Optimizing living donor nephrectomy

Eligibility and surgical techniques

Nienke Dols

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Chapter 1
Introduction

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Kidneys serve as a natural filter and provide homeostatic functions, for instance the control of reabsorption of water, glucose, and amino acids, regulation of electrolytes, preservation of acid-base balance and blood pressure, and they produce specific hormones. They are situated in the retroperitoneum, under the diaphragm, behind the peritoneum which encloses the biggest part of the intestines. Direct branches of the abdominal aorta, the left and right renal artery, take care of blood supply of around 20 percent of the cardiac output. They are surrounded by a renal capsule, fascia of Gerota, and perirenal fat. Patients diagnosed with end-stage renal disease (ESRD) have problems with most of the aforementioned functions of the kidneys.

Kidney disease leads to morbidity and mortality. Haemodialysis and peritoneal dialysis can lead to long-term survival and may bridge patients to kidney transplantation. However, there is an enormous impact on life expectancy and quality of life. Renal transplantation from living donors confers several advantages as compared to dialysis and transplantation from deceased donors, including improved long-term patient survival, better quality of life, immediate functioning of the transplant, better transplant survival, and the possibility of transplanting before dialysis is necessary.

Kidney transplantation is the therapy of choice for patients with ESRD and provides the best chance on long-term survival and a relative normal life. Rene Kuss and Joseph Murray performed the first successful kidney transplantations with a live donor in France and the United States respectively. By that time the major drawback was rejection, and the invention of adequate immunosuppressive therapy in the 1960s enabled deceased donor kidney transplantation, preventing dangerous operations performed on healthy donors. Enough deceased donors were present in that time, but twenty years later a discrepancy occurred between organ demand and supply. There was an increasing number of patients with ESRD and a stagnating number of available transplants. Average waiting time for a kidney from a deceased donor increased significantly and up to twenty percent of the patients had to be removed from the list annually, mainly because of mortality and worsening condition. This encouraged a new interest in live donor kidney transplantation. Expansion of living kidney donation is only possible by continuous innovations and research in all aspects surrounding it, such as screening of the donor, perioperative care and last but not least the surgical technique. These innovations have limited the discomfort to the donor and incited live donation.

Complications from kidney donation can be divided into those arising immediately from the operation, and those which may emerge many years after the kidney was donated. Surgical mortality with living kidney donation is extremely low. In one study of over 80.000 live kidney donors, surgical mortality was 3.1 per 10.000 donors, a rate that has been unchanged over the last 15 years. Overall long-term survival after donor nephrectomy is the same as similar matched individuals who did not undergo surgery. Although 50 percent of the functioning renal mass is removed after unilateral nephrectomy, compensatory hypertrophy in the remaining normal kidney returns the glomerular filtration rate to approximately 70 percent of baseline at 10 to 14 days and approximately 75-85 percent of baseline at long-term follow-up. In addition, long-term follow-up studies have not shown a progressive loss of glomerular filtration over time. [1-4]

Donor wellbeing has increasingly become a priority, and therefore the surgical technique and eligibility criteria are being optimized continually. Surgical practice has evolved from the open lumbotomy, through mini-incision muscle-splitting open (MIDN), to minimally invasive laparoscopic techniques. Over the last years many changes have been introduced in the field of living kidney donor nephrectomy. Laparoscopic donor nephrectomy is now the gold standard. There are different minimally invasive techniques, including standard laparoscopic, hand-assisted laparoscopic, hand-assisted retroperitoneoscopic, pure retroperitoneoscopic, and robotic-assisted living donor nephrectomy. Different centres have different visions and experience on which technique to use.

Boundaries for acceptance of kidney donors are shifting, as health of living kidney donors at long-term follow-up is good, and the procedure is considered to be safe. Donors with higher age or kidneys with multiple arteries, higher Body Mass Index (BMI) or moderate hypertension are nowadays accepted.

1. ELIGIBILITY FOR LIVING DONOR NEPHRECTOMY

Age

Due to the increasing shortage of deceased kidney donors, it is important to try to expand and maximize the living donor pool, and reconsidering the relative contra-indications for donation. Nowadays, older living donors may be candidates for kidney donation. Certainly, they would not have been selected in the past. Controversy remains, as age related changes in the kidney may result in a decline in renal function over the years, and the combination of aging and a donor nephrectomy is not properly investigated. Therefore questions have risen about the outcome of older living kidney donors and especially the decline in estimated glomerular filtration rate (eGFR) after donation. Older donors may also have an increased risk of perioperative complications. They often have a higher 'American Society of Anaesthesiologists score' (ASA-score), more comorbidity, a higher incidence of hypertension and a higher BMI, all possibly contributing to a higher risk of perioperative problems. In **Chapter two** we describe the results of a comparative study between younger and older living kidney donors.

Multiple arteries

Another issue is the use of kidneys with multiple arteries. The rationale was to avoid vascular and ureteral complications by using only kidneys with single arteries. But as there were possible doubts about the use of the right kidney, many centres favoured left donor nephrectomy even in the presence of multiple arteries. Live donor kidneys with multiple arteries are associated with surgical complexity for removal and a possibly increased rate of recipient ureteral complications. Multiple arteries may increase operation time and risk for the donor. Accessory lower pole arteries are associated with a higher rate of recipient ureteral complications indicating the importance of arterial imaging.

Nowadays there is one prospective and some retrospective studies comparing single and multiple arteries. All studies included a relative small number of donors with multiple arteries. All studies indicate the safety and feasibility of donor nephrectomy with more than one artery. Two studies indicate more renal arteries are associated with more ureteral complications in the recipient, and especially accessory underpole arteries. [5-10] **Chapter three** describes the different imaging techniques and the outcome and clinical consequence for multiple arteries and veins in our centre.

Side selection

Preoperative meticulous preparation for these operations has become increasingly important, as anatomy may influence surgical outcome and safety. There is still a dilemma whether right or left laparoscopic donor nephrectomy is to be preferred if both kidneys have equal anatomy. Right-sided donor nephrectomy has been associated with shorter renal vein and renal vein thrombosis in the recipient, but this is never proven in literature. Reluctance towards the right side arose when Mandal *et al*. described worse outcome for right kidneys, with significantly more renal vein thrombosis in the recipient. One RCT, one prospective and five retrospective studies concluded that right-sided donor nephrectomy is also justified, and some studies indicate the superiority of the right side. A shorter renal vein possibly leads in theory to a difficult anastomosis, but in practice it turns out better than expected.[11-17] We describe our results regarding left versus right-sided laparoscopic donor nephrectomy in **Chapter four**.

Body Mass Index

Obese donors are a true challenge for the laparoscopic surgeon. In addition to the technical challenges of positioning and instrumentation, longer operation time, surgeons may also face a higher incidence of anaesthetic, and postoperative complications. Studies suggest that laparoscopic donor nephrectomy is usually safe in selected obese donors. Obese donors have higher baseline cardiovascular risk and warrant risk reduction for long-term health. Furthermore obesity acts on renal function, it accounts for an increase in glomerular filtration rate with less elevated or even decreased effective renal plasma flow, and filtration fraction is therefore increased. The filtration fraction is a predictor for renal function loss. Together with donor nephrectomy this might be harmful on long-term follow-up, especially because the incidence of overweight and obesity is increasing. While early operative results are encouraging, careful study of obese donors, especially for the long-term renal effects, is advocated.

2. SURGICAL TECHNIQUES

Different surgical techniques are being used in different centres. Which surgical technique to use depends on the experience of the surgeon, but there is evidence that minimally invasive techniques are preferred above open donor nephrectomy. **Chapter five** we elucidate the current practice of surgical techniques in transplant centres in Europe. We compared the outcome of questionnaires on surgical techniques with the results of our previous survey, conducted by Kok *et al*.[18] With all the improvements in surgical practice the main focus is safety and its determinants; eligibility criteria, intra-operative, post-operative and safety on long-term follow-up.[19, 20]

Mini-incision open donor nephrectomy

Mini-incision donor nephrectomy (MIDN) is a modification on the older open flank incision, with less incision length and muscle splitting rather than dividing. This resulted in reduced blood loss, shorter hospitalization, and preservation of continuity of abdominal muscles, only with marginally longer operation time, without compromising graft and recipient survival. This led to the preference of mini-incision techniques to classic flank incisions. Notwithstanding MIDN was a step forward, there were still disincentives to the open, not minimally invasive approach.[21-24]

Laparoscopic donor nephrectomy

Laparoscopic donor nephrectomy (LDN) is performed with the donor in lateral decubitus position. In short, a 10-mm trocar is introduced under direct vision. The abdomen is insufflated to 12-cm H_2O carbon dioxide pressure. A 30° video endoscope and 3 to 4 additional trocars are introduced. The colon is mobilized and displaced medially. Opening of the renal capsule and division of the perirenal fat is facilitated using an ultrasonic device. After identification and careful dissection of the ureter, the renal artery, and the renal vein, a pfannenstiel incision is made. An endobag is introduced into the abdomen. The ureter is clipped distally and divided. The renal artery and vein are divided using an endoscopic stapler. The kidney is placed in the endobag and extracted through the pfannenstiel incision.

Since MIDN was introduced, evidence has mounted that the laparoscopic approach may be superior to conventional open donor nephrectomy. Various non-randomized studies have led to the similar conclusion, despite longer operation times and longer warm ischemia time LDN results in shorter hospital stay, faster recovery, less pain, less blood loss, earlier return to work, and better quality of life as compared to the conventional open approach.[25-40] Several case series from large volume centres in the United States tried to prove the feasibility and safety of the laparoscopic technique. The remaining issues surrounding the use of laparoscopic donor nephrectomy, including long-term follow-up, complications, and donor and recipient safety, are gradually being solved. Five year follow-up of our previous conducted RCT comparing laparoscopic and mini-incision open donor nephrectomy is described in **Chapter six**.[41] Nowadays laparoscopy is the standard technique in a lot of centres for surgeons experienced in laparoscopic techniques. There is level I evidence for the superiority of LDN, but safety remains an issue.[19, 20, 42, 43]

Hand-assisted retroperitoneal approach

Hand-assisted retroperitoneoscopic (HARP) donor nephrectomy starts with the incision for the handport. (Figure 1) With the HARP technique the retroperitoneal space is created manually through the pfannenstiel incision. An endoscope is introduced and

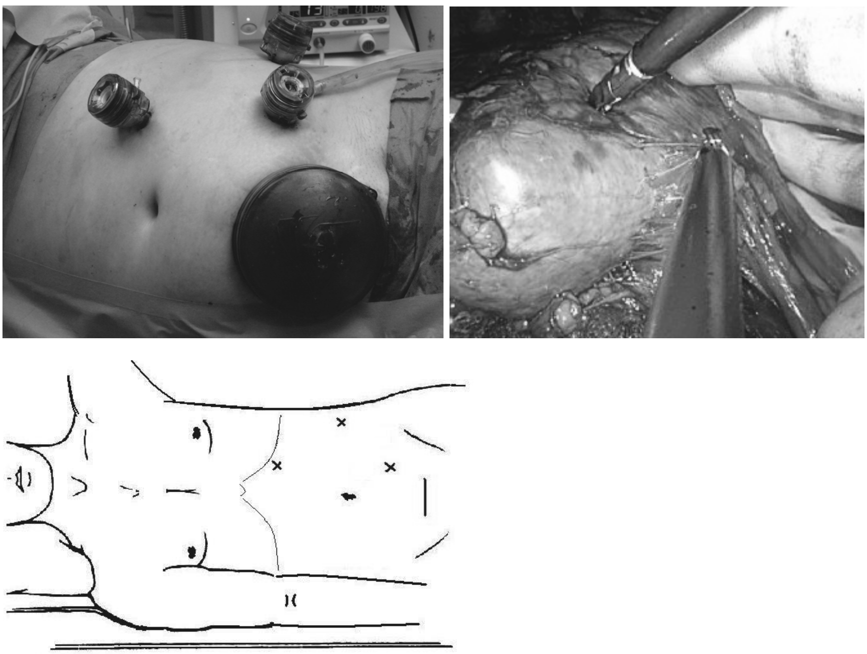

Figure 1. Hand-assisted retroperitoneoscopic donor nephrectomy and position of the trocars.

one or two other ports are inserted. The retroperitoneum is insufflated to 12-cm H_2O carbon dioxide pressure. Further dissection and preparation of the vascular structures is performed. The renal artery and vein are divided using an endoscopic stapler and the kidney is removed manually.

The advantages of hand-assisted donor nephrectomy above conventional laparoscopy include the ability to use tactile feedback, easier and rapid control of bleeding by digital pressure, better exposure and dissection of structures, rapid kidney removal. Overall, these advantages may lead to a shorter skin-to-skin- and warm-ischemia time.[44-46] With the retroperitoneal approach there is less chance to injure the intra-abdominal organs, because the peritoneum is not opened. This is an important advantage in times where safety of laparoscopic technique is still questioned. Possible disadvantages are more blood loss and a non-ergonomic position for the surgeon.

Data on hand-assisted retroperitoneal compared to laparoscopic donor nephrectomy are scarce. Only three small studies compare left-sided hand-assisted retroperitoneoscopic with laparoscopic donor nephrectomy. Outcome of most studies comparing different minimal invasive techniques are similar in terms of intra- and post-operative outcome for donor and recipient, and seems promising, but studies are small, too heterogeneous, and with low level of evidence. In the second part of this thesis the role for hand-assisted retroperitoneoscopic donor nephrectomy is clarified. **Chapter seven** describes the first results of HARP versus LDN in the Erasmus MC. These results supported us to perform the largest RCT on surgical technique for living kidney donation. In **Chapter eight** we outline the protocol of our randomised trial, comparing left sided hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy. The results of this trial are described in **Chapter nine**. We included only left-sided procedures in this trial for different reasons. The technique was, in that time, mainly described for left kidneys, possibly due to differences in anatomy and longer renal vein on the left side. Together with our experience with laparoscopy, with faster right-sided procedures, confirmed us to perform this RCT with only left-sided procedures. The first results of the study encouraged us to perform a feasibility study on the right side.

Together with the Technical University Delft, ergonomics are compared for a group of laparoscopic and hand-assisted retroperitoneal procedures, during some procedures in our randomised controlled trial (RCT) comparing laparoscopic and hand-assisted retroperitoneoscopic donor nephrectomy (HARP-trial). The outcome is discussed in **Chapter ten**.

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Chapter 2

Older live kidney donors: long-term safety

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ABSTRACT

The safety of older live kidney donors, especially the decline in glomerular filtration rate (GFR) after donation, has been debated. In this study we evaluated long-term renal outcome in older live kidney donors.

From 1994 to 2006 follow-up data of 539 consecutive live kidney donations were prospectively collected, during yearly visits to the outpatient clinic. Donors were categorized into two groups, based on age: <60 (n = 422) and ≥60 (n = 117). Elderly had lower GFR pre-donation (80 vs. 96 mL/min respectively, $p < 0.001$).

During median follow-up of 5.5 years, maximum decline in eGFR was 38% ± 9% and the percentage maximum decline was not different in both groups. On long-term follow-up, significantly more elderly had an eGFR <60 mL/min (131 (80%) vs. 94 (31%), $p < 0.001$). However, renal function was stable and no eGFR of less than 30 mL/min was seen. In multivariate analysis higher body mass index (HR 1.09, 95%CI 1.03–1.14) and more HLA mismatches (HR 1.17, 95%CI 1.03–1.34) were significantly correlated with worse graft survival. Donor age did not influence graft survival. After kidney donation decline in eGFR is similar for younger and older donors. As kidney function does not progressively decline, live kidney donation by elderly is considered safe.

INTRODUCTION

The outcomes of transplantation of kidneys derived from live kidney donors are superior with regard to early function and survival, as compared to transplants derived from deceased donors.[1-3] Live kidney donation is now generally accepted because the operation is safe, and donation does not lead to increased mortality rates at long-term.[4] Due to the worsening shortage of deceased kidney donors we are trying to expand and maximize our live donor pool, reconsidering the contra-indications for donation.

Nowadays, older live donors, obese donors and donors with minor comorbidity may be candidates for kidney donation. Certainly, they would not have been selected in the past. There is an ongoing shift towards the acceptance of these donors in order to bridge the gap between demand and supply of kidney transplants.[5, 6] Since a few years the percentage of older live kidney donors has also increased in our centre. (Figure 1) Controversy remains, as age related changes in the kidney may result in a decline in renal function over the years, and the combination of aging and a donor nephrectomy is not properly investigated. Therefore questions have risen about the outcome of older live kidney donors and especially the decline in glomerular filtration rate (GFR) after donation.

Older donors may also have an increased risk of perioperative complications. They often have a higher 'American Society of Anesthesiologist score' (ASA-score), a higher incidence of hypertension and a higher Body Mass Index (BMI), all possibly contributing to a higher risk of perioperative problems. Therefore, the aim of this study was to

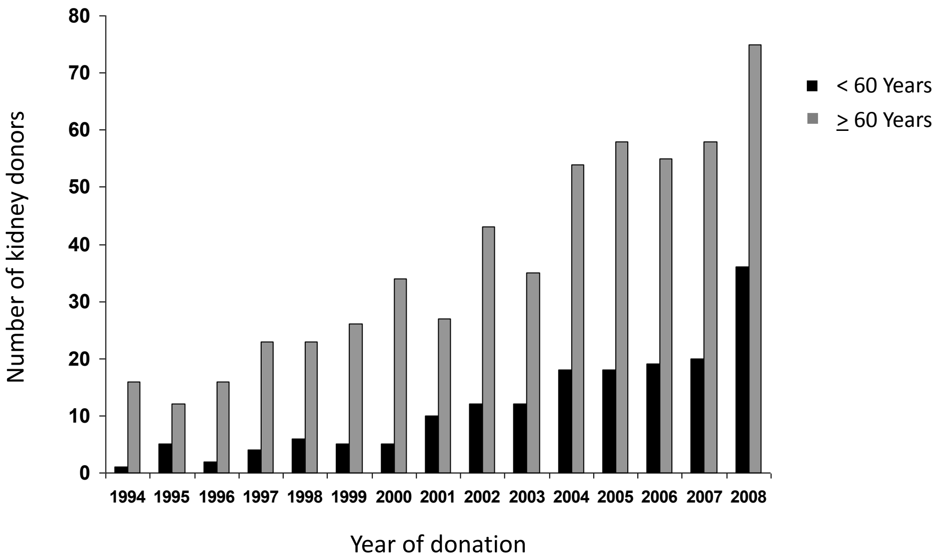

Figure 1. Number of live kidney donors in 2 age groups over the years 1994 to 2008 in Rotterdam.

evaluate short-term and long-term renal outcome after live kidney donation of older live kidney donors in comparison to the outcome in younger donors.

METHODS

Study population and data collection

In this study we included all 539 consecutive live kidney donors who underwent live donor nephrectomy at our centre from 1994 to 2006. Data of these donors and corresponding recipients were prospectively collected. Observation was until May 2010. All donors were preoperatively screened by a nephrologist, and subsequently by a medical psychologist, an anesthesiologist, and a cardiologist if indicated. Obese donors (BMI>30 kg/m^2) and donors with multiple arteries on both sides were not excluded from donating. Glomerular filtration rate (eGFR) was estimated by use of the Modification of Diet in Renal Disease formula (MDRD), which estimates GFR using three variables: serum creatinine, age, and gender.[7] The donor was discharged when a normal diet was tolerated and mobilization was adequate. Visits to the outpatient clinic were scheduled at three weeks, two months and one year following donor nephrectomy. Standard yearly follow-up consisted of blood analysis, blood pressure measurements, and urine analysis. Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg or the use of antihypertensive medication, according to the American Heart Association guidelines. Proteinuria was defined as > 0.3 g/l. In this study donors were categorized into two age groups: <60 years, and >60 years. This cut-off point was based on other articles.[8-12] Serum creatinine of the recipient was recorded preoperatively, during the first 14 days, day 21, 28 and every 3 months thereafter. Donor, graft and recipient survival were also recorded. The institutional review board approved the study.

Operative techniques

Open (until 1998), mini-incision open (from 2001 to 2006), and laparoscopic donor nephrectomy (from1997) were performed during this era. These techniques have been described previously.[13, 14] The donor and the corresponding recipient were operated on by the same team. After nephrectomy all kidneys were perfused with Eurocollins (Fresenius, Bad Homburg, Germany). Skin to skin time was defined as the time from the first incision until closure of the last incision. Warm ischemia time was defined as the time from closing the stapling device until back table perfusion of the kidney.

Statistical analysis

Categorical variables are presented as number (percentage). Continuous variables are presented as median (range). Categorical variables were compared with the Chi-square test; continuous variables were compared with the Mann-Whitney-U test. Death-censored graft survival and recipient survival was analyzed by Kaplan-Meier analyses and compared using the log-rank test. In a multivariate analysis, with backward elimination, we assessed the independent effects of donor and recipient variables on graft survival. We corrected for donor and recipient age, donor and recipient gender, donor BMI, number of arteries, number of previous transplants, mismatch-total, mismatch-DR, PRA, previous dialysis treatment. All analyses were conducted using SPSS (version 15, SPSS Inc., Chicago, USA). A P-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Baseline characteristics (Table 1)

Four hundred and twenty-two donors were younger than 60 years and 117 donors were 60 years or older. Older donors had a lower eGFR pre-donation, a higher body mass index (BMI), and a higher American Society of Anaesthesiologists- classification (ASA-classification) as compared to younger donors.

Table 1. Baseline characteristics of 539 live kidney donors, divided into two age groups over the years 1994 to 2006.

	<60 (n=422)	≥60 (n=117)	p-value
Gender: female	235 (56%)	69 (59%)	0.526
Age (years)	46 (18-59)	65 (60-90)	-
BMI* (kg/m^2)	25 (14-41)	26 (18-34)	0.035
GFR** (ml/min)	96 (54-173)	80 (54-146)	<0.001
ASA-classification# >1	69 (16%)	38 (33%)	<0.001
Operation: LDN^	264 (63%)	68 (58%)	0.151
Recipient			
Gender: female	163 (39%)	52 (44%)	0.263
Age	46 (8-76)	48 (19-81)	<0.001

* Body Mass Index, ** Glomerular Filtration Rate, # American Association of Anesthesiologists, ^ Laparoscopic Donor Nephrectomy.

Intra-operative data (Table 2)

Skin to skin time did not differ between the groups. Blood loss was significantly more in the oldest group and warm ischemia time was significantly shorter. Rates of minor and major intra-operative complications did not significantly differ. Major complications occurred in six younger donors (1%) including two bleedings, one of the stapled artery, which necessitated conversion and blood transfusion with three packed cells and two fresh frozen plasma's, and one diffuse bleeding, which resulted in a laparotomy five

Table 2. Short-term follow-up of 539 live kidney donors, divided into two age groups.

	< 60 (n=422)	≥60 (n=117)	p-value
Skin to skin time (min)	192 (84-420)	185 (94-395)	0.444
Warm ischemia time (min)	5 (1-20)	4 (1-13)	0.024
Blood loss (ml)	180 (0-3000)	230 (0-1285)	0.011
Conversion*	17 (6%)	3 (4%)	0.588
Complications minor	20 (5%)	10 (9%)	0.115
Complications major	6 (1%)	2 (2%)	0.820
Hospital stay (days)	3 (1-31)	4 (2-15)	0.012

* As a percentage of the donors who underwent LDN.

hours after donation to control bleeding. One splenic lesion occurred, which needed conversion and splenectomy. Three intestinal lesions occurred, two needed resection of a small bowel segment and one serosal lesion of the colon was sutured. In the youngest group there were 17 conversions (4%), two conversions are mentioned above. Bleedings (n=9), lack of overview due to intra-abdominal fat (n=3), and technical problems (n=2) necessitated the other conversions.

In the oldest group there were two major complications (2%), a splenic lesion, which necessitated splenectomy, and a bleeding from the rectus abdominis, which needed a re-operation the next day. There were three conversions (3%) in the oldest group; two resulted in an open procedure; one due to bleeding of the caval vein and one due to inadequate overview caused by intra-abdominal fat. In one procedure there was a conversion to a hand-assisted procedure, due to bleeding of the renal vein.

Post-operative data and long-term follow-up

The median follow-up was 5.5 years. Donors in the older group had a significantly longer hospital stay. Postoperative complications did not significantly differ between groups (3.8% and 4.3%). In the youngest group five donors developed pneumonia. These were successfully treated with antibiotics. One donor developed a pneumothorax which could be treated conservatively. Two donors developed a urinary tract infection, which were treated successfully with antibiotics; Four donors developed an incisional hernia, which needed mesh placement. Two donors developed a wound infection of the pfannenstiel incision, which were treated conservatively, one donor had an exacerbation of his known asthma, and one donor developed an infection of the mesh that was used to correct a incisional hernia from an earlier appendectomy. In the oldest group one donor developed a pneumonia, which was successfully treated with antibiotics; two donors had a wound infection of the pfannenstiel incision, treated effectively with antibiotics. Two donors developed an incisional hernia, one of the pfannenstiel incision, and one of the subcostal incision, both repaired with a mesh.

Older donors had a lower GFR before donation, but there were no differences in the mean maximum decline. (Figure 2, 3) The mean maximum decline in eGFR was 38% ± 9%.

At 5 years after donation, significantly more older donors had a GFR < 60 ml/min compared to younger donors (131 (80%) vs. 94 (31%, p<0.001). The renal function stabilized during follow-up and there were no donors with a GFR of less than 30 ml/min during follow-up. After donation 12 (10%) elderly developed hypertension versus 25 (6%) of the younger donors (p=0.56).

