PATIENT-REPORTED OUTCOMES FOLLOWING LIVING DONOR NEPHRECTOMY

Marit Helen Andersen

Doctoral Thesis
Faculty of Medicine, University of Olso, Norway
2008

The Interventional Centre and The Department of Surgery

Rikshospitalet HF

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 698

ISBN 978-82-8072-726-8

Cover: Inger Sandved Anfinsen.
Printed in Norway: AiT e-dit AS, Oslo, 2008.

Produced in co-operation with Unipub AS.
The thesis is produced by Unipub AS merely in connection with the
thesis defence. Kindly direct all inquiries regarding the thesis to the copyright
holder or the unit which grants the doctorate.

Unipub AS is owned by
The University Foundation for Student Life (SiO)

TABLE OF CONTENT

ACKNOWLEDGEMENTS

The present work was carried out at The Interventional Centre and The Department of Surgery, Rikshospitalet HF, Oslo, and financially supported by Southern Norway Regional Health Authority, The Department of Surgery and The Center of Patient Participation and Nursing Research at Rikshospitalet HF, The Norwegian Nurses' Association, The Norwegian Association for Kidney patients and Organ transplanted (LNT), and Harry W. Holm's Foundation.

Many people have been involved in this study and I am grateful to each and every one of them. First of all my thanks go to the donors who willingly took part in the study and taught me a lot about being a living kidney donor.

I would also like to express my deepest gratitude to all those who have supported me throughout this work. Erik Fosse, MD, DMSc, my main supervisor has provided valuable support at all stages of my thesis. His door has always been open and his encouragement has been invaluable. Also, I appreciate my two co-supervisors, professor Astrid Klopstad Wahl and professor Berit Rokne Hanestad for thorough support, encouragement and help, and for sharing with me their wide knowledge in quality of life-research. Thanks to Ole Øyen who has been my participating supervisor regarding living donor surgery. He has played a major role at all stages of the study.

I am grateful to my fellow researcher Lars Mathisen, with whom I have collaborated closely in all parts of the presented work. The co-operation with him has been appreciated.

Thanks also to the collaborative research team including Bjørn Edwin, Tor Inge Tønnessen, Gunnvald Kvarstein, Randi Digernes, Marijke Veenstra, Geir Aamodt and Fanny Bruserud.

Nephrologists at local hospitals in Norway have also contributed by recruiting potential donors to the study.

I am in debt to former head of the Department of Surgery Anstein Bergan, present head of the Department of Surgery Karl-Erik Giercksky, and Ellen Drolsum Finstad, for their leadership and support.

I wish to acknowledge the nursing staff at the Department of Surgery for their assistance during data-collection. I am grateful to my nursing collegues Kjersti Lønning, Käthe Meyer, Eva Alice Aadal, Kari Oustad and Annette Lennerling who shared their broad knowledge about living kidney donors with me.

Also, thanks to Trond André Aag, Aud Wenche Bakkeng and Tone Margrethe Sverresborg for data support.

Finally, I would like to thank my family. Special thanks to my children Maria, Andreas and Karina who have been a highly loved source of joy. I am grateful for the support my husband Lars provided during these years. This thesis would note have been possible without his encouragement, love and patience.

Oslo, April 2008

SUMMARY

The purpose of this study was to assess clinical and patient-reported outcomes following living kidney donor nephrectomy, with particular emphasis on patient-reported outcomes. A combination of quantitative and qualitative research methodology was used. In a randomized, controlled trial of 122 donors we compared laparoscopic and open donor nephrectomy, focusing on donor safety and per - and postoperative complications (Paper I), postoperative pain and convalescence (Paper I and II), and health status and overall quality of life at 1, 6 and 12 months follow-up (Paper III). The results demonstrated that the conventional open donor nephrectomy is superior to laparoscopic donor nephrectomy with regard to donor safety. Yet, an uncomplicated laparoscopic donor nephrectomy has important short-term advantages such as less analgesic requirements, less postoperative pain, better health status and a shorter sick leave as compared to the open approach. However, long-term follow-up only revealed significant differences in favour of laparoscopy when adjusting for reoperations and conversions. We therefore conclude that long-term benefits are hard to prove in favour of the laparoscopic technique. To explore the donors' narrative experiences of going through donor nephrectomy, we in-depth interviewed 12 donors at one week (Paper IV) and at one year (Paper V) after donation. A positive feeling about being a donor was the dominant theme in both interview series. Though experiencing disincentives from surgery during the first postoperative period, the donors expressed that they were back to normal health condition a year after surgery, also confirmed by our quantitative investigation. Donors experiencing unsuccessful recipient outcome did not regret donation. On the contrary they remained confident in themselves, thinking they did what they could do to help a close family member.

LIST OF ORIGINAL PAPERS

Paper I.
Øyen O, Andersen M, Mathisen L, Kvarstein G, Edwin B, Line P-D, Scholz T, Pfeffer PF. Laparoscopic versus open living-donor nephrectomy: experiences from a prospective, randomized, single-center study focusing on donor safety. Transplantation 2005; 79: 1236-1240.

Paper II.
Andersen MH, Mathisen L, Øyen O, Edwin B, Digernes R, Kvarstein G, Tønnessen TI, Wahl AK, Hanestad BR, Fosse E. Postoperative pain and convalescence in living kidney donors - laparoscopic versus open donor nephrectomy: a randomized study. American Journal of Transplantation 2006; 6: 1438-1443.

Paper III
Andersen MH, Mathisen L, Veenstra M, Øyen O, Edwin B, Digernes R, Kvarstein G, Tønnessen TI, Wahl AK, Hanestad BR, Fosse E. Quality of life after randomization to laparoscopic versus open living donor nephrectomy: long-term follow-up. Transplantation 2007; 84: 64-69.

Paper IV
Andersen MH, Mathisen L, Øyen O, Wahl AK, Hanestad BR, Fosse E. Living donors' experiences 1 wk after donating a kidney. Clinical Transplantation 2005; 19: 90-96.

Paper V
Andersen MH, Bruserud F, Mathisen L, Wahl AK, Hanestad BR, Fosse E. Follow-up interviews of 12 living kidney donors one yr after open donor nephrectomy. Clinical Transplantation 2007; 21: 702-709.

INTRODUCTION

Kidney transplantation is the optimal treatment for patients with end stage renal disease (1). There are two sources of kidneys for transplantation, deceased donors and living donors. Several studies show that kidneys from living donors provide superior immediate and long-term function, do not require prolonged waiting times, and are more cost - effective than those from deceased donors (2-4). However, the use of living donors for kidney transplantation not only affects patients with end stage renal failure, but also the healthy persons who volunteer to donate. The main objection to living kidney donation is that it exposes the healthy donor to the risks of major surgery and a life with just one kidney (5, 6). The available evidence, mainly from retrospective surveys, suggests that donor nephrectomy is generally very safe, with a perioperative mortality of about 0, 03 % (7). Postoperative problems associated with kidney donations are pain related to the wound and temporary occupational disability (8 -10). Careful, prospective follow-ups of large numbers of living donors have been uncommon, so the knowledge of the situation of going through living donor nephrectomy has been incomplete (11, 12), and in particular as seen from the donors' perspective. In Norway almost 40 % of all renal transplants are performed with organs from living donors (13) and efforts are made to increase the share of living kidney donors to increase the number of kidneys available for transplantation. At Rikshospitalet HF open donor nephrectomy has been the established treatment for living kidney donors. However, since 1998 laparoscopic donor nephrectomy has been experimentally performed at our hospital. In their report from 2000, Merlin et al concluded that the evidence-base for open and laparoscopic living donor nephrectomy has been inadequate to make recommendations regarding which technique is the best (11). The donors undergo the operation for altruistic reasons and the techniques are performed on healthy individuals. Hence, it is important to increase the knowledge base in this area. On this background we performed a broad evaluation project at our centre, including objective, subjective and economic donor outcomes. The present work investigates clinical and patient-reported outcomes following laparoscopic and open donor nephrectomy, with particular emphasis on patient-reported outcomes. The use of patient preferences to evaluate medicine and health care interventions is becoming more accepted in the medical community, and in particular with regard to clinical trials (14). The term patient-reported outcomes has now become accepted as important because it indicates interests in a number of outcomes and provides the patient's perspective on the treatment (15-18). Such outcomes can therefore be used both for comparative purposes in the evaluation of different treatments, and for descriptive purposes. Profiles of patient-reported data provide a source of information about the possible consequences of therapy, and this information can be shared with patients when deciding

which treatment may be the most suitable. To investigate clinical and patient-reported outcomes following living donor nephrectomy we applied a combination of a quantitative and a qualitative research approaches to shed light on different aspects regarding living donor nephrectomy

LIVING KIDNEY DONATION

The first successful living donor nephrectomy was performed in 1954 in Boston, USA (19). Since then, the number of living kidney donations has increased worldwide. In Norway kidney transplantation was established as a routine procedure in Norway in 1969 (20). Figure 1 demonstrates donor sources in Norway in the period 1969-2007.

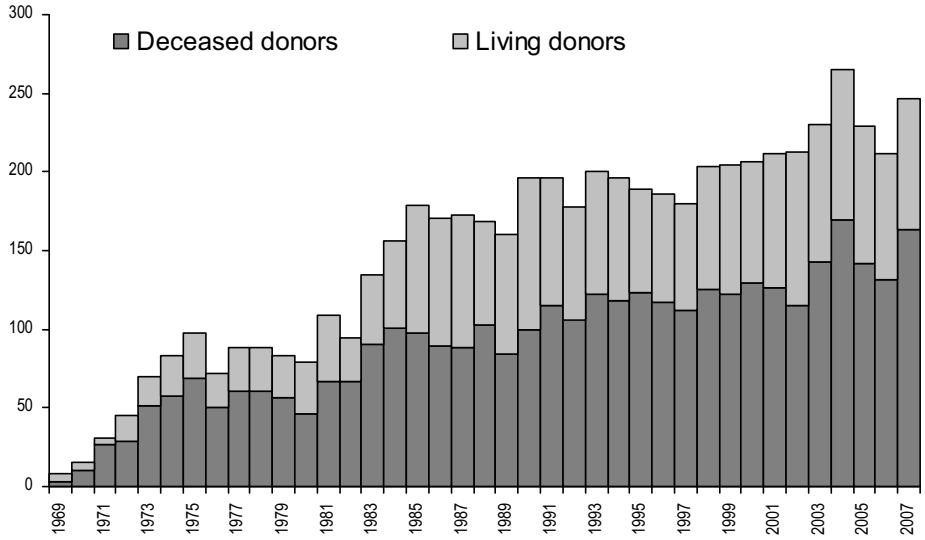

Figure 1. Kidney transplantations in Norway by donor source, dark grey bars indicate proportions of kidneys from deceased donors and grey bars indicate proportions of kidneys from living donors (figure adapted from Bakkan, 2008).

Advantages of living donor kidney transplantation

Living donor renal transplantation is superior to deceased renal transplantation in regard to graft and patient survival. Although the gap in graft survival between living related and deceased renal transplantation has narrowed considerably, living related donor grafts still have about 10 % better survival rate at 1 year and a significantly higher probability of function thereafter (21). There are

several reasons for this. First, living kidney donors have been fully screened and provide kidneys with a guaranteed high quality. Second, living kidney donation allows for transplant surgery to be scheduled to ensure optimal physical and emotional health of both the donor and the recipient. Third, these transplants are often pre-emptive, occurring before dialysis is necessary and allowing recipients to avoid waiting lists. Other important factors are that organs from deceased donors include the patho-physiological changes associated with brain death of the donor, maintenance in the intensive care unit and possibly extended cold ischemia times (22).

The donation procedure

Donor nephrectomy can be performed by either open or laparoscopic surgery and there are several techniques for both types. Open nephrectomy is performed by conventional retroperitoneal access through a flank incision at the level of costa 11 to 12, most often without rib resection. The donor is placed in an extended flank position (23). Laparoscopic nephrectomy is performed by a trans-peritoneal approach with the patient positioned in flank position with angulation. Six ports are used and the video-laparoscope is introduced through an infraumbilical port (24). The hand-assisted variation of the laparoscopic nephrectomy was developed to give surgeons greater tactile feedback and to facilitate the definition of tissue planes. It has been suggested that this may reduce the operating room time and allow transplant centres that lack advanced laparoscopic expertise to perform the donor surgery safely (25, 26). A few randomized (27, 28) and several non-randomized (29-35) studies have been performed to compare laparoscopic versus open living donor nephrectomy. In short, results suggest that the procedures are comparable regarding graft function. Further, as the open approach seems to be a very safe procedure, the laparoscopic approach is associated with a briefer convalescence and a better or equal quality of life as compared to the open approach.

Short and long-term risk following living kidney donation

Donor nephrectomy is associated with low morbidity and low mortality (36-42). Total morbidity, including minor complications, has been calculated to be roughly 10 percent (43, 44). Problems associated with kidney donations are postoperative pain and temporary occupational disability (45-49). Long term issues include the possibility of chronic pain, the risk of a slight rise in blood pressure and the increased incidence of proteinuria. Most series document about 5 % of the donor population with chronic pain or other problems directly related to nephrectomy (50). Yet, there is evidence that most donors recover well from the surgery and are back in normal health condition after donation (51-54). The psychosocial impact of donor nephrectomy has also been evaluated.

This includes a benefit in self-esteem and increased self-worth, and a strong donor-recipient relationship (55-58), but also a risk of sequel after the donation such as experience of stress and mild depression (59-65), and reaction to transplant failure or death of the recipient (66-67). Worries about medical costs and loss of income related to the donation process have also been documented (49).

Ethical and legal issues of living kidney donation

Living kidney donation raises many ethical issues. The key issue is whether the removal of a healthy kidney from a person constitutes harm. On the other hand, should not the autonomy of the donor who wishes to improve the quality of life of a closely linked individual be respected? Each case must be evaluated carefully to ensure minimum risk to the donor and maximum benefit to the recipient. Living donations historically have all been directed between family members and friends, are considered ethically acceptable (68-70), and are performed according to policies established at individual transplantation centres (71). In view of the potential risk to a living donor, it is generally accepted that all things being equal it is preferable to use deceased rather than a living organ donor. Moreover, other options are usually available to sustain life following end-stage renal failure. Article 19 of the Council of Europe Convention on Biomedicine stipulates that "living organ donation is only permissible where there is no suitable deceased organ available and no other alternative therapeutic method of comparable effectiveness" (72). Persons who donate a kidney should be competent, willing to donate, and free from coercion from other persons (73). Informed consent is required for major surgery and Appelbaum and Grisso describe four important principles for being competent to give a valid consent: i) the ability to communicate choices, ii) to understand relevant information about a treatment decision, iii) to understand the situation and the specific implications that it carries for one's future, and iv) to handle information rationally (74).

PATIENT-REPORTED OUTCOMES

The main focus in the present thesis is the evaluation of patient-reported outcomes following living kidney donation. The term patient-reported outcome addresses the source of the report rather than the content (18). It thus can be seen as an umbrella term to describe a broad spectrum of disease and treatment outcomes reported subjectively by the patient, such as health status measures, symptoms report and patient satisfaction with treatment (75, 76). Today patient-reported outcomes have evolved to include any endpoint derived from patient reports, both from the evaluation and comparison of treatments and for the assessment and management of individual patients.

Knowledge of patient experiences when treatment options are implemented serves to guide health personal so that interventions are timed, adjusted, and can contribute to the maximal benefit from surgery. A key challenge remains our ability to link patient-reported outcomes with clinical endpoints when new treatments are evaluated. The present work addresses this challenge by investigating patient-reported outcomes in a broad evaluation where objective and subjective assessments are investigated in patients going through living donor nephrectomy. Patient-reported outcomes were conceptualized as overall quality of life, health status, and disincentives related to surgery such as pain and the surgical scar. Also narrative donor experiences derived through in-depth interviews were part of patient-reported outcomes investigated in this thesis. The latter was integrated to get a more complete picture of the donors' situation. Phenomenological descriptions can provide health personal with different perspectives on a phenomenon as the focus is on individual experiences and how the persons express meaning about some aspects of their lives (77-79).

