Recurrence after radical and partial nephrectomy in high complex renal tumor using propensity score matched analysis

Hwanik Kim¹, Jung Kwon Kim¹, Changhee Ye¹, Joon Hyeok Choi³, Hakmin Lee⁴, Jong Jin Oh¹,², Sangchul Lee¹, Sung Kyu Hong¹,² & Seok-Soo Byun¹,²

We evaluated the recurrence after radical and partial nephrectomy in patients with RENAL nephrometry score [RENAL] ≥ 10. A total of 474 patients (radical nephrectomy [RN, n = 236] & partial nephrectomy [PN, n = 238]) in a single tertiary referral institution from December 2003 to December 2019 were assessed. Functional outcomes, defined as estimated glomerular filtration rate changes, relapse pattern, recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) were evaluated using propensity score-matched analysis. The predictors of recurrence and survival were assessed by Cox-regression analysis. 44 patients in the RN group and 88 in the PN group were included without significant differences in preoperative clinical factors after matching. The PN patients achieved significantly higher renal function preservation rates (p < 0.001). There were five recurrences in RN and six in PN. The PN patients revealed 5-year RFS rate (86.8%), 5-year CSS rate (98.5%), and 5-year OS rate (96.7%) comparable to the RN patients (RFS: 88.7% [p = 0.780], CSS: 96.7% [p = 0.375], and OS: 94.3% [p = 0.248]). Patients with a body mass index (BMI) ≥ 23 had lower 5-year RFS rates (85.5%) and OS rates (95.6%) than those with BMI < 23 (RFS: 90.0% [p = 0.195], OS: 100% [p = 0.117]) without significance. The significant predictor of recurrence was the pathologic T stage (hazard ratio [HR] 3.99, 95% confidence [CI] 1.10–14.50, p = 0.036). The significant predictor of death was the R domain of the RENAL (HR 3.80, 95% CI 1.03–14.11, p = 0.046). PN, if technically feasible, could be considered to preserve renal function in patients with RENAL ≥ 10. Nonetheless, PN needs to be implemented with caution in some patients due to the higher potentiality for recurrence and poor survival.

In the localized renal cell carcinoma (RCC), a partial nephrectomy (PN) or radical nephrectomy (RN), by tumor characteristics, is the treatment of choice for surgical candidates¹. PN is becoming the standard management of clinical T1 tumors² resulting in equivalent oncological outcomes as those of RN, functional preservation, and favorable survival benefit reported from several national database studies and meta-analyses³-⁴. Nevertheless, 20–40% of the patients treated for the localized case were reported to have recurrences⁵. In a multicenter study, Shah et al. observed that the disease recurred in 5.6% of the patients treated with PN for clinically localized RCC⁶. With the number of PN increasing in the last few years, growing attempts have been made to implement PN even for high complex renal tumors described by RENAL nephrometry score (RENAL), developed as a useful evaluation tool for predicting operative complexity posed by warm ischemic time (WIT) or postoperative complications⁷. Despite technological advances and the adoption of robotic surgical systems, few data on PN for high complex renal masses leave unmet need challenges. Furthermore, there is limited evidence on the recurrence of RCC in patients with high complex renal masses.

In this study, we aimed to investigate the predictors and patterns of RCC recurrence in patients with high complex tumors diagnosed as RCC and treated with PN or RN from a single center and assess the impact on recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS).

¹Department of Urology, Seoul National University Bundang Hospital, 82 Gumi-Ro, 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, South Korea. ²Department of Urology, Seoul National University College of Medicine, Seoul, South Korea. ³Biochemistry, College of Arts and Sciences, Boston College, Newton, MA, USA. ⁴email: ssbyun@snubh.org
Methods

Patient population. The Institutional Review Board of Seoul National University Bundang Hospital approved the current study (approval number: B-2007-625-102). A written informed patient consent was waived by the Seoul National University Bundang Hospital Institutional Review Board due to the retrospective nature of study. Personal identifiers were completely deleted such that data were analyzed anonymously. We reviewed our prospectively maintained institutional database of 3013 patients who underwent RN or PN between December 2003 and December 2019 at a single tertiary referral center. All methods were conducted in accordance with relevant guidelines and regulations (the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards).

