Tailor-made live kidney donation

Karel W.J. **Klop**

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Karel Willem Jan Klop

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Chapter 1 Introduction

K.W.J. Klop[1], N.F.M. Kok[1] and J.N.M. IJzermans[1]

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The kidneys are two bean-shaped organs, situated in the retroperitoneum, caudal of the diaphragm and behind the intestines. Blood supply is realized via the right and left renal artery, side-branches of the aorta. The kidneys serve several essential regulatory roles in the human body such as the regulation of electrolytes, maintenance of the acid-base balance, regulation of blood pressure and the production of specific hormones. By producing urine, the kidneys excrete waste products such as ureum and ammonium ; in addition the kidneys play a pivotal role in the reabsorption of water, glucose and amino acids.

Renal disease may lead to problems with most of the aforementioned functions and advanced renal disease may lead to renal insufficiency and severe morbidity. Kidney replacement therapy may consist of dialysis and kidney transplantation. Although dialysis may lead to long-term survival, this treatment has a limited beneficial effect on overall life expectancy and hampers the quality of life (QOL). As kidney transplantation has been demonstrated to have superior results on both outcomes, life expectancy as well as QOL, it is considered as the kidney replacement therapy of choice for end-stage renal disease.

The first kidney transplantations with living donors were performed in the early 1950s by Joseph Murray and Rene Kuss (1, 2). As no immunosuppressive therapy was available, transplant rejection proved the main hurdle to overcome. With the introduction of cyclosporin A in the 1970s the success rate of transplantation was increased significantly and even deceased donor kidney transplantation was restarted (3). Living donation lost its place due to the risks imposed on healthy donors. However, with the increasing demand for kidney grafts in the 1980's and a stagnating number of available kidneys,

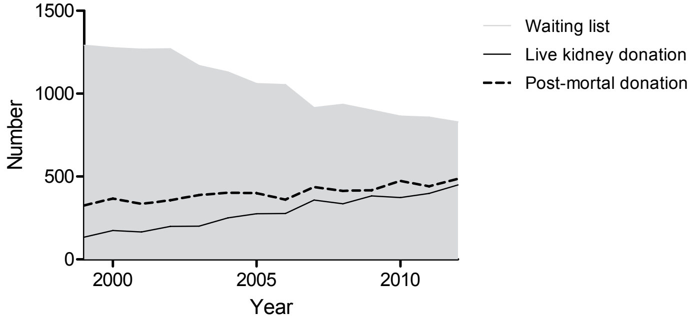

Figure 1. Dutch waiting list and number of transplantations

interest in live donor kidney transplantation was renewed (see figure 1).

Many studies since demonstrated that live kidney donation may offer several benefits for the recipient, including pre-emptive transplantation and better access to kidney transplantation, leading to increased graft survival. (4-6). In addition, as graft survival increases, dialysis and re-transplantation become less frequent, resulting in a clear financial benefit for society (7).

However, extension of the living donation program can only be legitimized if no harm is done to healthy donors, undergoing a surgical procedure for the benefit of others. To date, surgical mortality after live donor nephrectomy is reported to be 3.1 per 10.000 donors (8) and the complications leading to morbidity of the donors, short term as well as long term are limited. Overall long-term survival remains the same as in matched individuals that did not undergo a surgical procedure. Stimulated by these data, many programs were initiated to increase in live donor nephrectomy (9).

The extension of these programs has led to new ethical and clinical challenges. Due to an increase in non-directed donation, the relationship between donor and recipient becomes increasingly unclear (10). Furthermore, as donors are healthy individuals without an indication for a surgical procedure, safety and convalescence have become of paramount importance. Due to the persisting demand for donor kidneys, the eligibility criteria for live kidney donation have been extended (11). Data on live donor nephrectomy on donors with (minor) comorbidities remain scarce and of low quality. Thus, live kidney donation has become a widely studied subject, leading to continuous innovation on all fronts in the last decade.

Donor wellbeing, as discussed earlier, has become a priority. This implies that donor selection, the surgical technique, complication management, postoperative care, QOL and renal outcome need to be optimized. This can only be achieved if selection, treatment and follow-up are tailored to meet the needs of the individual donor.

Surgical techniques

The surgical technique used for live donor nephrectomy has evolved in the last decade. Classically, donor nephrectomy was an open procedure thattook place via a lumbotomy. This procedure requires a large flank incision and sometimes even a rib resection is deemed necessary. Mini-incision donor nephrectomy (MIDN) involves a much smaller incision and has a muscle splitting approach. MIDN results in reduced blood loss, shorter hospitalization and less donor discomfort, without compromising graft and recipient survival (12). The introduction of minimally invasive endoscopic techniques, such as laparoscopic donor nephrectomy (LDN) and hand-assisted retroperitoneoscopic donor nephrectomy (HARP), has again led to superior results with regard to pain, convalescence and QOL (13, 14). A survey conducted among European transplant surgeons by Kok *et al.* in 2004 demonstrated that different techniques were being used across Europe (15). **Chapter two** provides an updated overview and sets out the developments and the underlying incentives.

LDN was introduced in 1995 by Ratner *et al* (16). Reports on the superiority of LDN were, since then, published with increasing frequency. The superiority of LDN was also described in a Cochrane review (13). HARP was introduced in 2003 by Wadström *et al* (17). HARP theoretically combines control and speed of hand-guided surgery with the benefits of endoscopic surgery and retroperitoneal access. For these reasons, HARP was introduced as a potentially safer approach that is easier to implement (18). In order to legitimize the introduction of a new technique, it must be proven to be as good as, or superior to the 'golden standard'. For this reason we assessed the results of both LDN and HARP in a randomized fashion. The results for left-sided donor nephrectomy are described in **chapter three** and for right-sided donor nephrectomy in **chapter four**.

However, little is known on the learning curves of both HARP and LDN as no published evidence is available. Endoscopic donor nephrectomy is a complex procedure with potentially lethal complications. It requires the transsection of large blood vessels, maintaining adequate length of these vessels and prevention of collateral damage is crucial in a healthy donor. As is the case with any complex procedure, a certain level of experience is required to acquire an adequate level of competency (19). In **chapter five** we evaluate the learning curves of these two techniques in an experienced center and in a center initiating an endoscopic live donation program.

Post-operative outcome

Live donor kidney transplantation has a clear economic benefit over deceased-donor kidney transplantation and dialysis (7). The total financial benefit(with a median graft survival of at least 10 years) is $500,000 per donor, when compared to dialysis (20). Endoscopic techniques have been proven to be safe and result in less pain and increased QOL when compared to open techniques. Although LDN is a more expensive procedure, with regard to the use of disposables and duration of the procedure, it is still cost-effective when compared to open donor nephrectomy. The shorter convalescence time and the decrease in productivity loss make LDN a cost-effective procedure (21).

As cost and cost-effectiveness become increasingly important in modern healthcare, policy-makers and healthcare professionals are forced to make choices if several techniques are concurrently available. The benefits of HARP and LDN regarding safety, postoperative pain, convalescence and QOL are described in chapter three and chapter four. In order to provide an adequate and complete analysis of these techniques, we present the results of our cost-effectiveness analysis between LDN and HARP in **chapter six**.

Incisional hernias are a common surgical problem and may lead to significant surgical morbidity, such as increased pain, disability, decreased QOL and in some cases even intestinal obstruction and strangulation (22). Incisional hernia rates after MIDN range from 0.6% to 3%. For LDN different incisions are required, *i.e.* an Pfannenstiel incision an several incisions for trocar placement. Incisional hernia rates for these incisions have been described in literature and vary from 0.0% to 0.5% and 1% to 6% respectively. However, these rates were never described in 'healthy' donors. Furthermore, very little is known on donors' body image after the procedure. As there is no medical indication for the procedure, cosmesis may play a larger role than expected. In **chapter seven,** incision-related outcome after live donor nephrectomy is described. Incisional hernia rates are described for different incision types and body image and cosmesis were studied amongst donors.

Due to the increasing demand for kidney transplants, eligibility criteria for live donation have been extended (11). This is also described in **chapter two**. This has led to the inclusion of obese donors, donors with cardiovascular disease and elderly donors. Donor safety and graft and recipient survival have proven to be comparable to that of younger individuals, consequently encouraging the careful selection of elderly donors (23). Nonetheless, the preservation of QOL is also of paramount importance in elderly donors. So far, published evidence on QOL in elderly donors is scarce, inadequate and lacking longitudinal studies (24, 25). In **chapter eight** we quantify the effect of the surgical procedure on QOL in elderly donors.

Quality of life in live kidney donors is excellent in general, with scores comparable or superior to that of the general population (26, 27). However, there is evidence suggesting that a minority of donors experiences psychological distress or negative emotions after donation (28). Factors leading to a decrease in QOL postoperatively are unknown. The only study reporting on predictors of quality of life lacks baseline data, thus making these data hard to interpret due to the subjective nature of QOL (29). Identification of factors that influence postoperative QOL may have a clinical effect. Donors can be provided with better information and selection criteria may be adjusted according to anticipated outcome. In **chapter nine** we present the results of a multilevel analysis to identify factors associated with changes in QOL after live kidney donation.

Follow-up

The long-term effects of live kidney donation regarding kidney function, cardiovascular disease and QOL are not well studied. So far, some studies have demonstrated excellent long-term results without excess risk of end-stage renal disease or mortality (30, 31). Other studies have reported an increased long-term risk for end-stage renal disease and cardiovascular and all-cause mortality (32). Thus, the published evidence on long-term consequences after live kidney donationis contradictory. The quality of the published studies is marginal, lacking baseline data or having been conducted in a retrospective fashion. Furthermore, all these studies focus on healthy donors and fail to address the long-term effects of donation on donors with comorbidities; a very relevant topic in the perspective of recent developments. In **chapter ten** we describe the results of the ten-year follow-up regarding QOL and fatigue. In **chapter eleven** we present the protocol of the LOVE –study. With this study, that has already been initiated, we aim to fill the final hiatus in current knowledge.

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Chapter 2 Attitudes among surgeons towards live donor nephrectomy: A European update

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ABSTRACT

The increasing number of living kidney donors in the last decade has led to the development of novel surgical techniques for live-donor nephrectomy. The aim of the present study was to evaluate the current status of the surgical approach in Europe.

A survey was sent to 119 transplant centers in 12 European countries. Questions included the number of donors, the technique used, and the acceptance of donors with comorbidities.

Ninety-six centers (81%) replied. The number of living donors per center ranged from 0 to 124. Thirty-one institutions (32%) harvested kidneys using open techniques only. Six centers (6%) applied both endoscopic and open techniques; 59 centers (61%) performed endoscopic donor nephrectomy only. Lack of evidence that endoscopic techniques provide superior results was the main reason for still performing open donor nephrectomy. In seven centers, a lumbotomy is still performed. Seventy-two centers (75%) accept donors with a body mass index of more than 30 kg/m2, the median upper limit in these centers was 35 kg/m2 (range, 31-40). Donors with an American Society of Anesthesiologists classification higher than 1 were accepted in 55% of the centers.

Live kidney donation in general and minimally invasive donor nephrectomy in particular are more commonly applied in Northern and Western Europe. However, a classic lumbotomy is still performed in a minority of centers. Because minimally invasive techniques have been proven superior, more attention should be given to educational programs in this field to let many kidney donors benefit.

INTRODUCTION

Live kidney donor transplantations have stabilized waiting lists for kidney transplantation in some countries in Western Europe. As long as the rate of deceased donation does not change, increasing the number of live donors is the most realistic option to further reduce the number of patients awaiting kidney transplantation. In the Eurotransplant countries the number of live donor nephrectomies increased from 864 in 2005 to 1262 in 2010 (1, 2). The excellent results achieved with various minimally invasive variations of laparoscopic donor nephrectomy (LDN) form the base of this increase. With the introduction of these techniques, recovery is fast and quality of the live donor has been improved significantly. These surgical approaches include the retroperitoneoscopic technique with and without hand-assistance (3, 4), the fully laparoscopic techniques and the modified open donor nephrectomy using mini-incision techniques (5-7).

In 2006 we published the results of a survey on live donor nephrectomy in twelve countries in Northern and Western Europe. We evaluated the status of the surgical approach as of 2004 (8) and observed a great variation in the technique preferred within as well as between European countries. One of the most important reasons for still performing the open donor nephrectomy (ODN) was the assumed lack of evidence showing the superiority of LDN over ODN. Since then a number of randomized studies have been published demonstrating the superior results of LDN with regard to pain, postoperative recovery and quality of life (9-11). Some safety issues were mentioned as arguments against the introduction of new techniques. The aim of this study was to assess the current status of the surgical approach in Europe and evaluate the changes since 2004.

MATERIALS AND METHODS

A questionnaire was sent to 119 transplant centers in Austria, Belgium, Denmark, France, Finland, Germany, Ireland, the Netherlands, Norway, Sweden, Switzerland and the United Kingdom. In each center, a surgeon or a urologist was approached by mail and/or e-mail. The list of centers invited to participate in 2004 was updated using the websites of the national transplant societies.

In November 2010 questionnaires were sent out and in February 2011 non-responding centers were invited to participate for the second time. Remaining non-responding centers were approached individually by e-mail or by telephone. The questionnaire included issues on live kidney donation in four sections (table 3). Part A included questions on the number of kidneys that were transplanted from both deceased and living donors. Part B included questions on ODN and part C included questions on LDN. Part D focused on donors with co-morbidities. Both open and multiple-choice questions were included in the questionnaire. In most multiple-choice questions free text could be recorded for additional comments. Reported numbers were cross-checked using national databases from the British Transplantation Society, Eurotransplant, Scandiatransplant, Swisstransplant, Agence de la Biomédicine and the Transplant Newsletter 2010 from the Council of Europe (12).

We used descriptive statistics to present our data. Differences between groups were analyzed using a Mann-Whitney U test. Differences in measures at two different time points within the same group were analyzed using the Paired-Samples T-test. Analyses were conducted using SPSS (version 17.0.2, SPSS Inc., Chicago, USA). A P-value <0.05 was considered statistically significant.

RESULTS

We received ninety-seven replies (82%). One center expressed unwillingness to cooperate. Therefore, these results are based on ninety-six replies received from twelve countries. Surgeons who responded and stated their name at the end of the questionnaire were included in the acknowledgements with their affiliations.

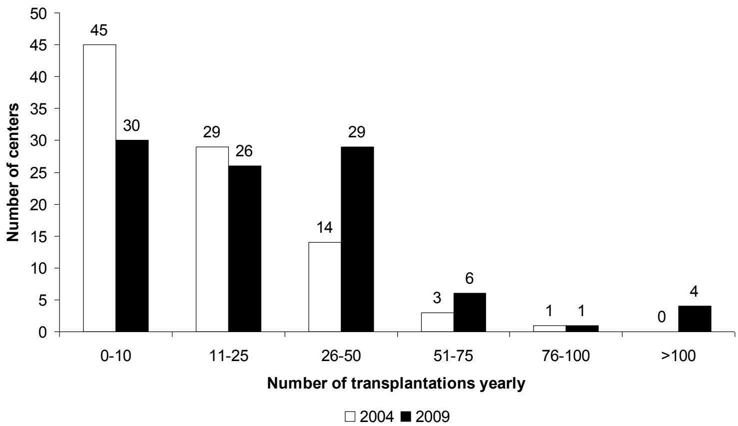

Figure 1. Case volume in responding centers in 2004 and 2009

Number of Transplantations

Figure 1 shows the case volume of the responding centers in 2004 and 2009. In 2009, 2824 live kidney donor transplantations were carried out in the 12 aforementioned countries. The responding centers were responsible for 2516 (89%) of these transplantations. In these 12 countries and the rest of Europe, 3589 live donor nephrectomies were performed. The responding centers accounted for 70% of these procedures (13). The median number of live kidney donor transplantations per center in 2009 was 20 (range 0-124). With regard to the annual number of live kidney donor transplantations in the last 5 years, 6% reported a decrease, 33% reported no changes and 61% an increase. The median increase in this last group was 50% (range 2-400%). Ninety-two percent of the centers had a registry of live donor nephrectomies.

The responding centers performed 6039 transplantations with kidneys originating from deceased donors in 2009. The median percentage of live donor kidney transplantations of the total number of kidney transplantations per center was 26% (range 0-82%). This percentage was below 10% in 18 centers (19%), between 10-25% in 27 centers (28%), between 25-50% in 44 centers (46%) and more than 50% in seven centers (7%).

Open Donor Nephrectomy

Thirty-seven centers (39%) reported to perform ODN. Thirty-one of these centers used open techniques exclusively. These 31 centers were responsible for 482 live donor

Table 1. Reasons for centers to stick to open donor nephrectomy

Reasons for:	No. of times mentioned (%)
Centers never performing LDN	(n=16)
Lack of evidence that LDN is better	9 (56%)
Evolution of ODN	4 (25%)
Other techniques hard to learn	1 (6%)
Safety	1 (6%)
Costs	1 (6%)
Other reasons	4 (25%)
Centers performing LDN simultaneously or in the past	(n=21)
Lack of evidence that LDN is better	7 (33%)
Evolution of ODN	7 (33%)
Other techniques hard to learn	2 (10%)
Safety	4 (19%)
Costs	0
Other reasons	4 (19%)

ODN, open donor nephrectomy; LDN, laparoscopic donor nephrectomy nephrectomies, nineteen percent of all live donor nephrectomies performed by the reporting centers. The median number of live donor nephrectomies per center in this group was 10 (range 0-82). Sixteen of these clinics had never tried a laparoscopic technique for live donation for reasons summarized in table 1. Lack of evidence that LDN was superior appeared to be an important reason to still prefer ODN. The other 15 centers had practiced endoscopic techniques in the past. The main reasons to perform ODN were the evolution of this technique in the center, safety and lack of evidence that LDN was superior. In seven of the aforementioned 31 centers, a lumbotomy was still performed. In six centers ODN and endoscopic techniques were used simultaneously, although ODN was preferred in these centers. The main reason to choose for an open approach in these clinics was also lack of evidence that LDN was superior.

Techniques of ODN

The preferred techniques used by the responding centers in both 2004 and 2009 are displayed in figure 2. Classic lumbotomy was defined as a 15-20 cm loin incision. A mini-incision donor nephrectomy (MIDN) was defined as a small flank incision varying from approximately 7cm in lean donors to 15 cm in obese donors. A fourth option was the pararectal vertical skin incision.

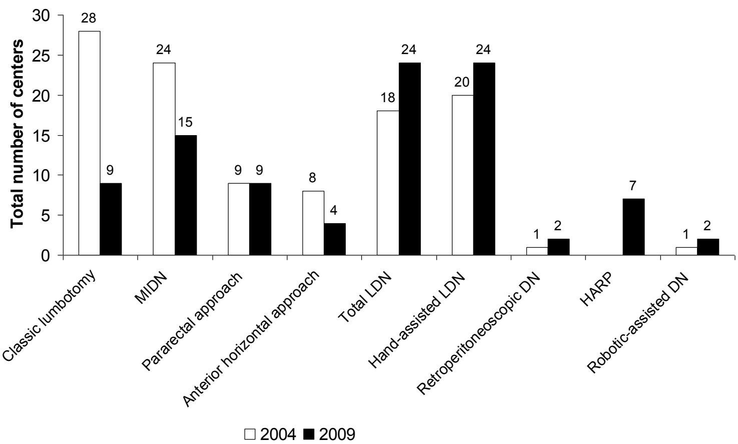

Figure 2. Preferred techniques in the responding centers in 2004 and 2009

Incisional Hernias and Incision Length

Incisional hernias were reported after all types of incision. Twelve centers in total reported to encounter incisional hernias. Two centers reported incisional hernias in 1% of the cases, three centers reported 2%, one center reported 3%, four centers reported 5% and two centers reported an incisional hernia rate of 10%. The median incision length for classic lumbotomy was 14 cm (range 11-20 cm). Median incision lengths for MIDN, transverse and vertical incisions were 10 cm (range 7-15 cm), 17.5 cm (range 15-20 cm) and 9 cm (range 7-18 cm) respectively. Median incision length in both the group with and without hernias was 10 cm (P=0.847).

Laparoscopic Donor Nephrectomy

Fifty-nine centers (61%) reported to prefer endoscopic techniques for donor nephrectomy, the preferred techniques used by these centers are displayed in figure 2. These centers were responsible for 1853 live donor nephrectomies, 74% of all live donor nephrectomies performed by the reporting centers. The median number of live donor nephrectomies per center in this group was 26 (range 0-124). This median was significantly higher than the median number of live donor nephrectomies per center in the group of centers performing only open techniques (P<0.001). Five of these centers started their laparoscopic programme in 2010 and one center in 2011. Therefore, data on numbers were available from 53 centers. In 2009, twenty-two centers performed 20 or less procedures, seven centers performed between 21 to 30 procedures, eight centers performed 31 to 40 procedures, five centers performed 41 to 50 procedures and 11 centers performed more than 50 laparoscopic procedures in 2009.

Experience

Seven centers (12%) performed less than 25 laparoscopic procedures up to and including 2009. Eight centers (14%) performed 25 to 50 procedures, seven centers (12%) performed 50 to 100 procedures, 10 centers (18%) performed 100 to 200 procedures and 25 centers (44%) performed more than 200 procedures, two centers did not report on this item. Twenty-four centers (41%) had introduced laparoscopic techniques to their transplantation programs since 2005. Thirty-seven centers (63%) stated that the introduction of laparoscopic techniques may have attributed to an increase of live kidney donation.

Instruments, Extraction Site and Conversion Rate

In three centers titanium clips were used to secure the renal vessels, in nine centers self-locking clips were used and in 43 centers an endostapler (TA or GIA) was used. The remaining centers used a combination of these three tools. For extraction of the kidney 40 centers (69%) used a Pfannenstiel incision. Other common extraction sites were sub-umbilical and antero-lateral. Only two centers used a mid-line incision for kidney extraction. In 13 centers an endoscopic procedure was converted to an open nephrectomy. The median conversion rate was 2% (range 1-7%). The median case volume in centers that converted one or more procedures in 2009 was significantly higher than centers that did not, 44 (range 7-115) and 20 (range 0-104) (P=0.006). There was no significant difference in years of experience between centers that did and did not convert (P=0.933).

Right-Sided LDN and Hand-Assistance

Eight centers (14%) performed left-sided LDN only. The median percentage of right-sided LDNs in the remaining centers is 27% (range 2-98%). Indications for right-sided donor nephrectomy are summarized in table 2. No relation was assessed between performing only left-sided LDN and years of experience (P=0.059) or case volume (P=0.091).

Table 2. Indications for right-sided laparoscopic donor nephrectomy and reasons for hand-assistance

Indication for:	No. of times mentioned (%)
Right-sided endoscopic DN	n=51
Multiple vessels on the left side	43 (84%)
Dependent on split function/kidney size	34 (66%)
Easier anatomy on the right side	27 ((53%)
Stenosis right renal artery	22 (43%)
Always right side	3 (6%)
Individual decision of surgeon	1 (2%)
Hand-assisted endoscopic DN	n=33
Shorter operation time	16 (48%)
Shorter warm ischemia time	10 (30%)
Easier than traditional LDN	9 (27%)
Safer with hand-assistance	7 (21%)
Donor/surgeon dependent	3 (9%)
Learning LDN setting	2 (6%)
Other	2 (6%)

DN, donor nephrectomy; LDN, laparoscopic donor nephrectomy

Thirty-three centers (56%) used some form of hand-assistance during LDN, reasons for hand-assistance are stated in table 2. No relation was found between the use of hand assistance and years of experience (P=0.247) or case volume (P=0.533).

Co-morbidities

Seventy-two centers (75%) accepted donors with a BMI above 30 kg/m2. Twenty-eight centers had no specific upper limit, as individual donor selection was at the discretion of the operating surgeon. In the remaining 44 centers the median upper limit was 35 kg/m2 (range 31-40). Eighty of the responding 96 centers (83%) accepted donors with hypertension. Donors with an ASA-classification higher than one were accepted in 55% of the centers.

Table 3. Questions on live donor nephrectomy

A. Number of kidney transplantations
How many kidney transplantations from a deceased donor were performed in your center in 2009?
How many kidney transplantations from a living donor were performed in your center in 2009?
Did these numbers change over the past 5 years?
Do you have a registration of live donor nephrectomies?
B. Open donor nephrectomy
Is the ODN technique preferred?
If yes, for what reason did you not experience other techniques?
What kind of open technique do you perform?
Do you have experience with other techniques than ODN?
Could you estimate you average incision length?
Do you see incisional hernias postoperatively?
C. Laparoscopic donor nephrectomy
Is LDN currently performed in your center?
If no, why not, If yes, what kind of technique?
In which year was LDN introduced?
In your opinion, has introduction of LDN contributed to increased live kidney donation in your center?
How many LDNs have been performed in your center in 2009 and in total?
How many percent of the LDNs in 2009 was converted to open?
Do you operate all donors laparoscopically?
Who does perform LDN in your center and how is your operation team composed?
Which extraction site is favored?
Which instrument is used to divide the renal vessels?
Is LDN restricted to left kidneys? If no, how many percent is right-sided LDN?
What indications do you use to perform right-sided LDN?
Do you use hand-assistance? If yes, for what reason?
D. Co-morbidities
Do you accept donors with a BMI of more than 30 kg/m^2? If yes, what is your upper limit?
Do you accept donors with hypertension? If yes, what are you limits?
Do you accept donors with ASA-classification > 1?

Developments

The percentage of centers using endoscopic techniques only increased from 45% in 2004 to 61% in 2009. The percentage of centers using open techniques only decreased from 55% in 2004 to 33% in 2009. The number of centers performing a classic lumbotomy decreased from 28 (30%) to 9 (9%). In 2004, 21/41 centers (51%) used some form of hand-assistance during donor-nephrectomy; in 2009 this increased to 33/58 centers (56%). In 2004, 20 out of 41 centers (49%) thought that the introduction of endoscopic techniques led to an increase of live kidney donors. Currently, 37 out of 59 centers (63%)

think the introduction of endoscopic techniques led to an increase of live kidney donation. The number of centers restricting LDN to the left kidney decreased from 12 (29%) to 8 (14%).

Matching Centers

In the study published by Kok *et al.* in 2006 the results were based on the replies from 92 different centers from 12 countries (8). Four of these centers no longer performed live kidney donation or merged with other centers by 2009. In the current study we received 71 replies from the 88 remaining centers (81%). In these centers the number of live donor kidney transplantations increased from 1169 in 2004 (81% of the total number operated on in these twelve countries) to 1920 (73%) in 2009. There was a significant increase in the median number of endoscopic donor nephrectomies per center in 2009 when compared with 2004, respectively 11.5 and 18 (P=0.028). The percentage of centers restricting LDN to the left side decreased from 32% in 2004 to 6% in 2009 (P=0.002). There was no significant difference in the percentage of centers using of hand-assistance, 48% in 2004 and 58% in 2009 (P=0.184).

DISCUSSION

The results of this survey confirm the increase of live donor kidney transplantations in Northern- and Western-Europe, more transplant centers are performing more live donor nephrectomies per year. A majority of the transplant centers stated that this increase may partially be due to the introduction of laparoscopic techniques; this is confirmed by a significant difference in median case volume between centers performing only open and only endoscopic techniques. The number of centers performing LDN and its variants has increased since 2004. A minority of the centers decided not to adopt minimally invasive endoscopic techniques. In the last 5 years a decrease of centers performing a classic lumbotomy can be noted.

The most important reason to choose for an open approach was lack of evidence favoring LDN. This finding is surprising since recent randomized trials have shown a shorter convalescence time, less pain and better quality of life after LDN when compared with ODN (9-11). Regarding safety and graft function, no significant differences were found between these techniques. Recently a Cochrane-review was published, confirming the results of these randomized trials. If the learning curve can be safely passed, laparoscopic donor nephrectomy offers significant advantages (14). The results of these trials show that benefit is to be gained by expanding the use of minimally invasive techniques. Another important argument provided by transplant centers that favor ODN is the evolution of this technique in their center. Two recent meta-analyses provided evidence that LDN may even be preferred over mini-incision techniques (15, 16). However, we would rather recommend a shift from classic lumbotomy to one of the less invasive open techniques than advocate that all donors should be operated on laparoscopically. In our opinion the benefit of mini-incision techniques over conventional open approaches is larger than the benefit of LDN over mini-approaches. However, the mini-incision techniques are harder to learn than (hand-assisted) laparoscopic techniques for the currently trained generation of surgeons and urologists. Therefore, investing time and money to incorporate (hand-assisted) LDN in the donation program may show to be beneficial for donors, hospitals and society.

The number of centers reporting on incisional hernias and the reported rate may be an underestimation. Donors do not necessarily return to the transplantation center to undergo a correction for an incisional hernia. Furthermore, duration of follow-up may differ between transplantation centers. However, incisional hernia rates after transverse incisions of the abdomen have been reported to be low (17).

Remarkably, 9 of the 59 centers (15%) performed endoscopic donor nephrectomy using self-locking clips for renal arterial control. A nationwide Class II recall of the Hem-o-lok locking clip by the Federal Drug Administration in the United States was issued in 2009 (18), *i.e.* before the survey. However, hemorrhagic deaths of live kidney donors from failure of these clips have been reported before then (19). The use of these clips to secure the renal artery, in contradiction to FDA recommendations is a major concern. The use of self-locking clips should be avoided in order to maximize donor safety.

This survey shows that about 54% of all centers use hand-assistance, this is comparable with the latest report from the United States (20). The most important arguments for using hand-assistance concerned reduction of the operating time, warm ischemia time and increased safety and control. These arguments confirm that hand-assisted LDN is not only used during the learning phase of LDN, but has become a true alternative with similar outcomes (21). Our results confirm this as there was no relation between the use of hand-assistance and years of experience or case volume. To date little evidence supporting either hand-assisted LDN or total LDN has been published. These current data indicate that the superior technique for kidney donation is still open for discussion and randomized controlled trials are needed to define the most appropriate approach that will optimize the safety and comfort of donors.

LDN is restricted to the left kidney in 14% of the centers. A significant increase in centers performing right-sided LDN was observed, in these centers approximately one third of all donor nephrectomies are right-sided. Indications for right-sided LDN were related to donor anatomy or split function. No centers mentioned shorter vessel length or renal vein thrombosis as reasons to prefer the left kidney over the right. Three centers always perform a right-sided donor nephrectomy when possible. These changes may reflect the effect of recent publications describing the feasibility and the superiority of right-sided LDN (22, 23). The results of this survey demonstrate that the prejudice against right-sided LDN is indeed declining in Western Europe. Fear for right renal vein thrombosis due to shorter vessel length seems ungrounded.

The eligibility criteria for live kidney donation have been extended. The vast majority of centers accept donors with a BMI above 30 kg/m2. In developed countries an increase in BMI is seen in the entire population. This inevitably leads to an increase of potential donors with a higher BMI. Although short-term results of obese donors are comparable to lean donors, more research is necessary to establish long-term outcomes (24). Donors with hypertension and/or an ASA classification of 2 or higher were also increasingly accepted. Long-term follow-up studies on live kidney donors have been published demonstrating excellent results. No detrimental effect on kidney function was observed, nor did donors show more hypertension than matched controls (25, 26). However, these studies all focus on healthy, carefully screened donors. More research is necessary on donors with (minor) co-morbidities.

We recognize that our study has the weakness associated with a retrospective survey. Given these limitations, the present study with a response rate of 82% representing nearly all live donor nephrectomies in the corresponding countries, provides the best possible reflection of the current status and is a realistic update.

In conclusion, live kidney donation in general and minimally invasive donor nephrectomy in particular is more commonly applied in Northern and Western Europe. However, a classic lumbotomy is still performed in a minority of centers. As minimally invasive techniques have been proven superior, this should be addressed through guidelines training and education in order to let all kidney donors benefit of minimally invasive approaches. The introduction of a prospective European registry focusing on surgical technique, donor selection and follow-up to evaluate and develop the current live kidney donation program is warranted.

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Chapter 3 Randomized controlled trial comparing hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy

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ABSTRACT

Laparoscopic donor nephrectomy (LDN) has become the gold standard for live-donor nephrectomy, as it results in a short convalescence time and increased quality of life. However, intraoperative safety has been debated, as severe complications occur incidentally. Hand-assisted retroperitoneoscopic donor nephrectomy (HARP) is an alternative approach, combining the safety of hand-guided surgery with the benefits of endoscopic techniques and retroperitoneal access. We assessed the best approach to optimize donors' quality of life and safety.

In two tertiary referral centers, donors undergoing left-sided nephrectomy were randomly assigned to HARP or LDN. Primary endpoint was physical function, one of the dimensions of the Short Form-36 questionnaire on quality of life, at 1 month postoperatively. Secondary endpoints included intraoperative events and operation times. Follow-up was 1 year.

In total, 190 donors were randomized. Physical function at 1 month follow-up did not significantly differ between groups (estimated difference, 1.79; 95% confidence interval, -4.1 to 7.68; P=0.55). HARP resulted in significantly shorter skin-to-skin time (mean, 159 vs. 188 min; P<0.001), shorter warm ischemia time (2 vs. 5 min; P<0.001) and a lower intraoperative event rate (5% vs. 11%, P=0.117). Length of stay (both 3 days; P=0.135) and postoperative complication rate (8% vs. 8%; P=1.00) were not significantly different. Potential graft-related complications did not significantly differ (6% vs. 13%; P=0.137).

Compared with LDN, left-sided HARP leads to similar quality of life, shorter operating time, and warm ischemia time. Therefore, we recommend HARP as a valuable alternative to the laparoscopic approach for left-sided donor nephrectomy.

INTRODUCTION

Recipient and societal benefits of live donor kidney transplantation are well established. Live kidney donation is increasingly performed in developed and developing countries to respond to the demand of kidney transplants. In 2008 more than 40% of the approximately 69.000 kidney transplants worldwide were donated by a live donor (1).

The benefits for recipient and society must be balanced against the potential harm to the donor (2-4). Live donors are healthy people who deserve a high standard of care. Screening of proper candidates for donation, improvement of the peri-operative course and social support after donation all contribute to the wellbeing of the donor. Preserving quality of life and safety of the donor and the graft should be the primary endpoints in research regarding live kidney donation. In a randomized controlled trial, we have previously shown that surgical technique had impact on the donor's quality of life (5). Laparoscopic donor nephrectomy (LDN) has become the preferred method to procure live donor kidneys because of less pain, shorter convalescence time and superior quality of life as compared to open approaches (3, 6-11). However, the safety of LDN has been debated because of an association with major intra-operative complications that rarely occurred during open donor nephrectomy (3, 11, 12). A recent survey in Europe clarified the demand for an easier approach (13). Hand-assisted retroperitoneoscopic nephrectomy (HARP) has been introduced as a safer approach that is easier to implement. HARP theoretically combines control and speed of hand-guided surgery with benefits of endoscopic technique and retroperitoneal access (5, 7-9, 11). The enormous shortage of organs from deceased donors will force centers and surgeons with limited experience to initiate or expand live donor kidney transplant programs. Concurrently a gradual shift occurs to older donors, obese donors and donors with mild co-morbidities to bridge the gap between demand and supply of organs. Therefore, it is warranted to define a standard surgical technique indicating the most effective approach. We compared both aforementioned approaches in a randomized controlled clinical trial.

