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REVIEW

Surgical approach and atypical recurrence after radical nephrectomy: considerations for cytoreductive nephrectomy in the metastatic setting

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Abstract

Radical nephrectomy (RN) remains an important therapeutic option in the management of renal cell carcinoma (RCC), including in the metastatic setting where cytoreductive nephrectomy (CN) may be pursued in select patients with good performance status and limited disease burden. While typical patterns of recurrence after CN are well established, atypical intraperitoneal recurrences (ATR) have emerged as rare but clinically relevant events in the era of improved systemic therapies and prolonged survival. In this structured literature review, we identified and analyzed 80 studies describing ATR after RN (localized or metastatic). We found that the majority of reported ATRs occurred following minimally invasive surgical approaches, including laparoscopic and robotic-assisted nephrectomy. Risk factors for ATR include high tumor grade, sarcomatoid differentiation, tumor necrosis, and potential surgical factors such as tumor spillage, specimen morcellation, and improper use of retrieval bags. Although technical breaches were implicated in several cases, ATR may also arise independent of these factors, likely reflecting the complex interplay between tumor biology, surgical approach, and host factors. The current evidence is limited by retrospective design, publication bias, and lack of standardization in reporting. Our findings underscore the need for future multicenter prospective studies with consistent definitions and long-term surveillance to better characterize ATR incidence and outcomes. Additionally, technical refinements such as strict adherence to oncologic principles, containment during specimen extraction, and avoidance of morcellation in high-risk cases may mitigate risk. As CN becomes more widely employed alongside modern systemic therapies, understanding and mitigating the risk of ATR will be critical in optimizing surgical decision-making in the metastatic RCC population.

Keywords: Renal cell carcinoma, cytoreductive nephrectomy, atypical recurrence, port-site metastasis, minimally invasive surgery

Introduction

Radical nephrectomy (RN) has historically been a cornerstone of treatment for renal cell carcinoma (RCC) across both localized and metastatic disease settings. In patients with metastatic RCC (mRCC), cytoreductive nephrectomy (CN) remains part of the management algorithm for select patients with limited metastatic disease and good performance status (*i.e.* International Metastatic Renal Cell Carcinoma Disease Consortium [IMDC] low risk) [1-3]. As systemic therapies have improved and overall survival has increased, atypical intraperitoneal recurrence (ATR), such as peritoneal carcinomatosis or port-site metastases, is being recognized [4, 5]. ATR is rare but clinically relevant, and its pathogenesis remains poorly understood. The emergence of ATR may reflect not only improvements in imaging and surveillance but also possible surgical factors and tumor biology, particularly in the context of minimally invasive approaches [6]. Although most published cases describe ATR following nephrectomy for localized RCC, the growing use of CN in the metastatic setting necessitates a closer examination of recurrence patterns in this high-risk population. This review synthesizes avail-

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able data on ATR following RN, highlights technical and tumor-related risk factors, and explores implications for surgical practice, particularly in patients undergoing CN for metastatic disease.

Methods

We conducted a structured literature search of the National Library of Medicine database (PubMed) from January 1962 to February 2025 using search terms related to renal cell carcinoma, nephrectomy, cytoreductive nephrectomy, peritoneal carcinomatosis, port-site metastasis, and atypical recurrence. Appropriate MeSH terms and appropriate nesting and Boolean operators were used to modify the search. We analyzed and reviewed 80 studies. Eligible studies included all reports of atypical intraperitoneal or port-site recurrence following RN, in either the localized or metastatic setting. Reviews, meta-analyses, and case reports/series were also included. Editorials, commentaries and letters to the editor were excluded. Data extracted included surgical approach, recurrence pattern, tumor characteristics, histology, and patient outcomes.