The complexity of surgery was defined by RENAL. Renal masses with an RENAL range of 4–6, 7–9, and 10–12 indicated low, moderate, and high complex lesions, respectively, as described by Kutikov and Uzzo. We strictly defined local recurrence as (1) the detection of a new enhancing lesion in the surgical bed of the original nephrectomy site(s) or regional lymph nodes (LN), which was identified by the urological oncologist or radiologist on:

Table 1. Baseline characteristics of the patients. RN radical nephrectomy, PN partial nephrectomy, BMI body mass index, DM diabetes mellitus, HTN hypertension, ECOG Eastern cooperative oncology group performance status, MDRD modification of diet in renal disease, GFR estimated glomerular filtration rate, R radius (maximal diameter), E exophytic/endophytic, N nearness to collecting duct system/renal sinus, A anterior/posterior location, L location relative to the polar lines.
Follow-up imaging or (2) the detection of a new enhancing lesion in the same region of the ipsilateral kidney as the original PN site (e.g., the PN site and the recurrence site were both in the lower pole)6. Systemic recurrence was defined as tumor development at systemic distant sites or in non-regional retroperitoneal LNs8.

After excluding 2569 patients with low (n = 742), moderate (n = 1283) complex, or unknown (n = 544) RCC complexity, 153 were initially diagnosed with metastatic RCC with high complex renal masses (44 cN1 cases, 82 cM1 cases, and 27 cN1M1 cases) and 291 with nonmalignant histology (110 angiomyolipomas, 60 oncocytomas, and 121 other benign cysts). Recurrence was noted in 61 of 474 patients (12.9%) with high complex renal masses who underwent RN (n = 236) or PN (n = 238).

All specimens were analyzed by dedicated urological pathologists. A positive surgical margin (PSM) was defined as the extension of the tumor to the inked surface of the resected specimen on the final pathology evaluation.

Follow-up protocol. According to the standardized institutional postoperative protocol, the patients were generally followed-up after surgery at least every 6 months in the first year, annually during the next 4 years, and every 2 years thereafter. The follow-up protocols consisted of computed tomography or magnetic resonance imaging studies and chest radiography. Renal functional outcomes defined as estimated glomerular filtration rate (eGFR) changes were followed.

RFS was defined as the interval between the date of surgery and the time of the first tumor recurrence. The cause of death was determined by the responsible physicians and death certificates. CSS was calculated from the date of surgery to the date of the last follow-up or death related to renal cell carcinoma. OS was calculated from the date of surgery to the date of the last follow-up or death due to all causes9.

Statistical analyses. The clinicopathological characteristics were compared between the patients who underwent RN and PN using the chi-squared test for categorical variables and the independent t test or Mann–Whitney U test for continuous variables. Kaplan–Meier survival analysis was used to calculate the survival estimates for RFS and OS. Further, the log-rank test was used to conduct comparisons between the groups. Univariate and multivariate Cox proportional hazard regression analyses were performed to evaluate the significant variables associated with the survival outcomes9. We conducted an additional analysis to determine if the body mass index (BMI) affected RCC recurrence or survival. The univariate results were used to determine the candidate variables for the final multivariate model in a backward model selection process. In all variables remaining in the final multivariate analysis, the p value was set to 0.05. To provide a further balance between radical and partial nephrectomies, we performed propensity score-matching (PSM). For a binary treatment indicator of the type of surgery (RN vs. PN), PSM was performed using age, sex, BMI, diabetes mellitus (DM) status, hypertension (HTN) status, Eastern Cooperative Oncology Group Performance Status (ECOG PS), Modification of Diet in Renal Disease-GFR (MDRD-GFR), tumor size, clinical T stage, operation technique, and RENAL. Matching variables were selected to balance the variables most likely influencing operative bias. Matching was performed using a 1:2 ratio between the RN and PN groups with a nearest neighbor-matching algorithm10. PSM was performed using the MatchIt extension package in R software (Vienna, Austria). All data were analyzed with SPSS version 22, and all tests were 2-sided with a p value of 0.05 considered statistically significant (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA).

Results

Patient demographics. Table 1 shows the patient baseline characteristics. Before the propensity score matching, we detected significant differences between the RN group and the PN group in terms of age, BMI, gender, HTN, chronic kidney disease (CKD), serum creatinine level, MDRD-GFR, tumor size, clinical T stage, RENAL, operation technique, and pathological classification. These preoperative clinical factor differences were eliminated by PSM. After PSM, the RN group and the PN group contained 44 and 88 patients, respectively. The median follow-up duration was 37.5 months in both groups (interquartile range (IQR) 12–60 months). There were no significant differences in the pathological results between the groups.