MATERIALS AND METHODS

Patients and setting

The details of design and methods for this randomized trial have been described previously (14). Donors who were operated in two Dutch university hospitals were approached to participate in the study. We only included donors who donated their left kidney for various reasons as reported before. Briefly, analyses of our center specific data on LDN had revealed that left-sided LDN was associated with significantly more intra-operative complications and longer warm ischemia and operation times as compared to right-sided LDN. We attempted to improve our results for left nephrectomy as the results for laparoscopic right nephrectomy were already excellent (15). HARP appears less advantageous for right nephrectomy as the working space is limited due to the liver.

All donors were preoperatively discussed in a multidisciplinary working group, consisting of surgeons, nephrologists and nurse practitioners. The anatomy of the renal parenchyma and vasculature of the kidneys was imaged by a combination of ultrasonography, and magnetic resonance angiography or computed tomography-angiography. The decision on the side of donor nephrectomy was based on the rule to leave the best kidney with the donor (15). If no difference existed between the kidneys, left-sided nephrectomy would be performed. Donors with extensive intraperitoneal surgery, *e.g.* small bowel surgery or colon resection, were primarily operated using a retroperitoneal approach and deemed ineligible for this study. The donor was eligible for inclusion in the study provided he was capable to fill out quality of life forms in Dutch. Eligible donors were informed on the study details and procedures. They provided written informed consent. The Medical Ethics Committees of both centers approved the study protocol and the study was registered in the Netherlands Trial Registry (NTR1433).

Randomization

All included donors were randomized after endotracheal intubation. The surgeon called the study coordinator to open the next numbered sealed opaque envelope provided by the trial statistician. The series of envelopes was prepared according to a computer generated randomization list using a (hidden) block size of four. There was no stratification by center. All involved health care professionals except for the members of the surgical team were unaware of the allocated procedure. As the incisions were similar in both techniques blinding of the operation site to prevent observer bias was not indicated. The performed procedure was not disclosed to the donor until one year after nephrectomy, if requested.

Anesthesia and surgery

From the night before surgery and during the operation anesthetic procedures were performed according to a strict protocol for medication, ventilation and fluid administration At the end of the operation donors received Patient Controlled Analgesia (PCA) with intravenous morphine The PCA-device was removed when morphine had not been required for at least six hours (5). All operations were performed by six credentialed surgeons. The surgeons had performed no less than 7 HARP procedures and 38 LDN procedures. As LDN was the standard technique and both centers performed between 60 and 153 live donor nephrectomies annually, experience with LDN was judged sufficient. The details of surgical techniques employed were previously described (8, 14).

Statistical considerations

The primary objectives of the study were quality of life and safety. Major complications would usually result in decreased quality of life. However, based on our data, the number of major complications affecting the postoperative course would be limited in either group (5). Therefore, we have chosen physical function, measured using the SF-36 questionnaire, as the primary end point at one month. A 7.5-point difference between HARP and LDN on this health concept was considered the minimal clinically relevant difference (5, 9). With a standard deviation of 18.4 points for LDN in our data set, an alpha of 0.05 and a beta of 0.20, we calculated that we had to randomize 95 donors to either group.

Safety, including both intra-operative complications, which are not regularly recorded in retrospective studies, and post-operative complications was defined as key secondary endpoint. We prospectively recorded any undesirable, unintended change of course during the operation and post-operatively. Intra- and postoperative complications were graded according to the modified Clavien-Dindo classification for surgical complications (16). Potential complications to the graft, such as a capsular tear or unintended ligation of a upper pole artery, are usually not included in a registration. However, these events play a role in evaluating outcome of kidney donation and were therefore recorded. All complications were recorded as previously described (5). Other secondary end points were operation times, pain scores and other quality of life dimensions.

Categorical variables were compared with the Chi square test. Continuous variables were compared with the Mann Whitney U test or Student's T test as appropriate. Repeated continuous variables were compared with repeated measurement ANOVA. Repeated measures were adjusted for baseline values, donor's sex and age. Analyses were conducted using SPSS (version 20.0, SPSS Inc., Chicago, USA). Data were analysed according to the intention to treat principle. A p-value <0.05 (two-sided) was considered statistically significant.

Data collection

After discharge, donors visited the outpatient clinic at three weeks, two months, three months and one year postoperatively. Serum creatinine of the donor was recorded preoperatively, and post-operatively on days one, two, three (if still admitted), three weeks, one year and annually thereafter. Glomerular filtration rate (eGFR) was estimated by use of the Modification of Diet in Renal Disease formula (17). Graft and recipient survival were recorded. Serum creatinine of the recipient was recorded preoperatively, during the first 14 days, day 21, 28 and every three months thereafter. The donor was discharged provided a normal diet was tolerated and mobilization was adequately.

In order to assess the effect of both operation types on physical and psychosocial health, donors were asked to complete forms quantifying quality of life and pain, using validated questionnaires (18). The SF-36 was administered preoperatively, and at one, three, six and 12 months postoperatively. The SF-36 is a multi-item scale that measures eight health dimensions: physical function, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. Scores for each of these health concepts range from 0 to 100, with higher scores indicating better quality of life. Physical function, the primary endpoint, comprises questions regarding physical health including whether the donor is able to carry shopping bags, can climb stairs and is able to walk short and longer distances. Pain and nausea were quantified using a visual analogue scale (VAS) questionnaire. Case record forms to record out of hospital complications, return to work and resumption of activities were sent as mentioned above. We assumed to encounter

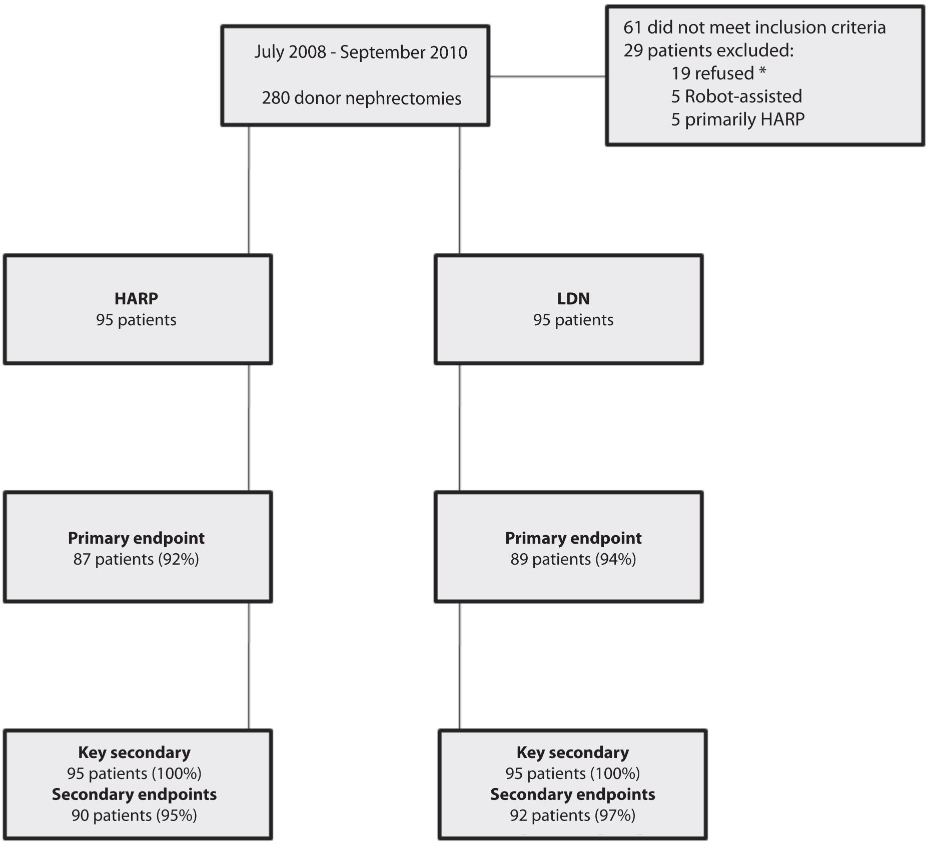

Figure 1. Flow-chart HARP-study.

almost all out of hospital complications by a combination of these case record forms and periodic visits to the outpatient clinic.

RESULTS

Between July 2008 and September 2010, 190 donors were randomized. In this period, 280 patients were eligible for donor nephrectomy. We were able to evaluate the primary endpoint in 176 of 190 participating donors (92.6%) of the donors at one month. Questionnaires not returned account for the missing data. An overview of in- and excluded donors is provided in figure 1. At three, six and twelve months, 88%, 87% and 86% of the quality of life forms were returned respectively. Baseline characteristics of the randomized donors are shown in Table 1.

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

	HARP (n=95)	LDN (n=95)
Donor		
Female	52 (55%)	46 (48%)
BMI (kg/m2)	26.0 (3.5)	26.2 (3.5)
Age (years)	52.8 (11.8)	52.4 (11.7)
ASA > 1	26 (27%)	19 (20%)
Arteries >1	17 (18%)	15 (16%)
Veins > 1	5 (5%)	9 (9%)
Pain	0.1 (0.4)	0.1 (0.5)
SF-36 Donor		
Physical function	93.8 (13.3)	94.2 (9.4)
Role physical	98.1 (13.0)	97.6 (14.7)
Bodily pain	95.9 (13.4)	95.9 (10.1)
General health	85.5 (13.1)	85.9 (11.5)
Vitality	81.5 (14.4)	82.2 (13.9)
Social functioning	93.5 (14.5)	94.3 (12.9)
Role emotional	95.7 (17.3)	97.5 (13.2)
Mental health	83.0 (12.8)	83.9 (12.3)
Recipient		
Female	40 (42%)	38 (40%)
Age (years)	48 (8-75)	49 (2-78)
Pre-emptive	29 (31%)	30 (32%)

Table 2. Quality of life at one month and one year after live kidney donation in both groups, mean (SD).

	One month postoperatively					One year postoperatively				
SF-36 dimension	**HARP**	**LDN**	**Adjusted difference (LDN minus HARP)**	**95%- CI**	**P-value**	**HARP**	**LDN**	**Adjusted difference (LDN minus HARP)**	**95%- CI**	**P-value**
Physical function	72.24 (19.94)	74.32 (19.23)	2.38	-3.48 to 8.25	0.423	94.70 (10.40)	93.95 (13.21)	-0.66	-4.04 to 2.73	0.701
Role physical	39.68 (44.43)	40.06 (39.23)	0.81	-12.17 to 13.79	0.902	94.16 (20.64)	91.07 (25.04)	-2.61	-9.84 to 4.62	0.477
Bodily pain	74.93 (18.12)	78.48 (20.48)	4.46	-1.30 to 10.21	0.128	95.46 (11.23)	93.06 (15.99)	-2.04	-6.13 to 2.06	0.328
General health	82·11 (13.00)	81.08 (13.82)	-1.55	-5.30 to 2.21	0.418	85.10 (14.40)	83.57 (16.59)	-1.95	-6.47 to 2.58	0.397
Vitality	67.37 (19.89)	66.53 (18.84)	-0.78	-6.35 to 4.79	0.783	78.27 (15.12)	77.55 (18.17)	-0.84	-5.51 to 3.83	0.722
Social functioning	77.73 (23.84)	78.09 (22.24)	0.28	-6.73 to 7.28	0.938	95.89 (9.95)	93.60 (15.09)	-1.78	-5.33 to 1.78	0.326
Role emotional	87.15 (29.83)	81.75 (35.63)	-6.30	-16.42 to 3.80	0.220	96.97 (16.39)	95.24 (18.76)	-1.87	-6.83 to 3.09	0.457
Mental health	84.27 (14.18)	86.49 (11.89)	1.68	-1.94 to 5.32	0.360	85.82 (13.73)	86.14 (13.30)	1.03	-2.97 to 5.04	0.611

Quality of life

The primary endpoint, physical function at one month, did not differ significantly between groups (Table 2). Raw data of physical function and the other dimensions of the Short Form-36 (SF-36) at baseline, one month and one year postoperatively are shown in Table 1 and 2 respectively. Physical function markedly decreased after the procedure. However, at three months postoperatively donors in both groups did not have significantly lower scores than at baseline. Preoperatively, but also at 3, 6 and 12 months postoperatively, live donors had superior physical function scores as compared to the average Dutch population (19). At these points in time physical function did not significantly differ between groups (figure 2). With regard to the other dimensions of quality of life, donors who underwent HARP had higher scores for vitality at three months (estimated difference -5.14, 95% CI -10.01 to -0.27). Other dimensions of quality of life did not differ between groups (not all data shown).

Within-group analyses showed that none of the scores for donors who underwent HARP

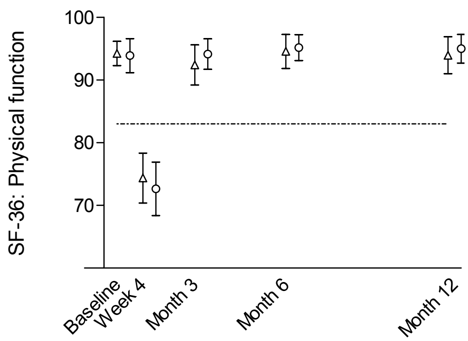

Figure 2. Physical function during one-year follow-up. The prespecified primary outcome, physical function at one month, did not significantly differ between groups. At other points in time no significant differences between groups were assessed either. Data are presented as means with corresponding 95 per cent confidence intervals. HARP and LDN are represented by dots and triangles respectively. The interrupted line represents the average for the Dutch population.

were significantly lower as compared to baseline at one year postoperatively. Mental health was significantly higher during follow-up. Bodily pain, general health, vitality, social functioning and role emotional returned to baseline levels at three months post-operatively. Role physical returned to baseline values at one year postoperatively.

Donors who underwent LDN also had better mental health scores postoperatively. General health and role emotional returned to baseline values at three months postoperatively. Role physical, bodily pain and social function returned to baseline levels at six months. At one year postoperatively the average score for vitality was still significantly lower (estimated difference 4.27, 95% CI 0.22 to 8.33).

Intra-operative data (Table 3)

Mean skin-to-skin time and warm ischemia time were significantly shorter in the HARP-group. Blood loss did not differ significantly. Intra-operative complication rate did not significantly differ between groups. Complications in the HARP group included a minor bleeding in the adrenal area requiring surgical intervention (grade 1) and four donors with total blood loss exceeding 500ml (grade 2a). One HARP procedure was converted to transperitoneal laparoscopy, because of inability to create a retroperitoneal plane due to adhesions after previous surgery. After conversion, the operation was uneventful. In the HARP group, none of the complications resulted in remaining dysfunction with the donor. Potential graft-related complications in this group included a kidney haematoma in four cases and the unintentional transsection of an accessory artery in two cases. Complications in the LDN group included a splenic laceration not requiring surgical intervention in three cases (grade 1), insertion of a mesh for a tearing fascia during closure in one case (grade 1), total blood loss exceeding 500ml in one case (grade 2a), a hemorrhage from the adrenal gland (300cc) in one case (grade 1), a splenic laceration that was oversewn in one case (grade 2b) and required the application of haemostatic sealant in two cases (grade 2b), serosal laceration of the small bowel in one case that was also oversewn (grade 2b), and an emergent conversion to open surgery due to a major haemorrhage in one case (grade 2c). Another procedure was converted to a hand-assisted transperitoneal approach because of adhesive perirenal fat and the inability to dissect the kidney from its perirenal fat Potential graft-related complications in this group included a kidney laceration in three cases, a kidney haematoma in two cases, the unintentional transsection of an accessory artery in four cases, an extended warm ischaemia time (WIT) (18 and 8 minutes) in two cases and an arterial dissection in one case. Ninety-two percent of the patients had no intra-operative complications. The only complication which influenced the postoperative course was the emergent conversions in the LDN group. This donor was readmitted for two days with reactive thrombocytosis and general malaise. The length of the Pfannenstiel incision was slightly but significantly longer for HARP.

Post-operative data (Table 3)

Postoperative complications in the HARP group included a wound infection in three cases, seroma in one case for which the donor was readmitted, painful scrotal swelling due to occult inguinal hernia in one case, a urinary tract infection leading to readmission and treatment with antibiotics in one case and a pneumonia in one case. One donor was readmitted and re-operated for a loop of small bowel that was trapped in a suture of the

Table 3. Intra and postoperative outcome (follow-up 1 year). Categorical data are given as No. (%) and continuous variables as mean (SD).

	HARP (n=95)	LDN (n=95)	P-value
Intra-operative			
Skin-to-skin time (min)	159 (42)	188 (39)	<0.001
Warm ischemia time (s)	150 (60)	288 (168)	<0.001
Conversion	1 (1%)*	2 (2%)**	0.414
Blood loss (ml)	214 (195)	193 (370)	0.629
Complications***	5 (5.3%)	11 (11.6%)	0.117
Grade 1	1 (1.1%)	5 (5.3%)	
Grade 2a	4 (4.2%)	1 (1.1%)	
Grade 2b	0	4 (4.2%)	
Grade 2c	0	1 (1.1%)	
Incision Pfannenstiel (cm)	9 (1)	8 (1)	<0.001
Graft-related complications	6 (6.3%)	12 (12.6%)	0.137
Post-operative			
Complications***	8 (8%)	8 (8%)	1.00
Grade 1	5 (5.3%)	3 (3.2%)	
Grade 2a	3 (3.2%)	4 (4.2%)	
Grade 2b	1 (1.1%)	1 (1.1%)	
Reoperations	1 (1%)	1 (1%)	1.00
Hospital stay (days)	3.7 (1.5)	3.4 (1.4)	0.187
Morphine requirement (mg)	23 (22)	24 (22)	0.828
One-year recipient survival	92 (97%)	94 (99%)	0.621
One-year death-censored graft survival	89 (94%)	86 (91%)	0.592
Post-operative pain			
Day 0	3.7 (2.2)	3.8 (2.1)	0.79
Day 1	2.6 (2.2)	2.8 (2.2)	0.61
Day 2	1.9 (1.8)	2.0 (1.8)	0.69
Day 3	1.5 (1.7)	1.8 (1.8)	0.38
Day 7	1.4 (1.8)	1.4 (1.7)	0.86
Day 14	1.0 (1.6)	0.8 (1.1)	0.14

*Converted to LDN

**One converted to hand-assisted laparoscopic, and one to an emergent open procedure

***Graded according to the adapted Clavien-Dindo scoring system

Pfannenstiel incision. Postoperative complications in the LDN group included a drop in haemoglobin from 14.5 g/dl to 8.5 g/dl not requiring a transfusion in one case, seroma in one case, a wound infection in one case and pneumonia in two cases. Readmissions included the aforementioned donor with emergent conversion and one donor presenting with rectal blood loss requiring observation only. One reoperation in the laparoscopic group was necessary because of a port-site hernia. 92% of the patients had no post-operative complications. Postoperative complication rate, total morphine requirement and length of hospital stay did not significantly differ between groups. During follow-up estimated glomerular filtration rates in donors and corresponding recipients did not differ between groups. Graft- and recipient survival did not differ either.

DISCUSSION

Mortality, morbidity and quality of life are the most important outcomes in modern medicine. The medical adagium "do not further harm" certainly applies to healthy live kidney donors. Live kidney donation has become ethically accepted because of the excellent results and the steep increase in the number of patients with end stage renal disease requiring transplantation. The evaluation of live donor nephrectomy is complex because graft- and recipient related outcomes also play an important role.

However, the three aforementioned donor related parameters remain most essential. In the present study mortality was zero. Estimated mortality after live donor nephrectomy is approximately 0.03% (20, 21). As the incidence of life-threatening complications, such as major hemorrhage, is very low, a study focusing on safety (ie. major complications) would need to include an extremely large number of donors to prove any potential benefit. Anticipating near zero mortality, this study focused on quality of life and donor safety, and will set a standard for the preferred operating technique for a wide range of centers with varying experience. Laparoscopy revolutionized live donor nephrectomy and certainly has contributed to the steep increase of the number of live donors. Recovery and quality of life were superior to both classic and modern open techniques (5, 8, 9). However, some severe intra-operative complications leading to major injury, and even death, have been described (11, 22). According to our own data, left-sided LDN was associated with a higher intra-operative complication rate as compared to right-sided LDN (15). Among these complications were a number of splenic injuries, occasionally resulting in splenectomy, and bowel lesions. Hand-assistance enables manual compression of bleeds, *e.g.* for emergent conversion, and finger-guided insertion of trocars, thereby protecting intra-abdominal organs. Retroperitoneal access results in fewer organs at risk; the intestines and the spleen are not encountered.

In the current study conversions and re-operations were rare. No significant differences in intra- and postoperative complication rate were observed between groups. However, higher-grade complications mainly occurred in the LDN group. Graft survival and graft function did not differ between groups up to one year. Potential graft-related complications did not significantly differ between groups. However, the clinical relevance of these potential complications cannot be assessed at short-term. The effect of shorter warm ischemia time on graft outcome in the HARP remains to be demonstrated. The mechanism, which is involved in graft function and graft survival is complex. However, there is consensus in the field of transplantation long warm ischemia times should rather be avoided (23). One-year graft survival is somewhat lower in the LDN-group as compared to the literature. However there is no statistical significant difference with the HARP-group. A possible explanation may be that all procedures were performed in tertiary referral centers, where highly sensitized and ABO-incompatible recipients are common among the patient population. Only larger cohort studies focusing on recipient outcome can reliably clarify any potential inference between type of nephrectomy and graft survival.

Improvements leading to less minor morbidity and shorter operation time and warm ischemia time only make sense if these do not adversely affect quality of life. In both groups baseline SF-36 scores are excellent as compared to the general population (19). This may be expected as a result of screening. Physical function at one month, the primary outcome of this study, did not statistically significantly differ between groups. However, equivalence by statistical means is not necessarily established. Like any clinical trial with a power of either eighty or ninety per cent a type two error may occur. With a sample size of 190 randomized donors it is unlikely that any relevant clinical difference exists.

In both groups donor nephrectomy had significant impact on most other dimensions, which is concordant with previous studies, most dimensions have recovered by three months (5, 24). We show in this series that donor nephrectomy may impact dimensions of quality of life up to one year postoperatively. As quality of life and mortality do not differ significantly between groups, morbidity is decisive to set the standard. Therefore, we have demonstrated that HARP is a valuable addition to the surgical armamentarium for left-sided live donor nephrectomy.

The advantages of HARP appear less obvious for right-sided LDN. Right-sided LDN has been proven to be substantially faster and safer at our institutes. Furthermore, in our experience right-sided HARP is hindered by the caudal position of the liver that limits the working space. Although we could not compare the learning curves of both techniques, both hand-assistance and the retroperitoneal plane facilitate the learning process of donor nephrectomy in our opinion. This is an important argument to support adaptation of the approach. In Europe, open donor nephrectomy is performed as the sole technique for live kidney donation in 30-40% of the centers (9, 13, 25). These centers may be reluctant towards introducing LDN mainly because of lack of evidence that laparoscopic techniques are better or the living transplant program is too small to master a complete laparoscopic approach. HARP seems a realistic option to offer all donors a safe, minimally-invasive approach. The long learning curve of LDN is indirectly shown by the reduced mean skin-to-skin time in our present study as compared to our former study. Even after 200 procedures, the operation time decreased without a significant change to the procedure. This is concordant with large case series published in literature (26). It is possible that the learning curves of the individual surgeons may have confounded the results of our trial. However, as data on learning curves for laparoscopic donor nephrectomy is limited and mainly includes large center reports, it is difficult to distinguish the individual learning curve from the center specific learning curve (*i.e.* the learning curve of the whole team). The positive effects of HARP on outcome may be underestimated by the relatively small experience with HARP before the start of the study. In our view the learning curve for HARP may be significantly shorter than the learning curve for LDN.

Reliable information is limited regarding the true, prospectively collected, complication and near complication rate of the surgical techniques in their learning curve (27). In the literature, proper evidence to support one of the aforementioned techniques is scarce. Only three small studies reported shorter operation times and warm ischemia times for HARP as main outcomes (28-30). We provide evidence that HARP is a valuable technique. In this relatively large study the randomized, blinded design avoided substantial bias. As we included donors with higher body mass index (BMI) (13.7% with BMI>30), advanced age (31.6% >60 years) and multiple vessels (arteries 16.8%, veins 7.4%), these results are applicable to the majority of donors. One of the main criticisms may be the relatively high intra-operative event rate in LDN as compared to large case series (26, 31). Accurate prospective scoring of the operation by an independent researcher present in the operating theatre may reveal significantly different outcomes on the operative course. In an era of transparency, it is open for discussion whether these events should be reported or not as they do not interfere with the recovery of the donor.

Recently published research has demonstrated the great discrepancy in the use of techniques between centers and countries within Europe (13, 25). With an increasing number of live donor nephrectomies being performed by an increasing number of transplant centers, the need for safe implementation of live donor nephrectomy is essential. In this study we demonstrate the shorter skin-to-skin time of HARP. Safety of the donor and the graft is at least comparable with LDN. Therefore, we recommend HARP as a valuable alternative to the laparoscopic approach for left-sided donor nephrectomy and thus an enrichment of the armamentarium.

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Chapter 4 Can right-sided hand-assisted retroperitoneoscopic donor nephrectomy be advocated above standard laparoscopic donor nephrectomy: A randomized pilot study

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ABSTRACT

Endoscopic techniques have contributed to early recovery and increased quality of life (QOL) of live kidney donors. However, laparoscopic donor nephrectomy (LDN) may have its limitations, and hand-assisted retroperitoneoscopic donor nephrectomy (HARP) has been introduced, mainly as a potentially safer alternative.

In a randomized fashion, we explored the feasibility and potential benefits of HARP for right-sided donor nephrectomy in a referral center with longstanding expertise on the standard laparoscopic approach. Forty donors were randomly assigned to either LDN or HARP. Primary outcome was operating time, and secondary outcomes included QOL, complications, pain, morphine requirement, blood loss, warm ischemia time, and hospital stay. Follow-up time was 1 year.

Skin-to-skin time did not significantly differ between both groups (162 vs. 158 min, P = 0.98). As compared to LDN, HARP resulted in a shorter warm ischemia time (2.8 vs. 3.9 min, P<0.001) and increased blood loss (187 vs. 50 ml, P<0.001). QOL, complication rate, pain, or hospital stay was not significantly different between the groups.

Right-sided HARP is feasible but does not confer clear benefits over standard right-sided LDN yet. Further studies should explore the value of HARP in difficult cases such as the obese donor and the value of HARP for transplantation centers starting a live kidney donation program. Nevertheless, HARP is a valuable addition to the surgical armamentarium in live donor surgery.

INTRODUCTION

Live kidney donation is increasingly accepted as the benefits for recipients are enormous and the risk of morbidity is low and mortality is rare (1). Minimally invasive endoscopic techniques have contributed to early recovery and increased quality of life (QOL) of live kidney donors (2-4). However, safety issues of laparoscopic donor nephrectomy (LDN) have been debated. In particular, major complications such as bleeding and visceral injury are more common in the laparoscopic era (5). Hand-assisted retroperitoneoscopic donor nephrectomy (HARP) has been introduced as a potentially safer alternative, combining the advantages of manual control with the benefits of retroperitoneal access and minimally invasive surgery (6-9).

We previously reported data of a prospective database indicating a higher intraoperative complication rate for left-sided LDN as compared to right-sided LDN (10). For this reason we explored the benefits of left-sided HARP. In the first 20 procedures, the operation time was significantly reduced as compared to LDN. In this series complication rates were lower but the difference did not reach statistical significance (11). We recently completed a randomized controlled trial in which left-sided HARP and LDN were compared (12). HARP appeared beneficial in terms of intraoperative safety (no visceral injuries, no life threatening bleeds) and shorter operating times. In the current pilot study we explored the feasibility and potential benefits of HARP for right-sided donor nephrectomy in a randomized fashion.

MATERIALS AND METHODS

Patients

All donors scheduled for right-sided donor nephrectomy at the Erasmus MC, University Medical Center in Rotterdam, the Netherlands, were eligible for inclusion in this study. All donors were discussed in a multidisciplinary working group. The anatomy of the renal parenchyma and vascular anatomy of the kidneys were visualized using a combination of ultrasound and magnetic resonance angiography (MRA) or computed tomography-angiography (CTA). If unilateral anatomical abnormalities *i.e.* ipsilateral arterial stenosis were present, that kidney was retrieved. If a significant difference in function was expected between both kidneys, based on size, the smaller kidney was retrieved. Reasons to remove the contralateral kidney included the presence of multiple arteries (including early or retrocaval branching), veins or ureters unilaterally. If no difference between the kidneys was assessed a right-sided nephrectomy was scheduled, according to preference (10, 13). If donors specifically asked for either a laparoscopic or a hand-assisted approach, they were not eligible for inclusion. Provided donors were 18 years or older and sufficiently understood the Dutch language, they were candidates for inclusion in this study. Eligible donors were informed on details of the study and procedures at our outpatient clinic by a transplant surgeon. They also received written information. Upon admission, the day before surgery, they provided written informed consent. The local medical ethics committee approved the study protocol and the trial was registered in the Dutch Trial Register (number: NTR3096).

Anaesthesia and Analgesia

Donors were prehydrated the day before surgery using intravenous crystalloids. Pre-operative donors received 1000 mg acetaminophen and were fitted with anti-embolic stockings during the operation. After endotracheal intubation anesthetic procedures were performed according to a strict protocol for medication, ventilation and fluid. Before clamping of the artery, 20 mg Mannitol was administered intravenously. No anti-biotic prophylaxis was given. At the end of operation donors received Patient Controlled Analgesia (PCA). This device enables the donor to administer intravenous morphine or piritramide from a 50-cc syringe (1 mg per ml) by pressing a button. Furthermore, two 500 mg acetaminophen tablets were offered four times daily until discharge. If the PCA-device had not been used during six hours, it was removed. Nausea was treated with granisetron one milligram up to three times daily.

Surgical Procedures

All procedures were performed in a high-volume live donor kidney transplantation center by five credentialed surgeons who were experienced in both procedures. The trial statistician provided a computer generated randomization list with a block size of four. He provided opaque, sealed envelopes to the study coordinator. There was no stratification. When the donor was under general anesthesia the research coordinator was called by telephone to open the envelope. After surgery, donors or their relatives were not informed on which donor nephrectomy technique was used. The incisions similar for both techniques, hence donors were fully blinded regarding the performed procedure.

A research fellow was present during all procedures to document intraoperative data such as blood loss, operation time and complications. Complications were defined as events requiring interventions or causing longer operating time or longer hospital admission. Skin-to-skin time was defined as the interval between incision and placement of the final suture. Warm ischemia time was defined as the interval between clamping of the first artery en the moment of flushing the kidney with UW-fluid at the back table. Blood loss was measured by both weighing all blood-stained surgical gauzes and measuring all collected blood by the suction device.

Both techniques have been described for left-sided donor nephrectomy before (11). For right-sided donor nephrectomy donors were placed in left lateral decubitus position. During LDN the camera and three to four additional trocars were introduced under vision. After identification and dissection of the kidney, ureter, and vascular structures, a Pfannenstiel incision was made. An endobag (Endocatch, US Surgical, Norwalk, USA) was introduced into the abdomen. The ureter was clipped distally and divided. The renal artery and vein were subsequently divided using an endoscopic linear stapler (EndoGia, US Surgical, Norwalk, CT, USA). The kidney was placed in the endobag and extracted through the Pfannenstiel incision. During HARP the Pfannenstiel incision was the first step. Using blunt dissection a retroperitoneal space was created and a Gelport (Applied Medical, Rancho Santa Margarita, CA, USA) was inserted. Blunt introduction of the first trocar between the iliac crest and the Gelport was guided by the operating surgeon's hand inside the abdomen. The additional trocars were placed under direct vision. Dissection of the kidney, ureter and vascular structures was similar to LDN but with hand-assistance and from a slightly different angle. The kidney was extracted manually. In both procedures the abdominal muscles and subcutaneous fascia were approximated. Skin wounds were sutured intracutaneously.

Recipients

Recipients and donors were allocated to different surgical wards, to minimize influence on donor recovery. All renal grafts were placed preperitoneally in the iliac fossa. Recipients received a calcineurin inhibitor based immunosuppressive regimen to avoid rejection. Recipient and graft survival were recorded up to one year, as well as estimated serum glomerular filtration rates (eGFR) pre- and postoperatively.

Data collection

The aforementioned research fellow recorded all pre-, intra- and post-operative data. Donors visited the outpatient clinic approximately one month after discharge. Intra-operative and postoperative complications were graded according to the modified Clavien grading system, described by Kocak *et al* (14). Donor eGFR was computed according to the four-variable modification of diet in renal disease (MDRD) formula preoperatively and postoperatively at day 1, 2, 3 (if the donor was still admitted) and one month and one year after surgery, at the first visit to the outpatient clinic. The donor was discharged from the hospital if a normal diet was tolerated and adequate mobilization was achieved.

In order to assess the effect of both surgical techniques on physical and psychosocial health, donors were asked to complete forms quantifying quality of life, pain, using validated questionnaires. The Short Form-36 (SF-36) was administered preoperatively, and at one month and one year postoperatively. The SF-36 is a multi-item scale that measures eight health dimensions: physical function, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. Scores for each of these health concepts range from 0 to 100, with higher scores indicating better QOL. Pain and nausea were assessed using a visual analogue scale (VAS) questionnaire during admission preoperatively and at day 1 and 2. Out of hospital they filled out forms at day 7 and 14. Donors had to choose a point on a 10 cm line (range from 0 or no pain to 10 or severe pain) which best corresponded with the experienced pain and nausea.

Statistical Considerations

Although we designed the current study to explore potential benefits, we have chosen a randomized concept in order to get comparable groups, thereby avoiding selection bias. With a low intra-operative complication rate for right-sided laparoscopic donor nephrectomy it would be unlikely to find any further reduction in intraoperative events (10). Serious adverse events including life-threatening bleeding and visceral injuries, or re-interventions are so rare in the current era of live donor nephrectomy that thousands of donors would have to be included in a randomized trial to demonstrate either a difference or similarity. The other potential measurable parameter that might have been influenced by HARP was operation time. We therefore chose skin-to-skin time as primary outcome. A difference of half an hour between the HARP- and LDN-group was considered to be clinically relevant. With an alpha of 0.05 and a beta of 0.20, we calculated that we had to randomize 20 donors in either group. However, twenty donors in either group would give an indication of the effect of HARP on operation times, complications, blood loss, pain, nausea and QOL to direct further studies. These outcomes were prespecified as secondary outcomes.

We attempted to incorporate all minor complications by attendance of a research fellow in the operation room and daily on the surgical ward. This strategy has led to relatively high rates of intraoperative complication rate in our previous studies. However, one should recognize that all minor events are scored, even those events which would not severely affect the intra-and postoperative course. These minor events are by definition underscored in all retrospective studies. Categorical variables were compared with the Chi square test. Continuous variables were compared with the Mann Whitney U test. Differences with regard to QOL dimensions were calculated with and without adjustment for baseline levels, gender and age. Analyses were conducted using SPSS (version 20.0, SPSS Inc., Chicago, USA). Data were analysed according to the intention to treat principle. A p-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Between April 2011 and January 2012 40 live kidney donors were randomized. Baseline characteristics are shown in table 1. Sixty-one donors were not eligible for inclusion (figure 1). Fifty-seven of these donors underwent left-sided donor nephrectomy. Four donors underwent right-sided donor nephrectomy but were not included in the study, including one donor whose command of the Dutch language was insufficient, one donor who did not wish to participate, one donor whose operation was specifically scheduled for LDN for educational purposes and one donor who had a neurostimulator on the right side precluding HARP. We evaluated the primary endpoint in 40 donors (100%) and QOL in 34 donors (85%) at one month and in 25 donors (63%) at one year.

