Incidence of Port Site Metastasis in Laparoscopic Radical Nephroureterectomy: Single-institution Experience

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OBJECTIVE
To address the incidence and potential risk factors of port site metastasis (PSM) in patients who underwent laparoscopic radical nephroureterectomy (RNU) for upper tract urothelial carcinoma.

MATERIALS AND METHODS
Between January 2013 and December 2018 laparoscopic RNU were performed in 240 patients at our institution, including 145 with renal pelvic tumor and 135 with ureteral tumor (40 patients have both tumor). Laparoscopies were performed through the transperitoneal approach in 28 patients, and retroperitoneal in 212 patients. Clinical data are retrospectively collected.

RESULTS
Perioperative and pathologic data are available in all 240 cases. After a mean follow-up of 12.6 months (range 3-45 months), 4 patients (1.7%) developed PSM following retroperitoneal RNU at an average of 4.3 months. Tumor stage is T2N0M0 in one, T3N0M0 in two, and T3N1M0 in one, respectively. Tumor grade are high-grade urothelial carcinoma in all. The incidence of PSM is 2.8% (4/145) and 0.7% (1/135) in renal pelvic and ureteral tumor, respectively.

CONCLUSION
We report a 1.7% incidence of PSM in upper tract urothelial carcinoma after laparoscopic RNU. We suggest that air leakage during retroperitoneal approach, high tumor stage (pT3) and grade, and advanced renal pelvic tumor with micrometastases could increase the potential risks of PSM.

patients, and retroperitoneal in 212 patients. No robot was used because a robotic system was not available at our institution.

For transperitoneal approach, the patient was in lateral position. Pneumoperitoneum with pressure of 14 mm Hg was created with a Veress needle. A 12-mm camera port was placed laterally to the rectus muscle at the level of the umbilicus. Remaining trocars were inserted under direct vision. Two 5-mm ports and one 12-mm port was inserted 3 cm upon and below the camera port, and at anterior axillary line slightly below the level of the camera port, respectively. For retroperitoneal approach, a 2-cm incision was cut at posterior axillary line below the costal margin. After blunt dissection of the muscles, operator could put in the forefinger to confirm the retroperitoneal space. An air sac was then inserted and injected with 800 mL air to expand the space of retroperitoneal cavity. With the guide of forefinger, a 5-mm port and 10-mm port were placed at anterior axillary line below the costal margin and 2-cm upon the crista iliaca at midaxillary line, respectively. A 12-mm port was then inserted in the first incision and interrupted suture of skin was performed to prevent air leakage (Fig. 1). For both approaches, the renal and proximal ureter were dissected under laparoscopy. The ureter was ligated with hem-o-lock at the distal position to prevent tumor spread to the bladder if the tumor was located in renal pelvic or upper ureter. The patient was then rearranged into supine position and open distal ureterectomy with excision of bladder cuff was performed. The dissected renal and proximal ureter were extracted through a 7-10 cm incision at lateral border of rectus muscles first. The distal ureter was subsequently dissected till the ureter within the bladder wall was completely exposed and the bladder mucosa around the ureteral orifice was extended outward with fan shape. The extended bladder mucosa was incised, and full-length ureter was then extracted. The defect of bladder wall was closed with two-layer continuous suture.

Four surgeons were involved in the reported procedure. There was no obvious intraperitoneal spillage at the time of surgery. No formal lymphadenectomy was performed and the specimen was extracted without using extraction bag.

Postoperative surveillance included physical examination, ultrasound, chest CT, and blood tests 3-6 monthly, and abdominal CT or magnetic resonance imaging 6-12 monthly, or when clinically indicated. Follow-up period is calculated from the date of operation to the date of the most recent documented examination. PSM is defined as tumor recurrence to the abdominal wall at 1 or more trocar sites, which was assessed with physical examination, Contrast-enhanced computerized tomography, ultrasound, magnetic resonance imaging and diagnosed with pathologic results.

RESULT

Demographic data, perioperative information, and final pathology results were available for all 240 patients. Patient characteristics and perioperative information are listed in Table 1 and postoperative pathologic outcomes are summarized in Table 2.