Figure 1. Postoperative renal function trends in glomerular filtration rate (GFR) preservation rates after radical nephrectomy and partial nephrectomy between the groups.
Figure 2. Kaplan–Meier curves for recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) between the groups. (A) RFS, (B) CSS, and (C) OS.
Effect of operation type (RN vs. PN) on renal function. There were significant differences in renal function between the two groups throughout the follow-up period (p = 0.001) (Fig. 1). At the follow-up 1 year after surgery, 90% eGFR preservation rates were found in 6.1% of the patients in the RN group and 70.2% of the patients in PN group (p < 0.001). Moreover, de novo CKD stage III or higher incidence rates at postoperative 1 year were seen in 41.1% of the patients in the RN group and 3.6% in the patients in the PN group (p < 0.001).

Effect of operation type and BMI on recurrence and overall survival. Among the patients in the post-propensity cohort, 11 patients (8.34%) were found to fit the criteria for recurrence. There were five systemic recurrences in the RN patients and six in the PN patients. There were no local recurrences. Five patients died during follow-up, which included three cancer-specific deaths in the RN group, and one cancer-specific death in the PN group. The PN patients had 5-year RFS rate (86.8%), 5-year CSS rate (98.5%), and 5-year OS rate (98.5%) comparable to the RN patients (RFS rate, 88.7% [p = 0.780]; CSS rate, 96.7% [p = 0.375]; OS rate, 94.3% [p = 0.248]). There were no differences in any type of survival between the two groups after PSM (Fig. 2).

In the BMI, before PSM, the 5-year RFS rate was significantly higher in patients with BMI ≥ 23 (88.8% vs. 73.4%, p = 0.001). After PSM, the patients with BMI ≥ 23 had lower 5-year RFS rates (85.5%) and OS rates (95.6%) than the patients with BMI < 23 (RFS, 90.0% (p = 0.195); OS, 100% (p = 0.117)) without significance (Supplementary Figure 1).

The significant predictor of recurrence was the pathologic T stage (hazard ratio [HR] = 3.99, 95% confidence [CI]: 1.10–14.50, p = 0.036) (Table 2). The significant predictor of death was the R portion of the RENAL (HR

### Table 2. Univariate and multivariate analysis for recurrence after nephrectomy.

|               | Univariate analysis | Multivariate analysis |
|---------------|---------------------|-----------------------|
|               | HR    | CI     | p value | HR    | CI     | p value |
| Age           | 1.01  | 0.96–1.06 | 0.689|
| BMI           |       |         |         |       |         |         |
| BMI < 23      | Ref   |         |         |       |         |         |
| 23 ≤ BMI < 30 | 3.48  | 0.44–27.48 | 0.237|
| BMI ≥ 30      | 4.5   | 0.28–72.21 | 0.288|
| BMI ≥ 23      | 3.56  | 0.46–27.83 | 0.226|
| Gender        |       |         |         |       |         |         |
| Male–Ref     | 3.17  | 0.97–10.37 | 0.057|
| DM           | 0.51  | 0.07–3.978 | 0.519|
| HTN         | 1.3   | 0.40–4.25 | 0.669|
| ECOG       | 1.89  | 0.75–4.76 | 0.177|
| Serum Cr      | 0.78  | 0.07–8.88 | 0.844|
| GFR           | 0.99  | 0.96–1.01 | 0.373|
| Tumor size    | 1.05  | 1.01–1.10 | 0.012|
| Op technique  |       |         |         |       |         |         |
| PN            | 0.82  | 0.25–2.71 | 0.751|
| Robot         | Ref   |         |         |       |         |         |
| Laparoscopy  | 0     | 0       | 0.984|
| Open         | 1.02  | 0.30–3.40 | 0.981|
| RENAL score   | 1.52  | 0.47–4.94 | 0.487|
| R            | 2.55  | 1.16–5.64 | 0.020|
| E            | 0.37  | 0.17–0.82 | 0.015|
| N             | 0     | 0       | 1.000|
| Pathologic T stage |     |         |         |       |         |         |
| pT1         | Ref   |       | 0.003  | Ref   |       | 0.036 |
| pT2–pT3     | 6.10  | 1.86–20.02 | 3.99 |
| 1.10–14.50 |       |         |         |       |         |         |
3.80, CI 1.03–14.11, p = 0.046 (Table 3). The patterns and management of recurrence between the groups are detailed in Supplementary Tables 1 and 2.