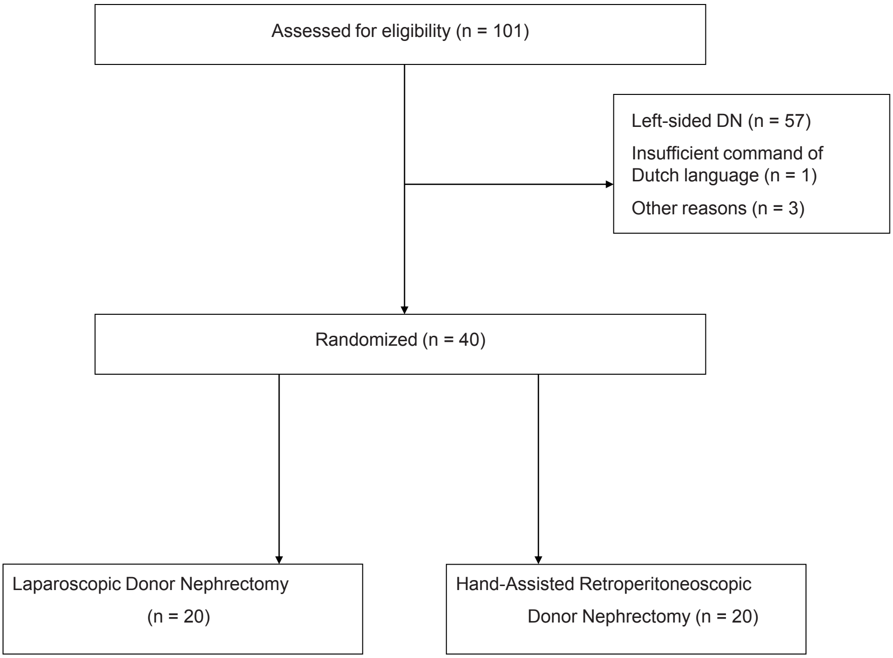

Figure 1. Trial flowchart

Intra-operative outcomes (table 2)

Median skin-to-skin time, the time between first incision and placement of the last skin suture, did not differ significantly between both groups. Median warm ischemia time was statistically significant shorter in the HARP-group. However, increased blood loss was observed. The HARP-group required a statistically significantly larger Pfannenstiel

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

	HARP (n=20)	LDN (n=20)
Donor		
Female	8 (40%)	15 (75%)
BMI - kg/m2	24.7 (19.8-34.1)	24.0 (18.5-32.5)
Age - years	47 (21-77)	49 (22-73)
ASA >1	9 (45%)	8 (40%)
Arteries >1	3 (15%)	3 (15%)
Veins >1	4 (20%)	2 (10%)
eGFR - ml/min/1.73m2	88 (59-114)	84 (63-126)
SF-36 Donor*		
Physical function	98.5 (3.7)	93.6 (12.3)
Role physical	93.8 (19.7)	90.0 (27.4)
Bodily pain	97.1 (13.2)	91.6 (15.7)
General health	86.7 (12.7)	86.9 (10.6)
Vitality	78.7 (11.3)	79.5 (13.3)
Social functioning	98.1 (6.1)	93.1 (14.3)
Role emotional	91.7 (26.2)	95.0 (16.3)
Mental health	69.3 (10.2)	69.5 (8.4)
Recipient		
Female	10 (50%)	7 (35%)
Age - years	50 (2-74)	54 (22-75)
Pre-emptive	9 (45%)	7 (35%)
eGFR - ml/min/1.73m2	9 (5-24)	9 (3-21)

* Data provided as mean (SD)

incision. Conversions were not necessary. The intra-operative complication in the LDN-group concerned an iatrogenic laceration of the bladder (grade 2b). Intra-operative complications in the HARP-group included the loss of a surgical gauze during the procedure requiring fluoroscopy (grade 1) and a haemorrhage of more than 500ml (grade 2a). One graft related complication occurred in the HARP-group, a laceration of the kidney capsule.

Postoperative outcomes (table 2)

The postoperative course was uncomplicated in 34 donors (85%). No significant differences were observed with regard to postoperative complication rate, reoperations, readmissions, hospital stay and total morphine or piritramide requirement. In the LDN-group one donor underwent exploratory relaparoscopy for a suspected haemorrhage. Since

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

	HARP (n=20)	LDN (n=20)	P-value
Intra-operative			
Skin-to-skin time (min)	162 (98-205)	158 (97-296)	0.98
Warm ischemia time (min)	2.8 (2-5)	3.9 (3-5)	<0.001
Blood loss (ml)	187 (25-500)	50 (0-260)	<0.001
Incision Pfannenstiel (cm)	10.0 (7.5-14.0)	8.5 (6.4-11.5)	0.016
Complications*	2 (10%)	1 (5%)	0.55
Grade 1	1 (5%)	0	
Grade 2a	1 (5%)	0	
Grade 2b	0	1 (5%)	
Graft-related complications	1 (5%)	0	0.31
Post-operative			
Complications*	3 (15%)	3 (15%)	1.00
Grade 1	1 (5%)	2 (10%)	
Grade 2a	1 (5%)	0	
Grade 2b	1 (5%)	1 (5%)	
Postoperative hospital stay - days	3 (2-4)	3 (1-6)	0.83
Readmissions	2 (10%)	0	0.15
Reoperations	0	1 (5%)	0.31
Morphine requirement - mg	9 (0-50)	16 (0-94)	0.58
Donor eGFR - ml/min/1.73m2			
Day 1	53 (38-67)	50 (34-82)	0.58
Month 1	54 (33-62)	55 (37-76)	0.59
Year 1	54 (34-79)	59 (38-86)	0.48
Recipient eGFR - ml/min/1.73m2			
Day 1	21 (8-61)	22 (5-38)	0.67
Month 1	48 (9-88)	51 (21-80)	0.61
Year 1	46 (18-90)	44 (15-78)	0.91
One-year recipient survival	18 (90%)	20 (100%)	0.16
One-year graft survival	19 (95%)	20 (100%)	0.31
Pain - VAS 0-10			
Day 1	2.8 (0-6.8)	3.1 (0-5.5)	0.95
Day 2	1.7 (0-4.9)	1.5 (0-7.5)	0.77
Day 3	1.4 (0-5.3)	2.1 (0-5.8)	0.50
Day 7	1.0 (0-4.9)	1.2 (0-5.4)	1.00
Day 14	0.8 (0-4.8)	0.5 (0-7.5)	0.88

* Graded according to the adapted Clavien-Dindo scoring system

no hemorrhage was found intraperitoneally, the Pfannenstiel incision was re-opened, exposing a preperitoneal hemorrhage. The donor was discharged 4 days after surgery.

Postoperative complications led to two readmissions in the HARP-group. One donor was readmitted to treat a retroperitoneal abscess by percutaneous drainage and antibiotics (grade 2b), the other donor was readmitted because of obstipation and was treated with laxatives (grade 2a). The other complication concerned a urinary tract infection requiring antibiotics (grade 1). In the LDN-group, postoperative complications included a urethral laceration during removal of the catheter (grade 1), a pneumonia requiring antibiotics (grade 1) and the haemorrhage described above (grade 2b).

At 1-year follow-up serum eGFR levels for donors and corresponding recipients and recipient survival did not differ between groups. One graft in the HARP-group was lost, this was due to technical problems during implantation. Re-implantation resulted in an extended warm ischemia time and hence to primary non-function and graft loss. However, no significant difference was observed between groups regarding graft survival. Two donors in the HARP group deceased during follow-up, one due to a gastric carcinoma and one due to cardiac problems. Pain scores did not significantly differ between both groups at any point in time. The median nausea score was 0 for both groups at any point in time; no significant difference between both groups were observed.

Quality of life

During one-month follow-up, six donors indicated that they did not wish to participate in the study anymore, three in either group. For this reason, at that moment quality of life was analyzed in 34 donors in total. There were no significant differences between

Table 3. Quality of life during follow-up, corrected for gender, age and baseline value. Data given as mean (SD).

	One month			One year		
	HARP (n=17)	**LDN (n=17)**	**P-value**	**HARP (n=11)**	**LDN (n=14)**	**P-value**
Physical function	67.8 (20.9)	67.1 (19.9)	0.99	93.8 (10.3)	88.6 (26.6)	0.22
Role physical	32.4 (36.2)	30.7 (37.6)	0.96	89.6 (29.1)	80.4 (39.4)	0.63
Bodily pain	73.2 (16.2)	71.9 (18.7)	0.78	90.2 (15.5)	84.1 (27.4)	0.50
General health	81.6 (16.4)	76.1 (13.2)	0.49	79.5 (20.7)	78.1 (21.8)	0.95
Vitality	64.7 (20.0)	58.8 (18.6)	0.51	72.7 (20.8)	74.8 (15.8)	0.59
Social functioning	76.5 (21.6)	77.2 (23.9)	0.49	90.6 (18.6)	92.0 (16.0	0.46
Role emotional	78.4 (40.7)	66.7 (45.4)	0.38	83.3 (38.9)	97.6 (8.9)	0.16
Mental health	65.5 (13.2)	60.9 (10.5)	0.26	63.6 (16.6)	63.0 (17.5)	0.90

groups regarding the quality of life dimensions at 1-month follow-up. During one year follow-up 2 donors emigrated and were unavailable for follow-up. In addition, 7 donors indicated that they no longer wished to participate in the study. At one-year follow-up, quality of life was analyzed in a total of 25 donors. After adjustment for age, gender and baseline values, we did not assess any significant differences during follow-up (table 3).

DISCUSSION

The safety of the graft after right-sided laparoscopic donor nephrectomy has long been debated. After an initial alarming report by Mandal *et al* (15), who described post-transplant renal vein thrombosis in 3 out of 8 grafts, we and others proved right-sided LDN to be safe (10, 13, 16). Moreover, right-sided LDN was easier to learn in our view. Favourable complication rates and shorter operation times as compared to left-sided LDN have directed our decision to retrieve the right kidney in case of identical anatomy between the two kidneys. We have always explained the benefits of right-sided donor nephrectomy by the frequent absence of side branches of the renal vein, the adjacent liver, which is easier to retract than the spleen, the hepatic colonic flexure, which is often easier mobilized than the splenic flexure, and the more caudal position of the kidney. In our experience, length of the right renal vein is never a contra-indication for right donor nephrectomy. Adequate positioning of the donor and stapling as close to the inferior caval vein as possible will aid in procuring sufficient length. A short renal vein after right-sided donor nephrectomy has never impeded implantation. However, transplant surgeons should adhere to the principle to leave the best kidney to the donor. There is an indication to remove the left kidney in more than half of the donors (10).

In contrast to the literature we previously reported a 19% intra-operative complication rate for left-sided LDN. This included primarily minor complications without consequences for the postoperative tract but also complications that could have had major consequences. Although we did think that many retrospective reports in the literature underestimated the true complication rate, our prospective data demanded a novel approach for left-sided kidney donation. Therefore we explored HARP for left-sided donor nephrectomy with stunning early results (11). In the first twenty procedures the operation times were significantly lower and the complication rate was lower, albeit not statistically significant due to a small sample size. In a recently conducted randomized controlled trial we confirmed the inferences of the pilot study. These included shorter operation time and warm ischemia time, the absence of major bleeds, visceral injury and exceptional long warm ischemia times, despite a long tradition of laparoscopic donor nephrectomy at our center, and a relatively short experience with HARP (12),.

Although our results for right-sided LDN were significantly better, we decided to explore the potential benefits for right-sided HARP in the current study. The results of this pilot study show that right-sided HARP is feasible. Furthermore, life-threatening bleeds and visceral injuries did not occur in the HARP group. The relatively high intra-operative complication rate is a result of the small sample size and an uncommon complication as a gauze that was lost. On the other hand, an intra-abdominal abscess that has to be drained is an uncommon postoperative complication after standard LDN. The intra- and post-operative complication rates for right-sided LDN were comparable to previous reports (10). No incisional hernias were observed, which is concordant with previously published research (17). For right-sided donor nephrectomy we did not observe a significant reduction in operation time using the hand-assisted retroperitoneoscopic technique. Warm ischemia times in this study were comparable to previous studies in our center and other reports in literature (11, 12, 18, 19). Warm ischemia time was significantly shorter in the HARP-group. The clinical relevance of this difference remains to be demonstrated as there are no reports on small differences in warm ischemia time and graft-related outcome in current literature. Nevertheless, warm ischemia times should be kept as short as possible. As may be expected when both techniques have the similar scars and operation time hospital stay and QOL did not differ between techniques.

Intra-operative blood loss was significantly higher in the HARP-group when compared to the LDN-group, 187 vs. 50 ml respectively. This may be explained by the more extensive mobilization of tissue during blunt dissection of the retroperitoneum, leading to increased blood loss. We do not judge this difference to be clinically relevant. In both groups all intra-operative complications were grade 1 or 2, *e.g.* non-life threatening or not leaving residual disability. Again all complications have been recorded adequately. Therewith we also included all adverse events with limited consequences for the post-operative course of the donor. To adequately asses a difference in safety, expressed by the complication rate between these techniques, a future study with complications as primary endpoint would be necessary. It seems unlikely that HARP will further reduce the low rate of complications for right-sided donor nephrectomy. Given the (historical) marginal difference in complication rates between these two techniques, such a future study would require a huge sample size. However, major vascular injuries may be dealt with quickly. Therefore, this technique likely reduces the risk of life threatening bleeds.

During right-sided HARP, presence of a large liver impedes adequate access to the upper pole of the kidney. Dissection of the upper pole in these cases was complex, requiring increased manipulation of the kidney, sometimes leading to iatrogenic peritoneal damage. In these cases, the sudden emergence of a pneumoperitoneum often resulted in a decrease of retroperitoneal space, hence in a decreased surgical working space.

In live donor surgery safety and quality of life are the most important factors when assessing differences between two surgical approaches. This pilot study was not designed and underpowered to reliably address differences in these outcomes. However, the small differences observed in this randomized single blind study are indicative of limited clinical differences. Bargmann *et al* previously investigated the addition of hand-assistance to transperitoneal laparoscopic donor nephrectomy in a similar designed study (20). They did not show a beneficial nor a detrimental effect of hand-assistance. We rather explored the retroperitoneoscopic approach as this approach technically avoids lesions to intraperitoneal organs.

The question may arise whether HARP may be helpful and if so in which donors. In this study age, obesity, and previous surgery did not preclude participation. HARP may be helpful in obese donors or donors suspected of having a fixed upper pole of the kidney, which we often experience in horse riders, motor cyclists and boxers. In these cases HARP may enable more traction. Furthermore, we would like to emphasize that all surgeons were very experienced in both techniques. Currently, more than 150 live donor nephrectomies are performed at our center annually, which is the highest volume of live donor nephrectomies in Europe. Potential positive effects of HARP on operation time and complication rate may have been blurred partially by abundant experience in the control arm. HARP may be beneficial for surgeons starting with endoscopic donor nephrectomy (21). HARP may be instrumental to safely negotiate the learning curve of endoscopic techniques. Future studies should be directed at HARP in the aforementioned groups and learning curve effects. In order to maintain the highest standard of care for these healthy individuals we advocate a donor oriented decision model when selecting a surgical technique. More prospective, comparative studies on all surgical techniques used for live donor nephrectomy are required to be able to implement such a model (22).

In our opinion, right-sided HARP is a valuable addition to the surgical armamentarium in live donor surgery. In addition to others we demonstrated that this technique is very safe and appears to have similar results as compared to standard LDN. Although HARP did not confer clear benefits over standard right-sided LDN in this randomized pilot study yet, we suggest that this technique has a place in live donor surgery and currently apply right-sided HARP in complex donors such as obese donors and donors with previous intra-abdominal surgery. The role of right-sided HARP in centers or surgeons at the beginning of their learning curve should be explored. Continental registrations may more likely than randomized controlled trials aid to resolve issues on safety of either technique. In order to maintain the highest standard of care for these healthy individuals we advocate a donor oriented decision model when selecting a surgical technique.

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Chapter 5 Learning curves in endoscopic donor nephrectomy

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Submitted

ABSTRACT

Laparoscopic donor nephrectomy (LDN) is a complex surgical procedure. Hand-assisted retroperitoneoscopic donor nephrectomy (HARP) combines the advantages of minimally invasive surgery, tactile feedback and a retroperitoneal approach. We explored the learning curves of either technique to be able to give a legitimate recommendation to centers initiating an endoscopic live donor nephrectomy program on which minimally invasive technique to adopt primarily.

Data on live donor nephrectomies was prospectively collected in one expert center and one center initiating an endoscopic live donor nephrectomy program. Both a center-specific and surgeon-specific analysis was performed.

The first 100 HARP procedures resulted in a decreased skin-to-skin time when compared to the first 100 LDN procedures, 188 vs. 290 minutes ($p<0.001$). A center with no prior experience in LDN averaged a time of 186 minutes. Complication rates were not significantly different, 4%, 10% and 5% respectively ($p=0.22$). Two surgeons with no prior experience in LDN achieved comparable skin-to-skin times (207 and 171 minutes) as more experienced surgeons. Complication rates did not differ significantly. Surgeons with little experience in LDN had a significant correlation between sequence number and skin-to-skin time ($p<0.001$ and $p=0.009$).

For centers either initiating a live donor program or changing their technique from open to endoscopic, we suggest to adopt HARP first. Supervision by experienced peers may help the introduction of HARP by centers initiating an endoscopic live kidney donation program.

INTRODUCTION

The surgical technique for live donor nephrectomy has evolved in the last decade. A variety of techniques is available to transplant surgeons, including several endoscopic techniques. The superiority of laparoscopic donor nephrectomy (LDN) over open donor nephrectomy has been established in terms of hospital stay, return to work and pain (1). However, several transplant centers across Europe still apply open techniques (2). Donor safety and the learning curve associated with LDN were reported by these centers to be important reasons to pursue open approaches (2).

Established advantages of hand-assisted donor nephrectomy include increased donor safety, tactile feedback, shorter operating time and reduced warm ischemia time (WIT) (3, 4). A retroperitoneal approach reduces the risk of iatrogenic visceral injuries and major bleeding. The hand-assisted retroperitoneoscopic donor nephrectomy (HARP) combines the aforementioned advantages. Since its introduction, several studies have described the superior results of HARP over laparoscopic and open donor nephrectomy (4-8).

Any new surgical procedure is subject to the effect of learning curve. The complexity of LDN is well known as it requires central transection of large blood vessels to maintain adequate length of these vessels for transplantation. Moreover, the transplant must remain intact and collateral damage to the healthy donor, who does not have any direct benefit from the procedure should be avoided at all cost. Thus, a high level of laparoscopic skills and experience is necessary. The advantages of hand-assistance have been proven to be even greater in laparoscopic novices (9, 10). For these reasons, the combined advantages of HARP may even be more valuable in centers initiating an endoscopic live donor nephrectomy program. The aim of this study was to gain further insight the learning curves for both LDN and HARP.

MATERIALS AND METHODS

Study population and data collection

The EMC harbors Europe's largest live kidney donation program. Since 1997 minimally invasive live donor nephrectomies have been performed on a regular basis. Data on all live donor nephrectomies were prospectively collected, and entered into a database. In March 2012, a proctoring program for HARP donor nephrectomy was initiated by the EMC for 2 surgeons in the UMCU. The latter surgeons had participated in our hands-on course on cadavers. Any previous experience in endoscopic donor nephrectomy was absent at the UMCU. Data on the procedures and follow-up were recorded during this program. These donor data included the following parameters: age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, relation to recipient, vascular anatomy, duration of the procedure, WIT, intraoperative complications, conversions, postoperative complications, and postoperative hospital stay. Reliable information on blood loss (*i.e.* gauze were not weighted) was not available in most of the cases in the UMCU donors and has thus not been included. Duration of the procedure was defined as skin-to-skin time. WIT was defined as the interval between clamping of the artery and flushing of the kidney with preservation solution. An intraoperative complication was defined as any intraoperative event requiring intervention or leading to a prolonged duration of the procedure. Major bleeding was defined as any bleeding leading to a blood loss > 500 ml or requiring conversion or transfusion. Donors were discharged when a normal diet was tolerated and mobilization was adequate.

Surgical techniques

Transperitoneal laparoscopic donor nephrectomy and hand-assisted retroperitoneoscopic donor nephrectomy were performed according to standard protocols as described previously (4, 11). In the former technique we did not apply hand-assistance at any stage and the kidney was removed via a Pfannenstiel incision using an endobag. The HARP approach started with a Pfannenstiel incision and insertion of a hand-port to facilitate hand-assistance during the whole procedure.

Statistical analysis

We performed a center-specific analysis and a surgeon-specific analysis. The center-specific analysis included 342 donors in four different consecutive series. The first series included the first 100 donors that underwent LDN at the EMC between December 1997 and April 2001 (first LDN). The second series consisted of the first 100 donors that underwent HARP at the EMC between November 2006 and May 2010 (first HARP). As we initially developed HARP for left-sided donor nephrectomy and we included most donors in a study randomizing donors between left sided HARP or left-sided LDN, most donors underwent left-sided nephrectomy in this cohort (12). The third series consisted of all donors that underwent LDN in 2010 in the EMC, 99 in total (concurrent LDN). The fourth series consisted of the first 43 donors that underwent HARP at the UMCU between March 2012 and November 2013.

For the surgeon-specific analysis we included the 30 first LDN and the 30 first HARP procedures of four transplant surgeons at the EMC, yielding 238 donors in total. We chose this number because 20-25 procedures are generally required to master full laparoscopic and hand-assisted laparoscopic colonic surgery (13, 14). We also included all

43 HARP procedures that had been performed by two transplant surgeons at the UMCU during the proctoring program.

Categorical variables are presented as a number (percentage). Continuous variables are presented as mean (standard deviation (SD)) or as median (minimum – maximum) as appropriate. Categorical variables were compared with the chi-square test; continuous variables were compared with the Mann-Whitney U test or a Student's T-test as appropriate. Correlations were assessed using Pearson's correlation coefficient. Between-group analyses were performed using a One-Way ANOVA. All analyses were conducted using SPSS (version 20.0.0.1, SPSS Inc, Chicago, USA). A P-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Center-specific analysis

Baseline characteristics

The baseline donor characteristics are summarized in table 1. Significant differences were observed regarding the side chosen for nephrectomy, donor age, American Society

Table 1. Baseline characteristics; categorical data presented as N (%), continuous data presented as mean (SD)

	First LDN N=100	First HARP N=100	Concurrent LDN N=99	HARP UMCU N=43	P-value
Female gender	49 (49%)	63 (63%)	62 (62%)	26 (61%)	0.150
Left-sided nephrectomy	28 (28%)	100 (100%)	51 (51%)	36 (63%)	<0.001
Age - years	46.6 (12.5)	53.0 (11.2)	53.0 (13.5)	51.8 (12.6)	<0.001
BMI - kg/m2	25.4 (3.4)	26.2 (3.3)	26.3 (3.3)	25.1 (3.4)	0.107
ASA-I	84 (84%)	69 (69%)	64 (64%)	36 (84%)	0.004
Single arterial anatomy	83 (83%)	81 (81%)	84 (84%)	34 (79%)	0.24
Single venous anatomy	90 (90%)	95 (95%)	96 (96%)	43 (100%)	0.07

SD, standard deviation; LDN, laparoscopic donor nephrectomy; HARP, hand-assisted retroperitoneoscopic donor nephrectomy; UMCU, university medical center utrecht; BMI, body mass index; ASA, American Society of Anesthesiologists

of Anesthesiologists-classification (ASA) and estimated glomerular filtration rate (GFR).

Table 2. Operative characteristics; categorical data presented as N (%), continuous data presented as mean (SD)

	First LDN N=100	First HARP N=100	Concurrent LDN N=99	HARP UMCU N=43	P-value
Skin-to-skin time - minutes	290.4 (64.9)	188.4 (49.6)	189.9 (51.3)	185.9 (37.4)	<0.001
WIT - minutes	8.0 (3.2)	3.0 (1.5)	4.9 (2.6)	3.43 (1.3)	<0.001
Blood loss - ml	320.7 (353.7)	209.0 (192.3)	138.2 (203.6)	NA	<0.001
Conversion	13 (13%)	2 (2%)	4 (4%)	0 (0%)	0.001
Per-operative complications	10 (10%)	4 (4%)	4 (4%)	2 (5%)	0.22
Major bleeding	7 (7%)	4 (4%)	3 (3%)	-	
Iatrogenic organ laceration	2 (2%)	-	1 (1%)	1 (2%)	
Other	1 (1%)	-	-	1 (2%)	
Postoperative stay - days	3.8 (2-9)	3.6 (1-10)	3.0 (1-11)	5.0 (2-16)	<0.001
Postoperative complications	6 (6%)	8 (8%)	8 (8%)	10 (23%)	0.009
Reintervention	1 (1%)	1 (1%)	1 (1%)	2 (5%)	0.324
Readmission	-	4 (4%)	3 (3%)	1 (2%)	0.283

LDN, laparoscopic donor nephrectomy; HARP, hand-assisted retroperitoneoscopic donor nephrectomy; WIT, warm ischemia time; erate NA, not available

Intra- and postoperative outcomes

An overview of all operative and postoperative characteristics is provided in table 2. Thirteen conversions were necessary in the first LDN group. Seven of these were emergent conversions to an open procedure due to major bleeding, in one case for a splenectomy and in one case due to ischemia of the lower pole of the kidney necessitating urgent flushing with preservation fluid. In the first HARP group there were two conversions, one emergent conversion to an open procedure for major bleeding and one conversion to a full laparoscopic procedure due to scar tissue in the pre-peritoneal surgical plane that could not be developed in a patient with a prior transabdominal hysterectomy. Four conversions took place in the concurrent LDN group, two emergent conversions to an open procedure for bleeding and two conversions to hand-assisted procedure for inadequate exposure. In the first LDN group the iatrogenic lacerations concerned a splenic injury for which a splenectomy was performed and a serosal bowel injury that was oversewn. The other complication was a conversion for lower pole ischemia as previously described. In the concurrent LDN group, the iatrogenic laceration concerned a splenic laceration. The iatrogenic injury in the University Medical Center Utrecht (UMCU) HARP group concerned an adrenal gland laceration without further consequences. The other complication was a patient that developed Horner's syndrome after epidural anesthesia.

Post-operative complications in the first LDN group included a pneumonia, a urinary tract infection, a superficial surgical site infection, neurapraxia in two cases and a post-operative bleed requiring reoperation in one case. In the first HARP group postoperative complications included a pneumonia, three urinary tract infections, three superficial surgical site infections and a persisting intestinal obstruction in one case requiring reoperation. Post-operative complications in the concurrent LDN group included a large hematoma in one case, one case of persisting intestinal obstruction, a superficial surgical site infection in 2 cases and a neurapraxia in one case. In one case the cardiologist was consulted for paroxysmal atrial fibrillation after the procedure. One donor experienced urinary retention for which a bladder catheter was inserted and one donor was re-operated for an incisional hernia and one donor developed a subfascial hematoma requiring reoperation. Postoperative complications in the HARP-UMCU group included 4 cases of pneumonia, 2 urinary tract infections, two cases of superficial surgical site infection and a subfascial hematoma and an incisional hernia both requiring reoperation.

Learning curve

Before introduction of the HARP technique 335 LDNs were performed in the Erasmus University Medical Center Rotterdam (EMC). Operating times decreased by increasing

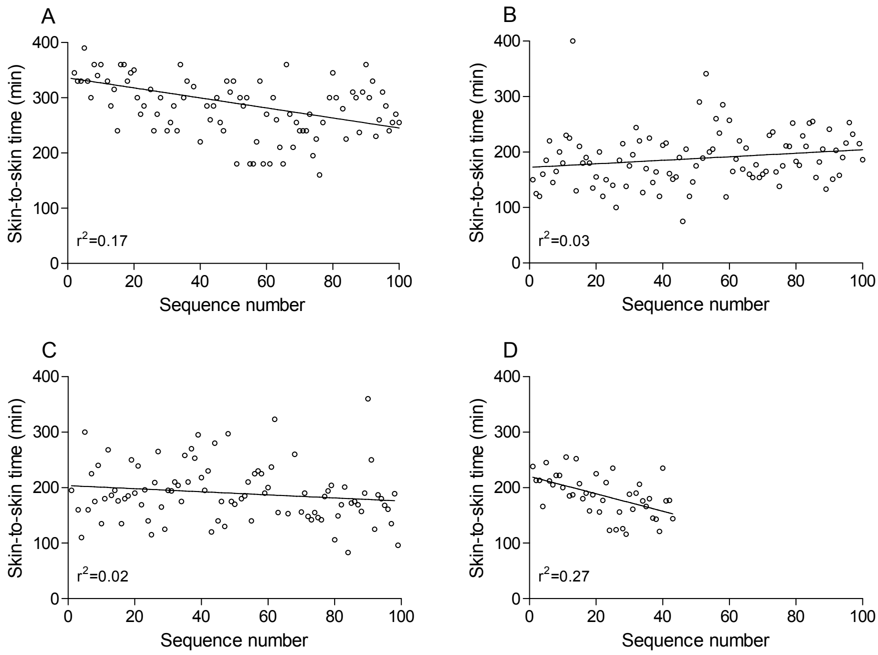

Figure 1. Skin-to-skin times and linear regression of first LDN (A), first HARP (B), concurrent LDN (C) and HARP-UMCU (D).

Table 3. Baseline donor and perioperative data and surgeon-specific differences between techniques. Data displayed as median (range) and number (%).

	Surgeon A			Surgeon B			Surgeon C			Surgeon D			Surgeon E	Surgeon F
	EMC												UMCU	
	LDN N=30	HARP N=28	P-value	LDN N=30	HARP N=30	P-value	LDN N=30	HARP N=30	P-value	LDN N=30	HARP N=30	P-value	HARP N=21	HARP N=22
Female gender	16 (53%)	20 (71%)	0.16	13 (43%)	16 (53%)	0.44	13 (43%)	14 (47%)	0.80	22 (73%)	18 (60%)	0.27	12 (57%)	14 (64%)
Age – years	48.6 (24-75)	49.3 (21-72)	0.47	55.8 (21-79)	47.4 (23-77)	0.05	53.9 (24-79)	57.0 (21-77)	0.51	57.1 (21-75)	52.7 (27-87)	0.65	52.0 (30-71)	52.0 (25-80)
BMI - kg/m2	24.4 (17.3-31.5)	25.7 (20.2-33.0)	0.08	26.6 (20.6-33.3)	27.1 (21.3-38.4)	0.46	24.2 (17.6-30.1)	24.5 (21.0-32.4)	0.99	25.0 (19.4-32.8)	26.4 (19.3-34.5)	0.11	25.5 (17.8-34.7)	24.1 (17.5-30.9)
ASA-I	24 (80%)	16 (57%)	0.06	18 (60%)	21 (70%)	0.42	19 (63%)	21 (70%)	0.58	25 (83%)	20 (67%)	0.14	20 (95%)	16 (73%)
Skin-to-skin time - min	300 (180-500)	200 (138-290)	<0.001	204 (140-323)	180 (110-253)	0.008	180 (105-340)	158 (75-400)	0.041	277 (130-478)	206 (100-341)	<0.001	207 (156-255)	171 (116-235)
WIT – min	8 (3-17)	3 (1-8)	<0.001	5 (2-21)	3 (1-4)	<0.001	5 (3-10)	3 (1-6)	<0.001	5 (2-13)	2 (1-3)	<0.001	4 (2-8)	3 (2-5)
Intra-operative complications	2 (7%)	2 (7%)	0.94	4 (13%)	3 (10%)	0.69	2 (7%)	1 (3%)	0.55	5 (17%)	3 (10%)	0.45	1 (5%)	2 (9%)
Major bleeding	1	1		1	3		-	1		2	3		-	-
Iatrogenic visceral injury	1	1		2	-		1	-		3	-		-	2
Other	-	-		1	-		1	-		-	-		1	-
Conversion	3 (10%)	1 (4%)	0.33	1 (3%)	-	0.31	1 (3%)	-	0.31	2 (6%)	-	0.15	-	-
Postoperative complications	3 (10%)	1 (3%)	0.33	3 (10%)	3 (10%)	1.0	2 (7%)	1 (3%)	0.55	2 (7%)	3 (10%)	0.64	1 (5%)	9 (41%)
Postoperative stay - days	3 (2-9)	3 (2-8)	0.003	3 (2-9)	3 (2-7)	0.88	3 (1-8)	4 (1-8)	0.31	3.5 (1-12)	3 (2-13)	0.13	4 (3-11)	4 (2-16)
Pearson's ρ (s-t-s time)	-0.34	-0.18		0.09	-0.64[1]		-0.42[2]	-0.23		-0.56[3]	-0.47[5]		-0.41	0.04
Pearson's ρ (WIT time)	-0.38	0.02		0.08	-0.07		-0.13	-0.38		-0.41[4]	-0.06		0.26	-0.09

EMC, Erasmus MC University Medical Center Rotterdam; UMCU, University Medical Center Utrecht; LDN, laparoscopic donor nephrectomy; HARP, hand-assisted retroperitoneoscopic donor nephrectomy; BMI, body mass index; ASA, American Society of Anesthesiologists

[1] p<0.001; [2] p=0.024; [3] p=0.001; [4] p=0.035; [5] p=0.009

sequence number in the first LDN-group (figure 1); a significant correlation was observed between sequence number and duration of the procedure in this group (Pearson's ρ = -0.409, $p<0.001$). In the first HARP-group, this correlation was not significant (Pearson's ρ = 0.184, p=0.07). In the concurrent LDN-group (Pearson's ρ = -0.157, p=0.13) and the HARP-UMCU-group (Pearson's ρ = 0.056, p=0.72) there was no significant correlation either. In the first HARP-group a decrease in blood loss and WIT was observed with increasing sequence number; Pearson's ρ was -0.318 (p=0.002) and Pearson's ρ was -0.357 ($p<0.001$) respectively (data not shown). In the other groups, these correlations were not observed.

Surgeon-specific analysis

Baseline characteristics

The baseline characteristics of the donors are summarized in table 3 and did not significantly differ baseline between techniques for the four surgeons performing LDN and HARP.

Intra- and postoperative outcomes

An overview of all operative characteristics is provided in table 3. A comparison between HARP and LDN was not possible for surgeon E and F as HARP was the only technique performed in that center. Of note, they had only performed open donor nephrectomies before starting with HARP and no LDN. For all other surgeons, a significant reduction in operation time and warm ischemia time was observed for HARP compared to LDN. No significant differences were observed for intra-operative complications, conversion rate and postoperative complications.

Learning curve

Surgeon A performed 249 LDNs before starting with the HARP technique. Surgeon B performed 2 LDNs before starting with the HARP technique. Surgeon C performed 2 LDNs before starting with the HARP technique and surgeon D performed 22 procedures before starting with HARP. The correlation between sequence number and skin-to-skin time is displayed in table 3. This correlation was significant for HARP for surgeon B and D, $p<0.001$ and p=0.009) respectively. For LDN this was the case in surgeon C and D, p= 0.024 and p=0.001 respectively. The correlation between sequence number and WIT is also displayed in table 4. The only significant correlation is the correlation for LDN for surgeon D (p=0.035). The skin-to-skin time of all surgeons and the corresponding linear regression for both procedure types is displayed in figure 2.

