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Retrospective Cohort Study

Learning curves of minimally invasive donor nephrectomy in a high-volume center: A cohort study of 1895 consecutive living donors

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ABSTRACT

Background: Few studies have investigated the learning curves of minimally invasive donor nephrectomy (MIDN) using the cumulative sum (CUSUM) analysis. In addition, no study has compared the learning curves of the different surgical MIDN techniques in one cohort study using the CUSUM analysis. This study aims to evaluate and compare learning curves for several MIDN using the CUSUM analysis.
Methods: A retrospective review of consecutive donors, who underwent MIDN between 1997 and 2019, was conducted. Three laparoscopic-assisted techniques were applied in our institution and included for analysis: laparoscopic (LDN), hand-assisted retroperitoneoscopic (HARP), and robot-assisted laparoscopic (RADN) donor nephrectomy. The outcomes were compared based on surgeon volume to develop learning curves for the operative time per surgeon.
Results: Out of 1895 MIDN, 1365 (72.0%) were LDN, 427 (22.5%) were HARP, and 103 (5.4%) were RADN. The median operative time and median blood loss were 179 (IQR, 139–230) minutes and 100 (IQR, 40–200) mL, respectively. The incidence of major complication was 1.2% with no mortality, and the median hospital stay was three (IQR, 3–4) days. The CUSUM analysis resulted in learning curves, defined by decreased operative time, of 23 cases in LDN, 45 cases in HARP, and 26 cases in RADN.
Conclusions: Our study shows different learning curves in three MIDN techniques with equal post-operative complications. The LDN and RADN learning curves are shorter than that of the hand-assisted donor nephrectomy. Our observations can be helpful for informing the development of teaching requirements for fellows to be trained in MIDN.

1. Introduction

Minimally invasive donor nephrectomy (MIDN) has emerged as the standard technique for living donor kidney transplantation. To date, several techniques have been introduced as MIDN, such as laparoscopic (LDN), hand-assisted retroperitoneoscopic (HARP), hand-assisted intraperitoneal, robot-assisted laparoscopic (RADN), and laparoendoscopic single-site donor nephrectomy [1]. For the safe performance of minimally invasive surgery, the importance of assessing surgical training and quality has recently been emphasized [2–4].

The cumulative sum (CUSUM) analysis, which is a useful tool for evaluating the learning curve for surgical procedures [5–7], has been adopted in minimally invasive surgery [8,9]. In addition, the learning curve for MIDN has been investigated using the CUSUM analysis [10–13]. However, no study has compared the learning curves of different MIDN techniques in one cohort study using the CUSUM analysis.

The aim of this study is to investigate the effect of surgeon volume on outcomes in MIDN and to determine learning curves for MIDN using the CUSUM analysis in a high-volume center in Western Europe. Furthermore, this study explores the necessary number of procedures for improving surgical technique in MIDN.

2. Materials and methods

2.1. Study design

A retrospective review was performed to investigate a prospectively

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collected database of 2089 consecutive living donors who underwent donor nephrectomy (DN) at our institution between January 1997 and June 2019. Out of 2089 DN, 1895 MIDN were included after excluding 194 open DN. All procedures were conducted by 37 primary surgeons including surgical residents, transplant fellows, and consultant surgeons. The present study was approved by the Ethics Committee at our institution and registered at the University Hospital Medical Information Network (UMIN000041405). The work was performed in accordance with the tenets of the Declaration of Helsinki and the STROCSS criteria [14].

2.2. Clinical data

From all enrolled living donors, the following data was collected: age, gender, body mass index (BMI), type of surgeon (surgical resident, transplant fellow, or consultant surgeon), type of DN (LDN, HARP, or RADN), side of DN (right or left kidney), operative time, blood loss, conversion rate to the other procedure, number of renal arteries and veins (single or multiple), incidence of postoperative major complications (Clavien-Dindo classification ≥ III), and postoperative length of stay (LOS). Postoperative major complications included those requiring surgical, endoscopic, or radiological intervention, with or without general anesthesia, and life threatening complications [15]. Conversion from LDN or RADN to hand-assisted DN was counted as conversion in this study.