Proteinuria was seen in 4 older donors after 1 year (n=98 (4.1%)), in 3 donors after 5 years (n=64 (4.7%)) and no donors showed proteinuria after 10 years (n=15). Proteinuria

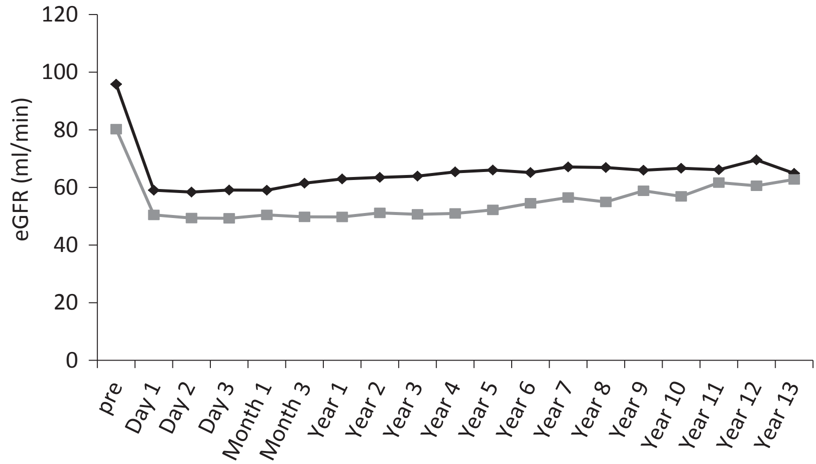

Figure 2. Median estimated glomerular filtration rate (eGFR) of 539 live kidney donors divided into two age groups. (Black line indicates <60; grey line indicates ≥ 60)

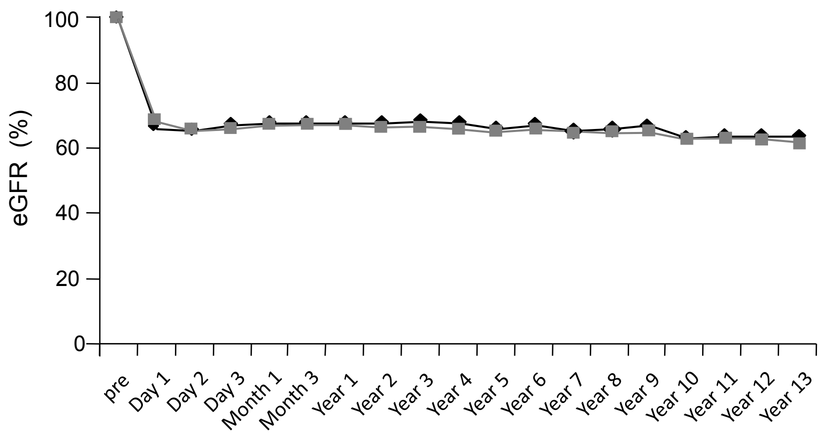

Figure 3. Percentual difference in estimated glomerular filtration rate (eGFR) of 539 live kidney donors divided into two age groups.100% is the baseline value. (Black line indicates <60; grey line indicates ≥ 60)

was seen in 12 younger donors after 1 year (n=354 (3.4%)), in 8 donors after 5 years (n=206 (3.9%), and in 6 donors after 10 years (n=94 (6.4%)). There are no significant differences between the groups at these time points (p-values: 0.91, 0.78, and 0.32).

Graft and patient survival

One and three year death-censored graft survival was 97% resp. 94% for kidneys derived from younger live donors, and 91% resp. 89% for those derived from older live donors (p=0.011 resp. p=0.008). There were 76 graft failures in the period studied. A higher donor BMI (p=0.003, Hazard ratio 1.085) and a higher mismatch-total (p=0.020, Hazard ratio 1.072) were independently associated with a shorter graft survival. (Table 3) Recipient survival did not differ between transplants derived from younger and older donors (p=0.072). Three older donors died during follow-up, one due to cancer, one due to a cardiac arrest and one unknown cause. One younger donor died 6 days after donor nephrectomy from thrombotic thrombocytopenic purpura. Eight younger donors died during follow-up, three due to cancer, one in a car accident, and four by an unknown cause.

Table 3. Multivariate analysis for the association between clinical variables and graft survival.

	Hazard ratio	95%-CI	P-value
BMI donor	1.085	1.029-1.144	0.003
Mismatch-total	1.172	1.025-1.340	0.020
Age donor	1.014	0.995-1.034	0.169
Age recipient	0.988	0.917-1.005	0.210
Gender donor	0.895	0.563-1.423	0.672
Gender recipient	0.906	0.565-1.452	0.810
Number of arteries	0.477	0.917-2.379	0.107
Number of previous transplants	0.881	0.539-1.438	0.894
Mismatch-DR	1.039	0.559-1.931	0.932
PRA	1.004	0.989-1.019	0.656
Previous dialysis	0.958	0.546-1.682	0.812

Data on donors older than 70 years

There were 25 (5%) donors of 70 years or older. The mean age in this group was 74 (70-90) years. We did not observe any significant differences in operative time, complications, conversions, or development of hypertension in comparison to the group younger than 70 years. Hospital stay was significantly higher for donors of 70 years or older (5 vs. 4 days, p<0.001), possibly explained by the social conditions needed to offer these donors adequate care in the home-situation.

DISCUSSION

Survival of live kidney donors in the years following nephrectomy has recently been reported favourable as compared to age-matched controls.[4] We add that surgical morbidity is acceptable, postoperative renal function is stable and the risk of hypertension is not higher than in the general population.

The Western world is aging. In Europe 17% of the inhabitants were 65 years or older in 2008. This percentage will rise to approximately 29% in 2050.[15] On the one hand this will lead to an increasing number of patients suffering from renal insufficiency, but also to an increasing number of older persons willing to donate. We provide evidence that healthy individuals in the older age category may undergo live kidney donation with good results for the donor as well as the recipient. Thus, live donation by older donors may offer an attractive option to further stabilize waiting lists for kidney transplantation.

More than 20% of the live donors in this study were 60 years or older. In our centre the mean donor age has increased over the last 15 years from 43 in the 1990s to 50 nowadays. We even included a group of 25 donors older than 70 years. The average age in this study is relatively high, in particular when compared to American studies.[16-18] Results of the present study may encourage other centres to include healthy older donors.

Several concerns have made doctors cautious of accepting older donors. These include possibly higher perioperative and postoperative complication rates, due to an increase in co-morbidity related to aging. Risk factors for renal and cardiovascular damage, such as hypertension and overweight, are more prevalent in the elderly. In concordance with the literature we do not report a difference in perioperative complication rate between younger and older donors.[16, 19-21] This may be the result of the selection process including donors with no or minor co-morbidity only.

Furthermore, information regarding the long-term renal consequences of reduced renal mass in healthy humans has mainly come from studies of veterans who lost a kidney as a result of trauma.[22] However, these veterans lost their kidney at relatively young age. Glomerular filtration rate (GFR) slowly declines over the years, with 5-10 ml/min per decade, leading to a further reduction of the residual capacity in donors.[23] In accordance with the literature, our data indicate that after an initial drop in kidney function there is no accelerated decline after donation, neither in young donors, nor in older donors.[20, 24, 25] None of the donations led to a GFR of less than 30 ml/min during follow-up, and the prevalence of hypertension was lower in comparison to the normal population. Proteinuria was rare in our study and did not differ between younger and older donors. Although isolated cases of renal failure have been described, no large study has shown evidence of progressive deterioration of renal function after live kidney donation.[25-29] We would like to extrapolate this for the older donors: live donation alone will not lead to renal insufficiency.

Some worrisome reports have been published on whether renal function of the transplanted graft may be compromised due to older age of the donor. The association of older donor age, and higher rejection rates and unfavourable graft survival has been debated.[9, 30] We did not assess an association between higher age and lower graft survival in the multivariate analysis. This is in concordance with recent literature.[9, 10, 12, 31-34] However, higher donor BMI and higher mismatch-total were independently associated with shorter graft survival. The latter association has been reported in literature.[35] Others did report BMI as a risk factor for graft failure, but the precise underlying mechanisms are not known.[36-38] Possibly, obesity-induced hyperfiltration and glomerular hypertension lead to renal damage and sclerosing glomerulopathy.[38] However, from the perspective of the recipient, transplantation from an older donor or with a higher BMI is probably nearly always preferred to both dialysis and transplantation from a deceased donor.[1-3]

Our study comprises a unique group, with a large group of older live kidney donors. We have described a cohort study with regular, yearly follow-up. One drawback is the time-frame of 13 years in which these donors are included. It should be noted that in this period there have been changes in all aspects of the live kidney donation and transplantation including a shift from related to unrelated donors, major changes in surgical technique and different immunosuppressive regimens in the recipient. Further follow up is indicated to evaluate the outcome of this shift in the near future.

In conclusion, live kidney donation by older donors may be considered safe as morbidity of the operation is limited, glomerular filtration rate does not progressively decline, and graft-survival is acceptable. We encourage accepting carefully selected older donors in living kidney donation programs.

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Chapter 3

Complex vascular anatomy in live kidney donation: imaging and consequences for clinical outcome

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ABSTRACT

Live donor kidneys with multiple arteries are associated with surgical complexity for removal and increased rate of recipient ureteral complications. We evaluated the outcome of vascular imaging and the clinical consequences of multiple arteries and veins.

From 2001 to 2005 data of 288 live kidney donations and transplantations were prospectively collected. Vascular anatomy at operation was compared to vascular anatomy as imaged by MRI or subtraction angiography and consequences of multiple vessels were investigated.

Simple renal anatomy with a solitary artery and vein was present in 208 (72%) kidneys. Sixty (21%) transplants had multiple arteries. Thirty (10%) transplants had multiple veins. MRI failed to predict arterial anatomy in 23 of 220 donors (10%) compared to 3 of 101 (3%) after angiography. The presence of multiple veins did not influence outcomes after nephrectomy in general. Multiple arteries did not affect clinical outcomes in open donor nephrectomy (N=103). In laparoscopic donor nephrectomy (N=185) multiple arteries were associated with longer operation times (245 vs. 221 minutes, P=0.023) and increased blood loss (150 vs. 100 ml, P=0.029). In general, neither multiple arteries nor vascular reconstructions influenced recipient creatinine clearance or ureteral complication rate. However, accessory arteries to the lower pole correlated with an increased rate of ureteral complications (47% vs. 14%, P=0.01).

Multiple arteries may increase operation time. Accessory lower pole arteries are associated with a higher rate of recipient ureteral complications indicating the importance of arterial imaging. Currently, both MRI and angiography provide suboptimal information on renal vascular anatomy.

INTRODUCTION

Minimally invasive donor nephrectomy has become the standard of care for live kidney donation.[1-4] Minimally invasive approaches include modified open and laparoscopic or retroperitoneoscopic approaches. These approaches have in common that the perception of renal anatomy is compromised as compared to conventional flank incisions due to loss of tactile sensation and/or impeded overview. Complex vascular anatomy may influence surgical outcome.[5] Therefore, preoperative planning of these operations has become increasingly important.

Live kidney donors are healthy individuals that deserve the least invasive and the least time consuming imaging with the best predictive value. Traditionally, the donor's renal anatomy was assessed by angiography with good results but significant consequences for the donor including radiation and a short stay in the hospital. Magnetic resonance imaging and Computed tomography have both been reported feasible alternatives.[6-11] In our hospital angiography was gradually replaced by MRI as this technique does not cause radiation and, in addition, provides information on venous anatomy.[12]

In this study we evaluated the diagnostic performance of our imaging to predict arterial anatomy during a 5-year period. Furthermore, we investigated the consequences of multiple arteries on clinical outcome therewith addressing the potential harm due to vessels missed on preoperative imaging.

METHODS

Patients

From January 1st 2001 to December 31st 2005 data of all laparoscopic and mini-incision open live kidney donations and corresponding transplantations were prospectively collected. Two-hundred-eighty-eight donor nephrectomies were performed. During this period three studies were performed after approval by the medical ethics committee. These included a radiological study comparing MRI and digital subtraction angiography (DSA) in an effort to image renal anatomy of live kidney donors, a prospective study addressing laparoscopic versus open donor nephrectomy and a randomized controlled trial addressing laparoscopic versus open donor nephrectomy. The main outcomes of these studies have been published previously.[2, 13, 14] Internal board review was obtained.

All donors were preoperatively screened by a nephrologist and subsequently by a medical psychologist, an anaesthesiologist, and cardiologist if indicated. Imaging consisted of ultrasound and either DSA or MRI, depending on planning only (i.e. the first available appointment directed imaging, as neither technique was considered superior), except for donors included in the aforementioned radiological study who underwent both DSA and MRI. Obese donors, donors with complicated renovascular anatomy or older donors were not restricted from either surgical technique. Right-sided kidney donation was not avoided. The results of the aforementioned studies led to a preponderance of MRI and laparoscopic donor nephrectomy since the second half of 2004.

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

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

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

Surgical techniques

The operative technique has been described previously.[14] Briefly, in LDN we applied an open technique to access the peritoneal cavity with the first trocar. A 30°-video-endoscope was used. Four additional ports were used on the right side including a 5mm-trocar in the epigastric region to retract the liver. On the left side three additional ports were created. Ultrasonic scissors (Ultracision, Ethicon, Cincinnati, USA) were used throughout the procedure. A pfannenstiel incision was made as extraction site. The renal vessels were stapled and the kidney was harvested with an endobag (Endocatch, US surgical, Norwalk, USA). Open donor nephrectomy was carried out using a muscle-splitting approach with an 8 to 15 cm incision (depending on BMI) running from the tip of the eleventh rib towards the umbilicus.

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

Data collection and statistical analysis

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

The true vascular anatomy as assessed during the operation and perfusion was considered as gold standard and compared to the vascular anatomy imaged by MRI or DSA. Therefore, sensitivity and specificity were calculated. Then, we analyzed the effect of additional arteries on clinical outcome, including the effect of misinterpreted accessory arteries. In all recipients a nuclear scan (MAG 3) of the transplant was performed one or two days after surgery. We were especially interested in the consequences of (missed) accessory arteries to the lower pole of the kidney. Previous concluded that vascular reconstructions may lead to an increased rate of ureteral complications.[5]

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

RESULTS

Preoperative imaging was performed in 278 of 288 donors in the Erasmus MC. CT or DSA of ten donors was performed elsewhere, including 4 donors participating in the cross-over program of the Dutch transplant centres. Baseline characteristics of the donors are outlined in Table 1.

Based on preoperative findings the right kidney was selected for removal in 156 (54%) donors. In 78% of the donors who underwent right-sided donor nephrectomy significant advantages in anatomy of the right kidney (arterial or venous) as compared to the left kidney, or ipsilateral stenosis of the artery and/or smaller size demanded procurement of the right kidney.

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

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

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

	Live donors and recipients (N=288)
Donor	
Gender (male; female)	114 (40%)/174 (60%)
Age (years)	50 (14)
Kidney (left; right)	132 (46%)/156 (54%)
ASA Classification (I :II :III)	220 (76%)/66 (23%)/2 (1%)
Body mass index (kg/m²)	26.2 (4.1)
Preoperative serum creatinine (µmol/l)	73 (13)
Recipient	
Relation (Living related; living unrelated; cross-over or anonymous)	173 (60%)/ 102 (35%)/13 (5%)
Gender (male; female; child)	173 (60%)/111 (39%)/4 (1%)
Age (years)	46 (15)
Preemptive transplantation (yes; no)	66 (23%)/222 (77%)
Preoperative serum creatinine (µmol/l)	793 (315)

Comparison of surgical anatomy and preoperatively imaged anatomy

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

Twenty-three MRIs (10%) were discordant with regard to arterial anatomy assessed intra-operatively as compared to 3 (3%) DSAs. The sensitivity of MRI and DSA was 0.61 and 0.81 respectively (Table 2A and 2B). The specificity of MRI and DSA was 0.98 and 1.00 respectively. The positive predictive value was 0.91 and 1.00 respectively. The negative predictive value was 0.89 and 0.97 respectively. Thirteen MRIs (6%) were discordant with regard to venous anatomy. Two other donors presented with multiple veins while the venous phase was imaged with an incorrect protocol allowing no judgment. In

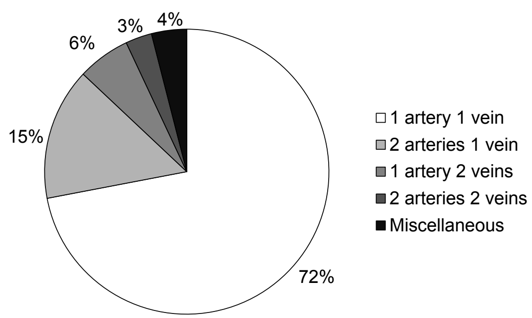

Figure 1. Variation in arterial and venous anatomy.

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

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

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

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

11 donors (11%) with a DSA multiple veins were discovered at surgery. All discordant findings are presented in Table 3. In cases in which DSA and MRI were both performed DSA revealed an additional accessory artery in one donor and doubt about the arterial anatomy in another donor. Accessory arteries were present in both donors.

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

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

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

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

Clinical consequences of multiple arteries

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

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

Nine smaller accessory arteries to the upper pole, one artery to the middle pole and one capsular artery were ligated. Postoperative nuclear imaging (MAG 3) showed

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

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

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

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

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

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

a defect that was smaller than 10% of the nephron mass in two transplants only. The other postoperative scans did not reveal loss of renal parenchyma at all, implying that sacrificing these branches was inconsequential. Arterial reconstruction after harvest of the transplant was performed in 40 cases (61%). Two or more arterial anastomoses were created in 15 transplants.

Arterial reconstruction after harvest of the transplant was performed in 40 cases (61%). Two or more arterial anastomoses were created in 15 transplants. Arterial reconstructions were not associated with ureteral complications. Accessory arteries to the lower pole however resulted significantly more often in ureteral complications (47% vs. 14% in the donors with multiple arteries but without an accessory artery to the lower pole, P=0.011) and ureteral reconstructions (27% vs. 6%, P=0.042).

Clinical consequences of arteries undetected at imaging

Three non-detected accessory arteries were ligated during kidney donation, one because of the small calibre (upper pole), one because of bleeding (lower pole) and one because it was not recognized at operation but at cold perfusion (lower pole). Discordant arterial anatomy did not adversely affect clinical outcomes of neither ODN nor LDN including complications, blood loss, operation time and ureteral complications in the recipient.

Clinical consequences of multiple veins

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

DISCUSSION

This study represents a detailed analysis of prospectively collected data on imaging renal vascular anatomy and subsequent surgical complications at one of the largest European transplant centers with regard to live kidney donor transplantations during a five-year period. We recently advocated laparoscopic kidney donation as the technique of choice.[2] In the current study multiple arteries were associated with prolonged operation time and warm ischemia time and increased blood loss in laparoscopic donor nephrectomy. However, despite a statistically significant association the clinical impact is limited. Our data confirm the feasibility of laparoscopic kidney donation in donors with multiple arteries as demonstrated by others.[5, 15-18] We add that arterial reconstructions do not necessarily result in detriment to the graft. However, lower pole accessory arteries often result in ureteral complications most probably because of an impaired ureteral blood flow.

As opposed to other radiological studies that focused on the accuracy of imaging we were more interested in the consequences for daily practice. Therefore the clinician and the radiologist both evaluated the radiological images and both MRI and DSA were included, because sometimes it was easier and faster to plan DSA and sometimes the other way around. The first step of imaging in potential live kidney donors is excluding disorders in the renal parenchyma and stenosis. The second step is planning the operation including which kidney best to harvest and what vascular anatomy to expect. The third step is quality control by comparing findings at surgery with the images. We focused on the latter aspects as MRI has already proven its value in detecting parenchymal abnormalities.[13] Observation during the operation, in particular during cold perfusion after nephrectomy, was considered the gold standard. Therefore we did not include data of DSAs and MRIs of the contralateral side remaining in the donor.

Because we know from our daily practice that the anatomy of branches of the renal vein including the gonadal vein, the adrenal vein and lumbar branches is highly variable and sometimes poorly visualized by our MRI scan, we did not attempt to incorporate these data. We acknowledge that these branches may be better visualized with CT.[19] The highly variable presence of these vessels always requires attention of the surgeon during donor nephrectomy. Although these branches can cause significant trouble including bleeds and difficulties to position the vascular endostapler, they do not affect postoperative transplant function. In right-sided kidney donation preoperative assessment of these branches may be helpful as these are usually absent. The same holds for accessory renal veins; these can be troublesome but can usually be sacrificed without any further consequence. Therefore, imaging should be primarily directed at detection of parenchymal abnormalities, arterial stenosis and accessory arteries.

MRI appeared less accurate in predicting arterial anatomy than DSA, failing in ten percent and three percent respectively. Although an important number of right kidneys was harvested, the percentage of discordant findings related to arterial anatomy was not different form the 12% assessed by Ames et al.[20] They reported an increased rate of arterial discordance in right kidney donation.

The presence of multiple veins remained undetected in about 11% of the donors if DSA was the sole imaging modality of the renal vessels, which is concordant with previous studies.[21] In our series the number of discordant scans was comparable to percentages in the current literature on imaging renal anatomy by either CT or MRI with rates of discordant scans ranging from 2 to 14 percent.[6-11, 20, 22] Interpretation of the diagnostic performance in all these studies included realizing that a single artery and single vein is present in the vast majority of cases, which influences the predictive value of any diagnostic tool.

Although discordant findings do not necessarily result in worse outcomes, it is clear that preoperative imaging of the donor can be improved. This could be accomplished by improved communication between radiologist and clinician,[10] tailored use of current techniques and further development of both MRI and CT. With regard to the second aspect we would like to draw attention to the 26 donors in our series that needed an additional DSA to rule out stenosis, because of claustrophobia or due to inability to comprehend breath-holding instructions. The sensitivity of CT to rule out stenosis may be higher as compared to the sensitivity of MRI. However, in hypertensive patients both modalities are inadequate to rule out stenosis.[23] Perhaps hypertensive donors should undergo DSA primarily. The motion artefacts of the current MRI imply that donors who do not understand instructions should be primarily imaged with CT or DSA. We acknowledge the increased risk of radiation, contrast allergy and contrast nephropathy if CT is used. Therefore we would suggest to image younger individuals in the fertile age using MRI. In older individuals (> 45 years) with good renal function (as may be expected from a potential donor) we advise to perform a CT, as the adverse effects of ionized contrast are relatively less hazardous. We also recommend CT in obese donors (BMI > 35), as vascular structures may be harder to identify in abundant fatty tissue. We acknowledge that these recommendations are not evidence-based yet.

Currently a single 'one-stop shop' modality for preoperative evaluation of potential live kidney donors simply does not exist. Future developments including stronger magnetic fields of MRI scans and more detailed CT scans will undoubtedly improve imaging of the live donor and change the spectrum of imaging.

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

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Chapter 4
Laparoscopic donor nephrectomy: a plea for the right-sided approach

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ABSTRACT

Laparoscopic donor nephrectomy (LDN) has become the preferred procedure for live donor nephrectomy. Most transplant surgeons are reluctant towards right-sided LDN (R-LDN) fearing short vessels and renal vein thrombosis.

In our institution selection of the appropriate kidney for donation was based on the same criteria that traditionally governed open donor nephrectomy. All intra- and post-operative data were prospectively recorded.

One hundred fifty-nine R-LDNs (56%) and 124 left-sided LDNs (L-LDN, 44%) were performed. Demographics did not significantly differ. Complications occurred in ten (6%) versus 23 (19%) procedures (R-LDN vs. L-LDN, P=0.002), resulting in 2 and 11 conversions respectively. Right-sided kidney donation was the only independent preventative factor for complications in multivariate analysis (P=0.008, Odds ratio 0.33). R-LDN was associated with shorter operation time (mean 202 vs. 247 minutes, P<0.001) and less blood loss (139 vs. 294 ml, P<0.001). Hospital stay was 3 days in both groups. With regard to the recipients, the second warm ischemia time was similar (29 vs. 28 minutes, P=0.699).

R-LDN is faster and safer than L-LDN and does not adversely affect graft function. R-LDN may be advocated to allow donors to benefit from the advantages of laparoscopic surgery.

INTRODUCTION

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

Right-sided LDN (R-LDN) has been associated with short vessel lengths and renal vein thrombosis in the recipient.[7] For this reason, many centres refrain from laparoscopically procuring right kidneys for transplantation even if multiple arteries are present on the left side.[6] However vascular anatomy of left-sided kidneys is more complicated and transplants with multiple arteries may lead to more ureteral complications.[8, 9] As other centres affirmed the conclusions, the aim of this study was to further investigate the role of R-LDN in live kidney donation.[10-12] In absence of contra-indications for right-sided kidney donation, R-LDN was chosen. We compared R-LDN to left-sided LDN (L-LDN).

METHODS

Study population and data collection

In this study we included all live kidney donors who underwent LDN at our centre between May 2001 and August 2007. During this time we prospectively collected data of all consecutive donors. A nephrologist screened all donors preoperatively. Renal anatomy was imaged using either digital subtraction angiography (DSA) or magnetic resonance angiography (MRA). Obese donors, older donors and donors with multiple arteries on both sides were not restricted from LDN.

A research fellow collected all intra-operative data on location. Postoperative data at the ward including complications and hospital stay, and data during follow-up were also prospectively recorded. Intraoperative and postoperative complications are scored according to the modified Clavien grading system described by Kocak et al.[13]

Visits to the outpatient clinic were scheduled three weeks, two months and one year following donor nephrectomy. The Institutional Review Board of the Erasmus MC approved this study.

Decision-making

Selection of the appropriate kidney for donation was based on the same criteria that have traditionally governed open donor nephrectomy. The decision to perform R-LDN or L-LDN was prospectively recorded. If imaging revealed unilateral anatomical abnormalities i.e. ipsilateral arterial stenosis that side was chosen. If there was an obvious difference in size, the smallest kidney was recovered. If possible the kidney with simplest vascular anatomy was removed i.e. we reviewed the number of renal arteries and the possibility of early branching. In case of a unilateral duplicated ureteral system the kidney with a single ureter was removed. If arterial and ureteral anatomy was similar, we tried to avoid venous anomalies including retro-aortic veins and circum-aortic veins. Finally, if none of the previous examinations revealed any difference, we usually selected the right kidney since branches (gonadal, adrenal and lumbar veins) to the right renal vein are uncommon.[9]

Surgery

Since 1997 total laparoscopic donor nephrectomy (without hand-assistance) has been performed at our institute. We started with L-LDN. After five left-sided nephrectomies the first R-LDN was performed because of multiple arteries on the left. Before the present study was initiated 100 LDNs had been performed with approximately 30% L-LDNs. The operative technique has been described previously.[14] Briefly, we applied an open technique to access the peritoneal cavity with the first trocar. A 30°-video-endoscope was used.

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

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

Statistical analysis

Categorical variables were compared with the Chi-square test; continuous variables were compared with the Mann-Whitney-U test. Logistic regression was applied to determine the independent effects of donor age, gender, ASA classification, side, body mass index, number of renal arteries and number of renal veins on the intra-operative and postoperative complication rate. In a multiple linear regression analysis we assessed the independent effects of these variables on operation time and blood loss. All analyses were conducted using SPSS (version 11.5, SPSS Inc., Chicago, USA). A P-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Kidney selection (Table 1)

Hundred-and-fifty-nine R-LDNs and 124 L-LDNs were performed. The right kidney was procured in 65 donors because of relative and absolute contra-indications on the left side. There were no reasons to favour one of the kidneys in 94 donors. In these donors the right kidney was selected. Miscellaneous reasons to remove the right kidney included two donors with a previous history of renal stones in the right kidney, a significantly smaller right kidney in two donors and, one donor with a cyst at the outer border of the left kidney. Miscellaneous reasons to select the left kidney included cortical tissue loss in two donors, multiple cysts in four donors, and in another donor there were doubts about vascular wall irregularities. Six times there was no reason to favour one of the kidneys and was chosen for the left one.