The concept of quality of life – origin and expansion

Of the most central concepts that fall within the term patient-reported outcomes are quality of life. This is a relatively new concept emerging from the political discussions in North America in the 1960s and has been widely debated during the last decades. The concept is used in a multitude of settings, and different professional groups attach different meanings to the concept. In medicine, the concept quality of life has gained more and more attention during the past 20-30 years as linking patient-reported health with clinical endpoints provides unique information for managing patient care (80). As quality of life-measurements allow for mapping of the impact of disease they have been used both for the evaluation and comparison of treatments and for the assessment and management of individual patients (81). Also, they complement traditional endpoints to evaluate the significance of a treatment effect from the patient's perspective; and thus can facilitate patient's involvement in treatment decision making. A universally accepted definition of quality of life has not been developed. Nevertheless, the majority of the researchers have agreed that quality of life is a subjective and multi-dimensional concept including dimension such as physical, psychological, social and spiritual dimensions (82-85).

An important recommendation for quality of life-research is to base studies on a conceptual model of quality of life that incorporates the multidimensionality of the concept and strengthens the link between theory and research (86). In the present thesis, we distinguished between different levels of quality of life, according to a model (Figure 2) developed by Spilker (87).

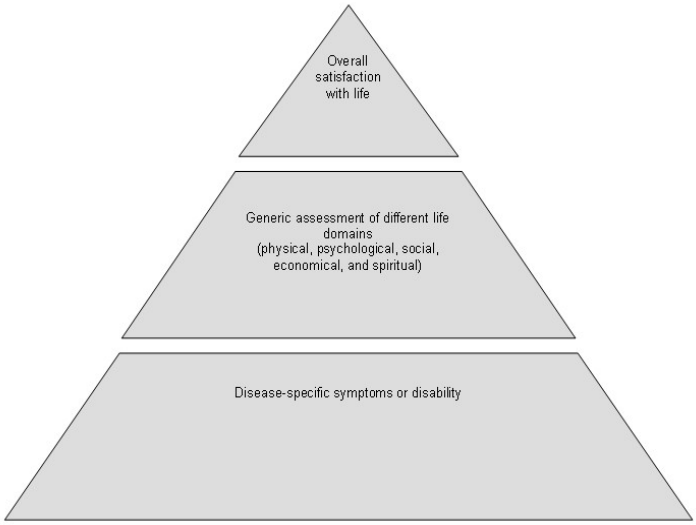

Figure 2. A model combining measurement of the overall, generic and disease related aspects of quality of life (Spilker, 1996).

Following this model, the quality of life definitions and measures can be grouped on three levels: i) the individual's overall satisfaction with life, ii) a generic level such as the individual's satisfaction with different life domains (physical, psychosocial and spiritual), and iii) disease specific symptoms or disability (87). Both the overall and generic level includes general domains, which are applicable to well and ill populations. The specific level focuses on the individual's perception of disease-related factors, such as disability caused by a specific disease. Dependent on the perspective, one level could impact on the other. Concepts such as disability, well-being, health and symptoms have been used interchangeable with the concept of quality of life. The relationship between these concepts is complex. It is quite clear that the concepts are related to each other. However, they are not the same (88, 89). In the present study the overall level is represented by The Quality of Life Scale-Norwegian (85, 90), the generic level is represented by the Short Form-36 (91) whereas several disincentives related to donor surgery, such as postoperative pain measured by the Visual Analogue Scale (92), represent the specific level.

Definitions

The following definitions of concepts are used in the present study:

- *Overall quality of life* is defined as a person's wellbeing that stems from satisfaction or dissatisfaction with areas that are important to him or her (93).

- *Health* is, by the WHO, defined to be 'a state of complete physical, mental, and social well-being, and not merely the absence of disease' (94).

- *Health status.* In this work the term *health status* includes the patients' perception of functioning, disability and well-being related to physical, mental and social health dimensions. These dimensions consist of eight concepts: physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role-emotional, and mental health (95).

- *Pain* is, by the International Association for the Study of Pain (IASP), defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (96).

AIMS OF THE STUDY

The overall aim of the present thesis was to investigate clinical and patient-reported outcomes following living donor nephrectomy, with particular emphasis on patient-reported outcomes. The objectives of the various papers comprising this study were:

- To assess the effect of laparoscopic versus open living donor nephrectomy on (1) operative time, warm ischemia time, length of renal artery and vein; (2) peri - and postoperative complications; and (3) the amount of analgesic administered and postoperative pain intensity as measured by a categorical verbal rating scale (VRS) at postoperative days 0 + 1(Paper I).

- To assess the effect of laparoscopic versus open living donor nephrectomy on (1) the amount of analgesic administered at postoperative days 0, 1 and 2; and (2) postoperative pain intensity as measured by a visual analogue scale (VAS) at postoperative day 2 (Paper II).

- To assess the effect of laparoscopic versus open living donor nephrectomy at 1 month postoperative on (1) numbers of donors reporting surgery related pain; (2) surgery related pain intensity as measured by a numeric rating scale (NRS); (3) use of pain medication during the last 24 hours, and during the last week; and (4) duration of sick leave (Paper II).

- To assess the effect of laparoscopic versus open living donor nephrectomy at 1, 6 and 12 months after donor surgery on (1) overall quality of life as measured by the Quality of Life Scale-Norwegian (QOLS-N); and (2) health status as measured by The Short Form-36 (SF-36) (Paper III).

- To assess the effect of laparoscopic versus open living donor nephrectomy on (1) the patients' perception of the surgical scar; (2) the donation's impact on personal finances; and (3) whether the patients would make the same decision to donate again (Paper III).

- To explore physical and psychosocial issues related to the patients' experiences of going through open donor nephrectomy at one week after surgery (Paper IV).

- To explore the patients' experiences of their physical and psychosocial health during the first year following open donor nephrectomy (Paper V).

RESEARCH QUESTIONS AND 0-HYPOTHESES

In the following the specific research questions and 0-hypotheses raised in this study are presented.

Paper I.

1. Is there a difference in the effect of laparoscopic versus open living donor nephrectomy on (1) operative time, warm ischemia time, length of renal artery and vein; and (2) complication rate and reoperations in the peri - and postoperative period?

0-hypothesis: There is no difference in the effect of laparoscopic versus open living donor nephrectomy on (1) operative time, warm ischemia time, and length of renal artery and vein; (2) complication rate and reoperations in the peri - and postoperative period.

2. Is there a difference in the effect of laparoscopic versus open living donor nephrectomy at postoperative days 0 + 1 on (1) the amount of parenteral morphine equivalents administered; and (2) pain intensity as measured by a categorical verbal rating scale (VRS), at rest and in motion?
0-hypothesis: There are no differences between groups at postoperative days 0 + 1 on (1) the amount of parenteral morphine equivalents administered; and (2) pain intensity as measured by a categorical verbal rating scale (VRS), at rest and in motion.

Paper II

3. Is there a difference in the effect of laparoscopic versus open living donor nephrectomy on (1) the amount of parenteral morphine equivalents administered at postoperative days 0, 1 and 2; and (2) pain intensity as measured by a visual analogue scale (VAS) at postoperative day 2, at rest and in motion?
0-hypothesis: There are no differences between groups on (1) the amount of parenteral morphine equivalents administered at postoperative days 0, 1 and 2 and; (2) pain intensity as measured by a visual analogue scale (VAS) at postoperative day 2, at rest and in motion.

4. Is there a difference in the effect of laparoscopic versus open living donor nephrectomy on surgery related pain at 1 month post donation on (1) numbers of donors reporting pain; (2) pain intensity as measured by a numeric rating scale (NRS) ; and (3) use of pain medication during the last 24 hours, and during the last week?
0-hypothesis: There are no differences between groups on surgery related pain at 1 month post donation on (1) numbers of donors reporting pain; (2) pain intensity as measured by a numeric rating scale (NRS); and (3) use of pain medication during the last 24 hours, and during the last week.

5. Is there a difference in the effect of laparoscopic versus open living donor nephrectomy on duration of sick leave?
0-hypothesis: There is no difference between groups on duration of sick leave.

Paper III

6. Is there a difference in the effect of laparoscopic versus open living donor nephrectomy on (1) overall quality of life as measured by the Quality of Life Scale-Norwegian (QOLS-N); and (2) health status as measured by The Short Form-36 (SF-36) at 1, 6 and 12 months after donor surgery?
0-hypothesis: There are no differences between groups on (1) overall quality of life as measured by the Quality of Life Scale-Norwegian (QOLS-N); and (2) health status as measured by The Short Form-36 (SF-36) at 1, 6 and 12 months after donor surgery.

7. Is there a difference in the effect of laparoscopic versus open living donor nephrectomy on (1) the patients' perception of the surgical scar; (2) the donation's impact on personal finances; and (3) whether the patients would make the same decision to donate again?
0-hypothesis: There are no differences between groups on (1) the patients' perception of the surgical scar; (2) the donation's impact on personal finances; and (3) whether the patients would make the same decision to donate again.

Paper IV

8. What are the patients' narrative experiences related to physical and psychosocial issues of going through open donor nephrectomy at one week after surgery?

Paper V

9. What are the patients' narrative experiences of their physical and psychosocial health during the first year following open donor nephrectomy?

METHODS

This thesis is based on three quantitative studies (Paper I-III) and two qualitative studies (paper IV and V).

Quantitative studies (Paper I-III)

Design

A prospective, randomized single centre trial was performed to compare clinical and patient-reported outcomes after laparoscopic versus open donor nephrectomy.

Pilotstudy

A pilot study was conducted prior to the main study with the purpose to assess a common standardized anaesthesia - and analgesia regime for both groups. A sample of 10 living donors participated. The patients were given medication according to the study regime and were asked to assess pain and symptoms postoperatively. The new regime demonstrated satisfactory anaesthetic and pain-release, and was established for all study patients.

Randomization

Information to nephrologists at local hospitals in Norway

Information letters including information about study aims and methods, were sent to all nephrologists at local hospitals before study start (in July 2000), and then a reminder at the start of the inclusion period in February 2001. In addition, information meetings were held with nephrologists at local hospitals in Norway, and surgeons and nephrologists at Rikshospitalet HF before and during study period.

Information to donors and inclusion

During initial evaluation for donation, nephrologists at local hospitals in Norway informed potential donors about the study, both verbally and in written text. Further, more extensive information was given to the donors at Rikshospitalet HF after admission, by the surgeons at the Department of Surgery. The inclusion was performed 1 - 4 days prior to donor surgery by the surgeons at the Department of Surgery.

Randomization procedure

To assure that the allocation of the treatment was carried out in an unbiased and random way, donors who fulfilled the inclusion criteria and had signed the informed consent form, were randomized to either laparoscopic or open donor nephrectomy. Well-established procedures were followed for the randomization process (97, 98). Due to a long inclusion period (from February 2001 to May 2004) the donors were randomized in blocks of 20. During the entire study period two persons, one researcher employed at the Department of Surgery, the other employed outside the department, randomly drew letters labelled either laparoscopic (10) or open technique (10), in blocks of 10 + 10. The letters were randomly mixed and blindly put into opaque envelopes pre-labelled with inclusion numbers of all participants. After having signed the informed consent form at Rikshospitalet HF, the donors were included by the surgeon and were allocated the next, sequentially pre-numbered randomization envelope.

Population and sample

The inclusion criteria were as follows: age 18 and older, and fulfilling existing criteria for donation with a single, left renal artery. The donors were not included if i) they had a history of extensive upper abdominal surgery, ii) there were findings suggesting right nephrectomy, and iii) they were not able to understand and speak Norwegian**.** There was no further selection. A total number of 240 living donor nephrectomies were performed during the inclusion period. Among the 118 donor nephrectomies not included in the study, there were two laparoscopic nephrectomies and 116 open nephrectomies. The reasons for performing open donor nephrectomy in 116 cases were: administrative circumstances (the two laparoscopic surgeons were not available), right kidney retrieval (due to multiple renal arteries on left side, incompatible kidney size) and extensive previous abdominal surgery. Obesity was not considered a contraindication. Less than five eligible donors were rejected for other reasons. A total of 122 living kidney donors were randomized to laparoscopic or open donor surgery. The laparoscopic and the open group were comparable with regard to age, sex, BMI and donor-recipient relationship. Mean age in the laparoscopic group was 46 years versus 45 years in the open group. The laparoscopic group consisted of 29 males and 34 females, whereas there were 26 males and 33 females in the open group. The attitude of the Norwegian population regarding laparoscopic versus open surgery was quite balanced during the study period, and the donors were informed that there was no hard evidence in favour of either procedure. Before surgery only one patient opted out and was excluded from the study as a consequence of being randomized to open donor nephrectomy. During follow-up there were five drop outs in the laparoscopic group, respective 3 in the open group. Reasons for drop outs in the laparoscopic group were: problems with reading and writing Norwegian (1), illness of a family member in the donor's family (1), not willing to participate in the study from the 6 months follow-up (1), and unknown reasons (2). Reasons for drop outs in the open group were: donors moving to another place (2), and unknown reasons (1). All reoperated and converted donors responded at all follow-ups and consequently were not among the drop outs of the study (Figure 3).

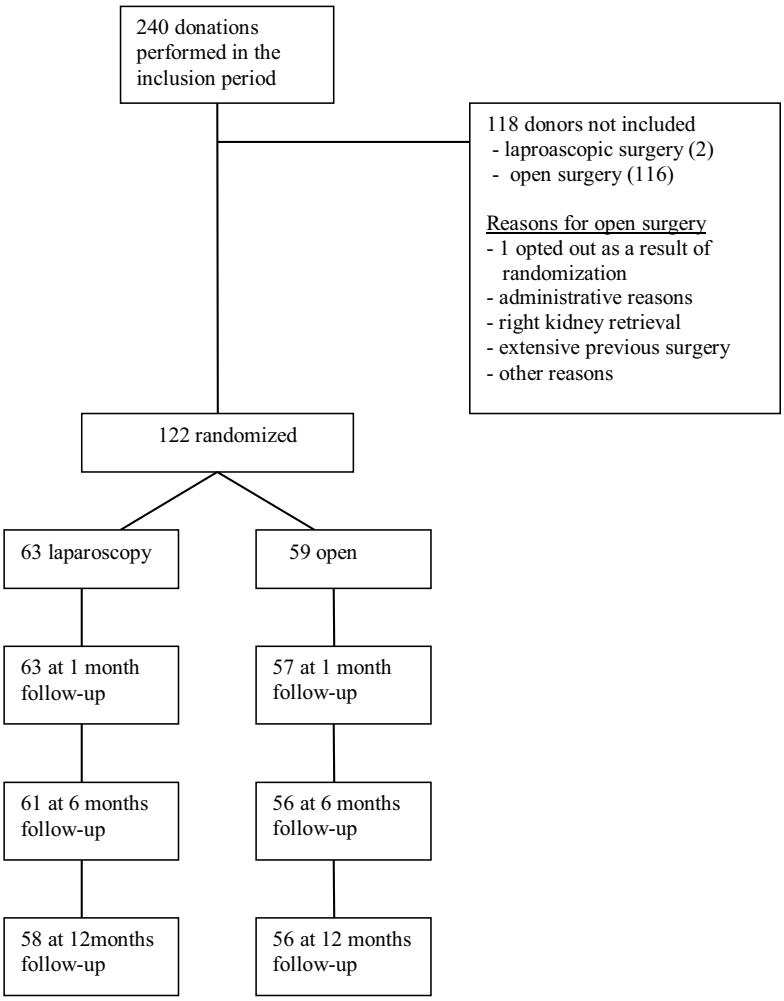

Figure 3. Flow of donors through the trial.