2.3. Surgical technique and training system

At our institution, MIDN included three techniques: LDN, HARP, and RADN, as details have previously reported [16,17]. LDN was performed with either the four- or five-trocar technique. Initially, the colon was mobilized, and perirenal fat was divided to identify the renal artery, renal vein, and ureter. After the transection of the ureter, renal artery, and renal vein, the donor kidney was extracted using the Endobag (US surgical, Norwalk, USA) through the Pfannenstiel incision. In HARP, a Pfannenstiel incision was initially made to create a retroperitoneal space, and a Gelport (Applied Medical, Rancho Santa Margarita, California, USA) was inserted. Dissection around the kidney, including the renal vessels and ureter, was performed with the three-trocar technique, and the kidney was removed by hand through the Pfannenstiel incision. RADN was performed with the da Vinci surgical system (Intuitive Surgical, Sunnyvale, California, USA). The trocars were inserted in a concave curve to create a top view. After the system was docked, the colon was mobilized to facilitate the dissection of the perirenal fat. The procedure afterwards was similar to LDN. In the case of a conversion from LDN or RALD to hand-assisted DN, a Gelport was inserted via the Pfannenstiel incision. Afterwards, the kidney was extracted manually through the Gelport.

Regarding the selection of MIDN procedures, surgeon experience and donor factors, such as BMI and kidney anatomy, were taken into account. In general, LDN was the first option used at our institution. In case with BMI ≥30, HARP was considered [16]. In 2009, RADN was introduced at our institution [17]. Initially, the indication to use RADN was a left-sided donor nephrectomy with a BMI below 30. The assumption was made that robot-assistance would not enhance the right-sided procedure since randomized controlled trials demonstrated an improvement only during left-sided procedures [18,19]. Therefore, the choice was made to include only donors with indications for left-sided donor nephrectomies. After 60 RADN, right-sided procedures have been performed occasionally.

Regarding our surgical training system, all fellows and residents were supervised by consultant surgeons who were qualified to conduct MIDN independently. The definition of consultant surgeons, transplant fellows, and surgical residents was described previously [7].

2.4. Statistical analysis

Firstly, donor characteristics and outcomes were compared between LDN, HARP, and RADN. Secondly, surgeon volumes were categorized into eight groups in LDN, six groups in HARP, and five groups in RADN based on the volume of procedures performed at our institution, and outcomes were evaluated based on the groups in each procedure. Lastly, the CUSUM analysis was performed to investigate learning curves for operative time per surgeon in MIDN and to identify the number of procedures necessary to reach optimal performance. In the CUSUM analysis, for each surgeon, the cumulative sums of the differences from the total cohort's mean were calculated in each procedure. A pooled average CUSUM was plotted to demonstrate the generalization of the results [7]. Data was presented as medians and the interquartile range (IQR) for continuous variables and as proportions for categorical data. Differences between groups were assessed using the Mann-Whitney *U* test for continuous variables and Fisher's exact test or the chi-square test for categorical variables. JMP version 11 software (SAS Institute, Cary, NC) was used for all statistical analyses. A P-value < 0.05 was considered statistically significant.

3. Results

3.1. Study cohort

The annual volume of MIDN between 1997 and 2018 is represented in Fig. 1. The overall characteristics and outcomes of all 1895 living donors are summarized in Table 1. Of these, 1365 (72.0%) were LDN, 427 (22.5%) were HARP, and 103 (5.4%) were RADN. In addition, 276 (15%) procedures were performed by surgical residents and transplant fellows, and 1619 (85%) were performed by consultant surgeons. The median operative time and blood loss were 179 (IQR, 139–230) minutes and 100 (IQR, 40–200) mL, respectively. The incidence of major complication was 1.2% with no mortality, and the median LOS was three (IQR, 3–4) days.

The outcomes in LDN, HARP, and RADN are also demonstrated in Table 1. Significant differences between the groups were found regarding BMI, side of DN, operative time, blood loss, and conversion rate. HARP was associated with a higher BMI of the donor, the use of left kidney, a shorter operative time, and higher blood loss. Furthermore, RADN were mostly performed by consultant surgeons, compared to LDN and HARP. However, the incidence of major complications and LOS did not differ between the groups.

