy. LDN was performed as previously reported [3, 4]. In recipients, the iliac vein is circumferentially mobilised and elevated slightly to enable implantation of the renal vein. No grafts or other special techniques were used to extend the renal vessels.

Statistical analysis

Statistical analysis was performed utilising the SPSS 9.0 (SPSS Inc., Chicago, IL) statistical software package. Comparisons of continuous data between right and left donor nephrectomy groups were performed using the Mann-Whitney test. Categorical data were reported as absolute numbers of patients and/or percentages and were compared using the Chi-square test. Analysis of serum creatinine values in the recipient was done by Mixed Model ANOVA after logarithmic transformation. A p-value of < 0.05 was considered to be statistically significant.

RESULTS

Demographic characteristics such as age, sex, Body Mass Index and origin (living related or unrelated) were comparable for both groups. In eight cases (6%) a transperitoneal hand-assisted approach was used, six on the right side (8%) and two on the left side (7%). LDN was initially performed on the left side. After five LLDN, the first RLDN was performed. Operative characteristics for RLDN and LLDN are shown in Table 1. Overall, mean operative time from skin incision to closure was significantly longer for LLDN ($p<0.001$). Median estimated blood loss, mean warm ischemia time, number of conversions and length of hospital stay was comparable for both groups. The number of postoperative complications, which resulted in additional therapy, was comparable for both groups.

The number of recipients with graft diuresis directly after declamping of the renal vessels is shown in Table 2 and was not significantly different between the two groups. In the postoperative period, 98% of the grafts were producing urine. Two recipients (RLDN) required postoperative hemodialysis.

There was one patient with an arterial thrombosis of the graft (1%). This consisted of a kidney that was procured via a RLDN and had developed the thrombosis one day postoperatively due to a problem of the arterial anastomosis, possibly an intima lesion. Laparoscopic procurement of this kidney graft, however, was uneventful.

The number of ureter complications such as obstruction or urine leakage was not significant different and decreased with time. The difference between the number of grafts lost between RLDN and LLDN was not significant; one graft developed an arterial thrombosis during implantation, three other recipients had graft loss for which no technical failure could be accounted for.

Mean serum creatinine of the recipient after logarithmic transformation is shown in Figure 1. Statistical analysis does not show any significant differences between the two groups after correction for pre-operative serum creatinine ($p= 0.15$).

Table 1. Operative characteristics. Data given are mean (range) except blood loss (median, range).

	Right LDN (n=73)	Left LDN (n= 28)	p- value
Operating time (min)[a]	218 (105-420)	280 (210-420)	P < 0.001
Blood loss (mL)	275 (50-2300[b])	250 (100-1000)	NS
Warm ischemia time (min)	7.9 (2-17)	8.2 (2-17)	NS
Conversion	6 (8%)	3 (11%)	NS
Minor bleedings	4	2	
Spleen lesion		1	
Insufficient overview	1		
Ischemia [c]	1		
Hospital stay (days)	3.6 (2-7)	4.4 (2-9)	NS
Post-operative complications	3 (4%)	3 (11%)	NS
Wound abces	2		
Exacerbation CARA	1		
Urine infection		1	
Pneumonia		1	
Laparotomy		1	

[a] Defined as time from skin incision to closure.

[b] One patient required blood transfusion due to a lesion of the epigastric vessels.

[c] clipping of an small arterial branch, to stop minor bleeding, resulted in ischemia of lower pole of the kidney.

Table 2. Graft function and survival. Data given are number of patients (percentage)

	Right LDN (n=73)	Left LDN (n=28)	p-value
Per-operative graft urine production	34/50 (68%)	17/22 (77%)	NS
Thrombosis	1 (1%)[a]	0 (0%)	NS
Ureter obstruction	2 (3%)	2 (7%)	NS
Ureter leakage	3 (4%)	2 (7%)	NS
Graft losts[b]	4 (6%)	0 (0%)	NS

[a] Arterial thrombosis

[b] First graft loss in the 56th LDN

DISCUSSION

To our knowledge, there have been no reports comparing large groups of RLDN to LLDN. However, the reluctance of transplant surgeons remains, excluding donors of laparoscopy when eligible to donate their right kidney.

In our study, operating time of LLDN was 60 minutes longer than for RLDN. The RLDN takes 218 minutes, which is comparable with other reported studies [5-7]. LLDN operating time, however, is longer than reported in most studies. The difference of 60 minutes can be explained by the fact that we initiated the LDN on the left side. Also, the total number of RLDN can reduce the learning curve and, subsequently, operating time. Recent operating time for left kidneys,

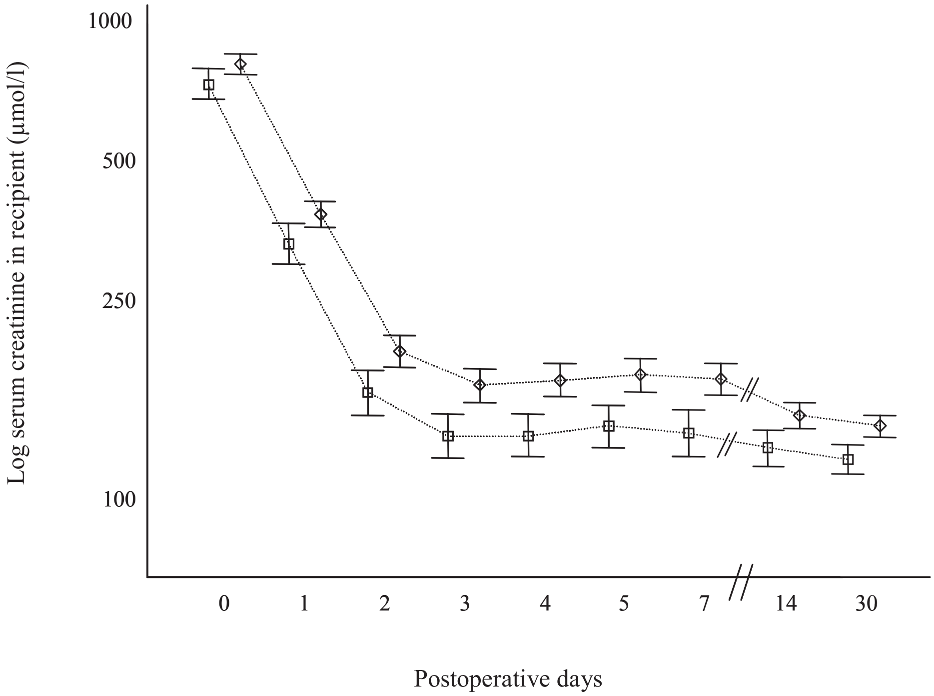

Figure 1. Geometric means of log serum creatinine (± standard error) according to post operative day and left LDN (open squares) or right LDN (open triangles). Day 0 represents preoperative values.

performed when the anatomy of the right kidney precludes its use, is now comparable to that of RLDN. RLDN did not result in additional per- or postoperative complications.

In all RLDNs performed, adequate length of renal vessels could be obtained. In addition, no problems occurred when performing the venous anastomosis. In contrast to other reported incidences of venous thrombosis in the right kidney [2, 7, 8], we found no venous thrombosis. Mean warm ischemia time was comparable for both groups but longer than reported in other studies [9, 10]. Considering graft function in recipients, there were no significant differences between the RLDN and LLDN groups regarding urine production subsequent to reperfusion, serum creatinine and graft survival. The higher number of ureter problems of LLDN grafts can be explained by the learning curve. Modification of dissection of the ureter, leaving the peri-ureteral tissue, resulted in a reduction the number ureteral complications.

We acknowledge the fact that LDN is not accepted by all surgeons as an alternative to open donor nephrectomy since LDN is associated with longer operating- and warm ischemia time, a learning curve and a possible increase in ureteral complications.

In this study there were no differences between RLDN and LLDN regarding conversions, complications, thrombosis, graft function and graft survival. We conclude right-sided laparoscopic kidney donation and subsequent implantation is safe with a low incidence of venous thrombosis. Therefore, reluctance toward right-sided donor nephrectomy is not justified and RLDN should not be avoided. A change in attitude towards RLDN enables donors suitable for right kidney donation to benefit from the advantages associated with laparoscopy.

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Chapter 3

Body image after laparoscopic or open donor nephrectomy

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ABSTRACT

Background: Laparoscopic donor nephrectomy (LDN) is thought to result in a better cosmetic outcome in the altruistic healthy donor compared to open donor nephrectomy (ODN). To our knowledge, there are no studies establishing the opinion of the donor with respect to their bodily appearance. This study investigates the body image of donors after ODN and LDN.

Methods: Donors operated between 1994 and 2001 were invited to fill out a Body Image Questionnaire. This questionnaire consists of two subscales, the body image score (BIS) and the cosmetic score (CS). 56 LDN and 69 ODN responded to the questionnaire (72% of 174 donors).

Results: Both groups were comparable for gender, current age and body mass idex (BMI). Time from donation until the time of this study (follow-up) was significantly longer for the ODN group. BIS and CS were found to be comparable for both groups. No associations were found between BIS or CS and follow-up duration. The same applied to gender, age and BMI.

Conclusion: Body image ratings of donors do not significantly differ after ODN or LDN.

INTRODUCTION

Because of the shortage of cadaveric kidneys, living kidney donors have become of major interest. Living kidney donation is associated with several advantages such as the superior graft survival and the elective nature of the procedure. The altruistic healthy donor must, however, undergo significant morbidity related to the donation. Minimal invasive techniques such as LDN are thought to bring better cosmetic results. Little is known about the attitude of donors towards their scar after open or laparoscopic kidney donation. Dunker et al. developed a "body image questionnaire" that consists of a body image scale and a cosmetic scale [1]. "Body image" is defined as person's perception of, satisfaction with and attitudes toward his or her body in general and to particular areas of the body. In this study we investigated donors body image after open and laparoscopic donor nephrectomy.

PATIENTS AND METHODS

Patient selection

Donors who were operated between January 1994 and May 2001 were selected. This period was chosen to ensure that the time from donation until this study was at least one year. After one year, the remodelling process of the scar was assumed to be complete.

A total of 174 donors were invited to participate in this study by sending them a letter accompanied by a body image questionnaire. The response rate was 72%; 56 donors underwent a LDN and 69 an ODN. The first laparoscopic donor nephrectomy was performed in 1997, the mean follow up for LDN donors was 3 years, the ODN donors 6 years.

The body image questionnaire has previously been described and applied by Dunker et al. where they compared laparoscopic-assisted and open ileocoloc resection and restorative proctocolectomy [1, 2] (Table 1). This questionnaire consists of questions regarding the attitude of the patients towards their bodily appearance (body image scale, items 1 through 5) and the degree of satisfaction with respect to the appearance of their scar (cosmesis scale, items 6 through 8). The body image scale (BIS) consists of five questions, which results in a total score with a minimum of 5 and a maximum of 20. The cosmetic scale (CS) consists of three questions which results for the total score in a minimum of 3 and a maximum of 24. Both scales are such that a higher score indicates a greater satisfaction.

Statistical analysis

Statistical analysis was performed using the SPSS 9.0 (SPSS Inc., Chicago, IL) statistical software package. Comparisons of continuous data between LDN and ODN donors were performed using the Mann-Whitney test. Categorical data were reported as absolute numbers of patients and/or percentages and were compared using the Chi-square test. Correlation of BIS and CS

Table 1. Body image questionnaire consisting of a body image score (items 1 through 5) and a cosmetic score (items 6 through 8). The minimum and maximum possible scores for the BIS are 5 and 20 respectively. In the CS, the minimum score is 3 and the maximum score 24. A higher score signifies a greater satisfaction with the bodily appearance (BIS) and physical appearance of the scar (CS).

1. Are you less satisfied with your body since the operation?
1= no, not at all
2 = a little bit
3 = quite a bit
4 = yes, extremely

2. Do you think the operation has damaged your body?
1 = no, not at all
2 = a little bit
3 = quite a bit
4 = yes, extremely

3. Do you feel less attractive as a result of your operation?
1 = no, not at all
2 = a little bit
3 = quite a bit
4 = yes, extremely

4. Do you feel less feminine/masculine as a result of your operation?
1 = no, not at all
2 = a little bit
3 = quite a bit
4 = yes, extremely

5. Is it difficult to look at yourself naked?
1 = no, not at all
2 = a little bit
3 = quite a bit
4 = yes, extremely

6. On a scale from 1 to 7, how satisfied are you with your scar?
1 = very unsatisfied
2 = quite unsatisfied
3 = a bit unsatisfied
4 = not unsatisfied/not satisfied
5 = a bit satisfied
6 = quite satisfied
7 = very satisfied

7. On a scale from 1 to 7, how would you describe your scar?
1 = revolting
2 = quite revolting
3 = a bit revolting
4 = not revolting/not beautiful
5 = a bit beautiful
6 = quite beautiful
7 = very beautiful

8. Could you score your own scar on a scale from 1 to 10?

with age, body mass index (BMI) and period between donation and the time of this study was determined using the Spearman correlation coefficient. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Donor characteristics are described in Table 2. Since the first LDN was performed in 1997, the time from donation to this study was significantly longer in the ODN group. ODN and LDN groups were comparable for gender, age and BMI at the time of this study. From the donors charts it was found that one LDN and one ODN donor developed a wound abces that required drainage. One ODN donor needed an operation to correct an incisional hernia.

The BIS was comparable for both groups (Table 3). Mean scores were high (approximately 97% of the maximum achievable score of 20). There were also no significant differences when the five items were analysed separately.

The CS was comparable for both groups with mean scores approximately 82% of the maximum achievable score of 24. When comparing the three questions separately, there were no significant differences. LDN and ODN donors scored their scar on a scale from 1 to 10 at 8.5 and 8.6 respectively (range 5 to 10 in both groups).

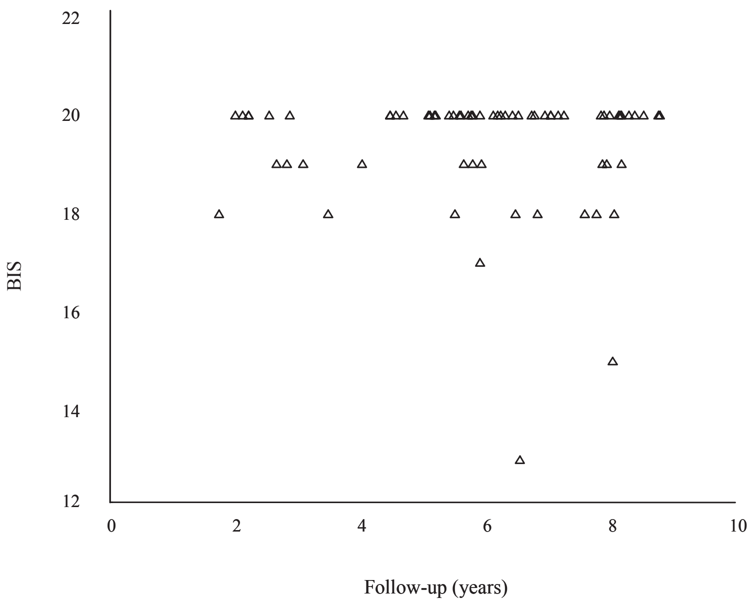
There were no associations between the BIS or the CS versus the duration of the period between donation and the time of this study (BIS versus follow-up shown in Graph 1). The difference in follow-up durations therefore does not bias the comparison of the two groups. We also found no relation between BIS or CS with gender, current age or BMI.