### Discussion

Several large retrospective studies have been conducted on the recurrence rates after surgical treatment of RCC. Notably, the majority of the data included patients with nephrectomy in the 1980s–1990s. All studies derived from institutional cohorts without hospital-based registries or population-based cohorts. Overall, the 5-year RFS rates were from 41.9 to 97.8%. However, the cohorts were diversely distributed in aspects of the disease stages and surgical methods (PN vs. RN and laparoscopic vs. open techniques). One contemporary cohort was comprised of 1541 patients who underwent PN for clinical T1a and T1b tumors from 1999 to 2008. Distant metastases were found in 59 patients (4.9%) after nephrectomy. The 5-year RFS rates were between 97.1 and 97.8% for clinical T1a and between 92.7 and 93.1% for clinical T1b tumors. Though no studies have directly compared the recurrence rates in previous versus more contemporary cohorts for localized RCC, the 5-year RFS is likely to be more than 90% in T1 patients following surgery. Unlike those results, our post-propensity cohort revealed a relatively lower 5-year RFS (RN: 88.7% vs. PN: 86.8%), but the results should be interpreted with caution as there were fewer patients at risk in each group at serial yearly follow-ups.

Local recurrence in the renal fossa after RN has been studied well. Itano et al. reported a 1.8% of local recurrence rate after RN. The 5-year CSS was poor at 28% in those patients but expanded with surgical resection of the recurrence. Thomas et al. reported that the pathological nodal stage at the original nephrectomy and the maximal diameter of the retroperitoneal recurrence were independent risk factors for CSS. Margulis et al. found the same recurrence rate (1.8%) in 2009 and correlated specific clinical factors with worse CSS. Compared to these results, the pre-propensity patients in the RN group in our study had no isolated local recurrences but eight (3.4%) had combined local and systemic recurrences. Seven had renal fossa recurrences and one had regional LN recurrence, all followed by concurrent or subsequent systemic metastasis. However, the post-propensity cohort showed only systemic recurrences.