Surgical techniques

All laparoscopic donor nephrectomies were performed in the flank position, with pneumoperitoneum at 9-11 mm Hg, trans-peritoneal access through 4-5 ports, and dissection mainly by means of a 5-mm ultrasonic knife. The first 17 laparoscopic donor nephrectomies were completed by conventional technique, using a basket for kidney extraction through a midline infraumbilical incision. The last 46 laparoscopic donor nephrectomies were completed by employing a modified, simple hand-assisted technique (99). During the final stages, the left hand

was introduced through a minimal incision (infraumbilical; without handport), to facilitate the handling and evacuation of the free kidney. Only a long left glove was needed for this modification. The required incision was of the same length as needed for basket extraction (6-9 cm). The open donor nephrectomies were performed by conventional retroperitoneal access through flank incision at the level of costa 11 to 12, and without rib resection. The length of the skin incision varied from 12 to 18 cm. Two different surgeons randomly performed the pure laparoscopic nephrectomies, one with extensive and one with moderate laparoscopic experience. After the shift to the hand-assisted technique, the surgeon with moderate laparoscopic experience was responsible for the laparoscopic procedures. Six different surgeons, all experienced transplant surgeons, randomly performed the open donor nephrectomies.

Peri - and postoperative analgesia regimen

All donors received anaesthesia and postoperative analgesia guided by the same protocol (100). At the start of the donor operation 8 mg dexamethason was administered intravenously as a single dose, while intravenous pro-paracetemol and ketorolac were started at the end of anesthesia. On the day of surgery and on postoperative day 1 and 2 the donors received pro-paracetamol 2 g x 4 and ketoralac 30 mg x 3 intravenously; thereafter oral medication; paracetamol 1 g x 4 and ketoralac 10 mg x 4. For the first postoperative days, a patient controlled analgesic pump (PCA) delivered intravenous opioid pain relief (ketobemidon) in bolus doses of 0, 1 mg/kg body weight, each dose trigged by the patient. PCA was discontinued between postoperative days 2-5, whereafter oral ketorolac was offered.

Data collection

Clinical data were collected through medical charts in the peri- and postoperative period. Patient-reported data were collected through bed-side interviews at postoperative day 0-2, and by questionnaires. Questionnaires were completed on admission 1-2 days prior to surgery (baseline), and were responded to by mail at 1, 6 and 12 months post donation. Figure 4 demonstrates strategy of data – collection.

Base-line	**Surgery**	**Postoperative days 0-2**	**1 month**	**6 months**	**12 months**
T0	**X**	**T1**	**T2**	**T3**	**T4**

Figure 4. Strategy of data collection. **X** = donor surgery, **T0 - T4** = data collection.

Clinical data

Donor safety and peri - and postoperative complications

To obtain data on donor safety and peri - and postoperative complications we collected data of operative time, warm ischemia time, length of renal artery and vein, perioperative incidents, reoperations, and conversions. We defined operative time as time elapsed from skin incision to placement of the final skin suture, and warm ischemia time as time elapsed from clamping of the renal artery to initiation of cold perfusion. Length of renal artery and vein was measured to the edge of the parenchyma in the hilus, without stretching. Data were obtained from medical charts.

The amount of ketobemidon administered at postoperative days 0-2

The amount of ketobemidon administered on postoperative 0-2 was obtained from medical charts and was reported as units of parenteral morphine equivalents (mg).

Patient- reported data

The Quality of Life Scale-Norwegian (QOLS-N). The QOLS-N is a 16 - item, domain specific instrument containing dimensions of physical and material well-being, personal development, relationship with others, social and civic activities, recreation, and independence (85). The scale measures overall quality of life and was chosen because it has been shown to provide broad information of overall quality of life. Also, it has been validated for use in Norwegian psoriasis patients (85). The QOLS-N has access to previous psychometric testing (101,102). Internal consistency by Cronbach,s alpha is reported at 0.8 (85). The instrument was developed empirically in the US by asking healthy people about their quality of life. In 1998 it was adapted by Burckhardt et al, and adapted for use in patients with chronic diseases. The QOLS-N yields a single sum score, range 16 to 112, with higher scores indicating better quality of life.

The Short Form – 36 (SF – 36). This instrument was chosen because it has been shown to be a valid, reliable and responsive questionnaire for assessing health status in both patients and healthy individuals (91). Internal consistency has been reported at 0.7 to 0.9 (91). Also the SF-36 has been found to be both sensitive and responsive when used to compare open and laparoscopic living donor nephrectomy (27, 28). The SF-36, which is based on the WHO definition of health, was developed in the US by the Medical Outcomes Study. The instrument is referred to as a generic measure because it assesses health concepts that represent basic human values that are relevant to everyone's functional status and well-being. It has been extensively used since the 1990s and remains one of

the most well-documented surveys currently utilised in the area of health status and quality of life-research. Respondents consider questions concerning health domains with regards to the four past weeks. The instrument has been translated to several languages, including Norway (103, 104). The SF-36 consists of 36 questions regarding self-reported aspects of health and includes 8 domains: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional problems, and mental health. The scores are transformed into a scale from 0-100. The higher the scores are, the better is the individual's health.

Postoperative pain.

As pain is an individual and subjective experience influenced by several factors, a central question discussed in the project group before study start was how to measure pain in the clinical, randomized study. An important goal was that all participants should receive a common, satisfying postoperative pain relief regimen. At the other hand, one main study objective was to detect possible differences in postoperative pain intensity between groups. We therefore chose a strategy including two main outcomes reflecting postoperative pain: i) measurement of the amount opioid (ketobemidon) administered daily by a PCA pump, and ii) pain intensity. By doing so, we could be able to detect possible differences between the groups in the immediate postoperative period even if the donors' pain intensity was reduced to a minimum level. Literature reviews performed before study start showed that amount of analgesics administered, and assessment of pain intensity, were common used endpoints in donor studies comparing lapaoscopic and open nephrectomy (8, 33, 105). Thus, our strategy of pain measurement would allow comparison of the pain results from our study to previous research in this area.

Measurement of pain intensity

Literature search showed that pain intensity in general is most commonly evaluated either by categorical rating scales, visual analogue scales or numerical rating scales (106-108). We chose the categorical verbal rating scale (VRS) and the Visual Analogue Scale (VAS) for the measurement of pain intensity during postoperative days 0-2 to get valid and reliable data, and to have the opportunity to compare the results to previous research. Pain intensity at 1 month post donation was evaluated using a numeric rating scale (NRS), by questionnaire mailed to the donors one month after donation. All three scales are considered valid and reliable with regard to postoperative pain intensity (108 -110).

At the postoperative days 0 + 1 pain intensity was assessed by using the five point VRS at rest and in motion. Expert nurses asked the patients to rate their pain intensity using the following response alternatives: 0 = no pain, 1 = weak pain, 2 = moderate pain, 3 = strong pain, 4 = very severe pain. There were several reasons for using the VRS in the immediate recovery period. First, before and during study period the VRS had been a standard regime in our department regarding postoperative pain assessment in patients who were delivered patient-controlled analgesia. Thus, the VRS was a established instrument, and well known by the health care personnell, including the expert nurses who collected these data. Second, previous studies have shown that this scale has satisfying psychometric properties (108, 109). Third, it is simple and quick to administer. It has been demonstrated that both patients and physicians are confident by using it (111, 112), thus the scale is commonly used.

At the postoperative day 2 when the donors usually ambulate to pain-triggering out-bed activities pain intensity was measured by the VAS (92). Two trained researchers performed the standardized bed-side interviews by using the 10-cm horizontal VAS-scale to measure pain intensity at rest and during a standardised cough - and deep breath exercise. Patients were asked to draw a vertical line through the scale at a point representing the level of pain intensity, anchored on the left with words signifying no pain (= 0), and on the right side with words signifying the worst imaginable pain (= 10). The VAS scale was chosen because this scale has in general become a standard with regard to pain assessment, the instrument has previously been validated (112), and has demonstrated important properties such as sensitivity, simplicity and reproducibility (108, 113). Also, it has been applied for the comparison of pain outcome following laparoscopic and open donor nephrectomy (105).

At 1 month post donation a central question was how many donors in the laparoscopic versus the open group who suffered from surgery related pain. In the 1 month questionnaire sent by mail, the donors were asked whether or not they had experienced surgery related pain the last 24 hours. Those answering “yes” were asked to indicate their pain intensity by using a 11-pointed numeric rating scale (NRS), with marks printed on the line with 0 signifying no pain and 10 the worst imaginable pain. A numerical rating format was chosen because this allows the patients to rate their pain a simple and precise way by their own at home (the VAS can be more difficult to use for self administration and without an assessor available). It moreover allows a more differentiated assessment and a finer gradation of pain as compared to the VRS. When it comes to psychometric properties Breivik et al (108) has demonstrated similar sensitivity of the NRS and the VAS with

regard to postoperative pain assessment. The patients were also asked in the 1 month questionnaire whether or not they had taken any oral analgesic drugs related to donor surgery during the last 24 hours, and during the last week.

Donor specific questions

At the 12 months assessment the donors were asked questions regarding their perception of the surgical scar, the donation's impact on personal finances, and whether the donors would make the same decision to donate again. To measure the donors' perception of the surgical scar we used a 10 cm horizontal Visual Analog Scale (92). Patients were asked to draw a vertical line through a scale anchored on the left-hand side with words signifying a very negative perception, and a very positive perception on the right-hand side. At 1, 6 and 12 months after donation the donors were asked to report on the occurrence of significant life events by answering the Life Events Index (114) and hereby were able to report on recipient death or graft failure. Finally, the donors were asked to report on their perception of the recipient's health.

Duration of sick leave

Duration of sick leave was calculated as numbers of weeks after discharge from hospital being off sick. Data on donor employment were collected at baseline. The donors were categorized as employed, students, or unemployed (out of work, housewives, or retired persons). Donors being employed and donors being students were included in the sick leave inquiry. Data from 93 donors (51 in the laparoscopic group, 42 in the open group) were collected by structured telephone interviews at about one year after donation. The donors were informed that the aim of the telephone interview was to gain knowledge about the duration of sick leave following donor nephrectomy. Following question was asked: "For how many weeks after hospital discharge were you on sick leave?" We registered the number of weeks of sick leave, and not number of days, because we considered it would be easier for the donors to give an exact answer to number of weeks away from work, compared to numbers of days. Besides, previous research on laparoscopic versus open technique has shown that weeks of sick leave following donor nephrectomy is a common used endpoint (33, 45).

The table below summarizes variables and instruments, numbers of items, response scales, time of data collection, and reliability estimates for main instruments measuring patient-reported outcomes in the present study.

Variables and instruments	Items	Response scales	Time of data collection					Cron-bach's alpha
			T0	T1	T2	T3	T4	
Overall quality of life QOLS-N; The Quality of Life Scale-Norwegian; 5 domains: physical and material well-being, personal development, relationship with others, participation in social, community and civic activities, and recreation (85).	16	Likert scale ranging from 1 (very dissatisfied) - 7 (very satisfied).	**x**		**x**	**x**	**x**	0,90
Health status SF-36; 8 domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health (91).	36	Different response scales: ordinal level and Likert response scales. Raw scores are trans-formed to 1 - 100. Higher scores indicate better health.	**x**		**x**	**x**	**x**	0,67-0,94
Postoperative pain <u>Postoperative days 0-2</u> VRS; verbal rating scale (106), at rest and in motion. VAS, visual analogue scale (92), at rest and in motion. <u>At 1 month post donation</u> Surgical related pain: NRS; numeric rating scale (108). Use of analgesic drugs the last 24 hours/the last week.	 2 2 1 1 2	 Categorical scale (0 - 4). A 10 cm line anchored on the left with words signifying no pain, on the right side words signifying the worst imaginable pain. Yes/no. Numeric rating scale (0 indicating no pain,10 indicating the worst pain). Yes/no.		 **x** **x**	 **x** **x** **x**			
Donor specific questions Donor - perception of the surgical scar, the donation's impact on personal finances, decision to donate again, and donor - perception of recipient health. Life Events Index (114).	4 8	Different response scales: 5 - point Likert scale, visual analogue scale, Yes/no.			 **x**	 **x**	**x** **x**	
Duration of sick leave.	1	Numbers of weeks of sick leave.	Telephone interview at about 1 year post donation.					

Table 1. Details of instruments measuring patient-reported outcomes.

Several variables were part of the randomized controlled trial. Table 2 provides a total overview of independent, dependent and confounding variables with regard to Paper I, II and III:

Variables		Paper I	Paper II	Paper III
Independent variable	Laparoscopic versus open donor nephrectomy.	**x**	**x**	**x**
Dependent variables	Operative time.	**x**		
	Warm ischemia time.	**x**		
	Length of renal artery and vein.	**x**		
	Perioperative incidents/reoperations/conversions.	**x**		
	Postoperative pain:			
	- amount of analgesic administrated	**x** [a]	**x**[b]	
	- pain intensity at rest and in motion	**x** [a]	**x**[c]	
	Surgery related pain at 1 month post donation:			
	- experience of pain? Yes/no		**x**	
	- pain intensity		**x**	
	- pain medication the last 24 hours? Yes/no		**x**	
	- pain medication the last week? Yes/no		**x**	
	Duration of sick leave (weeks).		**x**	
	Overall quality of life.			**x**
	Health status.			**x**
	Donor-perception of the surgical scar.			**x**
	The donation's impact on personal finances.			**x**
	Decision to donate again.			**x**
	Donor-perception of recipient health.			**x**
Confounding variables	Unsuccessful recipient outcomes/life events.	**x**	**x**	**x**
	Protocol violations of pain regimen.	**x**	**x**	**x**
	Not-blinded study.	**x**	**x**	**x**
	Shift from pure laparoscopic approach to hand-assisted approach in the laparoscopic series.	**x**	**x**	**x**

[a]Postoperative days 0+1
[b]Postoperative days 0-2
[c]Postoperative day 2

Table 2. Independent variables, dependent variables and confounding variables in the quantitative studies (Paper I, II and III).

Statistical analyses

The SPSS statistical package version 12.0 (SPSS, Chicago Illinois) was used for all statistical analyses.

Paper I

The primary endpoints of this study were operative time, warm ischemia time, renal artery and vein length, complications from surgery, and analgesic administered and pain intensity at postoperative

days 0 + 1. We used descriptive statistics in the comparison of donor characteristics. Student's *t* test was used to compare differences between groups with regard to surgical endpoints and analgesia - and pain data. A 5 % level of significance was considered statistically significant. Analgesia - and pain data were analysed both based on intention-to-treat data (the one patient converted from laparoscopic to open surgery as well as the reoperated patients were classified in the laparoscopic group), and on censored data. Since there were no major complications or reoperations in the open group, statistical inferences have not been considered meaningful for the comparison between groups.

Paper II

Primary endpoints were: the amount of postoperative analgesic administered and self-reported postoperative pain at postoperative days 0-2 and at 1 month post donation, and duration of sick leave. Power analysis revealed that 35 patients in each group would be required to detect 4-week post-operative pain differences found in previous studies (27), using a power of 80 % and a level of statistical significance of 5 %. Analysis was based on intention-to-treat. Accordingly, the one patient converted from laparoscopic to open surgery as well as the reoperated patients were classified in the laparoscopic group. Differences between the two treatment groups were analysed with χ^2-statistics and Fisher's exact test for categorical data. Continuous variables were analysed with Student's *t* test. Regarding the comparison of duration of sick-leave between the groups, two patients in the open group suffering from chronic backache were excluded from the data analyses. We used multiple linear regression analysis to test the effects of surgical technique on duration of sick-leave, adjusting for donor-recipient relationship and patients' socio-demographic characteristics.

