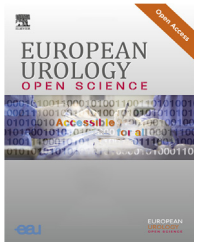
available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Kidney Cancer

Outcomes for Atypical Tumor Recurrences Following Minimally Invasive Kidney Cancer Operations

Paul Russo [a,*], *Kyle A. Blum* [a], *Stanley Weng* [a], *Niels Graafland* [b], *Axel Bex* [b,c,d]

[a] *Department of Surgery, Urology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [b] *Department of Urology, The Netherlands Cancer Institute, Amsterdam, The Netherlands;* [c] *Specialist Centre for Kidney Cancer, Royal Free London NHS Foundation Trust, London, UK;* [d] *Division of Surgery and Interventional Science, University College London, London, UK*

Article info

Article history:
Accepted April 10, 2022

Associate Editor:
M. Carmen Mir

Keywords:
Kidney cancer
Minimally invasive surgery
Nephrectomy
Recurrence

Abstract

Background: We managed a cohort of patients treated with minimally invasive surgery (MIS) for a kidney tumor presenting with atypical tumor recurrence (ATR) involving port sites, intraperitoneal carcinomatosis, and nephrectomy bed/perinephric tumor implants.
Objective: To determine the clinical characteristics, management, and oncologic outcomes for patients with localized renal cell carcinoma (RCC) who develop ATR following curative-intent MIS for partial or radical nephrectomy.
Design, setting, and participants: The study cohort comprised patients from 1999 to 2021 with localized RCC managed at Memorial Sloan Kettering Cancer Center (New York, NY, USA) after MIS for partial or radical nephrectomy who developed ATR. Outcome measurements and statistical analysis: We collected data on clinicopathologic characteristics, treatments, time to ATR, and overall survival.
Results and limitations: The median age of the 58 RCC patients was 61 yr. Forty-one patients (71%) were male, 26 (45%) had robot-assisted operations, and 39 (67%) had clear cell RCC. Twenty-nine patients had stage pT1 disease (50%) and ten (17%) had positive surgical margins. The most common ATR site was perinephric/nephrectomy bed implants (n = 28, 48%). Management included: surgical resection alone (n = 11, 19%), systemic therapy alone (n = 12, 21%), surgical resection and systemic therapy (n = 17, 29%), and palliative care (n = 8, 14%). At median follow-up of 59 mo (interquartile range [IQR] 28–92), the median time to ATR was 12 mo (IQR 5–28). Overall survival at 5 yr was 69.0% (95% confidence interval 57.4–83.1%) with only nine patients alive with no evidence of disease. Limitations include the potential for referral, detection, and selection biases, as well as uncertainty regarding the true incidence of ATR.

* Corresponding author. Department of Surgery, Urology Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Tel. +1 646 422 4393.
E-mail address: russop@mskcc.org (P. Russo).

https://doi.org/10.1016/j.euros.2022.04.005

Conclusions: ATR following MIS for partial or radical nephrectomy is an understudied, poor prognostic event which leads to a heavy treatment burden. Further investigation into its etiology and means of prevention is warranted.

Patient summary: Patients experiencing recurrence of kidney cancer in an atypical site require a heavy treatment burden and have a guarded overall prognosis. Continued research is needed to determine the precise incidence of these recurrences and identify methods for mitigating them.

1. Introduction

Minimally invasive surgery (MIS) for the treatment of kidney tumors has evolved over the past 30 yr, beginning with laparoscopic radical nephrectomy (RN) in 1991 [1], robot-assisted laparoscopic RN in 2000 [2], and the development of laparoscopic and robot-assisted partial nephrectomy (PN) over the past two decades [3]. Reported advantages of MIS include cosmetic incisions, shorter hospitalization, less pain, and more rapid return to normal activity. The short-term oncologic efficacy and safety metrics for MIS appeared to be similar to those for open approaches [4]. Today, robot-assisted laparoscopy for urologic cancers is the predominant form of MIS [5].

However, from the earliest experience with MIS in cancer, the literature is replete with reports of atypical tumor recurrence (ATR) involving port sites and intraperitoneal carcinomatosis emanating from hepatobiliary, gastrointestinal, and gynecologic primary tumors [6–10]. Although the precise ATR incidence is unknown, estimates range from 0.7% to 4% [10]. ATR following MIS has been reported in urologic oncology [11] involving prostate [12], bladder [13], testis [14], and kidney primary tumors [15,16]. There is controversy regarding whether technical factors during an MIS operation, tumor biology, or both cause ATR. Here we present our real-world experience in managing 58 patients who developed ATR following MIS PN or RN for localized kidney tumors (Fig. 1) and describe clinicopathologic characteristics, therapeutic interventions, and oncologic outcomes.