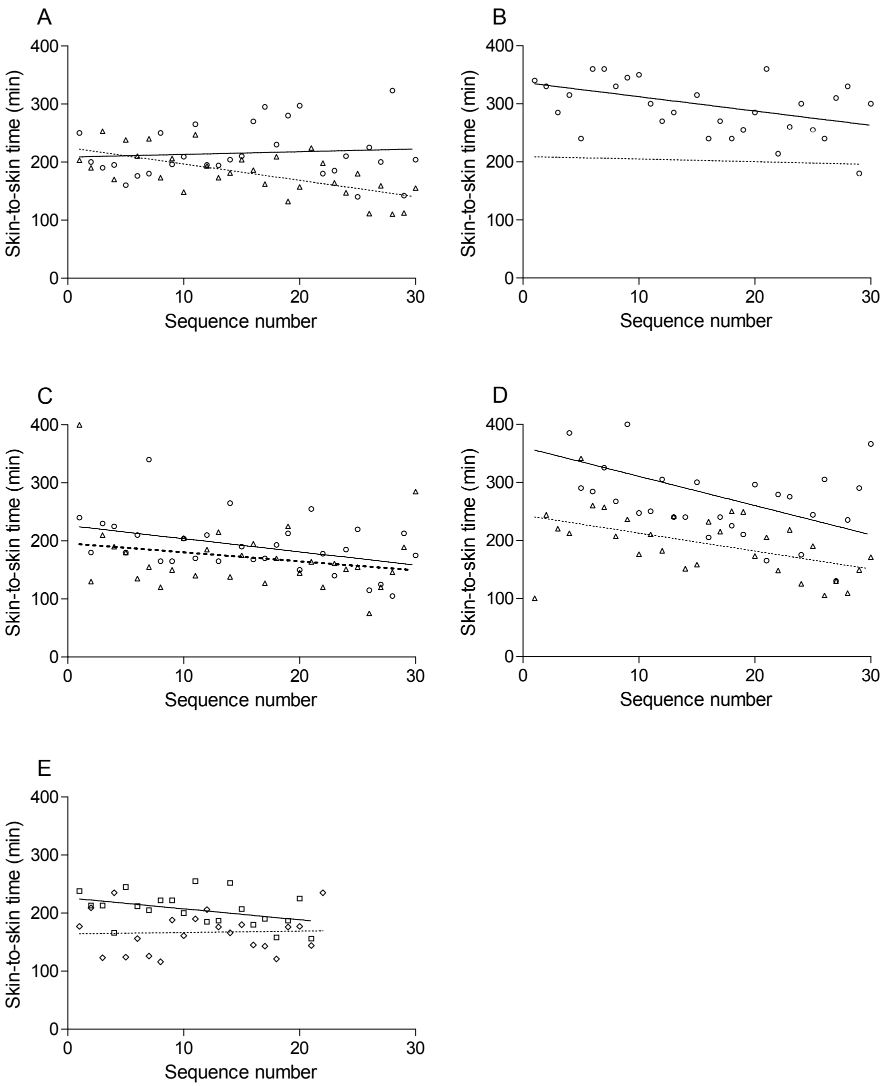

Figure 2. Skin-to-skin times and linear regression of all operating surgeons for both LDN (circles with line) and HARP (triangles with dashed line). In panel E skin-to-skin times and linear regression for HARP for both surgeon E and (squares with line) and F (diamonds with dashed line) are demonstrated.

DISCUSSION

To our knowledge, this is the first study to assess the learning curve associated with HARP and LDN. Our study confirms earlier findings regarding a shorter operating time and WIT for HARP compared to LDN and adds that this is also true for individual surgeons with a variety of experience in endoscopic donor nephrectomy (4). The EMC has extensive experience in LDN and HARP (2, 15). As LDN had been introduced almost a decade before HARP, most basic principles of endoscopic donor nephrectomy had been mastered and aided the introduction of HARP. We had the unique opportunity to prospectively monitor the learning curve of HARP in a university center that had recently changed their operative technique from open to laparoscopic. The UMCU initiated an endoscopic live donor kidney donation program.

Although randomized controlled trials provide the highest level of evidence, most trials do not include patients operated on during the learning curve of the surgeons. A fair comparison of surgical techniques is only possible with information on the learning curves of surgical techniques, but is often omitted. Large case-series from experienced centers have shown the long learning curve of LDN and the low conversion and complication rates that may be accomplished. Surveys and case series have provided data indicating that LDN was associated with a higher risk of (near) fatal complications as compared to conventional open donor nephrectomy. This probably reflects the complex surgical technique, but is also biased by a steep increase in live donor nephrectomies during the 1990s and 2000s in an era with altering inclusion criteria for live donation. Nevertheless, in particular a Norwegian trial showed the risk of major complications during laparoscopic donor nephrectomy (16). Centers initiating endoscopic programs for live kidney donation most probably cannot compete with the data of large volume expert centers that dominate the literature. Nevertheless, new programs are only valuable as good transplants are procured with limited harm to the donor in this era of ever expanding criteria for donation including donors with comorbidity and obesity.

The learning curve for an operation refers to the number of procedures that have to be performed to acquire an adequate level of competency. In general, a learning curve is steep in its initial portion followed by a long plateau, implying an experience dependent acquisition (17). The outcome measures used for the assessment of a learning curve differ. Skin-to-skin time is an adequate assessment of technical skills. However, besides surgical skills there are other factors that may affect skin-to-skin time such as patient (in this case: donor) selection and experience of the rest of the surgical team (13, 18). For this reason, we also assessed complication and conversion rates as indicators of the learning curve.

LDN and HARP are both techniques that can be safely performed when adequately adopted. LDN is a complex procedure requiring a long learning curve. HARP appears to efficiently reduce operation times, blood loss, warm ischemia times and visceral injuries at the beginning of the learning curve. This is also the case for (vascular) surgeons with limited laparoscopic experience (UMCU). This is indirect evidence as these surgeons only adopted HARP. However, operation times and warm ischemia times are superior as compared to the initial cohort at the EMC. All four individual comparisons between HARP and LDN were in favour of HARP with regard to skin-to-skin time and warm ischemia time. In the three later cohorts, conversions were rare, in particular for HARP. If a technique can further limit the chance of near fatal events (usually caused by uncontrollable bleeding from the renal vein, renal artery or aorta or a different, wrong surgical plane), it is extremely valuable in live donor surgery. Proctoring provides centers initiating an endoscopic live kidney donation program with a safe way to negotiate their learning curve, even when little prior endoscopic experience is present.

As selection criteria have changed over time (20), a selection bias has inevitably occurred in this study. The donors in the first HARP, concurrent LDN and the HARP UMCU group less often score ASA I, have a higher BMI and age when compared to the first LDN cohort. This is also the case for surgeon B-F when compared to surgeon A. However, as results are not inferior, and in most cases even superior in these groups, this does not seem to affect the outcome of this study. An explanation for this development may be due to the implementation of standardized protocols and development of new techniques and equipment. Also, the level of basic laparoscopic training has improved over time, with the inclusion of procedures of low, intermediate, and high complexity such as laparoscopic cholecystectomies, endoscopic inguinal hernia repair and laparoscopic colectomies, respectively, as part of surgical training (21, 22).

For centers either initiating a live donor program or changing their technique from open to endoscopic, we suggest to adopt HARP first. Although we did not observe a clinical benefit for HARP right donor nephrectomies in a randomized pilot, outcomes may be different in centers with less laparoscopic experience (23). We did not thoroughly explore hand-assisted transperitoneal laparoscopic donor nephrectomy at our center as we subjectively did not experience benefits over total transperitoneal laparoscopic donor nephrectomy. The literature is sparse on this subject. A small RCT by Bargmann *et al* did not show advantages nor disadvantages of either technique (24). Moreover, in very experienced endoscopic surgeons who master complex laparoscopic surgical procedures such as laparoscopic pancreatectomy and hemihepatectomy, learning curves for LDN may be significantly shorter. However, for the majority of surgeons performing live donor nephrectomy, HARP will be a technique which is safer and easier to learn.
Supervision by experienced peers may help the introduction of HARP by centers initiating an endoscopic live kidney donation program.

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Chapter 6 Cost-effectiveness of hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy: a randomized study

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ABSTRACT

Live kidney donation has a clear economical benefit over dialysis and deceased-donor transplantation. Compared with mini-incision open donor nephrectomy, laparoscopic donor nephrectomy (LDN) is considered cost-effective. However, little is known on the cost-effectiveness of hand-assisted retroperitoneoscopic donor nephrectomy (HARP). This study evaluated the cost-effectiveness of HARP versus LDN.

Alongside a randomized controlled trial, the cost-effectiveness of HARP versus LDN was assessed. Eighty-six donors were included in the LDN group and 82 in the HARP group. All in-hospital costs were recorded. During follow-up, return-to-work and other societal costs were documented up to 1 year. The EuroQol-5D questionnaire was administered up to 1 year postoperatively to calculate quality-adjusted life years (QALYs).

Mean total costs from a healthcare perspective were \$8935 for HARP and \$8650 for LDN (P=0.25). Mean total costs from a societal perspective were \$16,357 for HARP and \$16,286 for LDN (P=0.79). On average, donors completely resumed their daytime jobs on day 54 in the HARP group and on day 52 in the LDN group (P=0.65). LDN resulted in a gain of 0.005 QALYs.

Absolute costs of both procedures are very low and the differences in costs and QALYs between LDN and HARP are very small. Other arguments, such as donor safety and pain, should determine the choice between HARP and LDN.

INTRODUCTION

Live kidney donation offers several benefits, such as preemptive transplantation, better access to transplantation and increased graft survival (1-3). Furthermore, live kidney donation has a clear economic benefit over deceased donor transplantation and dialysis (4). The total economic benefit of live donor transplantation, with a median graft survival of at least 10 years, is well over $500,000, when compared with dialysis (5).

The surgical technique of live donor nephrectomy has evolved in the last decade, from the classic lumbotomy to several endoscopic techniques, including laparoscopic donor nephrectomy (LDN) and hand-assisted retroperitoneoscopic donor nephrectomy (HARP) (6). The endoscopic techniques have proven to be safe, lead to a shorter convalescence time, less pain and increased quality of life after the procedure, when compared with open techniques (7). Furthermore, endoscopic techniques are increasingly used across Europe and the United States of America (8, 9). When compared with mini-incision open donor nephrectomy, LDN is considered a cost-effective procedure. This applies to both the societal point of view and the health-care perspective (10).

HARP theoretically combines the control and speed of hand-guided surgery with the benefits of an endoscopic technique and retroperitoneal access. Hence, HARP has been introduced as a safer approach which is easier to implement when compared with LDN. However, manual dissection may increase postoperative pain and requires an expensive handport. Little is known on the cost-effectiveness of HARP. For this reason, we evaluated the cost-effectiveness of HARP versus LDN alongside a randomized, blinded clinical trial.

MATERIALS AND METHODS

Study design

The HARP-trial was a multi-center, randomized controlled, single-blind trial. Live kidney donors at the University Medical Centers in Rotterdam and Nijmegen in the Netherlands were considered eligible for participation in the study. Donors were included between July 2008 and September 2010. The study compared HARP and LDN. Details of the study design and surgical procedures are reported elsewhere (11).

Patients

All Dutch speaking donors who met the eligibility criteria for donating the left kidney were invited to participate in the HARP-trial. Exclusion criteria were a history of kidney surgery or adrenal gland surgery on the left side. In total 190 live kidney donors gave informed consent and were included in the study. Half of these patients (N=95) received HARP, the other half (N=95) received LDN.

Surgical techniques

All operations were performed by six credentialed surgeons. The surgeons had attended at least 10 HARP procedures. As LDN was the standard technique and both centers performed between 60 and 153 live donor nephrectomies annually, experience with LDN was judged sufficient. The details of surgical techniques employed were previously described (11, 12). Briefly, both procedures were performed with the donor placed in right-sided decubitus position. In LDN, the first trocar was introduced under direct vision, the abdomen was insufflated to 12-cm H2O carbon dioxide pressure and a 30º video endoscope and 3 to 4 additional trocars were introduced. The colon was mobilized and displaced medially, and opening of the renal capsule and division of the perirenal fat was facilitated using an ultrasonic device (Ultracision, Ethicon, Cincinnati, USA). After identification and dissection of the ureter, the renal artery and the renal vein, a Pfannenstiel incision was made. An endobag (Endocatch, US surgical, Norwalk, USA) was introduced into the abdomen. The ureter was clipped distally and divided. The renal artery and vein were divided using an endoscopic stapler (EndoGia, US Surgical, Norwalk, USA). The kidney was placed in the endobag and extracted through the Pfannenstiel incision. In HARP, we started with a 7-10 cm Pfannenstiel incision. After blunt dissection to create a retroperitoneal space, a Gelport (Applied Medical, Rancho Santa Margarita, California, USA) was inserted. Blunt introduction of the first trocar between the iliac crest and the handport was guided by the operating surgeon's hand inside the abdomen. CO2 was insufflated retroperitoneally to 12-cm H2O carbon dioxide pressure. Two other 10-12 mm trocars, just outside the midline inferior to the costal margin and in the flank respectively, were inserted to create a triangular shape. For dissection the aforementioned Ultracision device was used. Dissection of the kidney and dissection and cutting of the renal vessels and ureter were similar to transperitoneal donor nephrectomy but with hand-assistance and from a slightly different angle. The kidney was extracted manually.

Data collection

Direct Treatment Costs

Costs prior to admission to the hospital, including charges of screening and imaging, were not taken into account as these were similar for both techniques. Direct treatment costs constituted of personnel, material, and capital costs such as: total operating time, hospital days (prime and recurrent), capital costs associated with the operating theater for both procedures (monitors, endoscopic tower, sterilization etc.), personnel costs such as surgical costs (surgeon, assistant), anesthetics costs (anesthesiologist, assistant), operating nurses and material costs (disposables). Furthermore outpatient visits, general practitioner consultations, and home care related costs were included. Hospital overhead costs were added as a fixed percentage (20%) to the costs of the personnel in the operation room. Where possible, standard unit prices were used to improve generalization of the results and limit dependence on local negotiations between healthcare instances and the insurance companies (*i.e.,* standard prices were available for the cost of a day in a university hospital, the cost of a visit to the general practitioner) (13). If these prices were not available, real costs were determined (*i.e.* the costs of the endobag to retrieve the kidney). The trial coordinator in either center attended all operations from the arrival of the donor until leave to the recovery room. Together with the scrub nurse use of all instruments and other items such as the sheets to cover the operation field were documented. Costs of sterilization of reusable instruments, depreciation of hardware used during the procedures, salaries of anesthesiologist, surgeons, nurses and supporting personnel in the operation room were all included and expressed as a function of the time spent in the operation room. At the surgical ward, a standard price was counted for every day spent in (an academic) hospital according to the Dutch guideline (13). All costs related to the readmission of single donor including administration of intravenous antibiotics were added to the total in-hospital costs. Use of health care resources during follow-up were registered using case record forms that were administered preoperatively, 1, 2, 4, and 6 weeks postoperatively, and every 2 weeks thereafter until complete return to preoperative activity. Donors were asked whether or not they visited their general practitioner or a doctor in the hospital, or the emergency department. Participants were also asked to quantify these items. These data were cross-checked with data from the hospital's electronic patient system. For these resources, standard unit prices were available (13). If donors did not reply to the case record forms, we sent a reminder. If they did not respond to the reminder, we called them on the phone. As no differences in screening costs or costs related to the recipient, such as dialysis and immunosuppressive therapy, were expected, we did not attempt to incorporate these costs in our analysis. All costs were expressed in U.S. dollars ($).

Societal Costs

Additional burden to society was quantified by calculating productivity losses for donors who performed paid labor preoperatively using the friction costs method. The friction costs method assumes that an employee on sick leave is replaced if this sick leave takes too long. The friction costs period was set at 160 days on average based on 2008 figures (13). This implies that an employee on sick leave for more than 160 days would have been replaced. Productivity loss was fixed at an average of 80% of $48 per hour. With the aforementioned case-record forms data were gathered on preoperative occupation, including whether this occupation was physically demanding or not and whether the job was part-time or not. Up to every lost hour, productivity losses were documented, therewith also addressing those donors who started working part-time first and resumed regular working hours later. Because the donor's physical condition is known not be the only factor determining return to work, the day that patients resumed 90% and 100% of daily activities was also determined (14). We did not give any advice to the donors when to resume work. Use of societal care resources during follow-up were registered using case record forms that were administered preoperatively, 1, 2, 4, and 6 weeks postoperatively, and every 2 weeks thereafter until complete return to preoperative activity. Donors were asked whether or not they had housekeeping or home care, participants were also asked to quantify these items. Differences with regard to baseline were calculated and included in our analysis.

Effectiveness

Effectiveness was measured in terms of health-related quality of life (HRQoL). It was considered as single index utility, on a scale from 0 (representing death) to 1 (representing perfect health). The use of utility scores allows the calculation of QALYs and cost per QALY ratios. Utility scores were measured using the EQ-5D questionnaire (15). HRQoL of both surgical modalities was evaluated preoperatively and 7, 14, 28 days and 3, 6, 12 months postoperatively. In the EQ-5D, health status is described according to five attributes: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each attribute has three levels: no problems, some problems, or severe problems. The answers on the EQ-5D were transformed into a utility score using a scoring function (16). From these utility scores, QALYs were derived using the trapezium rule. One QALY means one year in perfect health. The trapezium rule is a way to approximately calculate the definite integral over a function f(x). The trapezium rule applied to QALYs is conducted by approximating the region under the function QALY = f(QALY*t) by a trapezium and calculating its area, In this equation t expresses the aforementioned EQ-5D measurement points.

Data Analysis and Statistical Considerations

Donors with missing values for the EQ-5D (N=15), costs of procedure (N=2) or productivity losses (N=5) were excluded from the analysis. This resulted in a total of 168 donors available for analysis. For this group, missing values for costs of medication (morphine, acetaminophen and tramadol use) were imputed using the series mean. For the other variables no items were missing. Categorical data are displayed as number (%) and continuous data as mean (standard deviation), unless stated otherwise.

For both groups, mean costs and QALYs were calculated. Differences in costs and QALYs between the groups were tested using Mann-Whitney U tests. In the cost-effectiveness analysis, incremental cost-effectiveness ratios (ICERs) were calculated by dividing the incremental costs of HARP versus LDN by the incremental QALYs of HARP versus LDN. The cost-effectiveness analysis was conducted from a health care perspective as well as a societal perspective, the latter including lost productivity, housekeeping and informal care.

Uncertainty concerning the costs and effects was handled using bootstrap analysis with 1000 replications (17). Bootstrap analysis is a method to deal with non-normality of two combined variables. By resampling with replacement from the original sample the chance that outliers significantly influence the cost-utility analysis becomes smaller. Incremental costs and effects for each replication were plotted in a cost-effectiveness plane from which a CEAC was derived. CEACs show the probability that a treatment is cost-effective, given different ceiling ratios. This ceiling ratio represents the maximum amount of money society is willing to pay for a QALY. To express costs in U.S. dollars, a currency exchange ratio of 1.3$ per euro was applied. Between-group analyses regarding the EQ-5D values were adjusted for baseline values and gender using SPSS mixed models. All analyses were conducted using SPSS (version 18, SPSS Inc., Chicago, USA). Bootstrap analyses were conducted in Microsoft Excel. Data were analyzed according to the intention to treat principle. A p-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Between July 2008 and September 2010, 190 donors underwent surgery according to the randomization. Three conversions occurred, two in the LDN-group and one in the HARP-group. During one-year follow-up response rates for quality of life ranged from

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

	HARP (n=82)	LDN (n=86)	P-value
Gender (female)	48 (59%)	44 (51%)	0.34
Age (years)	54.2 (11.0)	52.8 (11.5)	0.43
ASA Classification (>1)	24 (29%)	18 (21%)	0.21
Renal Arteries (>1)	14 (17%)	14 (16%)	0.89
Employed	52 (63%)	55 (64%)	0.94
Physically demanding work*	15 (29%)	30 (54%)	0.009

* Within employed

SD, standard deviation; HARP, hand-assisted retroperitoneoscopic donor nephrectomy; LDN, laparoscopic donor nephrectomy; ASA, American Society of Anesthesiology

93% to 86%. A total of 168 donors were included in the cost-effectiveness analyses (86 in the LDN-group; 82 in the HARP-group). Donors worked 35 hours (10-60 hours) on average in the LDN-group and 32 hours (4-58) in the HARP-group. Baseline characteristics are presented in Table 1.

Intra- and direct postoperative outcomes

The mean (SD) skin-to-skin time (time from incision to closure of the skin) was 159 (42) minutes in the HARP-group and 188 (39) minutes in the LDN-group ($p<0.001$). Mean postoperative hospital stay was 3.7 (1.5) days in the HARP-group and 3.4 (1.4) days in the LDN-group ($p=0.187$). Six postoperative complications (7%) occurred in the HARP-group, a conservatively treated wound infection in two cases, two cases of urinary tract infection, requiring re-admission in one case, a pneumonia requiring oral antibiotics in one case and a re-operation related to a small bowel obstruction due to enclosure in the Pfannenstiel suture. Five postoperative complications (6%) occurred in the LDN-group, a conservatively treated pneumonia in two cases, one re-admission for elevated liver enzymes and rectal blood loss (no treatment necessary) and one re-operation for the correction of a port-site hernia. Other readmissions or reoperations, due to incisional hernias or small bowel obstruction, did not occur.

Direct treatment costs

Direct treatment costs are summarized in Table 2. Personnel costs and costs for use of the operating theatre were significantly higher for LDN when compared with HARP. Disposables were significantly more expensive in the HARP-group when compared with the LDN-group. Other costs were similar for all categories. Both procedure costs and productivity losses were slightly higher for LDN than for HARP. Donors who underwent HARP had somewhat higher hospitalization costs. Fifty-five general practitioner visits took place in the LDN-group and fifty-seven in the HARP-group ($p=0.59$). Ninety-five visits to a medical specialist were required in the LDN-group and 101 in the HARP-group ($p=0.23$). Two readmissions of one and nine days were required in the LDN-group, in the HARP-group three readmissions of 3, 5 and 12 days were required.

Societal costs

Data on housekeeping, informal care, productivity loss, return to work and daily activities are presented in Table 2. No significant differences regarding extra housekeeping or informal care were observed. In some cases the lower border of the presented numbers is negative. This means that, for example, donors saved money on housekeeping due to the extra care they received from a relative or friend. On average, donors returned to work at day 52 in the LDN-group, compared to day 54 in the HARP-group. Fifty percent of all donors had returned to work by week 10. Donors who performed physically demand-

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

	HARP (n=82)	LDN (n=86)	P-value
Direct treatment costs (U.S. dollars)			
Costs of procedure	5,608 (3,171-7,132)	5,777 (4,116-7,784)	0.279
Costs of disposables	2,477 (1,234-3.286)	2,237 (1,476-3,112)	<0.001
Costs of operating theatre, personnel	2,409 (1,408-4,003)	3,540 (2,059-5,312)	<0.001
Costs of morphine	1 (0-9)	1 (0-8)	0.706
Costs of paracetamol (at home)	1 (0-4)	1 (0-7)	0.786
Costs of tramadol (at home)	0 (0-1)	0 (0-1)	0.850
Hospitalization	2,753 (748-7,475)	2,517 (1,495-7,475)	0.090
Reintervention	17 (0-1,435)	22 (0-1,879)	0.980
Treatment of complications	0 (0-3)	0 (0-7)	0.976
General practitioner visits	25 (0-400)	23 (0-437)	0.587
Medical specialist visits	215 (0-1,006)	186 (0-1,342)	0.233
Additional hospitalizations	182 (0-8,970)	87 (0-6,728)	0.605
Extra home care	131 (-2,093-3,731)	40 (0-1,365)	0.483
Total health care costs	8,935 (6,072-23,413)	8,650 (5,853-16,465)	0.252
Extra housekeeping	164 (-281-4368)	155 (-624-2,215)	0.815
Extra informal care	637 (0-7345)	460 (-488-2,373)	0.914
Productivity losses	6620 (0-34,811)	7,020 (0-39,026)	0.766
Total societal costs	16,357 (6,105-50,941)	16,286 (7,090-47,940)	0.785
Return to work (%)			
After 2 weeks	1 (2%)	1 (2%)	0.96
After 4 weeks	2 (4%)	2 (4%)	0.94
After 6 weeks	4 (8%)	6 (11%)	0.59
After 8 weeks	13 (25%)	16 (29%)	0.68
After 10 weeks	26 (50%)	28 (50%)	1.00
After 12 weeks	35 (67%)	37 (66%)	0.89
Complete resumption at day (range)	54.0 (8-174)	51.5 (14-169)	0.65
Activity level (at day)			
Resumption of 90% of daily activities	60.6 (7-365)	49.6 (7-180)	0.14
Resumption of 100% of daily activities	94.1 (14-365)	80.6 (7-365)	0.22

HARP, hand-assisted retroperitoneoscopic donor nephrectomy; LDN, laparoscopic donor nephrectomy ing work did not return to work later than those who did not have a physically demanding job (56 vs. 50 days, p=0.306). On average, male donors returned to work at day 45, female donors returned to work at day 59 (p=0.012). Four donors in the LDN-group and one donor in the HARP-group did not return to work within one year. No significant differences regarding resumption of daily activities were observed between groups.

Effectiveness

At day 7 and 14, the LDN-group had a significantly higher utility score, as measured on the EuroQol-5D (EQ-5D) (SDC, figure 1). At day 7, the estimated difference was 0.08 and at day 14 the estimated difference was 0.06 (p=0.020 and p=0.013 respectively). For donors who underwent LDN, Quality-Adjusted Life Years (QALYs) ranged from 0.61 to 1. On average, LDN yielded a total of 0.9394 QALYs. HARP yielded a total of 0.9341 QALYs (range 0.32 to 1). QALYs were not statistically significantly different between the two procedures (p-value 0.732).

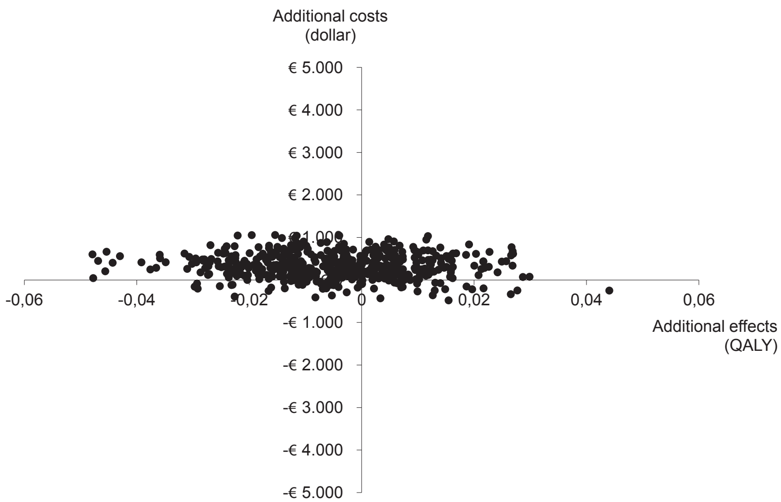

Figure 1. Cost-effectiveness plane from a health care perspective.

Cost-utility analysis

From a health care perspective, LDN was the least expensive procedure. Total health care costs were $8,650 for LDN and $8,935 for HARP. Consequently, HARP was $285 more costly than LDN, and resulted in 0.005 less QALYs. This implies that HARP was dominated by LDN. Bootstrap analyses showed considerable uncertainty surrounding the incremental costs and effects, presented in figure 1. The Cost-Effectiveness Acceptability Curve (CEAC) showed that, depending on the threshold, there was a 19% to 35% probability that HARP is cost-effective when compared with LDN (figure 2).

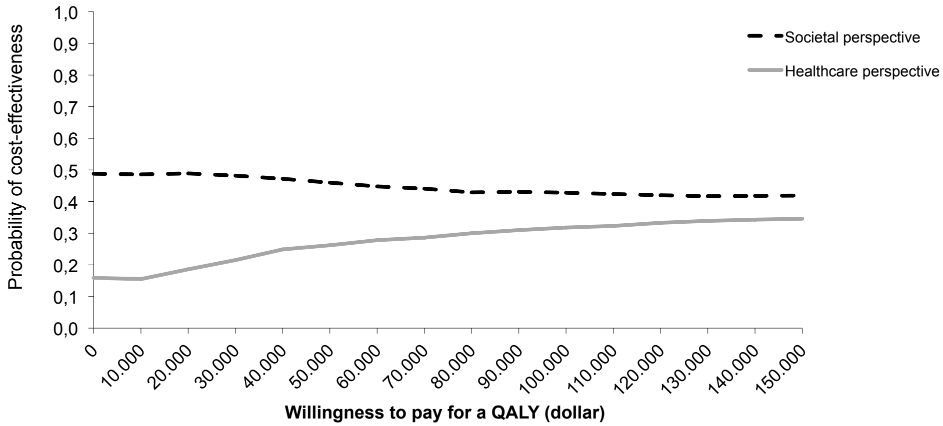

Figure 2. Acceptability curves for hand-assisted retroperitoneoscopic donor nephrectomy (HARP) versus laparoscopic donor nephrectomy (LDN) calculated from a health-care (continuous line) and societal perspective (dashed line). The x-axis represents the amount of money governmental organizations or insurance companies are willing to pay per QALY. The probability represents the chance that HARP is cost-effective at a certain amount. For example, if one is willing to pay up to $52,000 for one QALY, the probability that HARP is cost-effective can be determined by drawing a vertical line that crosses the x-axis at 52,000. The associated probabilities are the crossings between the vertical line and the two plotted lines; the probability that HARP is cost-effective is 0.28 from a health-care perspective and 0.49 from a societal perspective.

From a societal perspective, HARP was still the most expensive procedure, although the difference was smaller. Total societal costs were $16,286 for LDN and $16,357 for HARP. HARP was $70 more expensive than LDN. Since HARP was also 0.005 QALYs less effective, it was again dominated by LDN. Figure 3 shows the results of the bootstrap analysis. Again, there is considerable uncertainty about the incremental costs and effects. From a

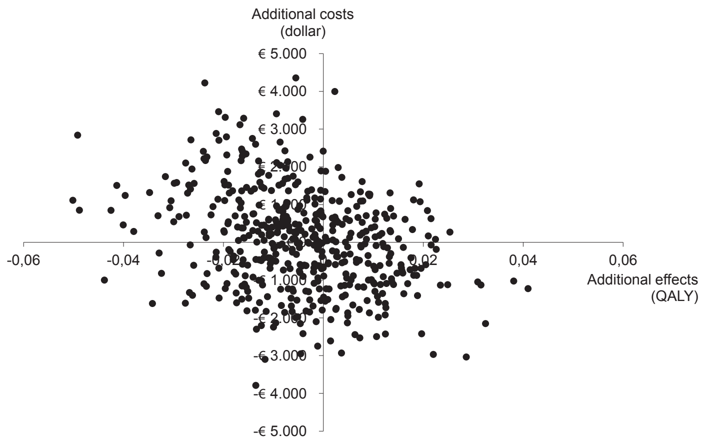

Figure 3. Cost-effectiveness plane from a societal perspective

societal perspective, the CEAC demonstrates that there is a 44% to 52% probability that HARP is cost-effective compared with LDN (figure 2).

DISCUSSION

Costs and cost-effectiveness play an increasingly important role in the evaluation of interventions. Policy makers and healthcare professionals are forced to make choices if several concurrent techniques are available. Choices should be based on patient safety, effectiveness and cost-effectiveness.

As the preoperative work-up was similar for both groups, these costs have not been taken into account in our analysis. All relevant costs regarding the admission, procedure, complications of the procedure and follow-up of the donor have been included in our analysis. By our knowledge this is the most extensive cost-effectiveness analysis on this subject, If a donor failed to report a GP visit or the use of analgesics at home, this would not significantly affect the outcome as the total number of included donors is high.

The significant difference in percentage of donors with physically demanding work within the employed group is remarkable but random and cannot be explained by some form of selection bias. As the percentage of donors returning to work within both groups is almost similar, and differences between groups are not significant, it is very unlikely that this had an impact on the total cost differences.

Procedure-related costs were not different between techniques. The differences between LDN and HARP in costs related to donation are diminutive. The total differences in costs from a health-care and societal perspective were $70 and $285 respectively, both in favor of LDN. These small differences were also observed on the CEACs. HARP yielded 0.005 QALYs less when compared with LDN. This difference in QALYs is minimal, as 0.005 QALYs equals two days in perfect health.

This study was conducted in two tertiary referral centers with abundant experience in LDN. Laparoscopic donor nephrectomy is a complex procedure. In our opinion the risk of major complications and the long learning curve have been important drawbacks for some centers and professionals to adopt LDN. HARP is apparently easier to learn (18), has a favorable intraoperative complication rate and has now been shown to be comparable in terms of costs and QALYs. We hypothesize that cost-effectivity of HARP compared with LDN may increase in low volume centers or centers at the start of their endoscopic donation program, as the anticipated reduction in operation time and severe complications is likely to be greater. A cost-effectiveness analysis of the Norwegian study addressing laparoscopic versus open donor nephrectomy showed that LDN was not cost-effective due to a large amount of money spent on the treatment of complications (19).

It is remarkable that work resumption takes rather long. In both groups, 50 percent of the donors have resumed work after 10 weeks. Furthermore, it takes approximately three months to resume all daily activities on average. Recovery is determined by multiple factors. We postulate that the psychosocial effects related to live donation influence the recovery of donors (20, 21). In the Netherlands there is a social system in which employers allow employees to receive paid sick leave after up to 13 weeks after donation and independent entrepreneurs are also entitled to reimbursement of foregone income during the same period (22). Hence, donors lack the financial incentive to restart work as quickly as possible.

The absolute costs of live donation are relatively low as compared to data published in a Norwegian study, but similar to our study comparing LDN with open donor nephrectomy (10, 19). In the former study, longer hospitalization, more productivity losses because of a lower mean age and the treatment of complications mainly explain the differences. In the latter study the complication rate was low and hospital stay after LDN was also 3 days on average. Although absolute costs are important in this era, we would like to emphasize that the costs of a live donation procedure are only a fraction of the costs related to the recipient including preoperative dialysis and immunosuppressive therapy.

In conclusion, both procedures appear to be economically acceptable techniques, with similar costs and QALYs. As measured differences between the current techniques are very small, other factors, such as ischemia time and safety, should determine the choice between HARP and LDN. Costs should not determine the technique.

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Chapter 7 Incision-related outcome after live donor nephrectomy: A single center experience

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ABSTRACT

Live donor nephrectomy is routinely performed. However, little is known regarding the incision-related outcome. The aim of the present study was to evaluate the prevalence of incisional hernias (IH) and to assess body image and cosmesis scores after donation. Questionnaires on IH, body image, and cosmesis were sent to all donors who underwent laparoscopic donor nephrectomy or mini-incision donor nephrectomy between January 2000 and December 2009.

In total, 444 replies were received (75%). Seven donors (1.5%) had undergone a surgical correction of an IH. Surgical site infection and steroid use appeared to be independent risk factors for the development of an IH ($p=0.001$ and 0.021, respectively). Body image and cosmesis scores were excellent. Elderly donors had significantly higher cosmesis scores when compared with young donors ($p<0.001$). Donor age of 60 years or higher, correction of an IH, and survival of the recipient appeared to be independent factors associated with a higher score on the cosmesis scale in multivariate analysis.

This is the largest study describing the prevalence of IH and cosmetic outcome after donor nephrectomy. The prevalence of IH after live donor nephrectomy is very low, and body image and cosmesis scores are excellent. Consequently, incision-related outcomes pose no barrier to live donor nephrectomy.

