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Review article

Port-site metastasis in laparoscopic gynecological oncology surgery: An overview

Vahan Manvelyan [a], Veerapol Khemarangsan [b], Kuan-Gen Huang [c, *], Aizura-Syafinaz Adlan [d], Chyi-Long Lee [c]

[a] Department of Operative Gynecology, Shengavit Medical Center, Yerevan, Armenia
[b] Department of Operative Gynecology, Charoenkrungpracharak Hospital, Bangkok, Thailand
[c] Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital at Linkou Chang Gung University College of Medicine, Kwei-Shan, Tao-Yuan, Taiwan
[d] Department of Obstetrics and Gynaecology, University Malaya Medical Centre, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

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ABSTRACT

Despite the low frequency, port-site metastases are associated with poor outcomes in patients and account for significant patient morbidity. They remain a challenging complication of laparoscopic procedures for gynecologic malignancies. A comprehensive, systematic search for published studies was conducted using the PubMed databases. Various mechanisms of port-site metastases are addressed in the relevant literature. The review of the articles points out that in the development of port-site metastases, the major role is played by biologically aggressive diseases, tumor manipulation, wound contamination, and surgery-related factors. The advantages of laparoscopic oncologic surgery are unquestionable. Further investigations of the mechanisms of port-site metastasis would contribute to the prevention of this insidious pathology.

Introduction

Laparoscopic surgery has been used for treatment of oncological patients for the past 30 years. The first reports concerning laparoscopy implementation in oncogynecology date back to the 1970s.[1–3] It is undebatable that laparoscopic surgery has numerous advantages. It affords a safe and less invasive modality for both diagnostic and major operative procedures.[4] Its safety and feasibility have been proved by numerous authors, who published their experience with total laparoscopic radical hysterectomy.[5–7]

Laparoscopy has several significant advantages in oncologic patients.[8–14] Oncologic and immunologic functions are much better preserved after laparoscopic surgery.[15–17] Additionally, specific to gynecologic malignancies, shorter intervals to postoperative treatments can also be listed as advantages to minimally invasive surgery.[18] Patients who undergo minimally invasive surgery can often begin adjuvant therapy relatively quickly after their initial surgery because of the shorter recovery time.[19]

As main complications of laparoscopic oncology, the authors mention vascular injuries, bowel injuries, genitourinary injuries, and port-site metastases (PSMs).[20,21] Nevertheless, Chi et al[22] found that both simple and complex laparoscopic procedures can be performed by a gynecologic oncology service with a low rate of complications. Among the mentioned complications, we consider PSMs rather important in laparoscopic oncology. Also, it should be underlined that PSM is a strong risk factor for peritoneal dissemination.[23] PSMs are associated with poor outcome of patients[24] and represent significant patient morbidity and end-of-life care issues.[25] All the above-mentioned factors highlight the high actuality of PSMs in today's laparoscopic surgery (Figure 1).

Incidence

The first paper describing the case of developing local tumor metastases after laparoscopy was presented by Döbrönte et al[26] in 1978. Following that, numerous data regarding this complication have been published in various surgical specialties. Zivanovic

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* Corresponding author. Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center, and Chang Gung University College of Medicine 5, Fu-Hsin Street, Kwei-Shan, Tao-Yuan 333, Taiwan.
E-mail address: kghuang@ms57.hinet.net (K.-G. Huang).

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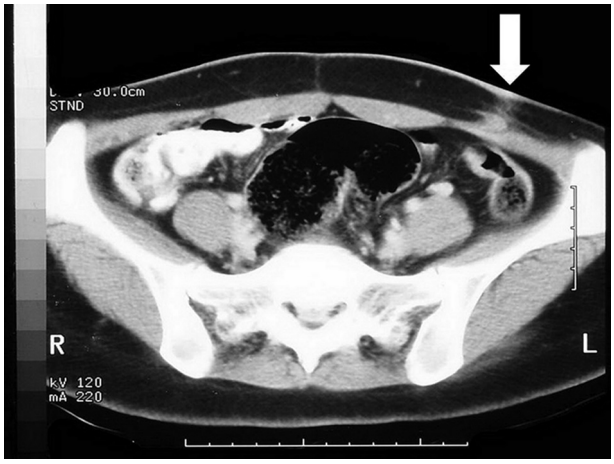

Figure 1. Arrow shows tumor metastasis over fascia and subcutaneous tissue. The overlying skin and parietal peritoneum are intact.