Results

Surgical approaches

RN involves the surgical removal of the kidney, often with surrounding structures such as perirenal fat, regional lymph nodes, and the ipsilateral adrenal gland. According to the American Urological Association 2021 guidelines, clinicians should consider a RN for "patients with a solid or Bosniak 3-4 complex cystic renal mass with increased oncologic potential suggested by tumor size, renal mass biopsy, and/or imaging." This procedure can be performed by an open incision or with a minimally invasive approach (laparoscopic or robotic). These techniques differ in terms of invasiveness, recovery time, surgical complexity, and clinical outcomes. According to the GRAND study [7], which analyzed data from nearly 194,000 patients in Germany who underwent RN between 2005 and 2021, 83% of procedures were performed using open technique, 15% were laparoscopic, and 2.2% were robotic. Notably, this study highlighted a steady decline in the use of open approaches since 2005.

In open RN, a large abdominal or flank incision of approximately 10-20 cm allows the surgeon direct access to the kidney. In laparoscopic RN, the surgeon makes several incisions in the abdomen to insert a camera and specialized instruments. Robotic-assisted RN builds upon the laparoscopic approach, using a robotic system to enhance precision and dexterity, particularly in complex cases. In a retrospective population-based cohort study from 2004 to 2013, minimally invasive surgery was not associated with differences in overall survival or disease specific survival compared to open surgical resection [8]. In addition, the total hospital cost has been noted to be higher when the robotic-assisted approach is applied compared to open [9]. However, studies have demonstrated both perioperative recovery and cosmetic advantages to minimally invasive RN compared to open-surgery in well-selected patients [10].

Patients with high tumor burden, extensive local inflammation, or peritoneal adhesions may present with technical challenges, particularly for minimally invasive procedures. These conditions can obscure anatomical planes, increase operative time, and elevate the risk of complications. The use of pneumoperitoneum (insufflation of the abdomen with CO_2) during minimally invasive procedures has been hypothesized to promote tumor dissemination, although clinical evidence is limited. There is also concern regarding port-site metastasis, especially in the context of advanced or poorly contained tumors. Furthermore, tumor handling during laparoscopic or robotic extraction must be meticulous to prevent capsule rupture or tumor spillage. These risks highlight the importance of careful patient selection and surgical technique in RN.

Defining atypical intraperitoneal recurrence

RCC most commonly metastasizes to the lungs, liver, bone, brain or lymph nodes, typically via hematogenous or lymphatic routes. Following RN in the localized setting, recurrences are mostly commonly found at these sites, or locally within the renal fossa itself, especially in the setting of positive surgical margin. Nearly half of all recurrences occur within two years of surgical intervention [11]. ATR following nephrectomy can be defined as any recurrence of disease in an unusual anatomic location or within an unexpected timeline relevant to typical metastatic pattern of RCC. Sites of ATR that have been described in literature to date include but are not limited to thyroid, bladder, skeletal muscle, skin, peritoneal implants, port sites, and various gastrointestinal organs [12-17]. The mechanism by which ATR occurs has been debated. It is ultimately likely multifactorial and varies between patients. Proposed mechanisms include: accidental deposition of cancerous cells directly into surgical wounds especially during specimen extraction, aerosolization of tumor cells within the peritoneal cavity during insufflation or desufflation, immunomodulation from pneumoperitoneum, escape of tumor cells in lymphatic or vascular pathways in a pressurized abdomen, and spread via instruments that have violated tumor margins [6, 18-20]. The etiology of ATR is also likely heavily influenced by tumor biology, histopathologic factors, and local wound factors [21, 22]. The exact incidence of ATR is unknown, however in the largest available case series on ATR following partial or RN we see that ATR is often associated with poor prognosis even with extensive multidisciplinary treatment strategies [18].

Incidence and patterns

ATRs have a generally undefined incidence, estimated to range from 0.9% to 4% [21]. In the largest cohort to date, Russo *et al*. examined 58 patients who underwent nephrectomy for localized disease and subsequently de-

