

Is port site metastasis a result of systemic involvement?

Samit Chaturvedi, Vikas Bansal, Rakesh Kapoor, Anil Mandhani

Department of Urology and Renal Transplantation, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

ABSTRACT

Aims: Port site metastasis (PSM) is an unwelcome consequence of laparoscopy for oncological procedures with uncertain etiology. We present the clinical evidence to prove that PSM is likely to be due to the hematogenous spread of tumor cells.

Materials and Methods: Six cases of port site metastasis, four following laparoscopic radical nephrectomy for localized renal cell carcinoma (RCC), one after laparoscopic radical prostatectomy done in two patients and one after laparoscopic partial cystectomy for tumor at bladder dome done in two were studied. One case of metastatic RCC with bilateral gluteal masses and two cases of open radical nephrectomy, with recurrence at the drain and incision site were also studied.

Results: During the median follow up of 59 months (range 24–120), 4/136 patients with RCC (1.47%) developed port site metastasis between 7–36 months after surgery. All six cases of PSM had advanced disease and recurrences at other sites, that is, peritoneum, omentum, bones, and lungs. None of the patients had isolated PSM. One patient of metastatic RCC, who did not have any intervention but repeated intramuscular injections of analgesics-developed bilateral gluteal masses, confirmed to be RCC on fine needle aspiration cytology. Two patients had metastasis at the incision site (one at the drain site) with distance, including cutaneous metastases.

Conclusions: Port site metastasis did not develop in isolation. There could be a likely existence of circulating tumor cells at the time of surgical trauma of penetrating nature, that is, port site or injection site, which manifest in some patients depending upon their immune response.

Key words: Laparoscopy, port site metastasis, recurrence

INTRODUCTION

After the first successful laparoscopic nephrectomy by Clayman *et al.* in 1991, there has been a rapid rise of laparoscopic procedures in urologic oncology.^[1] Despite various advantages of a minimally invasive approach, oncological safety of laparoscopy has been a point of debate due to occurrence of port site metastasis (PSM) and tumor seeding.^[2] Port site metastases are defined as recurrent cancerous lesions developing locally in the abdominal wall within the scar tissue at one or more trocar sites.^[2]

For correspondence: Dr. Samit Chaturvedi, Department of Urology and Renal Transplantation, Sanjay Gandhi Post Graduate Institute Of Medical Sciences, Lucknow – 226 014, Uttar Pradesh, India E-mail: samit.uro@gmail.com

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The exact pathophysiology of PSM is not known. Multiple factors have been hypothesized and most of them are linked to laparoscopy.^[3,4] Direct wound implantation, contamination of instruments, aerosolization of tumor cells, chimney effect, surgical technique, excessive manipulation of tumor, pneumoperitoneum, hematogenous spread, and local and systemic effects of the carbon dioxide pneumoperitoneum have been proposed. Even some have suggested gasless laparoscopy to reduce the incidence of PSM.^[3-6]

It would be difficult to prove that the factors related to laparoscopy have a direct cause and effect relationship for the development of PSM. Most of the series have been speculative in attributing the cause for development of port site metastasis to laparoscopic factors. We hereby propose a hypothesis that laparoscopic factors are least likely to be responsible for port site metastasis, which is rather a consequence of hematogenous spread of tumor cells.

MATERIALS AND METHODS

Study subjects

Study subjects included six cases of port site metastasis; four cases following laparoscopic radical nephrectomy for

localized renal cell carcinoma (RCC) and one each after laparoscopic radical prostatectomy and laparoscopic partial cystectomy for the tumor at the dome of the bladder. Study subjects also included one case of metastatic RCC who had repeated intramuscular injection at the bilateral gluteal region for pain and two cases of open radical nephrectomy, who had recurrence at the drain and incision sites.

