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*Research Article*

# Laparoscopic *versus* open radical nephrectomy in T2 renal cell carcinoma: A randomized control trial

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**Background: Laparoscopic Radical Nephrectomy (LRN) is the standard for treating patients with T1 Renal Cell Carcinoma (RCC) who are not candidates for nephron-sparing surgery. However, LRN is still considered controversial in patients with T2 tumors. The aim of the study was to compare the surgical and oncologic outcomes of LRN *vs* Open Radical Nephrectomy (ORN) in T2 RCC.**

**Material and Methods: Herein, 56 T2 patients with RCC were prospectively randomized to LRN or conventional ORN. The operative time, blood loss, perioperative complications, duration of hospital stay, postoperative pain score and duration, analgesic consumption, and short-term oncologic results were carefully reported.**

**Results: Demographic data including age, gender, weight, height and BMI were similar for both arms with p values=0.251, 0.769, 0.645, 0.382 and 0.336 respectively. The LRN group had less median operative blood loss (190 *vs* 500 ml, P=0.001), similar median operative time (150 min for ORN *vs* 180 min for LRN, p=0.102), similar time to start oral feeding (p=0.198) and lower postoperative pain score (3 *vs* 4.5, p=0.015). The median hospital stays were not statistically significant when comparing the ORN *vs* LRN (3 *vs* 2 days respectively, p=0.073), with no differences in perioperative morbidity rate (p=0.193). The Overall Survival (OS) was similar in both arms, 1 and 2 years OS for ORN and LRN was 77.3 %, 69% *vs* 87.6% and 74.1% respectively, p=0.615. Prognostic factors influencing the OS and LRFS showed that lymph node metastasis, medical comorbidities, amount of intraoperative blood loss, and age at presentation were independent prognostic factors.**

**Conclusion: LRN was superior in decreasing blood loss and postoperative pain while yielding similar oncologic outcomes.**

**Keywords:** Laparoscopic radical nephrectomy, open radical nephrectomy, minimal invasive surgery, renal cell carcinoma.

**List of abbreviations:** BMI: Body Mass Index; COVID: Corona Virus Disease; CT: Comuted Tomography; DFS: Disease Free Survival; LRN: Laparoscopic Radical Nephrectomy; ORN: Open Radical Nephrectomy;OS: Overall Survival; RN: Radical Nephrectomy; RCC: Renal Cell Carcinoma.

## INTRODUCTION

Surgery remains essential for patients with radio and chemo-resistant Renal Cell Carcinoma (RCC) (Robson, et al., 2017). Radical Nephrectomy (RN) remains the standard approach for treating unilateral RCC with a functionally normal contralateral kidney. The first report of LRN for a small renal mass was published in 1991 (Clayman, et al., 1991). Initially, LRN was reserved for small renal tumors (T1); however, it has now been extended to larger tumors (Conley, et al., 2009). The

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aim of LRN is still to follow the oncologic principles of Open Radical Nephrectomy (ORN), including removal of the kidney surrounded by the perinephric fat and enveloping Gerota's fascia, with or without performing adrenalectomy. However, LRN for larger (T2) renal masses has been reported in few retrospective and observational studies (Portis, et al., 2002, Lee, et al., 2018 and Dursun, et al., 2002). The advantages of LRN over ORN for T2 RCC were described in retrospective studies, which reported reduced blood loss, less postoperative pain, and shorter hospital stay. However, laparoscopic mobilization of large-sized tumors remains challenging.

The aim of the study was to compare the surgical and oncologic outcomes of LRN *vs* ORN in T2 RCC and hence, the current study was designed as a prospective Randomized Controlled Trial (RCT) to avoid selection or observer bias.

## MATERIALS AND METHODS

A randomized controlled phase II trial was designed, having a total sample size of 56 patients. The trial included patients from a single cancer institute, with radiologically detected T2 renal tumors who are candidates for surgical intervention.

All patients underwent preoperative workup, including complete blood count, comprehensive metabolic panel, and coagulation profile. Preoperative radiological assessment of the tumor using Computed Tomography (CT), with contrast and metastatic workup in the form of CT chest, was done for all patients. The aim of the study was explained to the patient before randomization. The patient signed informed consent. For both arms, the surgical procedure and possible complications were noted. All patients received perioperative second-generation intravenous cephalosporin antibiotic prophylaxis. Postoperatively, a thrombo-prophylaxis protocol was adopted for all patients until they were discharged.

