Safety and oncological outcomes for large (stage ≥T2b) and locally advanced renal cell carcinoma: comparison between laparoscopic and modified hand-assisted laparoscopic radical nephrectomy

Xudong Guo[1,2], Hanbo Wang[2], Yuzhu Xiang[2], Xunbo Jin[2] and Shaobo Jiang[2] (ORCID)

Abstract

Objective: To compare the operative and oncologic outcomes between hand-assisted laparoscopic radical nephrectomy (HALRN) and laparoscopic radical nephrectomy (LRN) for large (stage ≥T2b) and locally advanced renal cell carcinoma.

Methods: We retrospectively collected data from patients who underwent HALRN or LRN for stage ≥T2b renal cell carcinoma from January 2011 to January 2018 in our institution. The patients' demographics, perioperative parameters, and postoperative follow-up data were compared between the two groups. The survival outcome was estimated using the Kaplan–Meier method.

Results: The HALRN group comprised 78 patients, and the LRN group comprised 63 patients. The median operative duration was significantly shorter in the HALRN than LRN group. The two groups were equivalent in terms of the incision length, blood loss, complication rate, and duration of hospitalization. In the HALRN and LRN groups, the 5-year overall survival rates were 69.4% and 73.1%, the 5-year cancer-specific survival rates were 80.0% and 83.3%, and the 5-year progression-free survival rates were 66.4% and 74.7%, respectively, with no significant differences.

[1]Department of Urology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China
[2]Department of Urology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China

Corresponding author:
Shaobo Jiang, Department of Urology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, No. 9677 East Jingshi Road, Jinan 250014, P. R. China.
Email: jiangshaobo@sdu.edu.cn

Conclusions: Compared with LRN, HALRN may offer a shorter operative duration and equivalent surgical outcomes without sacrificing oncological efficacy. In addition, HALRN has specific advantages for extremely large and complicated renal tumors.

Introduction

Since the first laparoscopic nephrectomy was reported by Clayman et al.[1] in 1991, evidence of the benefits of this procedure has been continually demonstrated, and this surgery has rapidly become a standard approach for renal cell carcinoma (RCC). Hand-assisted laparoscopic radical nephrectomy (HALRN) was first introduced in 1997 with the intention of remedying the shortcomings of LRN, such as a lack of tactile feedback.[2] As a transition procedure from open surgery to pure laparoscopic surgery, HALRN has gained popularity in the early stage of the laparoscopic era. Many studies have revealed equivalent surgical and oncologic outcomes between HALRN and open procedures for RCC.[3,4] However, as surgeons have continued to gain experience, the advantages of tactile feedback and the shorter operative duration of HALRN have been gradually counteracted, especially in the treatment of conventional renal tumors. Nevertheless, for large and locally advanced renal cancer, HALRN still has inherent advantages over LRN.

Numerous studies have compared the surgical outcomes and oncological efficacy between LRN and open radical nephrectomy and between HALRN and open radical nephrectomy in the treatment of stage T2 and T3 RCC.[5–7] However, there have been few direct comparisons between HALRN and LRN for large (stage ≥T2b) and locally advanced renal tumors. This study was performed to report our modified HALRN technique and compare the surgical and oncological outcomes between HALRN and LRN in the treatment of stage ≥T2b RCC.

Patients and methods

This was a nonrandomized, retrospective, single-institution study. All patients who underwent HALRN or LRN at our urology center with a pathological diagnosis of stage T2b, T3a, or T4 RCC from January 2011 to January 2018 were enrolled in this study. We retrospectively analyzed the patients' characteristics (sex, age, body mass index (BMI), tumor size, tumor stage, and tumor grade) and perioperative parameters (operative duration, blood loss, incision length, complication rate, and duration of hospitalization). Postoperative complications were recorded using the Clavien–Dindo classification.[8] This study adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants. This study was approved by the local ethics committee of Shandong Provincial Hospital (ID SWYX: No. 2020-141, approved 22 March 2020). Information such as patient names, medical

record numbers, national identity numbers, and contact information was de-identified in this study.