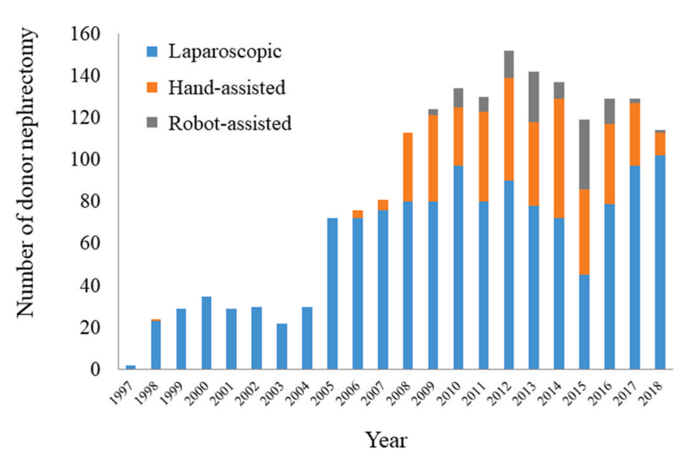

Fig. 1. Annual volume of minimally invasive donor nephrectomy between 1997 and 2019.

Table 1
Characteristics of minimally invasive donor nephrectomy between 1997 and 2019.

Variables	Total	LDN	HARP	RADN	P value
No. of patients	1895	1365	427	103	
Age (years)	52.5 (42.3–61.4)	51.8 (41.1–61.2)	54.6 (45.3–62)	54.0 (40.3–62.4)	0.001
Gender					
Male	833 (44%)	606 (44%)	185 (43%)	42 (41%)	0.74
Female	1062 (56%)	759 (56%)	242 (57%)	61 (59%)	
BMI (kg/m^2)	25.8 (23.5–28.7)	25.3 (23.1–28)	28.2 (25.4–31.4)	23.9 (22–26.3)	<0.001
No. of operator	37	37	13	6	–
No. of MIDN by type of surgeon					
Fellow/resident	276 (15%)	209 (15%)	65 (15%)	2 (2%)	<0.001
Consultant surgeons	1619 (85%)	1156 (85%)	362 (85%)	101 (98%)	
Side of nephrectomy					
Right	706 (37%)	619 (45%)	67 (16%)	20 (19%)	<0.001
Left	1189 (63%)	746 (55%)	360 (84%)	83 (81%)	
Operative time (minutes)	179 (139–230)	184 (140–250)	165 (134–202)	180 (146–223)	<0.001
Blood loss (mL)	100 (40–200)	65 (20–150)	200 (100–315)	78 (20–150)	<0.001
Conversion[a]	72 (3.8%)	62 (4.5%)	6 (1.4%)	4 (3.9%)	0.005
No. of artery (n = 1818)					
Single	1448 (80%)	1030 (80%)	341 (80%)	77 (75%)	0.46
Multiple	370 (20%)	258 (20%)	86 (20%)	26 (25%)	
No. of vein (n = 1818)					
Single	1656 (91%)	1158 (90%)	400 (94%)	98 (95%)	0.014
Multiple	162 (9%)	130 (10%)	27 (6%)	5 (5%)	
Postoperative major complications	23 (1.2%)	17 (1.3%)	6 (1.4%)	0 (0%)	0.27
Length of stay (days)	3 (3–4)	3 (3–4)	3 (3–4)	3 (3–4)	0.59

LDN laparoscopic donor nephrectomy, *HARP* hand-assisted retroperitoneoscopic donor nephrectomy, *RADN* robot-assisted laparoscopic donor nephrectomy, *MIDN* minimally invasive donor nephrectomy, *BMI* body mass index.
[a] Conversion from LDN or RADN to hand-assisted DN was counted as conversion.

3.2. Learning curve in laparoscopic donor nephrectomy

In total, 1365 LDN were performed by 37 surgeons. The surgeon volumes of all of the surgeons were divided into eight groups: Group 1 (1–10), Group 2 (11–20), Group 3 (21–30), Group 4 (31–40), Group 5 (41–60), Group 6 (61–80), Group 7 (81–100), and Group 8 (101≥). The outcomes of these eight groups are demonstrated in Table 2. Although no significant differences were found in terms of postoperative major complications and LOS, operative time and blood loss were significantly different between the groups.

The CUSUM analysis of operative time in LDN is shown in Fig. 2A. CUSUM-LDN showed that the mean number of consecutive interventions necessary to reach proficiency in LDN was 23 procedures. After 23 procedures, there was a period of stable improvement in operative time.

3.3. Learning curve in hand-assisted retroperitoneoscopic donor nephrectomy

The surgeon volumes of the 13 surgeons in HARP were divided into six groups: Group 1 (1–10), Group 2 (11–20), Group 3 (21–30), Group 4 (31–40), Group 5 (41–50), and Group 6 (51≥). The outcomes, categorized into six groups, are shown in Table 3. There were significant differences in operative time and blood loss; however, there were no differences in postoperative outcomes including major complications and LOS.