The comparison between renal pelvic tumor and ureteral tumor presented no obvious difference in most results. However, the postoperative pathology revealed that the percentage of advanced tumors (stages T3 and T4) was notably higher in patients with renal pelvic tumor than ureteral tumor (64.2% vs 11.1%) in our study.

The average time from diagnosis to definitive surgery was 5 days (range 4-7 days). During the mean follow-up of 12.6 months (range 3-45 months), it was found that 4 patients (1.7%) developed PSM between 1 and 8 months after surgery, including 3 patients with renal pelvic tumor and 1 with both renal pelvic and ureteral tumor. All 4 patients underwent retroperitoneal laparoscopy and only 1 of them revealed positive margin. None of the patients presented with incision site metastasis.

Patient 1 is a 71-year-old male with both renal pelvic and ureteral tumor, along with bladder tumor history. He was diagnosed with clinical stage T2N0M0 (high-grade invasive urothelial carcinoma) after surgery with positive bladder cuff margin. The patient developed with PSM and recurrent bladder tumor 7.5 months after surgery. The presentation was palpable masses in left lumbar posterior axillary line with no pain or hematuria. Palliative transurethral resection of bladder tumor and

Figure 1. Interrupted suture of the port site at posterior axillary line. (Color version available online.)
abdominal tumor resection was performed because recommendation of radical cystectomy was rejected. Histopathologic examination of the abdominal tissue revealed high-grade invasive urothelial carcinoma. Patient’s condition deteriorated soon after reoperation, accompanying with liver metastasis and multiple bone metastases. The total follow-up was 17 months till the patient’s death.

Patients 2 (47 years old) and 3 (59 years old) are both female patient with renal pelvic tumor, whose postoperative clinical stage was T3N0M0 (high-grade invasive urothelial carcinoma). Patient 2 presented with multiple painless masses at right abdominal anterior axillary line and right lumbodorsal posterior axillary line port sites 1 month after initial surgery. Pathologic biopsy of the 2 sites demonstrated the existence of tumor cells which is consistent with high-grade urothelial carcinoma. The patient eventually succumbed to death after 2-month follow-up because she refused to receive chemo- or radiotherapy. Patient 3 presented with painless mass at left lumbodorsal posterior axillary line port site 4.5 months after surgery which was confirmed by biopsy for high-grade invasive urothelial carcinoma and was demonstrated with lung metastasis by CT. The patient was still under radiotherapy till the end of our study.

Patient 4 is a 75-year-old male with renal pelvic tumor. The postoperative pathology showed high-grade papillary urothelial
carcinoma with clinical stage T3N1M0. The resected perihilar lymph nodes revealed tumor metastasis which may be a risk factor of subsequent PSM. He was diagnosed with bladder tumor and metastasis at right abdominal anterior axillary line port site (pathology diagnosis with high-grade urothelial carcinoma) 4 months after initial laparoscopy. The patient received limited curative effect from chemotherapy due to severe bone marrow suppression and finally succumbed to multiple metastasis 3 months after detection of PSM.

DISCUSSION

PSM as a troubling occurrence associated with poor prognosis after laparoscopic surgery has been receiving attention since first reported in 1978.3 Despite it being reported in various malignancies, the accurate incidence of PSM is difficult to ascertain due to the limited number of large studies with long-term follow-up. Some specific procedures and tumors have been associated with a higher incidence of PSM, such as 0%-5% for gynecological cancer, and 0%-4% for colorectal cancer.4 Nevertheless, the incidence of PSM in urologic laparoscopy has not been well defined.

Certain researchers have argued that the incidence of PSM following laparoscopic radical resection of renal carcinoma is variable, and the incidence may be as high as 21%.9 However, the majority of researchers still regard PSM as a rare event, along with an estimated incidence of 0.09%-0.35% in urologic oncologic laparoscopy reported in large contemporary series.8,10 Micali et al8 collected clinical data from 19 urologic centers, involving 10,912 patients who underwent laparoscopic resection for urinary malignant tumors and found that only 13 cases (0.09%) developed postoperative tumor metastasis, including 10 cases of PSM and 3 cases of retroperitoneal dissemination. Wherein, they did not identify a single case of PSM in the available clinical data of 2604 patients who underwent radical nephrectomies.