Before the operation, all patients underwent enhanced abdominal computed tomography (CT) with three-dimensional reconstruction to observe the size, shape, boundary, and location of the renal tumors. Patients with distant metastases or tumor emboli that extended into the inferior vena cava as demonstrated by the preoperative examinations were excluded from this study. Patients with a known history of renal inflammatory disease or abdominal surgery were not excluded but were more likely to be assigned to the HALRN group.

The operations were performed by two surgeons with extensive experience in both HALRN and LRN, and all operations were performed via a transperitoneal approach. The decision regarding the surgical approach (HALRN or LRN) was made preoperatively according to the patient's condition, the characteristics of the tumor, and the surgeon's experience-based judgment on the feasibility of the technique. Lymphadenectomy was performed only when the preoperative imaging examination or intraoperative exploration led the surgeon to suspect lymph node enlargement. Adrenalectomy was performed when the tumors were located at the upper pole of the kidney or when adrenal involvement was suspected.

We modified the positions of the hand port site and trocar sites to facilitate the operation. The patient was placed in the lateral jackknife position with sufficient padding for the brachial plexus, knees, and ankles. The operating bed was flexed to an angle of 60° to achieve optimal exposure. For right-sided HALRN, a 7-cm paraomphalic vertical incision was made lateral to the rectus abdominis muscle for placement of the hand-assist device. A 12-mm trocar was then inserted inferior to the costal margin at the midclavicular line, a

second 12-mm trocar was inserted inferior to the first trocar beside the rectus abdominis, and an extra 5-mm trocar was inserted immediately under the xiphoid for the liver retractor when adrenalectomy was necessary. For left-sided HALRN, an oblique hand port incision was made one finger-breadth inferior to the costal margin, and two 12-mm trocars were then inserted at the anterior axillary line and lateral border of the rectus muscle at the level of the umbilicus (Figure 1). The surgical procedure was performed in accordance with previously reported standard steps.[7] In the LRN group, the laparoscopic procedures and trocar positions were consistent with the previously described standard transperitoneal approach.[9] At the end of the procedure, the specimen was completely removed with a laparoscopic specimen bag via the hand-assist device incision or through the extended subcostal port site in the LRN group.

TNM staging was based on the 8th TNM classification of the American Joint Committee on Cancer (2017 version), and the nuclear grade of the tumor was determined by the Fuhrman classification system.[10,11] Follow-up was performed 1, 3, 6, and 12 months after surgery; every 6 months for 5 years; and then annually thereafter. The assessments included physical examination, blood biochemical examination, ultrasonography, abdominal CT, and chest CT. Other examinations were individualized if necessary. Survival data were mainly obtained from the electronic records of our institution or telephone follow-up. Overall survival (OS) was defined as the time from surgery to death of any cause. Cancer-specific survival (CSS) was defined as the time from surgery to death directly resulting from RCC. Progression-free survival (PFS) was defined as the time from surgery to identification of local recurrence or distant metastases with radiographic evidence.
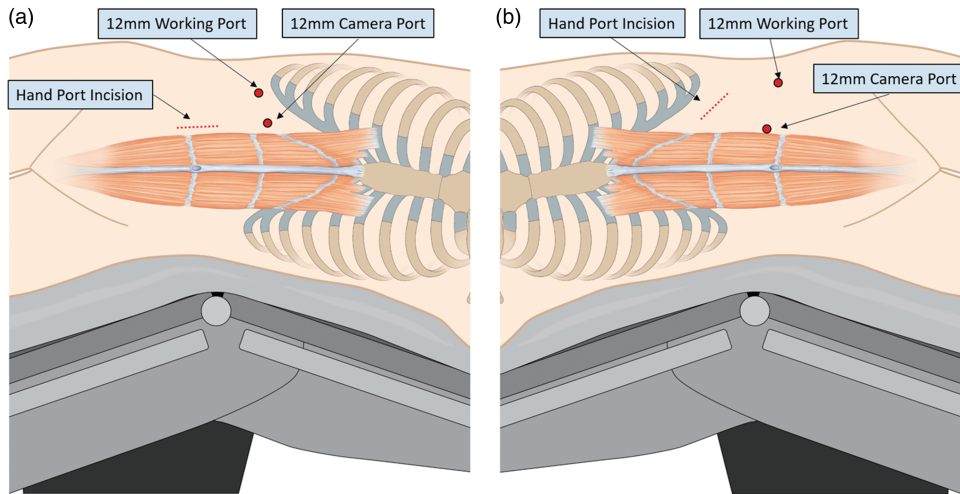
Figure 1. Hand port placement and trocar sites for hand-assisted laparoscopic radical nephrectomy (right-handed surgeon). (a) Right renal cell carcinoma and (b) Left renal cell carcinoma.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were compared between groups using the unpaired t-test (normally distributed data) or Mann–Whitney U test (non-normally distributed data). Categorical variables were analyzed using the chi-square test or Fisher's exact test. Survival curves (OS, CSS, and PFS) were estimated using the Kaplan–Meier method, and survival distributions were compared using the log rank test. A P value of <0.05 was considered statistically significant.

