Port Site Metastasis and Tumor Seeding in Oncologic Laparoscopic Urology

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Tumor seeding and port site metastasis remain a valid concern during laparoscopic procedures for urologic malignancies. A systematic review of all cases reported in published studies was performed. A MEDLINE search identified 17 English studies reporting a total of 29 cases of port site metastasis or tumor seeding secondary to urologic laparoscopic procedures in the past 20 years. Many factors contribute to port site metastases and tumor seeding. Nevertheless, we believe that only proper preoperative criteria, along with cautious intraoperative judgment, will keep port site metastasis to a minimum in the future.

The oncologic safety of laparoscopic procedures for malignancies has been widely questioned. Concerns about port site metastasis and tumor seeding have limited the use of laparoscopy in the treatment of malignancies. For many years, the mistaken belief that laparoscopic procedures might result in a greater incidence of tumor seeding than their open counterpart has justified the persecution of the laparoscopist who performed these procedures in the setting of malignancy.[1]

The advantages of a minimally invasive approach have been well established. Shorter convalescence and decreased analgesic requirements, along with better cosmesis results, favor minimally invasive procedures. However, no oncologic benefit for a minimally invasive approach to surgical resection of cancer has been established.[1–3] For this reason, careful patient selection is critical to keep tumor seeding to a minimum. However, laparoscopy is currently used to treat an ever-increasing number of malignancies at many numerous centers worldwide with oncologic results comparable to those of open procedures.[2,3]

What is the real association between tumor seeding and laparoscopic procedures in urology? Are there predisposing factors? Can it be prevented?

It was Dobronte *et al.*[4] in 1978 who made the first report of a port site metastasis after laparoscopy. Implantation at the place of penetration of the pneumo-needle and the trocar by the mediation of ascites-containing cells of a malignant ovarian cyst adenoma was reported.[4]

We performed a MEDLINE search for English-language studies reporting tumor seeding or port site metastasis associated with laparoscopic procedures performed in the setting of urologic malignancies. Also, current in vitro and in vivo studies, along with clinical trials, were analyzed concerning the association of tumor seeding and port site metastasis with laparoscopy. The Mesh terms used were "laparoscopy," "urology," "port site metastases," "tumor seeding," and "tumor recurrence."

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INCIDENCE

The reported incidence of tumor seeding and port site metastasis in the published surgical data ranges from 0.6% to 21%.[1,5] Ziprin *et al.*, as reviewed by Curet[1] reviewed 27 studies, each with a minimum of 50 cases, from 1993 to 2001 and found an overall incidence of only 0.71%. They suggested that the incidence of port site metastases after laparoscopic surgery was similar to that seen after open surgery.[1] However, in the urologic data, few reports of tumor seeding and port site metastasis have been published.[6] Rassweiler *et al.*[3] found an incidence of 0.18% in 1098 patients who had undergone laparoscopic procedures for urologic malignancies between 1992 and 2002. More recently, in an international survey by Micali *et al.*,[7] a total of 18,750 laparoscopic procedures were reviewed, of which 10,912 were for cancer. The incidence of port site seeding was 0.09% (10 cases) and that of peritoneal spread was 0.03% (3 cases). The investigators concluded that tumor seeding after laparoscopic oncologic surgery is rare and does not appear to be greater than what has been historically reported for open surgery. In a recent review by Lee *et al.*,[8] a similar incidence was reported.

At our institution, 1280 laparoscopic procedures have been performed for malignancies in the past 10 years. Two patients presented with tumor seeding, for an incidence of 0.1%.

ETIOLOGY

Multiple theories have tried to explain the development of port site metastases. However, no single hypothesis can

be blamed as the sole cause of tumor seeding. Many factors would appear to facilitate tumor seeding in the setting of laparoscopic surgery.[1,5,8–10] The factors related to tumor seeding and port site metastases can be divided in three categories: tumor related, wound related, and operative related.[1,5]

Tumor-Related Factors

The biologic aggressiveness of the tumor as represented by the grade and stage might play a critical role in determining the possibility of tumor seeding.[3,7,11] Transitional cell carcinoma (TCC) grade 2 and 3 have accounted for most port site metastases reported in urologic studies.[3,6,7] In an international survey on tumor seeding in urologic laparoscopy, 7 of 13 port site metastases were represented by TCC. Of the 7 cases, 4 were simple nephrectomies with incidental TCC and 3 were nephroureterectomies for suspected TCC. All but 1 case were grade 3 tumors. A retrieval bag was used to extract the surgical specimen in all but 1 case (incidental TCC, Stage pT1, grade 2). The remaining 6 cases were 4 laparoscopic adrenalectomies for lung metastases (Stage pT4, grade 3) and 1 pelvic laparoscopic lymphadenectomy for squamous penile cancer (Stage pT2, grade 3) and retroperitoneal lymph node dissection for NSGCT (Stage IIC).[3,7]