veloped ATR: 32 (55%) patients underwent laparoscopic surgery, while 26 (45%) underwent robotic surgery for their primary tumor. Clear cell carcinoma was the most common histology (67%), followed by sarcomatoid (17%) and rhabdoid (6.9%). In this patient cohort who developed ATR, most had localized disease at the time of nephrectomy: 29 (50%) had pT1 tumors, 6 (10%) had pT2, and 21 (36%) had locally advanced pT3 tumors. A total of 36 (62%) patients had recurrence within 18 months, 16 (28%) between 18 and 60 months, and six (10%) at > 60 months. Tumor recurrence was incidentally identified in 83% of cases (*i.e*. asymptomatic on imaging), with 57% occurring at distant sites. The nephrectomy bed or perinephric tumor implants were affected either alone in 48% of patients or alongside intraperitoneal and port-site metastases in 29%. Port-site metastases were observed in 22% of cases, appearing in isolation in 5% and with other metastatic sites in 17%. In 12% of patients, intraperitoneal metastases represented the only site of abdominal tumor recurrence. Unfortunately, this recurrence information was not specified between the robotic and laparoscopic cases. There was no significant difference in the time to recurrence between patients with clear cell RCC (ccRCC) (median 8 months, IQR 5–21) and those with non–ccRCC. At a median follow-up of 59 months, 21 patients (36%) had died (median time to death: 36 months), 28 (48%) were alive, and 9 (16%) had no evidence of disease. The overall 5-year survival from the time of ATR to last follow-up or death was 58.4% (95% CI: 45.2–75.5%) at a median follow-up of 41 months. Notably, all patients with low-grade tumors were alive at last follow-up despite experiencing ATR [18].

There are also a handful of case reports describing laparoscopic surgeries with atypical intraperitoneal recurrences. Most commonly, these come in the form of port site metastases. However, there are other descriptions of recurrence as peritoneal masses, intrahepatic, renal fossa, or bony pelvis [17, 23-26]. Only one case report describing atypical peritoneal recurrence in an open surgical approach exists at this time, with Ohtaki *et al*. describing the growth of an abdominal wall desmoid tumor beneath the incision site after removal of ccRCC. Two robotic cases outside of Russo *et al*.'s larger study have been reported. In Song *et al*.'s study, a 68-year-old man developed a port-site metastasis five months after undergoing robot-assisted partial nephrectomy (PN) for a 4 cm right renal mass (stage T1aN0M0). The isolated peritoneal recurrence at the camera-port site was confirmed to be RCC upon biopsy. Additionally, the port site metastases occurred without specimen bag rupture or even extraction of the specimen through the port in question [27]. Meanwhile, Beauvaut *et al*. in a prospective multicenter study reported long-term oncological outcomes after robotic PN for RCC. Among 110 patients was one case of peritoneal carcinomatosis, but no port-site metastasis was observed [28] (Table 1).

Risk factors for recurrence

Previous studies have demonstrated that renal masses smaller than 4 cm are more likely to remain localized to the kidney [32]. In the case of ccRCC and papillary RCC, tumors larger than 3 cm are associated with an increased risk of metastasis [33]. This review explores a range of tumor sizes reported in the literature. The Russo *et al*. study of 58 patients discovered a median tumor size of 5.9 cm [18], while single-patient case reports examining ATR reported tumor size of 2.5 cm, 5.5 cm, and 4 cm, respectively [25-27].

High nuclear grade has been established as an independent risk factor for RCC recurrence [29, 34]. We found that the majority of reported cases of atypical recurrence involve high-grade tumors. Russo *et al*. reported that 43 of 58 (74%) had high grade tumors (grade and 4). Similarly, Dhobada *et al*. noted a grade 3 tumor that resulted in port site metastasis [25], while Pandey *et al*. highlighted a grade 4 tumor that led to ileocecal junction and ovary metastasis ipsilaterally [31].

Sarcomatoid differentiation in RCC is also correlated with an increased rate of recurrence and poor prognosis [35, 36]. This is attributed to several factors, including a high tumor mutational burden especially in cancer driver genes [37], frequent presentation at an advanced or metastatic stage and limited efficacy of targeted therapies [35]. In Russo *et al*., 10 of 58 patients (17.2%) exhibited sarcomatoid differentiation [18]. Gradecki and Gru reported a case of ccRCC that initially lacked sarcomatoid features but was later presented with a predominantly sarcomatoid pattern upon metastasis to the skin [38]. Although sarcomatoid RCC represents approximately 5% of RCC cases [39], further studies are warranted to investigate sarcomatoid pattern as a potential risk factor for atypical recurrence, given its underlying aggressive nature. However, aside from tumor necrosis, there are not well-established radiographic features to predict sarcomatoid histology, and renal mass biopsy is not routinely performed prior to RN. Thus, the ability to anticipate sarcomatoid histology to guide surgical modality is limited. Furthermore, the sensitivity of RMB to detect sarcomatoid histology is limited [40]; it has been reported that only about 30-50% of cases ultimately identified at final pathology are detected on RMB [41].