Results

In total, 141 patients were included in this study (HALRN group, n = 78; LRN group, n = 63). The patient's demographics and histological results are summarized in Table 1. There were no significant differences in age, sex, or BMI between the two groups. The median operative time was significantly shorter in the HALRN group than in the LRN group (96 vs. 126 minutes,

respectively; $P < 0.01$). The median incision length for specimen retrieval was comparable between the HALRN group and LRN group. The two groups also showed an equivalent blood loss, duration of hospitalization, and complication rate. When considering subgroups by pathologic T stage (T2b vs. T3a/T4 subgroups), none of the perioperative parameters differed between the subgroups with the exception of the operative time $(P < 0.01)$. No patients in either group underwent conversion to open surgery. However, two patients in the LRN group underwent conversion from laparoscopic surgery to hand-assisted laparoscopic surgery because of failure to progress: one patient with a stage T3a tumor underwent conversion because of dense adhesions between the tumor and the colon, and one patient with a stage T4 tumor underwent conversion because of tumor invasion of the liver. Thirty-one (39.7%) patients in the HALRN group and 29 (46.0%) patients in the LRN group underwent combined adrenalectomy. Lymphadenectomy was performed in seven (9.0%) patients in the HALRN group and

Table 1. Patient and tumor characteristics.

Variable	HALRN (n = 78)	LRN (n = 63)	P
Patient characteristics			
Sex			
Male	47 (60.3)	36 (57.1)	0.71
Female	31 (39.7)	27 (42.9)	
Age, years	61.5 (42–78)	61 (45–76)	0.67
BMI, kg/m^2	24.84 (18.29–31.42)	23.62 (18.17–31.92)	0.43*
Tumor characteristics			
Laterality			
Right	40 (51.3)	27 (42.9)	0.32
Left	38 (48.7)	36 (57.1)	
Tumor size, cm	12 (5.8–19)	11.5 (5.5–16)	0.48
Pathological stage			
pT2b	38 (48.7)	33 (52.4)	0.86
pT3a	35 (44.9)	27 (42.9)	
pT4	5 (6.4)	3 (4.8)	
Tumor grade			
1	5 (6.4)	4 (6.3)	0.80
2	35 (44.9)	27 (42.9)	
3	33 (42.3)	25 (39.7)	
4	5 (6.4)	7 (11.1)	
Tumor histology			
Clear cell	67 (85.9)	56 (88.9)	0.60
Other	11 (14.1)	7 (11.1)	

Data are presented as n (%) or median (range).
HALRN, hand-assisted laparoscopic radical nephrectomy; LRN, laparoscopic radical nephrectomy; BMI, body mass index
*Mann–Whitney U test.

five (7.9%) patients in the LRN group. Table 2 shows the operative and postoperative outcomes.