Furthermore, in a review by Tsivian and Sidi,[6] of the 9 reported cases of port site metastases, 7 (78%) were associated with high-stage or high-grade tumors. In the present review, of the 31 reported cases, 14 (45%) correspond to TCC (Table 1).

Wound-Related Factors (Local Immune Response)

When the first cases of tumor seeding were reported, many investigators hypothesized over the possible immunologic role of this surgical approach, and the appropriateness of this approach was again questioned in the setting of malignancy. In a clinical study by Wichmann *et al.*,[12] the immunologic effect of laparoscopic and open colorectal surgery were prospectively compared. A total of 70 patients with colorectal diseases were prospectively enrolled, 35 patients each for laparoscopic and open surgery, respectively. Their findings indicated a less pronounced pro-inflammatory response to surgical trauma in patients after minimally invasive surgery. Also, the nonspecific immune response appeared to be less affected by laparoscopic surgery compared with open surgery, and the specific cell-mediated immunity was equally affected.[12]

In a review by Novitsky *et al.*,[13] the net immunologic advantage of laparoscopic surgery was assessed. Many comparative studies of cellular immunity after laparoscopic and conventional surgery have demonstrated an immunologic advantage conferred by laparoscopy. Decreased perioperative stress could be particularly important for oncologic patients, and this advantage translated into diminished perioperative tumor dissemination and better cancer outcomes.[13]

More recently, Ost *et al.*[14] performed an extensive review on the basic physiologic responses associated with pneumoperitoneum. The investigators concluded that, although conflicting data exist from animal and human studies, a general trend is present toward systemic immune preservation and peritoneal immune depression during insufflation-based laparoscopy. This altered peritoneal immune response could be an adverse event contributing to the rare development of port site metastasis.[14]

Most investigators have agreed that additional studies are necessary to elucidate the immune response during laparoscopic procedures and how this might play a role in the incidence of tumor seeding and port site metastases.[11,12,14–16]

Surgery-Related Factors

Pneumoperitoneum. In an effort to determine the role of carbon dioxide-induced tumor cell aerosolization in tumor seeding, Ikramuddin *et al.*[17] attempted to document this in a human model. A suction trap filled with saline was attached to an insufflation site on the port, the carbon dioxide effluent was directed through the saline, and the specimen was concentrated for later Papanicolaou stain. A total of 35 specimens were obtained; of these 15 (37%) had malignant disease. Five patients had carcinomatosis, and staining revealed a large number of malignant cells. Malignant cells were not found in any other patient. One patient, who displayed cellular aerosolization, developed a port site recurrence. The investigators concluded that malignant cells are aerosolized but only during laparoscopy in the presence of carcinomatosis and that it is unlikely that tumor cell aerosolization contributes significantly to port site metastasis.

In a study performed by Jingli *et al.*,[18] peritoneal lavage cytology was performed for 36 patients with colorectal cancer during colorectal laparoscopic surgery and for 45 patients with colorectal cancer during conventional surgery. The cytology specimens were examined twice: immediately after opening the peritoneal cavity and just before closure of the abdomen. Malignant cells were not detected in the carbon dioxide filtrate gas. The incidence of positive cytology findings during laparoscopic surgery was 33.33% in the prelavage and 8.33% in the postlavage. The incidence of positive cytology findings during conventional surgery was 33.33% in the prelavage and 11.11% in the postlavage. The investigators concluded that during colorectal laparoscopic surgery, the carbon dioxide pneumoperitoneum does not affect tumor cell dissemination or seeding and that the laparoscopic techniques used in colorectal cancer surgery are not associated with a greater risk of intraperitoneal dissemination of cancer cells than the conventional technique.