INTRODUCTION

Live kidney donation has become widely accepted in many countries. In 2009, approximately 46% of the transplants worldwide were derived from a live donor, [1]. Surgical approaches have evolved over the last two decades. Laparoscopic donor nephrectomy (LDN) and mini-incision donor nephrectomy (MIDN) have gradually replaced nephrectomy by classic flank incisions [2-3]. From a surgeon's point of view it is important to assure donor safety, recovery and quality of life after live donor nephrectomy. These parameters have been studied extensively in randomized controlled trials (RCT) focusing on surgical techniques and excellent results have been described for both techniques. However, superior results regarding recovery and quality of life have been reported following LDN [4-8].

Incisional hernias (IHs) are a common surgical problem leading to significant morbidity, such as pain, disability and in some cases even intestinal obstruction and strangulation. Furthermore, IH repair is associated with significant costs and a decrease in quality of life [9-10]. Incisional hernia rates after the different MIDN techniques have been described in literature ranging from 0.6% to 3% [11-12]. Although LDN is routinely performed, little is known on the prevalence of IHs after this procedure. Incisional hernia rates after a low transverse abdominal incision (such as the Pfannenstiel incision used for kidney extraction) have been described to vary between 0.0 and 0.5% [13-14]. The incidence of port-site IHs after laparoscopic procedures ranges from 1% to 6% [15-17].

As live kidney donors are healthy individuals with no direct benefit of the procedure, it is important to study every aspect of live kidney donation. Donor satisfaction is usually discussed in relation to graft and recipient survival. However, incision related outcome, body image and cosmesis may be important factors when assessing donor satisfaction. Although minimally invasive procedures are thought to provide better cosmetic results, little is known on the donors' perception of their body image or cosmesis after donation, especially at long term. The aim of this study was to evaluate the long-term incision-related outcome after live donor nephrectomy.

MATERIALS AND METHODS

Patients

All donors that underwent either MIDN or LDN between January 2000 and December 2009 at the Erasmus MC, University Medical Center in Rotterdam, The Netherlands were approached by (air) mail. Questionnaires were sent out in March and April 2011; nonrespondents were contacted by phone in June 2011. If donors had undergone a surgical correction of an IH, the appropriate hospital was contacted to acquire the official report of the procedure. After donor nephrectomy, donors were seen at the outpatient clinic at three weeks, three months and one year postoperatively. Thereafter, donors could return for annual follow-up visits if they desired. All gathered data was crosschecked in the hospital's electronic patient system.

Data collection

All eligible donors received a body image questionnaire (BIQ, attached as supplement). This BIQ has been developed by Dunker *et al.* and since then been applied to assess outcome regarding scars in surgical patients and in live kidney donors in particular [18-20]. The BIQ consists of two subscales, the body image scale (BIS) and the cosmesis scale (CS). The BIS was based on 5 questions investigating the attitude of donors towards their bodily appearance, which resulted in a total score between 5 and 20. The CS was based on three questions regarding the degree of satisfaction with the appearance of the donor's scar. The total score on this subscale was between 3 and 24. On both subscales, a higher score indicates greater satisfaction. Furthermore, all donors received a questionnaire on their postoperative course. Questions regarded IH-related complaints, general practitioner or hospital visits for these complaints. Exposure to known demographic and both endogenous and exogenous risk factors were assessed [21] (table 1).

During the aforementioned period of inclusion, a RCT ran in our center [5]. BIQs were acquired during the follow-up of this trial at the following moments: month 1, month 6 and month 12. Donors that completed the BIQ at all these time points, as well as during the follow-up of this study, were included for a separate analysis.

Table 1. Questions on development of incisional hernia.

1. Have you experienced any complaints of pain or bulging of the surgical scar since surgery?
2. Did you notice any of these complaints during sneezing or coughing etc.?
3. If yes, have you seen a GP for these complaints?
4. Was an incisional hernia diagnosed? If yes, have you undergone surgical correction?
5. Was one of the surgical wounds opened after nephrectomy due to an infection?
6. Did your GP prescribe you any antibiotics for a wound infection?
7. Do you have diabetes?
8. Are you a smoker? If yes, for how long and how many do you smoke?
9. Are you taking or have you been taking prednisone before or since the surgery? If yes, for what reason?
10. What is your weight and length?

GP, general practitioner

Surgical technique

MIDN was introduced in our center in 2000; between 2001 and 2004 both MIDN and LDN were practiced in the context of a trial [5]. After this trial, LDN was adopted as our standard technique.

Retroperitoneal MIDN was performed with the patient placed in a lateral decubitus position and the operating table maximally flexed; a horizontal 10–15 cm skin incision was made anterior to the 11th rib towards the umbilicus. The fascia and muscles of the abdominal wall were split, attempting to avoid harm to the intercostal nerves. The peritoneum was displaced medially. The kidney was dissected and arterial and venous structures were identified. After dissection, the ureter was divided and ligated distally. The renal artery and vein were divided using a stapler. Thereafter, the kidney was extracted, flushed with University of Wisconsin solution (ViaSpan; Barr Laboratories, Pamona, NY, USA) and stored on ice. The fascia was closed with a continuous polygactin 910 suture (Vicryl V-34; Ethicon GmbH, Norderstedt, Germany). The skin was sutured intracutaneously using a poliglecaprone 25 suture (Monocryl 4-0; Ethicon GmbH).

LDN was performed with the donor in lateral decubitus position. In short, a 10-mm trocar was introduced under direct vision. The abdomen was insufflated to 12-cm H2O carbon dioxide pressure. A 30° video endoscope and a 10-12 mm trocar were placed. Two or three additional 5-mm trocars were introduced. The colon was mobilized and displaced medially. Opening of the Gerota's fascia and division of the perirenal fat was facilitated using an ultrasonic device or diathermia. After identification and careful dissection of the ureter, the renal artery, and the renal vein, a Pfannenstiel incision was made. Skin and subcutaneous fat were incised transversally. The vertical plane between the rectus muscles was developed and the peritoneum was opened. Average length of the Pfannenstiel incision was 8 cm. An endobag was introduced into the abdomen. The ureter was clipped distally and divided. The renal artery and vein were divided using an endoscopic stapler and the kidney was placed in the endobag and extracted through the Pfannenstiel incision. Thereafter, the kidney was extracted, flushed with University of Wisconsin solution and stored on ice. The peritoneum was closed with a continuous polydioxanone suture (PDS 3-0; Ethicon GmbH). The rectus abdominis muscles were approximated using an interrupted polygactin 910 suture (Vicryl 3-0; Ethicon GmbH). The fascia was closed with a continuous Vicryl V34 suture. Fascial defects caused by 10-12mm ports were sutured using an interrupted polygactin 910 suture (Vicryl 0-UR6; Ethicon GmbH). All skin defects were sutured intracutaneously using a Monocryl 4-0.

Statistical considerations

Statistical analysis was performed using SPSS 20.0 statistical package (SPSS, Chicago, Illinois, USA). Differences in continuous variables were compared with a Mann-Whitney U test. Categorical variables were analyzed using a Chi-square test. Correlations were determined using a Spearman correlation coefficient. Backward multivariate analysis was performed using a generalized linear model. A p-value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, 716 live donor nephrectomies were performed at our center. In this period, four open donor nephrectomies, 109 MIDNs, 83 hand-assisted retroperitoneoscopic procedures, and 520 LDNs were performed. Of the 520 donors that had undergone LDN, 14 donors had deceased and 7 had emigrated; therefore 499 donors were available for follow-up. Of the 109 donors that had undergone MIDN, 7 had deceased and 6 had emigrated. Therefore 96 donors were available for follow up. None of the donor deaths were related to the donation procedure. 74 donors (77%) responded in the MIDN group. 370 donors (74%) responded in the LDN group. Total response rate was 75% (figure 1). There was significant difference in median age between responders and non-responders, 53.6 (18.1-78.5) and 45.0 (20.9-79.70) respectively ($p<0.001$). Furthermore, a significant difference was assessed in BMI, a median of 26.0 (16.5-39.4) for responders and 26.9 (17.5-41.0) for non-responders ($p=0.01$).

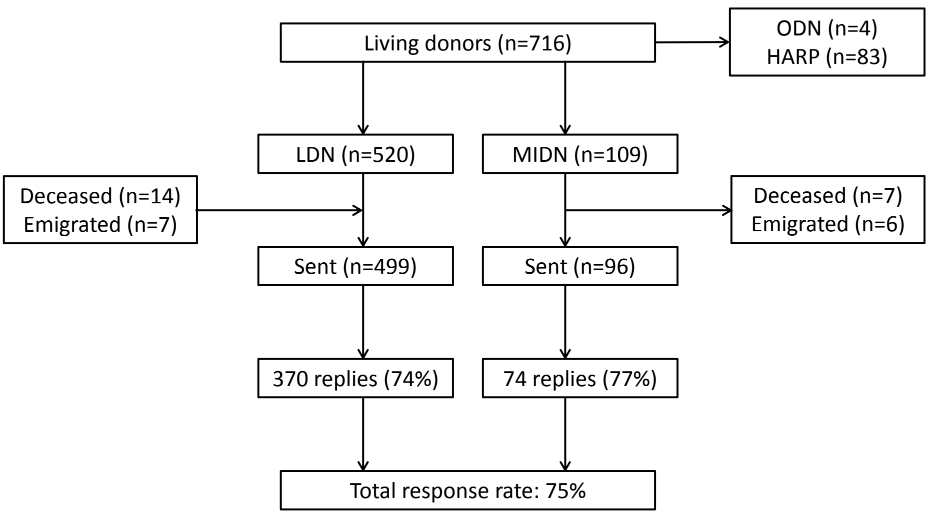

Figure 1. Study flow diagram.

Baseline

Baseline characteristics of all donors are shown in table 2. Median follow-up of the cohort was 6 years (2-11 years), median interval between donor nephrectomy and IH correction was 1.3 years (0.1-3.3 years). No significant differences between groups were found at baseline.

Table 2. Baseline characteristics. Categorical data are given as No. (%) and continuous variables as median (range).

	LDN (n=370)	MIDN (n=74)	P-value
Donor:			
Female	206 (56%)	50 (68%)	0.06
Age (years)	54.0 (18.1-78.5)	50.5 (21.9-75.4)	0.08
BMI (kg/m2)	26.0 (16.5-39.4)	26.5 (18.7-36.2)	0.39
Right-sided nephrectomy	202 (55%)	41 (55%)	0.89
History of hernias [a]	26 (5%)	4 (5%)	0.61
Recipient:			
Graft survival [b]	344 (93%)	68 (92%)	0.80
Recipient survival [b]	350 (95%)	67 (91%)	0.27

LDN: Laparoscopic Donor Nephrectomy; MIDN: Mini-Incision Donor Nephrectomy;
BMI: Body Mass Index
[a] Inguinal, umbilical and incisional hernia.
[b] Recipient and graft survival were measured accordingly to donor follow-up data. Median follow-up was 6 years.

Incisional hernias & Risk factors

In total, seven donors (1.5%) reported to have undergone surgical correction of an IH. Six corrections took place in the LDN-group (1.6%) and one correction took place in the MIDN-group (1.4%), this difference was not significant (p=0.87). Three donors had a port-site IH (0.7%); two donors had a hernia of the Pfannenstiel incision (0.4%). One donor had an IH of an old McBurney incision that was used for extraction (0.2%) and the one donor in the MIDN-group developed an incisional hernia of a flank incision (0.2%). None of the remaining donors had symptoms of an IH. The interval between the first and last correction was 9 years. IH corrections were equally distributed during follow-up, *i.e.* there was no higher incidence of IH corrections shortly after the introduction of either technique.

Seventeen donors (4.6%) developed a surgical-site infection (SSI) in the LDN-group vs. 2 donors (2.7%) in the MIDN-group; this difference was not statistically significant (p=0.46). Post-operative SSI occurred significantly more often in the IH-group (p=0.001).

Also, steroids were used significantly more often in the group with IH (p=0.021). Steroids were used for chronic obstructive pulmonary disease in 4 donors, severe eczema in 2 donors, gout, idiopathic thrombocytopenic purpura and sarcoidosis. For other IH risk factors, no significant association was assessed (table 3).

Table 3. Risk factors and body image and cosmesis scores. Categorical data are given as no. (%) and continuous variables as median (range).

	No IH (n=437)	IH (n=7)	P-value
Wound infection	17 (4%)	2 (29%)	0.001
Steroid use	8 (2%)	1 (14%)	0.021
Smoking	254 (58%)	4 (57%)	0.88
Diabetes	7 (2%)	0	0.56
Previous history of hernia [a]	30 (7%)	0	0.47
BMI after donation (kg/m2)	26.0 (18.0-47.6)	27.3 (22.6-39.4)	0.09
LDN	364 (83%)	6 (86%)	0.87
Body Image Score	20 (5-20)	19 (16-20)	0.27
Cosmesis Score	20 (3-24)	17 (10-21)	0.07

[a] Inguinal, umbilical or incisional hernias
LDN, laparoscopic donor nephrectomy

Body image & Cosmesis

The median score on the BIS for the whole group was 20 (range 5-20), the median score on the CS for the whole group was 20 (range 3-24). Scores were high; approximately 44% of the donors reported the maximum achievable score of 20 on the BIS and 14% of the donors reported the maximum achievable score of 24 on the CS. The BIS and CS were comparable between both groups (table 3). When rating their own scar on a scale from 1 to 10, the median score of donors in the IH-group was 6 (range, 5-10) the median score in the non-IH-group was 8 (range, 1-10), this difference was not significant (p=0.25). No correlation was observed between BIS or CS and duration of the period between donation and time of study (p=0.80 and p=0.31, respectively). No correlation was found between BIS or CIS and gender, BMI pre- or postoperatively and follow-up time. A significant correlation was found between age and CS (Spearman's ρ=0.22, p<0.001), indicating a higher score with higher age. Donors with an age of 60 or higher (n=125) had a significantly higher median score on the CS when compared with younger donors (n=319), 21 and 19 respectively (p<0.001).

A multivariate analysis was performed to identify factors associated with a higher score on the CS and BIS. Donor age of 60 or higher, absence of an incisional hernia and survival of the recipient appeared to be independent factors associated with a higher score on the CS (Table 4). Regarding the BIS, no significant associations were found in a multivariate analysis.

Table 4. Results of the uni- and multivariate analysis regarding the cosmesis scale.

	Univariate		Multivariate	
Variable	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**
Sex	1.35 (0.96-1.89)	0.088	1.37 (0.97-1.95)	0.08
Age 60≤	1.03 (1.02-1.05)	<0.001	1.03 (1.02-1.05)	<0.001
BMI after donation	0.97 (1.17-4.42)	0.22		
Graft survival	1.24 (0.59-2.57)	0.57		
Recipient survival	1.81 (0.35-3.61)	0.095	2.10 (1.03-4.26)	0.041
Absence of incisional hernia	3.88 (0.91-16.59)	0.067	4.45 (1.02-19.39)	0.046

OR, Odds Ratio; CI, Confidence Interval

Combined data

The BIQ was completed at month 1, 6, 12 and during the follow-up of this study by 111 donors. Median follow-up of these donors in this study was 7 years (range 5-9). BIS- and CS-scores did not change significantly during follow up (figure 2). There were no significant differences regarding technique on any of the scales at any follow-up moment.

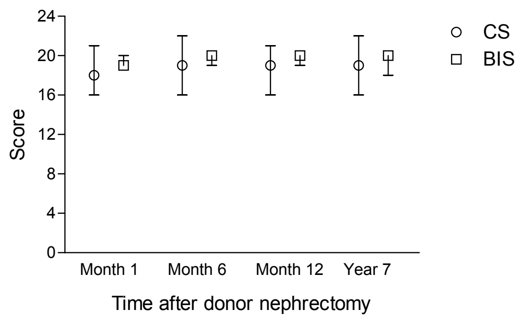

Figure 2. BIS- and CS-scores during follow-up; median, interquartile range

DISCUSSION

To our knowledge, this is the largest study that describes the prevalence of IH and cosmetic outcome after LDN and MIDN. Furthermore, there is no study reporting on long-term follow-up regarding this topic. As absolute incidence of IH and port-site IH are very low, studies should include a large sample. Since no data was available on the prevalence of IH after LDN, results were compared with the prevalence of IH in general laparoscopic procedures [12-15]. The prevalence of IHs of the low transverse incision (Pfannenstiel) and after MIDN in this study was comparable to reports in literature. The prevalence of port-site IHs in this study was lower than numbers reported in literature. Remarkably, no significant difference regarding the prevalence of IH's between groups was observed.

In our analysis, risk factors associated with the development of IH were the use of steroids and SSI; these risk factors for IH have been described before [13]. The reported reasons for taking steroids varied greatly. Although our analysis demonstrated a relation between the use of steroids and the development of an IH, the significance of this finding should be carefully interpreted. More research on this topic is needed in a larger sample with donors that developed an IH.

Overall, donors were very satisfied with their body image. Scores for both LDN and MIDN did not differ significantly. Data on the BIS and CS have been published previously by Lind *et al* [20]. Fifty-six donors reported on their body image after a mean follow-up of 3.4 years; the mean scores on the BIS and CS were 19.5 and 19.7, respectively. The scores in our study were comparable to these results. No association was found between follow-up time and BIS- and CS-scores. BIS- and CS-scores do not increase or decrease with time, indicating that these excellent results are achieved at both short and long-term follow-up. It is possible that donors value their own recovery and successful treatment of the recipient above their own body image and cosmetic outcome.

Elderly donors may be less concerned with bodily appearances, as was demonstrated by our multivariate analysis. Furthermore, death of the recipient adversely affects the donor's cosmetic outcome. It appears that the scars of a 'futile' procedure are experienced as cosmetically inferior, then when the recipient would still be alive. Correction of an IH is associated with lower scores on the CS, for obvious reasons. An individual's body image is apparently not influenced by external factors, in contrast to cosmesis.

This study had to be performed using questionnaires, in order to reach the majority of our donor population. A possible bias was therefore introduced, since results are dependent on donors' memory. However, an IH correction is, in general, an event that will be remembered well. Because this cohort study was performed retrospectively, non-symptomatic IHs may possibly have been missed. Nevertheless, the clinical relevance of diagnosing a non-symptomatic IH in a donor with excellent body image scores is questionable. Although significant differences were found between responders and non-responders regarding age and BMI, the clinical relevance of these differences is very questionable.

Donor safety, convalescence, quality of life after surgery and cosmesis determine the success of live donation programs. Sufficient reports on most of these topics are available, however little is known on cosmesis and body image. We did not expect incision-related outcome to differ significantly from other endoscopic procedures. Nevertheless, as live kidney donors do not directly benefit from the procedure, it is essential to study all aspects of laparoscopic donor nephrectomy to adequately inform donors during screening. We attempted to fill this hiatus in current knowledge.

The prevalence of IHs after live donor nephrectomy is very low. Risk factors for the development of an IH are SSI and the use of steroids; these risk factors have been described before. In general, BIS- and CS scores are excellent, these scores do not change significantly during follow-up. Body image and cosmesis are not influenced by the surgical technique. It appears that donors are more concerned with the well-being of the recipient, than with their own cosmetic outcome. Furthermore, elderly donors report significantly better cosmetic outcome. In conclusion, incision-related outcomes pose no barrier to live donor nephrectomy.

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Chapter 8 Quality of life of elderly live kidney donors

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ABSTRACT

Expanding the use of elderly live donors may help meet the demand for kidney transplants. The aim of this study was to quantify the effect of the surgical procedure on the quality of life (QOL) of elderly donors compared with younger donors.

Alongside three prospective studies (two randomized) running between May 2001 and October 2010, we asked 501 live donors to fill out the Short Form-36 questionnaire preoperatively and at 1, 3, 6, and 12 months postoperatively. We defined live donors 60 years or older as elderly. Between-group analyses regarding QOL were adjusted for baseline values and gender.

One hundred thirty-five donors were older and 366 donors were younger than 60 years. The response rate was high, with 87% at 12 months postoperatively. Elderly donors less often scored as American Society of Anaesthesiology classification 1 (60% vs. 81%; P<0.001) indicating a higher rate of minor comorbidity. At 1 month postoperatively, between-group analysis showed a significant advantage in QOL in favor of the elderly group regarding the dimensions “bodily pain” (7 points; P=0.001), “role physical” (18 points; P<0.001), and “vitality” (5 points; P=0.008). At 3 months, “bodily pain” (3 points, P=0.04) and “role physical” (8 points, P=0.02) were still in favor of the older group. At 6 and 12 months, “physical function” was in favor of the younger group (3 and 5 points, respectively; P=0.04 and P<0.001).

This study demonstrates that elderly donors recover relatively fast. The perspective of excellent postoperative QOL may help convince elderly individuals to donate.

INTRODUCTION

Live kidney donation has become increasingly accepted globally. It is considered to be safe and does not lead to increased mortality during follow-up (1). In 2009 approximately 46% of the 71,418 kidney transplants worldwide were derived from live donors (2). Live kidney donation offers a number of benefits, including pre-emptive transplantation, better access to transplantation for recipients, increased graft survival and a reduced financial burden on society (3-6). These potential benefits must be balanced against potential harm to the donor. During live donor nephrectomy, individuals are exposed to all the risks associated with general anaesthesia and major abdominal surgery. For this reason, donor safety, and preservation of quality of life are of paramount importance when performing these procedures.

Due to the increasing demand for kidney transplants, eligibility criteria for live donation have extended (7, 8). This has led to inclusion of elderly live donors that would not have been selected in the past. Since donor safety, graft and recipient survival have proven to be comparable to that of younger individuals, the careful selection of elderly donors in live donation programs is encouraged (9). Nonetheless, data on quality of life in elderly donors is scarce and often inadequate, and longitudinal studies are lacking (10, 11).

Ageing of the population is a global issue. The worldwide population aged 65 or above is projected to increase with 77% to 973,000,000 by 2030 (12, 13). In anticipation of this development, all aspects of live kidney donation should be assessed in this population. The aim of the present study was to quantify the effect of the surgical procedure on the quality of life (QOL) of elderly donors compared with younger donors.

MATERIALS AND METHODS

Study population and data collection

In this study we included 501 live donors on whom pre- and postoperative data on QOL was available. These donors had been included in 2 randomized trials and 1 prospective study that ran between May 2001 and October 2010 at the Erasmus Medical Center in Rotterdam and the University Medical Center in Nijmegen, both tertiary referral centers in the Netherlands. Data of all these donors was prospectively collected (24-26). For one of the trials and the prospective study, all donors were eligible for inclusion provided they were capable of filling out the questionnaires. For the other trial, all left-sided donors were eligible for inclusion provided they were capable of filling out the questionnaires. All donors were pre-operatively screened by a nephrologist, a medical psychologist, and anaesthesiologist and a cardiologist on indication. Obese donors or donors with a complex anatomy were not excluded. At the end of the procedure, patients received Patient Controlled Analgesia (PCA). This device enabled the donor to administer intravenous morphine from a 50-cc syringe (1 mg morphine per ml) by pressing a button. Furthermore, two 500 mg acetaminophen tablets were offered four times daily until discharge. The PCA-device was removed when morphine had not been required for at least six hours. Donors were discharged when a normal diet was tolerated and mobilization was adequate. Re-admission, re-interventions, length of stay and per- and postoperative complications were scored prospectively. We defined live donors > 60 years as elderly, based on other reports (9, 27, 28). If any significant differences would be found between groups, a subgroup analysis in the elderly group would be performed regarding quality of life. Thereafter, donors aged 70 or higher would be compared with donors aged 60-69.The institutional review boards approved these studies.

Operative techniques

Mini-incision open donor nephrectomy (2001-2006), standard laparoscopic donor nephrectomy (from 1997) and hand-assisted retroperitoneoscopic donor nephrectomy (from 2007) were performed in the aforementioned period. These techniques have been described earlier (26, 29).

Postoperative data and QOL

The Short Form-36 (SF-36) is a validated and commonly used tool to measure health-related QOL (30). This questionnaire consists of eight dimensions: PF, role limitations due to physical health problems (RP), BP, GH, VI, SF, role limitations due to emotional problems (RE) and MH. The dimensions PF, RP, BP and GH are most sensitive to changes in physical performance and physical well-being. The dimensions VI, SF, RE and MH mainly attribute to mental functioning and emotional well-being. Scores for each of these health concepts range from 0 to 100, with higher scores indicating better QOL. Donors were asked to fill out the SF-36 questionnaire preoperatively and at 1, 3, 6 and 12 months postoperatively. A 5-point difference on a dimension is considered to be the minimally clinically relevant difference (30). Pain was quantified using a visual analogue scale (VAS) questionnaire. Donors had to pick a point on a 10 cm line which best corresponded with the experienced pain and nausea. The distance on the line corresponds with pain and ranges from zero (no pain) to ten (severe pain). VAS-questionnaires were filled out at baseline and at day 1, 3, 7 and 14. For the resumption of 90% and 100% of daily activities, a questionnaire was used that has been described earlier (31, 32). Donors received a questionnaire on the resumption of daily activities at baseline and at week 1, 2, 4, 6, 8 and 10. Thereafter, they received a questionnaire at month 3, 4, 5, 6, 9 and 12 or until daily activities were fully resumed.

Statistical analysis

Categorical variables are presented as a number (percentage). Continuous variables are presented as mean (standard deviation). Categorical variables were compared with the chi-square test; continuous variables were compared with the Mann-Whitney U test. Between-group analyses regarding QOL were adjusted for baseline values and gender using SPSS mixed models. Within-group analyses were performed with the paired samples T-test. In this analysis a p-value >0.05 is considered as a return to baseline as no significant difference was present. A full cohort analysis was performed to avoid loss of data. All analyses were conducted using SPSS (version 20.0.0.1., SPSS Inc, Chicago, USA). A P-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Baseline characteristics

One hundred thirty-five donors (27%) were older and 366 (73%) younger than 60 years. On average, 41 young donors were included yearly, ranging from 13 to 63. In the elderly group, 15 donors were included yearly on average, ranging from 9 to 26. Fifty-eight percent of the young and 52% of the elderly donors were included before 2006. Elderly donors were less often classified as American Society of Anaesthesiology-classification (ASA-classification) one (p<0.001) and were more often genetically unrelated to the recipient (p=0.043). The response rate in both groups was high. In the young group, the response rate was 94%, 89%, 86% and 84% at 1, 3, 6 and 12 months postoperatively respectively. In the elderly group this was 99%, 99%, 99% and 98% at 1, 3, 6 and 12 months postoperatively respectively. Table 1 shows all baseline characteristics.

Quality of life

Baseline

Average baseline SF-36 scores of both young and elderly donors were higher than the average of the general Dutch population on all 8 dimensions (Figure 1). At baseline, SF-36 scores were not significantly different between groups except for the dimension physical function (PF). Young and elderly donors scored 95.2 and 89.5 on average respectively (p<0.001).

Between-group analysis

QOL during follow-up was assessed on all 8 dimensions. At one month postoperatively, between-group analysis showed a significant advantage in QOL in favour of the elderly group regarding the dimensions bodily pain (BP) (estimated difference 7 points,

Table 1. Baseline characteristics. Categorical data are displayed as No. (%), continuous data are displayed as mean (standard deviation).

	Young n=366	Elderly n=135	P-value
Female	194 (53%)	76 (56%)	0.51
Age - years			
<40	98 (27%)	-	
40-60	268 (73%)	-	
60-70	-	104 (77%)	
70<	-	31 (23%)	
GFR - mL/min			
Baseline	87.7 (17.8)	74.0 (14.2)	<0.001
Δ Baseline - 1-year	17.2 (23.7)	17.7 (19.5)	0.85
ASA-classification:			<0.001
1	296 (81%)	81 (60%)	
2	69 (19%)	52 (39%)	
3	1 (0.3%)	2 (1.5%)	
BMI - kg/m2	26.0 (3.8)	26.1 (3.1)	0.92
Living related	216 (59%)	61 (45%)	0.043
Procedure:			0.17
MIDN	85 (23%)	34 (25%)	
LDN	218 (60%)	69 (51%)	
HARP	63 (17%)	32 (24%)	
Postoperative complications	34 (9%)	13 (10%)	0.91
Re-admissions	4 (1%)	0	0.22
Re-operations	1 (1%)	1 (1%)	0.46
Hospital stay - days	3.6 (1.5)	3.8 (1.6)	0.11

GFR, glomerular filtration rate; ASA, American society of anesthesiologists; MIDN, mini-incision donor nephrectomy; LDN, laparoscopic donor nephrectomy; HARP, hand-assisted retroperitoneoscopic donor nephrectomy

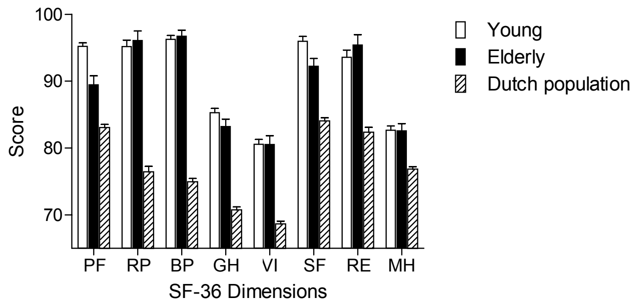

Figure 1. SF-36 scores at baseline. Data displayed as means (standard error of the mean).

p=0.001), role physical (RP) (estimated difference 18 points, $p<0.001$) and vitality (VI) (5 points, p=0.008). At 3 months, BP (3 points, p=0.04) and RP (8 points, p=0.02) were still in favour of the older group. At 6 and 12 months, PF was in favour of the younger group (estimated difference 3 and 5 points respectively, p=0.04 and $p<0.001$). At the various time points all other dimensions did not differ between groups (table 2).

Within-group analysis

One month after surgery, elderly donors had returned to baseline on the dimension mental health (MH) (p=0.55) Young donors did significantly better on this dimension at one month follow-up, when compared with baseline (p=0.004). At 3 months elderly donors had returned to baseline on the dimensions PF (p=0.21), BP (p=0.14), general health (GH) (p=0.65), social functioning (SF) (0.59) and role emotional (RE) (p=0.16). At month 3, young donors returned to baseline on the dimensions GH (p=0.18) and RE (p=0.07). At 6 months elderly donors had returned to baseline on the dimensions RP (p=0.16) and VI (p=0.26). At month 6, young donors returned to baseline on the dimension SF (p=0.25). For the dimension PF, young donors returned to baseline at month 12 (p=0.22). For the dimensions RP, BP and VI, young donors did not return to baseline within one year after the procedure. An overview of these results is provided in table 3.

Quality of life: Subgroup analysis

Between-group analysis

As significant differences were found between groups, a subgroup analysis was performed. We compared donors aged 70 or higher with all donors aged between 60 and 69. No significant differences were found between groups in this subgroup analysis.

Within-group analysis

Return to baseline was assessed, as described earlier, in the group aged 70 or older and the group of donors aged between 60 and 69. One month after surgery, donors aged 70 or higher had returned to baseline on the dimensions GH (p=0.51), SF (p=0.08) and MH (p=0.57). The donors aged between 60 and 70 returned to baseline on the dimension MH (p=0.70) at month 1. At 3 months, donors aged 70 or higher had returned to baseline on the dimensions PF (p=0.76), RP (p=0.87), BP (p=0.95), VI (p=0.81) and RE (p=0.29). At month 3, donors between the age 60 and 69 returned to baseline on the dimensions PF (p=0.19), GH (p=0.95), BP (p=0.07) and SF (0.19). At 6 months these donors had returned to baseline on the dimensions RE (p=0.74) and VI (p=0.53). On the dimension RP, donors aged between 60 and 69 did not return to baseline within one year after the procedure.

Table 2. Between-group analysis, SF-36 scores on all 8 dimensions during follow-up. Data presented as mean (standard deviation).

	Month 1			Month 3			Month 6			Month 12		
	Young	**Elderly**	**P-value**	**Young**	**Elderly**	**P-value**	**Young**	**Elderly**	**P-value**	**Young**	**Elderly**	**P-value**
Physical function	71.7 (19.8)	72.1 (20.7)	0.98	91.4 (13.1)	89.3 (17.7)	0.56	93.7 (11.3)	87.3 (20.7)	**0.035**	94.5 (11.4)	86.6 (20.5)	**<0.001**
Role physical	35.3 (38.8)	53.0 (43.3)	**<0.001**	79.1 (35.8)	87.9 (28.4)	**0.017**	88.9 (26.8)	93.9 (18.8)	0.09	91.5 (25.2)	89.0 (27.9)	0.33
Bodily pain	73.6 (20.9)	81.3 (19.0)	**0.001**	90.7 (17.5)	95.1 (14.0)	**0.042**	92.8 (15.4)	95.4 (13.0)	0.12	94.4 (14.2)	95.1 (13.7)	0.67
General health	80.2 (14.7)	80.3 (14.0)	0.51	83.6 (16.1)	83.8 (14.7)	0.69	85.1 (15.9)	83.7 (14.6)	0.80	85.1 (16.3)	81.9 (15.6)	0.25
Vitality	63.9 (19.6)	69.4 (18.4)	**0.008**	73.5 (19.2)	77.9 (17.7)	0.08	76.0 (18.7)	79.8 (15.1)	0.06	76.9 (18.1)	77.3 (17.3)	0.91
Social function	75.7 (23.4)	78.6 (22.7)	0.17	89.3 (18.2)	91.2 (16.7)	0.33	92.2 (15.8)	91.9 (13.7)	0.95	92.4 (16.6)	91.9 (15.7)	0.95
Role emotional	79.0 (36.1)	74.8 (39.8)	0.21	90.1 (27.0)	91.2 (26.1)	0.95	92.9 (22.1)	93.8 (19.7)	0.95	95.0 (19.2)	92.5 (24.3)	0.08
Mental health	84.8 (13.6)	83.0 (15.6)	0.21	85.2 (13.8)	86.3 (13.8)	0.38	86.0 (13.6)	84.4 (13.4)	0.16	86.0 (14.0)	83.4 (15.5)	0.20

Table 3. Within-group analysis, return to baseline. Data presented as difference (p-value).

	Young (n=366)	Elderly (n=135)
Physical function	Month 12 (p=0.22)	Month 3 (p=0.21)
Role physical	Not within 12 months	Month 6 (p=0.16)
Bodily pain	Not within 12 months	Month 3 (p=0.14)
General health	Month 3 (p=0.18)	Month 3 (p=0.65)
Vitality	Not within 12 months	Month 6 (p=0.26)
Social function	Month 6 (p=0.25)	Month 3 (p=0.59)
Role emotional	Month 3 (p=0.07)	Month 3 (p=0.16)
Mental health	Month 1 (p=0.004)*	Month 1 (p=0.55)

* Mental health is significantly better than baseline at Month 1 and thereafter

Pain

Elderly donors experienced significantly less pain postoperatively. At day 1 after surgery, elderly donors scored significantly lower on the VAS when compared with the young donors, 2.5 vs. 3.4 respectively (p<0.001). On day 3, elderly donors scored 1.6 on average while young donors scored 2.1, this difference was also statistically significant (p=0.016). Measurements at day 7 and 14 were not statistically significant. Post-operative pain-scores for both groups are displayed in figure 2.