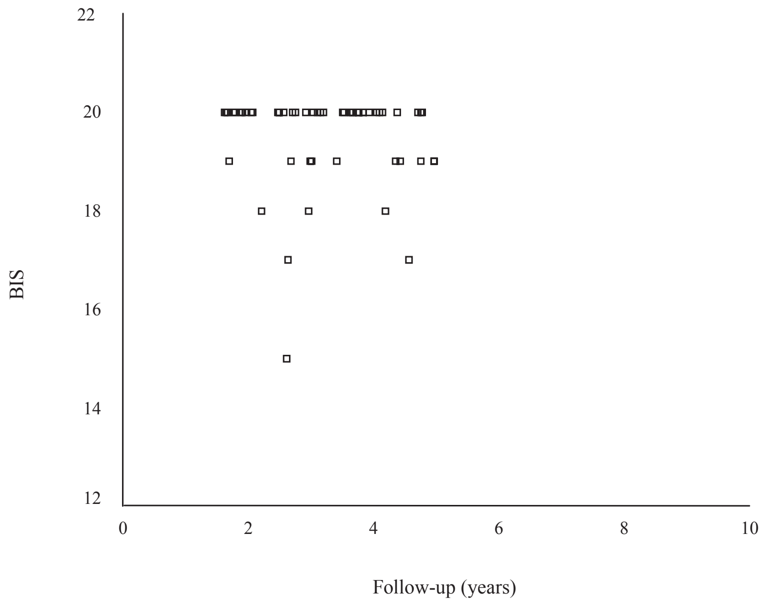
Table 2. Donor characteristics. Data are are given as number of donors (percentage) or as mean (range).

	LDN (56)	ODN (69)	p-value
Gender			
Male	26 (46%)	32 (46%)	1.0
Female	30 (54%)	37 (54%)	
Age (years)	51.9 (27-78)	54.5 (27-81)	0.17
BMI	21.9 (16-30)	23.1 (16-31)	0.09
Follow up (years)	3.4 (1.8-5.1)	6.1 (1.9-8.9)	<0.001

Table 3. Body image and cosmetic scores in donors. Data are given as mean (range).

	LDN (56)	ODN (69)	p-value
Body image score	19.5 (15-20)	19.4 (13-20)	0.74
Cosmetic score	19.7 (11-24)	19.8 (11-24)	0.80





Graph 1. BIS score of living donors after ODN (open triangles) or LDN (open squares) versus duration of follow-up.

DISCUSSION

LDN was introduced to decrease morbidity in the donor and potentially increase the number of living donors. Multiple studies report a better cosmetic result after LDN. To date, the opinion of the donors on the cosmetic result has not objectively determined. This study was performed to investigate donors' body image after ODN and LDN. Data from this study show that the ratings of BIS and CS were comparable after ODN and LDN. Furthermore, BIS and CS were not associated with donor age, gender, BMI or time from donation till execution of this study.

Contrary to Dunker et al., we found no differences in body image after an open or laparoscopic procedure. This discrepancy can be caused by the nature of the operation. The actual donor nephrectomy is preceded by a long process of decision making and counselling. This altruistic character might result in the situation where the donor feels the health of the recipient is superior to that of him- or herself. It is even conceivable that a large scar gives a donor more prestige in the eyes of friends and family. Also, many researchers assume that a larger scar automatically gives an inferior cosmetic result in the opinion of the donor. However, a discrepancy between the opinion of the patient and the observer are not uncommon. Low levels of concordance were found between observers' and patients' ratings in a study on cosmetic outcomes of breast conserving treatment for breast cancer [3].

Since this study was performed in a retrospective cohort study, ODN and LDN groups were not from the same time period. It is possible that results of the ODN group were more favorable. Donors in the open group have had more time to adapt and accept their scar, which might result in a higher BIS and CS. However, we found no association with time and the BIS or CS. Donors did not rate higher score when the donation was longer ago. This applied to both groups.

Finally, the response rate was 72% and we should interpret the results keeping that in mind. It might be possible that the non-responders group consisted mainly of dissatisfied donors although our medical registration system does not show donors with wound complications in this group. This is why we are currently performing a prospective study comparing ODN and LDN, determining the BIS and CS at one year after donation.

In conclusion, LDN does not seem to result in a superior body image compared to ODN, in the opinion of the donor.

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Chapter 4

Live donor nephrectomy and return to work. Does the operative technique matter?

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ABSTRACT

Background: Several studies report an earlier return to work after minimal invasive kidney donation compared to open donor nephrectomy. However, this variation in outcome might be influenced by other factors than the surgical technique used, such as the advice given by the physician regarding return to work. In this study we compare the absence from work after open (ODN), laparoscopic (LDN) and hand-assisted donor nephrectomy (HA) performed in the Netherlands, in relation to the advice given.

Methods: Questionnaires containing questions about return to work or return to daily activities were sent to 78 donors from three hospitals. In the HA and ODN hospitals, advice on full return to work was three months. In contrast, advice given in the LDN hospital was 6 weeks.

Results: After LDN, donors resumed their work after 6 weeks, 5 weeks faster compared to ODN ($p=0.002$) and HA ($p<0.001$). Complete return to work occurred 9 weeks sooner in the LDN group compared to the ODN and HA group (both $p<0.001$). In the unemployed group, there was no significant difference in length until full return to daily activities.

Conclusion: Return to work is influenced by the advice on return to work, given by the physician as well as the morbidity associated with the surgical approach.

INTRODUCTION

The number of available post-mortal kidneys remains stable and is insufficient to match the number of organs required to reduce the waiting list for kidney transplantation. Living (un) related donation represents a large potential supply of organs and, as a consequence, has the potential to reduce the shortage. The discomfort associated with open donor nephrectomy (ODN) however, may deter potential living donors from volunteering. Laparoscopic donor nephrectomy (LDN) represents an alternative to the conventional open method and is associated with less morbidity, shorter length of stay and earlier return to work [4-7]. However, this technique is associated with a long learning curve, discouraging transplant surgeons from applying this technique. The hand-assisted (HA) technique was introduced to make the laparoscopic procedure easier and faster to master, thus resulting in more widespread acceptance by surgeons and increased availability to donors. It is believed morbidity of the hand-assisted technique is comparable to LDN since both techniques result in equivalent incisions. Unfortunately, LDN and HA are associated with increased costs induced by the use of disposable instruments and increased operating time compared to ODN [2, 9]. However, a shorter hospital stay and earlier return to work can compensate these costs.

Studies reporting on convalescence period after kidney donation are mainly performed in the United States, where health care insurance and employment structures are very different from those in the Netherlands. Also, it is questionable to take return to work as an indirect measurement of the invasiveness of the procedure. Indeed, the advice given by the physician might influence return to work more than the morbidity related to the surgical approach. The aim of this study was to evaluate the duration of absence from work for LDN, HA and ODN in relation to the attitude and advice of the supportive care team.

MATERIALS AND METHODS

Patient selection

Three hospitals in the Netherlands, all with extensive operative experience in the field of live kidney donation, supplied a list of patients who had donated a kidney in the period from 25/01/00 through 01/10/01. The list contained information such as operating date, date of birth, gender and addresses. Data on the LDN was provided by the Erasmus Medical Center (EMC), those of the HA group by the University Hospital Amsterdam (AMC) and the ODN group by the University Hospital Nijmegen (St Radboud). A letter accompanying the questionnaire explained the donors participation was on a voluntary basis and would not have any consequences for follow-up and treatment. Questionnaires were sent to 25 donors who were operated in the EMC, 29 donors who were operated in the St Radboud and to 24 donors who were operated in the AMC. The questionnaire contained questions about employment, full or part-time work, return to work (partly or completely back to pre-operative hours) and, when unemployed, full resumption of normal activities. Time to return to work was defined at two moments; on the first day of resuming work after a sick-leave period (return to work) and when donors resumed work according to their pre-operative hours (full return to work).

Follow-up of the donors was in St Radboud and AMC mainly done by a nephrologist. In the EMC, the surgeon performed the follow-up at 3 weeks and 3 months, after which the donors where referred to a nephrologist for annual follow-up. Both St Radboud and AMC informed donors the expected duration until return to normal activities or work would be three months. The EMC informed donors they where expected to resume normal activities or work after 6 weeks. However, in all three centers the decision to go back to work was left to the donor.

Operating technique

Open donor nephrectomy

The patient is placed in a full lateral decubitus position by flexing the operating table, gaining maximum access between the iliac crest and the ribs. The method used in this study consists of an extra-peritoneal approach, with a flank incision just above or below the twelfth rib, cutting the muscles, without resection of the rib. Gerota's fascia is opened and the kidney is mobilised to get access to the renal vessels. After clamping of the renal vessels as close to the aorta and caval vein as possible, these structures and the ureter are cut. The organ is removed through the incision and is placed in a basin filled with cold preservation fluid. A needle is placed in the artery, and the kidney is flushed with a 4 °C preservation solution until the venous effluent is clear and the kidney is discoloured.

Laparoscopic (transperitoneal) donor nephrectomy

The patient is positioned on the operating table similar to the open approach allowing a conversion to lumbotomy, if necessary. After a subumbilical open introduction of a 10 mm Hasson-trocar, pneumoperitoneum is established by insufflation of carbon dioxide with an abdominal pressure of 12 mmHg. A 10 mm 30º video endoscope is inserted and the abdomen is inspected. Under direct vision, a 10 mm trocar and three to four 5 mm trocars are placed and instruments can be introduced. A 5 mm endo-babcock clamp is used for retraction of the liver or spleen. Retraction is secured by grasping the lateral abdominal wall. The hepatic or splenic flexure of the colon is mobilised using a 5 mm curved ultrasonic device (Ultracision®, Ethicon, Sommersville, NJ) and retracted medially, exposing the kidney. Gerota's fascia is opened and the renal vein and ureter are identified and dissected. The anterior and posterior aspects of the kidney are both freed as well as the upper pole from adjacent attachments and structures. At this point, the kidney is allowed to fall medially and the renal artery, which is identified behind the renal vein, is dissected towards the aorta. The vessels are encircled with a rubber vessel loop to enable gentle traction and correct positioning of the stapling device. Dissection of the ureter, including the peri-ureteral tissue and the ureteral arterial branch, is carried on to the crossing with the iliac artery. The left gonadal, lumbar and adrenal veins are clipped and divided. The adrenal gland is released from the medial superior aspect of the renal capsule using the ultrasonic device. Preparations are then being made for extraction of the kidney by making a Pfannenstiel incision of about 5 cm. Through this incision, an extraction device (Endocatch, US Surgical, Norwalk, CT) is inserted. After administration of 5000 U of heparin the ureter is clipped and divided. The renal vein and artery are divided using a linear vascular stapler (EndoGIA 30®, US Surgical, Norwalk, CT). Anticoagulation is then reversed with protamine. The kidney is placed in a specimen bag and brought out through the 5 cm incision and flushed with cold preservation fluid.

After closure of the incision, pneumoperitoneum is re-established and the abdomen is inspected. After complete haemostasis, the trocars are removed and the incisions are closed.

Hand-assisted donor nephrectomy

The procedure is performed as previously described in an article by Bemelman et al. [1]. A Pfannenstiel incision of approximately 7.5-8 cm is made correlating with the size of the surgeons glove. This incision is used to mobilise the coecum or sigmoid and the distal ureter. Subsequently, the hand port is installed (Omniport, Advanced Surgical Concepts, Co., Wicklow, Ireland), and the left hand is inserted. A pneumoperitoneum of 12 mm Hg is established. Two 10- to 11-mm trocars are introduced, respectively, subumbillically and in epigastrio. The operation is further conducted in the same order as the laparoscopic procedure. After dissecting and dividing of the ureter and the vessels, the kidney is removed with the aid of the hand-assisted device and perfused with cold preservation fluid.

Statistical analysis

Statistical analysis was performed using the SPSS 9.0 (SPSS Inc., Chicago, IL) statistical software package. Comparisons of continuous variables between laparoscopic, hand-assisted and open donor nephrectomy were performed using the Mann-Whitney test. Categorical data was reported as absolute number of patients and/or percentage of the group studied and was compared using the Chi-Square test. Correlation of age with return to work for each group was determined using the Spearman correlation coefficient. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Of the 78 questionnaires that were sent to living kidney donors, 73 were returned (94%) and all were analysed. The analysed LDN group consisted of 25 donors, the HA group of 22 donors and the ODN group of 26 donors.

Demographic data is listed in Table 1. There were no significant differences between the three groups for gender, employment and the type of employment (full- or part-time). Employed donors in the HA group are generally younger compared to the ODN and LDN groups (p<0.001, respectively p=0.013). In the unemployed group, ODN donors are generally older than LDN and HA (p=0.034, respectively p=0.004).

As shown in Table 2, return to work, either partly or completely back to pre-operative hours, was accomplished 6 weeks after LDN. This was significantly shorter than ODN and HA, which were respectively 12 and 10 weeks. Also, full return to work (100% of preoperative hours) was significantly shorter in the LDN in contrast to ODN and HA. ODN did not differ from HA for either outcome. There was no significant correlation of age with time until complete (100% of preoperative hours) return to work for either groups (all p>0.15, Figure 1). The same applied to 'partly' return to work.

Table 1. Demographic variables. Data given are number of patients (percentage) or median (range)

	Open donor nephrectomy (ODN) n=26	Laparoscopic donor nephrectomy (LDN) n=25	Hand-assisted donor nephrectomy (HA) n=22
Gender			
Men	15 (58%)	12 (48%)	9 (41%)
Women	11 (42%)	13 (52%)	13 (59%)
Employed			
Yes	15 (58%)	19 (76%)	14 (64%)
No	11 (42%)	6 (24%)	8 (36%)
Employment			
Full-time	12 (80%)	11 (58%)	9 (64%)
Part-time	3 (20%)	8 (42%)	5 (36%)
Age (Years)			
Total group	52 (37-74)*	46 (25-65)°	38 (25-63)
Employed group	48 (37-58)*	45 (25-62)#	34 (25-47)
Unemployed group	65 (48-74)	54 (25-65)§	52 (36-63)¥

* p< 0.001 vs. HA, # p= 0.013 vs. HA, § p= 0.034 vs. ODN, ¥ p= 0.004 vs. ODN, ° p=0.01 vs. ODN

Table 2. Employment and absence from work. Data given are median (range).

	Open donor nephrectomy (ODN)	Laparoscopic donor nephrectomy (LDN)	Hand-assisted donor nephrectomy (HA)
Employed	N=15	N=19	N=14
Return to work[1] (weeks)	12.0 (3-22)*	6.0 (0.5-25)	10.0 (5-21)#
Return to work[2] (weeks)	15.0 (4-32)#	6.0 (0.5-33)	15.0 (5-36)#
Unemployed	N=11	N=6	N=8
Full recovery (weeks)	4.3 (0-13)	4.5 (3-10)	5.2 (0-8)

* p= 0.002 vs. LDN, # p< 0.001 vs. LDN

[1] Partly or completely back to pre-operative hours, [2] Completely back to pre-operative hours

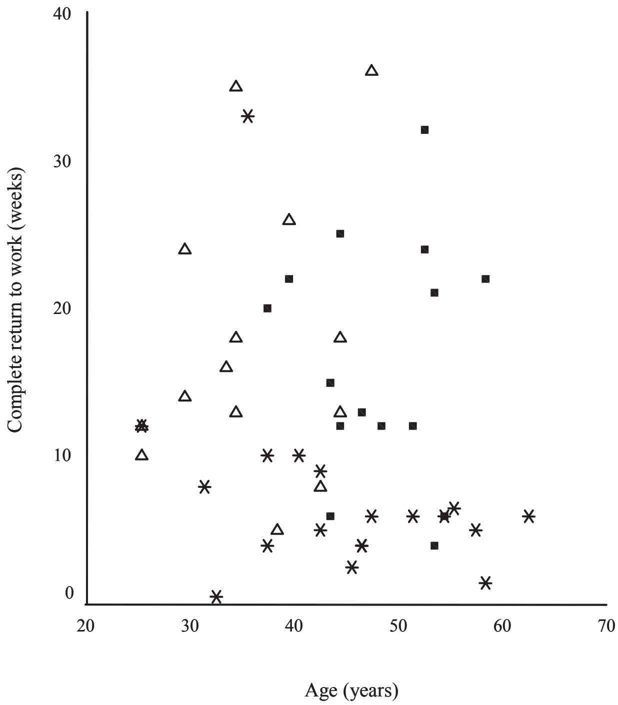

Figure 1. Graph showing correlation of age with return to work after LDN (stars), ODN (closed squares) and HA (open triangles).