### Table 3. Univariate and multivariate analysis for overall survival after nephrectomy.

|                      | Univariate analysis | Multivariate analysis |
|----------------------|--------------------|----------------------|
|                      | HR     | CI     | p value | HR     | CI     | p value |
| Age                  | 1.01   | 0.94–1.08 | 0.887 |        |        |        |
| BMI ≥ 23             | 44.06  | 0.01–151,827.2 | 0.362 |        |        |        |
| Gender               |        |        |        |        |        |        |
| Male—Ref             | 2.74   | 0.39–19.50 | 0.314 | 2.74   | 0.39–19.50 | 0.314  |
| DM                   | 3.54   | 0.59–21.22 | 0.166 | 3.54   | 0.59–21.22 | 0.166  |
| HTN                  | 4.41   | 0.49–39.56 | 0.185 | 4.41   | 0.49–39.56 | 0.185  |
| ECOG                 | 0.06   | 0–2103.6  | 0.599 | 0.06   | 0–2103.6  | 0.599  |
| Serum Cr             | 0.79   | 0.01–48.91 | 0.912 | 0.79   | 0.01–48.91 | 0.912  |
| GFR                  | 0.99   | 0.95–1.03  | 0.991 | 0.99   | 0.95–1.03  | 0.991  |
| Tumor size           | 1.03   | 0.97–1.09  | 0.378 | 1.03   | 0.97–1.09  | 0.378  |
| **Op technique**     |        |        |        |        |        |        |
| PN                   | 2.88   | 0.45–18.61 | 0.266 | 2.88   | 0.45–18.61 | 0.266  |
| Robot                | Ref    |        |        | Ref    |        |        |
| Laparoscopy          | 0      | 0      | 0.990 | 0      | 0      | 0.990  |
| Open                 | 1.54   | 0.25–9.62 | 0.644 | 1.54   | 0.25–9.62 | 0.644  |
| **RENAL score**      | 1.17   | 0.11–8.50 | 0.880 | 1.17   | 0.11–8.50 | 0.880  |
| R                    | 3.8    | 1.03–14.11 | 0.046 | 3.8    | 1.03–14.11 | 0.046  |
| E                    | 0.32   | 0.09–1.08  | 0.066 | 0.32   | 0.09–1.08  | 0.066  |
| N                    | 0      | 0      | 1.000 | 0      | 0      | 1.000  |
| a                    | Ref    |        | 0.868 | Ref    |        | 0.868  |
| p                    | 0.54   | 0.06–5.42 | 0.603 | 0.54   | 0.06–5.42 | 0.603  |
| x                    | 0.75   | 0.08–7.41 | 0.806 | 0.75   | 0.08–7.41 | 0.806  |
| L                    | 0.22   | 0.02–2.40 | 0.212 | 0.22   | 0.02–2.40 | 0.212  |
| **Pathologic T stage** |        |        |        |        |        |        |
| pT1                  | Ref    |        | 0.141 | Ref    |        | 0.141  |
| pT2–pT3              | 4.37   | 0.61–31.16 |        | 4.37   | 0.61–31.16 |        |
As mentioned, few studies have been conducted on local recurrence after nephrectomy for high complex renal masses. All were limited by the small number of patients in the cohorts and provided broad and variable definitions of local recurrence. From an observational study of 360 sporadic and nonfamilial patients with T1 tumors who received laparoscopic partial nephrectomy, Kreshover et al. reported that 4.4% of the patients experienced local recurrence in the retroperitoneum or the operated kidney. In a contemporary retrospective study by Thompson et al., the definition of local recurrence was a mass in the operated kidney. They found a 3.4% local recurrence rate in cT1a tumors (36 of 1057) and a 6.4% for cT1b tumors (21 of 326) after open PN. The another contemporary review of 279 patients with a mean follow-up of 25 months (IQR 7–43) by Garisto et al. reported that 4.3% of the total patients had recurrences, 4.43% and 3.95% in the robot-assisted PN and the open PN groups, respectively (p = 0.6). They also observed that both the open and robotic approach led to a significant decrease in postoperative eGFR. Our cohort with propensity score matching showed an RFS rate similar to a large sample-sized study of a population with highly complex renal masses but had longer follow-up and better preserved renal function. The RFS rates of patients with high complex renal masses did not differ significantly by treatment approach in the current study.

The association between BMI and mortality has been observed in patients with RCC across several cohorts. It is well known that obese patients with localized clear cell RCC who are treated with nephrectomy survive longer than those with normal weight according to the World Health Organization (WHO) categorization (BMI 18.5–24.9 kg/m²), a phenomenon known as the obesity paradox. A meta-analysis of patients with RCC who underwent nephrectomies showed higher OS in overweight or obese versus normal-weight patients (pooled HR 0.57, CI 0.43–0.76). A recent study reported differences in the tumor microenvironment in obese patients relative to normal patients. Although we evaluated the effect of BMI on tumor recurrence or survival, we only found a significant RFS difference in the pre-propensity cohort. While this finding might be attributed to significantly different demographics between the groups, our unexpected findings are supported by other studies and we confirmed that the obesity paradox also applied to our cohort.

The current study had some limitations, including the retrospective nature and single-center design with a small comparison group. In addition, the results may not be replicated in patients with a solitary kidney or metastatic RCC, as we only included patients with non-metastatic bilateral kidneys. Despite these limitations, to our knowledge, this was the first study identifying preoperative clinical factors associated with the recurrence and survival of RCC patients with high complex renal masses, overcoming the relatively low number of patients.

Conclusions
In patients with RENAL ≥ 10, PN should be performed to preserve renal function if technically feasible. We can confidently propose broadening the PN indication to include high complex tumors, regardless of the surgical difficulty. Nevertheless, PN should be done with caution in some cases due to the higher potential for recurrence and poor survival. Longer follow-up studies with larger cohorts and randomized controlled trials are expected to verify these findings.