Resumption of daily activities

Data on the resumption of 90% of daily activities was missing in 43 cases (9%); data on the resumption of 100% of daily activities was missing in 55 cases (11%). In the young group, 7 donors (2.1%) did not resume 90% of their daily activities within one year. In the elderly group, 5 donors (3.8%) did not resume 90% of their daily activities within one year; this difference was not statistically significant. In the young group, 11 donors

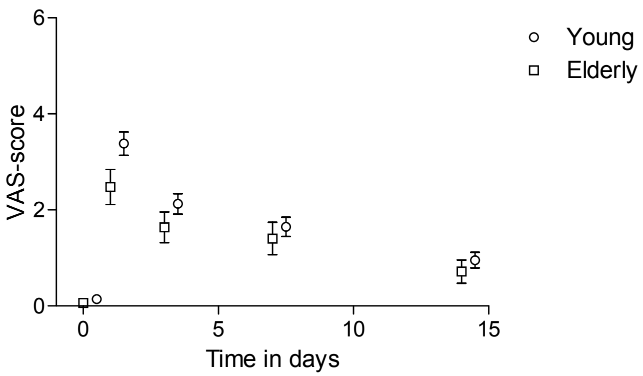

Figure 2. Pain intensity on the VAS; data displayed as mean (95% CI)

(3.4%) did not resume 100% of their daily activities within one year. In the elderly group, 7 donors (5.5%) did not resume 100% of their daily activities within one year; this difference was not statistically significant. In the remaining young donors, 90% of daily activities were resumed at day 55 on average, in elderly donors this was at day 49 (p=0.20). Hundred percent of daily activities were resumed at day 90 on average in young donors, for elderly donors this was day 77 (p=0.09).

DISCUSSION

This is the largest prospective follow-up study reporting on the live kidney donor's QOL, pain and resumption of daily activities. The results of this study demonstrate that donors have a superior QOL on all 8 dimension of the SF-36 questionnaire, when compared to the general Dutch population (14). Pain scores are comparable to earlier published results after live donor nephrectomy (15, 16). A very small proportion of donors does not resume 100% of daily activities within one year of the procedure.

The elderly donors that were deemed eligible for donation in this study were very healthy individuals. Therefore it is possible that a selection bias has occurred. However, our renal transplant team has liberally accepted donors with minor comorbidities, anatomic anomalies and elderly donors throughout the study period. The latter is reflected by a constant inclusion of elderly donors in the aforementioned period. Furthermore, we stress that ASA-classification is significantly higher in the elderly group as might be expected in the general elderly population. We previously reported a significant difference in QOL after laparoscopic and mini-incision donor nephrectomy. In the current study the percentage of donors undergoing either technique did not significantly differ. Several studies suggest poor long-term graft outcome when using elderly donors (17). As live kidney donation is safe, cost effective and can be performed electively or even pre-emptively and transplantation is preferred over dialysis, the use of elderly live donors can be justified from the perspectives of recipient, donor and society.

Elderly donors had significantly better QOL scores postoperatively on the dimensions bodily pain, role physical and vitality at month 1 and 3. As all between-group analyses have been adjusted for baseline values, this cannot be explained by pre-existing differences. A decline in QOL in younger donors has been described before (10, 18, 19). Furthermore, the results of this study demonstrate that elderly donors recover to baseline sooner than young donors on all dimensions except general health, role emotional and mental health. We hypothesize that, as elderly donors do not have a family to take care of or a daytime job to attend, they do not run into their disabilities as soon as younger donors do. Retirement may have a positive effect on recovery simply because retired donors have more time for planning and performing daily activities and therefore experience less limitations. Another explanation may be that elderly donors can put the negative experiences surrounding donation including pain, nausea and delayed recovery into perspective, as they have a lifetime of different experiences behind them. Furthermore, as people become older, they are less likely to focus on the physical aspects of their health and value their qualitative aspects higher (20). Although donors were included from three prospective studies , we acknowledge that we cannot completely rule out an effect of selection of elderly donors as we did not record all potential donors which were not selected. Therefore, we should be cautious to extrapolate superior quality of life to all potential elderly donors. However, we would rather like to stress that quality of life dimensions also return to preoperative values in elderly donors. Moreover, postoperative quality of life appears at least comparable to the quality of life of younger donors. The latter reached significantly higher scores on the physical function dimension at month 6 and 12. However, elderly donors had already returned to baseline by 3 months. A further increase would not be expected.

Subgroup analysis of donors aged 70 or higher demonstrated no significant differences between groups. This affirms our hypothesis that elderly donors do not run into their disabilities as soon as younger donors. Within-group analysis demonstrated that donors aged 70 or higher recovered to baseline faster on 5 out of 8 dimensions. This endorses the hypothesis that one’s perspective on quality of life changes with increasing age.

Elderly donors experience significantly less pain on day 1 and day 3 postoperatively. It has been established that postoperative pain has an effect on recovery and is strongly associated with reduced QOL (21-23). Therefore, another explanation for the observed differences may be explained by the differences in pain or pain perception between young and elderly donors. We did not address return to work, as the majority of the Dutch population retires at the age of 65. Full resumption of daily activities takes place within 3 months in general, with a small but non-significant advantage for elderly donors.

As opposed to most studies, which had a retrospective design, a small sample size of elderly donors or lacked pre-donation values, we have prospectively gathered data on a relatively large sample of elderly donors at various points in time, including baseline (11). Comparison of QOL data to the general population alone does not make sense, because baseline values of live donors are higher in general as a result of the selection process for donation. Data of donors older than 70 years must be carefully interpreted since this group is small and these donors will have most probably undergone careful selection. However, the data of this group seem to indicate that donation does not result in permanent reduced quality of life in very old donors.

The results of this study demonstrate that elderly donors have better postoperative QOL scores and return to their baseline value faster than young donors. This effect was also demonstrated when comparing donors above 70 years of age with donors aged 60 to 70. Furthermore, elderly donors experience significantly less pain during the first days after the procedure and the vast majority of all donors resume all of their daily activities. As the impact of age on donor safety has already been established and the results of this study demonstrate no disincentives regarding quality of life, elderly donors can safely be included in live donation programs. Furthermore, the perspective of excellent postoperative quality of life may convince elderly individuals to donate.

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Chapter 9 A multivariate analysis of health-related quality of life after live kidney donation

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Submitted

ABSTRACT

Live kidney donation has been proven to be a safe procedure with a very low mortality rate. There is evidence suggesting that the majority of live kidney donors experience a quality of life (QOL) comparable to or even superior to that of the general population. Nevertheless, identification of factors associated with a decrease in QOL would improve information to the donor, donor selection and convalescence.

Data on QOL on 501 live donors that were included in 3 prospective studies between 2001 and 2010 was used. The SF-36 was used to measure QOL up to one year after the procedure. Effects on both the mental (MCS) and physical component scale (PCS) were analyzed. Hierarchical linear regression analyses was applied for longitudinal analyses of the data.

Quality of life at baseline was significantly better for both the PCS and MCS when compared to the general Dutch population ($p<0.001$). Factors associated with a change in health-related QOL were BMI ($d=-0.17$), gender ($d=-0.14$), age ($d=-0.14$) and recipient and graft survival ($d=0.10$).

Overall QOL after live donor nephrectomy is excellent. Expectations towards a decreased postoperative QOL within the first year are unjustified and should pose no barrier to live kidney donation. Factors associated with QOL should aid physicians in adequately selecting and informing donors.

INTRODUCTION

The benefits of live kidney donation for recipients are well documented (1-4). The continuous demand for donor kidneys has led to an increase in live kidney donation and to the inclusion of donors with co-morbidities (5, 6). Live kidney donation has been proven to be a safe procedure with a very low mortality rate (7, 8). Furthermore, there is evidence suggesting that the majority of live kidney donors experience a quality of life (QOL) comparable to or even superior to that of the general population (9-11). Due to the development of new immunosuppressive drugs and minimally invasive surgical techniques, the selection of potential donors has changed. Eligibility criteria have become more flexible and other factors, such as convalescence and QOL, are becoming increasingly important. Nevertheless, little is known on long-term outcomes of QOL in this population, especially in donors with pre-existing comorbidities (12).

Published research suggests that a minority of donors experience psychological distress or negative emotions after donation (13, 14). Identification of factors associated with minor outcome would improve information to the donor, donor selection and convalescence. So far, there is only one study reporting on predictors of QOL (15). Although this study comprises a very large sample, it is lacking baseline data. QOL is a subjective concept and therefore differences between baseline and follow up are more informative than absolute numbers at follow up. This study aimed to identify factors associated with changes in QOL after live kidney donation, and has sufficient numbers of observations, including those at baseline.

METHODS

Study population and data collection

In this study we included 501 live kidney donors of whom pre- and postoperative data on QOL was available. These donors had been included in 2 randomized trials and 1 prospective study that ran between May 2001 and October 2010 at the Erasmus Medical Center in Rotterdam and the Radboud university medical center in Nijmegen, both tertiary referral centers in the Netherlands. Data of all these donors was prospectively collected (7, 16, 17). For one of the trials and the prospective study, all donors were eligible for inclusion provided they were capable of filling out the questionnaires (16, 17). For the other trial, all left-sided donors were eligible for inclusion provided they were capable of filling out the questionnaires (7). All donors were pre-operatively screened by a nephrologist and a medical psychologist, anaesthesiologist and a cardiologist on indication. Obese donors or donors with a complex anatomy were not excluded. At the end of the surgical procedure, patients received Patient Controlled Analgesia (PCA). This device enabled the donor to administer intravenous morphine from a 50-cc syringe (1 mg morphine per ml) by pressing a button. Furthermore, two 500 mg acetaminophen tablets were offered four times daily until discharge. The PCA-device was removed when morphine had not been required for at least six hours. Donors were discharged when a normal diet was tolerated and mobilization was adequate. Re-admission, re-interventions, length of stay and pre- and postoperative complications were scored prospectively. The institutional review boards and medical ethics committees respectively approved these studies.

Operative techniques

Mini-incision open donor nephrectomy (2001-2006), standard laparoscopic donor nephrectomy (from 1997) and hand-assisted retroperitoneoscopic donor nephrectomy (from 2007) were performed in the aforementioned period. These techniques have been described earlier (7, 18).

Postoperative data and QOL

The Short Form-36 (SF-36) is a validated and commonly used tool to measure health-related QOL (19). This questionnaire has been reported to have good reliability and validity in the Dutch population (20). The SF-36 consists of eight dimensions: physical function, role limitations due to physical health problems, bodily pain, general health, vitality, social function, role limitations due to emotional problems and mental health. The first four dimensions are most sensitive to changes in physical performance and physical well-being. By using the scores on these four dimensions a summary score can be computed, the physical component score (PCS). The latter four dimensions mainly attribute to mental functioning and emotional well-being. By using the scores on these four dimensions a summary score can be computed, the mental component score (MCS). The component scores are computed by normative comparison and standardized to the Dutch population. A score of 50 is the reference score for the Dutch population of the same age and gender, indicating the average of the Dutch population. A score below 50 indicates inferior quality of life and a score above 50 indicates superior quality of life. The eight dimensions of the SF-36 can also be analyzed separately. In this study this would lead to a surplus of data, not aiding to the comprehensibility of this study. Moreover, multiple tests would have been necessary. For this reason component scores were used.

Donors were asked to fill out the SF-36 questionnaire preoperatively and at 1, 3, 6 and 12 months postoperatively. Pain was quantified using a visual analogue scale (VAS) questionnaire. Donors had to indicate a point on a 10 cm line which best corresponded with the experienced pain. The distance on the line corresponds with pain and ranges from zero (no pain) to ten (severe pain). VAS-questionnaires were filled out at baseline and at day 1, 3, 7 and 14. For our analyses pain at days 7 and 14 were used.

Statistical analysis

Mixed modelling, also known as random effect modelling, multilevel or hierarchical linear regression analyses, was applied for longitudinal analyses of the data. Mixed modelling can efficiently handle data with missing and unbalanced time-points. It corrects for bias when absence of data is dependent on characteristics that are present in the models (21). First, saturated models were postulated with physical and mental quality of life as dependent variables. The saturated models included age, gender, body mass index (BMI), relationship, ASA-classification, procedure type, postoperative complications, pain, kidney functioning (GFR), recipient and graft survival, time, linear, quadratic and logarithmic and all interactions with time as fixed effects. For recipient and graft survival, only cases of directed donation could be analyzed. Also, the moment of loss of both recipient and graft with regard to the moment of follow-up was taken into account in the analyses. The deviance statistic (22) using restricted maximum likelihood (23) was applied to determine the covariance structure. The saturated model was reduced by eliminating insignificant fixed effects, taking into account that interaction effects ought to be nested under their respective main effects (24). The significance of the difference between the saturated model and the parsimonious final model was determined with the deviance statistic using ordinary likelihood. Statistical analyses were performed with SAS (version 9.2, Cary, NC, USA).

Effect sizes (Cohen's d) were computed using Equation 1, in which the difference between the estimate at time point t and the baseline score was divided by the estimated baseline standard deviation. An effect size between 0.20 and 0.50 was considered a small effect, between 0.50 and 0.80 a medium effect and above 0.80 a large effect.

RESULTS

Population characteristics

In total, 501 donors were eligible for inclusion in this study. Response rates at month 1, month 3, month 6 and month 12 were 95%, 84%, 82% and 81% respectively. An overview of all population characteristics is provided in table 1.

Quality of life

The final parsimonious mixed models are presented in Appendix A. The combination of linear, quadratic and logarithmic time effects are not readily insightful. For ease of

	MIDN n=119 (24%)	LDN n=287 (57%)	HARP n=95 (19%)	Total n=501 (100%)
Female	73 (61%)	145 (51%)	52 (55%)	270 (54%)
Age - years	51.6 (±12.8)	50.1 (±12.8)	52.8 (±11.8)	50.9 (±12.6)
ASA-classification:				
1	85 (71%)	223 (78%)	69 (73%)	377 (75%)
2	33 (28%)	63 (22%)	25 (26%)	121 (24%)
3	1 (0.8%)	1 (0.3%)	1 (1.1%)	3 (1%)
BMI - kg/m^2	26.1 (±3.5)	26.0 (±3.8)	26.0 (±3.5)	26.0 (±3.7)
Directed donation	116 (98%)	254 (89%)	85 (90%)	455 (91%)
Postoperative complications	13 (11%)	24 (8%)	7 (7%)	44 (9%)
Pain intensity day 1	3.47 (±2.22)	3.15 (±2.29)	2.66 (±2.17)	3.13 (±2.27)
Pain intensity day 3	2.41 (±2.03)	1.96 (±1.95)	1.56 (±1.66)	2.00 (±1.93)
Pain intensity day 7	1.91 (±1.88)	1.48 (±1.85)	1.46 (±1.79)	1.58 (±1.85)
Pain intensity day 14	1.07 (±1.80)	0.77 (±1.29)	1.04 (±1.58)	0.89 (±1.48)
1-year graft survival	117 (98%)	273 (95%)	92 (97%)	482 (96%)
1-year recipient survival	116 (98%)	275 (96%)	92 (97%)	483 (96%)

ASA, American society of anesthesiologists; BMI, body mass index; MIDN, mini-incision donor nephrectomy; LDN, laparoscopic donor nephrectomy; HARP, hand-assisted donor nephrectomy

interpretation the estimates resulting from these effects at the various time-points are presented in Table 2. In the upper rows the estimates are presented as the mean of the covariates age and BMI, for females, without postoperative pain, no graft loss and without comorbidity and complications. In the rows below the additional effects for males, a higher age, a higher BMI, postoperative pain, graft loss, comorbidity and postoperative complications are given. The course of both the PCS and MCS during follow-up is demonstrated in figure 1.

Physical component scale

For the PCS, donors report a significantly better QOL than the general Dutch population at baseline. A large decrease in the PCS occurs after the operation, that increased significantly in the months thereafter. After one year still a small decrease (d = -0.24) compared to baseline was noted.

Gender - Males have a non-significant 0.4 higher score at baseline (p=0.17) and a reduction of 0.13 each month (p=0.02). Although this reduction compared to women is significant the resultant estimated difference is not significant at any time, because of the somewhat higher starting score.

Table 2. Estimates and effect sizes

	Physical component			Mental component		
	Estimate	***d*** [2)]	***p-value***	**Estimate**	***d*** [2)]	***p-value***
No covariate effects [1)]						
Baseline	57.6			52.1		
1 month	46.9	-1.60	<0.0001	52.0	-0.01	0.90
3 months	54.6	-0.42	<0.0001	54.3	0.28	<0.001
6 months	55.7	-0.25	<0.0001	54.8	0.35	<0.001
12 months	55.8	-0.24	0.0005	54.6	0.32	<0.001
Additional covariate effects						
Males						
Baseline	58.0	0.10	0.17	53.8	0.22	0.003
1 month	47.4	0.08	0.26	53.7	0.22	0.003
3 months	54.8	0.04	0.57	56.0	0.22	0.003
6 months	55.5	-0.02	0.79	56.6	0.22	0.003
12 months	54.9	-0.14	0.19	56.3	0.22	0.003
Age + 10 years additional						
Baseline	57.1	-0.03	0.32	52.4	0.04	0.23
1 month	47.1	0.03	0.37	52.2	0.02	0.58
3 months	54.9	0.05	0.25	54.3	-0.01	0.83
6 months	55.7	0.01	0.81	54.7	-0.02	0.44
12 months	54.9	-0.14	0.006	54.3	-0.04	0.22
BMI + 5 kg/m² additional						
Baseline	57.3	0.00	0.98			
1 month	46.7	-0.02	0.77			
3 months	54.0	-0.04	0.40			
6 months	54.5	-0.09	0.11			
12 months	53.5	-0.17	0.02			
Pain + 2, additional [3)]						
1 month	44.4	-0.38	<0.0001			
3 months	52.4	-0.32	<0.0001			
6 months	54.2	-0.23	0.0001			
12 months	55.4	-0.05	0.47			
Graft loss, additional [3)]						
1 month	45.7	-0.18	0.53			
3 months	56.3	0.26	0.04			
6 months	58.2	0.39	0.003			
12 months	56.4	0.10	0.73			
Complications [3)]						
1 month	41.0	-0.91	0.0001	49.4	-0.34	0.02
3 months	51.9	-0.41	0.03	51.6	-0.34	0.02
6 months	54.4	-0.19	0.36	52.2	-0.34	0.02
12 months	53.9	-0.29	0.19	51.9	-0.34	0.02
Comorbidity						
Baseline (no time effects)	55.5	-0.28	0.002			

[1)] Effects at mean of covariates age and BMI for females without pain, no graft loss, comorbidity and no complications.

[2)] Cohen's d, effect size compared to baseline, for covariates additional effect sizes

[3)] In principle there were no differences at baseline

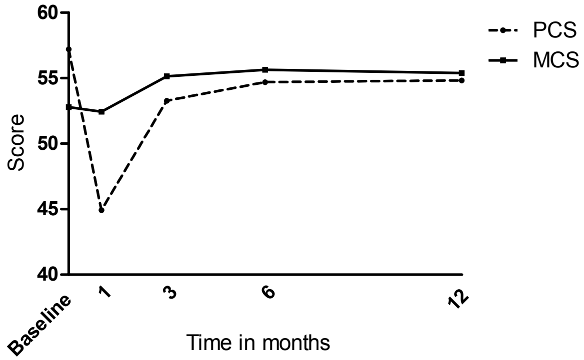

Figure 1. Scores on the PCS and MCS

Age - For interpretation of the age effect we chose to present the effect of a donor 10 years older than the mean age (*i.e.* 50.9 + 10 years) at baseline. No significant differences were found until one year, when a minimal (d = -0.14) decrease occurred.

BMI - The additional BMI effect is presented for a donor 5 kg/m^2 above the mean (*i.e.* 26 + 5 kg/m^2). No significant effect were found until one year, when a minimal (d = -0.17) occurred.

Pain - Donors suffering pain postoperatively, reported a mean VAS-score of 1.8. Hence we present the effects of an increased VAS-score of 2 points. An additional reduction of PCS scores was found after the operation, returning to baseline level after one year.

Loss of the graft - Loss of the graft resulted in a temporal increase of PCS scores at 3 and 6 months. No significant difference was retained after one year.

Complications - Patients with one or more post-operative complications demonstrated a much lower estimate one month after the operation (d = -0.91), but this effect reduced to a non-significant small effect at one year.

Co-morbidity - Co-morbidity resulted in a small decrease of 1.8 compared to patients without co-morbidity, independent of the time-point.

Other covariates - No significant effects were found with regard to death of the recipient and glomerular filtration rate (GFR).

Mental Component Scale

For the MCS, donors report a significantly better QOL than the general Dutch population at baseline and at any moment during follow-up (52.0 to 54.8 vs. 50.0 respectively, p<0.001).

Operation type - Overall, the mini-incision open donor nephrectomy had 2.3 higher scores and standard laparoscopic donor nephrectomy had 1.6 higher scores than hand-assisted retroperitoneoscopic donor nephrectomy.
Gender - Males had an overall 1.7 higher score than females.
Age - Older donors reported a non-significant higher MCS score at baseline. Though a small significant decrease in course of time was found, this did not result in a different score from donors with the mean age at any time.
Complications. Overall, post operative complications induced a small significant reduction in MCS scores.
Other covariates - No significant effects on the MCS scores were found for post-operative pain, death of the recipient, loss of the graft, GFR and co-morbidity.

DISCUSSION

To our knowledge, this is the largest, prospective study assessing QOL in a multivariate fashion with time interactions. The results of this study demonstrate that scores on both the PCS and MCS after donation are excellent. Furthermore, QOL is significantly better, both before and after donation, when compared with the general Dutch population. This has been confirmed by earlier reports (9-11). This emphasizes that baseline data are essential. For the PCS, donors do not completely return to their baseline value within one year. Nevertheless, they perform significantly better than the Dutch general population from month 3 on. Regarding the MCS, donors perform significantly better at baseline when compared to the general Dutch population. During follow-up the score on the MCS improves and remains significant. The latter finding implies a relative improvement in mental health after donation.

There are three possible explanations for the decrease of the PCS from baseline to follow up. First health could be reduced because of the donation. This is unlikely as no investigations so far has found any relevant average reduction in health. Second, it could be that donors are only recruited when they are in excellent physical condition. The reduction in PCS could then be interpreted as 'a regression to the mean'. r = 0.062), this second explanation is not also very likely, as the PCS score is not a criterion for donor ship. Thirdly, the potential donors could give strategic or '(socially) desirable answers': they know that donors are only selected if they are in good physical health and therefore they adjust their answers in that direction. Moreover, as the high scores at baseline only occur in the PCS, which is the most relevant for the inclusion criterion, and not in the MCS, the third explanation is a good candidate to explain the high scores at baseline.

Our study extends earlier findings on the relationship between excess body weight at time of donation and QOL (15). According to our data there is inversely proportional relation between BMI and QOL. An increase in BMI of 5 kg/m^2 at baseline would result in a decrease in QOL on the PCS of 0.09 per month. Although the effect of this relation is small (d=0.17), this finding is clinically relevant. There is an obvious relation between BMI and QOL, as obese individuals score lower on SF-36 dimensions as bodily pain and vitality(25). However, even when adjusting for baseline, this effect is still significant, implying an even worse QOL. No significant relation was observed between BMI and the MCS. This is important when counseling potential live donors.

This study also presents new information on QOL after live donor nephrectomy. Our data suggest a temporary increase in QOL in case of graft loss. Although this effect only lasts until 6 months after donation, it may be considered a small but significant effect. A possible explanation for this observation may be what psychologists refer to as cognitive dissonance. This implies that individuals who hold two or more contradictory beliefs, experience cognitive dissonance. In this case deterioration of the recipient and relative recovery of the donor, thus resulting in a contradictory increase in QOL. Another explanation may be that donors place their own physical discomfort into perspective when they see their recipient deteriorate.

Gender, age, BMI, co-morbidity, and graft loss are factors that affect postoperative physical QOL. Females have a marginally different QOL compared to males. This difference should not influence the selection of the donor as the difference is very small, not significant and it would instantly rule out half of the donors. A higher age at time of donation has only a minimal negative effect (d=0.14) on QOL at one year. This confirms the excellent quality of life we observed in donors previously (26). Hence, physicians should not restrain from selecting elderly donors. Co-morbidity is associated with a lower physical QOL. Therefore, transplant physicians should carefully select donors with co-morbidities. Relationship between donor and recipient does not directly influence QOL after the procedure. In case of directed donation, graftloss does influence postoperative QOL. As it is impossible to anticipate these factors, they should not influence selection criteria. A higher BMI is associated with a decrease in QOL. Thus, obese donors should not be selected if superior donors are available or obese donors should be stimulated to lose weight before donation.

This is the first study to assess factors associated with QOL in a prospective fashion. The strengths of this study are the large sample size and the fact that QOL was measured at baseline and at various time-points during follow-up. This allowed us to study factors that differentially influenced QOL up to one year post-operatively. As this is a relatively short follow-up time this may also be a limitation of this study. We do not expect any major changes in QOL after one year that may still be related to the procedure. We did not observe worrisome effects at 3 to 5 years after donation in a follow-up study of a randomized controlled trial on minimally invasive donor nephrectomy (27). Nevertheless, we are currently performing a 10-year follow-up study on QOL to determine this. Furthermore, changes in BMI should be studied with relation to QOL to establish if weight-loss after the procedure will result in a better QOL.

In conclusion, overall QOL after live donor nephrectomy is excellent. Expectations towards a decreased postoperative QOL within the first year are unjustified and should pose no barrier to live kidney donation. Factors associated with a change in health-related QOL were BMI, gender, age and graft survival. Although differences in QOL scores after one year are small, additional research has to reveal the long-term effects.

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Appendix A. Effect estimates of the final mixed models

Effect	Estimate	[95% CI]	P-value
Physical component scale			
Intercept	57.3	[56.7 ; 58.0]	<.0001
Linear time	-61.1	[-68.5 ; -53.6]	<.0001
Time squared	1.41	[1.22 ; 1.59]	<.0001
Log time	20.9	[16.6 ; 25.3]	<.0001
Log time squared	72.2	[64.2 ; 80.1]	<.0001
Male	0.63	[-0.27 ; 1.54]	0.1703
Male * linear time	-0.13	[-0.23 ; -0.00]	0.0201
Age (centered)	-0.018	[-0.055 ; 0.018]	0.3196
Age * Linear time	-0.025	[-0.038 ; -0.013]	0.0001
Age * log time	0.091	[0.0307 ; 0.150]	0.0031
BMI (centered)	-0.002	[-0.141 ; 0.137]	0.9807
BMI * linear time	-0.018	[-0.033 ; -0.003]	0.0157
Co-morbidity	-1.83	[-2.98 ; -0.69]	0.0017
Post operative complications	-9.99	[-15.41 ; -4.57]	0.0003
complications * linear time	-0.840	[-1.643 ; -0.036]	0.0406
complications * log time	7.09	[1.63 ; 12.55]	0.0109
Pain	-1.35	[-1.94 ; -0.76]	<.0001
Pain * linear time	0.099	[0.0380 ; 0.160]	0.0015
Graft loss	-5.09	[-11.67 ; 1.49]	0.1293
Graft loss * linear time	-1.06	[-1.99 ; -0.13]	0.0249
Graft loss * log time	7.21	[1.40 ; 13.02]	0.0151
Mental component scale			
Intercept	52.1	[51.3 ; 52.9]	<.0001
Linear time	-9.99	[-17.08 ; -2.67]	0.0073
Time squared	0.225	[0.039 ; 0.412]	0.0178
Log time	6.18	[1.61 ; 10.75]	0.0081
Log time squared	11.05	[3.56 ; 18.54]	0.0039
Male	1.70	[0.60 ; 2.80]	0.0025
Age (centered)	0.029	[-0.019 ; 0.076]	0.2345
Age * log time	-0.024	[-0.044 ; -0.0038]	0.0198
Complications	-2.689	[-5.006 ; -0.371]	0.023

BMI, body mass index; CI, confidence interval

Chapter 10 Ten-years follow-up on quality of life of a randomized controlled trial comparing laparoscopic and mini-incision open live donor nephrectomy

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Submitted

ABSTRACT

We aimed to compare the ten-year follow-up between live kidney donors after laparoscopic and open donor nephrectomy. One-hundred live kidney donors were followed-up ten years after participating in a single blind, randomized controlled trial that ran in two tertiary referral centers in the Netherlands. Participants were randomly assigned to either laparoscopic donor nephrectomy (LDN) or to mini incision muscle splitting open donor nephrectomy (MIDN).

The primary outcome was fatigue using the physical fatigue score of the multidimensional fatigue inventory 20 (MFI-2). Secondary outcomes were physical function using the SF-36, kidney function, incidence of hypertension, and survival of donor, recipient and graft.

After a median follow-up time of ten years, clinical data were available for 50 donors of the MIDN group (100%) and 47 donors of the LDN group (94%), laboratory data were available for 46 donors of the MIDN group (92%) and 44 donors of the LDN group (90%), and quality of life data were available for 37 donors in both groups (74%). Nine donors died during follow-upof unrelated causes to donation, and one donor was lost to follow-up. Quality of life showed a significant difference at ten-year follow-up in role emotional scores of the SF-36 between the LDN (99.1) and MIDN (84.7) group (p=0.002). Between the MIDN and LDN group there was no significant difference in kidney function (74.5 mL/min versus 79.9ml/min) and the incidence of new-onset hypertension (30% versus 27%), p=0.45 and p=0.459 respectively. Overall donor (91%), recipient (82%), and graft survival (66%) did not differ (p=0.885, p=0.127, and p=0.123 respectively) between both groups.

Donor outcomes including quality of life scores are excellent ten years after live kidney donation. Kidney function appears stable and hypertension does not seem to occur more frequently.

INTRODUCTION

In the last two decades live donors have rapidly become a major source of kidney transplants. The benefits for the recipients of live kidney donor transplantation are clear and include superior transplant quality and timing of the transplantation. The donor does usually not have any direct benefit and is exposed to harm of the surgical procedure. Laparoscopic donor nephrectomy has become the standard of care for live kidney donors (1-3). This approach has proven to limit discomfort, shorten length of hospital stay, and enable faster recovery with less fatigue and better quality of life (QOL) up to one year after donation (4). As opposed to recipients, donors are often discharged from further follow-up within months after the operation. Data on kidney function is scarce. However, it is unlikely that the donors' kidney function will differ from the kidney function of patients who underwent nephrectomy for other indications. Reports on long-term quality of life are even more rare. Most studies lack baseline data, have a retrospective design and do not have long-term follow-up. To establish the surgical standard of care in this era, we conducted a randomized controlled trial comparing laparoscopic and mini-incision open donor nephrectomy (MIDN) between 2001 and 2004. Both techniques clearly had an impact on the quality of life. We previously reported results three to five years after donation (5). We now present the data of these donors ten years after donation to evaluate the course of this impact.

METHODS

Study population

All 100 donors of our randomized trial comparing laparoscopic and mini-incision open live donor nephrectomy were included (4, 5). All donors have preoperatively been screened by a nephrologist, surgeon, social worker, and an anesthesiologist, and underwent imaging by angiography, MRI or ultrasonography to evaluate the vascular anatomy of both kidneys. If both kidneys were deemed suitable, the right kidney was procured for transplantation. The pre-, peri- and post-surgery procedures were described previously (4). An amendment to the protocol was written and approved by the medical ethics board to evaluate the ten-year follow-up data of all donors. Donor survival was checked in the Municipal Registry, ten years after donation, all donors who were still alive were contacted by mail and telephone to fill out questionnaires. Of the deceased donors the date and cause of death was recorded.

Surgical procedures

Donors were operated in two Dutch tertiary referral centers of which 50 were randomized to MIDN and 50 to LDN. Both techniques have previously been described (4). In summary, in LDN four to five trocars were inserted under direct vision into the peritoneal cavity. After mobilization of the hemicolon Gerota's fascia was opened and the kidney was dissected from the perirenal fat. After identification and dissection of the ureter and renal vessels, a Pfannenstiel incision was made as extraction site. Subsequently, the ureter was clipped and divided, and the renal vessels were divided with a stapler. The kidney was extracted using an endobag (Endocatch, US surgical, Norwalk, USA). In MIDN, the retroperitoneal cavity was accessed with an incision varying from 10-12 cm anterior to the 11th rib, by splitting the oblique and transverse abdominal muscles. A mechanical retractor was used to allow sufficient access. From the lateral side of the kidney Gerota's fascia was opened, and the kidney and its structures were dissected from the perirenal fat. Subsequently, the ureter and renal vessels were divided and the kidney was extracted. The fascias of the abdominal wall were sutured after which the skin was closed intracutaneously.

Data collection

After discharge the donors visited the outpatient clinic for a follow-up at three weeks, two months, three months and one year. Thereafter a yearly visit to the outpatient clinic was advised to evaluate kidney function. All donors have prospectively been followed since donation. Data on serum creatinine, blood pressure, weight, used medication and medical history were collected. Hypertension was defined according to the World Health Organization definitions. For donors aged <45: systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg; for donors aged >45: systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg and/or for both age groups the use of antihypertensive medication (6). The estimated Glomerular filtration rate (eGFR) was measured according to the Cockcroft Gault formula (7).

To evaluate the physical and psychosocial outcome among the MIDN and LDN donors of this randomized trial, donors were asked to fill out validated questionnaires on QOL (Short Form-36; SF-36) and fatigue (Multidimensional Fatigue Inventory-20; MFI-20). Previously, these questionnaires had been conducted preoperatively, at one month, three months, six months, one year, and once between three to five years (4, 5). For the current study questionnaires to all donors were sent at ten years after donor nephrectomy. The SF-36 is a validated and commonly used scale to measure health related QOL in eight health concepts: physical function, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. Scores for each of these concepts range from 0 to 100, with higher scores indicating better QOL. A five-point difference between LDN and MIDN on any health concept was considered the minimal clinically relevant difference (4, 8).

The MFI-20 includes 20 items ranging from one to five, which are divided into five scales: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. The total score per scale ranges from 4 (no fatigue) to 20 (exhausted) (9).

Recipients

Preperitoneal placement of the renal transplant in the iliac fossa was the standard surgical technique. Recipient survival, graft survival and serum creatinine levels were recorded during follow-up. Glomerular filtration rate was estimated according to the Cockcroft Gault formula (7).

