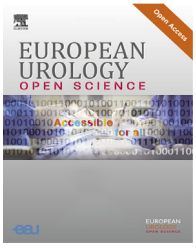
available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Opinion: Open Science

The Decision to Surgically Resect Recurrent Renal Cell Carcinoma: More Evidence that Careful Case Selection by Surgeons Is Associated with Better Survival

Paul Russo *

Department of Urology, Weill Cornell School of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

In the 80 yr since surgeons began resecting kidney cancer, our understanding of this disease has dramatically expanded. Once thought to be a single cancer, dubbed the "internist's disease" because of its capricious clinical behavior, usually advanced at presentation, kidney cancer is now understood to be a complex family of more than 30 different tumors with unique pathological and genomic features. The oncological threat ranges from benign (20%) to indolent (25%) to highly malignant (54%) [1]. Today's modern imaging led to tumor size and stage migration, the era of incidentaloma, the acceptance of kidney-sparing operations, and, in parallel, the development of minimally invasive surgery (MIS) and ablative techniques [2]. For patients with stage 4 disease, current systemic therapies, including tyrosine kinase, mTOR, immune checkpoint, and HIF2α inhibitors, have led to a fourfold improvement in overall survival (OS) in comparison to historical controls [3]. However, 30–40% of patients with localized disease eventually experience recurrence and surgeons are asked to play a critical role in their care. Nomograms and risk assessment models developed using clinical, serological, and hematological parameters can be used to stratify patients as having low, intermediate, or high risk of recurrence and are critical for patient counseling and clinical trial design [4].

In their study published in *European Urology Open Science*, Marconi et al. [5] used the RECUR multi-institutional kidney cancer registry involving 15 European centers to determine if local treatment of recurrence (LTR) provides a survival benefit. A total of 3039 patients with localized renal cell carcinoma (RCC) were treated with curative intent using partial nephrectomy (PN) or radical nephrectomy (RN) (>1000 had MIS) between 2006 and 2011. Resectable disease was defined as solitary metastases, oligometastases, and renal fossa or renal recurrence. A total of 505 patients (18%) developed recurrence, of whom 245 (8%) had resectable disease and 260 (8.5%) had "nonresectable disease". Of the 245 patients with resectable disease, 97 (3.2%) underwent surgical metastasectomy (n = 89), radiotherapy (n = 5), or ablation (n = 3), and, for the purposes of this study, were compared to 79 patients (6%) managed with palliative intent. It is assumed that clinician discretion (selection) led to the decision not to treat the latter patients. An additional 69 patients (2.3%) were excluded from the analysis because of missing data. The median overall survival (OS) was 70.3 mo for the LTR group versus 27.4 mo for the no-LTR group. The authors stratified analyses by risk of recurrence, which, as expected, favored the LTR cohort and was consistent across high-, intermediate-, and low-risk groups. On multivariable analysis, LTR, low versus high risk, and longer time to recurrence were all associated with longer OS.

Surgical case selection plays a fundamental role in localized, advanced, and recurrent kidney cancer. The patient's age, tumor size and location, renal functional status, and comorbidities affect the initial decision to operate and whether to recommend PN or RN. Surgeons must define the intent of the operation (curative, cytoreductive, palliative) from the outset. Similarly, medical oncologists use case selection in deciding when to commence systemic therapy in stage 4 disease, often delaying treatment in well patients with slow progression [6] or not treating at all following complete metastasectomy. In this report there is

DOI of original article: https://doi.org/10.1016/j.euros.2022.11.008

* Corresponding author at: Department of Urology, Weill Cornell School of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Tel. +1 646 422 4391; Fax: +1 212 988 0760.
E-mail address: russop@mskcc.org

https://doi.org/10.1016/j.euros.2023.01.006

much evidence of surgical case selection, with obvious disparities between the LTR and no-LTR patients leading to the marked difference in OS. In comparison to the LTR group, the no-LTR group was significantly older at recurrence (69 vs 64 yr), had fewer low- and intermediate-risk features (41.7% vs 62.9%), had a shorter time to recurrence (24 vs 31 mo), had fewer pT1 cases (17.7% vs 39.2%), had more pT3 cases (70.2% vs 38.1%), had more abdominal recurrences (46.4% vs 27.8%), and had more N+ cases (8.9% vs 2.1%).