Received: 5 August 2020; Accepted: 18 January 2021
Published online: 03 February 2021

References
1. Motzer, R. J. et al. NCCN guidelines insights: kidney cancer, version 2.2020. J. Natl. Compr. Cancer Netw. 17(11), 1278–1285 (2019).
2. Ljungberg, B. et al. European Association of Urology Guidelines on renal cell carcinoma: the 2019 update. Eur. Urol. 75, 799–810 (2019).
3. Pierorazio, P. M. et al. Management of renal masses and localized renal cancer: systematic review and meta-analysis. J. Urol. 196, 989–995 (2016).
4. Ristau, B. T. et al. Partial nephrectomy is not associated with an overall survival advantage over radical nephrectomy in elderly patients with stage Ib–2 renal masses: an analysis of the national cancer data base. Cancer 124, 3839–3848 (2018).
5. Speed, J. M., Trinh, Q. D., Choueiri, T. K. & Sun, M. Recurrence in localized renal cell carcinoma: a systematic review of contemporary data. Curr. Urol. Rep. 18(2), 15 (2017).
6. Wood, E. L. et al. Local tumor bed recurrence following partial nephrectomy in patients with small renal masses. J. Urol. 199(2), 393–400 (2018).
7. Kutikov, A. & Uzzo, R. G. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J. Urol. 182, 844 (2009).
8. Mouracade, P. et al. Patterns and predictors of recurrence after partial nephrectomy for kidney tumors. J. Urol. 197(6), 1403–1409 (2017).
9. Kim, J. K. et al. Comparison of robotic and open partial nephrectomy for highly complex renal tumors (RENAL nephrometry score ≥ 10). PLoS ONE 14(1), e0210413 (2019).
10. Brethorst, A. W. et al. Robotic partial nephrectomy vs minimally invasive radical nephrectomy for clinical T2a renal mass: a propensity score-matched comparison from the ROSULA (Robotic Surgery for Large Renal Mass) Collaborative Group. BJU Int. 126(1), 114–123 (2020).
11. Lane, B. R., Campbell, S. C. & Gill, I. S. 10-year oncologic outcomes after laparoscopic and open partial nephrectomy. J. Urol. 190(1), 44–49 (2013).
12. Ignano, N. R., Blute, M. L., Spotts, B. & Zincke, H. Outcome of isolated renal cell carcinoma fossa recurrence after nephrectomy. J. Urol. 164(2), 322–325 (2000).
13. Thomas, A. Z. et al. Surgical management of local retroperitoneal recurrence of renal cell carcinoma after radical nephrectomy. J. Urol. 194(2), 316–322 (2015).
14. Margulis, V. et al. Predictors of oncological outcome after resection of locally recurrent renal cell carcinoma. J. Urol. 181, 2044 (2009).
15. Putka, S. P. et al. Renal fossa recurrence after nephrectomy for renal cell carcinoma: prognostic features and oncological outcomes. BJU Int. 119(1), 116–127 (2017).
16. Kreshover, J. E., Richstone, L. & Kavoussi, L. R. Renal cell recurrence for T1 tumors after laparoscopic partial nephrectomy. J. Endourol. 27, 1468 (2013).
17. Thompson, R. H. et al. Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. Eur. Urol. 67, 252 (2015).
18. Garisto, J. et al. Robotic versus open partial nephrectomy for highly complex renal masses: comparison of perioperative, functional, and oncological outcomes. Urol. Oncol. 36(10), e471-e471.e9 (2018).
19. Sanchez, A. et al. Transcriptomic signatures related to the obesity paradox in patients with clear cell renal cell carcinoma: a cohort study. Lancet Oncol. 21(2), 283–293 (2020).
20. Choi, Y. et al. Body mass index and survival in patients with renal cell carcinoma: a clinical-based cohort and meta-analysis. Int. J. Cancer 132, 625–634 (2013).
21. Donin, N. M. et al. Body Mass Index and survival in a prospective randomized trial of localized high-risk renal cell carcinoma. Cancer Epidemiol. Biomark. Prev. 25(9), 1326–1332 (2016).
22. Hakimi, A. A. et al. An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. J. Natl. Cancer Inst. 105(24), 1862–1870 (2013).
23. Albiges, L. et al. Body Mass Index and metastatic renal cell carcinoma: clinical and biological correlations. J. Clin. Oncol. 34(30), 3655–3663 (2016).

Author contributions
H.K., J.K.K. and S.S.B. conceived the study. C.Y., J.H.C, H.L., J.J.O., S.L. and S.K.H. participated in the analysis and interpretation of results. H.K. and S.S.B. wrote the manuscript, with all authors reading and approving the final manuscript.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-021-82700-8.

Correspondence and requests for materials should be addressed to S.-S.B.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2021