In the unemployed group, time to full return to daily activities similar to preoperative activities, was comparable for all three groups.

DISCUSSION

Since the number of post-mortal kidneys falls short to the number required by the number of patients waiting for a kidney transplantation, living donation represents a large supply of organs. However, the altruistic, healthy donor is exposed to morbidity associated with the donor nephrectomy, which may deter potential donors from donating. A long convalescence period and absence from work may also be an important disincentive to the potential donor. Studies show a reduced discomfort and convalescence of the donor after laparoscopic or hand-assisted donor nephrectomy [3-8]. Question remains if correlation of the surgical technique with the reduction in convalescence is valid or if the decrease is mainly caused by the socio-economic behaviour of the donor.

Several American studies show a return to work after 2.3 to 3.9 weeks in the LDN group compared with 5.3 to 7.4 weeks in the ODN group [3, 4, 6]. In another report, donors returned to work after 3.5 weeks after HA compared to 4.1 weeks after ODN [8]. In our study, absence from work is considerably longer for all groups compared to American studies. This might be caused by the difference in social and insurance structures. In the Netherlands, donors receive paid sick-leave from work so there is no stimulus to restart work as quickly as possible. Also, advice from physicians regarding return to work may be different from that given in the United States. A Swedish study, comparing ODN and LDN, showed a duration of sick-leave of 6 weeks in the laparoscopic group compared to 7 weeks in the open group. Time away from work of our LDN group is comparable with that of the LDN group from the Swedish study. However, we have found a much longer absence for the open group.

When comparing absence from work of the HA group from our study and that of an American study, we find a (mean) difference of more than 3 months (3.5 vs. 17.7 weeks) [8]. The age of both groups is comparable (37 vs. 38 years) and does not explain this discrepancy. The dissimilarity could be a result of a difference in social and economical structures of the United States and the Netherlands. Also, hand-assisted donors, in this study, are informed prior to operation they will probably not work for three months. It seems the donors comply with this advice.

Although the hand-assisted procedure was introduced as an operating technique accompanied by the same benefits as LDN, in this study, the HA group differs significantly with regard to absence from work compared to the LDN group. Wolf et al. showed a comparable morbidity after hand-assisted and laparoscopic nephrectomy [10]. This indicates that the difference found in return to work between the LDN and ODN group is probably caused by the difference in advice prior to operation. The donors of the LDN group were informed they probably would not work for 6 weeks, contrary to the HA group who where told they would be absent for three months.

Contrary to the literature [11], donors of the HA group refrained from work as long as the donors from the ODN group. The comparable variables in time away from work for HA and ODN group suggests a corresponding morbidity for both operating techniques. However, this is unlikely since the incision of the HA is much smaller and the abdominal wall muscles are not divided. A reason for the similar results of HA and ODN could be that both groups received the same advice from their physicians related to the expected duration of sick-leave (based on their own experience).

We have found no difference in duration until full recovery in the unemployed group. This indicates donor recovery periods are similar for all groups but return to work is dependent on the advice given by the care-takers.

This study demonstrates that in a well-defined population there is a great variance in return to work after a live donor nephrectomy. Question remains if this variation in outcome is caused by the morbidity related to the surgical approach or a difference in the advice given to the donor with regard to return to work. Considering the comparable morbidity after HA and LDN, the difference in return to work may be a reflection of attitude and expectation of the physician more than the actual recovery period of the donor. It is remarkable the actual duration of sick-leave of all groups correlates with the advice given by the physician. Secondly, it is important to note that recovery is similar in the non-employed group.

In conclusion, this study shows that the approach and the advice of the physician to the donor regarding the moment of resumption of work has a great influence on the convalescence period and in particular the actual return to work. In order to perceive return to work as an indirect measure of the invasiveness of the procedure, all donors should receive similar advice. It is important to realise that advice and stimulation from the physician on return to work influences the outcome. All studies comparing morbidity and convalescence period of surgical techniques should define a methodological standardisation with regard to this advice given to the donors. Only then can we determine if a more rapid convalescence is caused by a socio-economic policy or the surgical technique used.

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Chapter 5

The effect of laparoscopic and open donor nephrectomy on the long term renal function in donor and recipient: a retrospective study

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ABSTRACT

Background: Pneumoperitoneum, as used in laparoscopic donor nephrectomy (LDN), may result in negative effects on renal function in donor and recipient. This study compares long-term serum creatinine in donor and recipient after laparoscopic and open donor nephrectomy (ODN).

Methods: A retrospective analysis of 120 LDN and 100 ODN donors and their recipients was performed. Serum creatinine of donor and recipient was recorded and analysed. The follow-up period post-transplantation was 3 years.

Results: Serum creatinine in the recipients was significantly higher in the LDN groups the first week after transplantation. Serum creatinine in the donor was significantly higher in the LDN group at 1 day, 3 months and 1 year post transplant. Finally, creatinine levels remained 40% higher compared to preoperative values in both donor groups.

Conclusion: LDN results in higher short-term serum creatinine levels in donor and recipient. Long-term serum creatinine levels were comparable after LDN or ODN in donor and recipient.

INTRODUCTION

The therapy of choice for end stage renal failure is kidney transplantation. Unfortunately, the number of cadaveric kidneys required for transplantation is exceeding the number of available kidneys. The use of kidneys from living donors might reduce the shortage of donor kidneys. Living (un)related donor kidney transplantation is associated with advantages such as reduced waiting-list period, elective nature of the operation and better graft and patient survival compared to cadaveric kidney donation [1]. Open donor nephrectomy (ODN) is associated with a mortality of 0.03% and considerable morbidity [2]. In order to reduce morbidity and potentially increase the number of living donors, various alternative techniques were introduced. Ratner et al. performed the first laparoscopic donor nephrectomy (LDN) in 1995 [3]. Several studies show a reduction in hospital stay, pain and return to work comparing laparoscopic to open donor nephrectomy [4-8]. Other techniques currently applied are the hand-assisted and retroperitoneal approach.

Establishing a pneumoperitoneum is necessary when performing a transperitoneal laparoscopic donor nephrectomy to provide sufficient working space and overview of the operating area to the surgeon. This pneumoperitoneum is, however, accompanied with important negative hemodynamic effects. Intra-abdominal pressure due to gas insufflation results in decreased renal flow and subsequent renal ischemia in the graft and the remaining kidney in the donor [9]. The impact of pneumoperitoneum on the kidney function in donor and recipient remains controversial. Some studies show a decreased short-term graft function in recipients of laparoscopically procured kidneys [10, 11], while other studies show no difference [12, 13]. Studies, investigating long-term renal function in kidney donors after open donor nephrectomy show a deterioration in renal function of about 30% [2, 14].

Considering the potentially increased renal ischemia during laparoscopic donor nephrectomy compared to open kidney donation, we were interested in determining whether long term serum creatinine would be significantly higher after laparoscopic donor nephrectomy compared to open donor nephrectomy in both the donor and the recipient.

MATERIAL AND METHODS

Patient selection

A retrospective analysis of all living (un)related kidney donors and their recipients, operated between 04-01-1994 and 12-03-2002, was performed. In this period, a total of 220 donor nephrectomies were carried out of which 120 in a laparoscopic (of which 8 with the hand-assisted technique) and 100 in an open fashion. LDN was performed as previously reported with intra-abdominal pressures of 12 mm Hg [15]. All removed kidneys were transplanted. Because the first LDN at our institute was performed in December 1997, the follow up period of the

LDN group was shorter than that of the ODN group. Analysis was performed until three years follow-up for both groups.

Data from donors were collected from medical records and consisted of age, gender and operating technique. Serum creatinine levels were available preoperatively and on days 1, 2, 21, 90, 365, 730 and 1095 postoperatively. These serum creatinine levels were statistically analysed as discussed below.

Data collected from recipients consisted of age and gender. Serum creatinine levels were available preoperatively and on days 1, 2, 3, 4, 5, 7, 14, 28, 180, 365, 730 and 1095.

Statistics

Statistical analysis was performed using the SPSS 10.0 (SPSS Inc., Chicago, IL) statistical software package on an 'intention to treat' basis. Analysis of serum creatinine levels of donor and recipient was done after log-transformation to approximate normal distribution. Repeated measurements ANOVA using the PROCMIXED procedure from SAS showed that the differences of donors and recipients depended on the day for serum creatinine levels. Therefore, an univariate analysis of variance was performed per day. Preoperative serum creatinine levels were determined as baseline values and analysed as covariate into the univariate analysis. Using regression analysis we adjusted for differences between the two groups (age and origin).

Analysis of donor and recipient age was done using the Mann-Whitney test. Categorical data such as gender and origin were reported as absolute numbers of patients and/or per-

Table 1. Donor and recipients characteristics are given as number of patients (percentage) or mean (range). # insufficient data available for analysis.

	LDN (122)	ODN (100)	p-value
DONOR			
Gender			
Male	56 (47%)	43 (43%)	0.68
Female	64 (53%)	57 (57%)	
Age (years)	47 (20-76)	48 (20-77)	0.70
BMI	25.5 (17-35)	25.8 (16-37)	0.76
Operating time (min)	236 (105-420)	157 (75-310)	< 0.001
Warm ischemia time (min)	7.7 (2-17)	#	

	LDN (122)	ODN (100)	p-value
RECIPIENT			
Gender			
Male	74 (62%)	52 (52%)	0.15
Female	46 (38%)	48 (48%)	
Age (years)	45 (16-73)	40 (18-71)	0.002
Origin donor			
Related	68%	88%	0.001
Un-related	32%	12%	

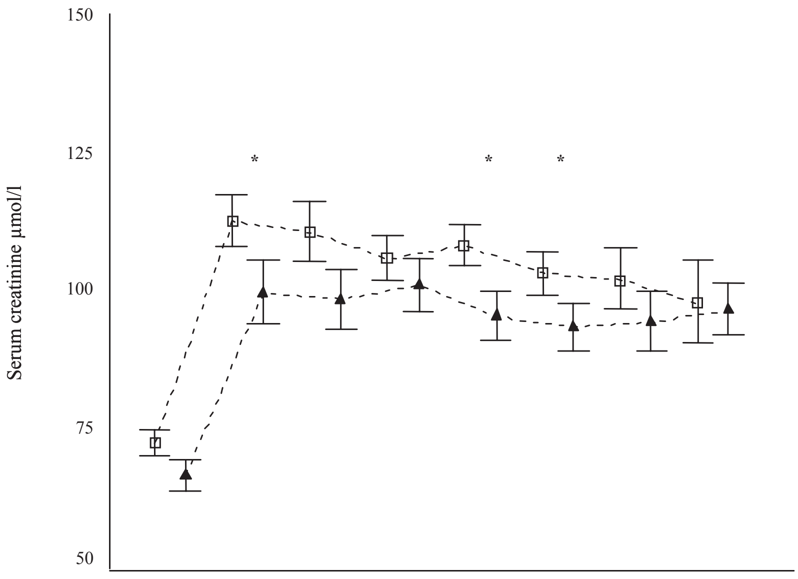
centages and were compared using the Chi-square test. A P-value of <0.05 was considered to be statistically significant.

RESULTS

There were no significant differences between LDN and ODN donor-groups for age and gender (Table 1). Operating times were significantly longer in the LDN group (Table 1).

Comparing log serum creatinine, LDN donors had significantly higher serum creatinine levels on postoperative day 1 (p=0.034), day 90 (p=0.008) and 1 year (p=0.031) compared to ODN donors (Figure 1). In both groups serum creatinine remained approximately 40% higher than preoperative values (Figure 2).

In recipients, gender was not significantly different between the ODN and LDN groups. The LDN recipients, however, were significantly older than the ODN group. Also, the percentage of living unrelated donations was significantly higher in the LDN recipients. With regard to log serum creatinine, we found significantly higher values in recipients of LDN kidneys compared to ODN kidneys in the first week post-transplant (Figure 3).



DAY:	0	1	2	21	90	365	730	1095
LDN#	120	99	103	98	113	94	62	33
ODN#	99	73	81	88	94	83	69	66

Figure 1. Geometric mean serum creatinine (micromol/l) with 95% CI of living kidney donors in time (open squares= LDN, closed triangles=ODN). * = p-value < 0.05 after correction for the difference in baseline values. Day 0 represents preoperative values.

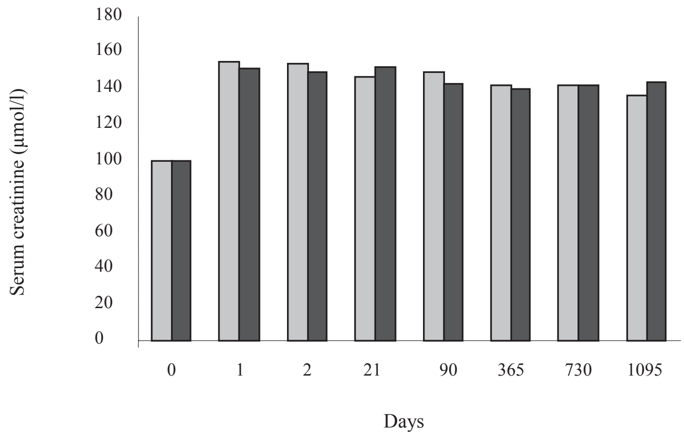


Figure 2. Bar chart representing serum creatinine (percentage) of the donor in comparison to pre-donation values in time (light grey bars =LDN, dark grey bars =ODN). Day 0 represents preoperative values.

DISCUSSION

Ever since the first successful laparoscopic donor nephrectomy, the safety of this procedure for donor and recipient has been questioned. It is commonly known that pneumoperitoneum, necessary for the laparoscopic technique may cause intra operative adverse cardiovascular and renal effects [9]. This study was conducted to investigate renal function (serum creatinine) in donor and recipient after ODN and LDN. We found a significantly higher serum creatinine in LDN donors on day 1, 3 months and 1 year after donation. Also, serum creatinine post-donation remained 40% higher than preoperative values. In recipients, serum creatinine was significantly higher in the LDN group during the first week after transplantation.