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

R-LDN (n=159)	Number (%)
Fibromuscular dysplasia right artery	2 (1%)
Stenosis right artery	8 (5%)
Multiple arteries and retrocaval vein on the left side	2 (1%)
Multiple arteries on the left side	27 (17%)
Very early branching left artery	4 (3%)
Double ureteral system on the left side	3 (2%)
Multiple veins on the left	5 (3%)
Retro-aortic vein on the left side	5 (3%)
Circum-aortic vein on the left side	4 (3%)
Miscellaneous	5 (3%)
Facultative	94 (59%)
L-LDN (n=124)	**Number (%)**
Stenosis left artery	9 (7%)
Multiple arteries on the right side	45 (37%)
Branching right artery behind vena cava	45 (37%)
Double ureteral system on the right side	2 (2%)
Multiple veins on the right	9 (7%)
Miscellaneous	8 (7%)
Facultative	6 (5%)

Demography (Table 2)

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

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

	Right (N=159)	Left (N=124)	P-value
Donor			
Male	65 (41%)	65 (53%)	0.053
Age (years)	50 (13)	50 (13)	0.975
ASA Classification>1	40 (25%)	25 (20%)	0.322
Body mass index (kg/m^2)	26.4 (4·1)	25.8 (3·9)	0.405
>1 Renal Artery	41 (26%)	29 (24%)	0.692
>1 Renal Vein	27 (17%)	13 (11%)	0.120
Recipient			
Male	102 (64%)	78 (63%)	0.403
Age (years)	48 (14)	47 (15)	0.429
Pre-emptive transplantation	44 (28%)	38 (31%)	0.584

Intra-operative outcomes (Table 3)

The complication rate was significantly lower for R-LDN. Complications in this group included two serosal lesions of the colon, sutured laparoscopically, a small bowel perforation and a bladder lesion. There were four bleeds (110 ml, 180 ml, 265 ml, 500 ml), one from the renal vein, one from an ovarian vein and one diffuse bleed after removal of the kidney. A bleed from the renal artery, due to failure of the stapler, required a conversion. Two times an artery to the lower pole was unintentionally cut; one required a conversion to a muscle-splitting approach. Complications on the left side included 8 bleeds (425 ml, 600 ml, 700

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

	Right (N=159)	Left (N=124)	P-value
Complications	10 (6%)	23 (19%)	0.002
Conversion to open	2 (1%)	11 (9%)	0.002
First warm ischemia time (minutes)	5.6 (2·3)	6.5 (3·5)	0.188
Time until kidney removal (minutes)	156 (47)	199 (56)	<0.001
Skin to skin time (minutes)	202 (47)	247 (56)	<0.001
Blood loss (ml)	138 (268)	294 (503)	<0.001
Second warm ischemia time (minutes)	29 (11)	28 (9)	0.699

ml, 860 ml, 2000 ml, 2300 ml, 2700 ml, and 3500 ml, six times from the renal vein or its tributaries, one persistent bleeding of the renal capsule and one from peri-aortic lymph nodes). Five superficial splenic injuries were treated conservatively. In one donor procedure an accessory lower pole artery was unintentionally cut. No impact on the graft function in the recipient was noted. Two serosal lesions of the small intestine occurred during suprapubic incision, a subcapsular haematoma of the kidney and unintentionally cutting the ureter during the procedure. Six conversions were necessary to treat the bleeds mentioned before. Five L-LDNs were elective conversions because of massive adhesions, lack of an adequate view due to abundant adipose tissue (n=3) and persistent bleeding of the renal capsule. In ten of eleven conversions the kidney was extracted by a muscle-splitting incision. A true emergent conversion using a lumbotomy was performed in one donor only.

Operation time and blood loss were favourable in R-LDN. Warm ischemia time was comparable between groups.

Right-sided nephrectomy was independently associated with fewer intra-operative complications (p=0.008, Odds ratio 0.33, Table 4). Right-sided nephrectomy (p=0.001), a solitary renal artery (p=0.002), and female gender (p=0.002) were independently associated with shorter operation time (data not shown).

Table 4. Multivariate logistic regression analysis for the association between clinical variables and intra-operative complications.

	Odds ratio	95%-CI	P-value
Male	1.99	0.908-4.350	0.086
Age	1.02	0.984-1.049	0.324
ASA classification >1	1.06	0.409-2.734	0.908
>1 Renal Artery	1.34	0.548-3.258	0.524
>1 Renal Vein	0.64	0.170-2.419	0.511
BMI	1.02	0.922-1.131	0.688
Right kidney	0.33	1.336-6.673	0.008

Post-operative outcomes (Table 5)

Post-operative complication rate and hospital stay did not significantly differ between groups. Complications after R-LDN included two major complications; the small bowel perforation described previously was undetected until two days after donor nephrectomy and required a subumbilical midline laparotomy. One donor with a known history of cardiac problems developed a fatal myocardial infarction post-operatively in the recovery room. This donor had concealed his cardiac complaints pre-operative according to his family. Minor complications included migraine (n=1), urinary tract infection (n=1), postoperative fever (n=2), wound infections treated with oral antibiotics (n=3), pneumonia (n=1) and a small pneumothorax which did not demand further treatment.

Table 5. Post-operative outcomes of R-LDN vs. L-LDN. Categorical data are presented as number (percent). Continuous data are presented as mean (SD).

	Right (N=159)	Left (N=124)	P-value
Donor			
Complications	11 (7%)	15 (12%)	0.150
Minor complications	9 (6%)	9 (7%)	0.629
Major complications	2 (1%)	6 (5%)	0.144
Postoperative hospital stay (days)	3.3 (1·2)	3.5 (1·5)	0.515
Recipient			
Immediate urine production*	141 (89%)	111 (90%)	0.833
Ureteral complications	23 (15%)	15 (12%)	0.602
Re-operation due to ureteral complications	6 (4%)	7 (6%)	0.570
Lymphocele	7 (4%)	7 (6%)	0.784
Arterial thrombosis	2 (1%)	1 (1%)	1.000
Acute Rejection	17 (11%)	19 (15%)	0.282

* 6 missing values

Major complications following L-LDN included two re-laparoscopies (presumed continuous bleeding), re-laparotomy (splenectomy after iatrogenous splenic injury), re-admission to intravenously treat a wound infection, and two incisional hernias requiring laparoscopic correction. Minor complications included one pneumonia and four wound infections all treated with oral antibiotics. One donor had temporarily sensibility loss of the lateral skin of the thigh. Three received a blood transfusion. Intraoperative and postoperative complications are summarised in table 6.

One recipient of a left kidney lost his graft on the first day due to an arterial thrombosis. One recipient of a right kidney developed renal artery thrombosis and lost the graft at the first postoperative day due to what turned out to be a factor V Leiden clotting

Table 6. Intraoperative and postoperative complications of R-LDN and L-LDN with grading by severity.

Grade	Percentage of all complications right side (n = 20)*,**	Percentage of total series (n= 159)	Complications	Patients (n)
1	65.0 (n= 13)	8.2	Blood loss < 500 ml	3
			Lower pole artery unintentionally cut	1
			Urinary tract infection	1
			Post-operative fever	2
			Wound infection	3
			Pneumonia	1
			Pneumothorax	1
			Migraine	1

Table 6. Intraoperative and postoperative complications of R-LDN and L-LDN with grading by severity. (continued)

Grade	Percentage of all complications right side (n = 20)*,**	Percentage of total series (n= 159)	Complications	Patients (n)
2	33.3 (n= 6)	3.8		
2a	0	0	0	0
2b	22.2 (n= 4)	2.5	Serosal lesion colon	2
			Small bowel injury	1
			Bladder lesion	1
2c	11.1 (n=2)	1.3	Renal arterial injury	1
			Lower pole artery unintentionally cut	1
3	0	0	0	0
4	5.0 (n= 1)	0.6	Myocardial infarction	1

Grade	Percentage of all complications left side (n= 33)*,***	Percentage of total series (n= 124)	Complications	Patients (n)
1	54.5 (n= 18)	14.5	Splenic injury superficial	5
			Lower pole artery unintentionally cut	1
			Subcapsular haematoma kidney	1
			Pneumonia	1
			Wound infection	4
			Elective conversion	5
			Temporary lateral thigh numbness	1
2	42.4 (n= 14)	11.3		
2a	3.0 (n= 1)		Blood loss > 500 ml	1
2b	21.2 (n= 7)		Serosal lesion small intestine	2
			Ureter unintentionally cut	1
			Wound infection	1
			Renal vein injury	1
			Presumed continuous bleeding	2
2c	18.2 (n= 6)		Renal artery injury	2
			Renal vein injury	2
			Lumbar vein injury	2
3	3.0 (n= 1)	0.8	Splenectomy secondary to splenic injury	1
4	0	0	0	0

* Complications of R-LDN and L-LDN of 20 and 32 donors respectively.
** One donor with a R-LDN had a re-operation due to small bowel injury, the highest grade was scored.
*** Five donors with a L-LDN had an intraoperative complication resulting in post-operative complication, the highest grade was scored.

disorder. The other recipient of a right kidney lost the graft at day 24, also due to arterial thrombosis. Renal vein thrombosis did not occur in any recipient. Other outcomes of the recipients were similar (Table 5). Most kidneys of both sides immediately functioned after reperfusion. Glomerular filtration rates of recipients of right versus left kidneys did not differ (data not shown). During follow-up (range 5 months to 7 years) eight recipients died in the R-LDN group and five in the L-LDN group. Causes of death in recipients in the R-LDN group were myocardial infarction (n=4), varicella zoster virus infection and sclerosing peritonitis, untreatable sepsis, B-cell lymphoma of the brain, and one patient was abstained due to multiple vascular problems. Causes of death in recipients in the L-LDN group were untreatable sepsis (n=3), respiratory insufficiency, and cerebral lymphoma. In addition to the aforementioned losses due to thrombosis, 8 grafts were lost. In the R-LDN group four grafts were lost, due to chronic allograft nephropathy, vascular-, humoral- and chronic rejection. In the L-LDN group four transplants were lost, due to a spreading gynaecological infection, chronic allograft nephropathy, vascular rejection necrosis and reactivation of the hemolytical uremic syndrome.

DISCUSSION

R-LDN should be implemented in live kidney donation programs to offer all donors the benefits from LDN and to procure optimal grafts. Moreover, we believe that right-sided laparoscopic donor nephrectomy may be advocated. In three out of four recent randomised trials addressing laparoscopic versus open live kidney donation, LDN was restricted to left kidneys with a single artery.[3, 15, 16] Our data show that selection of the right kidney was inevitable in ten donors due to a certain degree of stenosis or fibromuscular dysplasia of the renal artery at the right side. Furthermore, 27 right kidneys with single arteries could be procured instead of left kidneys with multiple-arteries. This facilitated both the nephrectomy and the implantation and may have avoided ureteral complications.[8]

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

Two common reasons influence many surgeons not to perform R-LDN. First, a positive association of laparoscopically procured right kidneys and renal vein thrombosis has been reported.[7] However, the absolute number of renal vein thrombosis has been very low and did not allow firm inferences. Data may be biased by selection of right kidneys. Most transplant centres have started with L-LDN and R-LDN is often performed as an exception only. In various reports by high volume centres the percentage of right kidney procurement is lower than 5%.[17-19] Second, in many centres a laparoscopic surgeon performs the nephrectomy and another surgeon transplants the kidney. The second surgeon (i.e. the transplant surgeon) has to be satisfied with vessel lengths and vessel quality. In our experience shorter and presumed weaker right renal veins do never cause problems during implantation. We believe that the prejudices of transplant surgeons against the short vessels of R-LDN are a more likely reason that the laparoscopic procurement of right kidneys is limited, rather than incidental thrombosis.

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

The intra-operative complication and conversion rates for L-LDN in our study appear notably high. The prospective registration with a research fellow recording all events in the operation room certainly attributes to these relatively high rates. Retrospective single centre reports mainly described L-LDN and report low conversion rates and low intra-operative complication rates.[17-19] We would like to stress that most reported complications required brief, conservative treatment only and are likely to be underscored in retrospective studies. Safety of the donor and the graft is of utmost importance during live donor nephrectomy. As a result, in our opinion it is necessary to document any adverse event lengthening operation time or hospital stay or causing potential danger to donor or graft. We realise that this approach may sometimes blur the true detriment a kidney donor may have from some reported complications (i.e. a small splenic injury without any consequence). Furthermore, good results with mini-incision open donor nephrectomy at our centre has led to a low threshold for elective conversion to a muscle splitting open approach when nephrectomy appears not easy.[14]

Ideally, a randomised trial would assess the superiority of R-LDN over L-LDN. However, as indicated there is a good reason to procure one of the kidneys in approximately 70% of the donors. The remainder could be randomised, but accrual of participants would be slow. Nevertheless, Minnee et al. performed a small randomised study for hand-assisted laparoscopic donor nephrectomy (HALDN). The operating time of HALDN of the right kidney is significantly shorter than HALDN of the left kidney. They did not assess differences in complication rates and graft survival between left and right-sided donor nephrectomy.[20] The absolute number of patients was small and therefore conclusions with regard to complications and renal vein thrombosis in the recipient cannot be drawn.

Our report is the first that includes a relatively high number of R-LDNs, and therefore allows inferences with regard to complication rates and recipient renal vein thrombosis.

Right-sided nephrectomy appeared the only baseline factor that decreases the number of complications. Thrombosis of the right renal vein did not occur. Our report, together with the current literature on R-LDN, rebuts the arguments of Mandal et al. against R-LDN.[7]

To avoid the learning curve of LDN as a potential confounder in this study (L-LDN was learned first in our institute), we decided to test the selection protocol only after enough experience had been gained with both techniques.

We have previously reported the feasibility of R-LDN and also showed good results, at least partly because of the later introduction of R-LDN.[9] Many American and European centres still prefer not to perform R-LDN.[6] As our data not only indicate the feasibility but also the superiority of R-LDN, the current study may remove prejudices against laparoscopic procurement of right kidneys. Adopting R-LDN is for the benefit of the surgeon and the donor.

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Chapter 5

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 centres in 12 European countries. Questions included the number of donors, the technique used, and the acceptance of donors with comorbidities.

Ninety-six centres (81%) replied. The number of living donors per centre ranged from 0 to 124. Thirty-one institutions (32%) harvested kidneys using open techniques only. Six centres (6%) applied both endoscopic and open techniques; 59 centres (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 centres, a lumbotomy is still performed. Seventy-two centres (75%) accept donors with a body mass index of more than 30 kg/m^2, the median upper limit in these centres was 35 kg/m^2 (range, 31-40). Donors with an American Society of Anaesthesiologists classification higher than 1 were accepted in 55% of the centres.

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 centres. 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-donor kidney 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 life of the live donor has been improved significantly. These surgical approaches include the retroperitoneoscopic technique with and without hand assistance, the fully laparoscopic techniques, and the modified open donor nephrectomy using mini-incision techniques.[3-7]

In 2006, we published the results of a survey on live donor nephrectomy in 12 countries in Northern and Western Europe. We evaluated the status of the surgical approach as of 2004 and observed a great variation in the technique preferred within and between European countries.[8] 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.

METHODS

A questionnaire was sent to 119 transplant centres in Austria, Belgium, Denmark, France, Finland, Germany, Ireland, the Netherlands, Norway, Sweden, Switzerland, and the United Kingdom. In each centre, a surgeon or an urologist was approached by mail and e-mail. The list of centres 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 centres were invited to participate for the second time. Remaining non-responding centres were approached individually by e-mail or by telephone. The questionnaire included issues on live kidney donation in four sections (Table 1). 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 comorbidities. Both open and multiple-choice questions were included in the questionnaire. In most multiple-choice

Table 1. Questions on live donor nephrectomy

A. No. of kidney transplantations
How many kidney transplantations from a deceased donor were performed in your centre in 2009?
How many kidney transplantations from a living donor were performed in your centre in 2009?
Did these numbers change during 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 your average incision length?
Do you see incisional hernias postoperatively?
C. Laparoscopic donor nephrectomy
Is LDN currently performed in your centre?
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 centre 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 centre 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?

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 Biomedicine, 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, IL). A P value G0.05 was considered statistically significant.

RESULTS

We received 97 replies (82%). One centre expressed unwillingness to cooperate. Therefore, these results are based on 96 replies received from 12 countries. Surgeons who responded and stated their name at the end of the questionnaire were included in the acknowledgments with their affiliations.

Number of Transplantations

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

The responding centres 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 centre was 26% (range, 0%-82%). This percentage was below 10% in 18 centres (19%), between 10%-25% in 27 centres (28%), between 25%-50% in 44 centres (46%), and more than 50% in seven centres (7%).

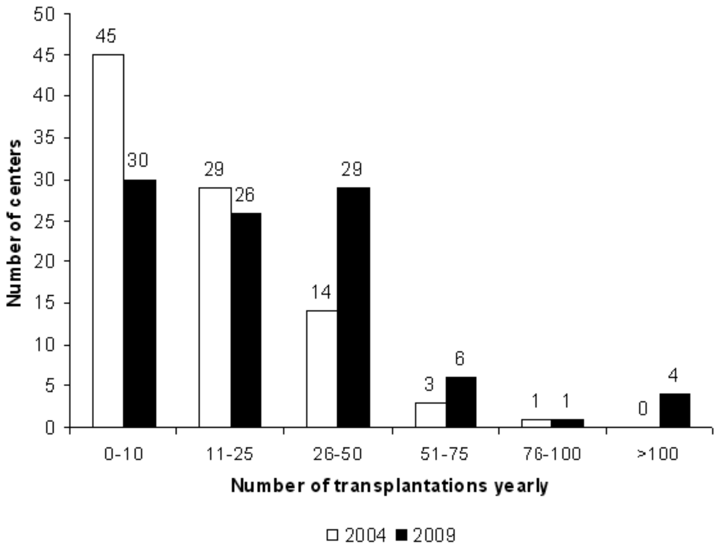

Figure 1. Case volume in responding centers in 2004 and 2009.

Open Donor Nephrectomy

Thirty-seven centres (39%) reported to perform ODN. Thirty-one of these centres used open techniques exclusively. These 31 centres were responsible for 482 live-donor nephrectomies, nineteen percent of all live-donor nephrectomies performed by the reporting centres. The median number of live-donor nephrectomies per centre 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 2. Lack of evidence that LDN was superior seemed to be an important reason to still prefer ODN. The other 15 centres had practiced endoscopic techniques in the past. The main reasons to perform ODN were the evolution of this technique in the centre, safety, and lack of evidence that LDN was superior. In 7 of the aforementioned 31 centres, a lumbotomy was still performed. In six centres, ODN and endoscopic techniques were used simultaneously, although ODN was preferred in these centres. The main reason to choose for an open approach in these clinics was also lack of evidence that LDN was superior.

Table 2. Reasons for centers to stick to open donor nephrectomy.

Reason	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)

LDN, laparoscopic donor nephrectomy; ODN, open donor nephrectomy.

Techniques of ODN

The preferred techniques used by the responding centres 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 was defined as a small flank incision varying from approximately 7 cm in lean donors to 15 cm in obese donors. A fourth option was the pararectal vertical skin incision.

Incisional Hernias and Incision Length

Incisional hernias were reported after all types of incision. Twelve centres in total reported to encounter incisional hernias. Two centres reported incisional hernias in 1% of the cases, three centres reported 2%, one centre reported 3%, four centres reported 5%, and two centres 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 mini-incision donor nephrectomy, 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 groups with and without hernias was 10 cm (P=0.847).

Laparoscopic Donor Nephrectomy

Fifty-nine centres (61%) reported to prefer endoscopic techniques for donor nephrectomy; the preferred techniques used by these centres are displayed in Figure 2. These centres were responsible for 1853 live-donor nephrectomies, 74% of all live-donor nephrectomies performed by the reporting centres. The median number of live-donor nephrectomies per centre in this group was 26 (range, 0-124). This median was significantly higher than the median number of live donor nephrectomies per centre in the group of centres performing only open techniques (PG0.001). Five of these centres started their laparoscopic program in 2010; and one centre, in 2011. Therefore, data on numbers were available from 53 centres. In 2009, 22 centres performed 20 or less procedures, 7 centres performed between 21 and 30 procedures, 8 centres performed 31 to 40 procedures, 5

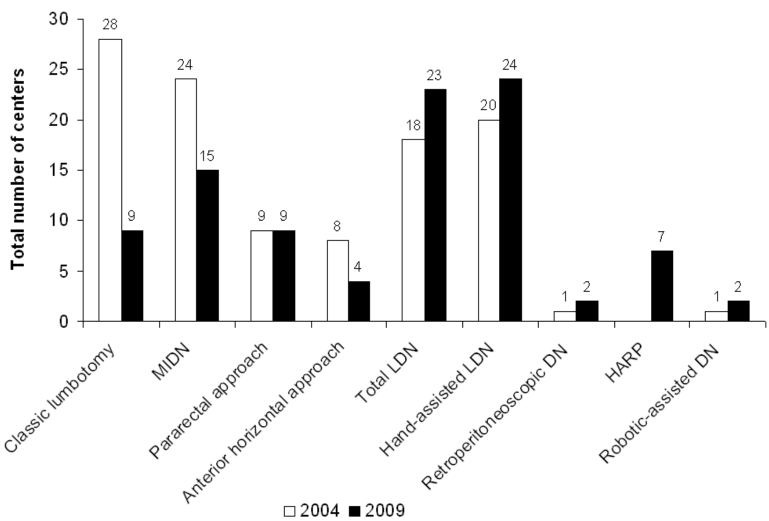

Figure 2. Preferred techniques in the responding centers in 2004 and 2009. LDN, donor nephrectomy; HARP, hand-assisted retroperitoneoscopic donor nephrectomy; LDN, laparoscopic donor nephrectomy; MIDN, mini-incision donor nephrectomy.

centres performed 41 to 50 procedures, and 11 centres performed more than 50 laparoscopic procedures.

Experience

Seven centres (12%) performed less than 25 laparoscopic procedures up to and including 2009. Eight centres (14%) performed 25 to 50 procedures, 7 centres (12%) performed 50 to 100 procedures, 10 centres (18%) performed 100 to 200 procedures, and 25 centres (44%) performed more than 200 procedures; 2 centres did not report on this item. Twenty-four centres (41%) had introduced laparoscopic techniques to their transplantation programs since 2005. Thirty-seven centres (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 centres, titanium clips were used to secure the renal vessels; in nine centres, self-locking clips were used; and in 43 centres, an endostapler was used. The remaining centres used a combination of these three tools. For extraction of the kidney, 40 centres (69%) used a Pfannenstiel incision. Other common extraction sites were subumbilical and anterolateral. Only two centres used a midline incision for kidney extraction. In 13 centres, an endoscopic procedure was converted to an open nephrectomy. The median conversion rate was 2% (range, 1%-7%). The median case volume in centres that converted one or more procedures in 2009 was significantly higher than centres that did not, 44 (range, 7-115) and 20 (range, 0-104) ($P=0.006$), respectively. There was no significant difference in years of experience between centres that did and did not convert ($P=0.933$).

Right-Sided LDN and Hand Assistance

Eight centres (14%) performed left-sided LDN only. The median percentage of right-sided LDNs in the remaining centres is 27% (range, 2%-98%). Indications for right-sided donor nephrectomy are summarized in Table 3. No relation was assessed between performing only left-sided LDN and years of experience ($P=0.059$) or case volume ($P=0.091$). Thirty-three centres (56%) used some form of hand assistance during LDN; reasons for hand assistance are stated in Table 3. No relation was found between the use of hand assistance and years of experience ($P=0.247$) or case volume ($P=0.533$).

Table 3. Indications for right-sided laparoscopic donor nephrectomy and reasons for hand-assistance.

Indication	No. of times mentioned (%)
Right-sided endoscopic DN (n=50)	
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 (24)
Donor/surgeon dependent	3 (9)
Learning LDN setting	2 (6)
Other	2 (6)

DN, donor nephrectomy; LDN, laparoscopic donor nephrectomy.

Comorbidities

Seventy-two centres (75%) accepted donors with a body mass index (BMI) above 30 kg/m^2. Twenty-eight centres had no specific upper limit because individual donor selection was at the discretion of the operating surgeon. In the remaining 44 centres, the median upper limit was 35 kg/m^2 (range, 31-40). Eighty of the responding 96 centres (83%) accepted donors with hypertension. Donors with an American Society of Anaesthesiologists classification higher than 1 were accepted in 55% of the centres.

Developments

The percentage of centres using endoscopic techniques only increased from 45% in 2004 to 61% in 2009. The percentage of centres using open techniques only decreased from 55% in 2004 to 33% in 2009. The number of centres performing a classic lumbotomy decreased from 28 (30%) to 9 (9%). In 2004, 21 (51%) of 41 centres used some form of hand assistance during donor-nephrectomy; in 2009, this increased to 33 (56%) of 58 centres. In 2004, 20 (49%) of 41 centres believed that the introduction of endoscopic techniques led to an increase of live kidney donors. Currently, 37 (63%) of 59 centres think that the introduction of endoscopic techniques led to an increase of live kidney donation. The number of centres restricting LDN to the left kidney decreased from 12 (29%) to 8 (14%).

Matching Centres

In the study published by Kok et al.[8] in 2006, the results were based on the replies from 92 different centres from 12 countries. Four of these centres no longer performed live kidney donation or merged with other centres by 2009. In the current study, we received 71 replies from the 88 remaining centres (81%). In these centres, the number of live donor kidney transplantations increased from 1169 (81% of the total number operated on in these 12 countries) in 2004 to 1920 (73%) in 2009. There was a significant increase in the median number of endoscopic donor nephrectomies per centre in 2009 when compared with 2004, 11.5 and 18 (P=0.028), respectively. The percentage of centres 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 centres using 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 centres are performing more live donor nephrectomies per year. Most transplant centres stated that this increase may partially be because of the introduction of laparoscopic techniques; this is confirmed by a significant difference in median case volume between centres performing only open and only endoscopic techniques. The number of centres performing LDN and its variants has increased since 2004. A minority of the centres decided not to adopt minimally invasive endoscopic techniques. In the last 5 years, a decrease of centres performing a classic lumbotomy can be noted. The most important reason to choose for an open approach was lack of evidence favouring LDN. This finding is surprising because 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, LDN 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 centres that favour ODN is the evolution of this technique in their centre. 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 centres reporting on incisional hernias and the reported rate may be an underestimation. Donors do not necessarily return to the transplantation centre to undergo a correction for an incisional hernia. Furthermore, duration of follow-up may differ between transplantation centres. However, incisional hernia rates after transverse incisions of the abdomen have been reported to be low.[17] Remarkably, 9 (15%) of the 59 centres performed endoscopic donor nephrectomy using self-locking clips for renal arterial control. A nationwide class II recall of the Hem-o-lock locking clip by the Food and Drug Administration in the United States was issued in 2009, that is, before the survey.[18] However, hemorrhagic deaths of live kidney donors from the failure of these clips have been reported before then.[19] The use of these clips to secure the renal artery, in contradiction to Food and Drug Administration recommendations, is a major concern. The use of self-locking clips should be avoided to maximize donor safety. This survey shows that approximately 54% of all centres 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 also become a true alternative with similar outcomes.[21] Our results confirm this because 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 centres. A significant increase in centres performing right-sided LDN was observed; in these centres, approximately one-third of all donor nephrectomies are right-sided. Indications for right-sided LDN were related to donor anatomy or split function. No centres mentioned shorter vessel length or renal vein thrombosis as reasons to prefer the left kidney over the right. Three centres 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 of right renal vein thrombosis caused by shorter vessel length seems ungrounded. The eligibility criteria for live kidney donation have been extended. The vast majority of centres accept donors with a BMI above 30 kg/m^2. 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 an American Society of Anaesthesiologists 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) comorbidities. 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, are more commonly applied in Northern and Western Europe. However, a classic lumbotomy is still performed in a minority of centres. Because minimally invasive techniques have been proven superior, this should be addressed through guidelines training and education to let all kidney donors benefit from 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 6

Long-term follow-up of a randomized trial comparing laparoscopic and mini-incision open live donor nephrectomy

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ABSTRACT

Long-term physical and psychosocial effects of laparoscopic and open kidney donation are ill defined. We performed long-term follow-up of 100 live kidney donors, who had been randomly assigned to mini-incision open donor nephrectomy (MIDN) or laparoscopic donor nephrectomy (LDN). Data included blood pressure, glomerular filtration rate, quality of life (SF-36), fatigue (MFI-20) and graft survival.