Paper III

As in Paper II, the analyses were based on intention-to-treat. The main outcomes were overall quality of life and health status. A two-sided alpha of 0, 05 and 80 % power was used for tests of statistical significant differences between groups. A moderate effect expectancy for between-groups differences was set at 0, 6. Assuming a drop out of 10 % during the one-year follow-up, the necessary sample size to detect a 0, 6 effect expectancy would be 50 patients in each group. Ten point change on 0-100 scales for measures of health status was regarded as clinically significant. Differences between treatment groups were analysed using Fisher's exact test for categorical data and Student's *t* test for continuous data. Longitudinal analyses of overall quality of life and health status were performed using Repeated Measures Analysis of Variance, and paired *t* tests from

baseline to 1, 6 and 12 months after surgery. Change scores for the QOLS-N single sum score and the SF-36 subscales were calculated as the baseline score minus the postoperative score; a positive change indicating worsening and a negative change indicating improvement. Effect sizes were calculated as the standardized response mean (SRM), which is the mean change score divided by the standard deviation of the change score. A SRM of 0.2 - 0.5 was considered 'small', 0.5-0.8 'moderate' and > 0.8 'large' (115). We used a 5 % level of significance.

Ethical considerations

There may be ethical aspects involved in inviting living kidney donors to be randomized to either laparoscopic or open donor nephrectomy. However, the attitude of the Norwegian population regarding laparoscopic versus open surgery was quite balanced before and during study period. All donors were informed that there was no hard evidence in favour of either procedure. The questionnaires used were considered not to cause psychological distress for the participants. The study has followed the ethical guidelines of the Declaration of Helsinki (116) and was approved by the Regional Committee for Medical Research Ethics in South Norway. The participants signed informed consent, were guaranteed anonymity and confidentiality, and the right to withdraw form the study at any time.

Qualitative studies (Paper IV and V)

As the purpose of Paper IV and V was to explore narrative donor experiences of going through open donor nephrectomy, qualitative research methodology was chosen for these sub-studies. Qualitative research is suited to gain understanding of people's lived worlds, and how people assess the world around them (117). According to Malterud the notion "qualitative" refers to quality in the sense of features, character, nuances and complexity, or nature of the phenomenon under study (118). Hence, qualitative methods might be applied on a descriptive level, and are more appropriate for understanding than for explanation. The aim of qualitative research is to investigate the meaning of social phenomena as experienced by the people themselves in their own context and, and in their natural setting (119).

Design

An explorative qualitative design with a phenomenological approach was chosen because this approach allows for the description of experiences as fully as possible as the persons in focus lived them. Thus, phenomenological research elicits the essence of concrete events and experiences that have a narrative form including descriptions of a person's thoughts, feelings and actions (120). In

the present study the phenomenon of interest was the donors' experiences of going through living donor nephrectomy the first year after surgery. Thus, the donors were prospectively followed for one year by in-depth interviews at one week and at one year after donor surgery. By doing so we were able to catch the immediate donor experiences of going through open donor nephrectomy (the short-term perspective), and to reflect donor experiences during the first year post donation (the long-term perspective).

Participants

Twelve Norwegian donors undergoing open donor nephrectomy during the period February – September 2003 at Rikshospitalet HF, and not participating in the ongoing randomized donor study, were recruited for the qualitative part of the study. Potential informants received information about the study, both orally and in writing, at the hospital. All donors asked gave their approval. The donors, who were consecutively selected to assure variety, were all above 18 years of age and were able to speak and understand Norwegian. The sample contained a broad variation in demographic characteristics such as age, gender, relationship to the recipient, settlement and occupation. The one-week and the one-year patient sample were identical.

Data collection

One-week interviews

The one-week interviews were performed during February-September 2003, in a closed room with a relaxed atmosphere at Rikshospitalet HF while the donors still were in hospital, usually the day the donor departed. The interviews, which were audio-taped, were conducted using a semi-structured interview guide and lasted for approximately one hour. The interviews started with a briefing about the purpose of the study. Then the informants were asked to narrate their immediate experiences of going through donor nephrectomy. Examples of questions were: "How will you describe your immediate recovery from donor surgery?", or "How will you describe being both a patient and a relative during the hospital stay?" A semi-structured interview guide, based on previous research on living kidney donation and clinical experience in the field, guaranteed that pre-determined issues were covered during the interviews (Figure 5).

One - week interview guide
• Preparation: Experiences of the decision - making process. Experiences of preparing for donating.
• Recovery from surgery: Experiences of being a fit individual and going through major operation. Experiences of the physical and mental recovery from surgery. Experiences of informational needs.
• Donor – recipient relationship: Experiences of the donor – recipient relationship. Experiences of being both a patient and a relative.
• Health assessment: Experiences of having one kidney left. Future outlook on own health.

Figure 5. The one-week interview guide.

Before ending the interviews the informants were asked if they had anything to add. After the interviews the donors had the opportunity to contact the researchers to discuss their experience of the interview situation.

One-year interviews

The follow-up interviews were carried out by telephone at one year post donation by two researchers during February – September 2004; one of the researchers also performed the interviews-series at the hospital one year before. A semi-structured interview guide was used, containing questions related to their experiences of own physical and psychosocial health, the donor-recipient relationship, transplantation outcomes of the recipient, and the medical follow-up of the donors (Figure 6). The interviews lasted for 30-50 minutes. In the body of the interview the the participants were asked to narrate their donor experiences using questions like: “How will you describe your physical condition the first year after the donation?” or “What is your experience of your medical follow-up during the first year after donation”? Also, probes were used to stimulate narration, such as: “What did you think then”? Before ending the interviews the informants were asked if they had anything to add. After the interviews all informants were invited to contact the researchers to add donor experiences, or to raise questions about the interview situation.

One - year interview guide
• Physical donor health Experiences of the physical condition the first year after donation.
• Mental donor health Experiences of the donors' mental health the first year after donation. Experiences when transplantation fails.
• Donor – recipient relationship: Experiences of the donor - recipient relationship the first year after donation. Experiences of the donor's role during convalescence.
• Medical follow up Experiences of the medical follow-up from the health care system.

Figure 6. The one-year interview guide.

Analysis

The recorded and transcribed data material from both interviews was analyzed in a phenomenological tradition. This process includes five steps described by Kvale (121). Initially the text of the separate interviews was carefully read through to get a general impression of the data material. Then, the natural units of meaning as expressed by the living donors were determined by the researcher. Third, the theme that dominated a natural meaning unit was stated as simply as possible. The donor's answer was read without prejudice and the statements were thematized. The fourth step consisted of interrogating the meaning units in terms of the specific purpose of the study: to answer how the living kidney donors experienced going through living donor nephrectomy. The themes of the meaning units were addressed with respect to such questions as, "What does this statement tell about living kidney donor – experiences?" In the fifth step, the essential themes of the entire interview were tied together in a descriptive statement. The method thus involves a condensation of the expressed meanings into more and more essential meanings of the structure and style of being a living kidney donor.

Ethical considerations

The ethical guidelines of the Declaration of Helsinki (116) were followed in all part of the research process. Both the initial interview study and the follow-up study were approved by the Regional Committee for Medical Research Ethics in South Norway. All participants were provided with oral

and written information about the aim of the study. The participants signed informed consent, were guaranteed anonymity and confidentiality, and the right to withdraw form the study at any time.

RESULTS

Paper I

In this paper we summarized the results from the prospective, randomized study, with particular emphasis on donor safety, peri - and postoperative complications, and immediate postoperative pain at postoperative days 0 + 1, laparoscopic versus open donor nephrectomy. There were significant differences in favour of the open group on operative time, warm ischemia time, and artery - and vein length ($p < 0.01$). Five major postoperative complications resulting in reoperations occurred in the laparoscopic group. These were caused by moderate bleeding from a port site (1), a forgotten sponge in the infraumbilical incision (1), jejunal perforation (2) and incarceration of bowel in a port site (1). There were no major complications in the open group. At postoperative days 0 + 1 the amount of ketobemidon administered were significantly in favour of the laparoscopic procedure ($p < 0.02$). Also there was a significant difference in favour of laparoscopy on pain intensity in motion as measured by the VRS at postoperative days 0 + 1 ($p < 0.02$).

Paper II

Paper II aimed to compare postoperative pain and convalescence, laparoscopic versus open donor nephrectomy, at postoperative days 0-2, and at 1 month after surgery. There was a significant difference in favour of the laparoscopic group regarding the amount of ketobemidon administered at day of surgery ($p < 0.01$), but no differences between groups at postoperative day 1, and day 2. No difference was observed between groups on pain intensity at postoperative day 2, at rest or in motion. One month post donation significantly fewer donors in the laparoscopic group reported surgery related pain ($p < 0.02$), or had used analgesics the last 24 hours ($p < 0.05$). The donors undergoing laparoscopic surgery reported significantly less pain intensity as compared to the donors in the open group at one month post donation ($p < 0.002$). The duration of sick-leave was significantly shorter in the laparoscopic group ($p < 0.01$).

Paper III

In Paper III the aim was to compare overall quality of life and health status at 1, 6 and 12 months after surgery, and donor specific questions, laparoscopic versus open approach. While no significant

differences were found between groups in QOLS-N scores at any time points, we found a significant difference in favour of laparoscopic surgery regarding the SF-36 subscale bodily pain at one month postoperatively ($p < 0.05$). Analysis based on intention-to-treat revealed no long-term differences between groups in SF-36 scores. Both groups reached baseline scores in most subscales at 12 months. When subtracting the re-operated donors and the one converted donor of the laparoscopic group, significant differences in favour of laparoscopy were revealed in the subscales bodily pain at 6 months ($p < 0.05$) and social functioning at 12 months ($p < 0.05$). QOLS-N scores at 12 months were significantly lower compared to baseline, but the changes did not exceed five points. No significant differences between groups were found concerning the donors' perception of the surgical scar, the donation's impact on personal finances, decision making, or the donors' perception on recipient health. Concerning the latter, 91% of the donors in the laparoscopic group reported the recipient health to be about as expected or better, respective 87 % in the open group, with no significant difference between groups.

Paper IV

The aim of paper IV was to explore physical and psychosocial issues related to living kidney donors' experiences of going through open donor nephrectomy at one week after surgery. The results showed that all the participants had a positive attitude about the donation a week postoperatively. Their wish to donate was related to an altruistic perception of improving the life of another person. Thus, the participants considered the donation to be a very meaningful action. The donors' main concerns related to the surgical experience were dealing with postoperative pain and nausea. Those suffering from nausea experienced that they were not adequately prepared to deal with this burden. Some participants also expressed that being a patient and a relative at the same time could be a stressful experience. When it came to the donor-recipient relationship, this was described as close and warm. The donors had a positive outlook on own future health and expected to have regularly follow-up's by the health care system after hospital discharge.

Paper V

In Paper V we explored donor experiences regarding physical and psychosocial health during the first year following donor nephrectomy. Though several participants experienced physical disincentives longer than expected post donation, all participants expressed an overall positive experience about being a donor a year after transplantation. Emotional distress, such as mild depression and feeling of loss, was reported. Donors experiencing unsuccessful recipient outcome suffered from severe physical and mental reactions. Yet, these donors reported that they were back

to normal condition a year later, remaining confident in themselves thinking they did what they could do to help a close family member. They did not regret donating a kidney.

DISCUSSION

There is a growing need for organs and many transplant centres have responded to this situation by expanding the living donor options. In Norway efforts are made to increase the donor pool and to continue the extensive use of living kidney donors. To date, there has been a lack of large, prospective follow up studies of the situation of living kidney donors. Thus, a major challenge facing this work was to expand the knowledge base in this area and the overall aim of the present work was to investigate clinical and patient-reported outcomes following living donor nephrectomy. A combination of quantitative and qualitative research approaches was applied to perform a broad evaluation. The quantitative approach was designed to assess the effect of laparoscopic versus open donor nephrectomy on clinical and patient-reported outcomes. In a randomized clinical trial of 122 donors we prospectively collected data at baseline, in the immediate postoperative period, and at 1, 6 and 12 months after surgery. The qualitative investigation was designed to prospectively explore experiences through in-depth interviews of 12 donors at one week and one year after surgery. In the following main results from the quantitative and the qualitative investigation will be discussed and put into the existing knowledge base within this area. Next, several methodological considerations and implications for clinical practice will be discussed. At the end of the section areas for future research are proposed.

Main results (Paper I-III)

Operative time, warm ischemia time, length of renal artery and vein, and peri - and postoperative complications

Paper I mainly focused on donor safety, laparoscopic versus open approach. Not surprisingly, there were significant differences in favour of the open approach regarding operative time, warm ischemia time, and vessel lengths (Paper I). Thus, the results from our randomized study give support to previous reports (2, 27, 28), suggesting that the conventional open nephrectomy is superior to laparoscopy when it comes to operative time, warm ischemia time, and vessel lengths . However, while no major complications occurred in the open group, there was a high rate of major complications and reoperations in the laparoscopic series. Despite the fact that laparoscopic

nephrectomy obviously removes some important disincentives to live donation this technique may increase the risk of acute complications. In the present study two surgeons performed the laparoscopic nephrectomies and reoperations occurred in both the surgeons' series. Yet, one may question if the experience of the laparoscopic surgeons has impacted on the results. The one with extensive experience performed 8 laparoscopic nephrectomies, resulting in one early reoperation on postoperative day 1. Of the 55 nephrectomies performed by the one with moderate laparoscopic experience there were 4 early reoperations between postoperative days 2-10, and 1 conversion to the open technique. Although it is hard from our study data to draw any conclusion when it comes to experience and complication rate, it is likely that experience and training play an important role with regard to donor safety following laparoscopic surgery. In a recently published review article of open versus laparoscopic donor nephrectomy it is stated that many complications following laparoscopic surgery are attributed to the learning curve rather than true differences in the techniques (122). In another report, Vallancien et al claim that a minimum of 50 difficult operations are necessary to acquire adequate skill in laparoscopy, with a decrease in blood loss and operating time, provided such operations are performed sufficiently frequently. To train, the surgeon should perform at least 1 case a week during the first year of experience (123). Many researchers report comparable numbers of complication rates when comparing the two approaches (28, 30, 33, 34). This could be attributed to less complication rates in their laparoscopic series as compared with our series, or that there may be a tendency to underreport complication rates. The latter has also been debated by others (41). However, some researchers performing retrospective studies have similar to us, documented higher complication rates in their laparoscopic series (2, 45). Our randomized study gives support to these findings and thus brings important data into the existing knowledge base in this area, demonstrating that the laparoscopic technique should be introduced with great caution.

Postoperative analgesics and pain intensity, duration of sick leave

The main findings regarding pain data mainly were in favour of the laparoscopic group. Thus, when it comes to the administration of ketobemidon and pain intensity measured by the VRS at postoperative days 0 + 1, the results from Paper I and II give support to previous research (8, 27-29, 33, 105, 124-128), demonstrating considerable donor advantages of the laparoscopic approach in the immediate postoperative period. There were some minor violations of the analgesic protocol. Yet, when we subtracted the donors with minor violations of the analgesic protocol, and the reoperated and converted donors, the results remained unchanged. The pain data from this randomized study are important as laparoscopic donor nephrectomy was introduced to cause minimal harm to living kidney donors. It is likely to believe that the small skin incision resulting

from the minimal invasive technique causes less pain as compared to the larger incision used for the standard open technique. Our findings thus highlight an important benefit of laparoscopic surgery, as the ethics of live donation imply that the morbidity of the procedure should be as low as possible (129). Opposite to the VRS scores at postoperative days 0 + 1, we found no differences between groups on the VAS pain intensity scores at postoperative day 2 (Paper II). This was surprising, and one may reflect on possible explanations. First, it could be that that the postoperative pain management disguised actual differences between groups at postoperative day 2. Second, though the VAS in general has become a standard instrument for measuring pain intensity, it may be that the VRS could be a better instrument for use also at postoperative day 2 since the VRS already was an established instrument before study start, and is easy to use and to understand both for the staff and the patients (111, 112). Third, there is also a possibility that no difference actually existed between groups at postoperative day 2. Still, the latter may be difficult to understand since our findings at 1 month post donation revealed that donors following the laparoscopic approach reported significantly less surgical pain. Previous research supports our 1-month pain results (27, 29, 33). Further, we found that the donors in the laparoscopic group had a significant shorter sick leave, compared to donors following open surgery. Since two informants in the open group reported that chronic backache, and not the donor surgery, was the reason for their prolonged sick leave period these were excluded from the data analyses of sick leave duration. In an additional analysis (intention-to-treat) we included the two informants in the open group suffering from chronic backache. Results showed an even greater difference between groups in favour of the laparoscopic surgery. Our findings regarding the VRS scores and duration of sick leave support Ruiz-Deya claiming that traits of recovery usually translate to time off work (130). Other studies from different countries, both randomized (27) and non-randomized (29, 33, 124) have documented shorter sick leave following the laparoscopic approach. Thus, our findings support previous research suggesting that laparoscopic donor surgery removes or diminishes important disincentives to live donation.