2. Patients and methods

Following institutional review board approval, we queried our prospectively maintained nephrectomy database for patients with localized (N0M0) renal cortical tumors who underwent curative-intent MIS PN or RN between 1999 and 2021 and developed ATR. ATR is defined as metastatic disease in sites not typical for the natural history of kidney cancer and includes port sites, intraperitoneal carcinomatosis, and nephrectomy bed/perinephric tumor implants. Local ATR was defined as recurrence in the perinephric region, and distant ATR as recurrence elsewhere in the abdomen or carcinomatosis. Clinical data for patients receiving care at Memorial Sloan Kettering Cancer Center (MSKCC; New York, NY, USA) were obtained from the electronic medical record. For patients who underwent their initial MIS PN or RN at an external institution but received subsequent care at MSKCC, clinical and pathological documentation was obtained before their transfer.

Data for baseline demographic characteristics (age, sex, race), tumor characteristics (size, histological subtype, grade, stage, surgical margin status), and surgical characteristics (laparoscopic or robot-assisted PN or RN) were recorded. Treatment for patients with ATR included surgical resection, systemic therapy (tyrosine kinase inhibitors, mTOR inhibitors, immune checkpoint inhibitors, chemotherapy), thermal ablation, radiation therapy, and best supportive care.

Descriptive statistics, including the median and interquartile range (IQR), were used to summarize perioperative patient characteristics. The last available follow-up data were collected to generate survival projections. The main objective was to analyze time to ATR, which was calculated as the time from the initial MIS PN or RN to the time of first ATR. The secondary objective was to determine overall survival (OS) reported from both the initial MIS and from the time of ATR. OS estimates were computed using the Kaplan-Meier method from time of MIS PN or RN to death or last follow-up. Outcomes were compared using Wilcoxon rank-sum and log-rank tests. Analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Data for 58 patients treated for ATR after MIS PN or RN, ten of whom received all of their care at MSKCC, were analyzed (Table 1). Twenty-six patients (45%) underwent robot-assisted operations. The median age was 61 yr (IQR 54–69) and patients were predominantly male (71%), and White (88%). The median primary tumor size was 5.7 cm (IQR 4.0–8.0). Tumor detection was incidental in 24 patients (41%), while 23 (40%) had local symptoms and six (10%) had systemic symptoms. Thirty-nine patients (67%) had clear-cell RCC (ccRCC) and 43 (74%) had high-grade disease. Nineteen patients (33%) had non–clear-cell RCC (nccRCC). Twenty-nine patients (50%) had pathologic stage pT1 disease (median tumor size 4.3 cm, IQR 3.2-5.8, 13 T1a, 16 T1b), 23 (79%) of whom underwent PN, and six (26%) had positive surgical margins. Of the remaining patients, six (10%) had stage pT2 disease (median tumor size 9.5 cm, IQR 8.1–10.9) and 21 (36%) had stage pT3 disease (median tumor size 8.0 cm, IQR 4.6–9.5). Information on pT stage was not available for two patients. Of the 21 cases with pT3 disease, 18 were pT3a and three were pT3b, and 17 (81%) had ccRCC. Positive surgical margins were present in ten patients (17%, seven pT1 and three pT3), eight of whom had undergone MIS PN. Of these ten patients with positive margins, two (20%) had sarcomatoid features and five (50%) had high-grade cancers (four ccRCC and one unclassified on pathology).

Recurrence details are summarized in Table 2. The median time from the index operation to ATR diagnosis was 12 mo (IQR 5–28 mo; Fig. 2A). Thirty-six patients (62%) experienced recurrence within 18 mo, 16 (28%) between 18 and