Tsivian *et al.*[19] compared abdominal wall scar implantation of intraabdominal inoculated tumor cells after laparoscopic trocar insertion and pneumoperitoneum with standard laparotomy and the patterns of tumor

Table 1. Single reports on port site metastases and tumor seeding in urologic published studies

Investigator	Cases (n)	Operation	Tumor Type, Stage, Grade	Bag Specimen Retrieval	Morcellation	Other Risk Factors	Treatment	Outcome
Stolla *et al.*,[32] 1994	1	PLND	Bladder TCC pT3G2	No	No	Lymph node capsular rupture	CHT and RT	Dead in 9 mo
Andersen *et al.*,[33] 1995	1	Transperitoneal laparoscopic bladder biopsy	Bladder TCC T1G2	No	No	Cystostomy during transurethral bladder tumor resection.	Cystectomy, CHT, and RT	Dead 1 yr after cystectomy
Bangma *et al.*,[34] 1995	1	PLND	PCa T3N1	No	No	Local spillage	Radioactive strontium therapy	Dead in 8 mo
Altieri *et al.*,[35] 1998	1	PLND	Bladder TCC T3G2	No	No	No	Cystectomy, patient declined CHT	Dead in 3 mo
Ahmed *et al.*,[36] 1998	1	Nephrectomy	Kidney TCC T3G3-G4	No	No	No	CHT	NS
Otani *et al.*,[37] 1999	1	Nephrectomy	Unsuspected TCC, G3 within tuberculous atrophic kidney	Yes	No	Bag specimen retrieval was attempted but bag was torn	Family declined CHT	NS
Fentie *et al.*,[38] 2000	1	Nephrectomy	RCC T3N0G4	Yes	Yes	No	Port site metastasis resection	Alive after 35 mo
Landman and Clayman,[39] 2001	1	Nephrectomy	RCC T1N0G2	Yes	Yes	No	Immunotherapy	NS
Castilho *et al.*,[40] 2001	1	Nephrectomy	RCC T1N0G2	Yes	Yes	Ascites	Immunotherapy	Dead in 8 mo
Wang *et al.*,[41] 2002	1	Cystectomy	Unsuspected SCC in ovarian dermoid cyst	Yes	No	Tumor rupture during dissection	Surgical debulking and CHT	Dead within 19 mo
Ong *et al.*,[42] 2003	1	Transperitoneal nephroureterectomy	Kidney TCC pT1NxMxG3	Yes	No	Perforation of pelvis during previous ureteroscopy	Wide excision of 3 port site metastases	Alive after 18 mo
Chen *et al.*,[43] 2003	1	Nephrectomy hand assisted	RCC T2N0M0	No	No	No	Immunotherapy	Died in 2 mo
Matsui *et al.*,[44] 2004	1	Retroperitoneal nephroureterectomy	SCC pT3N0M0	No	No	No	Wide excision of 1 port site metastasis and CHT	Alive after 6 mo
Iwamura *et al.*,[30] 2004	1	Retroperitoneal nephrectomy	RCC T1bN0M0	No	No	No	RT	NS
Micali *et al.*,[7] 2004	13	Adrenalectomy (4) Simple nephrectomy (4) Nephroureterectomy (3) PLND (1) RLND (1)	Lung metastasis T4G3; incidental TCC (3) T1G3, (1) T2G3 TCC T3G3 Squamous penile cancer T2G3 NSGCT IIc	1 No 3 Yes 1 No 3 Yes Yes Yes Yes	NS	NS	NS	Died within 6 mo NS Died within 26 mo Died within 4 mo Died within 6 mo

Table 1. (continued)

Investigator	Cases (n)	Operation	Tumor Type, Stage, Grade	Bag Specimen Retrieval	Morcellation	Other Risk Factors	Treatment	Outcome
El-Tabey and Shoma,[45] 2005	1	Cystectomy (robot-assisted)	Bladder TCC T3bN0M0G3	Yes	No	No	Patient declined further treatment	NS
Dhobada *et al.*,[46] 2006	1	Transperitoneal nephrectomy	RCC T2N0M0G3	Yes	No	No	NS	NS
Present series	2	Partial nephrectomy (1) RLND (1)	RCC T1N0M0G3 Mixed germ cell tumor T3N0M0	Yes Yes	No No	No No	Symptomatic Wide excision and CHT	Died within 1 mo Alive after 4 mo

PLND = pelvic lymph node dissection; TCC = transitional cell carcinoma; CHT = chemotherapy; RT = radiotherapy; PCa = prostate cancer; RLND = retroperitoneal lymph node dissection; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; NSGCT = nonseminomatous germ cell tumor.

dissemination in the peritoneal cavity in a mouse model. They concluded that the pneumoperitoneum does not change the intraabdominal distribution of renal cell carcinoma implants and that laparotomy and trocar insertion with pneumoperitoneum do facilitate scar metastasis and, therefore, pneumoperitoneum alone cannot be incriminated in the pathophysiology of port site metastases during laparoscopy.