A clinical study by Ratner et al., comparing graft function in recipients after ODN and LDN, showed a higher serum creatinine on day 2 and 3 in the laparoscopic group [11]. Also, Nogueira et al. found a significant higher serum creatinine during the first week after transplantation in recipients of laparoscopically procured kidneys [10]. In accordance with their findings, we also found higher serum creatinine levels in recipients of laparoscopically procured kidneys in the first week after transplantation. After the first week, however, serum creatinine levels were comparable until three years post-transplant. There seems to be a short-term graft dysfunction in kidneys after laparoscopic donor nephrectomy compared to the kidneys from open donor nephrectomy. The laparoscopic and open groups in this study differ significantly with respect to the origin of the donor (living related or unrelated). It is, however, not very likely that this difference is the main causal factor for the short-term graft dysfunction. Terasaki et al. reported similar graft survival rates of unrelated kidney grafts compared to related kidney grafts [1]. With respect to the age, studies show a decreased graft survival in younger recipients

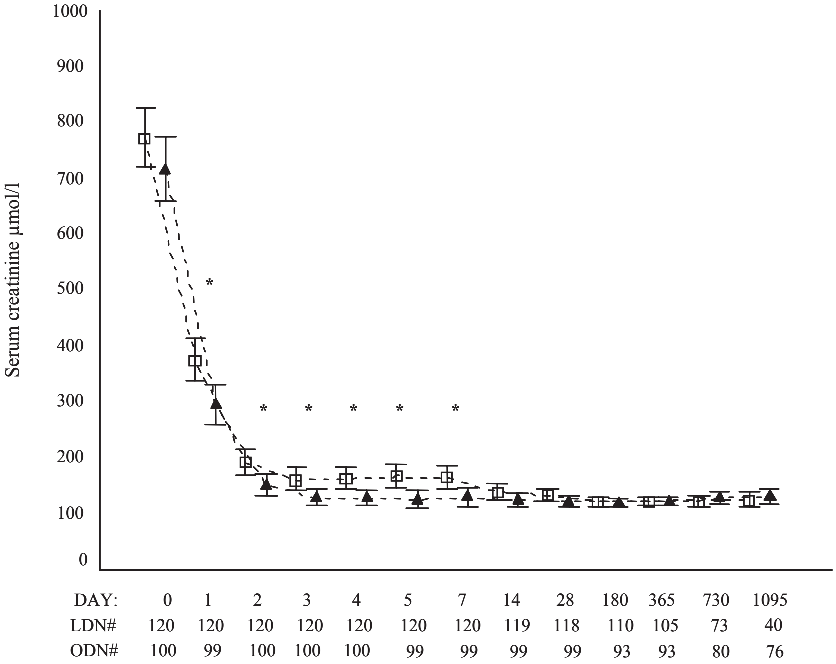


Figure 3. Geometric mean serum creatinine (micromol/l) with 95% CI of recipients in time (open squares= LDN, closed triangles=ODN). * = p-value < 0.05 after correction for the difference in baseline values. Day 0 represents preoperative values.

compared to older recipients [16, 17]. The higher serum creatinine levels in the LDN group can not be explained by the age difference since the ODN group was younger. Finally, after adjusting for the differences between the two groups for age and origin, serum creatinine levels remained significantly higher the first week post-transplantation in the LDN group.

One very important discriminating factor between ODN and LDN is the pneumoperitoneum. This may explain the higher serum creatinine levels we found in the first week post-transplantation. In an animal model, Kirsch et al. showed that with an intra abdominal pressure (IAP) of 10 mmHg the blood flow in the caval vein was decreased by 54% and the aortic blood flow by 7% [18]. Also, urine output was decreased and creatinine levels were elevated. McDougall et al. demonstrated a significant decrease in renal vein flow concomitant with a drop in urine output at a pressure of 15 mmHg [19]. These effects persisted for several hours after desufflation. This transient renal dysfunction has been well documented and various mechanisms have been described to explain these changes, which are probably multi factorial. Proposed mechanisms include decreased cardiac output, renal vein compression, ureteral obstruction, renal parenchymal compression and systemic and regional hormonal effects. Cisek et al., in an animal model, performed renal reductive surgery and applied 20 mmHg IAP for 6 hours [20]. Dramatic drops in urine output (80%), GFR (63%), and renal blood flow (20%) were noted with concomitant acute renal failure related to tubular cell injury, without chronic renal failure.

These observed blood flow changes suggested the possibility of renal tubular damage secondary to ischemia as a cause of oliguria during pneumoperitoneum. Altintas et al. showed significant histologic changes in rabbit kidneys after only 1 hour of pneumoperitoneum with pressures up to 15 mmHg [21]. Several authors, however, report reduced urine output and GFR without chronic damage to the tubula. Lee et al. found no histologic damage after 5 hrs of pneumoperitoneum in a rat study, McDougall et al. confirmed a lack of histologic abnormality in kidneys rendered oliguric at pressures of 15 mmHg [22, 19]. To counteract the effects of pneumoperitoneum expert anaesthesiologists and intense volume management are of major importance [23]. Also, it should be noted that intra-abdominal pressures must be as low as possible, keeping in mind that retroperitoneal donor nephrectomy does not require pneumoperitoneum, avoiding any negative effects of increased intra-abdominal pressure.

A decreased renal flow due to increased intra abdominal pressure might not only have a negative effect on the graft, but also on the remaining kidney in the donor. Serum creatinine levels in donors were significantly higher after LDN. Renal clearance is determined by renal blood flow and GFR, both are deprived during pneumoperitoneum up to 75% [24]. This so called prerenal azotemia (insufficient renal blood flow) leads to hormone release, which enhances hormonal directed tubular reabsorption and induces systemic and renal afferent artery vasoconstriction. Normally, prerenal azotemia leads predominantly to tubular ischemia and could lead to acute renal failure [25]. Interestingly, it has been demonstrated that the autoregulatory behaviour of renal circulation is lost in laboratory animals with post ischemic acute renal failure [26].

Of interest is that in both groups serum creatinine levels remained 40% higher than preoperative levels for both groups, comparable to Goldfarb et al. who found an increase of approximately 30% [14]. After unilateral nephrectomy, in literature creatinine clearance decreases by approximately 35% [2, 14].

We acknowledge the fact that this is a retrospective study with significant differences in cohorts. Although, after adjusting for these differences with regression analysis the higher levels serum creatinine in LDN recipient the first week remained. We are currently monitoring LDN and ODN renal function in donor and recipient in a prospective fashion.

In conclusion, this retrospective study shows higher serum creatinine levels in recipients of laparoscopically procured kidneys in the first week after transplantation. It is reassuring that these levels normalise to comparable levels in ODN recipients, until three years post-transplantation. Serum creatinine was found to be higher in the first year after donation in LDN donors compared to ODN donors. Although serum creatinine from one year until three years post-transplant are comparable for LDN and ODN groups, serum creatinine levels remain approximately 40% higher than preoperative values.

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Chapter 6

Effect of prolonged warm ischemia and pneumoperitoneum on renal function in a rat syngeneic kidney transplantation model

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ABSTRACT

Background: Laparoscopic donor nephrectomy is associated with several advantages for the donor. Graft function, however, might be impaired due to use of pneumoperitoneum and prolonged warm ischemia. This study investigates the impact of pneumoperitoneum and prolonged warm ischemia on long term graft function in a syngeneic rat renal transplant model.
Methods: A total of 27 Brown Norway (BN) rats were randomized for transplantation of kidneys after three different procedures: no insufflation and no warm ischemia (group 1), no insufflation with 20 minutes warm ischemia (group 2) and one group with CO_2 insufflation and 20 minutes warm ischemia (group 3). Glomerular filtration rate (GRF), serum creatinine, urine volume, urine creatinine and proteinuria were determined monthly for one year. One year after transplantation, the grafts were removed for histomorphologic analysis.
Results: No significant differences in GRF, serum creatinine, urine volume and proteinuria were found comparing the three groups. Histologic analysis also showed no differences between the different groups.
Conclusion: Warm ischemia in combination with CO_2 pneumoperitoneum, as used in laparoscopic donor nephrectomy, does not result in a negative effect on the long-term graft function, in a syngeneic kidney transplant model.

INTRODUCTION

Laparoscopic donor nephrectomy (LDN) was performed for the first time in 1995 to decrease morbidity related to open donor nephrectomy (ODN) and, subsequently, to increase the number of living donors. Several retrospective studies have shown laparoscopic kidney donation to offer significant advantages for the donor such as decreased postoperative pain and faster recovery [1-7].

However, laparoscopic donor nephrectomy may be associated with a short-term impaired graft function compared to open donor nephrectomy [8-10]. This diminished graft function might be a result of several factors associated with laparoscopic donor nephrectomy. First, studies comparing LDN and open donor nephrectomy (ODN) show a longer warm ischemia time in the laparoscopic approach [4]. The effect of this longer warm ischemia time on the long term graft function should not be underestimated since Brennan et al. showed that warm ischemia is a dominant risk factor for poor early graft function after living kidney donation [11]. A second factor influencing the graft function might be the pneumoperitoneum necessary for laparoscopic donor nephrectomy. This pneumoperitoneum induces a reduction of renal blood flow, inducing ischemia [12, 13].

The objective of this study was to determine, in a syngeneic rat renal transplant model, whether prolonged warm ischemia combined with pneumoperitoneum, as in laparoscopically donated kidneys, results in reduced long-term renal function in the recipient.

MATERIALS AND METHODS

Animals

Male rats of the inbred Brown Norway (BN) strain, weighing 250-300 g and aged 10-12 weeks were obtained from Charles River, Someren, The Netherlands. Rats were bred under specific pathogen free conditions and kept at a temperature of 20-24 °C with a 50-60% humidity and a 12 hours light/12 hours dark cycle. The rats were fed with laboratory diet (Hope Farms, Woerden, The Netherlands) and had free access to water. The experimental protocol adhered to the rules as determined by the Dutch Animal Experimentation Act and was approved by the Committee on Animal Research of the Erasmus University Rotterdam.

Experimental design

A total of 27 rats were allocated into three groups as follows: one group without pneumoperitoneum and without warm ischemia (group 1, n=8), one group without pneumoperitoneum but with prolonged warm ischemia (group 2, n=10) and one group with both CO_2 pneumoperitoneum and prolonged warm ischemia (group 3, n=9). Rats randomized to pneumoperitoneum were insufflated with CO_2 at a pressure of 12mm Hg for two hours. Warm ischemia was induced by placing the kidney into a 37 °C phosphate-buffered saline (PBS) solution for 20 minutes, after which the kidney was implanted in the recipient. In the group without warm ischemia, the kidney was transplanted immediately. Serum creatinine, urinary creatinine, urine volume and urinary protein excretion per 24 hours were measured monthly for one year. After one year, all animals were sacrificed and the grafts were investigated histomorphologically by light microscopy.

Operative procedures

Kidney donor

Anaesthesia was established with pentobarbital sodium 20 mg/kg/h intraperitoneally (Nembutal®; Sanofi Sante Animale Benelux BV, Maassluis, The Netherlands), given every hour. The rat was placed on a heating path (Swetron AB), the abdomen was shaved and cleaned with 70% alcohol and dried with gauze. In the group with CO_2 insufflation, a 5-mm skin incision was made in the midline of the abdomen after which a 5-mm trocar (Ethicon Endo-Surgery, Cincinatti, OH, USA) was introduced and secured with a purse string suture. CO_2 insufflation was maintained for two hours. After this period, the trocar was removed and heparin (100 IU) was administered (in all groups). Subsequently, a unilateral left nephrectomy was performed through a small medial laparotomy. The kidney was placed into warm PBS for 20 minutes or transplanted immediately, depending on the group.

Kidney recipient

Syngeneic kidney transplantation was performed using a modification of the technique described by Fisher and Lee [14]. Recipient rats were anaesthetised with ether. Prior to implantation, a unilateral left nephrectomy was performed. The graft was implanted on the left side. During the implantation procedure, the graft was wrapped in a gauze moisturised with PBS. Both artery and vein were anastomosed in an end-to-side fashion using 9-0 prolene. The perioperative warm ischemia time in the recipient was approximately 30 minutes in all animals (during anastomosis). After revascularisation, the ureter was anastomosed end-to-end to the distal end of the recipient's own ureter using interrupted 10-0 prolene sutures.

Nephrectomy of the right kidney was postponed until one week postoperatively to ensure an optimal recovery of the recipient.

Functional measurements

Post-transplantation, recipient rats were placed in metabolic cages every month to collect urine and determine the 24 hours urine production. In addition, blood samples were taken to measure serum creatinine levels. Serum and urinary creatinine were determined using the Jaffe method without deproteinization. Urinary protein excretion was measured colorimetrically by addition of pyrogallol red [15].

The glomerular filtration rate (GFR) per 100 gram body weight was based on the clearance of creatinine. Creatinine clearance (ml/min) was calculated using the following formula:

$$Creatinine_{urine} \times Volume_{urine} \text{ per 24 hours} / Creatinine_{serum} \times 1440$$

Histology

After twelve months the grafts were harvested from the recipient, fixed in a 3.6% buffered formaldehyde solution after longitudinal dissection and embedded in paraffin. Sections of 1µm thickness were stained with hematoxylin and eosin, silver (modified Jones staining) and periodic acid Schiff (PAS). The slides were evaluated in a blind fashion by a nephropathologist (I.B.). Parameters taken into account to score the number of glomeruli with ischemic changes were: tuft collapse, glomerular basement wrinkling, mesangial expansion, splitting of Bowman's capsule, and global glomerulosclerosis. Parameters taken into account to score ischemia on the basis of tubulo-interstitial changes were: tubular atrophy and interstitial fibrosis (in combination with lymphocytic infiltrates). However, interstitial lesions were hardly present in this study group. Vascular changes did not occur at all. Also, hyalinosis was completely absent. The renal capsule and the ureter were always normal, without signs of inflammation or hemorrhage.

Therefore, the final categorization was predominantly based on the affected number of glomeruli and scored as follows:

0 no abnormal glomeruli
1 <5% abnormal glomeruli
2 5-20% abnormal glomeruli
3 20-50% abnormal glomeruli

Statistical analysis

Repeated measurements ANOVA using the PROCMIXED procedure from SAS was used to compare outcome variables (serum creatinine, proteinuria, GFR and urine volume per 24 hours). In this evaluation proteinuria per 24 hours was compared after log-transformation to approximate normal distribution. In case differences between groups were found to depend on the month of measurement, an independent samples t-test was performed for each month separately. In view of the number of comparisons made, the limit of significance was set at p=0.01. Scores of histomorphology were analysed using the Mann-Whitney test. A P-value of <0.05 was considered to be statistically significant.

RESULTS

Renal function

Figure 1 shows the results of serum creatinine, urinary production, proteinuria and GRF for all groups. The average level during follow-up of GFR, serum creatinine, urine volume, and proteinuria, did not significantly differ for group 1 versus group 2 (p=0.46, p=0.49, p=0.42 and p=0.98 respectively).