All operations were performed by the same surgical team lead by one fully trained surgeon, with experience in both open and laparoscopic surgeries. LRN was performed using a trans-peritoneal approach. Under the vision, a standard four-port technique was used after the insufflation and introduction of the Visi Port™ trocar (Covidien, Dublin, Ireland). ORN was performed by a standard subcostal incision using a standard approach. The total operative time (from skin incision to skin closure) and blood loss were calculated and documented for each patient in the study.

### Postoperative management

All patients received a paracetamol injection thrice a day for 24 hr or longer, depending on their needs. The pain was assessed on day 0 postoperatively, using a scale of 0-10, where 10 was considered the worst. Intraoperative and postoperative complications, hospital stay, and time to initiate oral feeding were recorded in a prospective electronic database. Histopathological examination, histological type of tumor, grade, and margin status were also recorded. Patients were followed up regularly according to the Egyptian NCI RCC follow-up protocol every 3 months for 2 years by physical examination and CT scan, then every 6 months thereafter or whenever indicated by clinical suspicion of recurrence or metastasis.

### Basis of sample size estimation and randomization technique

Sample size estimation was performed by G power (Faul, et al., 2007). A sample size of 56 (28 per group) is sufficient to detect a power of 80% and a significance level of 5%. Randomization using computer-generated numbers was concealed using the sequentially numbered, sealed opaque envelop technique. After randomization, the surgical approach was unconcealed for both the treatment team and patients enrolled in the study.

### Statistical analysis

Data were analyzed using IBM SPSS advanced statistics (Statistical Package for Social Sciences), version 23 (SPSS Inc., Chicago, IL). Numerical data were described as mean and standard deviation or median, interquartile range, or range, as appropriate. Numeric data were also explored for normality using the Kolmogrov-Smirnov test.

Comparisons between the 2 groups for normally distributed numeric variables were performed using the Student t-test and non-normally distributed numeric variables. The Mann-Whitney test tested comparisons between the two groups. The appropriate Chi-square or Fisher's exact test was used to examine the relation between qualitative variables. Kaplan-Meier curves were used to assess the survival curve. The Log-rank test was performed to compare survival curves. The multivariate Cox regression hazard model was used to indicate the independent prognostic factors using a stepwise model. Overall survival time was calculated from the day of patient registration to the date of death or the time of data analysis. Event-free survival time was calculated from the date of registration to the date of the first relapse, either local or systemic. P-value $\leq 0.05$ was considered significant, and all tests are two-tailed.

## RESULTS

The study included 56 patients randomized to 2 arms, with 28 patients each as shown in Figure 1. Both arms had no difference in patient demographics, comorbidities, tumor laterality nor history of surgeries as shown in Table 1. Preoperative imaging for all randomized patients showed a T2 renal mass. T2 RCC was diagnosis on postoperative pathological assessment in 89% of cases in the ORN arm (one patient downstaged to T1, two upstaged to T3) compared to 64% in the LRN arm (4 patients downstaged to T1 and two patients upstaged to T3). Among both arms, the maximum number of positive LN retrieved was 11/11. There was no statistical differences in the number of LNs retrieved (p=0.478) or the number of positive LNs (p=0.078) among both arms. The pathological maximum tumor diameter, T stage, N stage, or pathological subtype showed no statistically significant differences between the two randomized groups (p=0.789, 0.26, 0.252, 0.599 respectively). In both groups, adrenal-sparing nephrectomies were performed in patients without suspicion of involvement of the adrenal gland. The rate of adrenal preservation was 60.7% and 85.7% in the open and laparoscopic nephrectomy arms, respectively. This difference was statistically significant (p=0.035). There was no evidence of pathological adrenal gland involvement in any of the patients who had non-adrenal preserving nephrectomies.