Microleakage around ports, often known as the "chimney effect," might play a role in the incidence of port site metastasis. A greater growth of tumor in the face of gas-leaking ports was reported by Tseng *et al.* as reviewed by Curet[1] in a rat model. However, many investigators have postulated that a high number of aerosolized cells are required.[1]

Pneumoperitoneum and wound closure technique on port site tumor implantation was evaluated by Burns *et al.*[20] They implanted a standard quantity of rat mammary adenocarcinoma in a flank incision in Wistar-Furth rats. After 14 days, 1-cm incisions were made in each animal in three quadrants. One half of the rats were placed into a 60-minute carbon dioxide pneumoperitoneum. Then, the flank tumor was lacerated transabdominally in both groups. The three wound sites were randomized to closure of skin; skin and fascia; and skin, fascia, and peritoneum. The abdominal wounds were harvested en bloc on postoperative day 7. No difference was found in implantation between the pneumoperitoneum and no pneumoperitoneum rats. Within the no-pneumoperitoneum group, a significant increase ($P = 0.03$) was found in tumor implantation with skin closure alone compared with closure of all three layers. The investigators demonstrated that the closure technique might influence the rate of port site tumor implantation but that the use of a carbon dioxide pneumoperitoneum does not alter the incidence of port site tumor implantation.

In a recently published animal model, Halpin *et al.*[21] assessed tumor implantation at abdominal wound sites after manipulation of a solid abdominal tumor. Human colon cancer cells were injected into the omentum of hamsters. The hamsters were randomized to bivalve, crush, strip, or excision, with or without a pneumoperitoneum. No significant difference was found with or without the pneumoperitoneum. However, a difference was found between the groups with and without tumor manipulation. The investigators concluded that tumor implantation at trocar sites results from spillage of tumor during manipulation and not the pneumoperitoneum.

Several investigators have compared different insufflation gases, and even gasless laparoscopy has been studied in animal models. The findings have been contradictory, and many investigators found no difference in the incidence of port site metastasis with gasless laparoscopy or using different insufflation gases.[1,20–22]

Surgical Technique. It has been well established that tumor boundaries must be respected to perform an onco-

logically safe procedure. It was Mathew *et al.* who demonstrated that tumor manipulation increased tumor metastasis in both open and laparoscopic surgery.[1]

Also, Mutter *et al.*[23] evaluated the effect of tumor manipulation during laparoscopy compared with that of conventional laparotomy on the growth and spread of an intraperitoneal tumor in the rat in a randomized and controlled trial. They concluded that manipulation was the main factor acting on tumor dissemination in both groups. However, laparoscopic surgery had a beneficial effect on local tumor growth compared with laparotomy in the case of tumor manipulation.

Lee *et al.*[24] studied animals that underwent crushing of a subcapsular splenic tumor during laparoscopic exploration. They found a greater incidence of port site involvement in these animals versus those who did not undergo tumor crushing.[24] It is obvious that with increasing surgical skills, unnecessary tumor manipulation can be kept to a minimum. It was also Lee *et al.*[25] who reported that port site metastases decreased with surgeon experience in the same animal model. Another crucial aspect of the surgical technique is morcellation and specimen removal. Many investigators have postulated that, when correctly performed, morcellation of the surgical specimen is oncologically safe.[26–29]

Varkarakis *et al.*[27] recently evaluated 56 consecutive patients who underwent radical and simple transperitoneal laparoscopic nephrectomy. Morcellation specimens (n = 33) were extracted at the umbilical or lateral port sites and intact specimens (n = 23) through an infraumbilical incision. The investigators concluded that with proper technique, morcellation is safe for extracting renal tumors. However, such a specimen can be evaluated for histologic type but not for pathologic staging, limiting its use with TCC. Port site seeding is rare and does not appear to be more frequent than with open nephrectomy. Although morcellation is cosmetically more desirable, in the latter study, no significant advantage was found in operating time, pain, or the duration of the hospital stay. The choice of extraction method should be left to surgeon preference and patient choice.