UTUC as a highly aggressive pathological type has been associated with a higher incidence of PSM in urologic oncology. Rassweiler et al15 reported 6 cases (1.6%) of PSM in 377 analyzed patients occurring 3-12 months following laparoscopic nephroureterectomy and suggested that patients with advanced tumors (pT3, N+) should be better recommended to open surgery. In a series of 115 patients with UTUC and underwent laparoscopic RNU, Muntener et al11 reported a patient who developed PSM (0.9%) at all 3 port sites 12 months after surgery. In present study, 4 of 240 patients (1.7%) with UTUC developed PSM between 1 and 8 months after RNU. Three of the patients (3/4) were in T3 tumor grade and 1 (1/4) was in T2. All 4 patients revealed high-grade urothelial carcinoma with morphologic type of invasive in 3 and papillary in 1. Our outcome is consistent with the previous study and suggests that biological aggressiveness of the tumor, represented by grade and stage, could play an important role in possible tumor seeding determination.

Except tumor-related factors, the performance of laparoscopy is associated with a number of additional factors that may provoke metastasis, including the presence of carbon dioxide pneumoperitoneum, chimney effect, aerosolization of tumor cells, contamination of instruments or port sites, direct wound implantation, excessive or incomplete manipulation of tumor, hematogenous spread, and the particular method used to remove the specimen.12-15 However, no researcher has reported the relationship between laparoscopic approaches and PSM before.

Retroperitoneal laparoscopic RNU as a technically more difficult and challenging approach is conventionally performed at our institution. In our study, most patients underwent this approach to laparoscopy and, of interest, all patients who have PSM underwent this approach either. We came up with the explanation: Air leakage around the port would at posterior axillary line enhances the effect of “chimney effect.” “Chimney effect” is reported by Kazemier et al16 which means leakage of carbon dioxide alongside trocars causes a high local gas flow at the trocar wounds, which may contain aerosol tumor cells that may be viable, suggesting that continuous air leakage around the port would increase the number of tumor cells at the port site and promote metastasis. With regards to the present cases, 3 of the 4 cases were observed with metastasis around the port site at posterior axillary line. This is the port site which is incised for 2 cm in order to fit in the operator’s finger and locate the other 2 port sites. Compared to abdominal wall, the tissue of the lumbodorsal region is much thicker and with plentiful layers. Although the excessive defect of skin is closed after port placement (Fig. 1), the underneath structure including muscles and fascia is still open and mussy (Fig. 2). Continuous air leakage at this port site is inevitable and aerosol tumor cells wound more likely to remain in the subcutaneous tissues, which may increase the chance of subsequent PSM. For the other 2 port sites in retroperitoneal approach and port sites in intraperitoneal approach, the trocars are more fitting to the abdominal wall and the inner structure is clean and smooth.

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Figure 2. Inner structure of the port site at posterior axillary line. (Color version available online.)
The majority of studies considered that the use of specimen bags in laparoscopy could reduce portsite contamination and implantation. In present study, although no retrieval bag was used when extracting the specimen, none of the patients developed incision site metastasis after surgery. However, it may still increase the possibility of direct wound implantation and contamination of instruments.

Incomplete manipulation of tumor has been reported as a risk factor of PSM. In our study, a total of 7 patients revealed positive margin after surgery, and only 1 patient with positive bladder cuff developed PSM, accompanying with recurrent bladder. Besides, all 4 patients with PSM also had multiple systemic recurrences at the time of port site recurrence. The highly aggressive tumor metastasized within few months and was responsible for fatal outcome. So, port site recurrence might be associated with systemic recurrence in such high-grade aggressive tumor.