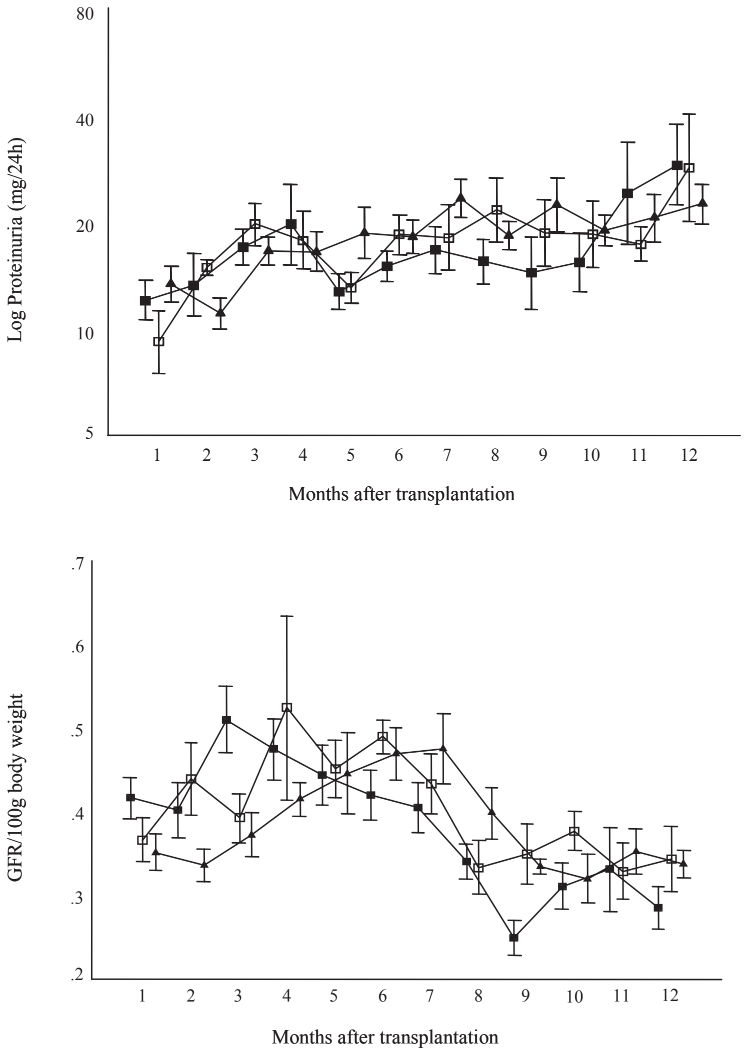
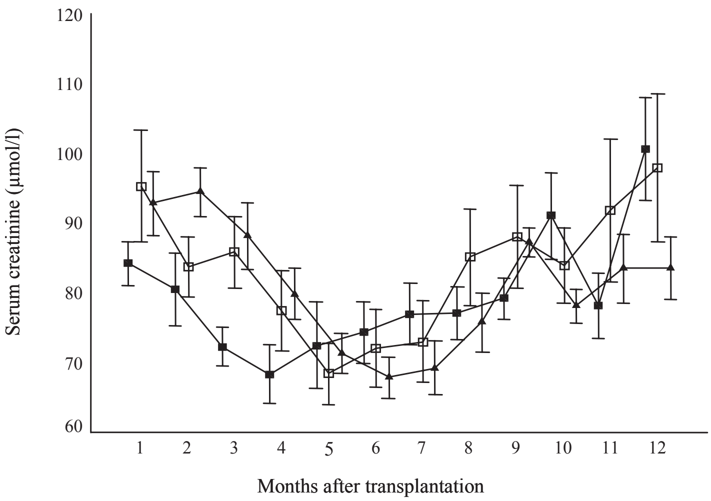
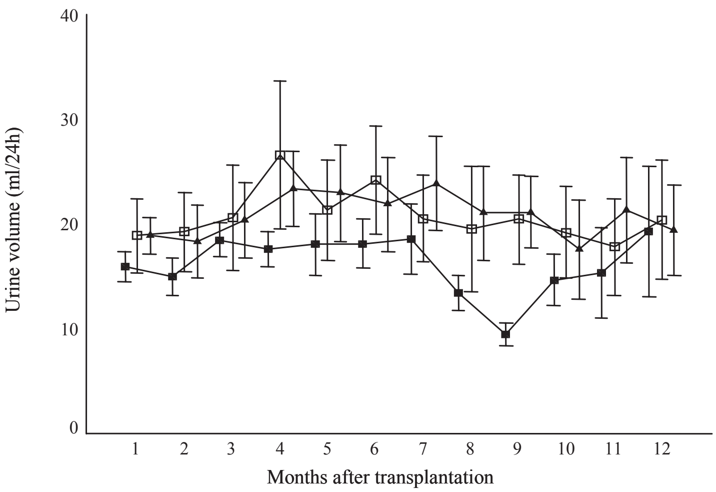


Figure 1. Renal function in recipients of kidneys from group no pneumoperitoneum, no warm ischemia (closed squares), group no pneumoperitoneum, 20 minutes of warm ischemia (open squares) and group 12 mm Hg pneumoperitoneum, 20 minutes warm ischemia (closed triangles). Data are represented as mean ± SEM (error bars).

Comparing group 2 and group 3, GFR, serum creatinine, urine volume, and proteinuria did not differ on the average level during follow-up (p=0.55, p=0.67, p=0.94 and p=0.58 respectively). Finally, comparing group 1 and group 3, GFR, serum creatinine, urine volume, and proteinuria did also not differ on the average level during follow-up (p=0.88, p=0.79, p=0.39 and p=0.61).





Histology

Figure 2 shows the distribution of histopathological scores for all groups. Mean scores of group 1, 2 and 3 were 0.9, 0.8 and 1.1 respectively. Statistical analysis showed no significant differences between the groups (Mann-Whitney test, group 1 versus group 2 p=0.61, group 2 versus group 3 p=0.38, group 1 versus group 3 p=0.65).

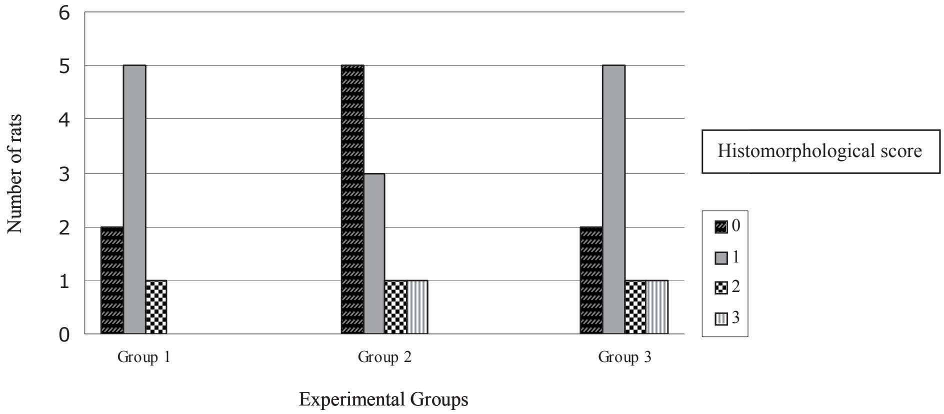


Figure 2. Histomorphological scores per rat in group 1 (no pneumoperitoneum, no warm ischemia), group 2 (no pneumoperitoneum, 20 minutes of warm ischemia) and group 3 (12 mm Hg pneumoperitoneum, 20 minutes warm ischemia) as determined by a nephropathologist (I.B.).

0 = no abnormal glomeruli
1 = <5% abnormal glomeruli
2 = 5-20% abnormal glomeruli
3 = 20-50% abnormal glomeruli.

DISCUSSION

Laparoscopic donor nephrectomy must be safe for the donor and warrant optimal graft function after procurement. It has been shown that LDN is technically feasible and can be performed safely in selected candidates. However, some studies showed a higher short-term serum creatinine in recipients of laparoscopically procured kidneys compared to recipients of open donor nephrectomy. Ratner et al. reported a higher serum creatinine in LDN recipients than in recipients receiving a kidney obtained by conventional methods, at postoperative days two and three [9], whereas Nogueira et al. reported a higher serum creatinine in LDN recipients at one week and one month post-transplant [8]. This difference in graft function may be caused by the pneumoperitoneum in combination with a prolonged warm ischemia time associated with LDN. The objective of this study was to determine the impact of CO_2 pneumoperitoneum during two hours combined with 20 minutes of warm ischemia on long-term graft function.

For this study, we used a syngeneic rat model, enabling us to investigate the influence of pneumoperitoneum and warm ischemia as an isolated factor on histomorphology and function of the kidney graft in the absence of an allogeneic response. We demonstrate that warm ischemia alone, or in combination with pneumoperitoneum has no negative effect on renal function or histomorphology in the recipient for the period of one year post-transplant.

When performing a transperitoneal laparoscopic donor nephrectomy, pneumoperitoneum is necessary to provide the surgeon with sufficient working space. There have been several experimental animal studies investigating the effect of pneumoperitoneum on the renal function. Hazebroek et al. showed that the type of insufflation gas, helium or CO_2, did not impair either short-or long-term renal function [16, 17]. The intra abdominal pressure (IAP), however, has a significant effect on the renal function. McDougall et al. and Kirsch et al. showed a decrease in urine output and GFR with increasing IAP's [18, 19]. A pneumoperitoneum of 15 mm Hg for four hours resulted in a decrease of renal blood flow to 70% of the baseline [13]. Even IAPs of 4 and 10 mm Hg resulted in a reduction of the renal circulation in the range of 34% and 41% respectively [20]. Finally, a significantly higher number of histopathological changes were found after pneumoperitoneum compared to a control group in which no CO_2 insufflation was performed [21]. These studies demonstrate that increased IAP, caused by insufflation of CO_2 gas, results in decreased renal blood flow and subsequent decreased urine output and GFR. This reduction in blood flow of the kidney may lead to ischemia and long-term decreased graft function.

A relatively long warm ischemia time in LDN is mainly caused by the time-consuming introduction of an extraction device and the extraction through a small Pfannenstiel incision. Jablonski et al. showed an elevation of serum creatinine and ureum on postoperative day 2 in 67% of the rats that were subjected to 30 minutes of renal warm ischemia [22]. They also showed that necrosis of the proximal convoluted tubule was present in kidneys after 30 minutes of warm ischemia. Cruzado et al. found a significant increase in serum creatinine levels and a significant decrease in creatinine clearance in rats that were subjected to 60 minutes of renal warm ischemia [23]. In LDN, warm ischemia times exceeding 30 minutes are uncommon. In our own clinical series, maximum warm ischemia time was 17 minutes which was due to technical difficulties during the extraction phase [24]. This is why we chose 20 minutes of renal warm ischemia for this experimental study, assuming this would reflect the maximum warm ischemia time in LDN. Comparing all three groups, we found no significant differences until one year post-transplantation. In addition, twenty minutes of warm ischemia did not result in a difference in histopathological changes, one year after renal transplantation. Thus, we conclude that 20 minutes of warm ischemia does not result in long term graft dysfunction.

Of interest is a study by Akbulut et al., who found that pneumoperitoneum of 12 mm Hg and 10 minutes of warm ischemia act synergistically to amplify oxidative stress in rat kidneys [25]. They suggest that this additive interaction of pneumoperitoneum and warm ischemia may cause renal damage in donor and recipient. However, we found no evidence of a synergistic effect of warm ischemia and pneumoperitoneum on renal function and histology in the recipient.

In summary, we conclude that a warm ischemia time of 20 minutes does not impair graft function and histomorphology during one year after renal transplantation in a syngeneic rat model. Most importantly, warm ischemia in combination with pneumoperitoneum does not result in an additive negative effect on long-term graft function.

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Chapter 7

Laparoscopic versus open donor nephrectomy: Ureteral complications in recipients

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ABSTRACT

Background: Laparoscopic donor nephrectomy (LDN) has proven to be safe and offer significant benefits to the donor compared to open donor nephrectomy (ODN). Of major importance is the effect of the surgical technique on the graft. Studies show an increased incidence of ureteral complications in recipients of laparoscopically procured kidneys. An operative reconstruction results in additional morbidity for the recipient. This study describes our experience with LDN and ODN regarding ureteral complications.

Methods: Living donors and their recipients, operated in the period January 1994 to April 2002, were included in this retrospective study. A total of 122 LDN and 77 ODN recipients were included.

Results: Fifteen (12%) LDN and 10 (13%) ODN recipients required a percutaneous nephrostomy drain. In total, 5 (4.1%) LDN and 5 (6.5%) ODN recipients needed a reconstruction of the ureter due to obstruction of the ureter or leakage of urine (p=NS, excluding the reconstructions due to technical errors). Operating time, warm ischemia and serum creatinine was comparable between recipients with- or without ureter complications requiring reconstruction.

Conclusion: Laparoscopic donor nephrectomy in our study was not associated with an increased incidence of ureteral complications in the recipient compared to open donor nephrectomy.

INTRODUCTION

Live donor nephrectomy is increasing due to a shortage of cadaveric kidneys. Also, live kidney donation offers several advantages such as increased graft survival and reduced waiting time for the recipient. Donors face a series of potential disincentives such as postoperative pain, hospitalization, cosmetic concerns and absence from work. In order to reduce these disincentives and lower the psychological barrier for donation, laparoscopic donor nephrectomy (LDN) was introduced in 1995 [1]. This technique significantly reduced the postoperative pain and convalescence period, compared to conventional, open donor nephrectomy (ODN) [2-6]. However, LDN might have a negative impact on the quality of the graft. Nogueira et al. reported a higher serum creatinine in LDN recipients at 1 week and 1 month post-transplant [7]. Furthermore, a higher incidence of ureteral complications after LDN compared to ODN has been reported by several studies [7-9]. Ureteral complications are associated with additional morbidity for the recipient, especially when resulting in surgical intervention. Although LDN offers several advantages to the donor, this technique should first of all be safe for the graft. LDN was introduced at the Erasmus MC in 1997 and has since been the operating technique of choice. This study describes our experience with LDN and ODN regarding ureteral complications.

MATERIALS AND METHODS

Patient selection

In the period of January 1994 to December 1997, 77 ODNs were performed. In December 1997 LDN was introduced as the procedure of choice for harvesting kidneys from living donors. From December 1997 to April 2002, 122 LDNs were performed. These 122 LDN and 77 ODN donors and their recipients were included in this retrospective study. We excluded one ODN and four LDN pediatric recipients and their donors (less than 16 years old).

The operating technique of LDN and ODN was described previously [10]. In short, LDN was performed in a transperitoneal fashion. Dissection of the ureter occurred with the use of an ultrasonic device. Dividing of the ureter was done at the level of the crossing with the iliac vessels using clips. ODN was performed in a retroperitoneal manner. Dissection of the ureter was performed with the use of scissors, whereas dividing of the ureter was done in the same fashion as in LDN using clips. In ODN and LDN, the ureter was dissected leaving as much peri-ureteral fat as possible but not including the gonadal vein. In recipients, the ureter was implanted in the bladder using an transvesical implantation technique. Two ODN recipients with a previous Bricker procedure required an alternative implantation.

Renal function of recipients after transplantation was monitored by daily measurement of serum creatinine and urine production. Routinely, all renal transplants were evaluated in the first days postoperatively with ultrasound and/or a 99m technetium mercaptoacetyl triglycyne renography. When a ureteral complication was suspected (increasing serum creatinine, reduced urinary output, painful graft), an ultrasound examination was performed. If the ultrasound showed dilatation of the pyelum or fluid collection (urine leakage), a percutaneous nephrostomy drain (PCN) was placed. Antegrade pyelography was used for follow up of the ureter lesion.

We retrospectively reviewed the computerized database and medical records of kidney donors and recipients. Recipients that developed a urological complication were identified. A ureteral complication was defined as a lesion requiring surgical reconstruction. Demographics of donor and recipient and serum creatinine of the recipient, at day 1, 2, 3, 4, 5, 7, 14, 28, 180 and 365, were also noted.

Sufficient data for analysis were available for 122 recipients who received a LDN kidney and 77 who received an ODN graft.

Statistical analysis

Statistical analysis was performed using the SPSS 10.0 (SPSS Inc., Chicago, IL) statistical software package. Data were analyzed on a intention to treat principle. LDN and ODN recipients with- or without ureteral complications were compared at each day separately using ANOVA with adjustment for the preoperative creatinine. All analysis of serum creatinine was done after log-transformation to approximate normal distribution. Comparisons of other continuous variables between LDN and ODN were performed using the Mann-Whitney U test. Categorical data were reported as absolute number of patients and/or percentage of the group studied and was compared using the chi-square test. A P-value of <0.05 was considered to be statistically significant.

RESULTS

In the period of January 1994 to April 2002, 77 ODN and 122 LDN and were performed. Demographics of donor and recipient are shown in Table 1.