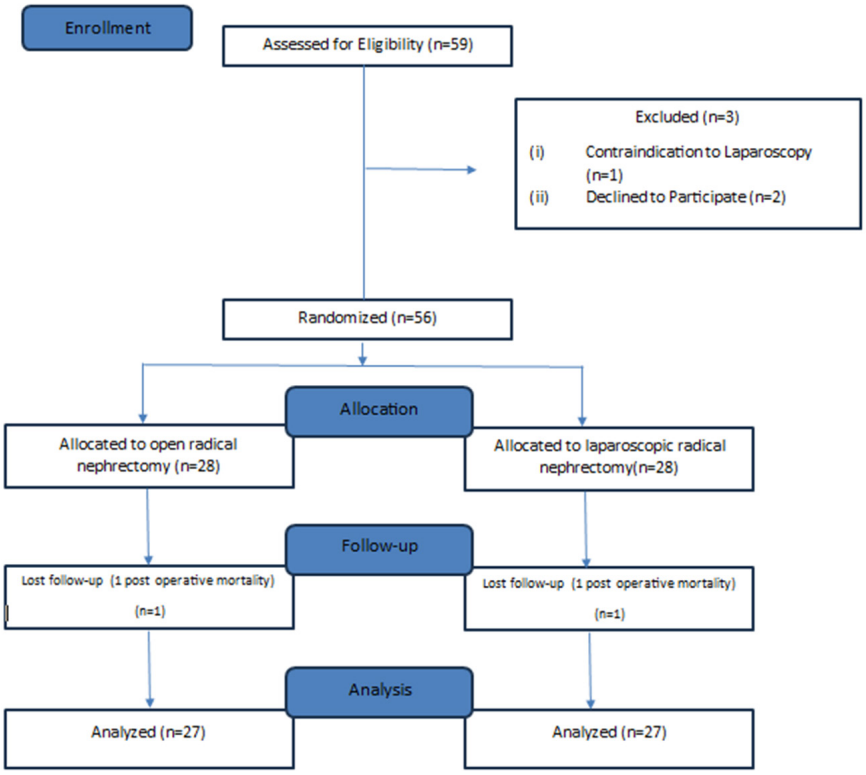


**Figure 1.** Analysis and diagnosis of renal cell carcinoma with two different surgical methods.

**Table 1.** Demographic characteristics of patients of the 2 randomized arms.

| Variable | All Patients | LRN | ORN | P |
|---|---|---|---|---|
| Age | 51.7 ± 15.7 | 49.0 ± 16.4 | 54.3 ± 14.2 | 0.251 |
| **Gender** | | | | |
| Male/ female | 29/27 | 14/14 | 15/13 | 0.769 |
| Weight | 87.9 ± 16.5 | 89.2 ± 17.0 | 86.6 ± 15.7 | 0.645 |
| Height | 156.5 ± 8.4 | 151.0 ± 7.1 | 160.3 ± 8.7 | 0.382 |
| BMI | 30.7 ± 6.1 | 31.6 ± 6.4 | 29.8 ± 5.4 | 0.336 |
| **Symptoms** | | | | |
| Asymptomatic | 16 (28.6%) | 7 (25%) | 9 (32.1%) | 0.554 |
| Symptomatic | 40 (71.4%) | 21 (75%) | 19 (67.9%) | |
| **Comorbidity** | | | | |
| No | 26 (46.4%) | 15 (53.6%) | 11 (39.3%) | 0.174 |
| Yes | 30 (53.6%) | 13 (46.4%) | 17 (60.7) | |
| **Laterality** | | | | |
| Right | 23 (41.1%) | 9 (32.1%) | 14 (59.0%) | 0.131 |
| Left | 33 (58.9%) | 19 (67.9%) | 14 (50.0%) | |
| **Past history of abdominal surgery** | | | | |
| No | 41 (73.2%) | 23 (82.1%) | 18 (64.3%) | 0.131 |
| Yes | 15 (26.8%) | 5 (17.9%) | 10 (35.7%) | |

The median total operative time in the ORN arm was 150 min (75-330 min). The median operative time for LRN was 180 min (range 75-420 min). This difference was not statistically significant (p=0.102). Intraoperative blood loss was significantly lower in the LRN *vs* ORN, having a median blood loss of 190 ml (range 30-2000 ml) *vs*. 500 ml (range 80-2500 ml) (p<0.001). The difference in blood transfusions was not statistically significant between both arms (p=0.352). Patients in the ORN arm started oral intake after a median of 1 day. In contrast, patients undergoing LRN started their oral feeding after median of 0 days (p=0.198).