Tumor necrosis has been associated with poor prognosis [42] and is considered an important risk factor for recurrence in RCC [43]. Pandey *et al*. described a case involving ccRCC with tumor necrosis that subsequently metastasized to the ileocolic junction and the ovary [31].

Tumor incision/spillage is a known risk factor for tumor recurrence and metastasis [44]. Thus, rigorous surgical technique is paramount to prevent tumor spillage during resection. Strategies to minimize tumor spillage include avoiding capsular or tumor incision and utilizing a specimen retrieval bag. In a retrospective study of Ito *et al*., none of the twelve patients who had accidental tumor incision during laparoscopic PN developed local tumor recurrence or port site metastasis. Consequently, the authors suggest that accidental tumor incision during laparoscopic PN may not be associated with tumor recurrence. However, given the small sample size, this finding warrants careful interpretation [45]. In contrast, Dhobada *et al*., noted a case of port-site metastasis following laparoscopic tumor

Table 1. Summary of reported cases and series describing atypical tumor recurrence (ATR) following radical or partial nephrectomy for renal cell carcinoma.

Study	Institution	N	Approach	Location	Stage/grade	Margin status	Histology	Outcome	Other factors
Russo *et al.* [18]	Memorial Sloan Kettering Cancer Center, New York, United States	58	Robotic and Laparoscopic	Numerous Described above	T1 50% T2 10.4% T3 36.2%	Neg 79.3% Pos 17.2%	CCC 67% Sarcomatoid 17% 6.9% Rhabdoid	Overall 5-yr survival from the time of ATR to last follow-up or death was 58.4%	
Castillo *et al.* [23]	Clínica Santa Maria, University of Chile, Chile	1	Laparoscopic	Port Site, peritoneal mass, multiple hepatic lesions	pT1, grade 3	Negative	N/A	Death 17 days after admission	
Masterson & Russo [17]	Memorial Sloan-Kettering Cancer Center, New York, United States	1	Laparoscopic	Port site and intra abdominal	pT1bNXM0	Negative	Papillary RCC	Multiple hepatic and peritoneal recurrences at 12 month follow up	
Greco *et al.* [26]	Martin-Luther-University, Germany	1	Laparoscopic	Port site	PT1a, high grade	Negative	Clear cell papillary carcinoma	No new metastases at 1 year	Intraoperative specimen rupture
Filizoglu *et al.* [29]	Kartal Dr. Lutfi Kirdar Hospital,Turkey	1	N/A	Left nephrectomy bed, pancreas	N/A	N/A	ccRCC	N/A	
Dhobada *et al.* [25]	Institute of Urology, Pune, India	1	Laparoscopic	Port site	T2N0M0	N/A	RCC	N/A	
Kumar *et al.* [24]	Sanjay Gandhi Postgraduate Institute of Medical Sciences, India	2	Laparoscopic	Port site, renal fossa, bony pelvis	T2N1M0 and T3aN1M0	N/A	RCC	N/A	One case converted to open intraoperatively
Ohtake *et al.* [30]	Kainan Hospital, Japan	1	Open	Abdominal wall desmoid tumor	pT3b	N/A	ccRCC	No recurrence or death at undefined follow up	
Pandey *et al.* [31]	Banaras Hindu University, India	1	N/A	ileocolic junction and the ovary	T2N0	Negative	ccRCC	Death 10 months after surgery	Lymphovascular invasion and tumor necrosis present
Song *et al.* [27]	Washington University SOM, United States	1	Robotic	Camera port site	T1aN0M0	N/A	RCC	N/A	
Beauval *et al.* [28]	Multi-Institutional, France	1/110	Robotic	Peritoneal carcinomatosis	pT1a R0	Negative	ccRCC	Death 18 months after surgery	