Overall quality of life, health status and donor specific questions

When it comes to overall quality of life we found no differences between groups at the QOLS-N scores at 1, 6 and 12 months. However, the health status investigation at 1 month demonstrated short-term benefits in favour of laparoscopy (Paper III), as the donors in the laparoscopic group reported significantly better SF-36 scores at the subscale bodily pain, also demonstrated in previous research (27-29). The 6 - and 12 months comparison of health status only revealed significant differences in favour of the laparoscopic group when we adjusted for re-operations and conversions (Paper III). When we subtracted the reoperated and converted donors in the laparoscopic group, we

found that the donors in the laparoscopic group reported significantly better at the subscale bodily pain (p = 0.032) at 6 months compared to the donors in the open group (n = 111). Also, we found a significant difference in social functioning at 12 months (p = 0.035) in favour of the laparoscopic group (n = 108). These findings may indicate that peri - and postoperative complications cause trouble for the patients for a long period after the donor surgery. This was also demonstrated at the follow-ups where the participants had the opportunity to write their own comments at the end of the questionnaires. Donors in the laparoscopic group experiencing peri - and postoperative complications commented on disincentives like pain and difficulties with performing their daily activities during the first year post donation. Nevertheless, while Perry's retrospective study showed significant differences on the SF-36 domains bodily pain, physical functioning and role emotional in favour of laparoscopic surgery at 6 - 12 months post donation (29), our intention-to-treat analysis did not demonstrate any long-term group differences. Moreover, our findings do not support the single blind, randomized trial of Kok et al, revealing significant long-term differences between groups in favour of laparoscopy on most SF-36 domains (28). However, Kok et al also performed a prospective investigation of psychosocial and physical impairment after mini-incision open and laparoscopic donor nephrectomy (131). The findings from this study are in line with our findings, demonstrating no differences in SF-36 scores at 6 and 12 months follow up. Buell et al have reported similar outcomes, finding no significant long-term differences in the SF-36 scores between their laparoscopic and open series (32). Nevertheless, given our findings, it could be that a study design permitting more frequent follow-ups during the first 6 postoperative months would have been a better strategy for comparing laparoscopic and open donor nephrectomy. The results with regard to sick leave showed that the majority of the donors were back at work within 2-3 months. Hence, it is reasonable to believe that the ability to detect important differences between groups would be largest within this period. Furthermore, it may be that a disease specific instrument for living kidney donors would have detected long-term differences between groups. As generic instruments tend to cover a wide range of conditions, disease specific instruments are designed to focus on symptoms and disabilities related to a specific disease or treatment (15). However, there is a lack of disease specific instruments tested for psychometric properties for use in this patient group. When it comes to donor-recipient relationship it is a possibility that this may impact on the donors' self reports on quality of life and health status. In the laparoscopic group, 19 % of the donors were not related to the recipient, respectively 22 % in the open group. We performed additional analyses of the unrelated donors' scores on health status and overall quality of life during follow-ups. Results showed a significant difference in favour of the laparoscopic group on the subscale bodily pain at 1 month post donation (p = 0,037). There were no significant differences

between groups with regard to other SF-36 scores, and QOLS-N at 1, 6 and 12 months. This indicates that in the present study the relationship to the recipient probably has played a minor role concerning donor reports on quality of life and health status.

Looking at the total sample, our follow-up results revealed that living donor surgery clearly impacted the donors' quality of life and health during the first month after surgery. In particular, the donors reported low 1 month-scores at the subscales role physical, bodily pain and vitality. The findings from our randomized series are important because previous reports from retrospective studies have concluded that the donors' quality of life was minimally affected by donor nephrectomy (42, 132). However, these studies were limited by the wide span of time since donation took place, and a retrospective design, and like that illustrate that different research designs may provide quite opposite study results. This may indicate that frequent, prospective follow-ups after surgery are necessary to provide reliable information of the consequences of going through donor nephrectomy. At 12 months our data demonstrated that most donors in both groups had returned to preoperative levels in most SF-36 subscales and were comparable to those in the general Norwegian population (104). Concerning the donors' attitude to the surgical scar one may reflect on why the donor scores were comparable in the two groups. Initially, we expected that the donors in the laparoscopic group would express a more positive attitude to the scar compared to donors in the open group as a consequence of the small laparoscopic incision. However, the altruistic character of donation raises the possibility of a situation in which the donors feels the health of the recipient is superior to that of him - or herself (133). This may explain why there were no differences between groups regarding attitude to the surgical scar. Our results are in line with previous studies (29, 134).

Main results (Paper IV-V)

In the qualitative studies (Paper IV and V), we explored donor experiences at one week and at one year after open donor nephrectomy. Though giving support to data derived from the randomized trial, the qualitative data above all provided knowledge of the lived experiences of going through donor surgery as narrated by the donors themselves. In the following results from Paper IV and V are discussed.

Overall attitude towards donation

One main finding in Paper IV and V was that the donors had an overall positive experience about being a donor. Although the donors reported on some negative experiences during the year after the

donation, the in-depth interviews explored that the donors' overall satisfaction and positive attitude towards the donation remained stable a year after surgery. Data from our research support previous reports (48, 58, 63, 65, 135, 136). The positive donor attitude may reflect several conditions related to live donation. The fact that the donors had been able to help a close family member may be thought of as very meaningful for most donors and may have ruled out possible negative feelings. Some donors also related the donation to own human existence, including increased self esteem, a resetting of values, and personal growth. Similar findings have been reported earlier (58). Other donors mentioned that the aspect of self-benefit was part of their positive donor experience: after the transplantation both the recipient's and the donor's life had become easier, or more active. These phenomena may contribute to explain why positive donor attitudes emerged as the dominant theme in both interview series. Reports from other studies support this assumption (61, 63, 65). Our findings put forward the importance of encouraging the donors to focus on positive donor consequences as this may strengthen the donors' coping strategies. However, as previously described in donor literature (58, 63), high rates of donor satisfaction may be biased by the donors' wish to present themselves in a socially desirable light, and to justify the pain and expense of having donated an organ. This phenomenon may have influenced on some of the donors' descriptions.

Donor-recipient relationship

The one-week and one-year data suggest that the donors expressed a continued sense of closeness with their recipients during the first year post donation. Concern and love were expressed repeatedly during both interview series. It was somewhat surprising that the donor-recipient relationship remained strong also a year after the donation. One might suppose that the donor experiences revealed in the present investigation, like disincentives from surgery, conflicting donor roles in the postoperative period, or unmet expectations regarding medical follow-up, would impact negatively on the relationship. Yet, previous research has demonstrated, in line with our findings, that the donor-recipient relationship in most cases remains stable, or more close, in the time after donation (48, 55, 63). An explanation may be that the donating process creates very strong bonds between the donor and the recipient. Also, significant persons in the donor's and the recipient's network including family, friends and health professionals probably act in a way that strengthen these bonds. Further, the result may also reflect a careful donor selection, and that the donors had been given enough time to reflect on their decision to donate pre donation. Finally, the donors who participated in the in-depth interviews were all close relatives to the recipient and this may be reflected in the strong donor-recipient relationship post donation. However, from a scientific view

one must not forget that our sample was small. It could be that a larger sample would explore more variations in the data, including descriptions of negative donor-recipient relationships. To sum up, our investigation suggests a strong and stable donor-recipient relationship during the first year post donation. Still, as the sample only consisted of 12 participants the results must be treated with caution.

Donor health post donation

Though a major finding was that the donors were back in normal health condition a year after surgery, several donors expressed that they experienced problems related to donor surgery longer than expected. The donors' health problems were related to emotional distress, physical disincentive and unsuccessful recipient outcome. Our qualitative data confirm previous research (45-49, 59, 66, 137). Transplant professionals must not underestimate the donors' transition from health to illness. According to Fehrman-Ekholm it is a dilemma resulting from the fact that the donors generally consider themselves to be healthy (50). Before the donation the donors are informed that donor nephrectomy is associated with very low morbidity and mortality. Moreover, a report concerning life insurance for kidney donors demonstrated that 36 of 38 insurance companies in the USA did not consider kidney donation to increase risks for medical problems in the donors (138). Opposite, several studies have documented adverse outcomes following living donor nephrectomy (7, 139-141). In order to bridge the gap between donor expectations and the risk of negative donor outcomes, and as the selection criteria for donors has become less restrictive, realistic information and education should repeatedly be offered to the potential donor. During the one-year interviews the donors expressed clear expectations of regular medical follow-up after hospital discharge. However, several informants experienced that these expectations were not always met. In a Swedish study of 451 donors it was reported that 51 % of the donors were not regularly examined after the donation (51). This study gives support to the present work and suggests the need for a common, mandatory donor follow-up by nephrologists after donor discharge from hospital.

Donor reactions when transplantation fails

One main finding revealed in paper V was the reactions of the 2 donors experiencing bad transplantation outcome. Their response pattern indicates that unsuccessful transplantation outcome may evoke severe reactions, and thus demonstrates the vulnerability of being a living kidney donor. Knowing that there was a strong bond between the donors and their recipients, and knowing that donors in general show great concern about the recipients, it is not hard to understand the donors' reactions. Though this result is limited by the small donor number, the seriousness of such events

can not be underestimated. As well, previous reports support our findings, suggesting that adverse recipient outcomes may result in negative feelings and grief by the donors (59, 66, 67). Potential donors need to be informed of all outcomes they may potentially face and harms may be minimized through careful donor selection. Also, health policies which fairly reimburse the donors for their non-medical expenses may help reduce undue stress. Our data revealed that there was a gap between the donors' needs of support and the help given from health professionals. Donor support and medical follow-up from health care team is essential. Recent studies have shown that the donor themselves requested such follow-up (57, 142, 143). For those facing adverse outcomes, early counselling may help alleviate psychosocial morbidity.

Methodological considerations

In the following methodological considerations related to the quantitative and the qualitative studies are discussed. In the end of the section the combination of the two different approaches will be commented on.

Quantitative studies

We used a randomized, controlled design. Random assignment creates two or more groups of units that are probabilistically similar to each other on the average. Ideally, any outcome differences that are observed between groups are likely to be due to treatment (144). Thus, the randomized trial is often referred to as the gold standard. Yet, many challenges occur when performing a randomized controlled trial in a clinical setting. In the following some important threats to reliability, validity and generalization in the present work are discussed.

Reliability

Reliability, or internal consistency, is concerned with error in measurement (107). According to Fayers, patients whose quality of life status has not changed should make very similar, or repeatable, responses each time they are assessed. If there is considerable random variability, the measurements are unreliable (15). Thus, assessment of reliability consists of determining that a scale or measurement yields reproducible and consistent results. Cronbach's alpha is the method used most widely for this purpose (145). When it comes to the reliability of postoperative pain measurements it is well-known that pain assessment is challenging. We performed pain assessments in a busy clinical setting in patients recovering from major surgery. In the present study some patients may have been uncomfortable with participating in bed-side interviews in the immediate

postoperative period while suffering from side effects of surgery. Also, we used two different instruments for assessing postoperative pain intensity in the recovery period (The VRS and the VAS) and it is possible that this caused confusion in the participants. This may have reduced reliability. Yet, to increase reliability of the pain assessments the donors were provided with oral and written information about the procedure in advance. Only few, trained researchers and expert nurses performed the standardized data collection procedure. Further, the bed-side interviews were scheduled at a quiet period of the day to secure a relaxed atmosphere during the pain assessment. Finally, the pain instrument used had previous been tested and had shown satisfying properties with regard to reliability (108, 109). Concerning overall quality of life and health status we judged reliability of the instruments used to be satisfying as Cronbach's alpha of of the QOLS-N ranged from 0.89 to 0.90, and of the SF-36 from 0.67 to 0.94, indicating intern consistency and stability of both instruments. Similar results have been found in other studies (85, 91).

Internal validity

Internal validity of a study refers to the extent to which it is possible to make an inference that the independent variable is truly influencing the dependent variable and that the relationship is not spurious (97, 146). A high degree on internal validity enables the researcher to rule out rival or alternative explanations to causal interpretation. To check the internal validity one can ask: "Was the effect observed on the dependent variable actually due to the action of the independent variable?" Though the design used in this study possesses a high degree of control because of the manipulation and the randomization and though we used valid instruments to measure patient reported outcomes, there were some important factors distorting the outcome variables of the study. The most important confounding variables threatening internal and external validity in the present study are illustrated in Table 2 and will be discussed in the following.

A limitation of our study design was that we did not directly integrate recipient data in our follow-up analysis. Previous research has shown that unsuccessful transplantation outcome influences the donors' health and quality of life (31, 49, 66). Some donors in the study sample experienced unsuccessful transplantation outcome during study period. This may be a threat to internal validity because unsuccessful transplantation outcome may have affected the donor scores at the questionnaires at 1, 6 and 12 months follow up. When we designed the study several reasons for not integrating recipient data were discussed. The donors were randomly allocated to laparoscopic or open surgery and it was likely to believe that randomization would distribute confounders equally between the two groups related to recipient outcome. Further, quantitative and qualitative follow-up

data on the donors were collected several times during the first year after donation and we considered it too demanding to collect recipient data paralleled to donor data. Finally, our design allowed for adjustment of changes in life events during the study period. The donors were asked to report on the occurrence of serious life events, such as illness and death of a close family member or friend, in the periods between the follow ups. The results showed that there were no significant differences between groups in donors reporting serious illness or death of a close family member or friend. Moreover, at 12 months the donors were asked to report on their perception of the recipient's health. Results showed no significant difference between the groups. As well, it is documented that adverse recipient outcomes most often occur more than a year after the transplantation (147-149). To sum up we believe that we, to a certain extent, were able to capture and control for a possible confounding variable of this study related to donor reactions in case of adverse recipient outcomes. Nevertheless, even if we believe that we to a certain extent were able to control for a possible confounding variable related to adverse recipient outcomes, we recommend integration of recipient data for future donor studies measuring patient-reported outcomes. Such data are informative and provide accurate information to allow for the adjustment for recipient outcomes on donor-data.

There were minor violations of the analgesic protocol. Examples of violations were discontinuation of ketorolac in two patients due to side effects, and intravenous doses of proparacetamol replaced by oral paracetamol. Protocol violations may have affected the results of the donors' pain ratings, and thereby reduced the internal validity of the study. To evaluate the effect of this error we subtracted the donors not following the analgesic protocol from the pain analyses. The findings with regard to postoperative pain remained unchanged. We therefore believe that violations of the analgesic protocol had only limited impact of the pain results.

A possible "Hawthorne effect" (77, 97) may have impacted the donors, and in particular the donors in the laparoscopic group. The present study was not blinded and the donors in the laparoscopic group knew that they were randomized to go through minimal invasive surgery. Also the donors' family, as well as the staff, were informed about the result of randomization. This could be a threat to internal validity in the way that these donors, their family, and the staff possibly expected the donors in the laparoscopic group to have a more rapid and easy recovery as compared with the open group, and thereby behaved in a particular manner. There may be a chance that this affected the responses of the donors in the laparoscopic group. It was difficult to rule out this effect in the present study since it in general is hard to fully obscure which surgical method have been used. Besides, blinding is only possible in the immediate postoperative period before the wound dressings

are removed, being of less importance in long-term assessments. However, the attitude of the Norwegian population regarding laparoscopic versus open surgery was balanced during the study period and the donors were informed that there was no hard evidence in favour of either procedure.