Study period

All cases were performed between December 1999 and December 2008. Patients with recurrences were assessed with computed tomography (CT) of the abdomen, chest x-ray, renal and liver function tests, and PET CT if required. The pattern of disease recurrence was studied along with the recurrences at the port, incision, and injection sites.

Initial laparoscopic approach

Laparoscopic nephrectomies were performed through the transperitoneal approach in 121 patients, retroperitoneal in five and combined approach (retroperitoneal renal artery clipping followed by transperitoneal nephrectomy) in ten patients. The standard three to four port approach was used. Similarly, partial cystectomy was done in two patients with localized tumor at the dome of the urinary bladder with lymphadenectomy. Laparoscopic radical prostatectomy patient was done outside our institute where the laparoscopic program was well established. Postoperative surveillance included history and physical exam, X-ray chest, ultrasonography, and blood tests 3–6 monthly and abdominal CT 1–2 yearly. Port site metastasis was diagnosed by physical examination, Contrast Enhanced Computerised Tomography (CECT), and pathological findings.

Specimen retrieval

A custom-made extraction bag (made from urobag) was used in all the cases for specimen retrieval without morcellation through a 5–7 cm incision. All the necessary precautions to avoid tumor spillage were taken.

RESULTS

The median age of the patients was 54 years (range 16–74 years). Out of 136 patients who underwent radical nephrectomy, laparoscopic procedures could be accomplished successfully in 103 (five by retroperitoneal approach), while in 33 patients, laparoscopy was converted to open procedure due to various reasons such as bleeding at the hilum, improper case selection, learning curve and finding lymph nodes during the surgery. There was no tumor violation or breach in the continuity as the threshold for conversion was very low at the initial stages.

During the median follow up of 59 months (ranging between 24–120), 4/136 patients with renal cell carcinoma (1.47%) developed port site metastasis between 7–36 months following the surgery [Figures 1 and 2]. Clinical stage, histopathological characteristics, and location of the PSM are given in Table 1. One of the two patients with mucinous adenocarcinoma of the bladder, who had partial cystectomy and lymphadenectomy presented with PSM along with distant metastasis at 13 months following the surgery [Table 1]. Similarly, one patient who had laparoscopic radical prostatectomy was presented with skeletal metastasis and PSM at left working port 5 months after the surgery. [Table 1]

All six cases of port site metastasis had advanced disease and recurrences at other sites too, that is, peritoneum, abdominal wall, omentum, bony pelvis, and lung. None of the patients had isolated port site metastasis. Four of six had metastasis within a year of initial laparoscopic surgery and rest two patients with RCC presented at 27 and 36 months each following laparoscopic radical nephrectomy.

Metastatic pattern in nonlaparoscopic procedure

Of 225 patients of renal cell carcinoma operated during the same period with open radical nephrectomy, we

Table 1: Port site metastasis following laparoscopic surgery

Type of tumor	Age in years	Initial pathological stage and type	Tumor size and location	Interval between surgery and metastasis	Port site recurrence	Other sites
Renal tumor	16	Clear cell RCC, T3aN1M0 Fuhrman's grade 3	5×5 cm central	7 months	Camera port at umbilicus	Renal Fossa, Bony pelvis and chest.
Renal tumor	74	Clear cell carcinoma T2N1M0 Fuhrman's grade 3	7.5×3.5 cm Inter polar	12 months	Right working port	Renal Fossa, right lung lower zone.
Renal tumor	35	Cystic RCC, T1N0M0 Fuhrman's grade 3	6×3cm	27 months	5 mm nonworking port	Mesenteric mass with lung metastasis
Renal tumor	50	Papillary type 2 T2 N1M0	7.5×6cm	36 months	5 mm nonworking port	Retroperitoneum, liver and lung and malignant ascites.
Prostate cancer	66	Adenocarcinoma pT3N1M0 Gleason 3+5	-	5 months	Left working port	Bone scan positive
Bladder cancer	67	Mucinous adenocarcinoma	3×3cm dome	13 months	Right working port	Local recurrence in the bladder and lung

picked up two cases of incision site metastasis [Table 2]. This may not represent the exact incidence in this group as attention was paid to look for incision site since 2008. One of those two patients had an incision and drain site recurrence along with other site metastatic lesions [Figure 3]. Another patient had multiple cutaneous metastases apart from recurrence at the incision site [Figure 4]. One patient of metastatic RCC, who did not have any intervention but repeated intramuscular injection in the gluteal region for backache, had bilateral gluteal masses, which were confirmed to be clear cell RCC on fine needle aspiration cytology [Figure 5].