Note: Details include surgical approach, recurrence location, tumor characteristics, margin status, histology, outcomes, and notable intraoperative or pathological findings. CCC = clear cell carcinoma; ccRCC = clear cell renal cell carcinoma; RCC = renal cell carcinoma; N/A = not available.

removal using a retrieval bag. This case report provides two critical considerations. First, the importance of proper and careful use of retrieval bags. Second, the potential limitation that retrieval bags may not entirely prevent microscopic tumor cell spillage [25].

Conversion from minimally invasive surgery to open surgery is associated with higher recurrence rates in colorectal [46] and liver tumors [47]. In this review, Kumar *et al.* noted that one of 33 patients who underwent conversion to open surgery, displayed port site metastasis [24]. Similarly, Ohtake *et al.*, reported a patient who developed an abdominal wall tumor following a laparoscopic nephrectomy converted to open surgery [30]. In both metastatic cases, severe bleeding was found as the primary reason for conversion.These findings align with previous studies suggesting that the underlying causes of conversion, such as intraoperative complications and more advanced tumor characteristics, are more directly associated with high recurrence rates instead of conversion itself [47, 48]. The current literature review further supports the premise that intraoperative challenges, rather than conversion, may be the principal contributing factor to recurrence.

Discussion

Best practices

Our review shows that the majority of ATR were associated with laparoscopic approaches. This trend may reflect a combination of procedural risk and higher representation in the literature due to increased volume of minimally invasive surgeries and uniform adoption among many urological specialists. The debate between laparoscopic and open surgery continues to evolve. Notably, the landmark Laparoscopic Approach to Cervical Cancer trial demonstrated that minimally invasive radical hysterectomy was associated with significantly lower overall survival compared to open abdominal surgery in early-stage cervical cancer [49]. These findings led to a shift in the standard of care, now recommending open abdominal radical hysterectomy for this patient population [50]. These findings illustrate the importance of surgical technique refinements, especially with respect to specimen handling, morcellation and instrumentation manipulation.

Morcellation is a technique often employed during minimally invasive procedures to facilitate specimen extraction through small incisions. However, in many oncologic surgeries, morcellation carries the risk of disseminating malignant cells, especially if performed without containment [51]. In RCC, a review of 16 cases of port-site metastasis following laparoscopic nephrectomy revealed that seven cases had identifiable technical causes: specimen morcellation (n = 3), failure to use an entrapment bag (n = 2), and tumor rupture (n = 2) [52]. The remaining nine cases had no clear technical etiology. While technical lapses may contribute to port site metastasis formation, the study concluded that underlying tumor biology, such as histologic subtype and metastatic potential, may play a more significant role in these cases. However, the risks associated with technical practices cannot be discounted.

The risks associated with uncontained morcellation have been well-documented in gynecologic oncology, particularly in instances of unsuspected uterine malignancy, where intra-abdominal morcellation has led to tumor dissemination and upstaging. This evidence has led to widespread recommendations against morcellation when malignancy is suspected [53]. Although port site metastasis are incredibly rare, urologic oncologic surgery would most likely benefit from similar cautionary practices, with avoidance of morcellation in high-risk renal masses and mandatory use of containment systems when specimen fragmentation is necessary. Although a few studies from the early 2000s suggest that morcellation was an effective minimally invasive surgical option for T1-2 and low grade RCC when performed carefully with proper specimen bagging and no intra-abdominal spillage, with Wu *et al.* (mean follow up 21 months) [54] and Lesani *et al.* (mean follow up 14.3 months) [55] finding no increased recurrence rates. This practice has largely been abandoned due to forfeiture of accurate staging, grading, margin status, and detection of aggressive histologic variants [54-61].

Cases related to entrapment bags may have some correlation with port site metastasis [52], however as mentioned above, the potential limitation of microscopic tumor cell spillage cannot be completed prevented by use of retrieval bags [25].