The CUSUM analysis of operative time in HARP identified a reduction of operative time after 45 procedures (Fig. 2B).

Table 2
Donor outcomes of 1365 patients undergoing laparoscopic donor nephrectomy.

	Group 1 (1–10)	Group 2 (11–20)	Group 3 (21–30)	Group 4 (31–40)	Group 5 (41–60)	Group 6 (61–80)	Group 7 (81–100)	Group 8 (101≥)	P value
No. of DN	178	99	100	87	151	140	140	470	
Age (years)	50.0 (38.4–60.0)	51.7 (45.3–59.3)	53.5 (40.8–64.1)	52.1 (41.4–61.5)	51.7 (40.9–62.1)	50.6 (39.0–61.8)	52.4 (42.4–62.7)	52.3 (41.7–60.1)	0.53
Gender (Male/Female)	85/93	46/53	41/59	40/47	72/79	54/86	58/82	209/261	0.75
BMI (kg/m^2)	24.9 (22.8–27.0)	25 (23.1–28.1)	24.9 (22.3–27.6)	26.2 (24.1–28.7)	25.4 (23.4–28.2)	25.6 (23.7–28.1)	24.9 (23.2–27.4)	25.5 (23.1–28.2)	0.08
Side of nephrectomy									
Right/Left	91/87	43/56	45/55	40/47	74/77	68/72	66/74	192/278	0.38
Operative time (minutes)	212 (167–304)	200 (139–259)	180 (145–255)	191 (151–226)	188 (143–240)	180 (141–240)	171 (132–211)	175 (127–249)	<0.001
Blood loss (mL)	90 (43–200)	100 (35–200)	100 (20–200)	88 (45–200)	70 (30–175)	100 (23–150)	50 (10–150)	50 (20–146)	0.039
Conversion	7 (3.9%)	5 (5.1%)	5 (5.0%)	8 (9.2%)	8 (5.3%)	5 (3.6%)	2 (1.4%)	18 (3.8%)	0.38
No. of artery (n = 1280)									
Single/Multiple	121/26	82/8	73/18	64/13	113/22	98/40	118/22	362/108	0.004
No. of vein (n = 1280)									
Single/Multiple	136/11	82/8	79/12	71/6	116/19	122/16	128/12	424/46	0.59
Postoperative major complications	1 (0.6%)	1 (1.0%)	2 (2.0%)	1 (1.2%)	1 (0.7%)	3 (2.1%)	0	7 (1.5%)	0.57
Length of stay (days)	3 (3–4)	3 (3–4)	3 (3–4)	3 (2–4)	3 (2–4)	3 (2–4)	3 (3–4)	3 (3–4)	0.68

DN donor nephrectomy, *BMI* body mass index.