In the postoperative period, 15 LDN recipients (9 recipients with a dilated pyelum and 6 recipients with fluid collections at ultrasound examination) and 10 ODN recipients (6 recipients with a dilated pyelum and 4 recipients with fluid collections at ultrasound examination) required a PCN (Table 1). In the LDN group, a PCN was placed 10 and 11 days (median) after transplantation in recipients with an obstruction or fluid collection respectively. Most PCNs were placed within 37 days after transplantation. However, in one LDN recipient, at a routine check-up, serum creatinine was elevated and ultrasound examination showed considerable widening of the pyelum. A PCN was placed 106 days after transplantation and a reconstruction was necessary for obstruction of the ureter. In the ODN group, a PCN was placed for

Table 1. Donor and recipient demographics. Data are given as number of patients (percentage) or median (range). * excluding ureter reconstructions due to technical errors.

	Laparoscopic donor nephrectomy (122)	Open donor nephrectomy (77)	p-value
Age donor (years)	48 (20-76)	49 (20-73)	NS
Gender donor			NS
Male	56 (46%)	32 (42%)	
Female	66 (54%)	45 (58%)	
Age recipient (years)	47 (16-73)	35 (18-67)	P<0.001
Gender recipient			NS
Male	76 (62%)	43 (57%)	
Female	46 (38%)	33 (43%)	
Origin			P<0.001
Living-related	84 (69%)	73 (95%)	
Living-unrelated	38 (31%)	4 (5%)	
PCN	15 (12%)	10 (13%)	NS
Ureter Reconstruction	6 (4.9%)	5 (6.5%)	NS
	5 (4.1%)*	5 (6.5%)*	NS

obstruction or fluid collection after 13.5 and 10.5 days (median) respectively. PCNs were inserted within 24 days of the transplantation. One ODN recipient was admitted one year after transplantation with complaints of his stomach and fatigue. Serum creatinine was elevated and ultrasound examination showed a wide pyelum and ureter. A PCN was placed (416 days after transplantation) and a reconstruction was eventually necessary. The time-point of PCN placement was not associated with the type of complication (obstruction or leakage) or whether or not the recipient eventually required a reconstruction, for both groups.

Of the recipients with a PCN, 5 (33% of all PCNs) in the LDN and 5 (50% of all PCNs) in the ODN group required surgical intervention. One LDN recipient required re-exploration the same day after transplantation due to urine leakage via the drain and did not receive a PCN prior to reconstruction. Possible insufficient drainage of the urine catheter resulted in secondary tearing of the vesico-ureteral anastomosis and subsequent leakage of urine. Considering the transvesical approach, we found no cystostomy leaks in the recipients.

In total, 6 (4,9%) LDN recipients (4 with a ureter obstruction, 2 with urine leakage) and 5 (6,5%) ODN recipients (5 with a ureter obstruction) needed reconstruction of the vesico-ureteral anastomosis, which is not significantly different (p=0.75, Table 1). Intra-operatively, we found fibrosis or necrosis of the ureter in all but one recipient. The one recipient without fibrosis was the patient with the urine leakage due to tearing of the vesico-ureteral anastomosis. Excluding technical errors as a cause of need for reconstruction, 5 (4.1%) LDN recipients and 5 (6.5%) ODN recipients required surgical reconstruction of the ureter due to fibrosis or necrosis of the ureter (p=0.51). There was no association of ureter reconstructions with the time-point of the transplantation (p=0.68).

In the LDN group, 4 recipients required a ureteroneocystostomy and 2 a pyelocystostomy for reconstruction of the ureter. In the ODN group, 1 recipient needed a pyelocystostomy, 2 recipients a ureterneocystostomy, 1 recipient a Boari flap and 1 recipient a proximal ureterpyelostomy for reconstruction. In 8 recipients (73%), the primary reconstruction surgery was successful. However, 2 ODN patients (one Boari flap and one pyelocystostomy) needed a second and one ODN patient a second and a third reconstruction.

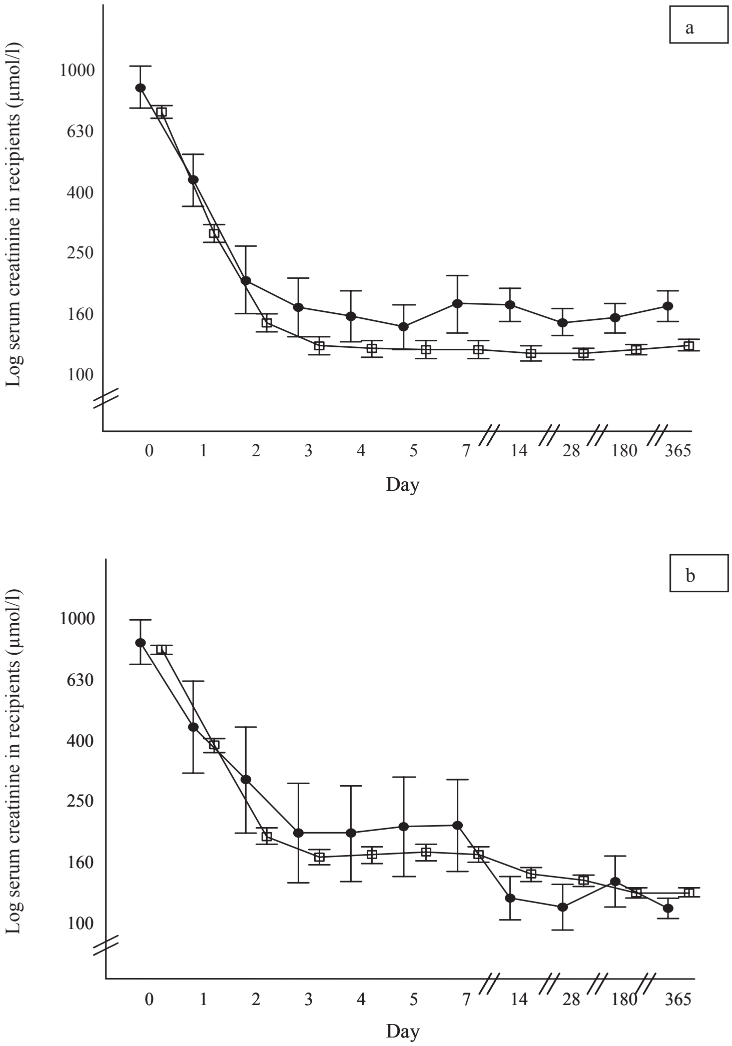

Figure 1. Graph showing log serum creatinine (µmol/l) of recipients with (closed circles) and without (open squares) ureteral complications after LDN (a) and ODN (b). Results are given for day 0 (pre-transplant), 1, 2, 3, 4, 5, 7, 14, 28, 180 and 365. Results are represented as mean ± 1 SEM of logcreatinine.

Operating time of LDN and ODN recipients and warm ischemia time of LDN recipients that developed a ureteral complication requiring surgical correction was comparable with that of recipients who did not develop a ureter complication. The mean warm ischemia time of LDN was 7.7 minutes. In open donor nephrectomy this time was not noted. There was no significant difference between left or right kidneys with regard to the need for a PCN or reconstruction.

Comparing serum creatinine in recipients with or without ureter reconstruction in the LDN and ODN group, there were no significant differences till one year follow up (Figure 1).

DISCUSSION

Several retrospective studies reported laparoscopic kidney donation to be associated with decreased postoperative pain and faster convalescence of the donor. Adversaries to the laparoscopic approach question the safety of this procedure with regard to potential damage to the organ which may be detrimental for the recipient [11]. They refer to articles reporting an impaired short-term graft function and a higher incidence of ureter complications of LDN kidney grafts [7, 9]. This study was performed to investigate the incidence of ureteral complications after LDN and ODN.

Data from this study showed that the number of PCNs and ureteral complications were comparable for both groups. Also, serum creatinine, in recipients requiring a reconstruction, was not significantly different than that of recipients without a reconstruction.

Studies comparing ureteral complications in recipients after ODN and LDN have reported different results. Two studies, performed by the University of Maryland, described a higher incidence of ureteral complications in LDN recipients (7.7% vs. 0.6% and 4.5% vs. 1.0%) [7, 9]. On the other hand, Ratner et al. found no significant differences in ureteral complications comparing ODN and LDN recipients (9.1% vs. 6.3% respectively) [12]. Similar to the latter study, we found a comparable incidence of ureteral complications (6.5% and 4.1% in the ODN and LDN group respectively, excluding technical errors as a cause of need for reconstruction). Since this study was performed using non-concurrent series, the number of reconstructions could be dependent on the experience of the surgeon. We found, however, no association of ureter reconstructions with time. Therefore we consider the outcome of the LDN not more favorable than that of the ODN group due to a learning curve of the surgeon. Operating time and warm ischemia were comparable for recipients with- or without reconstruction and are therefore not likely a causal factor for ureteral complications. Ureter obstructions requiring a reconstruction are thought to be caused by stripping of the peri-ureteral fat of the ureter with subsequent ischemia and fibrosis or a small caliber intravesical anastomosis. To ensure enough fat tissue and blood supply around the ureter, dissection of the gonadal vein and ureter together is suggested [13]. An additional benefit of this technique is that mobilization and dissection can be accomplished without grasping or touching of the ureter, thus avoiding tissue damage.

We do not dissect the ureter together with the gonadal vein and still the percentage of ureter complications is relatively low. The need for dissection of the ureter together with the gonadal vein is therefore open for discussion.

In this study, not all recipients that needed a PCN eventually required a surgical reconstruction of the ureter. It seems that in many cases, the ureteral complication necessitating a PCN resolved with time. Obstructions of the ureter due to blood clots in the pyelum or ureter, a hematoma compressing the ureter or edema of the vesicoureteral junction can cause a transitory obstruction. A small defect at the vesicoureteral anastomosis, causing urine leakage, can heal when urine is temporarily diverted by means of a PCN. We should keep in mind that intervention with PCN is an imprecise endpoint since the decision to place a PCN can be subjective.

Although we realize that the comparison of serum creatinine between the reconstructive and non-reconstructive groups was made with a small reconstructive group, the results implicate that the development and reconstruction of a ureteral complication does not impair graft function up to one-year post transplantation.

In conclusion, we find a comparable incidence of ureteral complications requiring reconstruction after LDN and ODN.

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Chapter 8

A randomized, blinded study comparing laparoscopic and minimal invasive open donor nephrectomy: The short term results

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ABSTRACT

Background: A well constructed randomized trial comparing laparoscopic and muscle-split open donor nephrectomy is lacking. To determine which operating technique is the procedure of choice we performed a randomized multicenter study comparing these two operating techniques with regard to peri-operative outcome, morbidity and convalescence. This article describes the short-term results.

Methods: A total of 100 donors were randomized for laparoscopic or muscle-split open donor nephrectomy. Donors and care takers were blinded for the operating technique used. Peri-operative data were recorded such as operating time, warm ischemia time and blood loss. In addition, peri- and postoperative complications were noted. Postoperatively, quality of life forms were filled out by the donor to determine pain and nausia. Finally, hospital stay was determined.

Results: Short term results show longer operating times and longer warm ischemia times. Donors experienced less pain after laparoscopic donor nephrectomy compared to the muscle split technique. Hospital stay was significantly shorter in the laparoscopic group.

Conclusion: Laparoscopic donor nephrectomy results in significant short term benefits for the donor compared to open muscle-split kidney donation.

INTRODUCTION

The shortage of cadaveric kidneys with increasing demand has resulted in renewed interest in living donors. Living donors represent a large potential pool of kidneys for transplantation, with superior outcomes compared to cadaveric kidneys [1]. Unfortunately, this is at the expense of the healthy altruistic donor with potential morbidity and a small risk of mortality [2,3]. In order to decrease morbidity, the laparoscopic donor nephrectomy was introduced by Ratner et al. in 1995 [4]. Several retrospective studies show decreased pain and a faster convalescence compared to kidney donation through a lumbotomy [5-9]. An alternative technique to this classical approach is the muscle-split incision, dividing rather than dissecting the abdominal muscles. Studies show a reduced morbidity compared to the lumbotomy [10].

Till this day no randomized studies haven been published comparing the laparoscopic and muscle-split donor nephrectomy. We performed a randomized multicenter study comparing these two operating techniques with regard to peri-operative outcome, morbidity and convalescence. This article describes the short-term results.

PATIENTS AND METHODS

Inclusion

The Medical Ethics Committee of the Erasmus Medical Center and the Medical Ethics Committee of the University Medical Center St Radboud both approved the study protocol.

Prior to randomization, a trial period in both participating hospitals was initiated to ensure adequate data collection and logistics. Potential problems were analysed and corrected. In both hospitals a trial coordinator was present. Living donors, aged over 18 year of age, with adequate knowledge of the Dutch language and willing to give informed consent were eligible for inclusion. Donors with previous operations to the kidney or adrenal gland or with radiological abnormalities necessitating a modified approach were not included.

All donors were screened by a nephrologist. Imaging of the kidneys was performed using ultrasound and Magnetic Resonance Angiography (MRA), allowing evaluation of arterial as well as venous anatomy. Donors were admitted and randomized one day preoperatively.

Prior to randomization, the left or right kidney was chosen for nephrectomy based on radiological examinations. In case of multiple arteries or veins in one kidney, the contralateral kidney was chosen. When the vasculature was equal in both kidneys, the smallest kidney was selected for removal. In case of equal size, the right kidney was chosen.

Randomization

Randomization was coordinated by the statistician using computerised allocation the day before operation. Also, one day preoperatively a select group (anaesthesiologist, surgeon and operating nurse) were informed on the randomized operating technique for donor nephrectomy. Apart from this select group no one was informed on which operating technique was used, including the staff on the ward and the patient.

Identical blood stained wound dressings were applied in the operating room covering potential laparoscopic and open donor nephrectomy wounds. A text stating "Do not remove" was written on the dressings. The dressings were removed on the day of discharge, after the quality of life forms were filled out. A sealed envelop containing information about the procedure performed was placed in the donors chart in a sealed envelop in case of emergency. Digital operation reports were not available until one week postoperatively ensuring the blinding of the medical staff and donor.

Anaesthesia and analgesia

All donors were pre-hydrated 10 hours preoperatively using intravenous crystalloids. The total amount of administered fluid was based on the donors length and weight. Preoperatively, donors were fitted anti-embolic stockings and received 1000 mg acetaminophen. Anaesthetic and fluid regiments were protocollised. One hour after commencing the operation, 20 mg Mannitol (100 cc, 20%) was administered to ensured adequate urination. With the exception of one donor that required endocarditis prophylaxis, no antibiotics were given. Postoperatively, all donors received a Patient Controlled Analgesia device (PCA) enabling the donor to administer intravenous morphine by pressing a button. Furthermore, 1000 mg acetaminophen tablets were offered to the donor four times a day until discharge. The PCA device was removed at the request of the donor and when morphine was not required for at least six hours.

Surgical procedures

In both centers there were two referent surgeons of whom at least one attended each operation in this study. These referent surgeons had performed at least thirty laparoscopic donor nephrectomies before the start of the trial, minimising the learning curve effect. All operations were attended by the trial coordinator of each center. Blood loss, operating times, use of instruments and complications were scored during the operation.

Laparoscopic donor nephrecomy

The patient was placed in a lateral decubitus position and the operation table was maximally flexed. Under direct vision, a 10-mm trocar was introduced subumbillically and the abdomen was insufflated until a 12-mm Hg carbon dioxide pressure was reached. A 30° video endoscope was introduced. Four additional trocars were placed and the colon was mobilised 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 and branches of the adrenal, gonadal and lumbar veins were clipped with titanium clips (Ligaclip, Ethicon, Cincinnati, USA) and divided. At this stage a 4-6 cm Pfannenstiel incision was made and an endobag (Endocatch, US surgical, Norwalk, USA) was introduced in the abdomen. The ureter was divided and 5,000 units of heparin were administered. Thereafter, 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 and stored on ice. Meanwhile, protamine was administered and the Pfannenstiel incision was closed in two layers. Again, the abdomen was insufflated. Hemostasis was ensured and the trocars were removed. All skin incisions were sutured intracutaneously.

