Outcomes of Atypical Tumor Recurrences Following Minimally Invasive Kidney Cancer Surgery

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Abstract

We looked after a group of patients who had Minimally Invasive Surgery (MIS) for a kidney tumor and had Atypical Tumor Recurrence (ATR) involving port sites, intraperitoneal carcinomatosis, and nephrectomy bed/perinephric tumor implants. The purpose of this study was to look at the clinical characteristics, management, and oncologic outcomes of patients with localized Renal Cell Carcinoma (RCC) who developed ATR after curative-intent MIS for partial or radical nephrectomy. Patients with localized RCC who developed ATR after MIS for partial or radical nephrectomy at Memorial Sloan Kettering Cancer Center (New York, NY, USA) from 1999 to 2021 were included in the study cohort. Measurement of outcomes and statistical analysis: We gathered information on clinicopathologic features, treatments, time to ATR, and overall survival.

The 58 RCC patients had a median age of 61 years. 41 patients (71%) were male, 26 (45%) underwent robot-assisted surgery, and 39 (67%) had clear cell RCC. 29 patients (50%) had stage pT1 disease, with ten (17%) having positive surgical margins.

Keywords: Non-Small Cell Lung Cancer (NSCLC) • Carbon-Ion Radiotherapy (CIRT) • Dose escalation • Efficacy • Toxicity

Introduction

Beginning with laparoscopic Radical Nephrectomy (RN) in 1991, robot-assisted laparoscopic RN in 2000, and the development of laparoscopic and robot-assisted Partial Nephrectomy (PN) over the last two decades, Minimally Invasive Surgery (MIS) for the treatment of kidney tumors has evolved over the last 30 years. Cosmetic incisions, shorter hospitalization, less pain, and a faster return to normal activity are among the reported benefits of MIS. The metrics for short-term oncologic efficacy and safety for MIS appeared to be comparable to those for open approaches. Robot-assisted laparoscopy for urologic cancers is now the most common type of MIS. However, reports of Atypical Tumor Recurrence (ATR) involving port sites and intraperitoneal carcinomatosis emanating from hepatobiliary, gastrointestinal, and gynecologic primary tumors have been reported since the beginning of MIS in cancer. Although the exact prevalence of ATR is unknown, estimates range from 0.7% to 4% [1]. ATR after MIS has been reported in urologic oncology with primary tumors of the prostate, bladder, testis, and kidney. There is debate over whether ATR is caused by technical factors during a MIS operation, tumor biology, or both. We describe clinicopathologic characteristics, therapeutic interventions, and oncologic outcomes from 58 patients who developed ATR after MIS PN or RN for localized kidney tumors. We searched 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 locations other than those seen in the natural course of kidney cancer, and it includes port sites, intraperitoneal carcinomatosis, and nephrectomy bed/perinephric tumor implants [2]. Recurrence in the perinephric region was defined as local ATR, and recurrence elsewhere in the abdomen or carcinomatosis was defined as distant ATR. The electronic medical record was used to obtain clinical data for patients receiving care at Memorial Sloan Kettering Cancer Center. Clinical and pathological data were collected from patients who had their initial MIS PN or RN at another facility but received subsequent care at MSKCC. Data were collected for baseline demographic characteristics (age, gender, and race), tumor characteristics (size, histological subtype, grade, stage, and surgical margin status), and surgical characteristics (laparoscopic or robot-assisted PN or RN). Surgical resection, systemic therapy (tyrosine kinase inhibitors, mTOR inhibitors, immune checkpoint inhibitors, and chemotherapy), thermal ablation, radiation therapy, and best supportive care were all options for patients with ATR [3].

To summarize perioperative patient characteristics, descriptive statistics such as the median and Interquartile Range (IQR) were used. To generate survival projections, the most recent available follow-up data were gathered. The primary goal was to examine time to ATR, which was calculated as the time between the initial MIS PN and RN and the first ATR.

The secondary goal was to calculate Overall Survival (OS) from both the initial MIS and the time of ATR. The Kaplan-Meier method was used to calculate OS estimates from the time of MIS PN or RN to death or last follow-up. Wilcoxon rank-sum and log-rank tests were used to compare outcomes. R version 3.5.3 was used for the analyses (R Foundation for Statistical Computing, Vienna, Austria) [4, 5].

We described 58 patients with locally advanced kidney tumors who developed ATR after MIS PN or RN. There was no consistent approach to ATR management that we could find. Rescue efforts for these patients resulted in a significant treatment burden, including 64% of patients requiring repeat operations, either alone or in combination with systemic therapy, and thermal ablation. However, of the 29 patients with T1 disease (50%) and ATR, nine have died as a result of the disease, 16 are still alive with the disease, and only four have no evidence of disease. These poor clinical outcomes suggest a significant change in the natural history of T1 disease in ATR patients.