Statistical analysis

Physical fatigue (MFI-20) had originally been defined as the primary outcome. Physical functioning (SF-36) had been defined as the most important secondary outcome. Con-

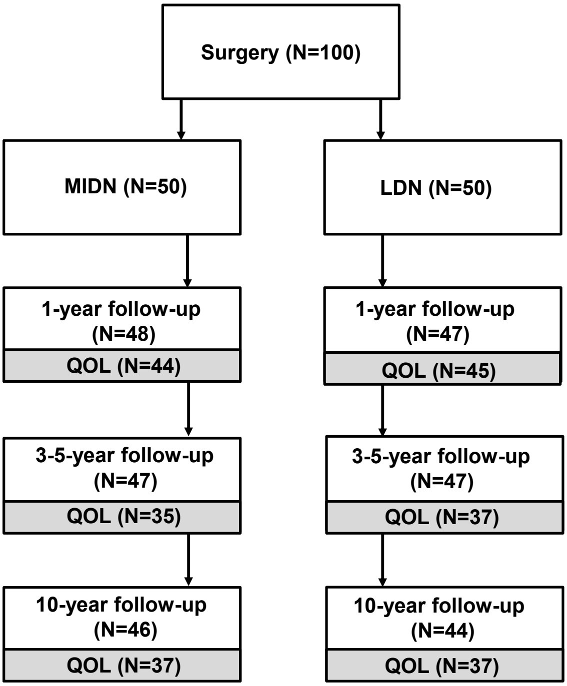

Figure 1. Flowchart of follow-up of 100 randomized live kidney donors. The follow-up boxes correspond with the number of donors of whom annually data on their kidney function and blood pressure was available. The QOL boxes represent the number of donors with available data on quality of life.

tinuous variables were compared with the Mann-Whitney-U test, categorical variables with the Chi-square test and repeated continuous variables with SPSS mixed models or the paired-samples T-test. Repeated measures were adjusted for baseline values, donor's gender and age. Survival was analyzed with a Kaplan-Meier analysis and between-group analysis was done with a log-rank test. All analyses were conducted using SPSS (version 22, SPSS Inc., Chicago, USA). A p-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Between November 2001 and February 2004, donors were randomly selected into two groups: 50 for MIDN and 50 for LDN. The follow-up period was between November 2011 and February 2014. Ninety-four percent of the donors were alive at ten years follow-up. Donor response rates with regard to the forms increased from 72% at three to five years post donation to 80% at ten years post donation as depicted in figure 1. There was no significant difference in response rate between MIDN and LDN donors. Median follow-up of the population was ten years (range 2-11 years). Nine donors have died according to the longest follow-up: six in the MIDN group and three in the LDN group (p=0.885). The overall donor survival is depicted in figure 2a. One donor died after two years of follow-up due to a car accident, one died after four years of follow-up of metastasized breast cancer, two died after seven years of follow-up of which one due to metastasized breast cancer and the other of metastasized lung cancer, one died after eight years of follow-up due to a cerebral vascular incident, one died after nine years of follow-up due to recurrence of breast cancer, two died after ten years of follow-up of which one to an aspergillus infection during chemo treatment for AML and the other of a cutaneous malignancy, and one died after 11 years of follow-up due to a ruptured aneurysm of the descending aorta. One donor in the LDN group lives abroad and was lost to follow-up. Baseline characteristics of the responders in both groups did not show a clinically significant difference (Table 1).

QOL and Fatigue (Table 2)

Previous follow-up results showed that all dimensions of QOL have returned to baseline in both groups (5). At ten-year follow-up none of the dimensions are at baseline levels in either group. The dimension role emotional was significantly in favor of LDN (p=0.002). Within-group analysis showed that in the LDN group all dimensions had lower values compared to baseline, except role emotional. Scores on all dimensions of the SF-36 at ten-year follow-up for both the MIDN and LDN group were not significantly different

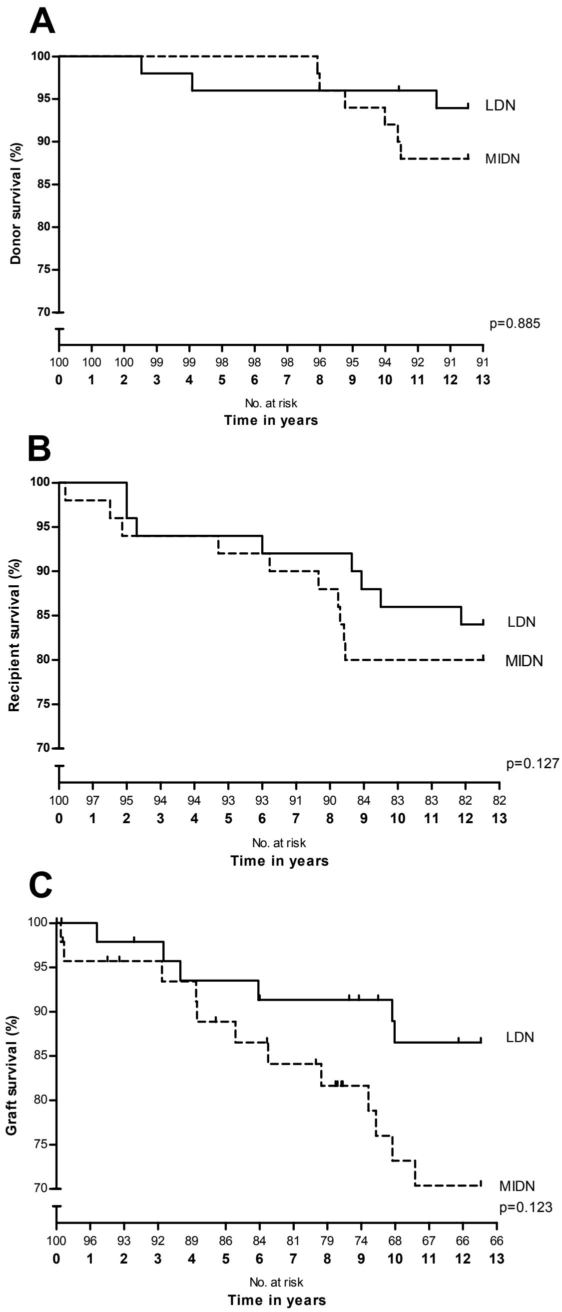

Figure 2. Longest follow-up survival of donor (A), recipient (B) and graft (C), divided between MIDN and LDN. The numbers at risk are shown on the x-axis.

Table 1. Long-term outcomes of donor and recipient. Categorical data are given as numbers (%) and continuous variables as median (range)

	MIDN (N = 46)	LDN (N = 44)	p-value
Donor			
Female (%)	20 (47%)	17 (46%)	0.57
Age (years)	58 (31-85)	59 (23-87)	0.73
eGFR (ml/min)			
Baseline	107.2 (29.3)	113.3 (30.0)	0.39
Follow-up	74.5 (27.2)	79.9 (25.0)	0.45
Hypertension (%)			
Baseline	2 (4%)	5 (10%)	0.44
New onset	14 (30%)	12 (27%)	0.459
BMI (kg/m²)			
Baseline	25.9 (3.5)	26.0 (4.5)	0.481
Follow-up	27.3 (3.8)	27.7 (4.8)	0.414
Recipient			
Ten-year graft survival[1]	71%	86%	0.111
Ten-year recipient survival	73%	87%	0.081

[1]Censored for death

when compared to scores at three to five years follow-up (5). The SF-36 physical functioning development during ten years of follow-up is shown in figure 3a.

On average, donors did not return to baseline during ten-year follow-up at any dimension of the MFI-20. At ten-year follow-up all dimensions of the MFI-20 did not show significant differences between the MIDN and LDN group. Scores on all dimensions of the MFI-20 at ten-year follow-up for both the MIDN and LDN group were not significantly different when compared to scores at three to five years follow-up (5). The MFI-20 physical fatigue development during ten years of follow-up is shown in figure 3b.

Kidney function

The eGFR was not significantly different between both groups at follow-up. As expected the ten-year follow-up measurements in both groups are significantly lower compared to the baseline measurements (p<0.001 for both groups). However, the ten-year follow-up measurements of the eGFR of all donors are not significantly different compared to the one-year measurements, median 76.4 and 76.1 ml/min respectively (p=0.86). The eGFR at follow-up was 70% of prenephrectomy values in the MIDN-group and 71% in the LDN-group. Seventeen donors (18.8%) had an eGFR between 30-60 ml/min. Within this group, eGFR at baseline was significantly lower when compared to donors with a higher eGFR, a median of 60 and 94 ml/min respectively (p<0.001). Also, age at follow-up was

Table 2. Quality of life of minimal invasive open donor nephrectomy (MIDN) versus laparoscopic donor nephrectomy (LDN). Raw data at baseline and 10-year follow-up [mean (SD)]. Estimated adjusted difference of means, 95% confidence intervals and p-values for the dimensions of the SF-36 and MFI-20 scales during 10-year follow-up. Negative differences regarding SF-36 indicate better quality of life following LDN. Positive differences regarding the MFI-20 indicate less fatigue following LDN.

	baseline		10-year follow-up		Estimated difference	95 % Confidence Interval	p-value
Dimension	**MIDN**	**LDN**	**MIDN**	**LDN**	**(MIDN minus LDN)**		
SF-36							
Physical function	90.3 (15.5)	94.8 (9.8)	83.8 (24.2)	88.8 (18.2)	-4.283	-12.8 to 4.2	0.321
Role physical	85.9 (31.8)	96.0 (13.7)	86.4 (31.1)	93.4 (19.0)	-6.132	-17.5 to 5.2	0.288
Bodily pain	94.4 (16.0)	95.5 (10.8)	86.5 (22.3)	89.3 (18.8)	-1.218	-9.7 to 7.3	0.777
General health	84.8 (14.2)	85.5 (13.4)	78.5 (19.4)	78.1 (20.2)	-1.937	-10.9 to 7.0	0.667
Vitality	76.2 (18.1)	83.7 (9.7)	74.5 (18.0)	78.8 (16.4)	-3.576	-10.8 to 3.7	0.331
Social functioning	85.0 (18.7)	95.0 (9.4)	88.9 (19.0)	91.1 (19.3)	-0.612	-8.9 to 7.7	0.884
Role emotional	88.7 (25.3)	91.3 (23.1)	84.7 (32.7)	99.1 (5.4)	-17.368	-28.1 to -6.6	0.002
Mental health	77.6 (15.2)	84.6 (9.8)	82.6 (14.3)	82.9 (14.9)	0.870	-5.1 to 6.9	0.774
MFI-20							
General fatigue	6.6 (3.6)	5.5 (2.0)	8.7 (5.0)	7.7 (4.4)	0.477	-1.4 to 2.3	0.616
Physical fatigue	5.9 (3.1)	5.0 (1.5)	7.8 (4.8)	6.9 (3.5)	0.728	-1.0 to 2.5	0.413
Reduced activities	7.1 (3.4)	6.5 (2.7)	8.1 (4.9)	7.4 (3.4)	0.526	-1.2 to 2.3	0.554
Reduced motivation	6.5 (2.9)	6.0 (2.1)	7.1 (4.0)	7.1 (3.0)	-0.612	-2.0 to 0.8	0.395
Mental fatigue	8.1 (4.6)	6.6 (3.1)	7.4 (4.5)	7.2 (4.0)	-0.357	-2.2 to 1.4	0.693

significantly higher in this group, a median of 75 and 57 years respectively (p<0.001). No significant differences with regard to BMI were observed within this group. After ten years 35 donors (38%) have lost over 6-34%of their eGFR. Within this group, eGFR at follow-up was significantly lower when compared to donors who lost less than the expected five percent of their eGFR, a median of 98.5 and 112.5 ml/min, respectively (p=0.004). None of the donors developed end-stage renal disease (ESRD) or required renal replacement therapy.

Incidence of hypertension

Hypertension preexisted in seven donors (two MIDN; five LDN), who were all treated medically. Twenty-six donors (14 MIDN and 12 LDN, p=0.742) developed high blood pressure after donation, which was adequately treated with medication. Eleven donors were treated with one anti-hypertensive drug, 11 donors with two anti-hypertensive drugs, two donors with three anti-hypertensive drugs, and one donor with four anti-

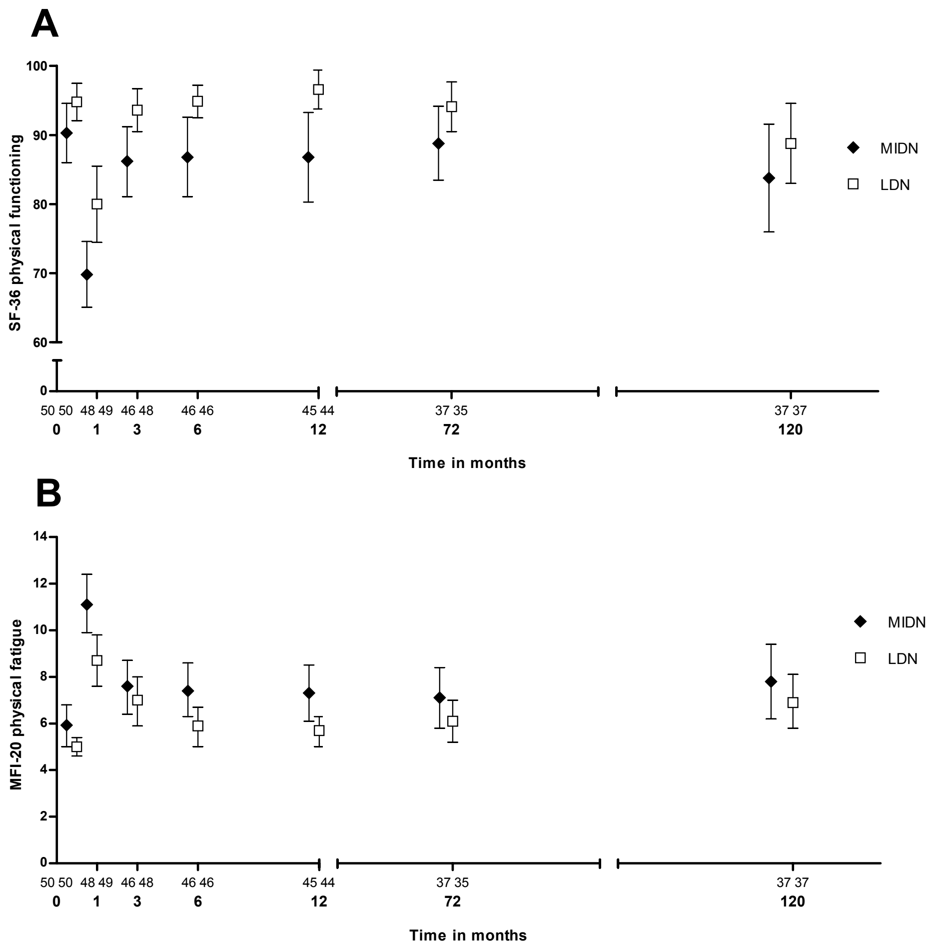

Figure 3. SF-36 physical functioning (A) and MFI-20 physical fatigue (B) development during ten-years of follow-up of randomized live kidney donors. Points indicate mean with 95% confidence interval.

hypertensive drugs. Data was missing in one case. These donors have a median eGFR at follow-up of 73.1 ml/min, the median eGFR in the group of donors without hypertension was 79.9 ml/min (p=0.136). Donors who developed hypertension were significantly older at time of donation when compared with donors who did not develop hypertension, mean age of 55 versus 45 years, respectively (p=0.001). No significant differences with regard to eGFR at baseline or BMI were observed. All seven donors with preexisting hypertension have well regulated hypertension. One donor still has the same medication, two donors received one additional antihypertensive drug, one donor received two additional antihypertensive drugs, and the other three have switched to other antihypertensive drugs. These donors have a median eGFR of 64.4 ml/min.

Body Mass Index

Body Mass Index (BMI) in both groups is significantly higher at follow-up (p-value <0.001). Between-group analysis did not show any significant differences at follow-up.

Recipients

Eighteen recipients died (ten MIDN and eight LDN, p=0.60) during follow-up of which nine had died during the previously reported three to five year follow-up period (5). One recipient (MIDN) died in the eighth year of acute dyspnoea. Six recipients died in the ninth year of follow-up, of which three recipients (two MIDN and one LDN) died of a metastatic cancer and the other three (two MIDN and one LDN) of a septic shock of an underlying infectious disease. Another recipient (LDN) died in the tenth year of follow-up of a cerebral vascular accident. The last death of a recipient (LDN) was in the twelfth year of follow-up of metastasized breast cancer. Ten-year survival for all recipients was 83%. The overall recipient mortality is shown in figure 2b. Between group analysis showed a ten-year survival of 80% in the MIDN group and 86% in the LDN group, respectively (p=0.261).

Additionally, eighteen recipients (twelve MIDN and six LDN, p=0.123) lost their grafts. Two recipients (two MIDN) lost their graft due to acute rejection, eight recipients (five MIDN and three LDN) due to chronic rejection, three recipients (two MIDN and one LDN) due to recurrence of kidney disease, two recipients (one MIDN and one LDN) due to non-compliance, and of three recipients (two MIDN and one LDN) the reason remains unknown. At ten-year follow-up 31 recipients were alive with a working graft in the MIDN group and 37 recipients in the LDN group. Between-group analysis showed a ten-year graft survival of 78% in the MIDN group and 86% in the LDN group respectively (p=0.318). Overall graft survival is shown in figure 2c.

DISCUSSION

This is the first prospective study to present the long-term consequences of live kidney donation on QOL and fatigue. After ten years of follow-up we expected that surgical technique did not influence outcomes. This hypothesis holds, except for the dimension role emotional of the SF-36. The latter is most probably not a true effect of surgery and might be related with the recipient outcome. The LDN group is associated with lower, though not significantly different, recipient mortality and graft loss (14 cases) compared with the MIDN group (22 cases). Rather interesting is the outcome of the whole group. Long-term outcome of live donor nephrectomy is excellent from the perspectives of both donor and recipient. The donor retains good quality of life and sufficient kidney function. The recipient has a good chance of ten-year survival with a functioning graft. We present unique data on a randomized cohort that has prospectively been followed annually after donation. We have included ten years follow-up data on renal function, hypertension, BMI, survival, QOL and fatigue. The response rate was excellent with 80 percent. As the cohort was randomized, baseline characteristics were not expected to significantly differ between groups. On average, live kidney donors have excellent life expectancy, do not have to fear further deterioration of kidney function or an increased risk of hypertension and have a better quality of life than the population. To our knowledge, all other studies have been conducted with a retrospective design. Quality of life has been polled at different times form donation and analyzed without paired control data in particular.

QOL in general was excellent. However, donors do not completely return to their baseline value for most of the dimensions on the SF-36 or MFI-20. The question remains whether this may be considered a general effect of aging, as it has been established that QOL depends on age (8), or that the measured decrease is the result of living with one kidney. Although the latter explanation is unlikely comparison with a matched control group that did not donate a kidney is necessary to provide a definite answer to this question.

The median eGFR ten years after LDN and MIDN was 79.9 and 74.5 respectively. These results are in line with other studies reporting on a mean follow-up of approximately ten years (10-15). Of all donors, 18.8% have an eGFR between 30-60 ml/min, which is a higher percentage compared to a study by El-Agroudy *et al.* of 0.9% (16). However, as baseline eGFR values were higher in the study by El-Agroudy, post-donation values were expected to be higher. Furthermore, the group of donors with an eGFR between 30-60 ml/min comprised significantly older donors and donors with an inferior eGFR at baseline. It has been established that nephrectomy will lead to a compensatory increase in eGFR in the remaining kidney to 70% of prenephrectomy values (17). Donors with low preoperative eGFR before nephrectomy are associated with a low eGFR at follow-up (12-14, 18). Najarian *et al.* showed a significant decline in creatinine clearance of live kidney donors after a mean follow-up of 16 years compared with baseline, however these results did not significantly differ compared to the siblings of these donors (19), Therefore, the observed decrease in eGFR in our study was expected and in accordance with previous reports. As opposed to most other studies we are able to report that eGFR is stable over time at various time points during follow-up. Most other studies did not include this continuous follow-up on eGFR and reported on a single point.

Of all donors, 28.6 % were diagnosed with new onset hypertension. In current literature the hypertension rate among live kidney donors after approximately ten years of follow-up range from 8.8-48.6% (10, 13). Our results are similar to the majority of the existing literature on live kidney donors (12, 14, 16, 20, 21). Vasan *et al.* showed that in their population based study the incidence of new-onset hypertension in their cohort with a mean age of 52 years, was 19% after a follow-up of four years. Also, with age the incidence of hypertension increased, especially in elderly due to the longer exposure time to develop hypertension (22). These findings are similar to other concordant literature on population bases studies, where the incidence of new-onset hypertension range from 20-30% after a follow-up of four years (23-25). Other studies with a longer follow-up up to ten years, showed an incidence of new-onset hypertension of 19-28% (26, 27). These results of non-donors are concordant with our findings. Donors with new onset hypertension have a mean eGFR of 69.8 ml/min, which is relatively good. All donors had well-regulated hypertension.El-Agroudy *et al.* show a better mean eGFR in their hypertensive donors, but this cohort had higher baseline values. BMI of our donors at follow-up was 27.5 (4.3), which is comparable with the current literature (11, 16). In order to assess the incidence of decreased kidney function and hypertension after donation compared to the incidence in the general population, a matched study comparing live kidney donors and healthy non-donors is required.

Of all donors, 9% died within a range of 2-11 years after donation. All donors died of unrelated causes to donation. This percentage is comparable to previously published results and comparable to the mortality rate in the general population (11, 12). Ten-year recipient and graft survival were excellent and comparable to concurrent literature (28, 29). There were no significant differences in graft and recipient survival.

A possible limitation of this study might have been a response bias. Donors who are not satisfied with the results of the procedure are less likely to respond to a survey. However, as response rates were excellent, even higher than the response rate after 3 to 5 years of follow-up (5), and follow-up time and baseline characteristics evenly distributed, it seems unlikely that these limitations have influenced the outcome of this study in a major way. Moreover, this cohort of 100 donors is too small to perform subgroup analyses on elderly donors and donors with minor comorbidity. Larger databases should be generated to conduct these analyses.

In conclusion donor outcomes including QOL and fatigue scores are excellent ten years after live kidney donation. Potential donors should not fear major negative changes at the long-term as kidney function appears stable and hypertension does not seem to occur more frequently. Recipient outcomes are excellent. These results are reassuring for the current practice of live kidney donation.

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Chapter 11 Long-term follow-up after live kidney donation : A matched controlled longitudinal study on renal function and quality of life – LOVE study

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ABSTRACT

The benefits of live donor kidney transplantation, such as pre-emptive transplantation, superior organ quality and increased graft survival are well-known. In light of the extension of donor eligibility criteria, these benefits must be balanced against the potential harm to the donor. Most of the previous studies suggest excellent long-term results and no excess risk of end stage renal disease (ESRD) in donors. However, these studies are lacking sufficient sample size, long-term follow-up, a prospective control group and donors with minor comorbidities. Recently, a study demonstrated an increased long-term risk for ESRD, cardiovascular, and all-cause mortality in live kidney donors. Thus, there is a need to further study the long-term consequences of kidney donation to guarantee the safety for live kidney donors.

The LOVE study is a single center prospective matched cohort study on long-term consequences after live kidney donation regarding kidney function. We will study individuals who have donated their kidneys from 1981 to 2010 in the Erasmus University Medical Center, Rotterdam, the Netherlands. In this time period 1080 individuals have donated their kidneys. All donors will be matched to four controls based on age, sex, ethnicity, BMI and comorbidity in a one to four . Baseline and follow-up data will be collected on kidney function, kidney-related comorbidity, quality of life and psychological outcome in all participants.

This study will provide evidence on the long-term consequences of live kidney donation for the donor.

INTRODUCTION

The benefits of live donor kidney transplantation, such as pre-emptive transplantation, superior organ quality and increased graft survival are well-known [1]. As a result live kidney donation has increased in the last decade [2]. Live donor nephrectomy is performed on healthy individuals who do not benefit directly from the procedure themselves. Consequently, these benefits must be balanced against the potential harm to the donor. Reports have been published on end-stage renal disease (ESRD) after live kidney donation [3, 4]. Due to extension of donor eligibility criteria, co-morbidities such as cardiovascular disease, obesity and higher age are no longer absolute contra-indications for donation [2, 5]. However, all these studies are based on short term follow-up and there is no evidence on follow-ups over 10 years for live kidney donation in general population. Furthermore, the quality of these early studies is marginal [6-10]. Individuals with minor co-morbidities are more often deemed eligible for donation, however, the occurrence of cardiovascular diseases takes years to emerge and might be missed during a short-term follow-up. Therefore evidence on long-term outcome is essential.

In 2011 Ibrahim *et al.* published a retrospective study on the long-term follow-up of 255 donors [11]. They demonstrated excellent long-term results and no excess risk of ESRD in donors. However, the study included a very small proportion of the total population of screened kidney donors. Their control group is matched for age, sex, ethnicity and BMI, but it is unclear how these controls were selected and if they were prospectively followed. Fournier *et al.* surveyed the largest and oldest population of 204 living kidney donors and found them to have a similar life span and kidney function to that of the general population [12]. A Swedish study supported these conclusions, however they did find that an increased proportion of the population developed hypertension and proteinuria [13]. A Norwegian study surpasses these results. Mjøen *et al.* compared their healthy donor population of 1901 donors with a median follow-up time of 24.9 years with a control group of potentially eligible donors based on their medical history. They concluded that live kidney donors have an increased long-term risk for ESRD, cardiovascular, and all-cause mortality [14]. The published evidence on the long-term consequences show contradicting results. Also, all these studies focus on healthy donors and fail to address the long-term effects of donation on donors with comorbidities.

Quality of life is a parameter that has been extensively studied in live kidney donors [15-17]. However, most studies that address this issue have been designed retrospectively. In this setting a baseline comparison is not possible, nor is it possible to adjust for time effects as donors do not receive the questionnaires at set time-points after donation. Unlike traditional measures of recovery, such as hospital stay and return to work, quality of life scores measure what donors experience themselves [18]. Quality of life scores after life kidney donation, in both the general and elderly population, are high [19, 20]. Nevertheless, reports on quality of life in donors with minor comorbidities and on the long-term are scarce.

Long term psychological outcomes after live kidney donation among donors are underexposed. Current published studies focus mainly on quality of life [21]. However, this is just a single aspect of the psychological well-being. An interesting question is to which extent the donation has had a positive effect on the psychological well-being of the donor. A limitation of previous studies is the lack of a representative control group due to donors usually being healthier compared to the normal population. Therefore a study among the donors and a suitable matched control group would be the design of choice.

Live kidney donation has been proven to be a safe and reliable procedure, with excellent outcome during 10 year follow up. The extending criteria for donation and the marginal quality of long-term follow-up studies have provided us with an gap in our current knowledge. Determining the long-term effects of physical and psychological well-being after live kidney donation is an essential part of further developing and expanding the live kidney donation program.

METHODS/DESIGN

Study objective

To determine the long term consequences of live kidney donation primarily regarding kidney function, and secondarily regarding survival, hypertension, diabetes mellitus, fatal and non-fatal cardiovascular events, quality of life and psychological well-being.

Hypothesis

Live kidney donation has no negative long-term consequences for the donor regarding kidney function, survival, hypertension, diabetes mellitus, fatal and non-fatal cardiovascular events, quality of life and psychological well-being when compared to an appropriate reference group.

Study questions

Primary question: Live kidney donation has no negative long term consequences for the donor regarding kidney function as compared to a representative control group.
Secondary question: Live kidney donation has no negative long term consequences for the donor regarding kidney related morbidity such as hypertension and diabetes.

Other secondary endpoints are: survival, blood pressure, incidence of fatal and non-fatal cardiovascular diseases, size of the remaining kidney, serum glucose, urine analysis on protein/creatinine ratio, microalbuminuria glucose and creatinine, quality of life and psychological well-being.

Study design

The LOVE study is a matched-controlled longitudinal study. The study started on August 19th 2013 and the duration of completing all follow up will be approximately three years. Approval of the Medical Ethical Committee has been obtained. Baseline characteristics on kidney function, BMI, pre-existing co-morbidity and medication of all donors will be checked and updated in accordance with the hospital's electronic patient system. Donors are invited by mail to come to the outpatient clinic for an extensive follow up appointment. Non-responders will be contacted again and non-participants will be asked to fill out and send back the questionnaire on their medical history as to analyze a potential selection bias. To strengthen our results, we aim for a response rate of 70% or higher.

Controls will be selected from the Rotterdam Study [22] and Study of Health In Pomerania (SHIP) [23] and matched for age, gender, BMI, ethnicity and pre-existing co-morbidity. A one on four match is our goal, however if the available data in the control group is insufficient, this will have to be revised downwards.

Kidney donors

All donors who donated their kidney between 1981 and 2010 at the department of surgery, Erasmus Medical Center, Rotterdam, the Netherlands or who participated in a cross-over program but had their full work-up here prior to the donation, will be eligible to be included in this study. All donors have preoperatively been screened by a nephrologist and surgeon, and underwent imaging by angiography, MRI or CT-scan. Data on prior medical history, medication use, BMI, blood and urine analysis regarding kidney function, and quality of life have been prospectively recorded. Since 1981, all live kidney donors have been entered into a database and are prospectively followed. Up to 2011, this database comprises 1080 live kidney donors. Data on baseline characteristics and perioperative factors have been gathered. In 2001, two randomized controlled trials on surgical techniques concerning live donors have been implemented and successfully completed at our center [24, 25]. Furthermore, two prospective cohort studies sampled from this population have taken place [26, 27]. Donors included in these trials have filled out questionnaires on quality of life pre-operatively and at set times after the procedure, using the SF-36 questionnaire and EuroQoL questionnaire. These are validated questionnaires for measuring health-related quality of life [28, 29].

Healthy individuals

Healthy individuals will be selected from the SHIP study and the Rotterdam Study cohort studies to cover the whole age range of the donors.

Donors aged 44 and younger will be matched with the SHIP study. This population-based cohort study was initiated in 1996 among inhabitants of West Pomerania in the northeast of Germany. Two main objectives were first, to assess prevalence and incidence of common risk factors, subclinical disorders and clinical diseases, and second to investigate the complex associations among these. Data on kidney function, blood pressure, BMI, medication, incidence of cardiovascular disease and diabetes, psychological well-being and quality of life have prospectively been recorded. The SHIP study comprises two cohorts aged 20-70 years. In our matched study, the first cohort will be used due to the longer follow-up. Multiple follow-up examinations of this first cohort were conducted between 1997 and 2012. In total, the first cohort consists of 4,310 subjects.

Donors aged 45 and over will be matched with The Rotterdam study. This prospective cohort study started in 1990 in the city of Rotterdam, the Netherlands. The study targets cardiovascular, endocrine, hepatic, neurological, ophthalmic, psychiatric and respiratory diseases. As of 2008, 14,926 subjects aged 45 years or over comprise the Rotterdam study. Data such as hypertension, serum creatinine, serum eGFR, cardiac events, survival, diabetes quality of life and psychological well-being have prospectively been recorded. The Rotterdam study comprises three different cohorts. We will use the second and the third cohort as controls. Multiple follow-up examinations of these two cohorts were conducted between 2000 and 2012. In total both cohorts consists of 6,943 subjects. Given the size of both studies, sufficient data on all study parameters will be available in our reference group.

Outcome measures

During the visit to the outpatient clinic the official consent form will be signed by the donor and study coordinator. During this visit the following parameters will be obtained.

Primary outcome: Kidney function in serum creatinine and eGFR (calculated with the MDRD and CKD-EPI formula).

Secondary outcome: Diastolic and systolic blood pressure as measured by datascope, incidence of hypertension and incidence of diabetes (checked and updated with questionnaire on medical history and hospital's electronic patient system). Other secondary endpoints: survival (checked and updated in accordance with the municipal administration), incidence of fatal and non-fatal cardiovascular diseases (checked and updated with questionnaire on medical history and hospital's electronic patient system), length, width and height of the remaining kidney by ultrasound (measured by an experienced ultrasonographer), serum glucose, urine analysis on protein/creatinine ratio, microalbuminuria, glucose and creatinine, quality of life (measured by EuroQoL and SF-12, that can be subtracted from any SF-36) and psychological well-being (for donors aged 45 years and higher with Hospital Anxiety and Depression Scale (HADS) [30], Center for Epidemiologic Studies Depression Scale (CESD) [31], Pittsburgh Sleep Quality Index (PSQI) [32], Questionnaires on Happiness and Life Satisfaction, and donors aged 44 years and lower with Beck Depression Inventory (BDI) [33]).

Evaluation of participating live kidney donors

During their follow up visit, blood and urine analysis will be done and donors will undergo two interviews regarding quality of life and their psychological wellbeing. Furthermore, an ultrasound of their remaining kidney will be performed. Participating donors will be reimbursed for their travel costs.

Unexpected outcomes

Unexpected outcomes will be reported to both the donor and the treating nephrologist, who will initiate subsequent examinations and treatment if needed. The general practitioner and any other treating specialist(s) will receive notice if needed.

Access to personal data

All personal data are coded into numbers. The coordinating investigator and the principal investigator are the only ones who have access to the coding system. All data are imported in a database, which is managed by the coordinating investigator. At the end of the study all data are analyzed together with the trial statistician.

DISCUSSION

High quality studies on long-term outcome after live kidney donation are not very common. Previous studies have suggested that live kidney donors have a normal life span, good health status and an excellent quality of life, no excess risk of ESRD and no consequences regarding diastolic and systolic tension and proteinuria [6, 7, 11-13]. However, these results have to be questioned due to the inferior methodological design of these studies. The majority of these studies are retrospective in design, have low sample sizes, no baseline data and lack an adequate control group. As donors are a highly selected healthy population, comparison to the general population might lead to an overestimation of long-term results. For this reason, a prospective study on long-term outcome, including baseline data and a representative control group, is the design of choice, as was suggested by one of the authors of these studies [10].

In the design of our study we tried to adhere to suggestions of previous studies. The current design of our study forces us to use two different control groups, as no single epidemiological study incorporating elderly individuals provided in the correct set of parameters. Nevertheless, this design will facilitate matching on age, sex, BMI, ethnicity and comorbidity in a one to four proportion. Previous studies in our center in the same population have always resulted in a high response rate [34, 35]. Although a selection bias can never be precluded, analysis of the non-responding group should provide us with a suggestion. All data of donors and healthy individuals are collected on baseline and prospectively during all follow-up moments. Our study population comprises numerous elderly donors and donors with minor co-morbidity. As this is a group that is generally underexposed in current literature, this study should clarify the ambiguities concerning the long-term results in this group.

With this study we have tried to overcome any limitation of previous studies. We aim to assess the long-term consequences of live kidney donation. This study will compare donors with a matched group of healthy individuals, regarding kidney function, kidney-related comorbidity, quality of life en psychological outcome.

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Chapter 12 Summary in English and Dutch

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SUMMARY

Chapter one provides the reader with an overview of developments in the field of live kidney donation. The necessity of live kidney donation is explained by the continuous demand for donor kidneys. This demand has led to the introduction of live kidney donation in the1980's and, subsequently, to innovation of techniques and an ethical discussion on the acceptance of live kidney donation. The clear advantages of live kidney donation as compared to post-mortal transplantation, including increased graft survival, pre-emptive transplantation and better access to transplantation, are outlined in this chapter. The continuous demand for donor kidneys and improvement of surgical techniques has also justified the extension criteria for donor selection. This has led to the inclusion of elderly and obese donors that would not have been selected in the past. As donors are healthy individuals who have no medical indication for nephrectomy, it is of paramount importance that all aspects of the procedure, *i.e.* the surgical technique, the post-operative outcome and follow-up, are optimized and extensively studied. Elderly and obese donors represent a cohort that is underexposed in current literature. This thesis aimed to study all factors that influence donor outcome. It provides health-care professionals with perspectives to approach live donor nephrectomy in an individualized fashion and gives insight in the opportunities and limitations of the living kidney program for those considering kidney donation.

Chapter two describes the surgical techniques currently used in Europe. Transplant centers do vary in the preference for different surgical techniques. Although there is evidence for the superiority of minimally invasive techniques, there are centers still performing open donor nephrectomy. We polled 119 centers in 12 different European countries of which 82% replied. The questionnaire consisted of questions on the number of donors, the acceptance of donors with comorbidities and the applied surgical techniques. The results of the questionnaire were compared with a previous survey of our group, conducted by Kok *et al* in 2004 (1). Thirty-two percent of the responding centers still performed a variation of open donor nephrectomy. The number of centers exclusively applying endoscopic technique increased from 45% in 2004 to 61% in 2009. In contrast with current knowledge, the argument most frequently mentioned for pursuing an open approach was lack of evidence for the superiority of endoscopic techniques.