Open muscle-split donor nephrecomy

The patient was placed in a lateral decubitus position and the operation table was maximally flexed. A 8-12 cm skin incision was made anterior to the 11th rib. The fascia and muscles of the abdominal wall were carefully divided in the longitudinal direction. 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. Meticulous dissection of the kidney followed, especially at the upper pole of the kidney to avoid damage to the adrenal gland and to the vascular pedicle. Ureter, renal vein and artery were identified and encircled with vessel loops. Gonadal, lumbar and adrenal vasular branches were divided if necessary. Thereafter, the ureter was clipped and divided. Before clamping and ligating of the renal artery and vein successively, 5,000 units of heparin were administered intravenously. The kidney was removed. Perfusion and storage were as aforementioned for laparoscopy. Prothrombine was given, and haemostasis was applied. The fascia of the abdominal muscles were closed using vicryl 1/0 (Ethicon Inc., Cincinnati, USA). The subcutaneous fascia was approximated and the skin was sutured intracutaneously.

Postoperative data

Postoperatively, the doctors on the ward kept the researchers informed twice daily in order to acquire accurate data during the hospital stay. Preoperatively and thereafter, donors were asked to fill out quality of life forms. The moment of discharge was determined by the donor on the condition that they had been to the bathroom, could eat normally and walk a flight of stairs. All patients were seen at the outpatient clinic at three weeks, three months and one year postoperatively.

Questionnaires

Baseline values of all questionnaires except the body image questionnaire were obtained the day before operation.

Pain and nausea were scored on a 0-10 (0 means no pain or nausea, 10 means the worst possible situation) visual analogue scale (VAS) preoperatively and at day 1, 3, 7 and 14.

Quality of life was assessed using EuroQol-5D, Short Form-36 (SF-36), and Multidimensional Fatique Inventory (MFI-20). The SF-36 and MFI-20 were filled out at month 1, 3, 6 and 12 postoperatively. The EuroQol-5D was also filled out at day 3, 7 and 14. Briefly, the EuroQol-5D consists of five dimensions; mobility, self care, daily activities, pain and state of mind. A so-called tariff score was calculated (1 is equivalent to excellent heath, 0 is equivalent to death). This is an overall score for all dimensions in which all factors were weighed according to the formula provided by the sector Public Health in the Erasmus Medical Centre Rotterdam. Furthermore, health status was scored on a 0-100 scale. Zero presents the worst and a hundred the best possible health status.

The body image questionnaire developed by Dunker et al. [11, 12] was filled out one year postoperatively to determine the attitude of the donors towards their bodily appearance after laparoscopic and muscle-spilt donor nephrectomy. Finally, all donors were sent return-to-work forms until full resumption of work to determine macro-economic costs.

In this article we describe the short term results of the VAS scores on pain and nausia.

Statistical Analysis

Power calculations by the statistician (WCJH) determined 50 donors were necessary in each arm to establish a difference of 0.6 standard deviations in the physical fatigue score on the MFI-20 with a power of 80% and an alpha of 0.05.

As primary outcome quality of life was determined. Secondary endpoints included length of postoperative hospital stay, pain medication, costs, operating times and renal graft function. Using the statistical program SPSS (version 12.0, SPSS Inc., Chicago, USA) categorical variables were compared with the Chi square test, continuous variables with the Mann Whitney U test and continuous variables with repeated measurements ANOVA. Repeated measures were corrected for baseline values, donor's sex and age. Continuous data were displayed as median (minimum-maximum) unless specified otherwise. Data were analysed on a intention to treat principle. A p-value <0.05 was considered statistically significant.

RESULTS

From November 2001 until February 2004 105 out of 163 donors were included in the Living Donors trial (LiDo). Among 58 not included patients were two donors who participated in a Cross-over program, which originated in 2003, and two donors who had planned frozen sections of abnormalities discovered at preoperative radiological examinations. After inclusion donation was cancelled in 5 cases. Fifty patients were included in each arm. Surgeons from the Erasmus Medical Center Rotterdam performed seventy-two kidney donation procedures

(34 laparoscopic and 38 muscle-split). Surgeons from the Radboud University Medical Center Nijmegen preformed twenty-eight donor nephrectomies (16 laparoscopic and 12 muscle-split procedures).

Demographics

Donor characteristics are shown in Table 1.

Table 1. Donor characteristics.

	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)
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)

Operative outcomes

Operative outcomes are displayed in Table 2. None of the laparoscopic procedures was converted to open nephrectomy. Kidney extraction time, skin-to-skin time and time in the operation room were significantly longer in the laparoscopic group (P<0.001). Warm ischemia time was lengthened in patients undergoing laparoscopic surgery (P<0.001). Blood loss was significantly less in the laparoscopic group (P<0.001). Intraoperative complications occurred in 6 (12%) and 3 patients (6%) in the laparoscopic and open group respectively (P=0.23). Complicated laparoscopies were caused by bleeding (n=3), colon lesion (n=1), bladder lesion (n=1), small capsular tear of the spleen. (n=1). Before closure all 6 aforementioned problems were laparoscopically solved and no interventions were demanded postoperatively. All 3 complications in the open group involved bleeding which were stopped during operation.

Postoperative outcomes

Postoperative outcomes are displayed in Table 2. In the first week following the operation patients in the laparoscopic surgery group recovered faster as reflected by earlier resumption of solid diet (P=0.01), less intravenous morphine requirement (P=0.005) and earlier discharge (P=0.003). When length of stay was corrected for social hospitalization (i.e. prolonged hospital stay without medical reason), patients undergoing laparoscopic surgery still required a shorter hospital stay (P=0.002). Nausea did not differ between the groups. Patients experienced significantly less pain at 1, 7 and 14 days following laparoscopy (P=0.04, P=0.03 and P=0.008 respectively). Postoperative complications following laparoscopy occurred in 3 patients (6%). One patient required a one-time blood transfusion, two patients presented with wound infections which were treated with oral antibiotics. In the open group three complications included urinary tract infection (n=1), a minor pulmonary infiltrate (both not not requiring intervention) and an infected retroperitoneal haematoma, which required readmission and administering of intravenous antibiotics. Cardiologic complications, bowel obstructions and incisional hernias did not occur. At one and two days postoperatively, serum creatinine levels were comparable for donors of both groups (p=0.81 and p=0.99 respectively).

DISCUSSION

Ever since Ratner et al. introduced the laparoscopic technique for living donor nephrectomy questions have been raised whether this technique should be the new standard. Many groups have reported their retrospective or prospective study results, however, a properly constructed randomized, multi-center trial is still lacking. In our search for a definite answer whether or not the laparoscopic donor nephrectomy is the procedure of choice, we chose to compare this technique to the muscle-split technique. This muscle sparing technique results in a reduction in morbidity and a faster convalescence compared to the lumbotomy. In order to determine

Table 2. Operative outcomes donors.

	Laparoscopic donor nephrectomy (N=50)	Muscle split donor nephrectomy (N=50)	P- Value
Conversion to open (No).	0	–	
Operation times (min)			
Time until kidney removal	181 (107-307)	117.5 (61-201)	<0.001
Skin-to-skin time	220.5 (135-354)	163.5 (92-298)	<0.001
Time in the operation room	289.5 (180-420)	226 (157-365)	<0.001
Warm ischemia time (min)	6 (2-14)	3 (1-6)	<0.001
Blood loss (ml)	100 (10-860)	240 (20-1800)	<0.001
Complications (No.%)			
Intraoperative	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
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

if the higher operating costs and longer learning curve associated with laparoscopic donor nephrectomy countervail against the benefits for the donor, a prospective randomized multicenter trail was conducted. This article reports the short-term results.

This study shows that laparoscopic donor nephrectomy compared to the muscle-split open donor nephrectomy results in longer operating and warm ischemia times. Furthermore, laparoscopic kidney donation is associated with a reduction in blood loss, morphine requirement, time until return to normal diet, hospital stay and pain compared to open donor nephrectomy.

In order to reduce morbidity related to open donor nephrectomy, several alternative techniques have been introduced. The muscle-split incision was designed to reduce postoperative pain and increase convalescence, perhaps equivalent to that of the laparoscopic technique.

Lewis et al. consecutively compared laparoscopic, muscle cutting minimal incision and open (with rib resection) donor nephrectomy [10]. They found a faster convalescence and less morphine requirements in the laparoscopic group compared to the mini-incision and open donor nephrectomy groups. Comparing the mini-incision to the open technique, the mini-incision resulted in better outcome for the donor regarding pain and convalescence. Perry et al. compared laparoscopic and mini-incision kidney donation techniques [13]. Their conclusion was a clear benefit in convalescence after laparoscopic donor nephrectomy. In our study, comparing a muscle-sparing mini-incision technique to laparoscopic donor nephrectomy, we found significant advantages for the donor. With equal numbers of complications, a decrease was found in blood loss, morphine use, time to normal diet, pain and hospital stay after laparoscopic donor nephrectomy. With the aid of the PCA, donors administed themselves 16 and 25 mg of morphine after laparoscopic and muscle split donor nephrectomy, respectively. This is comparable with the use of morphine reported by Ratner et al. [5] Also, hospital stay, blood loss and operating time are equivalent to the data published by other groups [13-15].

The long-term quality of life and return to work still need to be determined. Also, a cost analysis will establish the price of a potential benefit in quality of life. However, since we have established the short term benefits for the donor after laparoscopic donor nephrectomy, the laparoscopic technique should be the procedure of choice in experienced hospitals.

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Chapter 9

General discussion and conclusions

GENERAL DISCUSSION AND CONCLUSIONS

New developments in immunosuppression and operating techniques have made kidney transplantation the best available treatment for end stage renal failure. Because the number of available cadaveric kidneys falls short to the increasing demand [1] and since short – and longterm graft survival rates are higher after living donation compared to cadaver donor transplants [2], renewed interest has arisen in living donors. Living donors represent a large potential pool of organs for transplantation with the possibility of reducing the waiting list. Open donor nephrectomy has been the procedure of choice for living kidney donation for many years. However, the high morbidity related to this operating technique has resulted in a search for an alternative method to remove the donor kidney. Laparoscopy is associated with a number of advantages for patients such as a reduction in pain, hospital stay and sick leave. The laparoscopic donor nephrectomy may offer donors the same advantages, possibly resulting in an increase in kidney donors. However, before we can determine if laparoscopic donation is the procedure of choice, the advantages and safety for both donor and recipient must be established. In **Chapter 1** an overview is being given on the developments in kidney donation and the different operating techniques.

Since the initial report of laparoscopic kidney donation by Ratner et al. [3], many centers have adopted this technique and have published their early experience and results. A publication by Mandal et al. had a large impact on the laparoscopic right kidney procurement [4]. In their initial experience using the right kidney for transplantation, three out of eight renal allografts were lost due to venous thrombosis. These data resulted in several modifications in right-sided donor nephrectomy [4-6] and often precluded the use of laparoscopic right-sided donor nephrectomies. Moreover, multiple-artery left kidneys were chosen over right-sided single artery kidneys. In **Chapter 2** we describe our results comparing a left-sided laparoscopic donor nephrectomy group to the largest ever-published right-sided laparoscopic donor nephrectomy group. We found no venous thrombosis in both groups. The reluctance of many transplant surgeons toward right-sided laparoscopic donor nephrectomy is mainly based on a single article claiming a higher incidence of venous thrombosis. Our results and those of other recent articles have led to the conclusion that right-sided donor nephrectomy can be safely performed [7-10]. Therefore, every donor should be eligible for a laparoscopic approach, independent of the side chosen for kidney donation.

Many reviews on laparoscopic donor nephrectomy assume that the laparoscopic technique is associated with a better cosmetic outcome. This has been found to be true for many laparoscopic procedures. However, we should keep in mind that the donor nephrectomy is a unique procedure. Prior to donation, numerous factors influence the decision to donate a kidney to a loved one. In donors, the cosmetic aspect could be inferior to other aspects associated to kidney donation. This is why, in **Chapter 3**, we investigated the body image using the body image questionnaire (BIQ) [11] after laparoscopic and open donor nephrectomy. Body image was comparable in both groups even though the size of the scar was much larger in the open donor nephrectomy group. We hypothesize that the altruistic character of kidney donation may decrease the importance of the cosmetic result. It is conceivable that donors could place the health of the recipient superior to that of themselves. On the other hand, recipients could feel less guilty if the kidney donor has a smaller scar. Keeping in mind that laparoscopic and open donors are equally satisfied with their body image, the superior operating technique will be the one with the least morbidity for the donor and the highest safety for both donor and recipient.

Several studies have reported a faster return to work after laparoscopic donor nephrectomy compared to open donor nephrectomy [12-14]. However, these studies have been performed in the United States of America, where health care insurance and employment structures are different from those in the Netherlands. In **Chapter 4** we investigated the duration of sick leave after laparoscopic, hand-assisted and open donor nephrectomy in the Netherlands. We found an equally long period until full return to work in the hand-assisted and open donor nephrectomy groups (both 15 weeks). The laparoscopic group fully returned to work 6 weeks after the operation. In the un-employed groups, return to full recovery was approximately 4.5 weeks. This study showed two striking results. First, keeping in mind the nature of the operation, we expected to find similar sick-leave periods in the laparoscopic and hand-assisted groups. However, the hand-assisted donors stayed home more than twice as long as the laparoscopic donor group. Second, although the unemployed group stated they were fully recovered after approximately 4.5 weeks, the employed donors resumed their work much later. We hypothesize that the duration of sick leave is highly correlated with the advice given by the healthcare provider. This fact may lead to a large bias in series comparing operating techniques. The results of this study have led to neutral advice on return to normal activities and work in our prospective, randomized trial, avoiding bias.

An important difference between laparoscopic and open donor nephrectomy is the pneumoperitoneum. Pneumoperitoneum in laparoscopy is necessary to provide sufficient working space. Increased intra-abdominal pressure due to pneumoperitoneum results in decreased renal blood flow and urine output [15-18]. The first criterion for accepting an alternative operating technique rather than the conventional open donor nephrectomy is the safety for donor and graft. The new technique must not have a negative effect on renal function in both donor and recipient. In **Chapter 5** we compare long-term serum creatinine in donors and recipients after laparoscopic and open donor nephrectomy. We found higher levels of serum creatinine in recipients the first week post-transplantation. After this week serum creatinine levels were comparable for both groups. Furthermore, we found an increase of 40% of serum creatinine in kidney donors after donation. This increase was still apparent at three years post-donation. Two other studies have also described higher short-term serum creatinine levels in the laparoscopic recipients [19, 20]. As described by London et al., pneumoperitoneum results in a relative hypovolemic state leading to decreased blood flow and urine output [21]. This effect can be counteracted by prophylactic volume expansion. Currently, all our donors are prehydrated in an attempt to optimize renal function in donor and recipient.

Many authors emphasize the importance of short warm ischemia times in donor nephrectomy. It is unclear, however, if longer warm ischemia times, associated with laparoscopic donor neprectomy, have major clinical implications in the recipient. A study by Akbulut et al. showed that warm ischemia and pneumoperitoneum act synergistically to amplify oxidative stress in rat kidneys [22]. They state these results may have clinical implications in renal function in donor and recipient. In **Chapter 6**, we investigated the effect of prolonged warm ischemia on the long-term renal function in a syngeneic rat transplant model. Warm ischemia of 20 minutes alone, or in combination with pneumoperitoneum did not result in a decrease in renal function in the recipient. Keeping in mind this study was conducted in a syngeneic rat model, further research is necessary to investigate the impact of warm ischemia in an allogeneic transplant model. However, since clinical studies have shown comparable long-term renal function after open and laparoscopic donor nephrectomy [19, 23, 24] and we found no difference in renal function after considerably longer warm ischemia times, laparoscopic kidney donation seems to be safe for the recipient.