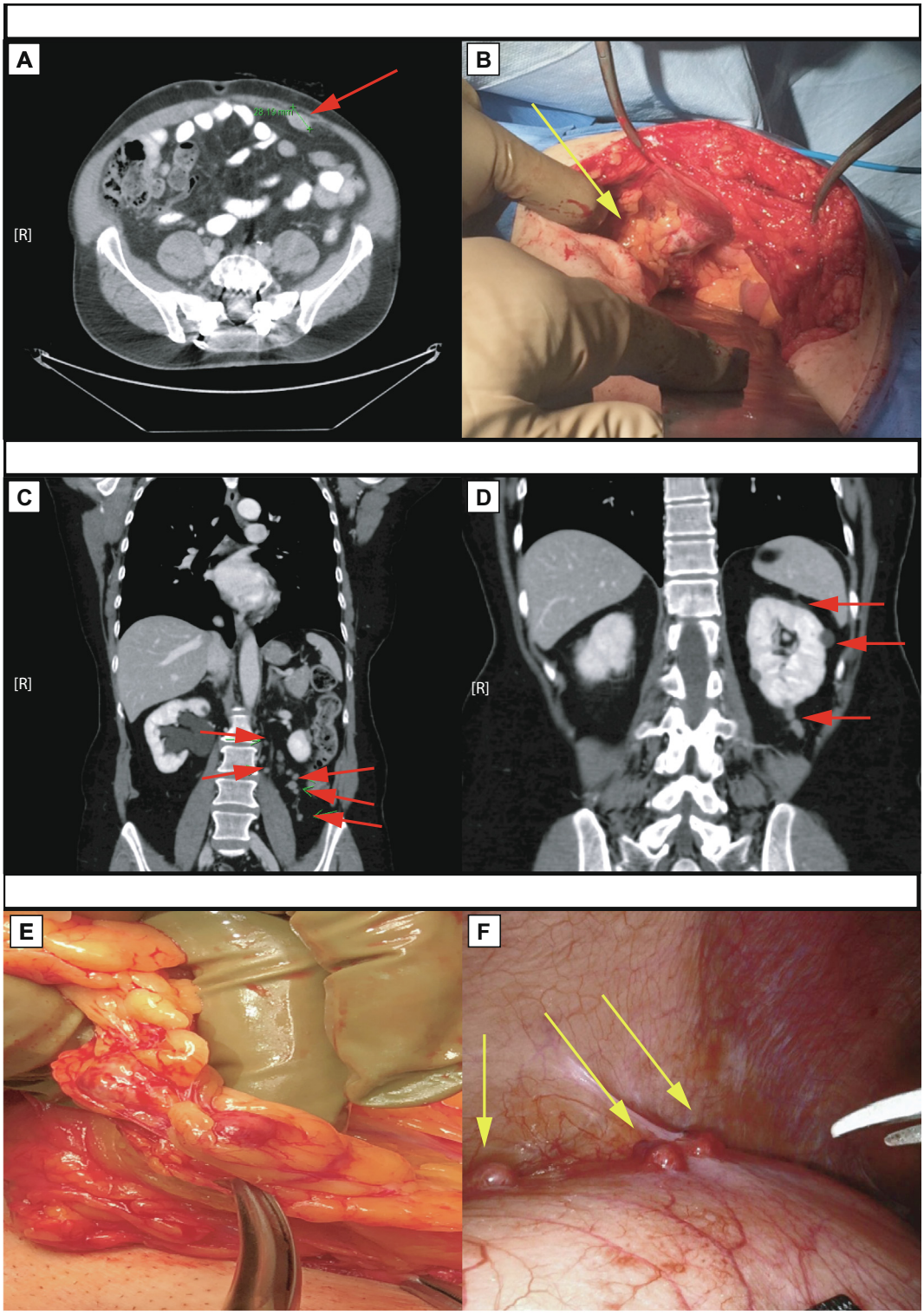


Fig. 1 – Atypical tumor recurrences following minimally invasive surgery for kidney cancer. (A) Computed tomography (CT) imaging and (B) gross view of a 2.8-cm port-site tumor. (C, D) Images for a 61-yr-old patient who underwent left robotic partial nephrectomy with perinephric implants on coronal CT. Implants are denoted by red arrows. (E) Omental implants. (F) Laparoscopic view of numerous peritoneal implants denoted by yellow arrows.

60 mo, and six (10%) at >60 mo (one at 231 mo), and five of these six had nccRCC histology. ATR was incidentally detected in 83% of cases, occurred at distant sites in 57%, and involved the nephrectomy bed/perinephric tumor implants alone in 48% or in conjunction with intraperitoneal and port-site metastases in 29% of cases. Port-site metastases occurred in 22% of patients and were isolated in 5% and with other sites in 17%. For 12% of patients, intraperitoneal metastases were the sole ATR. There was no significant difference in time to recurrence between the ccRCC

Table 1 – Summary of clinicopathologic characteristics

Parameter	Result
Patients (*n*)	58
Median age at procedure, yr (interquartile range)	61 (54–69)
Sex, *n* (%)	
Male	41 (70.7)
Female	17 (29.3)
Race, *n* (%)	
White	51 (87.9)
Other	2 (3.4)
Asian	1 (1.7)
Not available	4 (6.9)
Body mass index, *n* (%)	
Not obese (<30 kg/m^2)	31 (53.4)
Obese (≥30 kg/m^2)	25 (43.1)
Not available	2 (3.4)
Presentation, *n* (%)	
Incidental	24 (41.4)
Local	23 (39.7)
Systemic	6 (10.3)
Not available	5 (8.6)
Hospital type, *n* (%)	
Academic	42 (72.4)
Community	16 (27.6)
Laterality, *n* (%)	
Left	28 (48.3)
Right	30 (51.7)
Procedure type, *n* (%)	
Partial nephrectomy	30 (55.2)
Radical nephrectomy	28 (48.3)
Procedure technique, *n* (%)	
Laparoscopic	32 (55.2)
Robotic	26 (44.8)
Pathology reviewed, *n* (%)	
Yes	55 (94.8)
No	3 (5.2)
Histology, *n* (%)	
Clear cell	39 (67.2)
Non–clear cell	19 (32.8)
Sarcomatoid, *n* (%)	
No	48 (82.8)
Yes	10 (17.2)
Rhabdoid, *n* (%)	
No	54 (93.1)
Yes	4 (6.9)
Median tumor size, cm (interquartile range)	5.7 (4.0–8.0)
pT stage, *n* (%)	
T1	29 (50.0)
T2	6 (10.4)
T3	21 (36.2)
Not available	2 (3.4)
Fuhrman grade, *n* (%)	
Low (grade 1/grade 2)	8 (13.8)
High (grade 3/grade 4)	43 (74.1)
Not available	7 (12.1)
Margin status, *n* (%)	
Negative	46 (79.3)
Positive	10 (17.2)
Not available	2 (3.4)