After median follow-up of 6 years clinical and laboratory data were available for 47 donors (94%) in both groups; quality of life data for 35 donors (70%) in the MIDN group, and 37 donors (74%) in the LDN group. After 6 years, mean estimated glomerular filtration rates did not significantly differ between MIDN (75 mL/min) and LDN (76 mL/min, p = 0.39). Most dimensions of the SF-36 and MFI-20 did not significantly differ between groups at long-term follow-up, and most scores had returned to baseline. Twelve percent of the donors reported persistent complaints, but no major complications requiring surgical intervention. Five-year death-censored graft survival was 90% for LDN, and 85% for MIDN (p = 0.50).

Long-term outcome of live kidney donation is excellent from the perspective of both the donor and the recipient.

INTRODUCTION

In order to limit discomfort to the donor minimally invasive surgical techniques have become the standard of care for live kidney donation. Among various alternatives, these surgical approaches include mini-incision open donor nephrectomy (MIDN) and laparoscopic donor nephrectomy (LDN). The short-term consequences of these methods have been established.[1-5] Both open and laparoscopic techniques improve the convalescence of the donor, without detrimental effects on graft survival.[6-11] LDN results in faster recovery, less fatigue and better quality of life (QOL) of the donor up to 1 year after the donation procedure as compared to MIDN.[1] We previously reported the results of a randomized trial comparing open and LDN. One year after the donation QOL and fatigue scores were still in favour of LDN.[1] This warranted longer follow-up. Consequently, we analyzed physical and psychosocial outcomes in the same, randomized cohort 6 years after donor nephrectomy.

METHODS

Patients

All procedures were performed in two Dutch university medical centers. All eligible donors who were considered for randomization were informed about the two surgical approaches. Standard preoperative screening of donors included examination by a nephrologist, a transplant surgeon, a social worker and an anaesthetist. Renal ultrasonography, magnetic resonance angiography or digital subtraction angiography were performed to evaluate the vascular anatomy of the kidneys. If both kidneys were suitable for transplantation the right kidney was preferred for transplantation. Details of the inclusion criteria, randomization, surgical procedures and anaesthesia and analgesia have been published elsewhere.[1] Because our previous 1-year follow-up RCT showed remarkably favorable results for the LDN, as compared to MIDN, that became only apparent after analysis of the original data, we decided to write an amendment to the protocol in order to obtain post 1-year follow-up data of the donors. All donors were approached by mail and telephone on long-term follow-up post-donation. Consent of an internal review board was obtained.

Surgical procedures

Both techniques have been described previously.[1] Briefly, in LDN four to five trocars were introduced in the peritoneal cavity under direct vision. After opening of the renal capsule and division of the perirenal fat, the ureter and vascular structures were dissected. A Pfannenstiel incision was made as extraction site. The ureter was clipped and divided and the renal vessels were stapled. The kidney was recovered with an endobag (Endocatch, US surgical, Norwalk, USA). A horizontal 10–12-cm skin incision anterior to the 11th rib enabled MIDN. A mechanical retractor was used (Omnitract surgical, St. Paul, USA). The muscles of the abdominal wall were split. Gerota's fascia was opened on the lateral side of the kidney. After dissection of the kidney and its structures, the ureter, renal artery and vein were subsequently divided and the kidney was extracted. The fascias of the abdominal muscles were closed and the skin was sutured intracutaneously.

Data collection

After discharge donors had visited the outpatient clinic at 3 weeks, 2 months, 3 months and 1 year postoperatively. Thereafter they were requested to report for annual control visits. Prospective data on serum creatinine and blood pressure were collected. Glomerular filtration rate (GFR) was estimated according to the Cockcroft Gault formula.[12] Hypertension was defined according to World Health Organization definitions, that is, for donors <45 years of age: systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg; for age of >45 years: systolic blood pressure >160 mmHg and/or diastolic blood pressure >95mmHg and/or for both age groups the use of antihypertensive medication.[13] In order to assess the long-term effect of MIDN and LDN on physical and psychosocial health, donors were asked to complete forms quantifying fatigue, QOL and body image using validated questionnaires.[1] The Multidimensional Fatigue Inventory-20 (MFI-20, fatigue) and the Short Form-36 (SF-36, QOL) were administered preoperatively, and at 1, 3, 6 and 12 months postoperatively. We assumed that there would be no effect of time on the outcomes of between group comparisons because the hidden block size of the randomization list was four (i.e. in every group of four subsequent donations two laparoscopic and two open procedures had been performed). The MFI-20 includes 20 items, each item ranging from one to five. Each item is 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).[14] The SF-36 is a multi-item scale that measures 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 health 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.[1,15] The body image questionnaire (BIQ) was assessed at 1-year postoperatively and during long-term follow-up. BIQ consists of two scales: the body image scale (BIS) and the cosmetic scale (CS). The BIS consists of five questions evaluating the attitude of the patient toward his/her bodily appearance and scores the results on a scale ranging from 5 to 20. The CS consists of three questions assessing the donor's degree of satisfaction with respect to the appearance of the scar, and scores the results on a scale ranging from 3 to 24. For both scales higher scores indicate greater satisfaction.[16] The donor's retrospective experience of donation was evaluated with four non-validated questions evaluating the donor's retrospective experience of the surgery, retrospective experience of the donation, postoperative morbidity and alteration of the relationship with the recipient.

Recipients

Preperitoneal placement of the renal transplant in the iliac fossa was applied as the standard operation technique. Recipient survival, graft survival and serum creatinine levels were recorded during follow-up. GFR was estimated according to the Cockcroft Gault formula.[12]

Statistical analysis

Categorical variables were compared with the Chi square test, continuous variables with the Mann Whitney U test and repeated continuous variables with repeated measurement ANOVA. Repeated measures were adjusted for baseline values and for donor's gender and age. All analyses were conducted using SPSS (version 11.5, SPSS Inc., Chicago, USA). A p-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Fifty donors were randomly selected for MIDN and 50 for LDN, between November 2001 and February 2004. Baseline characteristics were not significantly different between groups.[1] Surgical outcome, postoperative complications and donor's QOL up to 1 year postoperatively have been described elsewhere.[1] Median follow-up of the donors was 6 years (range 1 to 8 years). One donor (MIDN) died after 4.5 years of follow-up due to breast cancer, and one donor (LDN) died due to a car accident 2 years after donation. Donor response rates with regard to the forms decreased from 89% at 1 year follow-up to 72% at 3–5 years post-donation (Figure 1). There was no significant difference in response rate between MIDN and LDN donors. Baseline characteristics of the responders in both groups did not significantly differ apart from a better response rate in older donors (median age 50 years) versus a median age of 45 years among non-responders (data not shown).

Long-term complications, residual kidney function and incidence of hypertension (Table 1)

The estimated GFR was not significantly different between both groups at any measured point in time. Hypertension pre-existed in seven donors (2 MIDN; 5 LDN). These donors

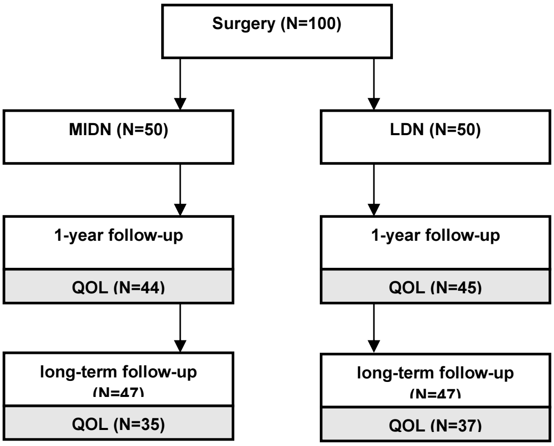

Figure 1. Flowchart of follow-up of 100 randomized live kidney donors. The white boxes represent the number of donors returning annually to the outpatient clinic and corresponding data on their residual kidney function and blood pressure. The grey boxes represent the available data on donor's quality of life (QOL).

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

		MIDN (N=47)	LDN (N=48)	P-Value
Donor				
Female (%)		24 (51%)	21 (44%)	0.27
Age (years)		52 (24-78)	53 (23-81)	0.77
Hypertension (%)				
Preexisted		2 (4%)	5 (10%)	0.44
New onset		3 (6%)	2 (4%)	0.53
GFR (ml/min)				
Pre-donation		107.2 (29.3)	113.3 (30.0)	0.39
Longest follow-up		73.9 (23.3)	77.3 (22.8)	0.61
Surgery				
Turned out better than expected		29 (82%)	32 (88%)	0.38
Donate kidney again		35 (100%)	37 (100%)	0.52
Relationship with recipient	Improved	11 (32%)	9 (24%)	0.19
	Unchanged	22 (62%)	28 (76%)	
	Deteriorated	2 (6%)	-	
Body Image Questionnaire				
Body Image Scale (BIS)	Year 1	20 (14-20)	20 (13-20)	0.40
	Follow-up	20 (13-20)	20 (18-20)	0.14
Cosmetic Scale (CS)	Year 1	18 (12-24)	20 (7-24)	0.14
	Follow-up	20 (12-24)	20 (9-24)	0.65
Recipient				
Five year graft survival*		85%	90%	0.50
Five year patient survival		86%	94%	0.33

*censored for death

were all treated medically. Five donors (3 MIDN; 2 LDN) developed high blood pressure during follow-up that was adequately treated with medication. All seven donors who were treated for hypertension at baseline did very well at long-term follow-up, and importantly the blood pressure was under control. Four donors took one and the same antihypertensive drug before and after donation and at long-term follow-up. Three other donors were treated with two anti-hypertensive drugs before the donation.

Two of these donors are still on the same medication, while one donor switched to two different antihypertensive drugs. At follow-up, 12% of the donors described residual disabilities. These included complaints about new onset high blood pressure (n = 2), meralgia paraesthetica (n = 1), psychological problems (n = 1) and pain at the scar site (n = 1) in the open group. In the laparoscopic group the complaints were general fatigue (n = 1) 'not related to the donation', hypertension (n = 1) and pain at the extraction incision (n = 1) in the laparoscopic group pain at the site of the Pfannenstiel incision (n = 2). These disabilities did not stop the donors from continuing their normal daily activities. If possible, all donors would have donated their kidney again. Long-term complications of surgery such as ventral hernias or bowel obstructions due to adhesions did not occur in either group.

Fatigue and QOL (Tables 1 and 2 and Figure 2A–C)

Not all dimensions of the MFI-20 returned to normal values in the course of time. Mean scores for physical and general fatigue did not return to baseline values in both groups (Figure 2A and B). However, between group analysis of the MFI-20 did not show statistically significant in-between-group differences at long-term follow-up. At 1-year follow-up physical fatigue was the only dimension that was significantly lower in the LDN Group ($p = 0.05$). Baseline health status of all donors was excellent and did not differ between groups.[1] At 1-year follow-up the dimensions physical function, vitality, social function and role emotional dimensions were significantly different in favor of LDN (p-values 0.03, 0.03, 0.04 and 0.007, respectively).[1] At long-term follow-up, the scores for all the dimensions of QOL as measured with the SF-36 returned to baseline in both groups (Figure 2C). Between-group analysis revealed a small difference in physical function only, in favor of LDN (Table 2). At follow-up the attitude toward bodily appearance (BIS) and appearance of the scar (CS) scores was not different between groups. These scores did also not significantly change over time (Table 1).

All donors retrospectively evaluated their donation in a positive way. The donor's attitude toward donation was not influenced by the applied surgical approach. Nor was it affected by transplant failure or by death of the recipient (data not shown).

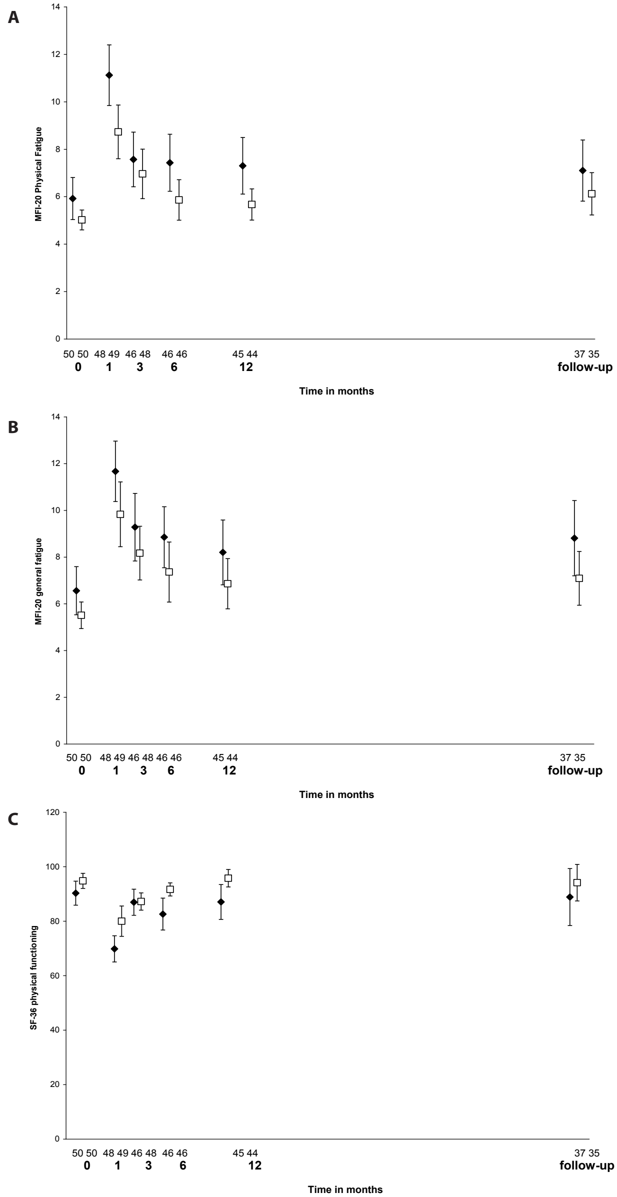

Figure 2. (A) Physical fatigue (MFI-20) during long-term follow-up displayed as means and corresponding intervals (closed diamonds, MIDN; open squares LDN). Numbers underneath the X-axis represent the number of donors evaluated at each point in time (left number MIDN; right number LDN donors). (B) General fatigue (MFI-20) during long-term follow-up displayed as means and corresponding intervals. (closed diamonds, MIDN; open squares LDN). Numbers underneath the X-axis represent the number of donors evaluated at each point in time (left number MIDN; right number LDN donors). (C) Physical functioning (SF-36) during long-term follow-up displayed as means and corresponding intervals. (closed diamonds, MIDN; open squares LDN). Numbers underneath the X-axis represent the number of donors evaluated at each point in time (left number MIDN; right number LDN donors).

Table 2. Quality of life of minimal invasive open donor nephrectomy (MIDN) versus laparoscopic donor nephrectomy (LDN). Raw data at one-year and long term 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 long-term follow-up. Negative differences regarding SF-36 indicate a better quality of life following LDN. Positive differences regarding the MFI-20 indicate less fatigue following LDN.

Dimension	One-year follow-up		Long-term follow-up		Estimated difference (MIDN minus LDN)	95% Confidence Interval	P-value
	MIDN	LDN	MIDN	LDN			
SF-36							
Physical function	87.0 (21.1)	95.8 (10.8)	88.8 (15.8)	94.1 (11.0)	-6.4	-12.3 to -0.5	0.03
Role physical	85.7 (32.7)	92.2 (26.0)	87.1 (30.0)	94.1 (19.5)	-5.1	-16.2 to 5.9	0.35
Bodily pain	91.7 (19.6)	97.5 (8.6)	92.2 (17.8)	91.7 (18.5)	-0.07	-8.3 to 8.1	0.99
General health	83.3 (18.1)	85.7 (15.9)	82.4(18.1)	84.6 (15.0)	-4.1	-11.1 to 2.9	0.24
Vitality	72.1 (19.7)	82.2 (13.2)	76.2 (18.7)	80.6 (14.4)	-3.8	-10.8 to 3.2	0.28
Social functioning	86.9 (22.7)	96.7 (9.0)	92.6 (17.6)	97.8 (9.0)	-4.8	-11.4 to 1.8	0.15
Role emotional	83.8 (35.8)	100.0 (0.0)	91.2 (23.7)	97.0 (17.4)	-5.6	-15.4 to 4.2	0.26
Mental health	67.2 (14.8)	68.6 (12.7)	65.9 (14.4)	67.8 (12.1)	-3.3	-8.9 to 2.2	0.23
MFI-20							
General fatigue	8.2 (4.4)	6.9 (3.6)	8.8 (4.5)	7.1 (3.4)	1.0	-0.61 to 2.7	0.22
Physical fatigue	7.3 (3.9)	5.7 (2.2)	7.1 (3.6)	6.1 (2.6)	0.56	-0.78 to 1.9	0.41
Reduced activities	7.6 (4.2)	6.0 (2.7)	6.6 (4.0)	6.4 (2.6)	0.23	-1.3 to 1.7	0.76
Reduced motivation	7.5 (4.5)	5.9 (2.7)	7.1 (3.9)	6.1 (2.3)	0.61	-0.62 to 1.8	0.33
Mental fatigue	8.5 (4.4)	6.4 (3.5)	7.7 (4.5)	6.4 (3.1)	0.79	-0.67 to 2.2	0.28

Recipients

Nine recipients died during the follow-up period. One recipient (LDN) died on the first postoperative day due to myocardial infarction. Two recipients (one MIDN and one LDN) died in the first year because of progressive infections related to their immune-compromised state. During the second year of follow-up, two other recipients died, respectively, due to myocardial infarction (MIDN) and adenocarcinoma of unknown origin in the liver and lung (MIDN). One recipient (LDN) died during the third year of follow-up because of plasma cell leukemia. Two recipients died in the fifth year after transplantation, one due to a metastatic lymphogenic bronchial carcinoma (MIDN), the other recipient died from an unknown cause. Another recipient (MIDN) died from a lung embolism in the sixth postoperative year. Five-year survival was 94% for LDN recipients and 86% for MIDN recipients ($p = 0.328$). Additionally, 10 recipients (6 MIDN, 4 LDN) lost their grafts due to rejection. Three-year death-censored graft survival rates were 87% for MIDN and 92% for LDN ($p = 0.525$). Five-year death-censored graft survival rates were, respectively, 85% for MIDN and 90% for LDN ($p = 0.498$). Serum creatinine levels decreased parallel wise to comparable levels without any significant differences between recipients transplanted with a kidney procured via open or via laparoscopic nephrectomy.

DISCUSSION

Long-term survival of live kidney donors compares favourably with the life span of age-matched controls.[17] However little is known about the long-term QOL following live donation. We here present unique follow-up data of a randomized cohort with a relatively high response rate. We also include follow-up data on hypertension and renal function of the donor. Regular, annual follow-up is rarely reported in other publications. Most other studies addressing the donor's QOL are more limited in scope because of their retrospective, cross-sectional data collection.[18-23] Comparison to baseline and evaluation of postoperative changes in QOL of the donor were not possible.[24,25] In addition, those results may be biased by low response rates.[22] None of the aforementioned studies have investigated the effect of the employed surgical technique on the QOL after the donation. For these reasons the assumption that QOL is not affected by donor nephrectomy is unfounded. Andersen et al. have shown that surgical technique influences several dimensions of QOL months after donation, but they did not assess differences at 1 year.[26] In contrast, in our previous study QOL at 1 year was superior in laparoscopically operated donors.[27] Therefore we attempted in the present study to acquire longer follow-up data of the same cohort. In both donor groups the QOL scores returned to baseline values indicating that, on average, the donor does not experience lasting harms of donation. Severe long-term complications requiring further surgical interventions did not occur. The reported residual disabilities may be considered relatively minor, and these residual disabilities would not have kept donors from another imaginary live donor nephrectomy. The applied surgical technique seems of minor importance to the donor at long-term follow-up. A minor difference in physical function may be considered irrelevant as the scores for donors in both the open and the laparoscopic group had returned to normal. Intriguingly, fatigue persisted for several years after live kidney donation. We question whether this is a result of living with one kidney, or a general effect of aging. QOL has been shown to depend on age.[15] No data on fatigue in live donors are available in the literature. A small subset of donors experienced residual disabilities. In this subset, scores in each domain of fatigue were median 1–4.5 points higher, indicating more fatigue. Because the number of donors in this group is too small to assess statistically significant results, presence of disabilities alone does not explain this. Further studies should elucidate these findings.

The QOL of the donor could presumably be affected by graft failure and death of the recipient.[23,24,28] However, the number of events (graft failure or recipient mortality) in our study is too small to properly assess such an influence. Nevertheless, it should be noted that such an adverse event did not influence the donor's willingness to donate the kidney again if asked to. This finding is consistent with the literature. Donors appear to regret donation in 1–5%.[19,23,24,29] Concordant with other studies there was no evidence of accelerated loss of kidney function after donation, regardless of the surgical technique used.[6,30,31]

The age- and gender-specific incidence of hypertension was somewhat lower than that of the Dutch population in general. This may be explained by a better preoperative health status of the live kidney donors as compared to that of the general population because of donor selection. Donor conception with respect to cosmetic outcome did not change over time and showed no between-group difference. The high scores on both BIS and CS indicate that cosmetic outcome perception appears to be excellent after both open and LDN.

The present study has two main limitations: the method of data collection (at different times during follow-up as outlined in the methods section) and the decreasing response rate to our QOL and fatigue forms. The non-responders of this study were mostly donors who had no complaints and possibly therefore did not appreciate the significance of completing the same questionnaires again. The responders were relatively older than the non-responders. In spite of these limitations we consider the results of the present study to be valuable, because the distribution of follow-up time and baseline characteristics is rather similar between LDN and MIDN groups.

The findings of this study offer an opportunity to provide useful information to prospective live kidney donors about what to expect of the surgical procedure and of the long-term outlook of their recovery. Interestingly, 12% of the donors in either group experienced their donor nephrectomy as worse than anticipated, indicating that there is still room for improvement in the mental preparation of live kidney donors. These results are essential prerequisites for expanding live kidney donation programs across the world.

In summary, serious long-term complications of living donor kidney donation did not occur, QOL scores returned to preoperative levels and donors were satisfied with the donation procedure. At long term, mode of surgical technique appears of minor importance to the donor at long-term, provided that a minimally invasive approach is applied. In conclusion the results of live kidney donation are excellent at long term.

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Chapter 7

Optimizing left-sided live kidney donation: hand-assisted retroperitoneoscopic as alternative to standard laparoscopic donor nephrectomy

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ABSTRACT

Laparoscopic donor nephrectomy (LDN) is less traumatic and painful than the open approach, with shorter convalescence time. Hand-assisted retroperitoneoscopic (HARP) donor nephrectomy may have benefits, particularly in left-sided nephrectomy, including shorter operation and warm-ischemia time (WIT) and improved safety. We evaluated outcomes of HARP alongside LDN. From July 2006 to May 2008, 20 left-sided HARP procedures and 40 left-sided LDNs were performed. Intra and postoperative data were prospectively collected and analysis on outcome of both techniques was performed. More female patients underwent HARP compared to LDN (75% vs. 40%, P = 0.017). Other baseline characteristics were not significantly different. Median operation time and WIT were shorter in HARP (180 vs. 225 min, P = 0.002 and 3 vs. 5 min, P = 0.007 respectively). Blood loss did not differ (200 ml vs.150 ml, P = 0.39). Intra and postoperative complication rates for HARP and LDN (respectively 10% vs. 25%, P = 0.17 and 5% vs. 15%, P = 0.25) were not significantly different. During median follow-up of 18 months estimated glomerular filtration rates in donors and recipients and graft- and recipient survival did not differ between groups. Hand-assisted retroperitoneoscopic donor nephrectomy reduces operation and warm ischemia times, and provides at least equal safety. Hand-assisted retroperitoneoscopic may be a valuable alternative for left-sided LDN.

INTRODUCTION

In 2007, approximately 500 candidates for kidney transplantation died while being on the waiting list in the Eurotransplant countries and more than 4000 in the United States. In addition, a considerable number of patients were removed from the waiting list because their clinical condition for undergoing transplantation had deteriorated by the time their turn for allocation of organ came about.[1,2] Live kidney donation is an important alternative for patients with end-stage renal failure and is to date the most effective method to solve the shortage of kidney donors in a number of countries, including the Netherlands. Laparoscopic donor nephrectomy (LDN) has become the preferred method to procure kidneys in live donors because of the reduced surgical trauma and reduced pain subsequently, shorter convalescence time and superior quality of life as compared with open approaches.[3-6] However, safety issues of LDN has been debated. We recently showed that right-sided LDN is easier to perform as compared with left-sided LDN.[7] Although right-sided LDN is preferred in our centre wherever the anatomical configurations of both kidneys are identical, aspects such as the presence of multiple arteries on the right side demand left-sided nephrectomy in approximately 50% of the donors. At our centre, we therefore introduced the hand-assisted retroperitoneoscopic approach (HARP) as an alternative for the left-sided LDN on the presumption that transplantation procedure as per this technique could be performed faster and the same would be at least as safe as the standard laparoscopic approach. In theory, HARP combines the control, dexterity and speed of the hand-guided surgery with the benefits of minimal invasive surgery, benefits of LDN including retroperitoneal access and reduced surgical trauma. Other smaller series have suggested certain advantages from the HARP technique over LDN such as shorter operation times and possibly fewer complications.[8-10] Based on these promising results of the HARP technique, we hypothesized that HARP might result in a better outcome in patients undergoing left-sided donor nephrectomy. Therefore, we evaluated the results of the first 20 left-sided HARP procedures alongside 40 left sided LDNs performed during the same timeframe.