The median postoperative pain scores recorded on the night of day 0 postoperatively were 4.5 and 3 in the ORN and LRN arms, respectively. The difference in postoperative pain scores was statistically significant (p=0.015). In the LRN arm, narcotics were used in only 7.4 % compared to 29.6% in the ORN. This difference was statistically significant (p=0.036). The median postoperative hospital stay for ORN patients was 3 days (range 2-10), while the LRN patients stayed between 1 and 4 days, with a lower median stay of 2 days (p=0.073). One patient in the ORN arm (3.6%) had an immediate postoperative complication (severe bronchospasm due to a post-COVID hyperactive airway). On the contrary, 17.9% of LRN had complications that included 14.3% conversion rate, and 3.6% (1patient) had ventricular tachycardia controlled by direct current shock. Converted patients were included in the LRN arm, as analysis of patients was done by intention to treat analysis. Out of 4 patients who were converted to ORN, 3 were due to marked bleeding and 1 due to large tumor size, limiting the progress with the laparoscopic sitting. One of the four converted cases immediately died postoperatively due to a massive myocardial infarction. One patient had postoperative adrenal vein bleeding, and another developed a mild wound infection. Both were delt with conservatively. No statistically significant difference was detected between both arms (p=0.193).The median follow-up time was 10.2 months. The 1 and 2-year OS were 77.6% and 69.0%, respectively, in the ORN arm compared to 87.6% and 74.1% for the LRN arm, with statistically insignificant differences (p=0.615). The presence of medical comorbidities, lymph node affection, and intraoperative blood loss were the only factors with significant prognostic impact on OS (p=0.002, 0.024, and 0.002, respectively). The LRFS were calculated in 54 patients (27 in each group (excluding the immediate postoperative mortality). There was no difference between the open and laparoscopy group in the LRFS in 1 and 2 years (p=0.529). The pathological N stage and the adrenal preservation were the only statistically significant factors affecting recurrence, with a p-value of 0.001 and 0.043, respectively. No distant metastasis was found in the study till the time of reporting, hense the LRFS was equal to Disease-Free Survival (DFS) as shown in Table 2.

**Table 2.** Univariate analysis of prognostic factors for RCC patients.

| **Variable** | **1-year OS (%)** | **2-year OS (%)** | **P** | **1-year LRFS (%)** | **2-year LRFS (%)** | **P** |
|---|---|---|---|---|---|---|
| Whole group | 82.6 | 70.8 | --- | 69.2 | 64.5 | --- |
| **Operative type** | | | | | | |
| LRN | 87.6 | 74.1 | 0.615 | 73.4 | 66.8 | 0.529 |
| ORN | 77.6 | 69 | | 65.6 | NR | |
| **Age (years)** | | | | | | |
| ≤ median | 92.9 | 87.1 | 0.389 | 85.7 | 85.7 | 0.001 |
| >median | 64.8 | 38.9 | | 48.2 | NR | |
| **Gender** | | | | | | |
| Male | 79 | 63.8 | 0.388 | 61.7 | 54 | 0.242 |
| Female | 86.4 | 77.8 | | 78.1 | 78.1 | |
| **Symptoms** | | | | | | |
| Asymptomatic | 85.2 | 73.1 | 0.776 | 78.6 | 78.6 | 0.215 |
| Symptomatic | 81.7 | 69.6 | | 64.5 | 57.4 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Comorbidity** | | | | | | |
| No | 100 | 91.7 | 0.002 | 79.3 | 79.3 | 0.068 |
| Yes | 66.8 | 50.1 | | 62.4 | 52.6 | |
| **Previous abdominal surgery** | | | | | | |
| No | 79.7 | 70 | 0.601 | 71.8 | 66.7 | 0.773 |
| Yes | 90.9 | 72.7 | | 61.1 | NR | |
| **Body Mass Index (BMI)** | | | | | | |
| ≤ 25 | 71.4 | NR | 0.778 | NR | NR | 0.031 |
| >25 | 79.7 | 64.4 | | 65.7 | NR | |
| **Maximum tumor size (cm)** | | | | | | |
| ≤ median | 86.4 | 86.4 | 0.082 | 81.9 | 81.9 | 0.267 |
| >median | 79.1 | 52.7 | | 56.2 | 46.9 | |
| **Laterality** | | | | | | |
| Right | 95.2 | 85.7 | 0.102 | 95.2 | NR | 0.063 |
| Left | 75.2 | 60.8 | | 52.7 | 52.7 | |
| **Total operative time** | | | | | | |
| ≤ median | 92.1 | 78.4 | 0.09 | 75.4 | NR | 0.337 |
| >median | 69.9 | 59.9 | | 58.8 | 58.8 | |
| **Blood loss** | | | | | | |
| ≤ median | 95 | 88.2 | 0.002 | 85.2 | NR | 0.008 |
| >median | 65.7 | 47 | | 48.5 | 38.8 | |
| **Intraoperative complications** | | | | | | |
| No | 85.1 | 72.3 | 0.248 | 75.8 | 70.8 | 0.016 |
| Yes | 62.5 | 0 | | NR | NR | |
| **Postoperative pain score** | | | | | | |
| ≤ median | 91.2 | 78.6 | 0.171 | 77.9 | 71.4 | 0.169 |
| >median | 78.2 | 65.2 | | 46.7 | 46.7 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Drain amount** | | | | | | |
| ≤ median | 92 | 79.3 | 0.218 | 78.3 | 78.3 | 0.018 |
| >median | 76 | NR | | 53.8 | 43.1 | |
| **Hospital stay (days)** | | | | | | |
| ≤ median | 79.5 | 70.4 | 0.315 | 69.8 | 64.4 | 0.601 |
| >median | 100 | 75 | | 58.3 | NR | |
| **Pathological T stage** | | | | | | |
| PT1 | 100 | NR | 0.366 | NR | NR | 0.318 |
| PT2a | 79 | 73.4 | | 71.8 | 71.8 | |
| PT2b | 87.1 | NR | | 68.9 | NR | |
| PT3 | 66.7 | NR | | NR | NR | |
| **Pathological N Stage** | | | | | | |
| N0 | 87 | 74.5 | 0.024 | 74.2 | 69.3 | 0.001 |
| N1 | NR | NR | | NR | NR | |
| **Pathological maximum size** | | | | | | |
| ≤ median | 82.6 | 75.7 | 0.683 | 76.4 | 76.4 | 0.466 |
| >median | 82.6 | 66.1 | | 62.4 | 53.5 | |
| **Pathological subtypes** | | | | | | |
| Clear cell | 77.1 | 66.1 | 0.607 | 68.9 | 68.9 | 0.997 |
| Chromophobe | 84.6 | 84.6 | | 69.4 | NR | |
| Papillary | 80 | NR | | 80 | NR | |
| Others | 100 | NR | | 65.6 | NR | |
| **Pathological grade** | | | | | | |
| Low grade | 85.7 | 57.1 | 0.97 | 50 | 50 | 0.502 |
| High grade | 77.8 | 66.3 | | 66.3 | 60.2 | |
| **Adrenalectomy** | | | | | | |
| No | 88.1 | 77.7 | 0.149 | 76.5 | NR | 0.132 |
| Yes | 70.6 | 57.1 | | 45.9 | 45.9 | |