Table 2 – Recurrence details

Parameter	Result
Patients (*n*)	58
Median time to recurrence, mo (interquartile range)	12 (5.3–28)
First recurrence presentation, *n* (%)	
Incidental	48 (82.8)
Local	6 (10.3)
Systemic	4 (6.9)
First recurrence location, *n* (%)	
Distant	33 (56.9)
Local	25 (43.1)
Atypical recurrence location, *n* (%)	
Perinephric/nephrectomy bed	28 (48.3)
Intraperitoneal	7 (12.1)
Port site	3 (5.2)
Perinephric/nephrectomy bed + intraperitoneal	10 (17.2)
Perinephric/nephrectomy bed + port site	6 (10.3)
Intraperitoneal + port site	3 (5.2)
Perinephric/nephrectomy bed + intraperitoneal + port site	1 (1.7)
Disease status at last follow-up, *n* (%)	
Alive with disease	28 (48.3)
Deceased	21 (36.2)
No evidence of disease	9 (15.5)

(median 8 mo, IQR 5–21) and nccRCC groups (median 18 mo, IQR 6–62; Wilcoxon rank-sum test, $p = 0.1$; Supplementary Fig. 1A). However, high-grade tumors recurred sooner than low-grade tumors (median 7 mo, IQR 5–18 vs median 31 mo, IQR 12–51; Wilcoxon rank-sum test, $p = 0.004$).

Multiple treatment modalities were used for the ATR patients (Table 3) and included surgery in 37 patients (64%), as the sole treatment in 11 (19%) and in conjunction with systemic therapy, thermal ablation, or radiation therapy in 26 (45%). Two or more surgical resections were performed in 37 patients (64%) and three or more in 13 patients (21%), while six patients (10%) underwent four or more resections. In two patients, ablation was repeated a second time. As summarized in Table 3, a full array of contemporary systemic therapies including tyrosine kinase, mTOR, and immune checkpoint inhibitors, interleukin 2, and chemotherapy were used alone or in combination.

After a median of 59 mo (IQR 28–92), 21 patients (36%) had died of disease (median time to death 31 mo, IQR 10–59), 28 (48%) are alive with disease (IQR 4.6–108 mo), and nine (16%) are alive with no evidence of disease (IQR 71–104 mo). Overall 5-yr survival from the time of the index MIS procedure to last follow-up or death was 69.1% (95% confidence interval [CI] 57.4–83.2%; Fig. 2B). Overall 5-yr survival from the time of ATR to last follow-up or death was 58.4% (95% CI 45.2–75.5%) at median follow-up of 41 mo (IQR 19–59). Disease-free status was achieved via surgery in eight patients (alone in four, combined with systemic therapy in three, and with thermal ablation therapy in one) and via systemic chemotherapy in a single patient. All deceased patients had documented RCC-specific deaths. The 5-yr OS was comparable between the ccRCC (67.3%, 95% CI 53.0–85.6%) and nccRCC (72.7%, 95% CI 54.9–96.3%) groups (log-rank test, $p = 0.5$; Supplementary Fig. 1D). Of the 29 patients with pT1 disease, the median time to ATR was 15 mo (IQR 7–34); nine have died of disease, 16 are alive with disease, and four have no evidence of disease. All the patients with low-grade tumors remain alive despite ATR (Supplementary Fig. 1F).

4. Discussion

We have described 58 patients with localized kidney tumors who developed ATR following MIS PN or RN. There was no consistent approach to the management of ATR that we could observe. Salvage efforts for these patients led to a large treatment burden, including repeat operations in 64%, either alone or in combination with systemic therapy, and thermal ablation. Only nine patients (16%) were rendered free of disease and 28 (48%) are surviving with evidence of disease. For patients with pT1 renal cancers, validated nomograms predict a 5-yr recurrence rate of <5% [17,18].