METHODS

Patient population

Between July 2006 and May 2008, 143 live kidney donors were operated at our center. The anatomy of the renal parenchyma and the arterial and venous anatomy of the kidneys were imaged by a combination of ultrasonography (US), and either magnetic resonance angiography (MRA) or computed tomography-angiography (CTA). Wherever the imaging studies revealed unilateral anatomical abnormalities i.e. ipsilateral arterial stenosis, that side was chosen. If multiple arteries (including early branching), veins or ureters were present unilaterally, the contralateral kidney was selected for removal. Eighty-three donors underwent right-sided LDN and were not included in the present analysis. The first 20 left-sided HARP operations were performed and compared with the procedures of 40 donors that underwent left-sided LDN during the same period. The reasons to opt for either type of operation were based on the anatomy, BMI, and previous abdominal operations. Discussions were held with all patients in a working group, wherein they were informed about the details of the various procedures and asked for consent. The Institutional Review Board of the Erasmus MC approved the study.

Surgical techniques

Both procedures were performed with the donor placed in right decubitus position. LDN was performed as described earlier.[11] In short, a 10-mm trocar was introduced under direct vision. The abdomen was insufflated to 12 cm water column pressure of carbon dioxide. A 30° video endoscope and three to four additional trocars were introduced. The colon was mobilized and displaced medially. Opening of the renal capsule and division of the perirenal fat were facilitated using an ultrasonic device (Ultracision, Ethicon, Cincinnati, OH, USA). After identification and careful dissection of the ureter, the renal artery and the renal vein, a Pfannenstiel incision was made. An endobag (Endocatch, US surgical, Norwalk, CT, 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, CT, USA) and the kidney was placed in the endobag and extracted through the Pfannenstiel incision. In HARP procedure, we started with a 7- to 10-cm Pfannenstiel incision. After blunt dissection to create a retroperitoneal space, the Gelport (Applied Medical, Rancho Santa Margarita, CA, USA) was inserted. Blunt introduction of the first trocar between the iliac crest and the handport was guided by the operator's hand inside the abdomen. Carbon dioxide was insufflated retroperitoneally to 12 cm water column pressure. Two other 10–12 mm trocars were inserted just outside the midline inferior to the costal margin and in the flank respectively, to create a triangular shape. For dissection the aforementioned UltraCision device was used. Dissection of the kidney and renal vessels was performed in procedure similar to transperitoneal donor nephrectomy but with handassistance and from a slightly different angle. The kidney was removed manually.

Outcome

A research fellow prospectively recorded operation- and warm ischemia time, intra- and postoperative complications and blood loss during the procedure. In addition, the donor was examined daily after the donation by the research fellow and clinical parameters, including pain scores were noted. Intraoperative and postoperative complications were graded according to the modified Clavien grading system described by Kocak et al.[12] Serum creatinine was recorded preoperatively, and postoperatively on days 1, 2, 3 (if still admitted) and approximately 3 weeks and annually thereafter. Glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease formula, which estimates GFR using four variables: serum creatinine, age, race, and gender.[13] Graft and recipient survival were recorded. Serum creatinine of the recipient was recorded preoperatively, during the first 14 days, day 21, 28 and every 3 months thereafter. The donor was discharged provided a normal diet was tolerated and mobilization was adequate. Postoperative hospital stay was calculated with and without correction for time spent in hospital as a result of nonmedical reasons (i.e. lack of homecare). Postoperatively, visits to the outpatient clinic were scheduled at 3 weeks, one year and yearly thereafter.

Statistical analysis

Categorical variables are presented as number (percentage). Continuous variables are presented as median (range). Categorical variables were compared with the chi-squared test. Continuous variables were compared with the Mann–Whitney U-test. All analyses were conducted using SPSS (version 15.0, SPSS Inc., Chicago, IL, USA). A P-value <0.05 (two-sided) was considered statistically significant.

RESULTS

Baseline characteristics

Twenty donors underwent HARP and 40 donors underwent LDN. More female patients underwent HARP as compared with LDN (75% vs. 40%, $P = 0.02$). Other baseline characteristics did not differ between groups (Table 1).

Intraoperative data

Median skin-to-skin time was shorter in the HARP group compared with the LDN group (180 min vs. 225 min, $P = 0.002$). Warm ischemia time was significantly shorter for the HARP group (3 min vs. 5 min, $P = 0.007$). Blood loss was minimal, and did not significantly differ between groups. Intraoperative complication rates for HARP and LDN (respectively 10% vs. 25%, $P = 0.17$) did not significantly differ between groups (Table 2). Intraoperative complications graded according to the modified Clavien grading system are displayed in Table 3.

Postoperative data

Postoperative complication rates for HARP and LDN (respectively 5% vs. 15%, $P = 0.25$) did not significantly differ between groups (Table 4). Postoperative complications

Table 1. Baseline characteristics of donors who underwent hand-assisted retroperitoneoscopic donor nephrectomy (HARP) and laparoscopic donor nephrectomy (LDN) and the corresponding recipients. Categorical data are presented as number (percentage). Continuous data are presented as median (range).

	HARP (n=20)	LDN (n=40)	P-value
Gender: female (%)	75	40	0.02
BMI (kg/m^2)	26 (19-32)	27 (20-36)	0.28
Age (years)	57 (36-72)	53 (30-71)	0.10
Solitary artery(%)	75	80	0.63
Solitary vein(%)	100	85	0.19
ASA-classification >1	35	25	0.42
Recipient			
Gender: female(%)	35	42	0.57
Age	53 (21-74)	51 (20-79)	0.79
Relation			
Living related(%)	40	45	0.91
Living unrelated(%)	35	30	
Cross-over(%)	25	25	
Pre-emptive(%)	45	30	0.16

Table 2. Intra-operative data of hand-assisted retroperitoneoscopic (HARP) versus laparoscopic donor nephrectomy (LDN). Categorical data are presented as number (percentage). Continuous data are presented as median (range).

	HARP (n=20)	LDN (n=40)	P-value
Skin to skin time (min)	180 (115-370)	225 (130-410)	0.002
Warm ischemia time (min)	3 (2-9)	5 (1-23)	0.007
Conversion	1 (5%)	1 (2.5%)	0.61
Blood loss (ml)	200	150	0.39
Complications	2 (10%)	10 (25%)	0.17

in the laparoscopic group included three wound infections, incisional hernia of the infra-umbilical port 2 months after donation (Re-operation and primary closure), epidermiolysis resulting from plasters, and temporary disorder in heart rhythm, which eventually needed monitoring without therapy. In the HARP group, one procedure was complicated by wound infection of the Pfannenstiel incision. In all recipients, urine production was noted before closure of the wound.

Mid-term outcome

During a median follow-up of 18 months, estimated glomerular filtration rates in both donors and recipients did not differ (Figs 1 and 2). Graft- and recipient survival did not significantly differ between recipients who received a graft procured by HARP and LDN respectively (Table 4).

Table 3. Intraoperative complications of HARP and LDN with grading by severity.

HARP	Grade*	Percentage of all complications (n = 2)	Percentage of total series (n= 20)	Complications	Patients (n)
	1	0	0	0	0
	2	100 (n= 2)	10	0	2
	2a	50 (n= 1)	5	Lumbar vein injury	1
	2b	0	0	0	0
	2c	50 (n= 1)	5	Lumbar vein injury, conversion	1
	3	0	0	0	0
	4	0	0	0	0
LDN	**Grade***	**Percentage of all complications (n = 10)**	**Percentage of total series (n= 40)**	**Complications**	**Patients (n)**
	1	50 (n= 5)	12.5	Blood loss < 500 ml	5
	2	50 (n= 5)	3.8		5
	2a	10 (n= 1)	2.5	Blood loss >500 ml	1
	2b	30 (n= 3)	7.5	Small bowel injury	1
				Bladder lesion	1
				Ureteral injury	1
	2c	10 (n= 1)	2.5	No overview, conversion to hand-assisted LDN	1
	3	0	0	0	0
	4	0	0	0	0

* 1 Non-life-threatening complications
2a Complications requiring only use of drug therapy, blood loss >500 mL or Hb drop >2 g/dL and/or resulting in hemodynamic instability or Hb <8 g/dL, readmission to hospital for medical management or prolongation of hospital stay for more than three times median length of stay.
2b Complications requiring additional therapeutic intervention (ie operation for bowel obstruction, interventional radiologic procedure) or readmission to the hospital for intervention.
2c Complications requiring open conversion of LDN for patient management
3 Any complication with residual or lasting functional disability
4 Leads to renal failure or death in the donor

Table 4. Post-operative data of hand-assisted retroperitoneoscopic (HARP) versus laparoscopic donor nephrectomy (LDN). Categorical data are presented as number (percentage). Continuous data are presented as median (range).

	HARP (n=20)	LDN (n=40)	P-value
Complications	1 (5%)	6 (15%)	0.25
Hospital stay (days)	3 (2-7)	4 (1-7)	0.19
Recipient survival*	19 (95%)	37 (93%)	0.71
Graft survival	17 (85%)	36 (90%)	0.44

*All recipients died with functioning transplants.

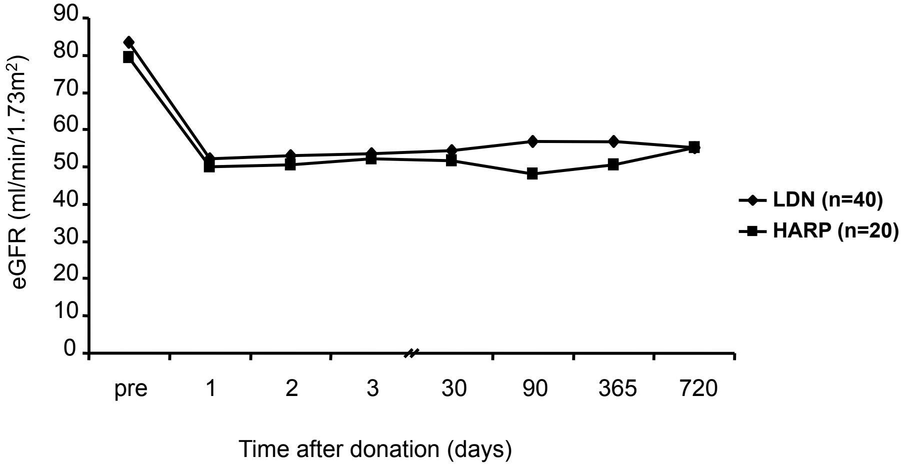

Figure 1. Estimated glomerular filtration rate after live kidney donation (MDRD-formula).

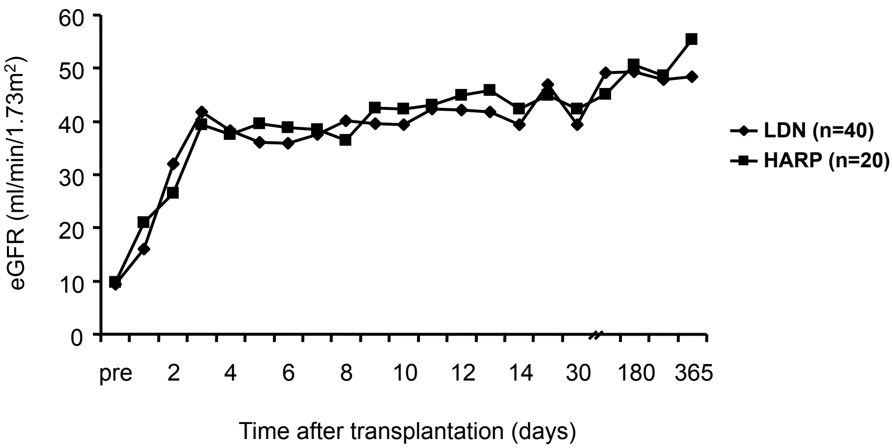

Figure 2. Estimated glomerular filtration rate after live kidney transplantation (MDRD-formula).

DISCUSSION

Live kidney donation is an important alternative for patients with end-stage renal failure and is to date the most effective way to solve the shortage of donor kidneys in a number of countries, including the Netherlands, We aim for perfection in operative technique for the healthy population of live kidney donors. This study shows that HARP donor nephrectomy is associated with shorter operation and warm ischemia times and offers at least equal safety in a selected group of patients. These results indicate that HARP may be a valuable alternative for left sided LDN at least in well-defined cases. Hand-assisted retroperitoneoscopic donor nephrectomy seems to be associated with certain advantages over the laparoscopic transperitoneal approach including easier and rapid control of bleedings by digital pressure, better exposure and dissection of structures (in particular the upper pole of the kidney), less chance of injuring intra-abdominal organs, more control in the stapling phase and easy and fast removal of the kidney. The surgeon's tactile feedback may be advantageous for vascular control. Overall, these advantages may lead to a shorter skin to skin- and warm ischemia time.[8-10] Part of the advantages is as a result of the hand-assistance, the remainder a result of the retroperitoneal access. Possible disadvantages include inferior ergonomics for the surgeon and possible higher pain scores through hand-manipulation. The possible association between pain and hand-assistance has only been described in one study comparing the laparoscopic and HARP technique. This study did not show a difference in pain scores and morphine requirement.[9] In the past, we successfully applied a mini-incision, retroperitoneal open approach with excellent results regarding safety. To determine the best approach for live donor nephrectomy to minimize discomfort to the donor, we performed a randomized controlled trial comparing mini-incision versus LDN. Laparoscopic donor nephrectomy results in a better quality of life compared with mini-incision open donor nephrectomy but equal safety and graft function.[4] We previously reported our data on left-sided versus right-sided LDN, with more intraoperative complications in the former group.[7] To improve our results, we searched for an alternative for left-sided donor nephrectomy. In the current approach, we try to combine the best of all techniques; retroperitoneal access, minimal invasiveness, a Pfannenstiel incision and manual control. Possible disadvantages of this approach concern tears in the peritoneum and postoperative pain resulting from continuous stretch of muscles and skin in the suprapubic region. Most tears occur where the peritoneum is firmly attached to the abdominal wall along the midline, the iliac crest, and the splenic corner. However, this does not have to be disadvantageous, and the operation could always proceed in the normal way. Data on HARP donor nephrectomy are scarce. Our results are concordant with other nonrandomized cohort studies. Only two studies compare left-sided HARP with LDN.[8,9] Sundqvist et al. performed a prospective study, comparing HARP (n = 11), LDN (n = 14) and open donor nephrectomy (n = 11). Hand-assisted retroperitoneoscopic donor nephrectomy had a significantly shorter operation time compared to LDN (145 min vs. 218 min, $P < 0.05$). Gjertsen et al. performed a retrospective study, comparing HARP (n = 11), LDN (n = 15) and open donor nephrectomy (n = 25). Reduced operation time was observed for the HARP group compared with the LDN (166 min vs. 244 min). Two centers posed the HARP approach as an alternative for right-sided donor nephrectomy.[14,15] Other centres published a retrospective comparison between retroperitoneoscopic donor nephrectomy and historical open controls.[15,16] Safety of the LDN is still debated, with most frequent complications of visceral and vascular lesions.[17-20] Many centres in Europe implemented the LDN, but there are still a lot of centers where open donor nephrectomy is performed. Among the reasons to stick to the open donor nephrectomy are the learning curve and the issues of safety associated with the LDN. The aforementioned advantages with regard to the safety of HARP position HARP between mini-incision open and transperitoneal endoscopic approaches. Even in the learning curve, as these are the fist 20 HARP-procedures at our centre, we experienced excellent results, with minimal complications. This underlines our statement that minimally invasive techniques should be preferred over the open techniques; for those centres that did not adopt the LDN, HARP may become a feasible alternative.[4-6] Obviously, the design of this study has its drawbacks including the retrospective analysis. Probably some issue associated with selection of suitable donors for the HARP technique led to more females in the HARP group.[21] To address a potential statistically significant reduction of complications, the sample size of this study is clearly too small. Randomized controlled trials addressing safety, pain and quality of life of the donors are needed. In conclusion, early results of the left-sided HARP technique are promising. Therefore, this technique is an interesting alternative to the transperitoneal laparoscopic approach.

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Chapter 8

Hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy: HARP-trial

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ABSTRACT

Transplantation is the only treatment offering long-term benefit to patients with chronic kidney failure. Live donor nephrectomy is performed on healthy individuals who do not receive direct therapeutic benefit of the procedure themselves. In order to guarantee the donor's safety, it is important to optimize the surgical approach. Recently we demonstrated the benefit of laparoscopic nephrectomy experienced by the donor. However, this method is characterized by higher in hospital costs, longer operating times and it requires a well-trained surgeon. The hand-assisted retroperitoneoscopic technique may be an alternative to a complete laparoscopic, transperitoneal approach. The peritoneum remains intact and the risk of visceral injuries is reduced. Hand-assistance results in a faster procedure and a significantly reduced operating time. The feasibility of this method has been demonstrated recently, but as to date there are no data available advocating the use of one technique above the other. The HARP-trial is a multi-centre randomized controlled, single-blind trial. The study compares the hand-assisted retroperitoneoscopic approach with standard laparoscopic donor nephrectomy. The objective is to determine the best approach for live donor nephrectomy to optimize donor's safety and comfort while reducing donation related costs. This study will contribute to the evidence on any benefits of hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy.

INTRODUCTION

Transplantation is the only treatment offering long-term benefit to patients with chronic kidney failure. As the number of patients suffering end stage renal disease (ESRD) increases, the recruitment of more kidney donors is important.[1] Live kidney donation is the most realistic option to reduce donor shortage on short- and long-term. Increasing the number of donors will decrease the number of patients on the waiting list and consequently reduce patient's mortality. Implementation of live donation offers the possibility to transplant before the kidney disease reaches the terminal phase, necessitating dialysis. Thus, this so called pre-emptive transplantation may prevent unnecessary surgical interventions to establish dialysis (including costs and mortality) and dialysis related complications. In the last decade the number of non-related live kidney donations is rising. Among these donors are family and friends of the recipient, and even anonymous donors; the ethical basis for live kidney donation is altering. The looser the connection between the donor and recipient is, the less clear the profit for the donor is.

Live donor nephrectomy is performed on healthy individuals who do not receive direct therapeutic benefit of the procedure themselves. In order to guarantee safety for the donors, it is important to optimise the surgical approach. Recently we demonstrated the benefit of laparoscopic nephrectomy (LDN) to the donor. However, this method is characterised by higher in-hospital costs, longer operating times and requires a well-trained surgeon.[2] The hand-assisted retroperitoneoscopic technique (HARP-technique) may be an alternative to a complete laparoscopic, transperitoneal approach. The peritoneum remains intact and the risk of visceral injuries is reduced. The hand-assistance results in a faster procedure and a significantly reduced operating time.[3-7] The feasibility of this method has been demonstrated recently, but as to date studies advocating the use of one technique above the other are lacking. This randomised controlled trial compares the hand-assisted retroperitoneal approach to the current standard, the transperitoneal laparoscopic technique, to define the most optimal approach.

We recently proved that laparoscopic kidney donation is beneficial for the donor. In comparison to minimally invasive open techniques, laparoscopic kidney donation is associated with a better quality of life, less pain, shorter in hospital stay and earlier return to work. This method is expensive for the hospital, has a long operating time and requires an experienced, well-trained, surgeon.[2, 8, 9] Other studies showed a possibly increased rate of life threatening complications, such as injuries to the intestines and bleeding.[10, 11] A surgical approach that is easier to learn and applicable in the majority of donors (i.e. selection of donors is not required) with similar benefits as the transperitoneal laparoscopic approach is warranted.

The hand-assisted retroperitoneoscopic approach may be a viable alternative. With this method the surgeon inserts his hand to create a retroperitoneal space, which is thereafter insufflated with gas. The peritoneum stays intact and tactile sensation remains. The chance of a complication to the intestines is very small. Furthermore, this technique is easier and quicker to learn for the surgeon than the laparoscopic approach. There is no randomized controlled trial comparing both techniques for the effectiveness.[3-6]

METHODS

Study objective

To determine the best approach for live donor nephrectomy i.e. to optimise donor's safety and comfort while reducing donation related costs.

Study design

The HARP-trial is a multi-centre, randomised controlled, single-blind trial. We have stratified per centre. The study started on July 24th 2008 and the duration of the inclusion will be approximately 3 years. The study compares hand-assisted retroperitoneoscopic donor nephrectomy and standard laparoscopic donor nephrectomy. In total 190 live kidney donors will be included in the study. Approval of the medical ethical committee of both centres was obtained.

Randomisation will take place after endotracheal intubation, by means of telephonic consultation of the study coordinator. A computer generated randomisation list with hidden block size is made for each centre by the statistician. The donor and the physicians involved in the postoperative period are blinded to the surgical technique until one year after donor nephrectomy. The operating theatre is not accessible for people who do not join the operating team. An independent surgeon evaluates the donor on the outpatient clinic before operation. As the extraction incision is similar in both techniques, we did not attempt to cover the wounds with a standard pattern of bandages.[12] All donors fill out the questionnaires until one year after donation, the Short-form 36 (SF-36), Euroqol (EQ-5D), Visual Analogue Scale (VAS) and a questionnaire about work and homecare.

Patient selection

All, properly Dutch speaking, live kidney donors who are medically capable of donating their left kidney can be included in the HARP-trial. Informed consent is mandatory. All types of live kidney donors can participate in the study, i.e. related, unrelated, altruistic and cross-over live kidney donors.

Exclusion criteria are a history of kidney surgery or adrenal gland surgery on the left side.

All potential donors are informed about the study at the outpatient clinic. For further information the patient can refer to the research fellow, transplant surgeon, or the independent physician. If a patient does not sign the informed consent form, the patient is not included in the study and therefore will be operated via the standard protocol. A live kidney donor can always withdraw his or her consent at anytime during the study.

Hypothesis

The left-sided hand-assisted retroperitoneal approach will lead, with a similar or better quality of life, to fewer complications, and reduced operating times and costs.

Study Questions

Primary question: Does left-sided hand-assisted retroperitoneoscopic donor nephrectomy lead to a similar or better quality of life as compared to left-sided transperitoneal laparoscopic donor nephrectomy?

Secondary question: Is the retroperitoneoscopic technique safer (conversions and complications) than the transperitoneal technique?

Other secondary endpoints: pain perception, return to work, operation time, cost-effectiveness from both a societal and health care perspectives (costs per quality adjusted life year).

Pilot study

The Erasmus Medical Centre Rotterdam harbours one of the largest European live kidney donor transplantation programs. On a yearly basis 75 to a 100 laparoscopic donor nephrectomies are performed. Our strategy is to improve the results of live kidney donation by optimizing the surgical technique with decreased complication rates and costs. The infrastructure, raised in earlier studies, led to the formation of a multidisciplinary team, with a high standard of care and surgery. In the previous study on live kidney donation running at our centre we compared the laparoscopic technique to the mini-incision muscle-splitting technique.[2] Laparoscopic donor nephrectomy resulted in early recovery, less fatigue and a better quality of life. However, the laparoscopic technique was more expensive from a hospital point of view and demanded more experience from the surgeon. A pilot study with 60 live kidney donors showed the feasibility of the retroperitoneal hand-assisted approach.[3] Even in this small group operating time was significantly reduced. It seems feasible to expand the surgical armamentarium with this technique. However, we first have to demonstrate similar or better quality of life in comparison with the laparoscopic technique.

Surgical intervention

Both procedures were performed with the donor placed in right-decubitus position. LDN was performed as described earlier.[8] Shortly, a 10-mm trocar was introduced under direct vision. The abdomen was insufflated with carbon dioxide to 12 cm H_2O pressure.

A 30° video endoscope and 3 to 4 additional trocars were introduced. The colon was mobilized and displaced medially. Opening of the renal capsule and division of the peri-renal fat was facilitated using an ultrasonic device (Ultracision, Ethicon, Cincinnati, USA). After identification and careful 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 and the kidney was placed in the endobag and extracted through the pfannenstiel incision.

In HARP we started with a 7-10 cm pfannenstiel incision.[3] After blunt dissection to create a retroperitoneal space, the 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 operator's hand inside the abdomen. CO_2 was insufflated retroperitoneally to 12 cm H_2O pressure. Two other 10-12 mm trocars, respectively just outside the midline inferior to the costal margin and in the flank, were inserted to create a triangular shape. For dissection the aforementioned ultrasonic device was used. Dissection of the kidney and renal vessels was similar to transperitoneal donor nephrectomy but with hand-assistance and from a slightly different angle. The kidney was removed manually.

Outcome measures

Primary outcome: Physical functioning as a measure for quality of life one month after donor nephrectomy. This is one of the dimensions of the standardized SF-36 questionnaire. Physical functioning is measured by means of the complaints with daily physical activities, like walking stairs, carrying grocery bags, walking 500 meter, etc. The SF-36 is in our opinion a suitable parameter to measure post-operative recovery.[13]

Secondary outcome: Direct costs (costs for the hospital). Other secondary endpoints: conversion to open surgery, complications, pain perception, work resumption, other dimensions of quality of life (SF-36), cost-effectiveness from hospital and health care perspective.

Costs-effectiveness

In this effectiveness analysis the effect of the surgical procedure on quality of life of the donor and the costs for the hospital are the most important outcome measures. The donor is the central point of interest; therefore we chose quality of life as primary endpoint for the power calculation. Saving money, but with a worse quality of life for the donors is indeed not relevant.

Power calculation

A difference of 7.5 point in physical functioning (SF-36) is a relevant difference. In international literature, a five point difference is the minimal clinically relevant difference. [13] In our previous study, reviewers thought this difference of five points was too small. Ten points is a big difference, but in our previous study this difference was observed after one month. A difference of 7.5 is in the middle of these data. Physical functioning is expressed on a scale of zero till hundred. Zero means a very limited function and hundred means an unrestrained function. With a measured standard deviation of 18.4 points (reference for left-sided kidney donation in the last five years), an alpha of 0.05, and a beta of 0.2, 95 donors have to be enrolled in both groups (Altman, Practical statistics for medical research, Chapman&Hall/CRC, 1991). Hereby we test two-sided, because the hand-assisted technique could be similar or even better than the laparoscopic technique. All data will be analysed according to the 'intention to treat' principle. Costs and effectiveness will be combined with the Euroqol 5-D to express the difference between both techniques in quality adjusted life years (QALYs).

Treatment of participating live kidney donors

The donor is prehydrated with intravenous crystalloids before operation. On the morning of surgery antithrombotic stockings are given. The anaesthetist uses a standard protocol for live kidney donation anaesthesia (remifentanyl and propofol), intravenous policy, and respiration. One hour after the beginning of the operation, 20 mg mannitol is infused. During the operation the research-fellow notes warm-ischemia time, blood loss, and complications. Postoperative pain medication is measured through a Patient Controlled Analgesic (PCA; morphine) device. If the patient does not use the PCA for 6 hours, the PCA is stopped. The dosage regimen is registered. Patients can be discharged when they meet with the following criteria: The donor tolerates a normal diet, the donor is mobile (is able to walk stairs), the donor is adequate and oriented and the donor does not use intravenous medication.

All live kidney donors will be seen at the outpatient clinic after four weeks, three months and yearly thereafter. All donors are asked to fill out different questionnaires; we measure pain and nausea scores (VAS-score), quality of life (SF-36, EQ-5D), and a questionnaire on work and homecare. (Table 1)

Unexpected events

The live kidney donor is informed at the outpatient clinic on the background of the study, possible complications and the chance of conversion to an open approach. After both operations the donor may wake up having an extra scar caudal to the costal margin if the operation is converted to an open approach.