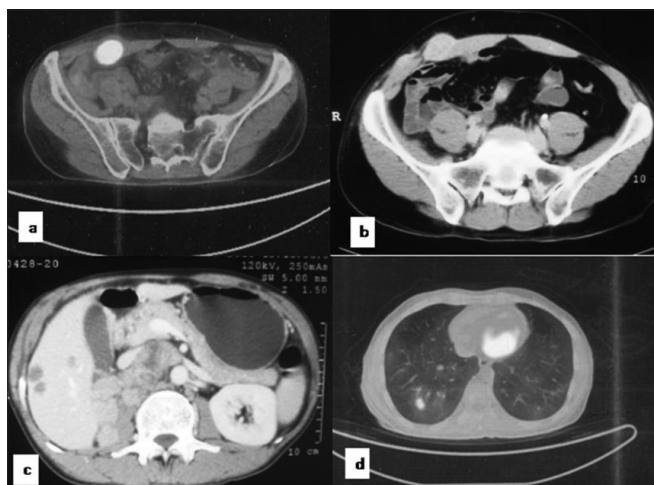


Figure 1: A case of renal cell carcinoma showing PSM on PET and NCCT (a, b) and distant metastasis in liver (c) and lung (d)

DISCUSSION

After the first reported case of PSM in 1978 by Debronte,^[7] the incidence in the published surgical literature has been reported in a wide range between 0.6% and 21%.^[8,9]

In urologic oncology, PSM was first reported in 1994 after laparoscopic lymphadenectomy for bladder cancer.^[10] The incidence in the contemporary urologic literature accruing a large number of patients of various urological malignancies has been reported from 0.09% to 0.73%.^[11,12]

The occurrence of port site tumor seeding after laparoscopy for malignant disease is a real concern. The initial high incidence reported in laparoscopic surgery done for gastrointestinal surgery and gynecology has not been

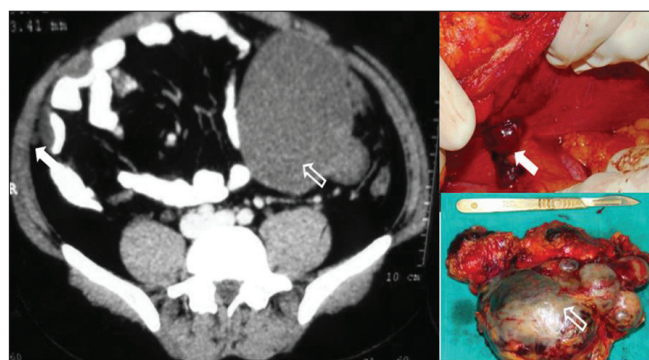


Figure 2: A case of RCC showing large mesenteric mass (arrow) and port site metastasis (solid white arrow)

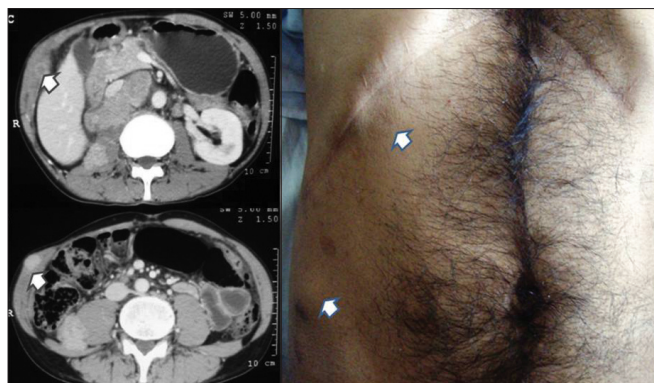


Figure 3: A case of open radical nephrectomy showing incisions site and drain site metastasis (marked with arrow)