et al,[27] in their noteworthy study, showed that PSMs were documented in 20 of 1694 patients (1.18%) who underwent laparoscopic procedures for a malignant intra-abdominal condition. In the investigation of Nagarsheth et al,[28] 83 patients with endometrial (39), ovarian (29), and cervical (14) cancers were subjected to laparoscopic treatment. The overall incidence of PSMs in gynecologic cancers in that was 2.3%. In the study of Martinez et al,[29] 1216 laparoscopic procedures were performed in women with endometrial end uterine cancers, and the incidence of PSM after laparoscopy for cervical and endometrial cancer was 0.43% and 0.33%, respectively.[29] Rassweiler et al[30] found an incidence of 0.18% in 1098 patients who had undergone laparoscopic procedures for urologic malignancies. Shoup et al[31] examined the incidence of PSMs for upper gastrointestinal tract malignancies and found that port-site implantation after laparoscopic procedures occurred in 0.79% of 1650 patients. Fleshman et al[32] noted an incidence of PSM in 0.9% in 435 patients who underwent laparoscopic-assisted colectomy. Summarizing, Terence et al[24] reviewed 17 studies, which included 11,027 cancer patients undergoing laparoscopic surgery or diagnostic laparoscopy, and pointed out that PSM is a rare phenomenon, occurring in less than 2% of patients.

Immune response

Data concerning immune response in the development of PSMs are rather rare. However, among the existing ones, the study of Ost et al[33] is of interest. In their study, mice and the syngenic murine bladder tumor cell line were used. The investigators subjected mice to either CO_2 pneumoperitoneum or midline incision. Peritoneal macrophages were collected. The tumor necrosis factor (TNF)-alpha levels were quantified. As the conclusion, the study showed that in a syngenic murine model, CO_2 pneumoperitoneum causes inhibition of peritoneal macrophage TNF-alpha secretion. Inhibition of peritoneal macrophage TNF-alpha secretion may be considered an adverse event contributing to the development of transitional-cell carcinoma PSM, especially if surgical oncologic principles are violated. Prior to this study, Gupta and Watson[34] reviewed the literature on immunological changes following laparoscopy and open surgery from Medline and concluded that despite a few contradictory reports, systemic immunity appears to be better preserved after laparoscopic surgery than after open surgery. However, the local intraperitoneal immune system behaves in a particular way when exposed to carbon dioxide pneumoperitoneum; suppression of intraperitoneal cell-mediated immunity has been demonstrated in a number of studies.[34] In addition to the abovementioned studies, Kuhry et al,[35] in their review article, argue that although laparoscopic surgery for colorectal malignancies may be associated with higher survival rates and lower recurrence rates because of improved immune function, it has also been related to high incidences of PSMs. Reviews in the literature have now shown that incidences of PSMs are comparable to incidences of wound metastases after open surgery.[35] Moreover, in their review article, “Immunological aspects of minimally invasive oncologic surgery,” Hegarty and Dasgupta[36] summarized that laparoscopy results in better overall preservation of immune function than open surgery. Also, a substantial number of recent studies on the topic of immune response in general and gynecologic surgery were identified from Medline by Holub,[37] with a conclusion stating that laparoscopic surgery better preserves the postoperative immunological functions compared with the open approach.

Nevertheless, Ost et al,[33] Kuhry et al,[35] Hegarty and Dasgupta,[36] and Holub[37] (referred by our group), as well as other investigators,[38–40] share a common opinion that the status of the immune response in laparoscopic procedures and its contribution in future development of the PSMs needs to be further investigated.

Pneumoperitoneum

Some investigations showed stimulation of tumor growth by intra-abdominal pressure.[40–43] Different pressures and their effect on tumor growth and PSMs in a rat model both *in vivo* and *in vitro* were investigated by Jacobi et al,[40] who showed that tumor cells incubated with CO_2 at 10 and 15 mmHg revealed a decreased *in vitro* intraperitoneal tumor growth in comparison with pressures at 0 and 5 mmHg. As for the studies *in vivo*, increased tumor growth could be observed at laparoscopy at 5 and 10 mmHg compared with the control group. Increase of subcutaneous tumor growth was observed at laparoscopy at 5, 10, and 15 mmHg compared with controls.[44] Nevertheless, other data demonstrated the stimulation of intra-abdominal tumor growth caused by high-pressure CO_2 and leading to increased pulmonary metastasis.[42]