Table 1. Time schedule for filling out the questionnaires

Time of evaluation	VAS	EuroQol	SF-36	Work and homecare
Preoperative	X	X	X	X
Postoperative				
Day 0	X			
Day 1	X			
Day 2	X			
Day 3	X	X		
Week 1	X	X		X
Week 2	X	X		X
Week 4		X	X	X
Week 6			X	X
Week 8			X	X
Month 3		X	X	X
Month 6		X	X	X
Month 12		X	X	X

If a donor has post-operative pain or discomfort of the bandages, they can be removed. All documentation will be marked with the HARP-trial logo. Information about the operation technique will be sealed in an envelope in the medical file. In case of unexpected events this envelope may be opened. Unexpected events are reported to the responsible physician and the study coordinator.

Access to personal data

All personal data are coded into numbers (1 to 190). The coordinating investigator and the principle 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 trial all data are analysed together with the trial statistician.

DISCUSSION

The hand-assisted retroperitoneoscopic technique may be an alternative to a complete laparoscopic, transperitoneal approach. The feasibility of this method has been demonstrated recently, but as to date there are limited data available advocating the use of one technique above the other.[3-7] This randomised controlled trial compares the hand-assisted retroperitoneal approach to the current standard, the transperitoneal laparoscopic technique to define the most optimal approach.

In comparison to minimally invasive open techniques, laparoscopic kidney donation is associated with a better quality of life, less pain, shorter in-hospital stay and earlier return to work. This method is time-consuming, leading to high hospital costs, and requires an experienced surgeon. Other studies showed a possibly increased rate of major, life threatening, complications, such as injuries to the intestines and bleeding.[10]

The hand-assisted retroperitoneoscopic approach may be a viable alternative. The chance of a complication to the intestines is very small, and hand-assistance could be beneficial for the control of bleedings. There is no randomized controlled trial comparing both techniques. Only three small studies compare left-sided hand-assisted retroperitoneoscopic with laparoscopic donor nephrectomy, but only with respect to clinical parameters.[3-5, 7] Wadstrom et al compared the LDN (n=11), hand-assisted laparoscopic technique (HALS) (n=14), and the HARP (n=18). The operation time with the HARP was significantly shorter than the LDN (141 vs. 270 min, $p<0.01$).[7] Sundqvist et al performed a prospective study, comparing HARP (n= 11), LDN (n= 14) and open donor nephrectomy (n= 11). Hand-assisted retroperitoneoscopic donor nephrectomy had a significantly shorter operation time compared to LDN (145 min vs 218 min, $p<0.05$).[5] Gjertsen et al performed a retrospective study, comparing HARP (n= 11), LDN (n= 15) and open donor nephrectomy (n= 25). Reduced operation time was observed for the HARP group compared with the LDN (166 min vs 244 min).[4] Dols et al performed a prospective study, comparing 20 left-sided HARP procedures and 40 left-sided LDNs. Median operation time and WIT were shorter in HARP (180 vs. 225 min, $p = 0.002$ and 3 vs. 5 min, $p = 0.007$ respectively).[3]

All other studies only described surgical outcome, and did not address quality of life of live kidney donors. Our main point of interest is to know whether the donors operated on with the hand-assisted retroperitoneal technique have a good quality of life afterwards. Therefore we will perform this randomised controlled trial comparing laparoscopic to hand-assisted retroperitoneoscopic technique, with physical function as a primary outcome.

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Chapter 9

Randomised controlled trial on living donors' comfort and safety during and after hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy

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ABSTRACT

Living kidney donation is the most realistic approach to diminish the shortage of donor kidneys and is increasing worldwide. In specialized centres laparoscopic donor nephrectomy (LDN) has become the gold standard to procure living donor kidneys. As safety issues and long learning curves are limiting its application, hand-assisted retroperitoneoscopic donor nephrectomy (HARP) has been suggested as an alternative, combining the control and speed of hand-guided surgery with the benefits of endoscopic techniques and retroperitoneal access. We evaluated the best approach to optimise the donors' comfort and safety.

In two Dutch tertiary referral centres, donors undergoing left-sided nephrectomy were randomly assigned to HARP or LDN. All donors were blinded to the surgical technique. Follow-up was one year. Primary endpoint was physical function at one month postoperatively, measured with the SF-36 quality of life questionnaire. Secondary endpoints included complications, operation times, pain scores and other quality of life dimensions.

Between July 2008 and September 2010 190 donors were randomised. HARP resulted in significantly shorter skin-to-skin time (mean (SD) 159 (42) vs. 188 (39) minutes, $p < 0.001$), shorter warm ischemia time (2 (1) vs. 5 (3) minutes, $p < 0.001$), and a lower intraoperative complication rate (8% vs. 23%, $p = 0.003$). Conversions were rare (1% vs. 2%, $p = 0.414$). Total morphine requirement (11 vs. 12 mg, $p = 0.833$), pain scores, length of stay (both 3 days, $p = 0.135$) and the postoperative complication rate (9% vs. 8%, $p = 1.00$) were not significantly different between HARP and LDN. Neither physical function at one month postoperatively (estimated difference 1.79, CI -4.1 to 7.68, $p=0.55$) nor any other quality of life dimension at any point in time significantly differed between groups. One-year patient and graft survival were not significantly different (97% vs. 99%, $p = 0.62$, 94% vs. 91%, $p = 0.59$ respectively)

As compared to laparoscopic donor nephrectomy left-sided hand-assisted retroperitoneoscopic donor nephrectomy leads to similar quality of life with fewer complications. We therefore recommend HARP as a safe and feasible technique for left-sided donor nephrectomy.

INTRODUCTION

Recipient and societal benefits of living kidney donor transplantation are clear. Optimal timing, including pre-emptive transplantation, prevents deterioration of the recipient on the waiting list. Superior organ quality results in longer mean patient survival as compared to recipients of deceased donor kidney transplants.[1-3] Quality of life is significantly better after transplantation as compared to patients on dialysis.[4, 5] The high initial costs of the procedure and immunosuppressive drugs soon outweigh the costs of prolonged dialysis.[6] Living 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 living donor.[7]

These benefits for recipient and society must be balanced against the potential harm to the donor.[8-10] Living donors are healthy people who deserve a high standard of care. Screening of proper candidates for donation, improvement of the peri-operative tract 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 living kidney donation. In a randomised controlled trial we have previously shown that the applied surgical techniques had impact on the donor's quality of life.[11] Laparoscopic donor nephrectomy (LDN) has become the preferred method to procure living donor kidneys because of less pain, shorter convalescence time and superior quality of life as compared to open approaches.[9, 12-17] However, the safety of LDN has been debated because of an association with major intra-operative complications that rarely occurred during open donor nephrectomy.[9, 17, 18] Hand-assisted retroperitoneoscopic nephrectomy (HARP) has been introduced as a safer approach which is easier to implement. HARP theoretically combines control and speed of hand-guided surgery with benefits of endoscopic technique and retroperitoneal access.[11, 13-15, 17] The enormous lack of organs from deceased donors will force centres and surgeons with limited experience to start or expand living kidney donor 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 clinical trial.

METHODS

Patients and setting

The details of design and methods for this randomized trial have been described previously.[19]

Donors who were operated in two Dutch university hospitals, the Erasmus MC, University Medical Center, Rotterdam and the Radboud University Nijmegen Medical Centre were approached to participate in the study.

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 (MRA) or computed tomography-angiography (CTA). The decision on the side of donor nephrectomy was based on the rule to leave the best kidney with the donor. Reasons to remove the contralateral kidney included: previous unilateral operations (e.g. adrenalectomy), large size mismatch between left and right kidney, and presence of multiple arteries (including early branching), veins or ureters unilaterally. If unilateral anatomical abnormalities were present, e.g. ipsilateral arterial stenosis, that kidney was procured. 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/she 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 centres approved the study protocol and the study was registered in the Netherlands Trial Registry (NTR1433).

Randomisation and masking

All included donors were randomised 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 randomisation list using a (hidden) block size of four. There was no stratification by centre. All involved health care professionals except for the members of the surgical team were unaware of the allocated procedure. The performed procedure was not disclosed to the donor until one year after nephrectomy.

Anesthesia

The evening before the operation, donors were prehydrated using intravenous crystalloids. Before the operation, donors received 1000 mg acetaminophen i.v. Donors were fitted with anti-embolism stockings during the operation. Prophylactic antibiotics were not prescribed. After endotracheal intubation, anaesthetic procedures were performed according to a strict protocol for medication, ventilation and fluid administration. Before clamping of the renal artery, 20 mg mannitol was administered intravenously. At the end of the operation 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. Nausea was treated with granisetron one milligram up to three times daily.

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 centres performed between 60 and 130 nephrectomies annually, experience with LDN was judged sufficient.

The details of surgical techniques employed were previously described.[14, 19] Briefly, both procedures were performed with the donor placed in right-decubitus position. In LDN, the first trocar was introduced under direct vision, the abdomen was insufflated to 12-cm H_2O carbon dioxide pressure and a 30° 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. CO_2 was insufflated retroperitoneally to 12-cm H_2O 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.

Kidney transplantation was conducted according the same technique in both groups, preperitoneal placement of the renal transplant in the iliac fossa was applied as the standard operation technique.

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.[11] 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.[11, 15] 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 and post-operative complications was defined as key secondary endpoint. A complication is any undesirable, unintended, and direct result of or event during an operation, which would not have occurred if the operation had gone as well as could reasonably be hoped for. We incorporated all minor and major complications, even if these events did not affect the donor in any way. All complications, including these 'near- complications', were scored by attendance of a research co-ordinator in the operation room and daily on the surgical ward. Due to this complication scoring system, we aimed to detect every complication, even the minor complications without any effect on the course for the donor. We cross-checked the medical records with the self reported complaints after the operation. The latter were recorded with case record forms every two weeks after the operation until work was completely resumed or, if the donor did not work, until all preoperative activities were completely resumed. 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 16.0, 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

A research fellow prospectively attended all operations and recorded all pre-, intra- and postoperative data. After discharge, donors visited the outpatient clinic at three weeks, two months, three months and one year postoperatively. Intra-operative and post-operative complications were graded according to the modified Clavien grading system described by Kocak et al.[20] 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, which estimates GFR using four variables: serum creatinine, age, race, and gender.[21] 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 (QOL) and pain (VAS), using validated questionnaires.[22] The Short Form-36 (SF-36, QOL) 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 QOL. 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. 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 nausea and ranges from zero (no pain or nausea) to ten (severe pain or nausea). 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 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. Sixty-one donors did not meet the inclusion criteria (did not speak Dutch properly, or did not meet criteria for side selection) and were not included in the present analysis. Twenty-nine donors underwent left sided donor nephrectomy, but were not included in the trial. These include five donors who were operated with a robot primarily, five donors with a history of extensive intra-

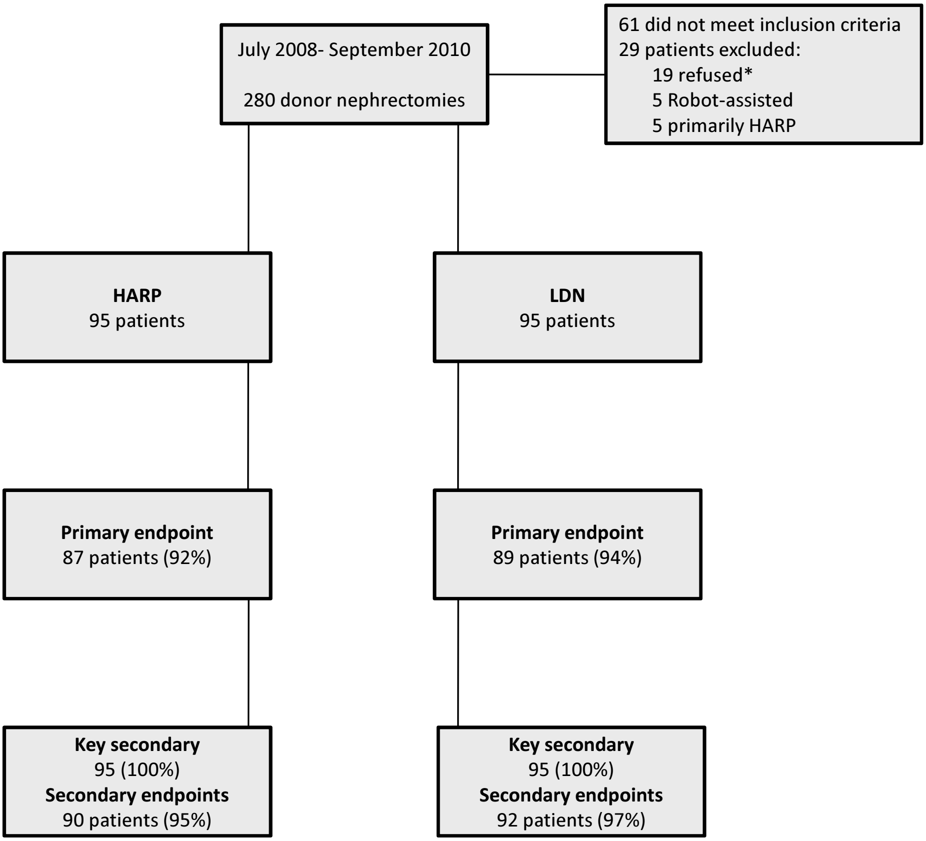

Figure 1. Flow-chart HARP-study.
*because of aversion against clinical studies, preference for the laparoscopic technique, and one due to moving to another country directly postoperative.

peritoneal surgery who were primarily operated with the HARP technique, nineteen donors who refused to participate in this study, because of aversion against clinical studies, preference for the laparoscopic technique, and one due to moving to another country postoperatively. 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. We have data on the key secondary outcome measures of all donors. Other secondary outcome measures, including pain scores on day 14, were available for 95.8% of the donors (Figure 1). At three months 88% of the quality of life forms were returned. At six months 87% of the forms were returned. At one year post-operatively 86% of the forms were returned. Baseline characteristics of the randomised 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/m^2)	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%)

*There are no significant differences between the groups.

Intra-operative data (Table 2 and 3)

Mean skin-to-skin time and warm ischemia time were significantly shorter in the HARP-group. Blood loss was minimal and did not differ significantly. HARP was associated with a significantly lower intra-operative complication rate. Complications were graded according to the modified Clavien grading system and measured as described in the methods section (Table 3). 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 LDN group two conversions were performed. One 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. The other procedure was emergently converted to open nephrectomy because of bleeding from the renal artery due to failure of the stapling device. 84.2% of the patients had no intra-operative complications. The length of the pfannenstiel incision was slightly but significantly longer for HARP.

Table 2. 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	159 (42)	188 (39)	<0.001
Warm ischemia time (min)	2.5 (1.0)	4.8 (2.8)	<0.001
Conversion	1 (1%)*	2 (2%)**	0.414
Blood loss (ml)	214 (195)	193 (370)	0.629
Complications	8 (8.4%)	19 (23.2%)***	0.003
Incision Pfannenstiel (cm)	9 (1)	8 (1)	<0.001
Post-operative			
Complications	9 (9%)	8 (8%)	1.00
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
Recipient survival	92 (97%)	94 (99%)	0.621
Death-censored graft survival (one year)	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
*** 3 major complications occurred in the LDN group, none in the HARP group

Post-operative data (Tables 2 and 3)

Postoperative complication rate, total morphine requirement and length of hospital stay did not significantly differ between groups. Post-operative complications led to two readmissions and one reoperation in the HARP group, where a small intestine was trapped in a suture of the pfannenstiel incision. One reoperation in the laparoscopic group was necessary because of a port-site hernia. 88.7% of the patients had no postoperative complications. 75.8%of the patients had no complications at all.

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.

Table 3. Intra and post-operative complications (follow-up 1 year) of HARP and LDN with grading by severity.

HARP Grade	Percentage of all complications (n= 17)	Percentage of total series (n= 95)	Complications	Patients (n)
1	58.8 (n=10)	10.5	Blood loss < 500 ml	3
			Upper pole artery unintentionally cut	1
			Wound infection (followed by an incisional hernia)	3
			Seroma	1
			Painful scrotal swelling due to occult inguinal hernia	1
			Renal vein injury (blood loss 300 cc)	1
2				
2a	35.3 (n= 6)	6.3	Blood loss > 500 ml	3
			Urinary tract infection (antibiotics)	1
			Re-admission, UTI and haematuria (4 days)	1
			Pneumonia	1
2b	5.9 (n= 1)	1.1	Re-operation: small bowel captured in pfannenstiel suture	1
2c	0	0	0	0
3	0	0	0	0
4	0	0	0	0
LDN Grade	Percentage of all complications (n =30)	Percentage of total series (n= 95)	Complications	Patients (n)
1	70.0 (n=21)	22.1	Blood loss < 500 ml	8
			Post-operative Hb 5·3 (no transfusion)	1
			Seroma	1
			Wound infection	1
			Laceration spleen (200, 100, 50, 50, cc blood loss)	4
			Laceration kidney (370 and 100 cc blood loss)	2
			Upper pole artery unintentionally cut	2
			Laceration adrenal gland (blood loss 400 cc)	1
			Long WIT due to technical reasons (22 min)	1
2				
2a	16.7 (n= 5)	5.3	Blood loss > 500 ml	1
			Re-admission (1 and 4 days, elevated liver enzymes and rectal blood loss, both needed no treatment)	2
			Pneumonia	2
2b	10.0 (n= 3)	3.2	Re-operation: Trocar herniation (resection 10cm small intestine)	1
			Laceration small intestine	1
			Lack of pneumoperitoneum during stapling due to pressing of the patient, bleeding 600 cc.	1
2c	3.3 (n=1)	1.0	Failure stapler renal artery (emergent conversion to open, 3500 cc blood loss)	1
3	0	0	0	0
4	0	0	0	0

Table 4. Quality of life at one month and one year after living 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

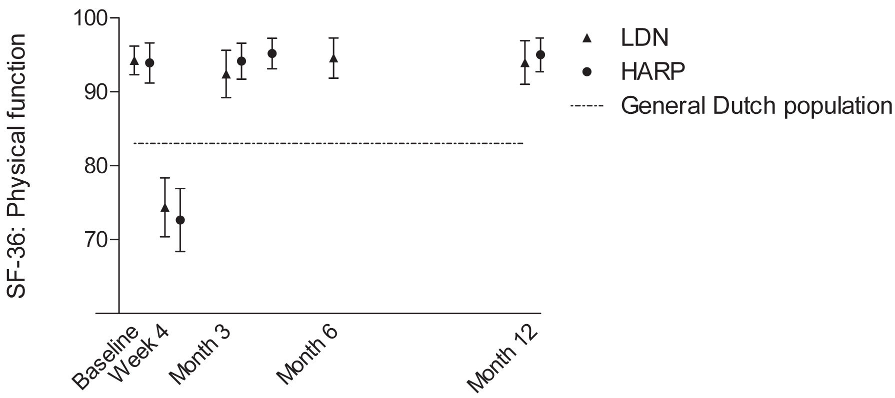

Figure 2. Physical function during one year follow-up. Mean (SD).

Quality of life

Raw data of the dimensions of the SF-36 preoperatively, and at one month and one year postoperatively are shown in Table 1 and 4 respectively. Physical function during one year follow-up is shown in figure 2. The primary endpoint, physical function, did not differ significantly between groups at one month (Table 4, Figure 2). At any other time points of the questionnaire physical function did not statistically significantly differ between groups. At three months donors who underwent HARP had higher scores for vitality (estimated difference -5.14, 95% confidence interval -10.01 to -0.27). Other dimensions of quality of life did not differ either between groups (not all data shown).

Within-group analyses showed that all scores for donors that underwent HARP were not significantly lower as compared to baseline at one year postoperatively. Mental health was even significantly higher during follow-up. Physical function, bodily pain, general health, vitality, social functioning and role emotional returned to baseline levels at three months postoperatively. Role physical returned to baseline values at one year postoperatively.

Donors that underwent LDN also had better mental health scores postoperatively. Physical function, 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 (mean difference 4.27, 95% CI 0.22 to 8.33).

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 living kidney donors. Living 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 living 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 living donor nephrectomy is approximately 0.03%.[23, 24] Anticipating near zero mortality, this study focused on morbidity and quality of life, and will set a standard for the preferred operating technique for a wide range of centres with varying experience. Laparoscopy revolutionized living donor nephrectomy and certainly has contributed to the steep increase of the number of living donors. Recovery and quality of life were superior to both classic and modern open techniques.[11, 14, 15] However, some severe intra-operative complications leading to major injury, and even death, have been described.[6, 17] According to our own data, left-sided LDN was associated with a higher intra-operative complication rate as compared to right-sided LDN.[25] Among these complications were a number of splenic injuries, occasionally resulting in splenectomy, and bowel lesions. Hand-assistance enables manual compression of bleeds 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. Major complications causing long lasting hospital admissions or permanent damage to the donor did not occur. However, significantly less minor intra-operative complications occurred after HARP. The effect of shorter warm ischemia time on graft outcome in the HARP has 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.[26]

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.[27] This may be expected as a result of screening. In both groups donor nephrectomy had significant impact on most dimensions, which is concordant with previous studies, most dimensions have recovered by three months.[11, 28] However, we show in this series that donor nephrectomy may impact dimensions of quality of life up to one year post-operatively. As quality of life and mortality do not differ significantly between groups, morbidity is decisive to set the standard. Therefore we advocate HARP as the approach of choice for left-sided 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 living kidney donation in 30% of the centres.[15, 29] These centres are 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.[30] Before the start of the study, the mean experience with HARP was only 10 procedures, indicating a steep learning curve. Reliable information is limited regarding the true, prospectively collected, complication rate of the surgical techniques in their learning curve.[31] 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.[32-34] We provide evidence that HARP is the preferred technique based on safety and quality of life. In this relatively large study the randomized, blinded design avoided substantial bias. As we included donors with higher body mass index (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 complication rate in LDN as compared to large case series.[30, 35] Accurate scoring by an independent researcher present in the operating theatre rather than by the surgeon may reveal significantly more intra-operative problems delaying the operation or causing harm to intra-abdominal organs or the graft. In this way we tried to avoid underscoring of complications. At present there is no clear or consistent definition of a complication in the surgical literature, but we tend to score all complications in this precise way, even the problems not affecting the intra or post-operative course of the donor.

In this era, safety and quality of life are of paramount importance. We therefore recommend HARP as the preferred technique for left-sided donor nephrectomy and advocate widespread introduction.

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Chapter 10

Ergonomics during live kidney donation: comparing the hand-assisted retroperitoneal and laparoscopic approach

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ABSTRACT

The rising number of healthy kidney donors requires the surgical approach to be optimized continuously. Laparoscopic donor nephrectomy (LDN) is preferred as it has better results for the donor, but it is more expensive and demands more surgical experience than the mini-incision approach. The hand-assisted retroperitoneoscopic (HARP) approach combines the control, dexterity, speed and retroperitoneal access of hand assisted surgery with the benefits of LDN. However, HARP possibly results in poor postures for the surgeon. The aim of this study is to compare the surgeon's body postures during HARP and LDN.

Ten HARP's and ten LDN's were randomly observed and recorded. The surgeon's postures were recorded from three locations in the operating room together with the image of the endoscope. Duration of static postures for the regions, shoulders, neck, elbows, wrists, and torso/back, outside the neutral zones were analysed by two observers using the software program Utilius VS Advanced Video Information System by CCC Campus-Computer-Center GmbH Leipzig. Surgeons were also asked to rate their physical discomfort for these body regions after performing surgery.

Nine HARP's and nine LDN's were analysed, performed by three surgeons. The overall average time (u:mm:ss) of the endoscopic part for HARP was 1:33:50 (SD 0:25:59) and for LDN 1:51:05 (SD 0:36:41). Comparing HARP and LDN, HARP showed mainly raised shoulders ('poor' and 'extreme': 17-88%), axial rotation of the torso/back ('poor' and 'extreme': 10-80%), and unergonomic wrists postures ('poor': 4-92%). LDN showed mainly unergonomic wrists postures ('poor': 2-81%). Subjective pain scores showed that physical discomfort after performing HARP were systematically higher than after performing LDN.

From a surgeon's ergonomic point of view, LDN seems to be superior. However, from a patient's point of view, left-sided HARP donor nephrectomy is recommended. To limit physical discomfort and physical impairment, ergonomic guidelines for the OR set-up should be followed.

INTRODUCTION

In 2010, 865 patients suffering from chronic kidney failure received kidney transplantation in the Netherlands.[1] However, 892 patients are still waiting for a kidney and approximately 1275 dialysis patients die each year. Live kidney donation seems an adequate option to reduce donor shortage.[2] In the last decade, the number of non-related live kidney donations is rising: in 2010, 55% of kidney transplantations performed in the Netherlands were from a live donor. Among these donors are family and friends of the recipient and even anonymous donors.[2] As these healthy donors do not receive any direct therapeutic benefit of the procedure their safety has to be guaranteed. This requires that the surgical approach is optimized continuously.[3]

The surgical approach has advanced from an open, through mini-incision, to a minimally invasive laparoscopic approach.[3] Literature shows adequate evidence that minimally invasive techniques are preferred as they result in less blood loss, shorter hospitalization, less morphine requirement, and better cosmetic results for the donor.[4, 5] Nevertheless, laparoscopic donor nephrectomy (LDN) is more expensive and demands more surgical experience than the mini-incision approach.[6] Therefore, an alternative for LDN was introduced: the hand-assisted retroperitoneoscopic (HARP) donor nephrectomy. HARP combines the control, dexterity, and speed of hand assisted surgery with the benefits of LDN, including retroperitoneal access and reduced surgical trauma.[7, 8] HARP is associated with shorter operation time and warm ischemia times and offers at least equal safety in a selected group of patients.[2]

Physical discomfort is mainly experienced if body postures are outside the ergonomic neutral zones.[9, 10] These neutral zones for the different body areas are shown in Figure 1. For laparoscopic surgery discomfort is mainly experienced in neck, back, and shoul-

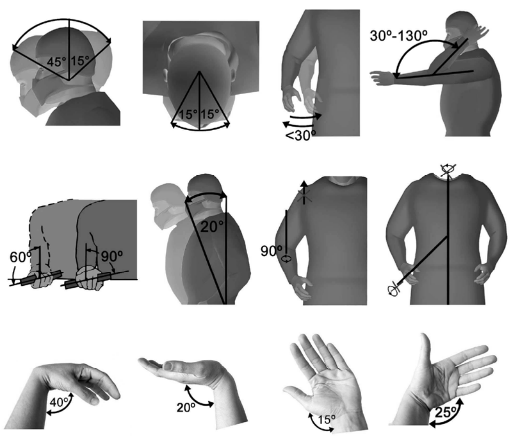

Figure 1. Neutral zones of different body areas.[10]

ders, which is predominately caused by static postures.[9, 11-14] HARP results in poor ergonomics and physical discomfort due static and poor body postures of the surgeon (lordotic position). Many surgeons experience back strain and muscle fatigue of the upper limbs.[7, 8, 15]

Static postures are also harmful.[13] Static working postures are defined as:"one or more body parts remaining in the same posture for at least 4 seconds".[16] These postures restrict the blood flow to the muscles, which results into muscular fatigue. In the short term, increasing discomfort may distract the surgeon from his task, leading to an increased error rate, reduced output, and accidents, which can be dangerous for the patient. In the long-term pathological changes in the muscles' soft tissue takes over, causing physical injury.[16, 17]

The aim of this study is to compare the body postures of the surgeon during HARP and LDN.