Figure 4: A case of open radical nephrectomy showing multiple cutaneous metastases

Table 2: Metastatic pattern in nonlaparoscopic surgery for renal cell carcinoma

Type of tumor	Age	Initial pathological stage and type	Tumor size and location	Interval between surgery and metastasis	Port site recurrence	Other sites
Renal tumor	55	Clear cell RCC, T3aN2M0 Fuhrman's grade 2	13×12 cm	10 months	Incision site	Local recurrence, cutaneous, and skeletal metastasis.
Renal tumor	52	Papillary cell carcinoma type 2 T4N1M0 Fuhrman's grade 4	16×8.5 cm	28 months	Right drain site	Retroperitoneal LN, Liver and lung metastasis.
Renal Tumor	53	Metastatic RCC on FNA	6×6 cm	-	Bilateral gluteal region	Lung carcinomatosis

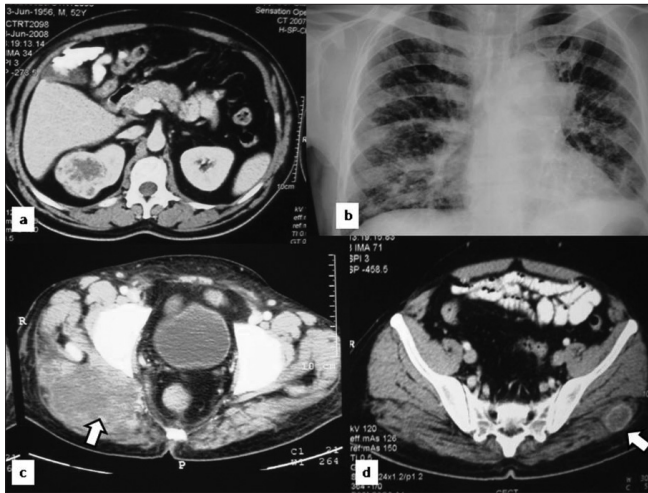


Figure 5: A case of metastatic RCC showing bilateral gluteal masses at the injection sites

seen in the same magnitude as in laparoscopic surgery done for urologic oncology. The exact pathophysiology of port site metastasis is not known, but various clinical and experimental studies have proposed factors such as natural tumor behavior, local wound factors, immune, and stress response of an individual and laparoscopy related factors.^[13]

Various factors related to laparoscopy have been studied but their role remains controversial. Though initially aerosolization of tumor cells and peri-port gas leakage (chimney effect) have been extensively reported to be the possible mechanism that can lead to tumor cell dissemination and PSM, recent literature has a contrary report as the quantity of tumor cells needed for port site metastasis formation was extremely high.^[14,15]

The moot question is whether port site recurrence is a result of implantation from the tumor being resected or it is an outcome of hematogenous spread. Local tumor cell implantation theory has not been proven and evidence supporting this mechanism is tenuous. Why would a properly removed T2/T3 renal cell cancer with no breach of tumor per se (proven by negative margin) have PSM? Why would one expect a PSM after diagnostic laparoscopy where tumor manipulation was absent?

When we looked at the magnitude of the problem of PSM, reported incidence from a single centre is 0.18% in 1098 patients, who had undergone laparoscopic procedures for urologic malignancies between 1992 and 2002.^[11] Similarly in an international survey by Micali *et al.*, on a total of 10 912 procedures done for various cancers the incidence of PSM was reported as 0.09%.^[12]

Unlike laparoscopic surgery, there is not much attention given to the pattern of recurrence after open radical nephrectomy. In one series the incidence of scar metastases after open radical nephrectomy has been reported as 0.4%.^[16]

This incidence is much higher than the cumulative incidence reported by Micali *et al.* and raises an important point about the association of laparoscopy per se with the occurrence of PSM.