Moreira etal[45] reported that as a result of insufflating gas' distension of abdomen, a high pneumperitoneal pressure is created, which in turn provokes movement of free peritoneal tumor cells, or may cause sloughing or dissemination of tumor cells from viscera into the peritoneal cavity. An increased blood flow of the anterior abdominal wall caused by intra-abdominal high pressure as a result of pneumoperitoneum can be a possible risk factor of PSMs because of the increased circulation.[46]

Carbon dioxide is the most commonly used gas for insufflations during laparoscopic surgery. It is nonflammable, inexpensive, colorless, readily available, and readily absorbed.[47] There are several conflicting results regarding intraperitoneal tumor growth as a result of CO_2 pneumoperitoneum. In particular, Jingli et al[48] presented a study where intraoperative 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. Cytology was examined twice: immediately after opening of the peritoneal cavity and just prior to closure of the abdomen. Malignant cells were not detected in the CO_2 filtrate gas. The incidence of positive cytology in the lavage of the instruments during laparoscopic surgery was 2.78%. The incidence of positive cytology during laparoscopic surgery was 33.33% in the prelavage and 8.33% in the postlavage. The incidence of positive cytology during conventional surgery was 33.33% in the prelavage and 11.11% in the postlavage. The conclusion was that during colorectal laparoscopic surgery, CO_2 pneumoperitoneum does not affect tumor cell dissemination and seeding.[48] In this study, laparoscopic techniques used in colorectal cancer surgery were not associated with a greater risk for

intraperitoneal dissemination of cancer cells than the conventional technique. Ishida et al[42] came to a similar conclusion after performing an investigation on rabbits, wherein the presence of a trocar may be a factor contributing to PSM, but CO_2 pneumoperitoneum appears not to be a factor.

Controversial data were presented by Hirabayashi et al,[49] who performed a study on 15 nude mice, which were injected with human gastric cancer (MKN 45) cells with further determining of the effect of pneumoperitoneum by using a scanning electron microscope to study the effects of how tumor cells disseminate to form PSMs after pneumoperitoneum. They found that pneumoperitoneum immediately results in peeling and destruction of the muscular layer of the abdominal peritoneum, increasing the propensity of tumor cell adhesion at port sites and subsequently healing process occurs, leading to scar formation with the presence of entrapped tumor cells. The conclusion of the study was that free cancer cells appear to attach to the injured port sites immediately after CO_2 pneumoperitoneum, and these are associated with the development of PSM after laparoscopic cancer surgery.[49]

Furthermore, the type of gas has also been shown to influence the rates of PSM with helium insufflations being the least likely compared to argon and nitrogen, which were more likely to be associated with PSM.[50]

Wound contamination

According to some authors, the tumor cell entrapment hypothesis is one of the etiologic development factors of the PSM. The essence of this hypothesis, presented in 1989, is that free cancer cells are capable of implanting on raw tissue surfaces including damaged peritoneal surfaces.[51] The tumor cells' destruction by the normal defense mechanisms could be prevented by fibrinous exudates that cover the raw tissue surfaces including damaged peritoneal surfaces in the postoperative period.

In laparoscopic procedures, the specimen is often extracted through a small wound that can increase tissue trauma, which may play a role in wound implantation.[52,53] The extraction of tumor through a small port site together with the leakage of CO_2 that occurs may induce movement of free tumor cells that have an increased propensity to implant in the traumatized tissue of the wound.[53] During the surgical procedure, ongoing passage and extrication of instruments that are contaminated by tumor material owing to the dissection process, may also explain its occurrence.[24]

Up to 70% of animal studies revealed tumor cell deposition in extraction wounds.[54] The survey of Paolucci et al[55] demonstrated that 55% of PSMs were found at the extraction port. Nevertheless, the same study also showed that an extraction bag was used in 11.5% of the patients who developed metastases at the extraction wound. The fact that PSM can be caused by other etiologic factors is proved in the same study. Although direct wound implantation likely plays a major role, there clearly are other etiologic factors because direct wound implantation does not explain the other 40% of patients who develop metastatic disease at nonextraction port sites. Another common port site where metastatic disease can be found is the operating port. Allardyce et al[56,57] found more tumor cells at operating ports than at assistants' ports, which suggested that wound implantation was caused by contamination of instruments. The studies show that concentration of the tumor cells in wound washings goes as high as 26% and that the tumor cells are able to recover from the gloves and instruments used during surgery.[58] Numerous investigators have shown instrument contamination with malignant cells.[52,56,59,60] Instrument contamination can occur by direct implantation of cancer cells after specimen manipulation. These cells can then contaminate the trocars, leading to PSMs.[54] Frequent changes of instruments may predispose to tumor wound implantation.[52,57]

It should be underlined that although conflicting data exist from animal and human studies, a general trend is observed toward systemic immune preservation and peritoneal immune depression during insufflation-based laparoscopy. This altered peritoneal immune response could also be an adverse event contributing to the rare development of PSMs.

