Kidney Cancer

Outcomes for Atypical Tumor Recurrences Following Minimally Invasive Kidney Cancer Operations

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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.

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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.

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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
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...
Tables 1 and 2 – Clinicopathologic Characteristics and Recurrence Details

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%, as the sole treatment in 11% 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 chemotheraphy 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).

**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/m²)       | 31 (53.4) |
| Obese (>30 kg/m²)           | 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)  |
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-

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**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 ( caboazitinib + 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 ( caboazitinib + 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.
otomy, 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 CO₂ 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, ablative, 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, Graalnd.

**Statistical analysis**: Blum, Weng.

**Obtaining funding**: Russo.

**Administrative, technical, or material support**: Blum, Weng.

**Supervision**: Russo.

**Other**: None.

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**Appendix A. Supplementary data**

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

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