MATERIALS AND METHODS

This study was performed in the Erasmus University Medical Centre (EMC) Rotterdam and was part of a randomized controlled trial (RCT) aiming to determine the best approach (LDN or HARP) to optimize donors' comfort and safety. In the EMC, each year 120 donor nephrectomies are performed, making it the largest centre in Europe for live kidney donor transplantation.[2]

Data collection

In total ten HARP's and ten LDN's were randomly observed and recorded from three locations in the operating room (OR). The cameras were mainly placed behind, in front, and besides the main operating surgeon, to obtain a full view of the surgeon's body postures (see Figure 2). The image of the endoscope was recorded as well. All video images were combined using a split screen (see Figure 2) and were stored on a hard disk. One observer (a MSc student Industrial Design Engineering) was present during each procedure to set-up the equipment and annotated unergonomic static body postures of the surgeons by means of a palmtop (HP iPAQ hx2490). Static body postures outside the neutral zones lasting ten seconds or more were marked. The unergonomic postures were time stamped to the video.

Immediately after performing the surgical procedure the surgeons were asked to rate their experienced physical discomfort in shoulders, neck, elbows, wrists, and torso/back using a 10-point Likert scale (with 1=no pain, 10=severe pain). They could also indicate other (physical) discomfort and make remarks.

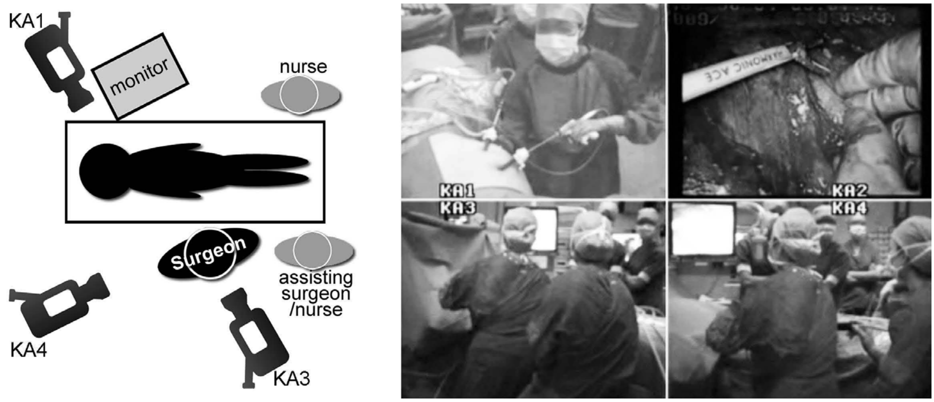

Figure 2. a) Set-up: location of the cameras. b) Output: video split screen.

Data analysis

The videos were analysed by two observers (LW/AA) using the software program Utilius VS Advanced Video Information System, Version 4.2.1 by CCC Campus-Computer-Center GmbH Leipzig. The annotations assigned during the observations were used as reference points to start analysing the unergonomic static postures outside the neutral zones. Only unergonomic postures during the endoscopic part of the procedure were included (recordings started when the endoscope was first entered into the abdomen and ended with the removal of the last trocars). Postures during the open parts of the procedure (e.g., enlarging incision for removal of kidney and dissection of the kidney) were excluded.

Both observers analysed one HARP and one LDN to obtain inter-rater agreement. Duration of the static body postures (longer than 10 seconds) outside the ergonomically neutral zones was recorded for the body regions shoulder, neck, elbows, wrists, and torso/back. These recordings were converted into a Microsoft Excel 2011 for Mac data sheet for further analysis.

RESULTS

In total 18 videos were analysed. One HARP and one LDN could not be analysed as data were corrupted or the image of the cameras was lost halfway during the procedure.

Participants

In total three surgeons, with different body lengths participated in this study.(Table 1) Participant1 performed four HARP's and five LDN's, participant 2 performed three HARP's and one LDN, and participant 3 performed two HARP's and three LDN's.

Table 1. Participants

Participant	Body length [cm]	Gender	Approach	
			HARP	LDN
1	183	Male	1,2,3,4	1,2,3,4,5
2	170	Female	5,6,7	6
3	160	Female	8,9	7,8,9*

LDN9 was converted to an open procedure, losing the image of the endoscope. Therefore, only the first 2 hours and 40 minutes were used for analyses.

Duration unergonomic postures

The total time of the endoscopic part of the procedure was divided into three ergonomic categories: 'good', 'poor' and 'extremely poor'. The overall average time (u:mm:ss) of the endoscopic part for HARP was 1:33:50 (SD 0:25:59) and for LDN 1:51:05 (SD 0:36:41).

Table 2 shows that during HARP both neck flexion and neck rotation outside the neutral zones were infrequently seen. Also during LDN few unergonomic neck flexions were seen. In contrast to most LDN's, LDN6 and LDN8 showed unergonomic neck rotations lasting 24 minutes (30% of the time) and 10 minutes (12% of the time), respectively.

During HARP, frequently one shoulder was raised: the arm controlling the laparoscopic instrument. For HARP, the shoulder was raised ranging from 36% of the total endoscopic time (HARP9: 23 minutes) to 88% of the time (HARP2: 'extremely poor' 31 minutes and 'poor' 40 minutes). During HARP1, HARP2, HARP5, and HARP8 an extremely raised shoulder was seen ranging from 4 minutes (HARP5) to 1 hour and 9 minutes (HARP8). For LDN shoulders were less often raised. Only during LDN1, LDN2 and LDN6 shoulders were raised, ranging from 8% to 19% of the total endoscopic time.

Unergonomic flexion of the elbows was seen during both HARP and LDN. For HARP this ranged from 6% of the endoscopic time (HARP1: 6 minutes) to 80% of the time for HARP6 ('extremely poor' 8 minutes and 'poor' 1 hour and 5 minutes). For LDN poor elbow postures ranged from (almost) none (LDN6, LDN7, and LDN9) to 73% of the time (LDN8: 1 hour and 4 minutes).

During HARP2 wrist postures were outside the neutral zones during 3 minutes (4% of the time). For the other HARP's unergonomic wrist postures were seen during 14% of the time (HARP1: 15 minutes) to 92% of the time (HARP9: 59 minutes). During LDN2 and LDN3 only few unergonomic wrist postures were seen (4 minutes and 2 minutes, respectively). However, during the remaining LDN's 20% of the time (LDN9: 32 minutes) to 81% of the time (LDN8: 1 hour and 11 minutes) unergonomic wrist postures were seen.

Torso abduction was infrequently seen during both HARP and LDN. Only during HARP8 the surgeon bent her torso in 19% of the time (21 minutes).

Table 2. Total duration of postures outside the neutral zones for different body regions [u:mm:ss] and percentage of total endoscopic time

HARP/LDN and Total endoscopic time	Subject	Posture	Neck: Flexion	Neck: Rotation	Subjective pain score Neck	Shoulder: Raised	Subjective pain score Shoulder (left, right)	Elbow: Flexion	Subjective pain score Elbow (left, right)	Wrist *	Subjective pain score wrist (left, right)	Torso: Abduction	Torso: Axial rotation	Subjective pain score back
HARP1 1:43:51		Extreme	--	--		0:19:12 (18%)		--		--		--	0:17:56 (17%)	
	1	Poor	0:00:27 (0%)	--	2	1:03:52 (62%)	1,4	0:06:01 (6%)	1,1	0:15:00 (14%)	5,1	--	1:05:09 (63%)	2
		Good	1:43:24 (100%)	1:43:51 (100%)		0:20:46 (20%)		1:37:50 (94%)		1:28:51 (86%)		1:43:51 (100%)	0:20:46 (20%)	
HARP2 1:20:44		Extreme	--	--		0:30:43 (38%)		--		--		--	--	
	1	Poor	--	--	2	0:40:01 (50%)	1,3	0:09:25 (12%)	1,1	0:03:00 (4%)	1,4	0:00:21 (0%)	--	--
		Good	1:20:44 (100%)	1:20:44 (100%)		0:10:00 (12%)		1:11:19 (88%)		1:17:44 (96%)		1:20:23 (100%)	1:20:44 (100%)	
HARP3 2:26:01	1	Poor	--	--	4	1:32:34 (63%)	1,4	0:25:11 (17%)	1,1	1:29:22 (61%)	1,3	0:00:36 (0%)	1:01:09 (42%)	3
		Good	2:26:01 (100%)	2:26:01 (100%)		0:53:27 (37%)		2:00:50 (83%)		0:56:39 (39%)		2:25:25 (100%)	1:24:52 (58%)	
HARP4 1:48:00	1	Poor	--	0:01:23 (1%)	1	0:57:25 (53%)	1,3	0:11:03 (10%)	1,1	0:26:01 (24%)	1,4	0:00:36 (1%)	0:57:38 (53%)	2
		Good	1:48:00 (100%)	1:46:37 (99%)		0:50:35 (47%)		1:36:57 (90%)		1:21:59 (76%)		1:47:24 (99%)	0:50:22 (47%)	
HARP5 1:14:00		Extreme	--	--		0:03:31 (5%)		--		--		--	--	
	2	Poor	--	--	7	0:56:23 (76%)	7,4	0:09:35 (13%)	2,2	0:48:51 (66%)	9,6	0:02:00 (3%)	0:43:08 (58%)	4
		Good	1:14:00 (100%)	1:14:00 (100%)		0:14:06 (19%)		1:04:25 (87%)		0:25:09 (34%)		1:12:00 (97%)	0:30:52 (42%)	
HARP6 1:31:30		Extreme	--	--		--		0:07:50 (9%)		--		--	--	
	2	Poor	--	--	9	1:13:12 (80%)	8,8	1:05:22 (71%)	4,4	0:47:24 (52%)	9,3	--	1:13:12 (80%)	7
		Good	1:31:30 (100%)	1:31:30 (100%)		0:18:18 (20%)		0:18:18 (20%)		0:44:06 (48%)		1:31:30 (100%)	0:18:18 (20%)	
HARP7 1:07:07	2	Poor	--	--	8	0:46:10 (69%)	8,7	0:04:51 (7%)	2,2	0:37:30 (56%)	2,7	0:01:02 (2%)	0:45:08 (67%)	7
		Good	1:07:07 (100%)	1:07:07 (100%)		0:20:57 (31%)		1:02:16 (93%)		0:29:37 (44%)		1:06:05 (98%)	0:21:59 (33%)	
HARP8 1:48:49		Extreme	--	--		1:08:37 (63%)		--		--		--	--	
	3	Poor	--	--	3	0:18:26 (17%)	4,6	0:44:17 (41%)	1,3	0:46:18 (43%)	3,6	0:20:57 (19%)	0:10:54 (10%)	7
		Good	1:48:49 (100%)	1:48:49 (100%)		0:21:46 (20%)		1:04:32 (59%)		1:02:31 (57%)		1:27:52 (81%)	1:37:55 (90%)	

Table 2 (continued)

HARP/LDN and Total endoscopic time	Subject	Posture	Neck: Flexion	Neck: Rotation	Subjective pain score Neck	Shoulder: Raised	Subjective pain score Shoulder (left, right)	Elbow: Flexion	Subjective pain score Elbow (left, right)	Wrist *	Subjective pain score wrist (left, right)	Torso: Abduction	Torso: Axial rotation	Subjective pain score back
HARP9	3	Poor	--	--	8	0:23:01 (36%)	3,9	0:48:15 (75%)	3,8	0:58:56 (92%)	3,9	0:00:47 (1%)	0:43:59 (68%)	--
1:04:24		Good	1:04:24 (100%)	1:04:24 (100%)		0:41:23 (64%)		0:16:09 (25%)		0:05:28 (8%)		1:03:37 (99%)	0:20:25 (31%)	
LDN1	1	Poor	0:02:33 (2%)	--	1	0:08:09 (8%)	2,1	0:30:05 (28%)	1,1	0:37:49 (36%)	1,2	0:02:33 (2%)	--	2
1:45:50		Good	1:43:17 (98%)	1:45:50 (100%)		1:37:41 (92%)		1:15:45 (72%)		1:08:01 (64%)		1:43:17 (98%)	1:45:50 (100%)	
LDN2	1	Poor	--	0:00:51 (1%)	1	0:10:37 (12%)	1,3	0:25:47 (29%)	1,1	0:04:09 (5%)	1,1	--	0:00:51 (1%)	1
1:28:22		Good	1:28:22 (100%)	1:27:31 (99%)		1:17:45 (88%)		1:02:35 (71%)		1:24:13 (95%)		1:27:31 (99%)	1:27:31 (99%)	
LDN3	1	Poor	--	--	2	0:03:29 (4%)	1,1	0:28:28 (31%)	1,1	0:02:00 (2%)	1,2	--	--	4
1:33:17		Good	1:33:17 (100%)	1:33:17 (100%)		1:29:48 (96%)		1:04:49 (69%)		1:31:17 (98%)		1:33:17 (100%)	1:33:17 (100%)	
LDN4	1	Poor	0:00:20 (0%)	--	1	0:01:06 (1%)	1,1	0:38:48 (47%)	1,1	0:49:33 (60%)	1,1	--	0:58:00 (70%)	1
1:22:29		Good	1:22:09 (100%)	1:22:29 (100%)		1:21:23 (99%)		0:43:41 (53%)		0:32:56 (40%)		1:22:29 (100%)	0:24:29 (30%)	
LDN5	1	Poor	0:00:10 (0%)	0:00:31 (0%)	2	0:00:10 (0%)	1,1	0:34:46 (28%)	1,1	1:04:41 (52%)	0,1	0:00:20 (0%)	0:04:01 (3%)	1
2:03:22		Good	2:03:12 (100%)	2:02:51 (100%)		2:03:12 (100%)		1:28:36 (72%)		0:58:41 (48%)		2:03:02 (100%)	1:59:21 (97%)	
LDN6	2	Poor	0:01:27 (2%)	0:23:30 (30%)	5	0:15:05 (19%)	2,2	--	2,2	0:49:11 (63%)	2,2	0:02:23 (3%)	0:11:37 (15%)	2
1:18:41		Good	1:17:14 (98%)	0:55:11 (70%)		1:03:36 (81%)		1:18:41 (100%)		0:29:30 (37%)		1:16:18 (97%)	1:07:04 (85%)	
LDN7	3	Poor	--	--	6	0:03:02 (2%)	6,6	0:01:14 (1%)	3,3	0:57:10 (32%)	8,8	0:00:28 (0%)	--	7
3:01:25		Good	3:01:25 (100%)	3:01:25 (100%)		2:58:23 (98%)		3:00:11 (99%)		2:04:15 (68%)		3:00:57 (100%)	3:01:25 (100%)	
LDN8	3	Poor	--	0:10:23 (12%)	4	--	3,5	1:03:35 (73%)	1,1	1:10:34 (81%)	1,1	0:01:41 (2%)	0:25:47 (30%)	3
1:26:47		Good	1:26:47 (100%)	1:16:24 (88%)		1:26:47 (100%)		0:23:12 (27%)		0:16:13 (19%)		1:25:06 (98%)	1:01:00 (70%)	
LDN9	3	Poor	0:00:56 (1%)	--	3	0:01:27 (1%)	3,3	0:02:13 (1%)	3,2	0:31:32 (20%)	3,3	0:01:04 (1%)	--	3
2:39:35		Good	2:38:39 (99%)	2:39:35 (100%)		2:38:08 (99%)		2:37:22 (99%)		2:08:03 (80%)		2:38:31 (99%)	2:39:35 (100%)	

Finally, axial rotation of the torso was mainly seen during HARP. During the majority of HARP's (HARP1, HARP4-7, and HARP9) the torso was rotated up to 80% of the time (HARP6: 1 hour and 13 minutes and HARP1: 'extreme' 18 minutes and 'poor' 1 hour and 5 minutes). LDN1-3, LDN5, LDN7, and LDN9 showed hardly any axial rotation of the torso. However, LDN4 showed axial rotation during 58 minutes (70% of the time).

Subjective pain score

Figure 3 shows that the physical discomfort experienced in the different body regions after performing HARP was rated systematically higher than after performing LDN. Especially physical discomfort in the right shoulder and right wrist after HARP (4.8) scored twice as high than after LDN (2.3).

Participant 1 also indicated physical discomfort in his right knee after performing all HARP's and after performing LDN1, LDN2, and LDN3 ranging from 4 to 5. For LDN5 he rated discomfort in his right knee with a 6. For LDN3 and LDN5 he also experienced discomfort between his shoulder blades, rating it a 4 and 3, respectively.

For HARP9, participant 3 indicated physical discomfort in her upper legs, knees, and between her shoulder blades (no ratings were given). For LDN7 she indicated discomfort in her right index finger (rating 8) and right hip (rating 6). For LDN8 and LDN9 she experienced discomfort in her knees (no ratings were given)

Table 2 also shows the participants' pain score after performing that particular procedure. Compared to the other participants, participant 1 rated his physical discomfort lowest for both HARP and LDN (average overall discomfort 2.0 and 1.3, respectively). Participant 2 gave the highest pain scores for HARP (average overall discomfort 5.7), and participant 3 gave the highest pain scores for LDN (average overall discomfort 3.7).

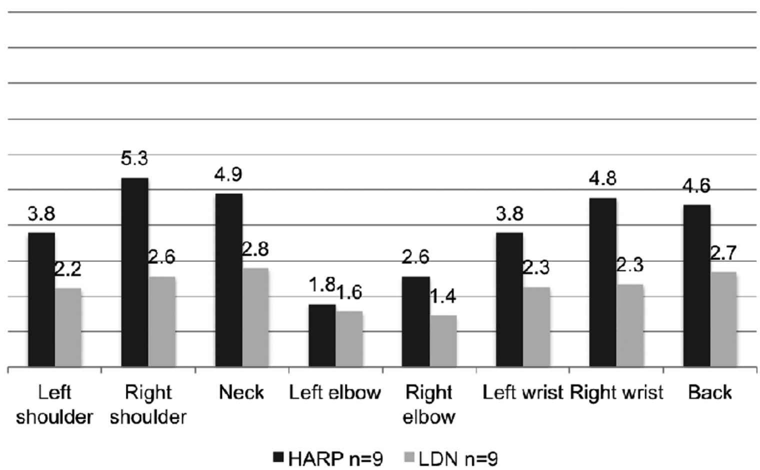

Figure 3. Average physical discomfort (scores 1-10) in different body regions after performing the surgical procedure.

DISCUSSION

This study showed that during both HARP and LDN unergonomic static postures were seen. The total time standing in unergonomic static postures would even more if the rule of 4 seconds would have been used. However, we only measured postures lasting 10 seconds or more as observing 4 sec in too short. Overall, for HARP the shoulder regions, back regions, and wrists were more dominant and for LDN the wrists. The subjective scores showed that HARP was perceived as more uncomfortable than LDN (average overall discomfort 3.9 and 2.2, respectively).

The body posture of participant 1 was characterized by a raised shoulder instead of a raised elbow (elbow was mostly held near the torso), which explains the low subjective rating in his elbows compared to his shoulders. Participant 1 also gave the lowest subjective pain scores for both HARP and LDN compared to the other participants. Although no specific reason could be observed, the surgeon's body length and whether the dominant hand was inside the abdomen could have played a role (participant 1 had his left hand in the abdomen, participants 2 and 3 their right hand). Furthermore, sex could have influenced the pain scores as well. Stomberg et al. have shown that female physicians suffer significantly more often from pain in the neck, shoulder, wrist, upper-back, and head after laparoscopy.[12]

Although no specific reason could be observed or was given, comparing data from the observations with the associated participants' pain scores showed some discrepancies. For HARP1, participant 1 rated physical discomfort in his shoulder with a 5 (14% of the time), which was higher compared to other HARP's. Discomfort in his back was rated a 2, but more time was spent in an unergonomic back posture (80% of time) compared to other HARP's that received a similar pain score. Pain scores for the wrist ranged from 0-1 for LDN4 and LDN5. Although these scores were comparable to other LDN's, more time was spent in an unergonomic wrist posture than during the other LDN's (52-60% of the time). For LDN4, discomfort in the back was rated a 1, although observation showed 70% of the time was spent in an unergonomic back posture. For HARP7, participant 2 rated discomfort in the wrist lower (rating 2.7) than for other HARP's although the observation showed similar time spent in an unergonomic wrist posture. Ratings for LDN7 were higher compared to the other LDN's performed by participant 3. For LDN8discomfort in the elbows and wrists were rated low (rating 1) despite spending considerable time in an unergonomic posture (73% and 81% of the time, respectively).

From a surgeon's ergonomic point of view, LDN seems to be superior. However, the preliminary results from the RCT show that left-sided HARP donor nephrectomy leads to excellent quality of life, fewer complications and is safer than LDN. Therefore, from a patient's viewpoint HARP is recommended as a safe and feasible technique. As long as the negative effects of unergonomic postures are not shown in the patients' outcome and surgeons continue to work through the pain, HARP will be the approach of choice.[11]

The observations showed that mainly the operating table and the instruments caused unergonomic posture. The monitor position and height did not present severe discomfort (although subjective ratings were relatively high – HARP= average 4.9; LDN= average 2.8). Manasnayakorn *et al* also have shown that the height of the operating table, the manipulation angle, and the instrument length influence the muscle workload and task performance during HARP.[15, 18] This study also showed that the intracorporeal to extracorporeal instrument-length ratio influenced the surgeon's posture.[7] Especially the short surgeons experienced more discomfort. Also the handle design, the handle size, and the cable at the back of the electrosurgical instrument influenced the surgeons' postures, which is in accordance with literature.[15, 18, 19]

One of the limitations of this study was the nature of the research set-up (observations). The aim was to measure duration of static body postures of five body regions without attaching sensors to the surgeon and with limited disruption of the procedure. Although surface electromyography (EMG) is possible, the participants did not opt for this method as this could distract them during surgery, and they were not mobile anymore (most EMG recording are performed during simulated tasks.[15, 18, 20, 21]). Szeto *et al* have shown that measuring merely neck and shoulder muscles activity by means of EMG did not interfere with the surgeons work.[22] However, in this study more regions had to be studied. Another limitation of this study is the minimum number of participants, and some participants only performing one or two LDN's or HARP's during the study period. However, the research type (RCT) did not allow us to select a specific surgeon or approach. Finally, during this study we focussed on the postures of the surgeon. However, the observations also showed unergonomic postures of the assisting surgeon and scrub nurse, which are also described in literature.[12, 23-25] Future research should therefore focus on the postures of the entire OR team.

To reduce physical discomfort and physical impairment, the OR set-up should be adjusted by the OR team to support them during surgery.[9] Recommendation for HARP entail an optimal operating surface height at 5 cm above elbow level, a shorter shaft length (250 mm instead of 330 mm), and a manipulation angle of 45-60 degrees to reduce to hand-to-target distance between extracorporeal and intracorporeal limbs.[7, 15, 18] For LDN it is recommended that the operating surface height is 64 to 77 cm above the level of the floor (0.7-0.8 times the elbow height).[10, 21] For both HARP and LDN the monitor should be placed straight in front of the surgeon, between 0,5m and arm's length (the viewing distance also depends on the monitor size), and between eye level and operating surface height (15 degrees downward).[13, 26] Also prevent people and equipment blocking the monitor.[26] Furthermore, for both approaches the location of the trocar ports, the position of the patient, and the type, and adjustability of the handle are important.[7, 13, 19, 26]

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Chapter 11
Summary

L.F.C. Dols

In this thesis we described the fundamentals of on the one hand selection of living kidney donors, on the other hand different aspects of surgical techniques.

Chapter one gives an overview of surgical improvements and the acceptance of donors in the field of living kidney donation. Kidney transplantation is the therapy of choice for patients with end-stage renal disease and offers the best chance on long-term survival and a good quality of life. In recent years a lot has changed in live kidney donation programmes. Expansion of living kidney donation is only possible by continuous innovations and research in various aspects including screening of the donor, perioperative care, surgical technique, long-term safety and transplant outcome. Innovations have limited the discomfort to the donor and incited live donation. Over the last two decades there has been a constant search to develop the optimal surgical technique for the living kidney donor. As opposed to many other operations the healthy living donor does not directly benefit from the operation. The attention to donor wellbeing and safety has become a priority. The criteria for acceptance of living donors have broadened over the years. Donors with complex vascular anatomy, older age, higher BMI and minor comorbidity do no longer preclude donation. Surgical practice has evolved from open lumbotomy, through mini-incision muscle-splitting open (MIDN), to minimally invasive laparoscopic techniques. In this chapter we describe the techniques practiced at the Erasmus MC in short, the mini-incision open, standard laparoscopic and hand-assisted retroperitoneoscopic donor nephrectomy. In literature, there is 'level 1' evidence that minimally invasive techniques are preferred to open donor nephrectomy. With all the improvements in surgical practice the main focus is safety, but this can never be properly studied because the sample size of such a study would be enormous. Acceptance of living kidney donors is broadened nowadays and research in intra-operative, post-operative and long-term outcome is needed to further specify the eligibility criteria.

Living donation by older donors may offer an attractive option to further stabilize waiting lists for kidney transplantation. The Western world is aging. In Europe the percentage of inhabitants of 65 or older will rise to approximately 29% in 2050. This will lead to an increasing number of patients suffering from renal insufficiency, but also to an increasing number of older persons willing to donate. The acceptance of older living kidney donors is debated, especially the supposed decline in estimated glomerular filtration rate (eGFR) after donation. As there is an ongoing shift towards the acceptance of these donors in order to bridge the gap between demand and supply of kidney transplants, we studied our cohort of living kidney donors over the years 1994 to 2006 in **Chapter two**. We outline that outcome after donor nephrectomy of older living kidney donors is not compromised. In a cohort of 539 consecutive donors, 422 donors < 60 years and 117 donors ≥ 60 years, short- and long-term transplant and recipient outcome is compared between older and younger donors. Elderly had a lower eGFR pre-donation, but decline in eGFR is not significantly different. Post-operative complications did not differ between both groups. At long-term we did not assess any differences with regard to proteinuria and hypertension. We addressed that there was no significant association between higher age and lower graft survival. In our study population graft survival inversely correlated with higher HLA-mismatch and higher Body Mass Index (BMI). As kidney function does not progressively decline and there are no differences in postoperative outcome, we conclude that living kidney donation is considered safe for the older donor.