The pathologic T stage and Fuhrman's nuclear grade were not significantly different between the HALRN and LRN groups. Among the 62 patients with stage T3a tumors, the HALRN group contained 24 patients with microscopic perinephric and/ or perihilar fat invasion and 11 patients with a segmental or main renal vein tumor thrombus, while the LRN group contained 19 and 8 patients with each, respectively. Among the patients with stage T4 tumors, the HALRN group contained three patients with adrenal invasion and two patients with psoas major muscle invasion, while the LRN group contained two patients with adrenal invasion and one patient with hepatic invasion. No positive surgical margins were reported.

The median follow-up duration was 49 months in the HALRN group and 52 months in the LRN group. By the end of the follow-up period, 23 (29.49%) patients in the HALRN group and 15 (23.81%) patients in the LRN group had developed local recurrence or distant metastasis. Most of the patients with metastasis received immunotherapy or targeted therapy. There was no statistically significant difference in terms of metastases between the two groups. During the follow-up period, 13 (16.7%) patients died of cancer-related

Table 2. Operative and postoperative outcomes.

Variable	Total			T2b			T3/T4		
	HALRN (n = 78)	LRN (n = 63)	P	HALRN (n = 38)	LRN (n = 33)	P	HALRN (n = 40)	LRN (n = 30)	P
Operative characteristics									
Conversions	0	2[a]	0.20*	0	0		0	2[a]	0.18*
Estimated blood loss, mL	80 (20–1200)	76 (20–1500)	0.72†	100 (20–800)	60 (20–300)	0.199†	80 (50–1200)	110 (20–1500)	0.091†
Operation duration, minutes	96 (68–196)	126 (95–185)	<0.01†	90 (68–196)	125 (98–175)	<0.01†	101 (70–185)	128.5 (90–185)	<0.01†
Incision length, cm	7 (7–11)	7 (5–12)	0.74†	7 (7–11)	8 (6–12)	0.171†	7 (7–10)	6.5 (5–11)	0.293†
Blood transfusion	7 (9.0)	5 (7.9)	0.83	4 (10.5)	2 (6.1)	0.500	3 (7.5)	3 (10.0)	0.712
Postoperative characteristics									
Postoperative complications									
No complications	54 (69.2)	45 (71.4)	0.96	26 (68.4)	24 (72.7)	0.817	28 (70.0)	21 (70.0)	0.956
Clavien grade I	13 (16.7)	11 (17.5)		6 (15.8)	5 (15.1)		7 (17.5)	6 (20.0)	
Clavien grade II	9 (11.5)	6 (9.5)		5 (13.2)	4 (12.1)		4 (10.0)	2 (6.7)	
Clavien grade IIIa	2 (2.6)	1 (1.6)		1 (2.6)	0 (0.0)		1 (2.5)	1 (3.3)	
Clavien grade IIIb	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Clavien grade IVa	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Clavien grade IVb	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Clavien grade V (death)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Length of postoperative stay, days	6 (5–10)	6 (5–11)	0.33†	6 (5–8)	6 (5–9)	0.856†	6 (6–10)	6.5 (6–11)	0.321†
Length of follow-up, years	49 (15–110)	52 (23–98)	0.95†	53.5 (21–110)	52 (24–98)	0.691†	46.5 (15–91)	51 (24–87)	0.444†

Data are presented as n, n (%), or median (range).

HALRN, hand-assisted laparoscopic radical nephrectomy; LRN, laparoscopic radical nephrectomy.

*Fisher's exact test.

†Mann–Whitney U test.