Our institutional experience with surgical resection of recurrent kidney cancer demonstrates the virtues of careful case selection. In our historical experience with 278 patients managed between 1980 and 1993, favorable features for 5-yr OS were a disease-free interval of >12 mo (54% vs 9%), involvement of a solitary organ versus multiple organ sites (54% vs 29%), and age younger than 60 yr (49% vs 35%), with resection of lung metastases associated with 50% OS [7]. Resection of an isolated brain metastasis was associated with 5-yr OS of only 18%. In our next report of 118 patients managed from 1989 to 2005, risk stratification based on performance status, lactate dehydrogenase, hemoglobin, and serum calcium segregated survival outcomes into good risk (76 mo), intermediate risk (25 mo), and poor risk (6 mo) [8], with a later study suggesting that the risk stratification was as important as the metastasectomy [9]. Lastly, in a study of complete metastasectomy in 138 patients managed from 1990 to 2013 across numerous organ sites, factors adversely affecting cancer-specific survival were a shorter interval from nephrectomy to recurrence, multiple tumors resected at a single site, larger tumors at the time of nephrectomy, and sarcomatoid histology [10]. In this study, performed during the expansion of MIS kidney surgery between 2006 and 2011, Marconi et al. [5] observed a higher rate of abdominal recurrences in the no-LTR group. This could speak to a growing concern related to atypical tumor recurrences following MIS PN and RN leading to port-site recurrence and carcinomatosis often not amenable to resection [11]. Intra-abdominal recurrence (peritoneal surface, carcinomatosis, port site, nephrectomy bed) could be a result of the natural history of the disease (metastatic disease), a technical failure at the time of surgery, or a combination of both. Insight into its origins could be obtained using molecular genetics to determine clonal similarity or differences, but treatment approaches would not differ whatever the mechanism. Unfortunately, the prognosis for patients with such intra-abdominal recurrence, previously considered an uncommon site of kidney cancer spread, is guarded despite attempted surgical resection or systemic therapies.

In the end, whether surgeons use the eye test or rely on risk stratification models and nomograms or the take home messages from studies like those described above, careful case selection, as was on full display in this article, could provide a clinical benefit for eligible patients with kidney cancer. For those patients not cured by repeat resection or not eligible for LTR, further improvement in systemic agents may one day convert their stage 4 disease to a chronic disease with prolonged survival.

Conflicts of interest: The author has nothing to disclose.

References

[1] Signoretti S, Flaifel A, Chen YB, Reuter VE. Renal cell carcinoma in the era of precision medicine: from molecular pathology to tissue biomarkers. J Clin Oncol 2018;36:3553–9.
[2] Russo P, Jang T, Eggener S, Pettus J, Karellas M, O'Brien F. Survival rates after resection for localized kidney cancer 1989–2004. Cancer 2008;113:84–96.
[3] Liao Y, Hou H, Han Z, Liu Y. Systemic therapies for metastatic renal cell carcinoma in the second-line setting: a systematic review and network meta-analysis. Medicine 2022;101:e30333.
[4] Klatte T, Rossi SH, Stewart GD. Prognostic factors and prognostic models for renal cell carcinoma: a literature review. World J Urol 2018;36:1943–52.
[5] Marconi L, Kuusk T, Capitanio U, et al. Local treatment of recurrent renal cell carcinoma may have a significant survival effect across all risk-of-recurrence groups. Eur Urol Open Sci 2023;47:65–72.
[6] Rini BL, Dorff TB, Elson P, et al. Active surveillance in metastatic renal cell carcinoma: a prospective phase 2 trial. Lancet Oncol 2016;17:1317.
[7] Kavolius JP, Mastorakos MD, Pavlovich C, Russo P, Burt ME, Brady MS. Resection of metastatic renal cell carcinoma. J Clin Oncol 1998;16:2261–6.
[8] Eggener SE, Yossepowitch O, Pettus JA, Snyder ME, Motzer RJ, Russo P. Renal cell carcinoma recurrence following nephrectomy for localized disease: predicting survival from time to recurrence. J Clin Oncol 2006;24:3101–6.
[9] Eggener S, Yossepowitch O, Kundu S, Motzer RJ, Russo P. Risk score and metastasectomy independently impact prognosis in patients with recurrent renal cell carcinoma. J Urol 2008;180:873–8.
[10] Jakubowski CD, Vertosick EA, Untch BR, et al. Complete metastasectomy for renal cell carcinoma: comparison of five solid organ sites. J Surg Oncol 2016;114:375–9.
[11] Russo P, Blum KA, Weng S, Graafland N, Bex A. Outcomes for atypical tumor recurrences following minimally invasive kidney cancer operations. Eur Urol Open Sci 2022;40:125–32.