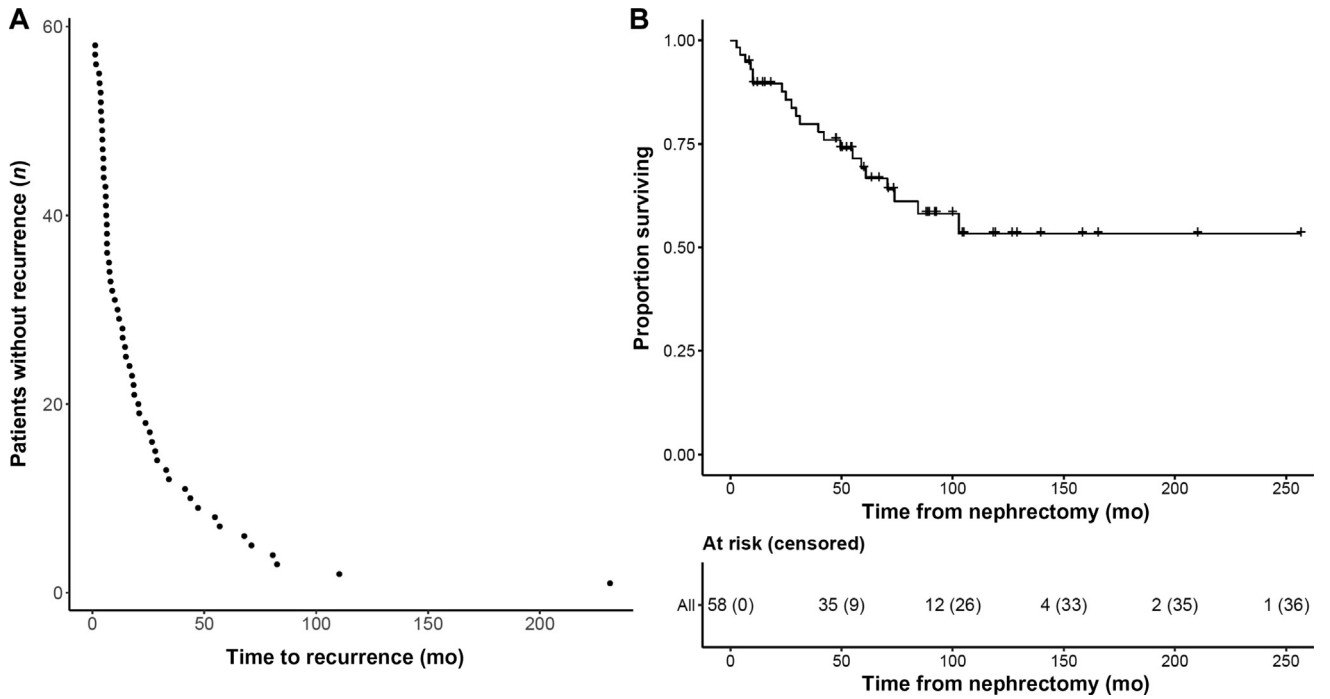


Fig. 2 – Oncologic outcomes. (A) The median time from the index operation to atypical tumor recurrence was 12 mo (interquartile range 5–28). (B) Kaplan-Meier overall survival curve (from the index minimally invasive surgery to last follow-up or death). The 5-yr overall survival estimate was 69.1% (95% confidence interval 57.4–83.2%).

Table 3 – Summary of salvage attempts

Treatment type	Patients, *n* (%)
Surgery alone	11 (19.0)
Systemic therapy alone	
TKI (sunitinib, pazopanib)	9 (15.5)
ICI (ipilimumab + nivolumab)	1 (1.7)
Immunotherapy (interleukin-2)	1 (1.7)
mTOR inhibitor (temsirolimus)	1 (1.7)
Radiation therapy alone	1 (1.7)
Surgery + systemic therapy	
TKI (sunitinib, pazopanib)	8 (13.8)
ICI (ipilimumab + nivolumab)	5 (8.6)
mTOR inhibitor (everolimus, temsirolimus)	2 (3.4)
TKI + ICI (cabozantinib + ipilimumab/nivolumab)	1 (1.7)
Chemotherapy (doxorubicin + gemcitabine)	1 (1.7)
Surgery + ablation	3 (5.2)
Surgery + systemic therapy + ablation	
TKI (pazopanib)	1 (1.7)
TKI + ICI (axitinib + pembrolizumab)	1 (1.7)
Surgery + systemic therapy + radiation	
TKI (pazopanib)	1 (1.7)
TKI + ICI (cabozantinib + nivolumab)	1 (1.7)
TKI + mTOR inhibitor (lenvatinib + everolimus)	1 (1.7)
Surgery + systemic therapy + ablation + radiation	
TKI + ICI (axitinib + pembrolizumab)	1 (1.7)
No treatment (supportive care)	8 (13.8)

ICI = immune checkpoint inhibitor; TKI = tyrosine kinase inhibitor.

However, for the 29 patients with T1 disease (50%) and ATR, nine have died of disease, 16 are alive with disease, and only four have no evidence of disease. These poor clinical outcomes suggest a significant alteration in the natural history for T1 disease among patients experiencing ATR.

MIS has evolved over the past 40 yr from a diagnostic operation in benign conditions (ectopic pregnancy) and cancer care (exclusion of peritoneal metastatic disease before open resection of visceral malignancies) to a therapeutic operation in both benign and malignant diseases [19]. Many curative-intent cancer operations across all subspecialties of surgical oncology are now performed via MIS [20]. However, the literature is replete with reports of ATR involving port sites and intraperitoneal carcinomatosis emanating from virtually all organ sites treated [6–15]. Interestingly, a large, randomized trial of adjuvant systemic chemotherapy in kidney cancer (ASSURE, ≥T1b) [21] and a study using Surveillance, Epidemiology and End Results (SEER) data linked to Medicare claims (≤T1b) [22] did not find significant differences in oncologic outcomes, including overall survival, cancer-specific survival, and local recurrence patterns, between open and MIS approaches.