Over the last 40 years, MIS has evolved from a diagnostic procedure in benign conditions (ectopic pregnancy) and cancer care (exclusion of peritoneal metastatic disease prior to open resection of visceral malignancies) to a therapeutic procedure in both benign and malignant diseases. Many curative-intent cancer operations are now performed using MIS in all surgical oncology subspecialties. However, reports of ATR involving port sites and intraperitoneal carcinomatosis emanating from virtually all organ sites abound in the literature.

Interestingly, no significant differences in oncologic outcomes, including overall survival, cancer-specific survival, and local recurrence patterns, were found between open and MIS approaches in a large, randomized trial of adjuvant systemic chemotherapy in kidney

cancer (ASSURE, T1b) and a study using Surveillance, Epidemiology, and End Results (SEER) data linked to Medicare claims (T1b). However, a large, randomized trial comparing open to MIS hysterectomy in stage 1 cervical cancer found that the latter 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 higher likelihood of locoregional recurrence (HR 4.26). In response to these reports, the US Food and Drug Administration (FDA) issued a warning about Robot-Assisted Surgical (RAS) devices in 2018, which was updated in 2021: "RAS devices have been cleared for use in certain types of surgical procedures commonly performed in cancer patients, such as hysterectomy, prostatectomy, and colectomy." These clearances are based on a 30-day patient follow-up. The FDA has not evaluated the safety or efficacy of RAS devices for cancer prevention or treatment based on cancer-related outcomes such as overall survival, recurrence, and disease-free survival." Recently reported robot-assisted RPLND for testis cancer-associated ATR resulted in a large treatment burden and poor clinical outcomes in patients with a 60-year survival potential [6].

In response to these emerging MIS-related oncologic concerns, major centers' gynecological oncologists have halted MIS hysterectomy in early-stage cervical cancer. Other centers, however, found no significant differences between MIS and open radical hysterectomy and continue to use MIS on a regular basis. Over the last two decades, our understanding of the diversity of renal cortical tumors has evolved, and we now know that they are a complex group of more than 30 tumors with distinct pathologic, genomic, metabolic, and metastatic capabilities. The ccRCC subtype accounts for 70% of metastasizing renal cortical tumors, whereas nccRCC metastasizes much less frequently but is more resistant to current systemic therapies. In our study, 39 patients (67%) had ccRCC and 19 (33%). Among the 28 patients. The etiology of ATR is unknown, but it is likely 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), tumor capsule violation during dissection or forced extraction through the abdominal wall, and extravasation of malignant cells into vascular and lymphatic spaces in a positive-pressure environment. A case series describing needle-tract seeding after percutaneous renal mass biopsy, which is considered a rare event in the current era of coaxial biopsy devices, lends support to the idea that renal tumor capsular violation can have a negative oncologic impact. Surgical experience and a surgeon's position on the MIS learning curve for complex operations like PN and RN is a difficult metric to measure, but missteps early in a surgeon's career could also contribute to ATR. Using extraction bags, minimizing trocar CO_2 leakage, avoiding tumor morcellation, cleaning instruments before reuse, changing gloves after tumor extraction, avoiding violation of the tumor's natural capsule, and cleaning port sites with povidone iodine are all ways to avoid MIS tumor-cell contamination. A positive surgical margin during MIS PN could theoretically lead to ATR via tumor cell aerosolization after inadvertent entry into the tumor and/or its pseudocapsule. The widespread use of MIS, now largely robot-assisted in urology, has required a significant commitment of medical center resources and operating room time, particularly in the United States and Europe. Dhanani et al. found no clear advantage for robot-assisted, laparoscopic, or open approaches in terms of intraoperative complications, conversion rates, and long-term outcomes in a recent systematic review of 50 studies of abdominopelvic operations involving nearly 5000 patients [7]. In the future, carefully designed clinical trials free of commercial bias and conflicts of interest will be required for the medical community to accurately assess the oncologic and economic value of these novel approaches, as well as their comparative effectiveness.

Conclusion

The exact incidence of ATR after MIS for kidney tumors is unknown. Our real-world experience with 58 patients, however, shows that when ATR occurs, there is a significant treatment burden involving reoperations, ablation, radiation, and systemic therapy, as well as a guarded prognosis for overall and recurrence-free survival. Understanding the mechanisms underlying ATR occurrence will help to address the recent FDA missive and improve informed consent by better describing all of the potential risks, benefits, and alternatives for patients and doctors considering MIS for kidney tumors.

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