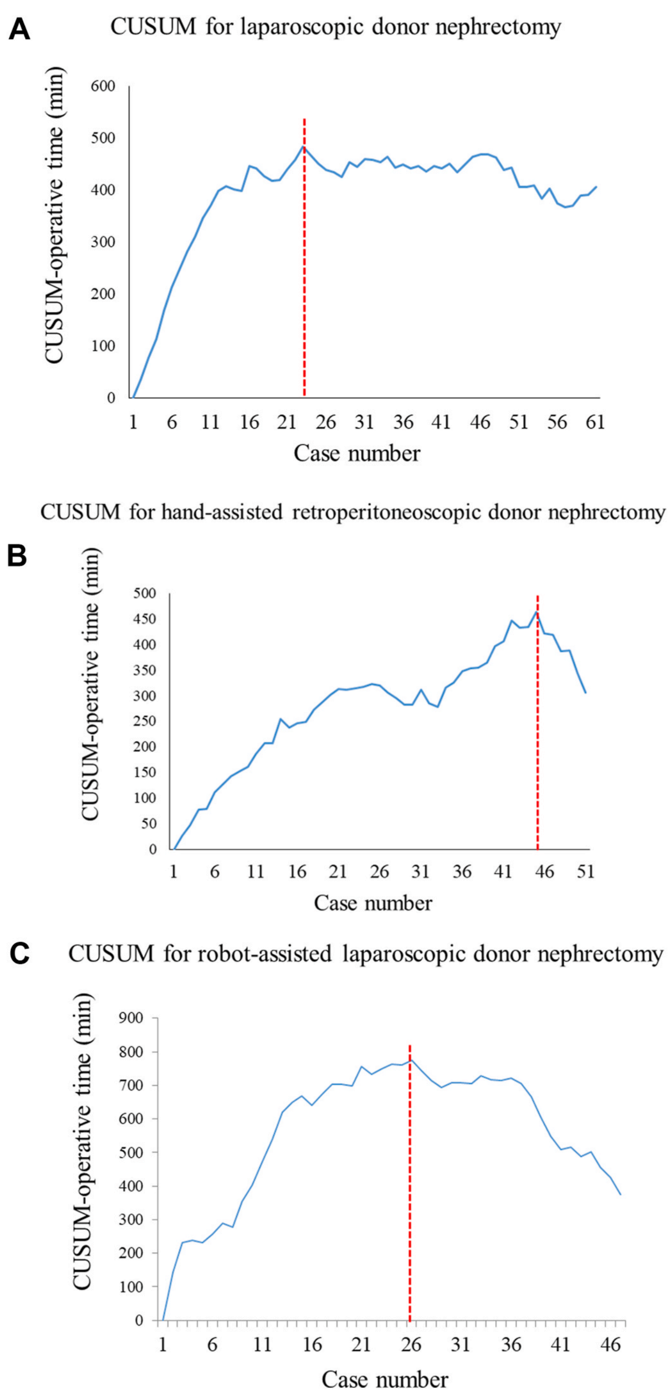

Fig. 2. The cumulative sum (CUSUM) analysis of operative time in minimally invasive donor nephrectomy. (A) Laparoscopic, (B) hand-assisted retroperitoneoscopic, and (C) robot-assisted laparoscopic donor nephrectomy.

3.4. Learning curve in robot-assisted laparoscopic donor nephrectomy

Six surgeons were involved in RADN as operators. Outcomes based on surgeon volumes, classified into five groups, are shown in Table 4: Group 1 (1–10), Group 2 (11–20), Group 3 (21–30), Group 4 (31–40), and Group 5 (41≥). Operative time was longer in Groups 1 and 2. Postoperative outcomes did not differ between the groups.

The CUSUM analysis of operative time in RADN found an increasing trend in the early phase and a period of steady improvement after 26 procedures, as shown in Fig. 2C.

3.5. The CUSUM analysis in minimally invasive donor nephrectomy

The CUSUM analysis of operative time in three different MIDN techniques is summarized in Fig. 3. Different numbers of procedures were required in each technique to reach proficiency: 23 procedures in LDN, 45 procedures in HARP, and 26 procedures in RADN.

4. Discussion

This is the first investigation into the learning curves of three surgical techniques of MIDN in a high-volume center in Europe. The present study is a large retrospective series of 1895 living donors who underwent MIDN that investigates the effect of surgeon volume on outcomes. We evaluated learning curves for three different MIDN techniques, using the CUSUM analysis, to obtain the necessary number for each procedure to improve surgical technique in MIDN.

A systematic review investigating the learning curve in LDN indicated that the learning curve, defined by decreased operative time, averaged 35 cases in LDN [2]. To date, only a few studies have evaluated the learning curve of LDN using the CUSUM analysis. In one study, the CUSUM model for hand-assisted LDN found a flexion point for decreasing operative time in 12 cases [12]. In another study, the CUSUM model demonstrated the initial learning phase of 32 cases in HARP [13]. However, there has been little investigation regarding the learning curve of pure LDN using the CUSUM analysis. Therefore, the present study indicates new findings; although the operative time of HARP was significantly shorter than LDN, a longer learning curve is required to reach proficiency in the HARP method. The longer learning curve for HARP could be influenced by a donor factor such as higher BMI in the HARP group, than a surgeon factor such as surgeons' experiences. In addition, anatomical factors, such as the number of renal arteries and veins, could influence the learning curves in MIDN, as these factors have been reported to predict the difficulty of LDN [20].

There is little evidence so far regarding the learning curve for RADN. A previous study investigating the learning curve of robotic hand-assisted DN has reported that the operative time and complications rate were significantly improved after the first 74 cases and has suggested that the learning curve was more than 100 cases [21]. However, the CUSUM model was not used to evaluate the learning curve of robotic hand-assisted DN in that study. In the present study, the operative time was significantly reduced after the first 26 cases, according to the CUSUM analysis, suggesting that 26 cases were required for the initial learning phase of RADN.