External validity

External validity refers to the generalizability of the research findings to other samples (77, 97). The central question when assessing the generalizability of a study is: are the findings relevant beyond the experimental condition? Both the representativeness of the participants and the experimental settings must be considered when judging whether the findings can be applied elsewhere (150). To assure that the sample of the study should be representative for Norwegian donors we made study participation as convenient and un-extraordinary as possible. Donors fulfilling the inclusion criteria were considered eligible for the study. Exclusion criteria were history of extensive upper abdominal surgery, findings suggesting right nephrectomy, and not understand and speaking Norwegian**.** There was no further selection. Information to potential donors across the country was spread by nephrologists at local hospitals. Also, all donors were informed about the study after admission to Rikshospitalet HF. As there is only one transplantation centre in Norway, and as there is a regular exchange of information between the local nephrologists and the transplant professionals at Rikshospitalet HF, we believe that almost all potential donors who fulfilled the inclusion criteria were informed about the study and were invited to participate. The main reasons for 118 donors not participating in the study during the study period were administrative circumstances (the laparoscopic surgeons were not available), right side chosen, and the donors had a history of extensive previous abdominal surgery. During follow-ups there were five drops out in the laparoscopic group versus 3 in the open group. Those donors being reoperated or converted to open surgery were not among the drop outs. We performed additional analyses of non responders to test baseline characteristics and scores of the main instruments. No statistically significant differences were found in donor characteristics, or in baseline scores of the main instruments between responders and the non responders. Additional to test for baseline scores, we tested the non responders' scores at one month follow-up. The results showed that scores of non responders' in the open group were comparable to the total sample. In the laparoscopic group three out of five non responders were comparable to the total sample, whereas two non responders had low scores at most of the SF-36 areas. Thus, it is possible that the two non responders in the laparoscopic group would have influenced negatively at the 6 - and 12 months assessments if they had responded to the long-term assessments. On the topic of sick leave one of the two non-responders was included in our analysis, reporting a sick leave period of 10 weeks. The other was unemployed (a housewife)

and thereby not part of the assessment. However, both non responders reported gave comments at the end of the 1- month questionnaire. One reported serious worries because of the course of the recipient (her husband). The other reported that she had suffered from chronic headache for many years. This may reflect that their low SF-36 scores were caused by problems not directly related to laparoscopic surgery.

The research situation is also essential when judging the generalizability of a study (97). The question is whether or not results obtained in one setting can be generalized to another setting. In the present study a particular anaesthesia and postoperative pain management was established to ensure that all donors received a common regimen guided by the same standardised protocol. After the study was ended this anaesthesia and postoperative pain management has been established as a standard regime for patients going through laparoscopic nephrectomy. However, when it comes to open surgery, the standard regime for these patients is epidural analgesia. According to Brink and Wood (150), if the effect obtained is applicable only to the specific setting of the study, the relevance of the findings beyond the experimental condition can be reduced. Since the study regime is not established as a standardized treatment for all living kidney donors, this may be a threat to the generalization of our pain results. Another threat to extern validity in the present work is the switch from a pure laparoscopic technique to a hand assisted laparoscopy during the study period. Today the hand assisted, and not the pure laparoscopic technique, is the established treatment with regard to laparoscopic donor nephrectomy. This may threaten external validity of the work. However, taking into account that the infra-umbilical incision and extent of dissection were comparable with both techniques, we believe that the impact on the donors' assessments were much the same. Earlier reports concerning laparoscopic surgery support this supposition (26, 151). Finally, the high complication rate in our laparoscopic series is a serious threat to extern validity. One may suppose that when no learning curve longer exists for the laparoscopic procedure at our centre, the complication rates are reduced. Previous reports support the assumption that a relationship exists between the surgeon's experience and the complication rate in the area of laparoscopic surgery (152-153). Thus, the occurrence of a high complication rate in the present study may not be representative for the future situation of laparoscopic donor nephrectomy at our centre, and thereby the external validity of the present study may be reduced. The high laparoscopic complication rate raises an important question: in the comparison of new and established surgical methods, at what time should randomized studies be performed? It is clear that the complication rate with regard to new surgical methods is reduced in centres with a high volume. The present randomized study was started three years after the introduction of laparoscopic donor nephrectomy at Rikshospitalet HF.

We were then still in the learning phase of the method and it is possible that the number of complications could have been lower at a later stage.

To sum up, although we used a prospective, randomized design, there are several threats to reliability, internal validity and external validity in the present study that may affect the findings. Consequently, caution should be used when drawing conclusions concerning the results of the quantitative part of the study.

Qualitative studies

Reliability and validity

As the concepts of accuracy and truth are relevant in all scientific work, the question of reliability and validity must also be raised within qualitative studies. Sandelowski and Barosso (154) and Kvale (121) discuss the components of rigor in qualitative studies and propose several strategies to enhance reliability and validity in qualitative research. These are literature searches ahead of the study, the use of brief and simple interview questions, avoiding leading questions, use of expert peer debriefing, and techniques for establishing consensus in the research team. In our qualitative approach we used several strategies to help ensure scientific quality of the study. The research questions and the interview guides were based on literature reviews and the researchers' experiences in the field. Still, in interview studies the researcher is himself (or herself) the research instrument (121), and to be a good interviewer one must be able to assist the informants in the unfolding of their narratives. This is important because it is during the interview phase that knowledge is constructed through the interaction of the researcher and the participant (121). Although the researchers in the present study had broad knowledge of the interview theme and previously had performed in-depth interviews, it was challenging to pose clear and short questions to the informants during the first interviews series. Another challenge was to allow the informants to finish what they were saying and to let them proceed at their own rate of thinking and speaking, and to tolerate pauses during the interviews. Also, avoiding leading questions and remembering to question critically to test the reliability and the validity of what was said, was easier said than done. To assure data quality, two researchers performed the interviews, one of them interviewing and the other adding supplementary questions when necessary. Though we attempted to standardize the interview situation it is possible that nonverbal cues from both researchers and respondents affected the respondent's answers. Also, the fact that the interviewers were affiliated to the transplant unit may have influenced the participants' descriptions. Follow-up interviews at one year were conducted by telephone because the donors were spread around the country. One may argue that in-depth interviews should be performed face-to-face. However, contact between the donors and the

researcher was already established during the one-week interviews, performed face-to face before the donors' discharge from hospital. During the data analysis phase we had regular meetings with clinical experts to get peer opinions and to assure an accurate reflection of the interview data. The experts represented transplantation professionals concerning the pre donation phase, donor surgery, and post donation follow-ups. A well-established method for data analysis was chosen (121) and we used multiple interpreters to ensure trustworthiness during this process. Alternative ways of interpreting, categorizing and organizing data were discussed carefully until consensus was established in the research team.

Transferability

The main objective of the qualitative studies was to provide rich descriptions of the unique situation of 12 donors going through living kidney donation, as narrated by the donors' themselves. A central question is: can the results be transferred to other living kidney donors? From a strictly scientific view the findings can not be generalized to other living kidney donors because they are based on a qualitative research methodology and a small sample size. Though the participants were consecutively selected for interviews, the sample contained a broad variation in demographic characteristics. However, the sample comprised 12 participants and it is likely to believe that a larger sample would have increased the variety of the findings. Yet, since large sample sizes represent much work in organizing and interpreting the data, and since we had a repeated research design (totally 24 in-depth interviews were performed in the period 2003-2004), we judged it to be too time consuming to have a larger sample. Nevertheless, Kvale warns against large quantities of data in interview studies because it can be hard to handle them in a meaningful way. In stead, the focus should be on the content, the depth, and the qualitative meaning of what is said (121). According to Malterud, the findings from a qualitative study are not thought of as facts that are applicable to the population at large. Rather they are descriptions, notions, or theories applicable within a specified setting (155). Thus, the results from our qualitative studies provide relevant, new knowledge and a deeper insight into the situation of 12 Norwegian donors, relevant both for potential donors and transplant professionals. Like that, the results may be transferable to clinical settings in which transplant professionals counsel living kidney donors in the different stages of the donation process.

Combining quantitative and qualitative methods

We performed a combination of methodological approaches to study the outcomes of living donor nephrectomy broadly and in depth. The main argument for a combined approach was that a mixed

model would enable us to profile the complexity of going through donor surgery, since diverse research methods may shed light on different aspects of a phenomenon. In addition to quantifying self-reported outcomes following donor nephrectomy the qualitative investigations allowed us to extract the meaningful content of the donor experiences narrated by the donors through personal interviews. The use of quantitative methods was appropriate in the comparison of two surgical methods of donor nephrectomy as the randomized, controlled trial provided us with specific information about the effect of surgery. Data from the qualitative studies gave in-depth descriptions of the reality of going through open nephrectomy as narrated by the donors themselves. Thus, in this thesis the two approaches can be thought of as complementary, providing transplant professionals with broad clinical knowledge based on different perspectives of the donors' situation. Another advantage of mixed models lies in the potential for enhancing validity of study findings. The quantitative and the qualitative studies in this thesis showed similar trends concerning donor health the first year after surgery. When researchers' hypotheses are supported by complementary types of data, they can be more confident about the validity of the results (97, 156).

However, the use of multiple research designs may also be challenging as the data derived from one design may demonstrate weaknesses of the opposite design. In the present study the qualitative data revealed severe donor reactions when transplantation failed. This finding demonstrated the importance of integrating recipient data in donor studies, and thus revealed a weakness in our quantitative investigation concerning the lack of recipient follow-up. On the opposite, one may argue that if we had performed the qualitative interviews before designing the quantitative study we probably would have integrated recipient data in our quantitative 1, 6 and 12 months follow-up. This demonstrates how mixed model also may strengthen the design of a study. Further, one could claim that the triangulation between quantitative and qualitative approaches generates confusion about the epistemological and ontological bases that underlie each distinct approach. Qualitative research is often seen to represent a distinctive paradigm compared to quantitative research (157, 158), drawing on text instead of numbers, applying procedures for interpretation of meaning instead of statistics to calculate probabilities, aiming for wholeness rather than details, and acknowledging the involvement of the researcher in the construction of knowledge (118). Yet, in the present study we experienced the similarities of the approaches to be more apparent than the differences as both approaches are based on solid epistemological traditions, aiming to aggregate new knowledge within a field by a systematic collection, organization and interpretation of data.

Implications for clinical practice

This thesis adds multidimensional assessments to the existing knowledge base in the area of living kidney donation, with particular emphasis of patient-reported outcomes. According to Osoba (159) patient-reported outcomes in clinical practice has been shown to lead to a better understanding of patients' concern with improvement in counselling and referral for required services. Potentially, such assessment should also be used to monitor the progress of a patient's disease and benefit from treatment. Data derived from this study affirm that attention should be further paid to several aspects of living kidney donation. Following strategies for clinical practice are proposed:

In several transplant centres the open technique is today the only established procedure regarding living donor nephrectomy. In the introduction of laparoscopic donor surgery it should be kept in mind that this method is still evolving. Essential factors for a successful laparoscopic approach are long-lasting experience within the field and technical expertise needed to perform the operation.

Concern has been raised about whether living donors are always completely informed about the risks that are involved regarding donor surgery. Clinical and patient-reported outcomes derived from our study, and others (160, 161), highlight the importance of correct and neutral preoperative information from health professionals to potential donors. Our findings revealed that the donors' decision process mainly was based on emotions and altruistic feelings. Further, a high complication rate was revealed in our laparoscopic series. Balanced information about the risks and benefits inherent in the donation process may be one way of promoting appropriate coping strategies for the donors. Also, it is important that the donors have sufficient time to reflect on the decision to donate.

The unique situation of caring for both the recipient and the donor while at hospital provides additional challenges for the transplant staff. It is clear from our study that the donors experienced concerns and worries regarding the recipient, resulting in less focus on own needs during recovery. Thus, it is vital for transplantation professionals not to underestimate the donors' needs, as well as donor transition from health to illness, and to organize donor programmes with as much focus on the donor as on the recipient. Some transplantation centres provide accommodation in a two-bedded side ward for the donor and the recipient. At our centre it has been a tradition to care for the donor and recipient in separate rooms within the same ward, so that if any clinical problems emerge they can be managed without emotional stress to the other part. Data from the in-depth interview series support the continuation of this tradition. According to our study results, the continuity of care after hospital discharge was missing for some of the donors, despite the health professionals' assurance

of medical follow-up after donation. This finding is supported by previous research (51, 66,162) and demonstrates the need of a mandatory medical follow-up on a regular basis for all donors, in accordance with the recommendations of the Amsterdam Forum on the care of the living kidney donor (163). In case of graft failure, or death of the recipient, an active approach is required by transplant professionals to give thoroughly support to the donors.

Future research

This thesis of clinical and patient-reported outcomes has illuminated complex factors into the core of living donor surgery. In light of clinical and methodological challenges raised by this study future research questions in this area are proposed.

Post surgery donor outcomes need to be studied further, both in a clinical and patient-reported perspective, and at a time when the laparoscopic surgeons have gained experience with the laparoscopic technique to rule out biases of the studies caused by learning curve, and thereby test the generalizability of our findings. Frequent follow-ups during the first postoperative months are necessary to assure that effects from surgery, and any anticipated changes, will be captured.

As most post donation follow-ups have been retrospective, it is essential that future studies have a prospective design. Such studies will benefit from a long-standing study approach, which implies finding out more about longitudinal consequences of living donor nephrectomy. Also, data on recipients' course should be collected paralleled, such as survival and acute rejection rates, to allow for the adjustment for recipient outcomes on donor-data.

There is a lack of translated, disease specific instruments tested for psychometric properties for use in living kidney donors. Hence, developing such instruments is essential to provide researchers and clinicians with useful and rich patient information, in addition to compare donor data across of countries.

The findings from our qualitative investigation indicated that being a donor may be a complex experience. More research is needed to fully understand the complex donor situations and donor reactions, and in particular when it comes to donor complication related to donor nephrectomy and adverse recipient outcome. Further series of repeated in-depth interviews are needed to fully understand donor needs. It is essential to have large enough samples to capture a variety in donor experiences.

At the very last, our study revealed that medical follow-up of living kidney donors varied within local health districts. Hence, there is a need to evaluate existing follow-up routines, both by data derived from health professionals and from donors. Standardized programmes should be established to ensure regular donor contact with local nephrologists post donation. An evaluation study of medical follow-up routines may be the first step in establishing a mandatory programme throughout the country.

CONCLUSIONS

1. The quantitative and the qualitative investigation of patient-reported outcomes following donor nephrectomy show that both laparoscopic and open living donor nephrectomy clearly impact the donors' overall quality of life and health status. However, a year after surgery the majority of the donors was back in normal condition and remained satisfied with their decision to donate.

2. The randomized trial demonstrates that conventional open donor nephrectomy is superior to laparoscopic donor nephrectomy with regard to donor safety. The high rate of complications in the laparoscopic series indicates that the laparoscopic technique should be introduced with great caution.

3. The short-term data support the view that an uncomplicated laparoscopic donor nephrectomy has important advantages such as less postoperative pain, better health status and a shorter sick leave period as compared with the open approach. The 6 - and 12 months data only revealed significant differences in favour of laparoscopy when adjusting for re-operations and conversions. We therefore conclude that long-term benefits are hard to prove in favour of laparoscopic surgery.

4. In-depth interviews revealed that a positive feeling about being a donor was the dominant theme in the donors' experiences at one week and at one year after the donation. Though experiencing disincentives from surgery during the first postoperative period, the donors expressed that they were back to normal condition a year after surgery, also confirmed by the quantitative investigation.

5. Donor reactions when transplantation failed were characterized by severe physical and mental reactions. Yet, the donors did not regret donation, but remained confident in themselves, thinking they did what they could do to help a close family member.

REFERENCES

1. Marson LP, Lumsdaine JA, Forsythe JLR, Hartmann A. Selection and evaluation of potential living kidney donors. In: Gaston RS, Wadström J, editors. Living donor kidney transplantation: current practices, emerging trends and evolving challenges. Oxon: Taylor & Francis, 2005.