Tumor recurrence at the incision site following open surgery has been reported in GI malignancy. In one study, the incidence of recurrence at the port and at the incision site was same, that is, 13 of 1650 (0.79%) laparoscopic procedures and 9 of 1040 (0.86%) laparotomies.^[17] In addition, reports have described tumor implantation in or near surgical sites in laparotomy scars, pelvic drain sites, and episiotomy scars in gynecologic malignancies.^[18-20]

Once viable tumor cells release into the circulation, disseminated cancer cells called “seeds,” would only colonize in an organ where microenvironments (soil) is conducive for their growth.^[21,22] The trauma caused at port insertion site leads to release of growth factors creating a premetastatic niche or fertile soil for the tumor cells to lodge there and grow. Tumor cells implant in much better way in the early stages of wound healing as they benefit from the release of growth factors.^[23,24]

It is a common parlance in urologist fraternity that if hematogenous spread is the reason for PSM then more often than not we should be seeing incision site metastasis following open radical surgery. Port site metastasis in laparoscopy is probably a bias as incision site metastasis is seen after open oncological surgeries also but are not talked about as often. A plausible reason for port site being a favored site for PSM could be that penetrating wounds are more prone to home circulating tumor cells as we saw in two of our cases, that is, drain site metastasis and metastases in the gluteal region.

Another reason to support PSM to be the consequence of hematogenous spread of tumor cells is that none of our patients had isolated port site recurrence and all six had disseminated disease. Similar observations were made by various authors who found that PSM as a solitary site of recurrence was rare and most probably it reflected the aggressive biology of malignant disease and the level of immunosuppression of an individual rather than the technical aspects of the laparoscopic approach.^[11,25,26] In one study on colon cancer surgery, it was found that laparotomy scar tumor implantation occurred in 13 of 1600 cases, of which the majority were accompanied by carcinomatosis. Isolated tumor deposits were noted in only 0.2% of their patients.^[27]

Moreover, in an isolated PSM, it is difficult to prove the presence of micrometastasis or emerging metastasis somewhere else. A follow up study would facilitate a further understanding of this concept of PSM being a result of hematogenous spread. In another interesting review of 31

cases of PSM in urologic malignancy, reported in English literature till 2008, it was found that the majority of the cases had higher stage and grades of tumors and most of them had widespread metastases too.^[28] Among the isolated PSM, where follow up was available in the reported cases, majority of them died within 1 year of the development of PSM.^[28]

Clinical evidence presented in this study favors hematogenous seeding of circulating cells, which home in at the site of injury and depending on the biological nature of the tumor cells, tumor cell load, and individual immune response, the process of homing and subsequent growth of the tumor cells results. However, one should not only continue to take necessary precautions during the laparoscopy for cancer surgery, but also should keep a very low threshold for conversion to open surgery. Choosing the right patient of cancer for laparoscopy and further understanding of mechanism of PSM would allay the anxiety of PSM after laparoscopic surgery. This hypothesis, that PSM is a consequence of hematogenous spread of tumor cells, can prospectively be studied by documenting circulating tumor cells and by doing proper follow up of all the cases that develop PSM. This would further shed some light on the exact mechanism of occurrence of PSM.

CONCLUSION

Port site metastasis after laparoscopic procedures for malignancy may not be the outcome of the laparoscopic technique as such. Most of the time it is associated with an advance stage of the malignancy and portends a poor prognosis. Based on the clinical evidence we present, we suggest that port site metastasis is an expression of an aggressive malignancy disease. Its occurrence is a result of homing in the circulating tumor cells at the site of injury and subsequent growth, depending upon the biological nature of the malignancy and local host factors.

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