However, a large, randomized trial in stage 1 cervical cancer compared open to MIS hysterectomy, the latter of which was associated with a 10.6% decrease in disease free survival (HR 3.74), a lower rate of overall survival (93.8% vs 99%, HR 6.00), and a greater likelihood of locoregional recurrence (HR 4.26) [23]. Of note, patients with recurrent cervical cancer were centered in 14 of the 33 centers suggesting that variability in surgical expertise could play a role in these findings. Two additional studies comparing open to MIS hysterectomy in early-stage cervical cancer, one with 2461 patients using the National Cancer Database and SEER [24], and the other a meta-analysis of 9499 patients [25], also reported significantly higher mortality rates for MIS treated patients. In response to these reports, the US Food and Drug Administration (FDA) issued a warning in 2018 regarding robot-assisted surgical (RAS) devices, updated again in 2021, as follows: "RAS devices have been cleared for use in certain types of surgical procedures commonly performed in patients with cancer, such as hysterec-

tomy, prostatectomy, and colectomy. These clearances are based on short-term (30 day) patient follow up. The FDA has not evaluated the safety or effectiveness of RAS devices for the prevention or treatment of cancer, based on cancer-related outcomes such as overall survival, recurrence, and disease-free survival." [26]. Recently reported robot-assisted RPLND for testis cancer associated ATR similarly led to a large treatment burden and poor clinical outcomes in patients with the potential for 60 years of survival and raised the question whether rapid recovery is ever worth even a small possibility for such catastrophic outcomes [14]. In response to these emerging MIS-related oncologic concerns, gynecological oncologists at major centers have suspended MIS hysterectomy in early-stage cervical cancer [27]. However, other centers reported no significant differences between MIS and open radical hysterectomy and continue to use MIS routinely [28].

Our understanding of the diversity of renal cortical tumors has evolved over the past 20 yr and we now know that these are a complex group of more than 30 tumors with distinct pathologic, genomic, metabolic, and metastatic capabilities [29]. The ccRCC subtype accounts for 70% of the renal cortical tumors that metastasize, whereas nccRCC metastasizes much less often but is more resistant to contemporary systemic therapies [30]. In our series, 39 patients had ccRCC (67%) and 19 had nccRCC (33%). Of the 28 patients who are alive with disease, 19 had ccRCC (68%) and nine had nccRCC (32%). Of the six patients who experienced relapse at >60 mo, five had nccRCC, including one patient diagnosed with intra-abdominal and port-site metastases at 231 mo (papillary type 1 RCC). The intrinsic malignant potential of the index tumor, as determined by histologic subtype, tumor grade, and the presence or absence of sarcomatoid features [31], probably contributes to the pace at which the ATR will progress to more widespread metastatic disease or remain static without subsequent metastatic progression. As shown in Supplementary Fig. 1F, all the patients with low-grade tumor remain alive.

The etiology of ATR is unknown but is probably multifactorial and could include direct wound implantation, tumor-cell contamination of surgical instruments, aerosolization of tumor cells escaping from an insufflated abdominal cavity (chimney effect), violation of tumor capsules during dissection or forced extraction through the abdominal wall, and extravasation of malignant cells into vascular and lymphatic spaces in a positive-pressure environment [32,33]. Case series describing needle-tract seeding following percutaneous renal mass biopsy, considered a rare event in the current era of coaxial biopsy devices, lends credence to the notion that renal tumor capsular violation can have an adverse oncologic impact [34]. Surgical experience and a surgeon's position on the MIS learning curve for complex operations such as PN and RN is a difficult metric, but misadventures early in a surgeon's experience could also contribute to ATR [7,10,12,19]. Maneuvers to prevent MIS tumor-cell contamination include the use of extraction bags, minimizing trocar CO_2 leakage, avoiding tumor morcellation, cleansing of instruments before reuse, changing of gloves after tumor extraction, avoiding violation of the tumor's natural capsule, and cleansing of port sites with povidone iodine [11]. The adverse impact of a positive surgical margin during MIS PN could also theoretically lead to ATR via aerosolization of tumor cells after inadvertent entry into the tumor and/or its pseudocapsule [35]. In a PN series, Shah et al. [36] found that a positive surgical margin (7.8% of patients) after either MIS or open surgery led to a 2.08-fold greater risk of recurrence. Ten patients (17%) in our study had positive surgical margins, of whom eight (six pT1 and two pT3) had undergone MIS PN and five had high-grade cancers.

Our study has significant limitations. It represents a small subset of patients managed at our center and is subject to referral, detection, and selection biases. We also understand that patients who experienced an unsatisfactory oncologic outcome following MIS PN or RN with ATR may seek specialized surgical and medical oncologic care at our center and that our experience may not reflect that of other general hospitals or medical centers. In the absence of central reporting of such events or a national registry, the precise incidence of ATR cannot be determined because the denominator is unknown. We know that local tumor recurrence due to disease natural history and/or technical issues can also occur following open kidney surgery [21,37,38]. However, perinephric seeding, peritoneal implants, and port-site metastases probably represent a unique pattern of recurrences related to the techniques and the surgical environment of kidney MIS. Research is ongoing to update our experience with local recurrence after both MIS and open kidney surgery to draw a more accurate comparison. Although we do not have a formal "control" group, during this study period we identified 19 patients (14 PN and five RN) who developed isolated local recurrences at our center (unpublished data). However, for this subset of patients, our data indicates that if ATR occurs after curative-intent MIS for kidney tumors, the ensuing clinical course predicts a heavy treatment burden and poor prognosis.