2. Odland MD, Ney AL, Jacobs Dm, et al. Initial experience with laparoscopic live donor nephrectomy. Surgery 1999; 126: 603-607.

3. Montgomery RA, Kavoussi LR, Su L, et al. Improved recipient results after 5 years of performing laparoscopic donor nephrectomy. Transplantation Proceedings 2001; 33: 1108-1110.

4. Lind MY, Ijzermans JNM, Bonjer HJ. Open versus laparoscopic donor nephrectomy in renal transplantation. British Journal of Urology International 2002; 89: 162-168.

5. Nicholson ML, Bradely JA. Renal transplantation from living donors. BMJ 1999; 318: 409-410.

6. Hartmann A, Fauchald P, Westlie L, Brekke IB, Holdaas H. The risk of living kidney donation. Nephrology Dialysis Transplantation 2003; 18: 871-873.

7. Ramcharan T, Matas AJ. Long-term (20-37 years) follow-up of living kidney donors American Journal of Transplantation 2002; 2: 959-964.

8. Ratner LE, Buell JF, Kuo PC. Laparoscopic donor nephrectomy: pro. Transplantation 2000; 70: 1544-1548.

9. Freedland SJ, Blanco-Yarosh M, Sun JC, Hale SJ, Elashoff DA, Litwin MS et al. Ketorolac-based analgesia improves outcomes for living kidney donors. Transplantation 2002; 73: 741-745.

10. Challinor P, Sedgewick J, editors. Principles and Practice of Renal Nursing. Cheltenham: Nelson Thornes Ltd., 2001.

11. Merlin TL, Scott D F, Rao MM, et al. The safety and efficacy of laparoscopic live donor nephrectomy: a systematic review. Transplantation 2000; 70: 1659-1666.

12. Ku JH. Health-related quality of life of living kidney donors: review of the short form 36-health questionnaire survey. Transplantation International 2005; 18: 1309-1317.

13. Westlie L, Leivestad T, Lien B, Meyer K, Fauchald P. How are living kidney donors doing? Tidsskrift for Den Norske Lægeforening 2003; 123: 1060-1062.

14 Patel KK, Veenstra DL, Patrick DL. A review of selected patient-generated outcome measures and their application in clinical trials. Value in Health 2003; 6: 595-603.

15. Fayers PM, Machin D. Quality of life. The assessment, analysis and interpretation of patient-reported outcomes. 2nd ed. Chichester: John Wiley & Sons Ltd., 2007.

16. Revicki DA, Cella D, Hays RD, Sloan JA, Lenderking WR, Aaronson NK. Responsiveness and minimal important differences for patient reported outcomes. Health and Quality of Life Outcomes 2006; 4: 70.

17. Leidy NK, Revicki DA, Geneste B. Recommendations for evaluating the validity of quality of life claims for labelling and promotion. Value in Health 1999; 2: 113-127.

18. Patrick DL. Patient-reported outcomes (PROs): An organizing tool for concepts, measures, and applications. Quality of Life Newsletter 2003; 31: 1-5.

19. Merill JP, Murray JE, Harrison JH, et al. Successful homotransplantations of the kidney between nonidentical twins. New England Journal of Medicine 1960; 262: 1251-1260.

20. Westlie L, Leivestad T, Holdaas H, Lien B, Meyer K. Report from the Norwegian National Hospitals Living Donor Registry: one - year data, January 1, 2002. Transplantation Proceedings 2003; 35: 777-778.

21. Ko DSC, Cosimi AB. The donor and donor nephrectomy. In: Morris PJ, editor. Kidney transplantation. Principles and practice. 5th ed. Philadelphia: W.B. Saunders Company, 2001.

22. Meier-Kriesche H-U, Kaplan B. Advantages of living donor kidney transplantation in the current era. In: Gaston RS, Wadström J, editors. Living donor kidney transplantation: current practices, emerging trends and evolving challenges. Oxon: Taylor & Francis, 2005.

23. Elias N, Delmonico FL, Ko DSC. Surgical aspects of renal transplantation. In: Pereira BJG, Sayegh MH, Blake P, editors. Chronic kidney disease, dialysis & transplantation. 2nd ed. Philadelphia: Elsevier Saunders, 2005.

24. Lumsdaine JA, Forsythe JLR, Lear PA. Living donation (renal). In: Forsythe JLR, editor. Transplantation Surgery: Current dilemmas. London: W.B Saunders, 2001.

25. Wolf JS Jr., Tchetgen MB, Merion RM. Hand-assisted laparoscopic live donor nephrectomy. Urology 1998; 52: 885-887.

26. Slakely DP, Wood JC, Hender D, Thomas R, Cheng S. Laparoscopic live donor nephrectomy: advantages of the hand-assisted method. Transplantation 1999; 68: 581-583.

27. Wolf JS, Merion RM, Leichtman AB, et al. Randomized controlled trial of hand – assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation 2001; 72: 284-290.

28. Kok NFM, Lind MY, Hansson BME et al. Comparison of laparoscopic and mini-incision open donor nephrectomy: single blind, randomised controlled clinical trial. BMJ 2006; 333: 221-224.

29. Perry KT, Freedland SJ, Hu JC, et al. Quality of life, pain and return to normal activities following laparoscopic donor nephrectomy versus open mini-incision donor nephrectomy. The Journal of Urology 2003; 169: 2018-2021.

30. Dahm F, Weber M, Muller B, et al. Open and laparoscopic living donor nephrectomy in Switzerland: a retrospective assessment of clinical outcomes and the motivation to donate. Nephrology Dialysis Transplantation 2006; 21: 2563-2568.

31. Giessing M, Reuter S, Deger S, et al. Laparoscopic versus open donor nephrectomy in Germany: impact on donor health-related quality of life and willingness to donate. Transplantation Proceedings 2005; 37: 2011-2015.

32. Buell JF, Lee L, Martin JE, et al. Laparoscopic donor nephrectomy vs open live donor nephrectomy: a quality of life and functional study. Clinical Transplantation 2004; 19: 102-109.

33. Lennerling A, Blohmé I, Östraat Ö, Lönroth H, Olausson M, Nyberg G. Laparoscopic or open surgery for living donor nephrectomy. Nephrology Dialysis Transplantation 2001; 16: 383-386.

34. Hiller J, Sroka M, Holochek MJ, Morrison A, Kavoussi LR, Ratner LE. Functional advantages of laparoscopic live – donor nephrectomy compared with conventional open – donor nephrectomy. Journal of Transplantation Coordination 1997; 7: 134-140.

35. Pace KT, Dyer SJ, Stewart RJ, et al. Health-related quality of life after laparoscopic and open nephrectomy. Surgical Endoscopy 2003; 17: 143-152.

36. Price DPT. Legal and ethical dilemmas in living donor kidney transplantation. In: Gaston RS, Wadström J, editors. Living donor kidney transplantation: current practices, emerging trends and evolving challenges. Oxon: Taylor & Francis, 2005.

37. Reimer J, Rensing A, Haasen C, Philipp T, Pietruck F, Franke GH. The impact of living-related kidney transplantation on the donor's life. Transplantation 2006; 81: 1268-1273.

38. Blohme I, Fehrman-Ekholm I, Norden G. Living donor nephrectomy. Complications rates in 490 consecutive cases. Scandinavian Journal of Urology & Nephrology 1992; 26:149-153.

39. Fehrman-Ekholm I, Dunér F, Brink B, Tydén G, Elinder CG. No evidence of accelerated loss of kidney function in living kidney donors: results from a cross-sectional follow-up. Transplantation 2001; 72: 444-449.

40. Vlaovic PD, Richardson RM, Miller JA et al. Living donor nephrectomy: follow-up renal function, blood pressure, and urine protein excretion. Canadian Journal of Urlogy 1999; 6: 901-905.

41. Wadström J. Living donor nephrectomy. In: Gaston RS, Wadström J, editors. Living donor kidney transplantation: current practices, emerging trends and evolving challenges. Oxon: Taylor & Francis, 2005.

42. Isotani S, Fujisawa M, Ichikawa Y, et al. Quality of life of living kidney donors: the short-form 36-item health questionnaire survey. Urology 2002; 60: 588-592.

43. Najarian JS, Chavers BM, McHugh LE, Matas AJ. 20 years or more of follow-up of living

kidney donors. The Lancet 1992; 340: 807-810.

44. Johnson EM, Remucal MJ, Gillingham KJ, Dahms RA, Najarian JS, Matas AJ. Complications and risks of living donor nephrectomy. Transplantation 1997; 64: 1124-1128.

45. Ratner LE, Kavoussi LR, Schulam PG, Bender JS, Magnuson TH, Montgomery R. Comparison of laparoscopic live donor nephrectomy versus the standard open approach. Transplantation Proceedings 1997; 29: 138-139.

46. Schostak M, Wloch H, Müller M, et al. Living donor nephrectomy in an open technique: a long-term analysis of donor outcome. Transplantation Proceedings 2003; 35: 2096-2098.

47. Duque JLF, Loughlin KR, Kumar S. Morbidity of flank incision for renal donors. Urology 1999; 54: 796-801.

48. Burroughs TW, Waterman AD, Hong BA. One organ donation, three perspectives: experiences of donors, recipients, and third part with living kidney donation. Progress in Transplantation 2003; 13: 142-150.

49. Johnson EM, Anderson JK, Jacobs C, et al. Long-term follow-up of living kidney donors: quality of life after donation. Transplantation 1999; 67:717-721.

50. Fehrman-Ekholm I. The psychosocial impact of donor nephrectomy. In: Gaston RS, Wadström J, editors. Living donor kidney transplantation: current practices, emerging trends and evolving challenges. Oxon: Taylor & Francis, 2005.

51. Fehrman-Ekholm I, Brink B, Ericsson C, et al. Kidneys donors don't regret. Transplantation 2000; 69: 2067-2071.

52. Westlie L, Fauchald P, Talseth T, Jakobsen A, Flatmark A. Quality of life in Norwegian kidney donors. Nephrology Dialysis Transplantation 1993; 8: 1146-1150.

53. Smith GC, Trauer T, Kerr PG, Chadban SJ. Prospective psychosocial monitoring of living kidney donors using the Short Form-36 health survey: results at 12 months. Transplantation 2004; 78: 1384-1389.

54. Chen CH, Chen Y, Chiang YJ, Wu CT, Chen HW, Chu SH. Risks and quality-of-life changes in living kidney donors. Transplantation Proceedings 2004; 36: 1920-1921.

55. Jacobs C, Johnson E, Anderson K, Gillingham K, Matas A. Kidney transplants from living donors: how donation affects family dynamics. Advances in Renal Replacement Therapy 1998; 5: 89-97.

56. Olbrisch ME, Benedict SM, Haller DL, Levenson JL. Psychosocial assessment of living organ donors: clinical and ethical considerations. Progress in Transplantation 2001; 11: 40-49.

57. Fisher PA, Kropp DJ, Fleming EA. Impact on living kidney donors: quality of life, self-image and family dynamics. Nephrology Nursing Journal 2005; 32: 489-500.

58. Corely MC, Elswick RK, Sargeant CC, Scott S. Attitude, self – image, and quality of life of living kidney donors. Nephrology Nursing Journal 2000; 27: 43-50.

59. Taghavi R, Mahdavi R, Toufani H. The psychological effects of kidney donating on living kidney donors (related and unrelated). Transplantation Proceedings 2001; 33: 2636-2637.

60. Eggeling C. Psychosocial implications for live – related donors. EDTNA/ERCA Journal 1999; 25: 19-22.

61. Pradel FG, Mullins CD, Barlett ST. Exploring donors' and recipients' attitudes about living kidney transplantation. Progress in Transplantation 2003; 13: 203-210.

62. Walsh,A. Living kidney donor experiences: implications for counseling EDTNA/ERCA Journal. 2004; 30: 196-200.

63. Schover LR, Streem S B, Boparai N, Duriak K, Novick AC. The psychosocial impact of donating a kidney: long – term followup from a urology based center. The Journal of Urology 1997; 157: 1596-1601.

64. Heck G, Schweitzer J, Seidel-Wiesel M. Psychological effects of living related kidney transplantation-risks and chances. Clinical Transplantation 2004; 18: 716-721.

65. Franklin PM, Crombie AK. Live related renal transplantation: psychological, social, and cultural issues. Transplantation 2003; 76: 1247-1252.

66. Haljamäe U, Nyberg G, Sjöström B. Remaining experiences of living kidney donors more than 3 yr after early recipient graft loss. Clinical Transplantation 2003; 17: 503-510.

67. Weizer N, Weizman A, Shapira Z, Yussim A, Munitz H. Suicide by related kidney donors following the recipient's death. Psychotherapy & Psychosomatics 1989; 51: 216-219.

68. Ethics Committee of the Transplantation Society. The consensus statement of the Amsterdam forum on the care of the live kidney donor. The Ethics Committee of the Transplantation Society. Transplantation 2004; 78: 491-492.

69. Nicholson ML, Bradley JA. Renal transplantation from living donors. British Medical Journal 1999; 318: 409-410.

70. Abecassis M, Adams M, Adams P, et al. Consensus statement on the live organ donor. JAMA 2000; 284: 2919-2926.

71 Hanto DW. Ethical challenges posed by the solicitation of deceased and living organ donors. The New England Journal of Medicine 2007; 356: 1062-1066.

72. Article 19. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine. 4 April 1997, Oviedo.

73. Beauchamps TL, Childress JF. Principles of biomedical ethics. 5th ed. New York: Oxford University Press, 2001.

74. Appelbaum PS, Grisso T. Assessing capacities to consent to treatment. The New England Journal of Medicine 1988; 319: 1635-1638.

75. Acquadro C, Berzon R, Dubois D, et al. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group Meeting at the Food and Drug Administration, February 16, 2001. Value in Health 2003; 6: 522-531.

76. Garrat A, Schmidt L, Mackintosch A, Fitzpatrick R. Quality of life measurement: bibliographic study of patient assessed health outcome measures. British Medical Journal 2002; 324: 1417.

77. Polit DF, Beck CT. Nursing Research: principles and methods. 7nd ed. Philadelphia: J.B. Lippincott Williams & Wilkins, 2004.

78. Marshall C, Rossman GB. Designing Qualitative Research. 4th ed. London: SAGE Publications, 2006.

79. Grbich C. Qualitative research in health. An introduction. London: SAGE Publications, 2003.

80. Willke RJ, Burke LB, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. Controlled Clinical Trials 2004; 25: 535-552.

81. Fayers PM, Sprangers MAG. Understanding self-rated health. The Lancet 2002; 359: 187-188.

82. Vallerand AH, Payne JK. Theories and conceptual models to guide quality of life related research. In: King Ch & Hinds PS, editors. Quality of life from nursing and patient perspective. Theory – Research – Practice. 2nd ed. Boston: Jones and Barlett Publishers, 2003.

83. Grant M, Ferrell BR, Sakurai C. Defining the spiritual dimension of quality of life assessments in bone marrow transplant survivors. Oncology Nursing Forum 1994; 21: 376.

84. Cella DF. Quality of life: Concepts and definitions. Journal of Pain and Symptom Management 1994; 9: 186-192.

85. Wahl A, Burckhardt C, Wiklund I, Hanestad BR. The Norwegian version of the Quality of Life Scale (QOLS-N). A validation and reliability study in patients suffering from psoriasis. Scandinavian Journal of Caring Sciences 1998; 12: 215-522.

86. Aaronsen NK, Meyerowitz BE, Bard M, et al. Quality of life research in oncology: Past achievements and future priorities. Cancer 1991; 67: 839- 843.

87. Spilker B. Introduction. In: Spilker B. (ed.) Quality of life and pharmacoeconomics in clinical trials. 2nd ed. New York: Raven Press, 1996.

88. Anderson KL, Burckhardt CS. Conceptualization and measurement of quality of life as an outcome variable for health care intervention and research. Journal of Advanced Nursing 1999; 29: 298-306.