## DISCUSSION

RN is the cornerstone for managing localized RCC. Widespread acceptance of LRN as the standard of care for radical nephrectomy has grown gradually. LRN is the standard of care for renal masses unsuitable for nephron-sparing surgery. The ongoing evolution and refinement of surgical techniques have significantly improved perioperative outcomes. The oncologic principles of LRN are the same as ORN. Initially, LRN was reserved for small renal tumors; however, it's now extending to larger tumors (Conley, et al., 2009). Many studies compared LRN *vs*. ORN in T1 tumors and proved their equivalent oncological outcomes (Gill, et al., 2000 and Gill, et al., 2001). Moreover, several studies have suggested a possible upper limit of 15 cm for attempting (Steinberg, et al., 2004). The role of laparoscopy in treating large T2 renal masses has been explored in observational and retrospective cohorts (Portis, et al., 2002, Lee, et al., 2018, Dursun, et al., 2002 and Hemal, et al., 2007). Despite the limitations of the retrospective nature of these studies, LRN has proven definite in T2 tumors. The general advantages of LRN over ORN include reduced blood loss, less postoperative pain, and shorter hospital stay. However, laparoscopic mobilization of large-sized tumors and their retrieval remains challenging. In the present study, The conversion rate was 3.6%. Meanwhile, the oncologic outcome of LRN in large T2 tumors needs to be compared to the standard ORN, preferably in prospective randomized studies.