The strength of this study is its large cohort, including 1365 LDN, 427 HARP, and 103 RADN, over a 23-year period. The investigation of the learning curvea for these different techniques is unique, and the CUSUM analysis identified different flexion points in each procedure. Previous studies have reported that hand-assisted DN was easier to learn and can reduce the learning curve compared to LDN [22,23]; however, our CUSUM analysis found strikingly opposite results.

There are many variables associated with clinical outcomes, such as hospital volumes and technical skills. The larger hospital volume at our institution might have had a beneficial effect on the clinical outcomes, as an association of hospital volume with better outcomes has been reported after surgical procedures including LDN [24,25]. In addition, the technical skill of each surgeon would be an important factor for the clinical outcomes after complex surgical procedures [26]; however, the assessment of each surgeon's skill was not possible due to the nature of this retrospective study.

Several limitations in this study should be acknowledged with respect to methodological issues, such as the use of a single center and retrospective data. Therefore, the results might be influenced by an information bias and a selection bias. Selecting donors with a BMI above 30 for HARP introduced a selection bias. We investigated surgeon experience in each procedure performed at our institution; however, the surgeons' levels of experience prior to practicing at our center were not

Table 3
Donor outcomes of 427 patients undergoing hand-assisted retroperitoneoscopic donor nephrectomy.

	Group 1 (1−10)	Group 2 (11–20)	Group 3 (21–30)	Group 4 (31–40)	Group 5 (41–50)	Group 6 (51≥)	P value
No. of DN	114	79	62	40	40	92	
Age (years)	53.4 (44.5–60.9)	54.9 (46.8–64.9)	51.3 (43.3–63.0)	52.8 (41.1–60.0)	56.8 (44.2–62.8)	56.4 (46.7–63.0)	0.18
Gender (Male/Female)	36/78	32/47	33/29	23/17	17/23	48/44	0.021
BMI (kg/m^2)	28.4 (25.2–31.0)	28.4 (25.2–31.6)	26.8 (24.7–31.6)	28.3 (24.4–31.8)	27.8 (26–30.4)	28.7 (26.2–32.5)	0.30
Side of nephrectomy							
Right/Left	14/100	13/66	16/46	2/38	5/35	17/75	0.06
Operative time (minutes)	186 (152–212)	179 (153–212)	158 (138–202)	170 (164–202)	162 (132–188)	131 (108–156)	<0.001
Blood loss (mL)	200 (100–345)	150 (80–365)	170 (100–285)	300 (100–450)	238 (128–350)	150 (50–225)	0.003
Conversion	1 (0.9%)	1 (1.3%)	2 (3.2%)	0	0	2 (2.2%)	0.43
No. of artery							
Single/Multiple	88/26	66/13	50/12	30/10	35/5	72/20	0.62
No. of vein							
Single/Multiple	110/4	72/7	57/5	39/1	39/1	83/9	0.22
Postoperative major complications	1 (0.9%)	0	1 (1.6%)	0	1 (2.5%)	3 (3.3%)	0.35
Length of stay (days)	3 (2–4)	3 (3–4)	3 (2–4)	3 (3–4)	3 (3–4)	3 (3–4)	0.46

DN donor nephrectomy, *BMI*, body mass index.

Table 4
Donor outcomes of 103 patients undergoing robotic-assisted laparoscopic donor nephrectomy.

	Group 1 (1−10)	Group 2 (11–20)	Group 3 (21–30)	Group 4 (31–40)	Group 5 (41≥)	P value
No. of DN	26	20	20	20	17	
Age (years)	56.1 (39.8–62.4)	57.2 (36.0–65.1)	52.2 (37.4–60.8)	53.9 (43.8–64.5)	52.8 (45.8–62.3)	0.86
Gender (Male/Female)	11/15	9/11	9/11	7/13	6/11	0.94
BMI (kg/m^2)	23.6 (21.7–24.7)	23.6 (21.9–25.3)	23.8 (20.3–26.4)	24.7 (22.3–27.2)	26.3 (22.8–28.5)	0.07
Side of nephrectomy						
Right/Left	3/23	1/19	1/19	10/10	5/12	<0.001
Operative time (minutes)	218 (175–257)	223 (168–246)	180 (159–203)	151 (137–194)	140 (127–166)	<0.001
Blood loss (mL)	100 (10–150)	100 (11–175)	50 (13–94)	100 (50–161)	50 (15–175)	0.56
Conversion	1 (3.9%)	2 (10.0%)	1 (5.0%)	0 (0%)	0 (0%)	0.35
No. of artery						
Single/Multiple	20/6	17/3	11/9	16/4	13/4	0.26
No. of vein						
Single/Multiple	24/2	19/1	20/0	19/1	16/1	0.66
Postoperative major complications	0	0	0	0	0	–
Length of stay (days)	3 (3–4)	3 (3–4)	3 (3–4)	3 (2.3–3)	3 (2–3)	0.06