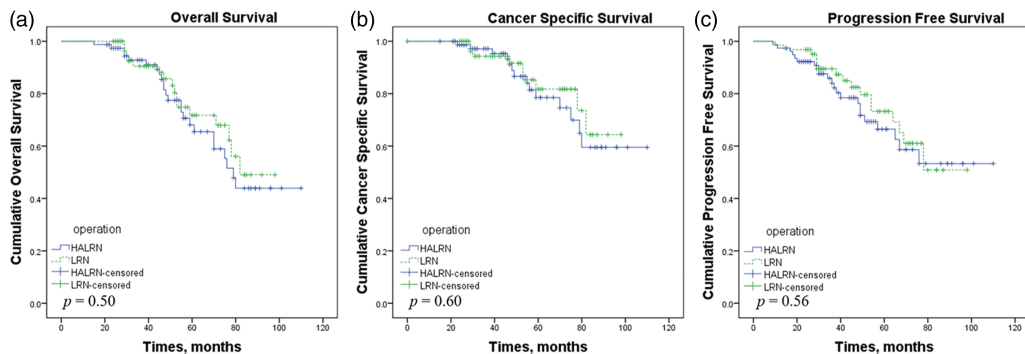[a]Two patients underwent conversion from laparoscopy to hand-assisted laparoscopy.

Figure 2. Kaplan–Meier analysis of (a) overall survival, (b) cancer-specific survival, and (c) progression-free survival according to surgery type among all patients.

diseases and 10 (12.8%) died of other diseases in the HALRN group, while 8 (12.7%) patients died of cancer-related diseases and 7 (11.1%) died of other diseases in the LRN group. There were no statistically significant differences in OS, CSS, or PFS between the HALRN and LRN groups (Figure 2). In the HALRN and LRN groups, the 5-year OS rates were 69.4% and 73.1%, the 5-year CSS rates were 80.0% and 83.3%, and the 5-year PFS rates were 66.4% and 74.7%, respectively. Furthermore, when the patients were stratified by pathologic T stage into T2b and T3a/T4 subgroups, neither subgroup showed appreciably different survival results (OS, CSS, and PFS) between the HALRN and LRN groups (Figures 3 and 4).

Discussion

HALRN still has inherent advantages for large tumors and complicated conditions. Some investigators consider HALRN to be the optimal technique for large tumors.[12] In patients with larger tumors, the working space is limited, which may restrict the dissection of the upper and dorsal part of the kidney during LRN. The excessive bulk and weight of the tumor may affect exposure of the renal pedicle. These limitations usually result in longer operating times and other technical difficulties. HALRN allows the surgeon to use his or her intra-abdominal hand to gain tactile sense, perform blunt dissection, and retract surrounding structures, making it easier to dissect the renal pedicle and upper and dorsal part of the kidney.[3] Additionally, for patients with a known history of renal inflammatory disease or abdominal surgery, extensive adhesions or close proximity between the renal mass and local structures is expected. The intra-abdominal hand enhances maneuverability for retraction and dissection, allowing for safer lysis of stony or hard bowel adhesions.