Early studies comparing laparoscopic and open donor nephrectomy reported an increased incidence of ureteral complications in the laparoscopic recipients [25, 26]. This caused great concern about the safety of the laparoscopic approach for the outcome of the kidney graft, in particular the ureteral anastomosis. In **Chapter 7**, the incidence of ureteral complications after laparoscopic and open donor nephrectomy is compared. Excluding technical errors as a cause of need for reconstruction, we found a comparable incidence of ureteral complications. Since the initial reports of high incidence of ureteral complications, operating technique modifications have been advocated. Dissection of the gonadal vein together with the ureter ensures sufficient blood supply to the ureter [27]. However, since we do not dissect the ureter with the gonadal vein and still find a low percentage of ureteral complications, the need for modification of the laparoscopic technique is open for discussion. Still, great care must be taken to leave as much peri-ureteral tissue as possible and not to dissect to far into the hilum of the kidney.

The question whether laparoscopic donor nephrectomy is definitively superior to the open technique can only be answered by prospective randomized trials. Unfortunately such trials are lacking. Simforoosh et al. have published preliminary results of a randomized clinical trial comparing open and laparoscopic donor nephrectomy [28]. However, this study and article do not comply with the general rules of a well-constructed randomized trial. Randomization, surgical techniques and selection of the donors are insufficiently described. There seems to be a selection bias since only left sided nephrectomies were performed on donors with a BMI of less than 28. Also, this study does not report on quality of life and costs. Finally, the laparoscopic technique is being compared to the traditional open procedure. Since the emergence of the 'muscle-split' incision, the open flank incision with or without rib resection seems obsolete. In **Chapter 8** we present the short term results of the first prospective, randomized, multicenter trial comparing laparoscopic and 'muscle-split' incision open donor nephrectomy. In an attempt to decrease bias in donor and health care providers on the ward, blinding was established. This study shows major advantages of the laparoscopic technique such as less blood loss, less pain and a shorter hospital stay for the donor, compared to the 'muscle-split' incision. Contrary, laparoscopic kidney donation results in an increase in operating time and warm ischemia times.

In conclusion, this thesis shows that laparoscopic donor nephrectomy is safe for donor and recipient. At the expense of little more time, donors benefit from less pain and a shorter hospital stay, compared to 'muscle-split' donor nephrectomy. Therefore, laparoscopic donor nephrectomy is the procedure of choice for living kidney donation.

DISCUSSIE EN CONCLUSIES

Dankzij ontwikkelingen in immunosupressiva en operatietechnieken is niertransplantatie de beste behandeling voor patienten met nierfalen. Door een tekort aan postmortale nierdonoren en toename van de wachtlijst [1] is er hernieuwde interesse ontstaan voor de levende nierdonor. Eveneens van belang is het feit dat de lange termijn transplantaatfunctie na levende nierdonatie beter is dan na postmortale donatie [2]. Lange tijd was de open nierdonatie via lumbotomie de procedure van keuze. Deze operatietechniek gaat echter gepaard met een hoge morbiditeit. In een poging deze morbiditeit te verminderen is er gezocht naar een betere operatietechniek. Laparoscopie is geassocieerd met voordelen zoals minder pijn, een kortere opnameduur en korter ziekteverlof in vergelijking tot open chirurgie. Laparoscopische nierdonatie zou mogelijk dezelfde voordelen kunnen bieden aan nierdonoren en wellicht het aantal donaties doen toenemen. Echter, voor we kunnen vaststellen of de laparoscopische nierdonatie de procedure van voorkeur is, is het van belang de voordelen en veiligheid van deze operatiemethode voor donor en ontvanger af te zetten tegen de standaard (open) techniek. In **Hoofdstuk 1** wordt een overzicht gegeven van de ontwikkelingen betreffende de nierdonatie en de chirurgische technieken.

Sinds de introductie van de laparoscopische nierdonatie door Ratner et al. [3] in 1995 hebben veel centra deze techniek toegepast en hun eerste ervaringen gepubliceerd. Een publicatie van Mandal et al. heeft een grote invloed gehad op de laparoscopische donatieprocedure van de rechter nier [4]. Zij rapporteerden veneuze trombose in drie van acht rechter laparoscopische nierdonaties. Deze gegevens resulteerden in een modificatie van de laparoscopische procedure voor de rechter nier [4-6]. Ook werd de laparoscopische techniek gereserveerd voor de linker donor nefrectomie en werden linker nieren met meerdere arteriën verkozen boven rechter nieren met één arterie. In **Hoofdstuk 2** beschrijven wij de resultaten van een studie waarin de linker laparoscopische donornefrectomie vergeleken wordt met de grootste ooit gerapporteerde groep rechter nierdonaties. De terughoudendheid van veel transplantatiechirurgen jegens de laparoscopische donornefrectomie rechts is voornamelijk gebaseerd op één artikel welke een verhoogd risico op veneuze trombose rapporteert. Wij vonden geen veneuze trombose in beide groepen. Onze resultaten, en inmiddels ook resultaten van andere studies, tonen aan dat laparoscopische nierdonatie van de rechter nier veilig is zonder verhoogde kans op veneuze trombose [7-10]. Daarom zou iedere donor in aanmerking moeten kunnen komen voor een laparoscopische benadering ongeacht de zijde van de te doneren nier.

Veel publicaties over laparoscopische donornefrectomie gaan ervan uit dat deze techniek geassocieerd is met een betere cosmetische uitkomst. Dit is waar voor veel laparoscopische procedures. Echter, de nierdonatie is een unieke situatie. Vele factoren beïnvloeden het besluit een nier te doneren. Het cosmetisch aspect zou een ondergeschikte rol kunnen spelen. Daarom hebben wij in **Hoofdstuk 3** het cosmetisch aspect na laparoscopische en open nierdonatie onderzocht met behulp van de 'Body Image Questionnaire' (BIQ) [11]. Het cosmetisch aspect was vergelijkbaar in beiden groepen, ondanks een veel groter litteken in de open groep. Wij veronderstellen dat het altruïstische karakter van de nierdonatie het belang van het cosmetisch resultaat kan verminderen. Het is denkbaar dat de donor het belang van de ontvanger voorop stelt. Daarentegen kunnen ontvangers zich minder schuldig voelen wanneer de donor een kleiner litteken heeft. In aanmerking genomen dat beide groepen even tevreden zijn over het cosmetisch resultaat, zal de operatietechniek van voorkeur diegene zijn met de laagste morbiditeit en de hoogste veiligheid voor donor en ontvanger.

Meerdere studies rapporteren een snellere terugkeer naar werk na laparoscopische donornefrectomie vergeleken met open nierdonatie [12-14]. Deze studies zijn echter met name uitgevoerd in de Verenigde Staten, waar ziekteverzuimregelingen en arbeidsvoorwaarden verschillen van die in Nederland. In **Hoofdstuk 4** inventariseerden wij de periode van ziekteverlof na laparoscopische, hand-assisted en open donornefrectomie. Wij vonden een vergelijkbare periode van afwezigheid van werk in de hand-assisted en open nierdonatie groepen (15 weken). De laparoscopische groep hervatte het werk echter al na 6 weken. In de niet-werkzame groep duurde de volledige terugkeer naar dagelijkse activiteiten ongeveer 4.5 week. Deze studie toonde twee opvallende resultaten. Ten eerste, de aard van de operatie in acht genomen, was de verwachting dat de periode van ziekteverlof gelijk zou zijn in de laparoscopische en hand-assisted groepen. Echter, de hand-assisted groep blijft twee maal langer thuis dan de laparoscopie groep. Ten tweede, de niet-werkende groep is volledig hersteld na 4.5 weken terwijl de werkende groep later aan het werk gaat. Wij veronderstellen dat de periode van ziekteverlof gecorreleerd is met het advies gegeven door de arts. Dit kan leiden tot bias in studies die operatietechnieken vergelijken. Het resultaat van deze studie heeft ertoe geleid dat er een neutraal advies wordt gegeven omtrent de duur van te verwachten ziekteverlof in onze prospectieve, gerandomiseerde studie.

Een belangrijk verschil tussen laparoscopische en open donornefrectomie is het pneumoperitomeum. Pneumoperitoneum in de laparoscopie is noodzakelijk om de chirurg voldoende overzicht en werkruimte te bieden. Verhoogde intra-abdominale druk kan leiden tot een vermindering van de renale bloedvoorziening en een afname van urineproductie [15-18]. Een eerste criterium voor het verkiezen van een alternatieve operatiemethode boven de conventionele methode is de veiligheid voor donor en transplantaat. Een nieuwe techniek mag geen nadelig effect hebben op de nierfunctie in donor en ontvanger. In **Hoofdstuk 5** vergelijken we het lange-termijn serum kreatinine in donoren en ontvangers na laparoscopische en open donornefrectomie. In deze studie vonden wij een hoger serum kreatinine in de eerste week na transplantatie in ontvangers van een laparoscopisch verkregen nier. Na deze periode waren de serum kreatinine niveaus vergelijkbaar voor beide groepen. In de donor vonden wij een toename in serum kreatinine van 40% na donatie. Deze toename was drie jaar na donatie nog steeds aanwezig. Twee andere studies beschrijven eveneens een hoger serum kreatinine in ontvangers na laparoscopische nierdonatie [19,20]. Zoals beschreven door London et al. resulteert pneumoperitoneum in een relatieve hypovolemie welke tot een afname van nierperfusie en urineproductie leidt [21]. Dit effect kan worden verminderd door profylactische volumetherapie. Tegenwoordig worden daarom alle donoren in het Erasmus MC geprehydreerd in een poging de nierfunctie in donor en ontvanger te optimaliseren.

Veel auteurs benadrukken het belang van een korte warme ischemietijd bij donornefrectomie. Het is onduidelijk of de langere warme ischemietijden welke gepaard gaan met laparoscopische nierdonatie klinische gevolgen hebben in de ontvanger. Akbulut et al. toonde aan dat pneumoperitoneum en warme ischemie synergistisch werken en zo oxidatieve stress kunnen versterken in nieren van de rat [22]. Zij stellen dat deze bevindingen klinische implicaties kunnen hebben in de nierfunctie van donor en ontvanger. In **Hoofdstuk 6** hebben wij het effect van lange warme ischemie op de lange termijn nierfunctie onderzocht in een syngeen ratten transplantatiemodel. Warme ischemie van 20 minuten alleen, of in combinatie met pneumoperitoneum resulteert niet in een afname van nierfunctie in de ontvanger. Gezien het feit dat deze studie verricht is in een syngeen model, is verder onderzoek in een allogeen model noodzakelijk. Echter, aangezien klinische studies gelijke lange-termijn nierfuncties tonen na laparoscopische en open donornefrectomie [19, 23, 24], en het feit dat wij geen verschil vonden na aanzienlijk langere warme ischemietijden, lijkt laparoscopische nierdonatie veilig voor de ontvanger.

Enkele studies waarin laparoscopische en open donornefrectomie worden vergeleken beschrijven een hogere incidentie van uretercomplicaties in de ontvanger [25, 26]. Dit heeft geleidt tot ongerustheid ten aanzien van de veiligheid van de laparoscopische procedure voor het transplantaat, met in het bijzonder de ureteranastomose. In **Hoofdstuk 7** vergelijken wij het aantal uretercomplicaties na laparoscopische en open donornefrectomie. Wij vonden vergelijkbare aantallen uretercomplicaties in beide groepen (waarbij uretercomplicaties ten gevolge van een technische oorzaak waren geëxcludeerd). Na de initiële meldingen over verhoogde incidentie van uretercomplicaties na laparoscopische donornefrectomie zijn er enkele modificaties van deze operatietechniek beschreven teneinde de incidentie van uretercomplicaties te verlagen. Dissectie van de vena gonadalis samen met de ureter zou voldoende bloedvoorziening van de ureter garanderen [27]. Echter, in het Erasmus MC wordt de ureter vrijgeprepareerd zonder vena gonadalis, en vonden in onze studie een laag percentage uretercomplicaties. De dissectie met medeneming van de vena gonadalis staat daarom ter discussie. Het lijkt met name van belang genoeg peri-ureteraal vet te behouden.

De vraag welke operatietechniek superieur is voor nierdonatie zal moeten worden beantwoord door middel van een prospectieve, gerandomiseerde studie. Helaas zijn er tot nog toe geen studies die deze vraag kunnen beantwoorden. Simforoosh et al. publiceerde voorlopige resultaten van een gerandomiseerde studie waarin laparoscopische en open donornefrectomie werden vergeleken [28]. Echter, de randomisatie, operatietechnieken en selectie van de donoren worden onvoldoende beschreven. Er lijkt sprake te zijn van selectiebias, aangezien alleen linkszijdige nierdonaties werden verricht bij donoren met een body mass index onder de 28. Tenslotte wordt in deze studie de laparoscopische techniek vergeleken met de open lumbotomie. Het toepassen van deze conventionele open methode lijkt obsoleet sinds het verschijnen van de 'muscle-split' techniek. In **Hoofdstuk 8** beschrijven wij de korte termijn resultaten van de eerste prospectief, gerandomiseerde multicenter studie waarbij laparoscopische en 'muscle-split' donor nefrectomie worden vergeleken. Bias door donor, artsen en verpleegkundigen werd vermeden door blindering. Deze studie toont aan dat laparoscopische nierdonatie gepaard gaat met een toename in operatieduur en een langere warme ischemietijd. Daarentegen is laparoscopische nierdonatie geassocieerd met voordelen voor de donor zoals minder bloedverlies, kortere opnameduur en minder pijn, in vergelijking met de 'muscle-split' techniek.

Concluderend kunnen wij stellen dat dit proefschrift aantoont aan dat laparoscopische donornefrectomie veilig is voor donor en ontvanger. Dankzij de investering van iets meer tijd en geld herstellen donoren sneller en ervaren zij minder pijn in vergelijking met donoren met 'muscle-split' donornefrectomie. Daarom is laparoscopische donornefrectomie de techniek van voorkeur bij levende nierdonatie.

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CURRICULUM VITAE

May Yvonne Lind werd geboren op 17 november 1975 te 's Gravenhage. Het Hoger Algemeen Vormend Onderwijs en het Voorbereidend Wetenschappelijk Onderwijs volgde zij aan het Rijnlands Lyceum te Wassenaar. De studie Geneeskunde werd aangevangen in 1995 aan de Erasmus Universiteit te Rotterdam. Tijdens deze studie was zij werkzaam in het studententeam van de afdeling Geriatrie van het Dijkzigt Ziekenhuis. Het afstudeeronderzoek werd verricht in het Sophia Kinderziekenhuis te Rotterdam bij Prof.dr. D. Tibboel. In 2001 behaalde zij het artsexamen (cum laude).

In 2001 kreeg zij een aanstelling als arts-onderzoeker op de afdeling Heelkunde van het Erasmus MC. Daar was zij verantwoordelijk voor het coördineren van de 'LiDo Trial', een gerandomiseerde studie naar open en laparoscopische nierdonatie. Naast deze studie verrichtte zij tevens de studies zoals beschreven in dit proefschrift. In 2003 begon zij met de opleiding tot algemeen chirurg in het Erasmus MC te Rotterdam (opleider: Prof.dr. H.J. Bonjer / Prof. dr. J.N.M. IJzermans). Sinds 1 maart 2005 vervolgt zij haar opleiding in het Sint Franciscus Gasthuis te Rotterdam (opleider Dr. C.H.A. Wittens).