Moreover, the benefits and limitations of LRN still need to be analyzed in large T2 RCCs to validate their effectiveness before being considered a standard of care. Hence, the current study was designed as a prospective RCT for such comparisons to avoid selection or observer bias, representing the first reported randomized clinical trial in contemporary literature. Two prospective non-randomized observational studies found no significant differences in patients demographics between the LRN and ORN control groups (Kwon, et al., 2011 and Khan, et al., 2019). Others detected no differences between obese (BMI>30) and non-obese patients for the surgical outcomes and conversion rates (Fugita, et al., 2004). In concordance with the present study, Kwon, and colleagues, in 2011, reported a similar mean operative time in both groups (209 min *vs*. 205 min, p=0.755) (Kwon, et al., 2011). Similarly, Khan and colleagues in 2019 reported an operative time of 187.5 *vs*. 163.6 min 13. Other studies showed significantly longer operative times in the LRN group than the ORN group (Hemal, et al., 2007 and Jeon, et al., 2011). Multiple studies have reported reduced blood loss and a shorter hospital stay for LRN patients (Steinberg, et al., 2004 and Kim, et al., 2006). In the present study, the ORN arm had a median blood loss of 500 ml compared to 190 ml for the LRN arm (p<0.001), which was attributed to the smaller incisions, less operative manipulation, more meticulous dissection, and larger and better visualizations of tissues and vessels. This was congruent with Jeon and colleagues in 2011 (Jeon, et al., 2011).There was no difference in the rate of intraoperative transfusion between both arms (p=0.352); 10.7% of patients needed a transfusion in concordance with standard rates of transfusion reported in RCC (ranging from 10% - 11%) (Henderson, et al., 2015).

In the present study, the median postoperative pain score on day 0 was significantly less in the LRN group (3 *vs*. 4.5, p=0.015) treated with less intense analgesia. The LRN group showed a significantly lower use of narcotics than the ORN group (p=0.036), similar to results reported by (Hemal, et al., 2007 and Khan, et al., 2019). The lower intensity of postoperative pain accelerates the postoperative recovery course and lessens the time needed to return to normal daily activity. In the ORN arm, one patient experienced an intraoperative complication compared to 5 patients in LRN (4 conversions to open surgery and one cardiac complication), yet the difference was not statistically significant (p=0.193).

Conversion to ORN was due to large tumor size in 1 patient and bleeding from the gonadal or renal pedicle in 3 patients. The rate of postoperative complications was similar in both arms. Kwon, Khan, and their colleagues had a similar complication rates in 2011 and 2019 (Kwon, et al., 2011 and Khan, et al., 2019). The current study shows a median postoperative hospital stay for ORN patients of 3 days compared to 2 days for LRN patients (p=0.073). Even if these results were not statistically significant, the overall length of hospital stay was lower when compared to the current literature (Jeon, et al., 2011). Less hospital stay has a crucial impact on the cost of inpatient stay and the time needed for patients to return to daily activities.

The median follow-up time in our study was 10.2 months. Laparoscopic and open nephrectomies had similar OS and LRFS (p=0.615 and p=0.529, respectively). The one and 2-year OS for the LRN arm were 87.6% and 74.1%, respectively, while they were 77.6% and 69.0 for ORN, respectively. Furthermore, many investigators also reported a similar 5-year OS rate, cancer-specific survival rate, and recurrence-free survival rate in the LRN and ORN (Portis, et al., 2002, Hemal, et al., 2007, Kwon, et al., 2011, Khan, et al., 2019 and Jeon, et al., 2011). These retrospective studies emphasized equivalent long-term survival for LRN patients compared to ORN patients. Despite the relatively few studies comparing the oncological, most published data confirm the oncological equivalence and feasibility of LRN and ORN. This study has limitations related to the relatively small cohort of patients and short follow-up. However, as a first reported randomized trial, the preliminary results showed similar oncological outcomes between LRN and ORN suggesting that more extensive similar studies will be required to define the laparoscopic approach as a gold standard for T2 RCC treatment.

## CONCLUSION

LRN proved its advantage in the management of T2 RCC by decreasing intraoperative blood loss and postoperative pain, while yielding similar oncologic outcomes. Therefore, the current study represents the first step in defining LRN as the gold standard surgical management of localized T2 RCC; furthermost extensive series with longer follow-ups will be required to confirm our results.

## DISCLOSURE

Dr. Tarek M. Zaghloul, Dr. Hatem Aboulkassem, Dr. Rasha M. Allam, Dr. Luca Pio, Dr. Ayatullah G. Mostafa, Dr. Amr M.

Selim, Dr.Walid M Fadllalla and Dr.Ashraf S. Zaghloul have no conflicts of interest or financial ties to disclose.

## ETHICAL DISCLOSURE

The authors state that they have obtained appropriate institutional review board approval. Informed consent has been obtained from all the participants involved.

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