The widespread adoption of MIS, now largely robot-assisted in urology, particularly in the USA and Europe, has come with considerable commitment of medical center resources and operating room time. However, in a recent systematic review of 50 studies of abdominopelvic operations involving nearly 5000 patients, Dhanani et al. [39] did not observe a clear advantage for robot-assisted, laparoscopic, or open approaches in terms of intraoperative complications, conversion rates, and long-term outcomes. Going forward, carefully conducted clinical trials, free of commercial bias and conflicts of interest, are essential for the medical community to accurately judge the oncologic and economic value of these innovative approaches and their comparative effectiveness [40].

As MIS approaches to kidney tumors expand, it is our hope that this report will encourage surgeons to scrutinize their kidney cancer data sets for evidence of ATR and create collaborations that will more accurately define its incidence to understand its potential causes and to create quality improvement strategies to prevent this highly morbid event.

5. Conclusions

The precise incidence of ATR following MIS for kidney tumors is unknown. However, our real-world management

of 58 patients indicates that when ATR does occur, there is a heavy treatment burden involving reoperations, ablation, radiation, and systemic therapy, and a guarded prognosis for overall and recurrence-free survival. Understanding the mechanisms underlying ATR occurrence will address the recent FDA missive [34] and improve informed consent by better describing all the potential risks, benefits, and alternatives for patients and physicians considering MIS for kidney tumors.

Author contributions: Paul Russo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Russo.
Acquisition of data: Blum, Weng.
Analysis and interpretation of data: Blum, Russo, Weng.
Drafting of the manuscript: Russo, Weng, Blum.
Critical revision of the manuscript for important intellectual content: Russo, Bex, Graafland.
Statistical analysis: Blum, Weng.
Obtaining funding: Russo.
Administrative, technical, or material support: Blum, Weng.
Supervision: Russo.
Other: None.

Financial disclosures: Paul Russo certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This work was supported by The Sidney Kimmel Center for Prostate and Urologic Cancers and in part through NIH/NCI Cancer Center Support Grant P30 CA0087848 and the Stephen P. Hanson Family Fund in Kidney Cancer Research. The sponsors played a role in data collection and management.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.04.005.