DN donor nephrectomy, *BMI* body mass index.

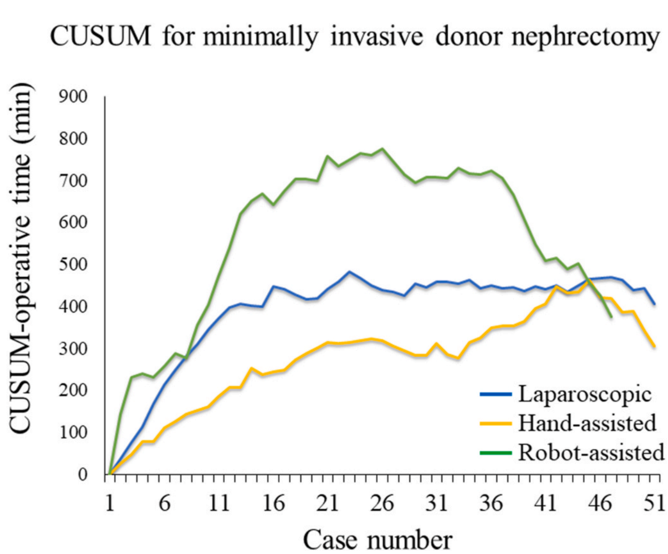

Fig. 3. The cumulative sum (CUSUM) analysis of operative time in minimally invasive donor nephrectomy.

evaluated. Prior experience at other centers could have affected the learning curves in MIDN. In addition, the findings from a high-volume center might not apply to a low-volume center. In our opinions, low-volume centers should confine themselves to one technique and master it, depending on the surgeons' levels of experience. Finally, although we have demonstrated the learning curves in MIDN, a prospective multicenter study should be performed to investigate the learning curves in MIDN.

5. Conclusions

This study investigates the learning curves of LDN, HARP, and RADN using the CUSUM analysis. Analysis has revealed that the learning curves were 23 cases in LDN, 45 cases in HARP, and 26 cases in RADN. The LDN and RADN learning curves are shorter than that of hand-assisted donor nephrectomy. Our observations can aid in informing the development of teaching requirements for fellows being trained in MIDN.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

The database used and/or analyzed during the current study are not publicly available, but can be available from the corresponding author on reasonable request.

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Ethical approval

The approval of the Ethics Committee of the Erasmus MC was obtained (MEC-2019-0373).

Unique Identifying number (UIN)

1. Name of the registry:UMIN-CTR.
2. Unique Identifying number or registration ID:UMIN000041405.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000047271.

Author contribution

Kosei Takagi: Conceptualization, Methodology, Formal Analysis, Investigation, Writing-Original Draft.

Hendrikus J.A.N. Kimenai: Resources, Data Curation, Writing-Review & Editing.

Turkan Terkivatan: Resources, Data Curation, Writing-Review & Editing.

Khe T.C. Tran: Resources, Data Curation, Writing-Review & Editing.

Jan N.M. Ijzermans: Conceptualization, Writing-Review & Editing, Supervision, Project Administration.

Robert C. Minnee: Conceptualization, Methodology, Writing-Review & Editing, Supervision, Project Administration.

Guarantor

Kosei Takagi.

CRediT authorship contribution statement

Kosei Takagi: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Hendrikus J.A.N. Kimenai:** Resources, Data curation, Writing - review & editing. **Turkan Terkivatan:** Resources, Data curation, Writing - review & editing. **Khe T.C. Tran:** Resources, Data curation, Writing - review & editing. **Jan N.M. Ijzermans:** Conceptualization, Writing - review & editing, Supervision, Project administration. **Robert C. Minnee:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, All authors have approved the final version of the article.

Declaration of competing interest

The authors declare that there are no conflicts of interest in this study.

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