In **chapter three** the results of a randomized controlled trial comparing left-sided standard laparoscopic donor nephrectomy (LDN) with hand-assisted retroperitoneoscopic donor nephrectomy (HARP). As HARP theoretically combines the control and speed of hand-guided surgery with the benefits of an endoscopic technique and retroperitoneal access, it was hypothesized that HARP would be safer and result in comparable quality

of life (QOL). In total, 190 left-sided donor nephrectomies were performed in two Dutch tertiary referral centers and follow-up during one year. Among other study parameters were skin-to-skin time, warm ischemia time (WIT), complications, QOL, return to work and costs. HARP did indeed result in a comparable QOL, a reduced skin-to-skin time and WIT. Furthermore, a significant reduction of intra/operative complications was observed. No significant differences were observed regarding pain, morphine requirement, length of stay and postoperative complications. One-year recipient and graft survival were comparable between groups. Therefore we recommend HARP as the preferred technique for left-sided donor nephrectomy.

As the results of right-sided laparoscopic donor nephrectomy were superior in our center, we decided to separately study the effect of HARP on right-sided donor nephrectomy. In **chapter four** we present the result of a randomized controlled pilot study. In this study, forty donors were randomly assigned to either LDN or HARP. Primary outcome was skin-to-skin time and secondary outcomes included QOL, complications, pain, morphine requirement, blood loss, WIT and hospital stay. Follow-up time was one year. No significant differences were observed in skin-to-skin time, QOL, complication rate, pain and hospital stay. HARP did result in a significantly shorter WIT and increased blood loss. We concluded that right-sided HARP is feasible but does not confer clear benefits over standard right-sided LDN. Further studies should evaluate the value of HARP in obese donors and in centers trying to initiate an endoscopic program.

In **chapter five** we discuss the learning curves of both HARP and LDN. Any new surgical procedure is subject to learning curve, *i.e.* to the number of procedures that have to be performed to acquire an adequate level of competency. As the advantages of hand-assistance have been proven to be even greater in laparoscopic novices, HARP may even prove to be more valuable in centers initiating an endoscopic live donor nephrectomy program. We prospectively collected data on live donor nephrectomies in one expert center and one center initiating an endoscopic program. The results of this study demonstrated that LDN and HARP are both techniques that can be safely performed when adequately adopted. HARP appears to efficiently reduce operation times, blood loss, warm ischemia times and visceral injuries at the beginning of the learning curve. Thus, HARP provides centers initiating an endoscopic live kidney donation program with a safe way to negotiate their learning curve, even when little prior endoscopic experience is present.

The costs and cost-effectiveness of both HARP and LDN are discussed in **chapter six**. When several concurrent techniques are available, and these techniques are comparable in terms of patient-related outcome, policy-makers and healthcare professionals are forced to make decisions. In these cases costs and cost-effectiveness play an increasingly important role in the evaluation of interventions. For this reason we performed an extensive costs and cost-effectiveness analysis. We included both direct and indirect treatment costs. Our analysis demonstrated no differences between HARP and LDN, absolute costs and quality adjusted life-years are similar for both techniques. We concluded that other factors, such as safety, ischemia time and QOL, should determine the choice between HARP and LDN.

Chapter seven describes the incision-related outcome after both LDN and mini-incision donor nephrectomy (MIDN). As little is known on the prevalence of incisional hernias, cosmesis and body image, a survey was conducted among live kidney donors. The prevalence of incisional hernias was very low and comparable to other reports on this subject. Independent risk factors for the development of an incisional hernia were a surgical site infection and steroid use. These factors have been associated with the development of incisional hernias before. Body image and cosmesis scores were excellent. Elderly donors had significantly higher cosmesis scores when compared with young donors. This might imply that elderly donors are less concerned with bodily appearances. Incision-related outcome should pose no barrier to live donor nephrectomy.

The donor selection criteria have extended in the last decade, leading to an increase of donors with comorbidities and elderly donors. Donor safety and recipient and graft survival have proven to be comparable with that of younger individuals. Nevertheless, little is known on QOL in elderly donors. In **chapter eight** we describe the results of a prospective study comparing QOL in 135 elderly donors with 366 younger donors. Elderly donors had better postoperative QOL scores and they returned to their baseline faster than young donors. Furthermore, elderly donors experienced significantly less pain during the first days after the procedure. The results of this study demonstrate no disincentives regarding QOL. Thus, elderly donors can be safely included in live donation programs in high volume centers with sufficient expertise.

Although QOL after live kidney donation is excellent in general, there are some reports on psychological distress or negative emotions after donation. Identification of factors associated with minor outcome would improve information to the donor, donor selection and convalescence. In **chapter nine** we present the results of a multivariate analysis designed to identify these factors. Factors associated with a change in health-related QOL one year after donation are body mass index (BMI), gender, age, recipient and graft survival. Large negative but mainly reversible effects only take place in the first month after donation; the long-term effects remain to be established. The effects measured are small, nevertheless they are clinically relevant. These factors should be taken into account during donor selection.

In **chapter ten** we discuss the results of a long-term follow-up study regarding fatigue and quality of life after both LDN and MIDN. We previously reported results three to five years after donation of a randomized trial comparing MIDN and LDN. Both approaches resulted in similar fatigue and QOL, except for physical function which is significantly better after LDN. Ten years after donation we re-evaluated the same parameters in the same cohort. The results of this study showed no difference in QOL between groups, except for role emotional. This between groups difference is hard to explain and most likely result of serendipity. More interestingly, quality of life scores have declined a decade after donation which may be expected as an effect of age. Estimated glomerular filtration rates did not decline on average. Furthermore, there were no significant differences in fatigue, new-onset hypertension, recipient survival and graft survival. These data demonstrate good long-term outcome after both MIDN an LDN and once more emphasize the long-term safety of live kidney donation.

The last chapter of this thesis, **chapter eleven**, provides the reader with the protocol for the LOVE-study. In this study we aim to assess the long-term consequences of live kidney donation, *i.e.* kidney function, hypertension, diabetes mellitus, QOL etc. As live kidney donors are a highly selected cohort, they should be compared with equally healthy individuals that have not donated. Controls will be selected from two different prospective cohort studies. Donors and controls will be matched for age, sex, body mass index, ethnicity and co-morbidity in a one on four fashion. The LOVE-trial has already initiated and the outcome will add new insight in the long term effects of live kidney donation

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SAMENVATTING

In **hoofdstuk één** wordt een overzicht gegeven van de ontwikkelingen op het gebied van nierdonatie bij leven. Vanwege de toenemende vraag naar donornieren ontstond er in de jaren tachtig hernieuwde interesse naar nierdonatie bij leven. Het gevolg hiervan was niet alleen dat de chirurgische technieken zich verder hebben ontwikkeld maar ook dat de ethische discussie rond nierdonatie bij leven nieuw leven werd ingeblazen. Nierdonatie bij leven heeft, vergeleken met postmortale donatie, enkele grote voordelen. De belangrijkste voordelen worden in dit hoofdstuk omschreven, zoals betere toegang tot transplantatie, langere overleving van de getransplanteerde nier en de mogelijkheid tot pre-emptief transplanteren. Levende nierdonoren zijn gezonde individuen die geen medische indicatie hebben voor een nefrectomie. Alle stappen in het proces verdienen optimale aandacht om de risico's op niet-gewenste effecten voor de donor zo klein mogelijk te maken. Dit betekent dat voorbereiding, chirurgische techniek, postoperatieve zorg en follow-up goed gedocumenteerd en onderzocht moeten worden.

Een ander gevolg van de toenemende vraag naar donornieren en de verbetering van de chirurgische technieken is verruiming van de inclusiecriteria. Dit heeft geleid tot de inclusie van oudere en dikkere donoren die in het verleden niet geschikt zouden worden bevonden voor het afstaan van een donornier. Deze groep donoren krijgt niet de aandacht die het verdient in de huidige literatuur. Het doel van dit proefschrift is om alle bekende factoren te onderzoeken die donorgerelateerde uitkomst beïnvloeden. We trachten medische professionals te voorzien van handvatten om nierdonatie bij leven zo 'tailor made' mogelijk te benaderen. Verder benadrukken we de mogelijkheden en beperkingen van nierdonatie bij leven.

Hoofdstuk twee geeft een overzicht van de chirurgische technieken die momenteel in Europa worden gebruikt. Transplantatiechirurgen in verschillende centra hebben een voorkeur voor uiteenlopende chirurgische technieken. Hoewel er bewijs is voor de superioriteit van minimaal invasieve technieken, zijn er nog steeds centra die open technieken gebruiken. Om dit nader te onderzoeken ontvingen 119 transplantatiecentra in 12 verschillende Europese landen een vragenlijst. De respons bedroeg 82 procent. De vragenlijst bevatte vragen over het aantal ingrepen, het accepteren van donoren met comorbiditeit en de toegepaste chirurgische techniek. De resultaten van deze vragenlijst werden vergeleken met de resultaten van een overeenkomstig onderzoek uit 2004 door Kok *et al.* (1). Het blijkt dat 32% van de aangeschreven centra nog steeds een open techniek gebruikt. Het aantal centra dat alleen een endoscopische techniek toepast is toegenomen van 45% in 2004 naar 61% in 2009. Ondanks de huidige kennis is de meest gerapporteerde reden om een open techniek te gebruiken gebrek aan bewijs voor de superioriteit van endoscopische technieken.

De resultaten van een gerandomiseerd onderzoek, waarbij linkszijdige laparoscopische donor nefrectomie (LDN) wordt vergeleken met handgeassisteerde retroperitoneoscopische donor nefrectomie (HARP), worden gepresenteerd in **hoofdstuk drie**. Theoretisch biedt HARP de controle en snelheid van open chirurgie, terwijl de voordelen van retroperitoneale toegang en minimale invasiviteit behouden blijven. Derhalve veronderstelden wij dat HARP zou leiden tot een veiligere ingreep en een vergelijkbare kwaliteit van leven (QOL). Er werden in totaal 190 linkszijdige donor nefrectomieën verricht in twee academische ziekenhuizen, de follow-up bedroeg één jaar. De duur van de ingreep, warme ischemie tijd (WIT), complicaties, QOL, arbeidsongeschiktheidsduur en kosten waren factoren die werden onderzocht. HARP leidde inderdaad tot een vergelijkbare QOL, een verminderde operatieduur en WIT. Er werd een significante vermindering van intraoperatieve complicaties geobserveerd. Wat betreft pijn, morfinebehoefte, opnameduur en postoperatieve complicaties werden er geen significante verschillen gevonden. De één-jaars overleving van zowel de ontvanger als van de getransplanteerde nier was vergelijkbaar voor beide groepen. Aan de hand van deze resultaten concludeerden wij dat HARP de voorkeur heeft bij linkszijdige donor nefrectomie.

Omdat de uitkomsten van rechtszijdige donornefrectomieën beter waren dan linkszijdige, werd besloten om de resultaten van HARP voor de rechterzijde separaat te onderzoeken. In **hoofdstuk vier** worden de resultaten van een gerandomiseerde pilot studie uiteengezet. In dit onderzoek worden de resultaten van LDN en HARP onderzocht in 40 gerandomiseerde donoren. De primaire uitkomstmaat was operatieduur en de secundaire uitkomstmaten waren QOL, complicaties, pijn, morfinebehoefte, bloedverlies, WIT en opnameduur. De follow-up tijd bedroeg één jaar. Significante verschillen werden niet gevonden wat betreft operatieduur, QOL, complicaties, pijn en opnameduur. HARP resulteerde wel in een significant kortere WIT en significant meer bloedverlies. Uit de resultaten concluderen we dat rechtszijdige HARP zeker haalbaar is, maar geen duidelijk voordeel biedt ten opzichte van LDN. De waarde van HARP bij obese donoren en in centra die een endoscopisch nierdonatie programma starten dient te worden vastgesteld in toekomstig onderzoek.

In **hoofdstuk vijf** worden de leercurves van zowel HARP als LDN geanalyseerd en besproken. Elke nieuwe chirurgische techniek is onderhevig aan een bepaalde leercurve. Dat wil zeggen dat er een aantal procedures dient te worden uitgevoerd om de procedure adequaat te kunnen verrichten. Aangezien er aanwijzingen zijn dat de meerwaarde van handgeassisteerd opereren nog groter is voor beginners in de laparoscopie, zou HARP extra waarde kunnen bieden in centra waar een endoscopisch nierdonatie bij leven programma wordt opgestart. De gegevens van één centrum met een hoog niveau van expertise en één beginnend centrum werden verzameld. Uit analyse van deze gegevens bleek dat zowel LDN als HARP veilig kunnen worden uitgevoerd wanneer de leercurve is doorlopen. HARP resulteert in een vermindering van operatieduur, WIT, bloedverlies en het aantal iatrogene viscerale letsels aan het begin van de leercurve. Op deze manier kan HARP bijdragen aan het veilig doorlopen van de leercurve in centra die een endoscopisch nierdonatie bij leven programma proberen op te zetten, zelfs wanneer er weinig algemene endoscopische ervaring is.

Kosten en kosteneffectiviteit van zowel HARP als LDN zijn onderwerp van discussie in **hoofdstuk zes**. Wanneer meerdere technieken beschikbaar zijn, en deze technieken vergelijkbaar zijn wat betreft patiëntgerelateerde uitkomsten, moeten medische professionals een keuze maken. In deze gevallen spelen kosten en kosteneffectiviteit tegenwoordig een steeds grotere rol. Om deze reden evalueerden wij de kosten en kosteneffectiviteit van zowel HARP als LDN. Voor een zo volledig mogelijke analyse werden zowel directe als indirecte kosten geanalyseerd. Uit de resultaten blijkt dat er geen verschillen zijn tussen HARP en LDN wat betreft kosten en zogenaamde quality-adjusted life years. Derhalve dienen andere factoren, zoals veiligheid, WIT en QOL doorslaggevend te zijn bij het kiezen voor HARP of LDN.

In **hoofdstuk zeven** worden de verschillen in incisie-gerelateerde uitkomsten tussen LDN en mini-incisie donor nefrectomie (MIDN) beschreven. Omdat er zeer weinig bekend is over de prevalentie van littekenbreuken, cosmetiek en het lichaamsbeeld na donatie werd er een enquête gehouden onder levende nierdonoren. De prevalentie van littekenbreuken was erg laag en vergelijkbaar met ander onderzoek naar dit onderwerp. Onafhankelijke risicofactoren voor het ontwikkelen van een littekenbreuk zijn het gebruik van corticosteroïden en het doormaken van een wondinfectie. Ook deze factoren zijn eerder beschreven binnen deze context. Scores wat betreft cosmetiek en het eigen lichaamsbeeld zijn uitstekend na donor nefrectomie. Oudere donoren scoren significant hoger dan jongere donoren waar het gaat om cosmetiek. Een mogelijke verklaring zou zijn dat oudere donoren de cosmetieke uitkomst minder belangrijk vinden.

De verruiming van de selectiecriteria voor nierdonatie bij leven heeft geleid tot de inclusie van oudere donoren en van donoren met comorbiditeit. Zowel de veiligheid van de donoren als de overleving van de getransplanteerde nier is vergelijkbaar tussen oudere en jonge donoren. Er is weinig bekend over QOL van oudere donoren. In **hoofdstuk acht** worden de resultaten van een prospectieve studie beschreven waarin de QOL van135 oudere donoren wordt vergeleken met die van 366 jonge donoren. Oudere donoren hebben betere QOL scores postoperatief en bij oudere donoren wordt het pre-operatieve niveau eerder bereikt dan bij jongere donoren. Opvallend is dat oudere donoren minder pijn ervaren in de eerste dagen na de ingreep. De resultaten van deze studie demonstreren dat QOL geen belemmering hoeft te vormen in de selectie van oudere donoren.

Hoewel QOL na nierdonatie over het algemeen als uitstekend wordt beschouwd, is er een aantal publicaties verschenen waarin neerslachtigheid en andere negatieve emoties na donatie worden gesuggereerd. Door identificatie van factoren die QOL op negatieve wijze beïnvloeden, kunnen donoren beter geïnformeerd worden en kan de selectie van donoren evenals hun herstel geoptimaliseerd worden. In **hoofdstuk negen** worden de resultaten van een multivariate analyse gepresenteerd waarmee wij trachten deze factoren te identificeren. Één jaar na donatie lijken body mass index (BMI), geslacht, leeftijd en het overleven van zowel de getransplanteerde nier als de ontvanger van invloed te zijn op QOL. De grotere negatieve effecten op QOL vinden vooral plaats in de eerste maanden na donatie, maar zijn alle reversibel. Voor een uitspraak over de lange-termijn effecten is aanvullend onderzoek nodig. Ondanks dat de gemeten effecten over het algemeen klein zijn, zijn deze wel klinisch relevant. Derhalve dienen de voornoemde factoren overwogen te worden bij het selecteren van donoren.

In **hoofdstuk tien** worden de lange-termijn resultaten wat betreft vermoeidheid en QOL na LDN en MIDN besproken. Eerder publiceerde onze groep over de 3-5 jaar resultaten na een gerandomiseerde studie over LDN en MIDN. Uit dat onderzoek bleek dat QOL en vermoeidheid vergelijkbaar waren in beide groepen. Dit ging niet op voor de dimensie 'physical function', deze was significant beter na LDN. In het huidige onderzoek, tien jaar na donatie, werden exact dezelfde parameters meegenomen. Dit onderzoek liet geen verschillen in QOL zien, behalve op de dimensie 'role emotional'. Dit verschil tussen de twee groepen laat zich moeilijk verklaren en berust waarschijnlijk op serendipiteit. De resultaten van deze studie laten wel zien dat QOL afneemt over een decennium, zoals verwacht zou kunnen worden bij het toenemen van de leeftijd. De gemiddelde nierfunctie veranderde daarentegen niet. Er werden verder ook geen significante verschillen gevonden met betrekking tot vermoeidheid, de incidentie van hypertensie en het overleven van de getransplanteerde nier en de ontvanger. Deze studie laat goede lange-termijn resultaten zien na MIDN en LDN en onderstreept de veiligheid van nierdonatie bij leven, ook op de lange-termijn.

In **hoofdstuk elf** van dit proefschrift presenteren wij het protocol van de LOVE-studie. Het doel van deze studie is om de lange-termijn consequenties van nierdonatie bij leven te onderzoeken. Onderzochte parameters in deze studie zijn onder andere nierfunctie, hypertensie, diabetes mellitus, QOL etc. Omdat levende nierdonoren vaak zeer gezonde individuen zijn, dienen zij vergeleken te worden met een vergelijkbaar gezond individu dat niet heeft gedoneerd. Onze controlegroep in deze studie is samengesteld uit twee verschillende prospectieve cohort studies. De donoren en de controles zullen één op vier worden gematcht wat betreft leeftijd, geslacht, BMI, etniciteit en comorbiditeit. De LOVE-studie is gestart en we verwachten dat de uitkomsten van deze studie ons extra inzicht zullen verschaffen in de resultaten na nierdonatie bij leven op lange termijn.

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Chapter 13 General discussion recommendations and future perspectives

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The enduring demand for kidney transplants has led to a renewed interest in live kidney donation. As there is no medical indication for the nephrectomy, donor safety is considered of paramount importance. All different aspects of live kidney donation have been extensively studied in the last decade, resulting in a refined technique. All gathered knowledge should result in an individualized approach, thus tailoring the entire procedure to the needs of the treating physician, society and especially the donor.

SURGICAL TECHNIQUES

The superiority of endoscopic donor nephrectomy over open techniques has been established. The results in our survey demonstrate an increase in minimally invasive donor nephrectomy in Northern and Western Europe. Nevertheless, open donor nephrectomy (ODN) is still common practice across Europe and the reason most mentioned for sticking to ODN was lack of evidence that laparoscopic donor nephrectomy (LDN) is better. In our opinion the evidence for the superiority of endoscopic techniques is based on solid research and transplant centers should be encouraged to adopt these minimally invasive techniques by guidelines and training programs. Several European transplant centers do not perform more than 25 procedures annually and a large proportion of these centers has not yet adopted a minimally invasive technique. Furthermore, self-locking clips are still being used to gain arterial control, this despite a nationwide recall after hemorrhagic deaths due to failing clips. The use of these clips should be discouraged as they may lead to fatal bleeding. Considering these issues one may plea for centralization of live donor nephrectomy to improve the quality of the living donation programs and to guarantee the safety of donors.

LDN is considered a very safe but complex procedure. As with any laparoscopic procedure, the risk of iatrogenic visceral injury is present. The so called 'hilar phase' is recognized as the most complex part of the procedure. Gaining control and length of all blood vessels while preventing hemorrhage requires experience. Furthermore, extraction of the graft during LDN may sometimes be troublesome, resulting in increased warm ischemia time (WIT). A retroperitoneal approach theoretically reduces the risk of visceral injury. Hand-assistance helps to distinguish anatomical structures and may facilitate easy control in case of a major bleed. Also, faster extraction of the graft is possible by manually retracting the graft through the Gelport. As hand-assisted retroperitoneoscopic donor nephrectomy (HARP) may combine these advantages, we assessed the value of HARP in a randomized fashion for both right end left-sided donor nephrectomy.

For left-sided donor nephrectomy we observed no significant differences in the number of intra- and postoperative complication rate between the laparoscopic approach and the HARP-technique. However, the complications occurring in the LDN group were more serious, as measured by the validated Clavien-Dindo classification system. Skin-to-skin time and WIT were significantly reduced when performing HARP. With regard to QOL, no significant differences were observed between groups. Therefore, we advocate HARP for left-sided donor nephrectomy. Future studies should identify which donors, such as obese donors or donors with comorbidities, specifically benefit from this technique. For right-sided donor nephrectomy only WIT was significantly reduced when performing HARP. No significant differences were observed for complication rate, skin-to-skin time and quality of life (QOL). Although right-sided HARP confers no clear benefits over right-sided LDN, we consider it a valuable addition to the surgical armamentarium. Especially in obese donors, where intra-abdominal fat may impede dissection, HARP may prove of additional value.

HARP appears to efficiently reduce operation times, blood loss, warm ischemia times and visceral injuries in centers and surgeons initiating an endoscopic live kidney donation program. This appears to be the case in both right- and left-sided donor nephrectomy. We tried to assess the learning curve in both a center initiating an endoscopic program and a center with abundant experience in LDN. Our analyses demonstrated that the advantages of HARP appear to be of minor significance in centers experienced in endoscopic donor nephrectomy. Nevertheless, as HARP does help surgeons to safely overcome their learning curve, right-sided HARP may indeed be a valuable addition to the surgical armamentarium.

POST-OPERATIVE OUTCOME

With the availability of several techniques to conduct a nephrectomy for living donation, policy makers and health-care professionals are forced to make choices for the approach to be preferred. Primarily, this choice should be based on patient safety. With little differences in patient safety, other factors such as QOL, cost-effectiveness and cosmesis have to be taken into account in making a decision. Outcome measurements as defined by costs and cost-effectiveness play an increasingly important role in the evaluation of interventions. Both LDN and HARP appear to be economically comparable techniques, both in absolute costs as well as quality-adjusted life years. Hence, cost and cost-effectiveness are not discriminating both approaches and cannot play a decisive role in choosing between HARP and LDN.

Little is known about the incision-related outcome after live donor nephrectomy. Donor satisfaction is usually discussed with regard to graft and recipient survival. Nonetheless, body image and cosmesis may be important factors when assessing donor satisfaction. Incisional hernias are a common surgical problem that may result in significant morbidity and a re-intervention to correct an incisional hernia results in extra costs and decrease in QOL. Our study demonstrated no difference in prevalence of incisional hernias between LDN and mini-incision donor nephrectomy (MIDN). A multivariate analysis revealed that risk factors associated with the development of an incisional hernia are surgical site infection and use of steroids. Donor scores on both the body image and cosmesis scale proved to be excellent and were not influenced by the surgical technique used. Elderly donors reported significantly better cosmetic outcome. It appears that donors are more concerned with their own physical recovery and the well being of the recipient than with the cosmetic outcome of the incision. Thus, we conclude that incision-related outcome may pose no barrier to live donor nephrectomy either.

Due to the continuous demand for kidney transplants, eligibility criteria for live donation have extended. This has led to the inclusion of elderly live donors that would not have been selected in the past. In these donors, safety as well as graft and recipient survival have been demonstrated to be comparable to that of younger individuals. However, very little is known on QOL in a selected group of elderly donors. As aging of the population is becoming more and more a global issue and more elderly people present as potential living kidney donors, research focused on the elder population is necessary. Results of our study demonstrate that elderly donors aged 60 years or older do have a better QOL and show a faster return to baseline value than younger donors. Furthermore, elderly donors experience less pain during the first days after the procedure. The impact of age on donor safety had already been established by our group and no difference was found between younger and elderly people. As the study presented in this thesis (chapter eight) demonstrated no disincentives with regard to QOL, we conclude that elderly donors can be safely included in live donation programs.

Despite all efforts, some donors still experience physical or psychological distress after donation. If we could identify factors playing a role in this process we could adapt our approach and improve the outcome for these donors. Therefore, a multivariate analysis on factors influencing QOL was performed and it was found that BMI, gender, age and recipient and graft survival play a significant role in post-operative QOL. However, the effect of these parameters on the overall outcome is very limited and the effect on long-term outcome is still unknown. The factors that can be influenced by the preoperative selection process include BMI and age, these factors should be weighed in the timing of the elective procedure and the surgical technique used. If multiple donors are available, physicians should rather select non-obese donors. Psychological counseling of obese donors during follow-up or striving for weight reduction may prove valuable in improving their outcome.

FOLLOW-UP

Little is known on the long-term effects of live kidney donation. Our group previously published data on QOL three to five years after donation of a randomized trial comparing MIDN and LDN. Both approaches result in similar scores on fatigue and QOL, except for physical function, found to be significantly better after LDN. Kidney function of the donor, graft and recipient survival showed no differences. Subsequently we measured scores on fatigue and QOL in the same cohort, ten years after donation. The results of this study showed no difference in QOL between groups, except for one dimension. This difference between MIDN and LDN is hard to explain and most likely a result of serendipity. It is more interesting to observe changes in the total cohort. As expected, quality of life scores have declined a decade after donation. This is probably an effect of age. Nevertheless, average QOL scores are excellent after donation.

Estimated glomerular filtration rates did not decline on average and there were no differences in fatigue, new-onset hypertension, recipient survival and graft survival. Furthermore, no donors developed end-stage renal disease. Our data demonstrate good long-term outcome after both MIDN an LDN. These result do not provide us with any disincentives towards live kidney donation and are, thus, reassuring for current practice. However, donors should be adequately informed on the odds of developing kidney failure, hypertension and other kidney-related comorbidity.

Thus, more research on live kidney donors compared with healthy individuals that have not donated is required. The LOVE-trial (chapter 11) was designed to study the long-term consequences of live kidney donation and to compare the outcome with data from matched controls. The primary outcome will be kidney function, secondary outcomes include survival, hypertension, diabetes mellitus, fatal and non-fatal cardiovascular events, quality of life and social well-being. Controls will be selected from two different prospective cohort studies. Donors and controls will be matched for age, sex, body mass index, ethnicity and co-morbidity in a one on four fashion. Our study population comprises numerous elderly donors and donors with minor co-morbidity. As this is a group that is generally underexposed in current literature, this study should clarify the ambiguities concerning the long-term results in this group. The acquired information will aid in adequately informing live kidney donors in the future and in decision-making for protocols extending inclusion criteria.

CONCLUSION AND FUTURE PERSPECTIVES

As the superiority of endoscopic techniques has been proven, all transplant centers should strive for the introduction of these techniques and adjust the individual approach guided by donor characteristics. Centralization of live donor nephrectomy may be advocated to increase the quality of surgical care. Several concurrent techniques, such as LDN and HARP are available to offer the best surgical technique to a donor. These techniques appear to be equal in terms of safety, quality of life, costs and recipient related outcome. HARP may be favored over LDN in case of left-sided donor nephrectomy, and appears to be a good alternative for centers initiating an endoscopic live kidney donation program. Right-sided HARP offers no advantages when compared with right-sided LDN, but may help centers initiating an endoscopic program or surgeons with little endoscopic experience to safely negotiate their learning curve. Elderly donors can safely be included in live donation programs and should, in cases where multiple equal donors are available, be preferred over younger donors. Also, physicians should rather select non-obese donors when multiple donors are available.

Live kidney donation is the way forward in renal replacement therapy. It has provided us with a means to meet the increasing demand for kidneys grafts. With the current knowledge transplant surgeons may select the appropriate donor, choose the most suitable technique, and perform the procedure in a safe setting with adequate aftercare to ensure the best outcome. The final blind spot in live kidney donation is the long-term consequences for the donor. Our research on this topic has provided us with reassuring data with regard to kidney related co-morbidity and QOL (chapter 10). However, research on potential risk of live kidney donation on long term (as defined by decades of follow up) is needed to give further insight in morbidity after donation by comparing donors with healthy non-donors. Establishing of these long-term consequences will define the boundaries of live kidney donation for the near future.

Chapter 14 Appendices

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Lieve broer en zusje, lieve Rick en Bel. Wat ben ik trots op jullie. Rick, ik kan je niet vertellen hoeveel respect ik voor je heb. Je hebt zo hard geknokt om te komen waar je nu bent en hebt nooit opgegeven. Ik ken weinig met mensen met zo veel charisma als jij. Één glimlach en iedereen gaat voor de bijl. Lieve Bel, ook jij hebt hard moeten werken en het niet altijd makkelijk gehad. Nu een fantastische nieuwe baan die je op het lijf geschreven is. Je bent mooi, slim, lief en grappig. Kortom, you have got it all…

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LIST OF PUBLICATIONS

Ten-years follow-up on quality of life of a randomized controlled trial comparing laparoscopic and mini-incision open live donor nephrectomy.
Klop KWJ, Janki S, IJzermans JNM, Dooper PhMM, IJzermans JNM, Kok NFM
Submitted

A multivariate analysis of health-related quality of life after live kidney donation.
Klop KWJ, van Busschbach J, Timman R, Dols LFC, Dooper PhMM, Weimar W, IJzermans JNM, Kok NFM.
Submitted

Learning curves in endoscopic donor nephrectomy
Klop KWJ, Kok NFM, Toorop R, Berger P, Dor FJMF, IJzermans JNM.
Submitted

Can right-sided hand-assisted retroperitoneoscopic donor nephrectomy be advocated above standard laparoscopic donor nephrectomy: a randomized pilot study.
Klop KWJ, Kok NFM, Dols LFC, Dor FJMF, Tran TCK, Terkivatan T, Weimar W, IJzermans JNM.
Transplant International, February 2014.

Randomized controlled trial comparing hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy.
Dols LFC, Kok NFM, d'Ancona FC, Klop KWJ, Tran TCK, Langenhuijsen JF, Terkivatan T, Dor FJMF, Weimar W, Dooper PhMM, IJzermans JNM.
Transplantation, January 2014.

Quality of life of elderly live kidney donors.
Klop KWJ, Dols LFC, Weimar W, Dooper PhMM, IJzermans JNM, Kok NFM.
Transplantation, October 2013.

Incision-related outcome after live donor nephrectomy: a single-center experience.
Klop KWJ, Hussain F, Karatepe O, Kok NFM, IJzermans JNM, Dor FJMF.
Surgical Endoscopy, August 2013

Cost-effectiveness of hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy: a randomized study.
Klop KWJ, Kok NFM, Dols LFC, d'Ancona FC, Adang EM, Grutters JP, IJzermans JNM.
Transplantation, July 2013.

Langer bestaande ruptuur van de patellapees
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Nederlands Tijdschrift voor Traumatologie, Februari 2013.

Intravesical versus extravesical ureteroneocystostomy in kidney transplantation: a systematic review and meta-analysis.
Slagt IK, Klop KWJ, IJzermans JNM, Terkivatan T.
Transplantation, December 2012

Response to: topical gentamicin does not provide any additional anastomotic strength when combined with fibrin glue.
Karatepe O, Klop KWJ.
American Journal of Surgery, October 2012

Attitudes among surgeons towards live-donor nephrectomy: a European update.
Klop KWJ, Dols LFC, Kok NFM, Weimar W, IJzermans JNM.
Transplantation, August 2012

Een man met peroperatief vrijkomende parasieten.
Klop KWJ, van Kanten AR.
Nederlands Tijdschrift voor Geneeskunde, Februari 2012

Ruptured pseudoaneurysm in a renal allograft after percutaneous biopsy.
Klop KWJ, Karatepe O, Weening JJ, van Agteren M, Dor FJMF.
Kidney International, February 2012

After-hours colorectal surgery: a risk factor for anastomotic leakage.
Komen N, Dijk JW, Lalmahomed Z, Klop KWJ, Hop W, Kleinrensink GJ, Jeekel H, Ruud Schouten W, Lange JF.
International Journal of Colorectal Disease, July 2009

PHD PORTFOLIO

Name PhD student: Karel W.J. Klop	PhD period:
Erasmus MC Department: Surgery	Promotor(s): Jan N.M. IJzermans
Research School: Molecular Medicine	Supervisor: Dr. N.F.M. Kok

1. PhD training

	Year	Workload (ECTS)
General courses		
- Principles of Methodology (NIHES)	2011	0.7
- Introduction to Data-Analysis (NIHES)	2011	1
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2011	1.5
- CPO Minicusrsus voor Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen	2011	1.0
Specific courses (e.g. Research school, Medical Training)		
- Hesperis Course Parijs/Bergamo	2011-2012	5
Seminars and workshops		
- ETFW (European Transplantation Fellow Workshop)	2011	2
Presentations		
- Boot Congres Maastricht	2012	4
- American Transplantation Congress, Boston	2012	4
- International Congress of the Transplantation Society, Berlin	2012	4
- SICOT, Riyadh	2013	4
- American Transplantation Congress, Seattle	2013	4
Conferences		
- Boot Congres Amsterdam	2011	1
- Chirurgendagen	2011	1
- ESOT-congres Glasgow	2011	2

2. Teaching

	Year	Workload (ECTS)
Lecturing		
- Lecture at Department of Hematology	2011	0.5
- Lecture at LiDo-course Rotterdam	2012	0.5
- Education for nurses/medical students	2011-2012	3
Supervising practicals and excursions, Tutoring		
- Examination of Basic Life Support (EHBO) of medical students	2012	1

CURRICULUM VITAE

Karel Willem Jan Klop werd op 2 januari 1985 geboren te Rotterdam. Hij groeide op in Middelburg in Zeeland en behaalde in 2002 zijn eindexamen VWO. Het hieropvolgende jaar behaalde hij zijn propedeuse Classical and Archeological Studies aan de University of Kent in Canterbury. In 2003 startte hij met de opleiding Geneeskunde aan de Erasmus Universiteit Rotterdam. Hij bracht ruim 3 maanden door in het Academisch Ziekenhuis in Paramaribo voor een keuze co-schap chirurgie. In januari 2011 behaalde hij cum laude zijn artsexamen. De twee jaar die volgden werden doorgebracht als arts-onderzoeker aan de afdeling Heelkunde. In deze periode werd de basis voor dit proefschrift gelegd. Het onderzoek heeft op verschillende congressen prijzen gewonnen, waaronder de 'Young Investigator Award' op zowel het Amerikaanse als Europese transplantatiecongres. In 2012 begon hij als arts-assistent in het IJsselland Ziekenhuis in Capelle aan de IJssel. In 2013 begon hij met de opleiding tot chirurg, ook in het IJsselland Ziekenhuis (opleiders: Dr. I. Dawson en dr. B.P.L. Wijnhoven). In zijn vrije tijd geniet hij erg van fietsen, hockeyen, muziek en koken.