Interestingly, the percentage of patients with advanced tumors (pT3, T4) in renal pelvic is notably higher than in ureter (64.2% vs 11.1%) at present study, and the incidence of PSM following renal pelvic tumor is also higher than ureteral tumor, with an occurrence rate of 2.8% (4/145) and 0.7% (1/135), respectively. This might be associated with an earlier occurrence of obstructed symptoms and earlier diagnosis in patients with ureteral tumors. On the other hand, direct invasion of high-grade renal pelvic tumor or tumor-caused upper tract obstruction could lead to increased pressure in the renal pelvis. The obstructed urine with viable tumor cells could reflux through peripheral kidney tubules, lymph-vessels, veins, and mesenchyme to reduce the pressure, which may increase the risk of local invasion and micrometastases. With intensive blood vessel and lymph-vessel surrounded, aggressive renal pelvic tumor with higher stage may be accompanied with a higher risk of vascular and lymphatic micrometastases compared to ureteral tumors, and more likely to experience “chimney effect” during the retroperitoneal laparoscopy, which could lead to a higher risk of PSM.

Growing evidence has been regarding neoadjuvant chemotherapy to a potential survival advantage and pathologic response for UTUC. But whether it plays a role in preventing PSM is not clear. Sakurai et al. reported a case of cTNM stage II (T2 N0 M0) gastric cancer followed by pTNM stage I (T1b N0 M0) after administration of an oral fluoropyrimidine drug for 2 weeks, who developed PSM 18 months after laparoscopic gastrectomy. In the present study, no patient received neoadjuvant chemotherapy since there were no significant sign of local invasion and metastasis during preoperative evaluation. Therefore, we advise cautious conclusion about the effect of neoadjuvant chemotherapy to preventing PSM.

PSM is a poor prognostic factor. When PSM occurs without identifiable technique-related factors in the operation, it is inevitable for multiple metastases to eventually develop. In our study, patient one survived for 10 months after the detection of portsite implantation relying on receiving gemcitabine and carboplatin (GC) chemotherapy while patient 2 survived only for 2 months without receiving any chemoradiation therapy. Patient 4 received sunitinib-targeted therapy because the recommendation of chemotherapy was rejected. Nonetheless the treatment was discontinued 2 weeks later due to bone marrow suppression which eventually lead to a limited lifetime of 3 months. Patient 3 remains in a stable condition at present (3 months after PSM) after receiving interventional treatment and chemotherapy. However, as this patient has been followed for a relatively short time, further observation is required. As a result, the prognosis of PSM in our study is generally poor with an overall survival of within 1 year, compared to an approximately 50% 1-year survival for metastatic renal cell carcinoma reported in the literature.

Although the exact cause remains unclear, the occurrence of PSM may be considered attributable to the combination of holistic and local factors. Measures to reduce the occurrence of PSM include strict abidance to the surgical guidelines for tumor resection, avoidance of air leakage at the portsite, use of impermeable specimen bags to remove the specimen under direct vision, irrigation of the laparoscopic instruments, and incisions with povidone-iodine when necessary, and enhancing the body immunity. Regular postoperative observation and examination are also recommended since timely detection of tumor recurrence or metastasis and subsequent administration of systemic chemotherapy are prerequisite for prolonging the life expectancy of patients.

The limitations of our study include its retrospective nature and the relatively short overall follow-up. Nevertheless, the development of UTUC is fairly aggressive, with typically short median time to fatal outcome reported in most series. In our cases, the average time to local recurrence (4.3 months) was relatively shorter than the mean follow-up time (12.6 months). Therefore, the possibility of missing a significant number of patients with PSM is pretty low. Besides, although no extraction port recurrence appeared in our series, the lack of retrieval bag is also a potential risk of PSM and local recurrence. The use of retrieval bag is highly recommended when extracting the specimen to better protect against metastasis.

CONCLUSION

In this single-institution experience, we report a 1.7% incidence of PSM in UTUC after laparoscopic RNU. Air leakage during retroperitoneal approach, high tumor stage (pT3) and grade, and advanced renal pelvic tumor with micrometastases are suggested to increase the potential risks of PSM. Due to an overall poor prognosis, urologists should be aware of this rare, but serious, complication in oncological laparoscopic surgery, for which precise preoperative imaging detection, cautious manipulation and regular follow up is necessary.

References