References

[1] Clayman RV, Kavoussi LR, Soper NJ, et al. Laparoscopic nephrectomy. N Engl J Med 1991;324:1370–1.
[2] Klingler DW, Hemstreet GP, Balaji KC. Feasibility of robotic radical nephrectomy—initial results of single-institution pilot study. Urology 2005;65:1086–9.
[3] Patel HD, Mullins JK, Pierorazio PM, et al. Trends in renal surgery: robotic technology is associated with increased use of partial nephrectomy. J Urol 2013;189:1229–35.
[4] Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European Association of Urology guidelines on renal cell carcinoma: the 2019 update. Eur Urol 2019;75:799–810.
[5] Ghani KR, Sukumar S, Sammon JD, Rogers CG, Trinh Q-D, Menon M. Practice patterns and outcomes of open and minimally invasive partial nephrectomy since the introduction of robotic partial nephrectomy: results from the nationwide inpatient sample. J Urol 2014;191:907–12.
[6] Curet MJ. Port site metastases. Am J Surg 2004;187:705–12.
[7] Schaeff B, Paolucci V, Thomopoulos J. Port site recurrences after laparoscopic surgery. A review. Dig Surg 1998;15:124–34.
[8] Maarschalk J, Robinson SM, White SA. Port site metastases following laparoscopic liver resection for hepatocellular carcinoma. Ann R Coll Surg Engl 2015;97:e52–3.
[9] Iavazzo C, Gkegkes ID. Port-site metastases in patients with gynecological cancer after robot-assisted operations. Arch Gynecol Obstet 2015;292:263–9.
[10] Tsivian A, Sidi AA. Port site metastases in urological laparoscopic surgery. J Urol 2003;169:1213–8.
[11] Castillo OA, Vitagliano G. Port site metastasis and tumor seeding in oncologic laparoscopic urology. Urology 2008;71:372–8.
[12] Micali S, Celia A, Bove P, et al. Tumor seeding in urological laparoscopy: an international survey. J Urol 2004;171:2151–4.
[13] El-Tabey NA, Shoma AM. Port site metastases after robot-assisted laparoscopic radical cystectomy. Urology 2005;66:1110.
[14] Calaway AC, Einhorn LH, Masterson TA, Foster RS, Cary C. Adverse surgical outcomes associated with robotic retroperitoneal lymph node dissection among patients with testicular cancer. Eur Urol 2019;76:607–9.
[15] Masterson TA, Russo P. A case of port-site recurrence and locoregional metastasis after laparoscopic partial nephrectomy. Nat Clin Pract Urol 2008;5:345–9.
[16] Song J, Kim E, Mobley J, et al. Port site metastasis after surgery for renal cell carcinoma: harbinger of future metastasis. J Urol 2014;192:364–8.
[17] Kattan MW, Reuter V, Motzer RJ, Katz J, Russo P. A postoperative prognostic nomogram for renal cell carcinoma. J Urol 2001;166:63–7.
[18] Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer 2003;97:1663–71.
[19] Lau WY, Leow CK, Li AK. History of endoscopic and laparoscopic surgery. World J Surg 1997;21:444–53.
[20] Chang J, Rattner DW. History of minimally invasive surgical oncology. Surg Oncol Clin N Am 2019;28:1–9.
[21] Lee Z, Jegede OA, Haas NB, et al. Local recurrence following resection of intermediate-high risk nonmetastatic renal cell carcinoma: an anatomical classification and analysis of the ASSURE (ECOG-ACRIN E2805) adjuvant trial. J Urol 2020;203:684–9.
[22] Auffenberg GB, Curry M, Gennarelli R, Blum KA, Elkin E, Russo P. Comparison of cancer specific outcomes following minimally invasive and open surgical resection of early stage kidney cancer from a national cancer registry. J Urol 2020;203:1094–100.
[23] Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895–904.
[24] Melamed A, Margul DJ, Chen L, et al. Survival after minimally invasive radical hysterectomy for early-stage cervical cancer. N Engl J Med 2018;379:1905–14.
[25] Nitecki R, Ramirez PT, Frumovitz M, et al. Survival after minimally invasive vs open radical hysterectomy for early-stage cervical cancer. JAMA Oncol 2020;6:1019. https://doi.org/10.1001/jamaoncol.2020.1694.
[26] US Food and Drug Administration. Caution when using robotically-assisted surgical devices in women's health including mastectomy and other cancer-related surgeries: FDA safety communication. Silver Spring, MD: US FDA; 2019. https://www.fda.gov/medical-devices/safety-communications/caution-when-using-robotically-assisted-surgical-devices-womens-health-including-mastectomy-and.
[27] Zhang Y, Chen S. Reconsider minimally invasive surgery for early cervical cancer. Ann Transl Med 2019;7:S111.
[28] Brandt B, Sioulas V, Basaran D, et al. Minimally invasive surgery versus laparotomy for radical hysterectomy in the management of early-stage cervical cancer: survival outcomes. Gynecol Oncol 2020;156:591–7.
[29] Signoretti S, Flaifel A, Chen Y-B, Reuter VE. Renal cell carcinoma in the era of precision medicine: from molecular pathology to tissue-based biomarkers. J Clin Oncol 2018;36:3553–9.

[30] Russo P. A well organised effort to metastatic non-clear-cell renal cell carcinoma. Lancet Oncol 2019;20:472–3.
[31] Molina AM, Tickoo SK, Ishill N, et al. Sarcomatoid-variant renal cell carcinoma: treatment outcome and survival in advanced disease. Am J Clin Oncol 2011;34:454–9.
[32] Johnstone PA, Rohde DC, Swartz SE, Fetter JE, Wexner SD. Port site recurrences after laparoscopic and thoracoscopic procedures in malignancy. J Clin Oncol 1996;14:1950–6.
[33] Sooriakumaran P, Kommu SS, Anderson C, Rane A. Port-site metastasis after laparoscopic surgery: what causes them and what can be done to reduce their incidence? BJU Int 2009;103:1150–3.
[34] Macklin PS, Sullivan ME, Tapping CR, et al. Tumour seeding in the tract of percutaneous renal tumour biopsy: a report on seven cases from a UK tertiary referral centre. Eur Urol 2019;75:861–7.
[35] Verhagen PCMS, Boevé ER. The European Association of Urology guideline on renal cell carcinoma (RCC) is not concise in its recommendation to perform partial nephrectomy in T1b RCC. Eur Urol 2019;76:132–3.
[36] Shah PH, Moreira DM, Okhunov Z, et al. Positive surgical margins increase risk of recurrence after partial nephrectomy for high risk renal tumors. J Urol 2016;196:327–34.
[37] Bruno JJ, James Bruno J, Snyder ME, Motzer RJ, Russo P. Renal cell carcinoma local recurrences: impact of surgical treatment and concomitant metastasis on survival. BJU Int 2006;97:933–8.
[38] Russo P, Jang TL, Pettus JA, et al. Survival rates after resection for localized kidney cancer: 1989 to 2004. Cancer 2008;113:84–96.
[39] Dhanani NH, Olavarria OA, Bernardi K, et al. The evidence behind robot-assisted abdominopelvic surgery: a systematic review. Ann Intern Med 2021;174:1110–7.
[40] Schiavone MB, Kuo EC, Naumann RW, et al. The commercialization of robotic surgery: unsubstantiated marketing of gynecologic surgery by hospitals. Am J Obstet Gynecol 2012;207:174.e1–7.