In addition to morcellation and bag use, prior reviews have additional recommendations to reduce risk of urological port site metastasis. These usually arise from manipulation of surgical instruments, which can be mitigated by sufficient technical preparation, avoidance of laparoscopic surgery with ascites present, proper trocar fixation without gas leakage, avoidance of tumor boundary, drain placement if needed before abdominal deflation, and thorough irrigation of instrumentation and port site wounds (including techniques for iodine irrigation) [51], much of which should be considered as part of standardized practice.

Notably lacking from the literature are reports of ATR following nephrectomy in the metastatic setting. Theoretically, distant metastasis and the presence of circulating tumor DNA with potential hematogenous seeding during surgery, along with the previously mentioned mechanisms such as tumor staging, spillage, necrosis, and high nuclear grade, might predispose to a higher rate of recurrence with cytoreductive nephrectomy compared to surgery for localized disease. In addition, the use of systemic immune therapies, such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), prior to cytoreductive nephrectomy is currently being studied [62, 63] and their respective roles in reducing tumor size through tissue necrosis. Their role in tissue necrosis may lead to increased friability during surgical resection and a higher risk of seeding and ATR. To date, this has not been reported. Interesting to consider is the rate of such ATR in the setting of preoperative/induction targeted molecular therapy, such as TKIs, which exert limited effects only during dosing, versus ICIs, which can exert prolonged effects due

to immune system priming and neoantigenicity [64]. Certainly, an improved understanding of the potential for ATR becomes increasingly important in guiding the sequencing of systemic therapy prior to or after cytoreductive surgery, as it not only influences metastatic progression but may also influence rates of ATR.

Future directions

The growing recognition of ATR following highlights several key areas for future investigation. First, the true incidence of ATR remains unclear and may be underrecognized due to inconsistent reporting practices and lack of long-term surveillance protocols tailored to detect these patterns. Prospective multicenter registries with standardized definitions of ATR and structures follow-up are needed to more accurately estimate incidence and evaluate oncologic outcomes.

Second, while our review suggests a higher prevalence of ATR among laparoscopic and robotic approaches [17, 23, 27], existing data are limited by publication bias and retrospective design. Comparative studies with adequate adjustment for cofounders including tumor characteristics, surgical technique, and use of containment systems are essential to determine whether minimally invasive approaches have an increased risk for ATR. In addition, specific ATR rates in the metastatic setting after induction ICI and TKI therapy followed by cytoreductive nephrectomy must be tracked and analyzed moving forward.

Third, given the heterogeneous biological behavior of RCC, there is a need to identify molecular or imaging biomarkers that can stratify patients by risk of ATR. Future studies should explore the utility of circulating tumor DNA, radiomics, and advanced molecular profiling to predict ATR and guide perioperative decision-making [37].

Finally, integrating evidence-based best practices into surgical training and perioperative protocols may reduce recurrence risk. Emphasis on specimen handling, avoidance of tumor morcellation without containment, and uniform use of retrieval bags should be part of standard operating procedures, especially in high-grade or sarcomatoid RCC. The development of technical guidelines and quality metrics for cytoreductive nephrectomy in the metastatic setting, especially in the context of the complete responses seen in the era of IO-IO and IO-TKI therapy, may enhance safety and promote superlative oncologic outcomes.

Conclusions

ATR after RN is an uncommon but clinically significant event, most often associated with high-grade tumors, sarcomatoid features, and minimally invasive approaches. While technical factors such as tumor spillage and morcellation may contribute, the multifactorial nature of ATR, including tumor biology and surgical technique, highlights the complexity of its pathogenesis. Although most available data are derived from nephrectomy for localized disease, the expanding role of CN in the management of mRCC highlights the need for heightened awareness of ATR in this population. Given the potential impact of emerging systemic therapies on tumor friability and recurrence patterns, further investigation into ATR following CN is warranted. Standardization of reporting, adherence to oncologic principles, and integration of risk-reduction strategies into surgical practice will be essential for optimizing outcomes in both localized and metastatic RCC.

Declarations

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