Preoperative knowledge of the anatomy is of utmost importance, because donor kidneys with multiple arteries are associated with surgical complexity for removal and an increased rate of ureteral complications in the recipient. In **Chapter three** we evaluated the outcome of vascular imaging and the clinical consequence of multiple arteries and veins. Vascular anatomy at the operation was compared to preoperative imaging by magnetic resonance imaging (MRI) and digital subtraction angiography (DSA). Of 288 kidneys, 21 percent had multiple arteries and 10 percent multiple veins. Failure to predict the arterial anatomy was seen in 10 percent of the donors with the MRI and in 3 percent of the donors with DSA in. Venous anatomy was discordant in 6 percent of donors with MRI and 11 percent of donors with DSA. Multiple vessels did not influence recipient creatinine clearance or ureteral complications in total. However, accessory arteries to the lower pole are correlated with an increased rate of ureteral complications, possibly due to a reduced blood flow to the ureter. In LDN multiple arteries were associated with increased blood loss, longer operation- and warm ischemia time, but these parameters do not have any clinical impact on outcome since major differences are absent. Thus, proper preoperative planning is especially important to detect accessory arteries to the lower pole.

Many centres have been reluctant towards right-sided laparoscopic donor nephrectomy (R-LDN). Initial literature on R-LDN described a possible higher risk of venous thrombosis and subsequently graft failure in the recipient due to a shorter renal vein. In various transplantation centers right-sided nephrectomy was performed with old fashioned open approaches, even during the first decade of the current millennium. In **Chapter four** we describe the outcome of 159 right-sided and 124 left-sided procedures. The right kidney was also selected for removal in case of similar anatomy. Intra-operative complications were less frequent in R-LDN, 6 versus 19 percent. In L-LDN more conversions were seen, although some were elective. In multivariate analysis R-LDN appears to be the only baseline factor decreasing the intra-operative complication rate. There was no difference in post-operative complications for donor or recipient, and importantly there were no cases of venous thrombosis. Adopting R-LDN is beneficial to the donor, recipient and surgeon.

All different centers have special preferences of the particular technique to be used. In **Chapter five** we report the current practice of surgical techniques in transplant centres in Europe. We compared the outcome of questionnaires on surgical techniques with the results of our previous survey, conducted by Kok *et al*. Eighty-two percent of 119 centres in twelve countries replied on our questionnaire about the number of donors, the acceptance of donors with comorbidities, and the applied surgical techniques. More centres adopted the minimally invasive endoscopic techniques, but still 32 percent solely performed a variation of open nephrectomy. The number of centres exclusively applying endoscopic techniques increased from 45 percent in 2004 to 61 percent in 2009. The most important reason for centres not to adopt endoscopy is the presumption of a lack of evidence of superiority, which is not stated in recent literature.

Long-term physical and psychosocial aspects after laparoscopic and open donor nephrectomy are ill defined in literature. In **Chapter six** we point out that both donor and recipient have an excellent long-term outcome after median of 6 years after operation. Using questionnaires to quantify quality of life (SF-36) and fatigue (MFI-20) we evaluated the cohort of donors and recipients of 50 MIDN and 50 LDN operations from a previous RCT comparing mini-incision and laparoscopic donor nephrectomy (70 percent response rate). Clinical and laboratory data of 94 percent of donors were available. In the previous study physical fatigue was less and physical function better after LDN after one year follow-up. This study did not show statistically significant differences between the groups in the various dimensions of the questionnaires and most scores returned to baseline. Twelve percent reported persistent complaints after donor nephrectomy, such as new-onset hypertension, psychological problems, and pain at the extraction site. There is a positive attitude amongst donors; all donors who filled out the questionnaire would donate again if this would have been possible.

Chapter seven describes the first results of the left-sided hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy at the Erasmus MC from July 2006 to May 2008. This technique can especially improve the results of left-sided nephrectomy, as the intra-operative results for this side are inferior to right-sided LDN. We must keep in mind that most intraoperative benefits in right-sided donor nephrectomy do not clinically influence the post-operative course of the donor. Twenty HARP procedures were compared with 40 LDN's. Median operation time and warm ischemia time were significantly shorter for HARP despite this was the initial experience with HARP and we had a long tradition of laparoscopic donor nephrectomy. Intra- and postoperative, complication rate did not significantly differ between groups. Kidney function was not different for donors and corresponding recipients either. HARP may be a valuable alternative to left-sided LDN.

In order to guarantee donor safety, it is important to optimize the surgical approach. Although the 'LiDo-trial' taught us the superiority of LDN over mini-incision muscle-splitting open donor nephrectomy, there still are some disincentives such as rare but severe complications, longer operating times, higher in-hospital costs and long learning curves of the surgeon. Hand-assisted retroperitoneal donor nephrectomy may be an alternative, as this possibly implies a shorter operation time and fewer complications since the retroperitoneal plane is away from intestinal organs. **Chapter eight** is our published protocol for the HARP-study, comparing 190 live donors, 95 in each group, who were operated with hand-assisted retroperitoneoscopic versus standard laparoscopic nephrectomy. The HARP-trial is a multicentre, randomized controlled, single blind trial, conducted at the Erasmus MC and the Radboud University Nijmegen Medical Centre. The objective of the study is to determine the best approach for live donor nephrectomy. We hypothesized that left-sided hand-assisted retroperitoneal approach would lead, with similar or better quality of life, to fewer complications, and reduced operating time. All donors were randomized and followed-up for one year with questionnaires at marked time points.

The results of this randomized controlled, blinded, trial comparing LDN and HARP are described in **Chapter nine**. One hundred and ninety left-sided living kidney donors were operated on between July 2008 and September 2010 in two tertiary referral centers. All donors filled out questionnaires about quality of life, pain and nausea and return to daily activities and work. The prerequisite, that HARP may not result in a worse quality of life, was attained. HARP resulted, above all, in a shorter warm-ischemia time, shorter operative time and significantly less intra-operative complications. Other outcome measures, such as pain, morphine requirement, length of hospital stay and post-operative complication rate did not statistically significantly differ between the groups. One-year patient and graft survival were not significantly different. HARP is therefore recommended as a safe and realistic technique for left-sided donor nephrectomy.

Although HARP is the recommended technique for left-sided donor nephrectomy, ergonomic position for the surgeon may be inferior to LDN, especially due to the hand-assistance in combination with endoscopy. In **Chapter ten** we describe the ergonomics during both procedures. We recorded ten procedures from both techniques, during the HARP-trial, from three different locations and linked them with the image of the endoscope and asked the surgeons afterwards to rate the physical discomfort per body region. An unergonomic position was scored as outside the neutral zones for the duration of ten seconds. HARP showed raised shoulders, axial rotation of the torso and wrist positions outside the ergonomic range and LDN mainly poor wrist postures. All three surgeons rated higher physical discomfort after performing a hand-assisted retroperitoneal procedure. Patient outcomes are pivotal. Surgeons' discomfort comes at a second place, but to limit discomfort and physical impairment, ergonomic guidelines for the operation room set-up should be followed.

Chapter 11
Nederlandse samenvatting

L.F.C. Dols

In dit proefschrift worden een aantal uitgangspunten beschreven met betrekking tot de selectie van levende nierdonoren enerzijds en de verschillende aspecten van chirurgische technieken anderzijds.

Hoofdstuk één toont een overzicht van alle verbeteringen in de chirurgische techniek en de veranderingen in de selectie van geschikte levende nierdonoren. Niertransplantatie is de beste therapie voor patiënten met eindstadium nierfalen, het geeft de beste kans op overleving op de lange termijn en een goede kwaliteit van leven. De afgelopen jaren zijn er veel veranderingen doorgevoerd in de programma's voor levende nierdonatie. Uitbreiding van deze programma's is alleen mogelijk indien wij continue innovatie en onderzoek ondersteunen in alle aspecten van de levende nierdonatie, zoals: selectie van de donor, perioperatieve zorg, chirurgische techniek, overleving op de lange termijn en transplantaat uitkomst. Innovaties op dit gebied hebben het ongemak voor de donor verminderd en hiermee de levende nierdonatie vooruit gebracht. De laatste jaren is er gezocht naar de optimale chirurgische techniek voor levende nierdonatie. Dit is mede gedreven door het ontbreken van een duidelijk voordeel voor de donor bij de operatie. Hierdoor hebben het welzijn en de veiligheid van de donor prioriteit voor het verder ontwikkelen van levende nierdonatie. De criteria voor de acceptatie van een levende nierdonor zijn over de jaren verbreed, tegenwoordig accepteren we donoren op hogere leeftijd, met co-morbiditeit, met complexe vasculaire anatomie, en met een hogere BMI. De chirurgische techniek is geëvolueerd van open lumbotomie, via een mini-incisie spiersparende open techniek naar minimaal invasieve endoscopische technieken. We beschrijven in dit hoofdstuk de technieken die worden gebruikt en lichten de technieken zoals gebruikt in het Erasmus MC toe. In de literatuur is 'level 1' bewijs dat de laparoscopische techniek de voorkeur heeft boven open nierdonatie. Met alle verbeteringen in chirurgische techniek komt de focus vooral te liggen op veiligheid. Dit kan niet goed onderzocht worden, omdat de steekproefgrootte van dit soort studies veel te groot zou zijn om in een centrum te verrichten. Om selectiecriteria nog doelmatiger te definiëren zijn onderzoeken naar perioperatieve en lange termijnuitkomsten nodig.

Levende nierdonatie door oudere donoren kan een optie zijn om de wachtlijst voor niertransplantatie te stabiliseren. De westerse wereld vergrijst. In Europa zal het aantal inwoners van 65 of ouder stijgen tot 29% in 2050. Dit zal leiden tot een toename in nierfalen, maar tevens tot veel potentiële nierdonoren. Er bestaat onduidelijkheid of ouderen als levende nierdonor kunnen worden geaccepteerd. Dit heeft in het bijzonder te maken met de vermeende daling in de glomerulaire filtratie snelheid (eGFR) na donatie. Vanwege de verruiming van de acceptatiecriteria voor oudere levende nierdonoren hebben we een cohort van donoren van 1994 tot 2006 onderzocht. Dit onderzoek wordt beschreven in **Hoofdstuk twee**. We onderschrijven dat de uitkomst na levende nierdonatie van oudere donoren niet gecompromitteerd is. We hebben de uitkomst van donatie op korte- en lange termijn voor de donoren en tevens de uitkomst van het transplantaat en ontvanger vergeleken in een groep van 539 donoren, van wie 422 jonger waren dan 60 jaar en 117 donoren 60 jaar of ouder. Ouderen hadden een lagere eGFR voor donatie, maar de afname in eGFR na donatie is niet significant verschillend tussen beide groepen. Er werden geen verschillen gevonden in postoperatieve complicaties en op de lange termijn werden geen verschillen gezien in de incidentie van eiwit verlies in de urine en hypertensie. Er is geen verband gevonden tussen hogere leeftijd en kortere transplantaat overleving bij de ontvanger. Er blijkt wel een kortere transplantaat overleving te bestaan bij een hogere genetische mismatch tussen donor en ontvanger en bij een hogere BMI van de donor. Aangezien de nierfunctie geen voortdurende daling laat zien en er geen verschillen bestaan in de uitkomst na de operatie, concluderen wij dat levende nierdonatie veilig is voor oudere donoren.

Preoperatieve kennis van de anatomie is zeer belangrijk, in het bijzonder bij nieren met meerdere arteriën, omdat deze geassocieerd zijn met een moeilijkere operatie en een mogelijk toegenomen kans op problemen met de ureter bij de ontvanger. In **Hoofdstuk drie** beschrijven wij een evaluatie van de uitkomst van beeldvorming van de bloedvaten en de klinische consequenties van nieren met meerdere arteriën en venen. De anatomie van de bloedvaten tijdens de operatie werd vergeleken met de beeldvorming voor de operatie. Beeldvorming was verricht met 'magnetic resonance imaging' (MRI) en 'digital subtraction angiography'(DSA). Van de 288 nieren had 21 procent meerdere arteriën en 10 procent meerdere venen. Een verkeerde inschatting van de arteriele anatomie bleek in 10 procent bij gebruik van MRI en in 3 procent bij DSA. Veneuze anatomie werd in 6 procent bij MRI en 11 procent bij DSA verkeerd voorspeld. Het hebben van meerdere vaten had geen invloed op de kreatinine klaring van de ontvanger of het totaal aantal ureter complicaties. Accessoire nierarteriën naar de onderpool zijn wel gecorreleerd met meer ureter complicaties, mogelijk door een verminderde bloeddoorstroming naar de ureter. In laparoscopische donor nefrectomie (LDN) zijn meerdere arteriën geassocieerd met meer bloedverlies, langere operatie- en warme ischemietijd, maar deze verschillen hebben geen evidente invloed op de klinische uitkomst. Goede preoperatieve beeldvorming blijkt in het bijzonder van belang voor het detecteren van onderpoolsarteriën.

Veel centra zijn terughoudend met rechtszijdige laparoscopische donornefrectomie (R-LDN). In oudere literatuur wordt een mogelijk hoger risico op veneuze trombose gezien met hierbij falen van het transplantaat. Dit zou mogelijk worden veroorzaakt door een kortere niervene aan de rechter zijde. In verschillende centra werd de rechtszijdige donornefrectomie met ouderwetse open technieken verricht, zelfs nog aan het begin van dit millennium. In **Hoofdstuk vier** beschrijven we de uitkomst van 159 R-LDN en 124 L-LDN procedures, waarbij de rechter-zijde werd gekozen in geval van vergelijkbare anatomie aan beide zijden. Intraoperatieve complicaties werden minder gezien bij R-LDN, 6 procent versus 19 procent. In L-LDN werden meer conversies gezien, waarvan sommige electief. In een multivariate analyse bleek R-LDN de enige factor die kon zorgen voor een vermindering van de intra-operatieve complicaties. Er werd geen verschil gevonden in post-operatieve complicaties voor donor of ontvanger, en er werd geen veneuze trombose gezien. R-LDN kan worden gebruikt en geeft een goed resultaat voor de donor, ontvanger en chirurg.

Transplantatiecentra hebben verschillende voorkeuren voor de te gebruiken operatietechniek. In **Hoofdstuk vijf** beschrijven we de huidige uitvoering van de chirurgische technieken in verschillende transplantatiecentra in Europa. We hebben de vragenlijsten over chirurgische techniek vergeleken met een eerder onderzoek uit ons centrum verricht door Kok *et al.* Tweeëntachtig procent van de 119 centra in twaalf landen reageerden op onze vragenlijst met vragen over onder andere het aantal levende donoren, acceptatie van donoren met comorbiditeit en de gebruikte chirurgische techniek. De meeste centra hebben de minimaal invasieve techniek aangenomen, maar nog steeds gebruikt 32% van de centra een vorm van open techniek. Het aantal centra dat uitsluitend minimaal invasieve technieken gebruikt is toegenomen van 45 procent in 2004 tot 61 procent in 2009. De belangrijkste reden voor centra om geen minimaal invasieve techniek te verrichten is de veronderstelling dat er geen sluitend bewijs voor is, wat overigens juist wel in de literatuur is beschreven.

Langetermijn fysieke en psychosociale aspecten na laparoscopische en open levende nierdonatie zijn weinig beschreven in literatuur. In **Hoofdstuk zes** beschrijven we dat de levende donor en ontvanger een uitstekend lange termijn uitkomst hebben na gemiddeld zes jaar na operatie. Door het gebruik van kwaliteit van leven (SF-36) - en vermoeidheid (MFI-20) vragenlijsten evalueerden we een cohort van 50 mini-incisie spiersparende en 50 laparoscopische operaties uit een eerder uitgevoerde RCT waarin deze twee technieken vergeleken werden (70% respons). Van 94% van de donoren waren klinische data en bloedwaarden bekend. In de oorspronkelijke studie werd vastgesteld dat in de laparoscopisch geopereerde groep na een jaar de fysieke vermoeidheid minder was en de fysieke functie beter. De huidige studie toont geen verschillen aan tussen de beide groepen over de verschillende dimensies van de vragenlijsten en de meeste scores zijn weer op het basis niveau van voor de operatie. Twaalf procent geeft aan blijvende klachten te hebben zoals een postoperatief ontwikkelde hoge bloeddruk, psychische problemen of pijn bij het litteken boven het schaambeen. Er is over het algemeen een positief beeld over het doneren van een nier; alle donoren die participeerden in het onderzoek, zouden opnieuw doneren indien dit mogelijk was.

Hoofdstuk zeven beschrijft de eerste resultaten van de linkszijdige handgeassisteerde retroperitoneoscopische versus de standaard laparoscopische nierdonatie in het Erasmus MC van juli 2006 tot mei 2008. Met deze techniek zou vooral voordeel te behalen zijn bij de linkszijdige operatie, aangezien de intraoperatieve resultaten minder goed zijn dan aan de rechter zijde, overigens zonder veel invloed is op het klinische beloop van de donor na de operatie. De perioperatieve uitkomsten van twintig HARP procedures werden vergeleken met de uitkomsten van veertig LDN procedures. De mediane operatietijd en warme ischemietijd waren significant korter voor de HARP. Er werden geen verschillen gezien in complicatie aantallen, zowel intraoperatief als postoperatief. De nierfunctie was niet verschillend voor beide groepen. HARP kan een waardevol alternatief zijn voor de linkszijdige laparoscopische donornefrectomie.

Om veiligheid te kunnen garanderen is het belangrijk de chirurgische techniek te optimaliseren. Hoewel de 'LiDo-trial' liet zien dat LDN superieur was aan de mini-incisie spiersparende techniek, zijn er nog steeds nadelen zoals: een langere operatietijd, een kleine kans op ernstige complicaties die bij open chirurgie zelden gedocumenteerd zijn, hogere kosten en er moet een chirurg beschikbaar zijn die gespecialiseerd is in laparoscopische nierdonatie. Handgeassisteerde retroperitoneale donornefrectomie kan een alternatief zijn met een mogelijk kortere operatietijd en minder complicaties doordat het vlak buiten het buikvlies om is en de chirurg zo minder makkelijk de organen, die binnen het buikvlies liggen, kan beschadigen. **Hoofdstuk acht** beschrijft ons gepubliceerde protocol voor de HARP-studie, waarin 190 levende nierdonoren, met 95 in elke groep, een nierdonatie ondergingen via laparoscopische (LDN) danwel handgeassisteerde retroperitoneoscopische (HARP) benadering. De HARP-studie is een multicentrisch, gerandomiseerd, enkel blind onderzoek wat uitgevoerd is in het Erasmus MC te Rotterdam en het UMC St Radboud te Nijmegen. Het doel van de studie was de beste techniek voor levende nierdonatie te definiëren. De hypothese was dat linkszijdige handgeassisteerde retroperitoneale benadering zal leiden tot een gelijke of betere kwaliteit van leven en daarbij minder complicaties geeft en een vermindering van operatietijd en kosten. Alle donoren zijn gerandomiseerd en werden vervolgd tot een jaar postoperatief met vragenlijsten op gezette tijden.

De resultaten van deze gerandomiseerde, geblindeerde studie waarbij linkszijdige LDN en HARP werden vergeleken wordt beschreven in **Hoofdstuk negen**. Honderdnegentig levende nierdonoren die geopereerd zijn tussen juli 2008 en september 2010 in twee tertiaire verwijzingscentra. Alle donoren hebben vragenlijsten ingevuld over de kwaliteit van leven, pijn, misselijkheid en de tijd tot terugkeer naar het werk. Er werd voldaan aan het uitgangspunt dat HARP in ieder geval geen slechtere kwaliteit van leven mocht hebben dan de LDN. HARP resulteerde in een kortere warme ischemietijd, kortere operatietijd en minder intra-operatieve complicaties. Andere uitkomstmaten, zoals pijn, benodigde hoeveelheid morfine, opnameduur en postoperatieve complicaties verschilden niet tussen beide groepen. Patiënt- en transplantaatoverleving waren niet verschillend tussen beide groepen één jaar na transplantatie. Daarom bevelen wij HARP techniek aan als benadering van keuze voor de donornefrectomie links.

Hoewel HARP de aanbevolen techniek is, zou de ergonomische positie van de chirurg mogelijk inferieur zijn aan de LDN, vooral door de handassistentie in combinatie met laparoscopie. In **Hoofdstuk tien** beschrijven we de ergonomie van beide ingrepen. Bij 10 procedures van beide technieken hebben we videobeelden gemaakt vanuit drie verschillende hoeken en koppelden dit aan het beeld van de camera. Achteraf is de chirurgen gevraagd het fysieke discomfort per lichaamsonderdeel met een cijfer aan te geven. Een niet ergonomische positie werd genoteerd indien deze buiten de neutrale ergonomische standen was voor de duur van tien seconden. HARP liet meer momenten met opgetrokken schouders, rotatie om de as en posities van de polsen buiten de neutrale zones zien. LDN liet frequent niet-ergonomische posities van de polsen zien. Alle drie de chirurgen gaven meer ongemak aan tijdens de handgeassisteerde retroperitoneale procedure. Aangezien alles om de patiënt draait, staat het ongemak van de chirurg op een tweede plaats. Om ongemak voor de chirurg zoveel mogelijk te voorkomen moeten ergonomische richtlijnen voor de opstelling van de operatiekamer worden opgevolgd.

Chapter 12

General discussion, recommendations and future perspectives

L.F.C. Dols

Wider acceptance of living donation and expanded eligibility criteria for donation has increased focus on risk factors that could impact safety of the living kidney donor. Key risk factors determining the level of safety can be found in pre-donation medical evaluation, the surgical procedure itself and the long-term consequences of living with one kidney.

Pre-donation medical evaluation

In 2004 the Amsterdam Forum set forth a comprehensive list of medical criteria that can be used in the evaluation of potential kidney donors.[1] Broader eligibility criteria made the decision to accept living donors even more challenging. Centers do not strictly follow the Amsterdam Forum criteria, as it is the responsibility of the nephrologist and surgeon to accept living kidney donors. Therefore the criteria are not uniform between centres. Future directions will have to focus on defining new and generally accepted eligibility criteria in order to guarantee a higher standard of care for the living kidney donation programs. We should address all determinants of safety (i.e. risk factors) that contribute positively to the process of pre-donation medical evaluation.

Risk factors for renal and cardiovascular damage, such as increasing age, hypertension, diabetes and overweight, are important in screening for a suitable kidney donor. With increasing age, co-morbidities are more frequent. Many centers impose age limits, according to data this should be no drawback in living donation and we should accept older donors. There is no higher perioperative complication rate, no higher rate of hypertension or decrease in GFR. The rate of change in GFR is not significantly different between older and younger donors, although older donors have age related changes in kidney function and therefore can have a lower GFR pre-donation. Older donors have established behavior patterns which make them good candidates in many aspects. Older donors have also less time to develop long-term complications. The risk on ESRD does not seem to be elevated in comparison to the normal population, but very long-term follow-up is sparse. Therefore older donors can be accepted, and when possible matching in donor and recipient age is advised.

Hypertension is a risk factor and can be encountered more frequently with increasing age. It is known that malignant hypertension is a strong predictor for cardiovascular risk and progressive renal insufficiency. Whether 'easily controllable' hypertension, without organ damage, poses a risk for renal function after donation, is less clear. In case of an isolated abnormality it poses little risk for kidney function, therefore donation should not be excluded up front.

Obesity is a risk factor for proteinuria and increased serum creatinine, as demonstrated by studies on long-term follow-up of uninephrectomized patients for other reasons than donation.[2] Recently, a meta-analysis concluded that donation of obese individuals is safe with regard to the perioperative process, but long-term follow-up lacks.[3] Obesity as a risk factor should certainly be taken into account as it is possibly more threatening than hypertension and older age. Obesity is associated with development of diabetes, cardiovascular and renal complications. Studies indicate obesity as an accelerant to some forms of glomerular disease. Obese donors have higher risks according to a hyper-filtration mechanism. We should encourage potential donors to lose weight, and not to gain weight after donation on long-term.

Side selection is of utmost importance to the safety of the process. Reluctance towards the right side is not based on evidence, and centers should always prioritize the best treatment for the donor. This includes adherence to the principle that the best kidney must be left to the donor. The choice for either side should be made reminding anatomical fundamentals and its impact on donor and recipient surgical procedure and outcome. If anatomical abnormalities, i.e. renal artery stenosis, are absent, right-sided donor nephrectomy is to be preferred when anatomy is less complex on this side.

Surgical procedures

Surgical techniques have been thoroughly studied and developed over the past decade. Endoscopic techniques should be applied in the majority of donors. Transplant surgeons should become familiar with these techniques. It is not acceptable to perform classic open donor nephrectomies in this era with different minimal invasive options. Nevertheless in Europe at least nearly 500 open donor nephrectomies were performed in 2010, with a significant number of classic open nephrectomies.[4] Above all nine of the questioned centers still use hem-o-lock self-locking clips in contrast to the recommendations of the Federal Drug Administration to abandon these for living kidney donation. This demonstrates a lack of knowledge and skills to accurately treat living kidney donors. Living donors should be treated in specialized centers to ensure this specific knowledge and a high frequency of operations. In general, we suggest HARP for left-sided donor nephrectomy. However subgroup analyses should determine which technique should be used in which donor, reminding the specific experience of a surgeon. HARP does not yet confer clear benefits on the right side. Indications for right-sided HARP should be defined. Recent developments include the robot-assisted laparoscopic donor nephrectomy, with advantages of 560-degrees rotatable instruments, the use of high definition 3D-technology, an enlarged image, computerized corrections of undesirable vibrations and an improved surgeon's ergonomic comfort. In the near future the position of the robot-assisted laparoscopic donor nephrectomy needs to be assessed. Especially for complex vascular anatomy we expect the robot to be beneficial. However, we expect that robot-assisted laparoscopic donor nephrectomy will never be proven cost-efficient. For efficient implementation of newly developed techniques, proctors from specialized centers could support shortening learning curves via training programs for colleagues.

Long-term consequences

With sufficient follow-up of past donors we have knowledge of all these individual factors, and importantly the combination of risk factors. On the basis of this knowledge we can develop a 'tailor-made approach' per donor. Due to continuous shifting of boundaries for living donation, it is difficult to decide when we have sufficient follow-up data. Practice of living kidney donation is too diverse in centres in Europe regarding eligibility criteria and surgical technique. An international database should be used to systematically include data of different centres. This provides us more insights in risk factors affecting mortality and morbidity of living kidney donation and will help us to only select those donors who have the best chance on a good outcome. As of today morbidity and mortality is difficult to study given the low incidence, therefore this requires a large sample size that goes beyond regional or national data registries. By using the extensive database we can identify risk factors for morbidity and mortality after donation and include all known and possible factors in a donor risk score model to predict the postoperative outcome preoperatively.

As long as there is no solution for kidney disease, dialysis techniques are inferior to transplantation, kidneys from living donors have better survival, and artificially grown kidneys or stem cell therapy are not daily practice yet, we have to keep optimizing predonation screening and surgical techniques.

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