We modified the positions of the hand port site and trocar sites to facilitate the operation. The right-hand port site was lateral to the rectus abdominis at the level of the umbilicus, and the left-hand port site was inferior to the costal margin. The overall position of the hand port incision was higher than that of conventional HALRN. The aim of this modification was to allow the intra-abdominal hand to be closer to the renal hilum, increase renal vascular control, and facilitate management of the upper pole of the kidney. We preferred to use a subcostal incision for the hand port device in left HALRN and for specimen removal in LRN because the incidence of incisional
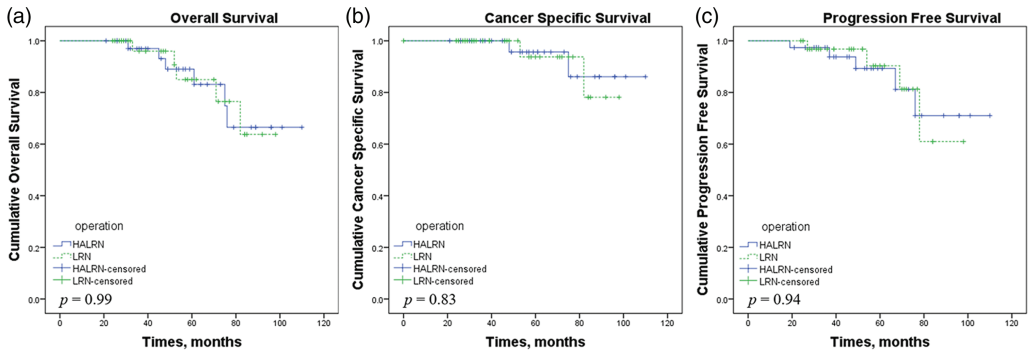
Figure 3. Kaplan–Meier analysis for patients with stage T2b cancer according to surgery type. (a) Overall survival. (b) Cancer-specific survival. (c) Progression-free survival.
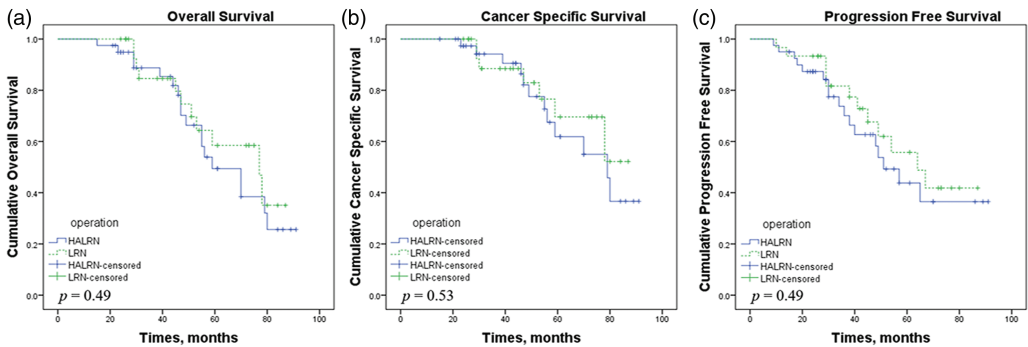

Figure 4. Kaplan–Meier analysis for patients with stage T3/T4 cancer according to surgery type. (a) Overall survival. (b) Cancer-specific survival. (c) Progression-free survival.

hernia is expected to be much lower with a subcostal incision than with a midline incision or Gibson incision. Additionally, an upper abdominal incision is easier to hide and thus achieves better cosmetic effects, especially for young women. Although patients with this incision were expected to experience more pain, the length of hospitalization was not significantly extended in previous studies.[13] In the present study, we found no significant difference in the length of hospitalization between the two groups.

The shorter operative time is the main advantage of HALRN over LRN and has been shown in previous studies.[3,14] In our study, the operative time was significantly shorter in the HALRN group than in the LRN group. A possible reason is that with the HALRN approach, blunt dissection was extensively employed throughout the procedure, which allowed for accurate identification of anatomical landmarks and rapid separation. Rapid management of the renal pedicle is another reason for the shorter operating time. For patients without tumor thrombi or suspicious renal hilar lymph nodes, the renal pedicle can be directly controlled by the inner hand and ligated en bloc with staples to avoid a sophisticated dissection of the hilar vessels and its related complications. These advantages also render HALRN a good alternative option for pregnant patients.[15] Domján et al.[16] considered HALRN to be the

preferred method during pregnancy. The hand port incision could avoid injury to the enlarged pregnant uterus by insertion of Veress needles. In addition, the hand in the abdomen might accelerate manipulations, thus shortening the time of increased abdominal pressure and anesthesia.