89. Hyland ME. A reformulation of quality of life for medical science. Quality of Life Research 1992; 1: 267-272.

90. Burckhardt CS, Woods SL, Schultz AA & Ziebarth M. Quality of life of adults with chronic illness: A psychometric study. Research in Nursing and Health 1989; 12: 347-354.

91 Ware JE, Kosinski M, Gandek B. SF-36 Health Survey: manual and interpretation guide. Boston: Health Institute, 2003.

92. Cline ME, Herman J, Shaw ER, Morton RD. Standardization of the Visual Analogue Scale. Nursing Research 1992; 41: 378-380.

93. Ferrans CE. Development of a quality of life index for patients with cancer. Oncolgy Nursing Forum 1990; 17: 15-21.

94. World Health Organization. Constitution of the world Health Organization. In Basic Documents. Geneva, Switzerland: WHO, 1948.

95. Ware JE, Sherbourne CD. The MOS 36-item Short-form health survey (SF-36). I. Conceptual framework and item selection. Medical Care 1992; 30: 473-483.

96. IASP (1994): IASP Pain Terminology. Classification of Chronic Pain, 2nd, IASP Task Force on Taxonomy, H. Merskey and N. Bogduk (editors). Seattle: IASP Press. 209-214.

97. Polit DF, Hungler BP. Nursing research: principles and methods. 6th ed. Philadelphia: Lippencott, 1999.

98. Altman D. Practical statistics for medical research. Washington DC: Chapman & Hall/CRC, 1997.

99. Øyen O, Line PD, Pfeffer P, Edwin B, Jørgensen PF, Foss A et al. Laparoscopic living donor nephrectomy: Introduction of simple hand-assisted technique (Without hand-port). Transplantation Proceedings 2003; 35: 779-781.

100. Øyen O, Andersen MH, Mathisen L, et al. Laparoscopic versus open living-donor nephrectomy: Experiences from a prospective, single-center study focusing on donor safety. Transplantation 2005; 79: 1236-1240.

101. Burckhardt CS, Archenholtz B, Bjelle A. Measuring the quality of life of women with rheumatoid arthritis or systemic lupus erythematosus: A Swedish version of the Quality of Life Scale (QOLS). Scandinavian Journal of Rheumatology 1992; 21: 190-195.

102. Burckhardt C, Anderson K, Archenholz B, Hägg O. The Flanagan Quality of Life Scale: evidence of construct validity. Health and Quality Outcomes 2003; 1: 59.

103. Ware JE Jr, Keller SD, Gandek B, Brazier JE, Sullivan M. Evaluating translations of health

status questionnaires. Interpersonal Quality of Life Assessment. International Journal of Technology Assessment in Health Care 1995; 11: 525-551.

104. Loge JH, Kaasa S. Short form 36 (SF-36) health survey: normative data from the general Norwegian population. Scandinavian Journal of Social Medicine 1998; 26: 250-258.

105. Wolf JS, Marcovich R, Merion RM, Konnak JW. Prospective, case-matched comparison of hand assisted laparoscopic and open surgical live donor nephrectomy. Journal of Urology 2000; 163: 1650-1653.

106. Stubhaug A, Breivik H. Post-operative analgesic trials: some important issues. In: Breivik H., editor. Baillière's Clinical Anesthesiology. London: Baillère Tindall, 1995; 9: 555-589.

107. McDowell I. Measuring health. A guide to rating scales and questionnaires. Oxford: Oxford University Press, 2006.

108. Breivik EK, Björnsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. Clin J Pain 2000; 16: 22-28.

109. Kunst G, Chrubasik S, Black AMS, et al. Patient-controlled epidural diamorphine for post-operative pain: verbal rating and visual analogue assessments of pain. European Journal of Anesthesiology 1996; 13: 117-129.

110. Cline ME, Herman J, Shaw ER, Morton RD. Standardization of the Visual Analogue Scale. Nursing Research 1992; 41: 378-380.

111. Kremer E, Atkinson JH, Ignelzi RJ. Measurement of pain: patient preference does not confound pain measurement. Pain 1981; 10: 241-248.

112. Price D, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983; 17: 45-56.

113. Huskisson EC. Visual Analogue Scales. In: Melzack R (editor). Pain Measurement and Assessment. New York: Raven Press, 1983.

114. Testa MA, Simonsen DC. Assessment of quality-of-life outcomes. New England Journal of Medicine 1996; 334: 835-840.

115. Cohen J. Statistical power analysis for the behavioural sciences. 2 nd ed. Hillsdale, NJ: Lawrence Erlbaum Hillsdale, 1988.

116. World Medical Association. Declaration of Helsinki. In: Beauchamp TL. Principles of biomedical ethics. 5th ed. New York: Oxford University Press, 2001.

117. Grimen H, Ingstad B. Qualitative research. In: Laake P, Benestad HB, Olsen BR. Research methodology in the medical and biological sciences. Amsterdam: Academic Press, 2007.

118. Malterud K. The art and science of clinical knowledge: evidence beyond measures and numbers. The Lancet; 2001: 397-400.

119. Burkett GL, Godkin MA. Qualitative research in family medicine. Journal of Family

Practitioner 1983; 16; 625-626.

120. Todres L. Clarifying the life-world: descriptive phenomenology. In: Holloway I, editor. Qualitative research in health care. London: Open University Press, 2005.

121 Kvale S. Interviews: an Introduction to qualitative research interviewing. Thousand Oaks, California: Sage, 1996.

122. Shokeir AA. Open versus laparoscopic live donor nephrectomy: a focus on the safety of donors and the need for a donor registry. The Journal of Urology 2007; 178: 1860-1866.

123. Vallancien G, Cathelineau X, Baumert H, Doublet JD, Guillonneau B. Complications of transperitoneal laparoscopic surgery in urology: review of 1,311 procedures at a single center. The Journal of Urology 2002; 168: 23-26.

124. Ratner LE, Kavoussi LR, Sroka M, et al. Laparoscopic assisted live donor nephrectomy - a comparision with the open approach. Transplantation 1997; 63: 229-223.

125. Waller JR, Hiley AL, Mullin EJ, Veitch PS, Nicholson ML. Living kidney donation: a comparision of laparoscopic and conventional open operations. Postgraduate Medical Journal 2002; 78: 153-157.

126. Bachmann A, Wolff T, Giannini O, et al. How painful is donor nephrectomy? Retrospective analysis of early pain and pain management in open versus laparoscopic versus retroperitoneoscopic nephretomy. Transplantation 2006; 81: 1735-1738.

127. Huynh PN, Hollander JB. Trends toward laparoscopic nephrectomy at a community hospital. Journal of Urology 2005; 173: 547-551.

128. Toother RL, Rao MM, Scott E, et al. A systematic review of laparoscopic live-donor nephrectomy. Transplantation 2004; 78: 404-414.

129. Truog RD. The ethics of organ donation by living donors. The New England Journal of Medicine 2005; 353: 444-446.

130. Ruiz-Deya G, Cheng S, Palmer E, Thomas R, Slakely D. Open donor, laparoscopic donor and hand assisted laparoscopic donor nephrectomy: a comparison of outcomes. Journal of Urology 2001; 166: 1270-1274.

131. Kok NFM, Alwayn IPJ, Tran KTC, Hop WJC, Weimar W, IJzermans JNM. Psychosocial and physical impairment after mini-incision open and laparoscopic donor nephrectomy: a prospective study. Transplantation 2006; 28: 1291-1297.

132. Peters TG, Repper SM, Jones KW, Walker GW, Vincent M, Hunter RD. Living kidney donation: revovery and return to activities of daily living. Clinical Transplantation 2000; 14: 433-438.

133. Lind MY, Hop WC, Weimar W, Ijzermans JN. Body image after laparoscopic or open donor nephrectomy. Surgical Endoscopy 2004; 18: 1276-1279.

134. Rodrigue JR, Cross NJ, Newman RC. Patient-reported outcomes for open versus

laparoscopic living donor nephrectomy. Progress in Transplantation 2006; 16: 162-169.

135. Stothers L, Gourlay WA, Liu L. Attitudes and predictive factors for live kidney donation: A comparison of live kidney donor versus nondonors. Kidney International 2005; 67: 1105-1111.

136. Jordan J, Sann U, Janton A. Living kidney donors' long-term psychological status and health behaviour after nephrectomy - a retrospective study. Journal of Nephrology 2004; 17: 728-735.

137. Weizer N, Weizman A, Shapira Z, Yussim A, Munitz H. Suicide by related kidney donors following the recipient's death. Psychotherapy& Psychosomatics 1989; 51: 216-219.

138. Spital AA, Jacobs C. Life insurance for kidney donors: another update. Transplantation 2002; 74: 972-793.

139. Bergman S, Feldman LS, Mayo N E, et al. Measuring surgical recovery: the study of laparoscopic live donor nephrectomy. American Journal of Transplantation 2005; 5: 2489-2495.

140. Gres P, Avances C, Iborra F, Mourad G, Guiter J. Long-term morbidity of living donor kidney harvesting. Progres en Urologie 2007; 17: 194-198.

141. Azar SA, Nakhjavani MR, Tarzamni MK, Faragi A, Bahloli A, Badroghli N. Is living kidney donation raly safe? Transplantation Proceedings 2007; 39: 822-823.

142. Sanner M. The donation process of living kidney donors. Nephrology Dialysis Transplantation 2005; 20: 1707-1713.

143. De Graaf Olson W, Bogetti-Dumlao JT. Living donors' perception of their quality of health after donation. Progress in Transplantation 2001; 11: 108-115.

144. Shadish WR, Cook TD, Campbell DT. Experimental and quasi-experimental designs for generalized causal inference. Boston: Houghton Mifflin Company, 2002.

145. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika 1951; 16: 297-334.

146. Lund T. Metodologiske prinsipper og referanserammer (Methodological principles and reference ramifications). In: Lund T, editor: Innføring i forskningsmetodologi (Introduction to Research Methodology). Oslo: Unipub forlag, 2002.

147. Davis CL, Delmonico FL. Living-donor kidney transplantation: a review of the current practices for the live donor. Journal of American Society of Nephrology 2005; 16: 2098-2110.

148. U.S. Transplant-Scientific Registry of Transplant Recipients: 2005 OPTN/SRTR Annual Report. Ann Arbor, MI: University Renal Research and Education Association with the University of Michigan, 2005.

149. U.S Renal Data System: 2005. Annual Data report. Available at www.usrds.org

150. Brink PJ & Wood MJ. Advanced design in nursing research. 2nd ed. California: Sage Publications, 1990.

151. Wolf JS, Moon TD, Nakada SY. Hand-assisted laparoscopic nephrectomy: comparison to standard laparoscopic nephrectomy. Journal of Urology 1998; 160: 22-27.

152. Kok NFM, Alwayn IPJ, Lind MY, Tran KTC, Weimar W, IJzermans JNM. Donor nephrectomy: mini-incision muscle-splitting open approach versus laparoscopy. Transplantation 2006; 81: 881-887.

153. Higashihara E, Baba S, Nakagawa K, et al. Learning curve and conversation to open surgery in case of laparoscopic adrenalectomy and nephrectomy. Journal of Urology 1998; 159: 650-653.

154. Sandelowski M, Barroso J. Handbook of synthesizing qualitative research. New York: Springer Publishing Company, 2007.

155. Malterud K. Qualitative research: standards, challenges, and guidelines. The Lancet 2001; 358: 483-488.

156. Green J, Thorogood N. Qualitative methods for health research. London: Sage Publications, 2004.

157. Miles MB, Huberman AM. Qualitative data analysis: an expanded sourcebook, 2nd ed. Thousand Oaks, California: Sage Publications, 1994.

158. Barbour RS. The case for combining qualitative and quantitative approaches in health services research. Journal of Health Services Research and Policy 1999; 4: 39-43.

159. Osoba D. Translating the science of patient-reported outcomes assessments into clinical practice. Journal of the National Cancer Institute, Monographs 2007; 37: 5-11.

160. Lennerling A, Nyberg G. Written information for potential living kidney donors. Transplantation International 2004; 17: 449-452.

161. Yi M. Decision - making process for living kidney donors. Journal of Nursing Scholarship 2003; 35: 61-66.

162. Siddins M, Hart G, He B, Kanchanabat B, Rao MM. Laparoscopic donor nephrectomy: meeting the challenge of consumerism? ANZ Journal of Surgery 2003; 73: 912-915.

163. A report of the Amsterdam Forum On the Care of the Live Kidney Donor: data and medical guidelines. Transplantation 2005; 79: 53-66.

ERRATA

Formal errors which have been corrected in the thesis:

Page 16: … at postoperative days **0, 1 and 2**; and (2) postoperative pain intensity as measured by a visual analogue scale (VAS) at postoperative day 2 **(Paper II).**

References

14. Patel KK, Veenstra **DL**, Patrick DL. A review of …
32. Buell JF, Lee L, Martin JE**, et** al. Laparoscopic…
40. Vlaovic PD, Richardson RM, Miller JA et al. Living donor nephrectomy: follow-up renal function, blood pressure, and urine protein excretion. Canadian Journal of **U**rology 1999…
45. Ratner LE, Kavoussi LR, Schulam PG, Bender JS, Magnuson TH, Montgomery R. Comparison of laparoscopic live donor nephrectomy versus the standard open approach. Transplantation **P**roceedings 1997…
56. Olbrisch ME, Benedict **S**M, Haller DL, Levenson JL…
82. Vallerand AH, Payne JK. Theories and conceptual models to guide quality of life related research. In: King Ch & Hinds PS, editors. Quality of life from nursing and patient perspective. Theory – **R**esearch – Practice…
83. Grant M, Ferrell BR, Sakurai C. **D**efining the spiritual…
131. Kok NFM, Alwayn IPJ, Tran KTC, Hop WJC, Weimar W, IJzermans JNM. Psychosocial and **p**hysical impairment after mini-incision open and laparoscopic donor nephrectomy: a prospective study. Transplantation 2006; 28: 1291-**1297.**
132. Peters TG, Repper SM, Jones KW, **W**alker GW, Vincent M, Hunter RD. Living kidney donation: re**c**overy and return…
135. Stothers L, Gourlay WA, Liu L. Attitudes and predictive factors for live kidney donation: A comparison of live kidney donor versus nondonors. Kidney **I**nternational 2005…

Papers, errata

<table>
<tr><td>Paper I</td><td>Page 1238, Table 2. Explanation text below Table 2, regarding analgesic requirements: “Values in brackets are intention-to-treat data… ”, should be replaced with “Values in brackets are cencored data…”</td></tr>
<tr><td rowspan="2">Paper II</td><td>Page 1439, Surgical techniques. Starting on line 6, the correct numbers are: “The first 17 laparoscopic donor nephrectomies…The last 46 laparoscopic...”</td></tr>
<tr><td>Page 1440, Table 2. The correct amount of analgesic requirement is:
<table>
<tr><td></td><td>Laparoscopy</td><td>Open Surgery</td><td>N</td><td>p-value</td></tr>
<tr><td>Day of surgery</td><td>13.1 (9.2)</td><td>17.8 (10.7)</td><td>63/59</td><td>0.010</td></tr>
<tr><td>First postoperative day</td><td>15.0 (13.4)</td><td>18.6 (15.4)</td><td>63/59</td><td>0.157</td></tr>
</table></td></tr>
<tr><td rowspan="3">Paper III</td><td>Page 65, Surgical techniques. Starting on line 3, the correct numbers are: “The first 17 laparoscopic donor nephrectomies …The last 46 laparoscopic…”</td></tr>
<tr><td>Page 66, Health status. Last paragraph, the correct text is: “SRM for changes from baseline to 12 months varied between 0 and .55, however, most effect sizes were less than .30, indicating no or irrelevant changes.</td></tr>
<tr><td>Page 67, Figure 1. 95 % CI should be replaced by Mean scores subscale SF-36.</td></tr>
</table>