However, it is logical to assume that the potential risk of tumor seeding is greater when morcellation is performed. Direct dissemination of tumor by contaminated instruments or by extraction without the use of an entrapment sac have also been well documented.[3,6–8,10,30,31] An increased number of tumor cells has been observed in ports with excessive manipulation. Ports used by the lead surgeon have been proved to have more tumor contaminant than either those used by the assistants or the port used for placement of the laparoscope.[5]

An entrapment bag should always be used for intact specimen extraction, because direct contact between surgical specimen and wound can facilitate tumor seeding. In this regard, the incision size plays a paramount role; an incision to small for specimen extraction can lead to tissue trauma and could be responsible for wound implantation.

REVIEW OF EXISTING DATA

To our knowledge, 17 studies in English have been published, reporting a total of 29 cases of port site metastasis or tumor seeding secondary to laparoscopic urologic procedures in the past 20 years. Table 1 summarizes these reports, along with 2 cases from our own series.[30,32–46]

When the cases were compared, aggressive tumor biology seemed to be the main factor associated with tumor seeding. Most cases reported were high-grade TCC. Other factors such as morcellation and absence of bag retrieval might also have been present.

PREVENTION

In recent years, the incidence of port site metastases reported in urologic studies has significantly decreased. Experienced laparoscopists and standardized techniques have allowed oncologically safe laparoscopic procedures. Despite this, many investigators have studied new methods to keep tumor seeding to a minimum. The injection of intraperitoneal agents to eradicate liberated tumor cells remains controversial.[47–51] The use of methotrexate, povidone-iodine, sodium hypochlorite, chlorhexidine-cetrimide, aspirin, and indomethacin has been postulated.[47–51] However, many of these suggestions are unproven, and peritoneal irritation secondary to these agents must not be underestimated. Recently, some investigators have proposed the use of heparin as an antiadhesion agent. Pross *et al.*[52] demonstrated that low-molecular-weight heparin given subcutaneously or combined intraperitoneal lavage and subcutaneous injections significantly inhibits intraabdominal tumor growth and intraperitoneal metastasis of adenocarcinoma cells in rats undergoing laparoscopy. Instillation of antiadhesion agents has been proposed in high-risk laparoscopic procedures with high-grade, high-stage disease or in situations in which the risk factors for port site implantation have been identified intraoperatively.[8]

Tsivian and Sidi[6] have suggested several measures to prevent urologic port site metastasis, including (a) sufficient technical preparation, (b) avoidance of laparoscopic surgery if ascites is present, (c) trocar fixation with avoidance of gas leakage along the trocar, (d) avoidance of tumor boundary violation, (e) cautious consideration of morcellation, (f) use of an impermeable bag if morcellation is done, (g) use of a bag for intact specimen removal, (h) drainage placement, if needed, before abdomen deflation, (i) povidone-iodine irrigation of the laparoscopic instruments, trocar, and port site wounds, and (j) suturing of 10-mm trocar wounds.

Concerning hand-assisted laparoscopy, Chen *et al.*[43] recommended the use of an impermeable specimen bag and that surgeons should not hesitate to extend the wound if resistance is met while removing the specimen from the hand port. Also, they suggested that because of

the risk of cancer cell spillage on the gloves, the operator might change to a new pair of surgical gloves after removal of the tumor before closing the wound. Additionally, traumatic manipulation should be carefully avoided, especially with a high-stage/high-grade tumor. Intraoperative tumoricidal agent lavage might be added in such high-risk patients. Finally, they suggested that better patient selection criteria are required.[43] Technically, it is feasible to perform hand-assisted laparoscopic nephrectomy for tumors larger than 7 cm. However, in regard to the incidence of tumor recurrence and prognosis, whether hand-assisted laparoscopic nephrectomy is suitable for tumors larger than 7 cm cannot be determined without more long-term clinical data. Schneider *et al.*[53] demonstrated a 50% decrease in the incidence of port site metastases when preventive measures were used and the risk of developing a port site recurrence was decreased by 7.7-fold.

CONCLUSIONS

Port site metastasis in the setting of urologic laparoscopic surgery is a rare occurrence. Multiple factors have been linked to tumor seeding; however, tumor grade and stage seem to be preponderant. Standardized oncologic techniques and preventive measures, including cytotoxic and antiadhesion agents, might help decrease the incidence of tumor seeding. Nevertheless, we believe that only proper preoperative criteria, along with cautious intraoperative judgment, will keep port site metastasis to a minimum in the future.

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