The authors of previous studies have often considered that the longer incision for HALRN than for LRN led to more abdominal pain and delayed postoperative recovery. In a prospective comparative study by Venkatesh et al.,[17] the HALRN incision was significantly longer than the LRN extraction incision (7.75 vs. 6.18 cm, respectively; $P < 0.05$). Notably, however, the tumor size was generally small in their study (mean size of 5.7 cm in the LRN group and 5.4 cm in the HALRN group). In the present study, both groups had similar incision lengths because of the large tumor sizes. Furthermore, HALRN may be associated with more blood loss, a higher complication rate, and a longer hospital stay than LRN. In reality, a number of studies have dispelled these viewpoints.[18] Our study showed equivalent results in terms of blood loss, complication rates, and hospital stays between HALRN and LRN.

In patients with large or locally advanced renal tumors, conversion to open surgery is usually performed because of serious intraoperative complications or technical difficulties. In particular, gaining control of tumor thrombi within the renal vein is still challenging in laparoscopic surgery. In one laparoscopic series, 50% of the patients required conversion to HALRN, and 16% required conversion to open surgery even with the assistance of intraoperative ultrasound monitoring.[19] In our experience, we usually use the inner hand to help identify the distal margin of the tumor thrombus and maneuver the thrombus back before applying vascular clips or endoscopic stapling devices. No patients in either group

of the present study underwent conversion to open surgery. However, two patients in the LRN group underwent conversion from laparoscopic to hand-assisted laparoscopic surgery because of dense adhesions attaching the tumor to the colon and liver. Previous studies have shown that in complex cases, LRN is more frequently converted to open surgery than is HALRN.[20,21] Thus, based on past experience, our recommended indications for HALRN are a tumor size of ≥ 10 cm, BMI of ≥ 30 kg/m^2, a renal vein tumor thrombus that extends to the junction of the inferior vena cava, adjacent organ invasion, and a history of renal inflammatory disease or abdominal surgery.

Many cohorts have demonstrated that the oncologic outcomes of HALRN are equivalent to those of LRN for localized RCC. Kawauchi et al.[5] retrospectively compared the oncologic outcomes of HALRN and LRN for stage T1 and T2 RCC and found no difference in the 5-year disease-free survival rate (92% vs. 91%) or CSS rate (92% vs. 94%) during a mean follow-up period of 41 and 75 months, respectively. In addition, several studies have revealed equivalent oncologic outcomes between LRN and open radical nephrectomy for large and stage T3 RCCs.[6,22] This is the first direct comparison of HALRN and LRN for large (stage $\geq$ T2b) and locally advanced renal tumors. In the current study, we found no statistically significant difference in OS, CSS, or PFS between the HALRN and LRN groups.

This study has several limitations. The major limitation is the nonrandomized, retrospective, single-institution study design. Additionally, the selection criteria for the type of surgery were not explicit and were mainly determined by the patient's condition and surgeon's preference. Furthermore, we only evaluated the outcomes of pathologically staged T2b, T3a and T4 RCC rather than clinically staged

disease. Finally, mild selection bias was present between the HALRN and LRN groups. Patients with a larger tumor size, larger tumor thrombi, and a history of renal inflammatory disease or abdominal surgery were more likely to be assigned to the HALRN group. Therefore, further randomized studies with larger sample sizes are needed to confirm the current findings. Nevertheless, compared with LRN, HALRN still had a shorter operation time and equivalent surgical outcomes.

Conclusion

Our study has revealed that HALRN is technically safe, feasible, and effective for large (stage $\geq$T2b) and locally advanced renal tumors. Compared with LRN, HALRN may offer a shorter operation time and equivalent incision length, blood loss, and duration of hospitalization without sacrificing oncological outcomes. In addition, HALRN has advantages when the tumor is very large, the situation is extremely complicated, or the patient's medical comorbidities demand a rapid procedure, and to a certain extent, HALRN may avoid unnecessary conversion to open surgery.

ORCID iD

Shaobo Jiang [iD] https://orcid.org/0000-0002-2389-4751

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