Tumor-related factors

There are several postulated causes for developing PSMs; of these, tumor aggressiveness appears to be the most favored. It is a truism of cancer biology that the more aggressive the tumor in terms of grade and stage, the more likely that tumor is to metastasize. Thus, the phenomenon of PSMs might simply reflect the biological aggressiveness of the primary tumor.[61]

In their article, “Risk factors contributing to early occurrence of port-site metastases of laparoscopic surgery for malignancy,” Wang et al[62] discovered that the majority of recurrences were in patients with adenocarcinoma cell type, advanced stage (far-advanced disease), and often with diffuse peritoneal carcinomatosis, and, consequently, concluded that PSMs may contribute to the highly aggressive nature of the disease.[62] We can meet practically the same conclusion in Abu-Rustum et al's[63] study—subcutaneous implantation appears to occur in patients with known metastatic disease and is detected in the setting of synchronous advanced intra-abdominal or pelvic metastasis and progression of carcinomatosis.

In spite of this, in a review article that analyzed 31 articles, which included 58 patients, Ramirez et al,[64] concluded that laparoscopic PSMs are a potential complication of laparoscopy in patients with gynecological malignancies, even in patients with early-stage disease. Meanwhile, Zivanovic et al[27] analyzed a prospective database of all patients undergoing transperitoneal laparoscopic procedures for malignant conditions performed by the gynecologic oncology service, in which 2251 patients were involved. The investigators arrived at a conclusion that the rate of port-site tumor implantation after laparoscopic procedures in women with malignant disease is low and almost always occurs in the setting of synchronous, advanced intra-abdominal or distant metastatic disease.[12] Moreover, Rassweiler et al[30] performed 1098 laparoscopic procedures for urological malignancies, and concluded that according to their experience the incidence of local recurrence and the risk of PSMs is low and seems to be mainly related to the aggressiveness of the tumor.

Martinez et al[29] estimated the incidence of clinically detected PSMs in patients with endometrial and cervical cancer treated at two gynecologic oncology services with extensive experience. During the study period, 1216 laparoscopic procedures for uterine cancer were performed. A total of 921 patients underwent laparoscopic staging for cervical cancer and 295 for endometrial cancer. The overall incidence of PSM in our institutions was 0.4% per procedure (5 patients), and the incidence of PSM after laparoscopy for cervical and endometrial cancer was 0.43% and 0.33%, respectively. Excluding patients with peritoneal carcinomatosis, the rate of port-site recurrence in our series lowered to 0.16%, and the rate of isolated PSMs dropped to 0%. The median time to the development of PSM was 8 months (range 6–48), the median overall survival from diagnosis for all patients was 26 months (range 7–30), and median survival from recurrence was 5 months (range 1–20). They concluded that although PSMs are recognized as a complication of laparoscopy for ovarian cancer, they are a rare complication of laparoscopic staging for endometrial and cervical cancer. The majority of patients with PSM presented with associated synchronous

disease.[29] Vergote et al[65] observed a high rate of PSMs after laparoscopy in patients with advanced ovarian carcinoma, as well. In addition to the abovementioned studies, there is a very interesting investigation byNagarsheth et al,[28] in which they determined the incidence of PSMs in patients undergoing laparoscopic procedures for gynecologic cancers. The charts of patients treated by laparoscopy for diagnosis, treatment, or staging of gynecologic cancer were studied. No patients without a histological or cytological diagnosis of cancer from the index procedure were included. Fisher's exact test was used for statistical analysis. Eighty-three patients were identified accounting for 87 procedures. The types of cancer treated included endometrial (39), ovarian (29), and cervical (14). Twenty procedures were performed for recurrence of ovarian or peritoneal cancer, and ascites was present in 10 cases. The conclusion was that the overall incidence of PSMs in gynecologic cancers in their study was 2.3%. The risk of PSMs is highest (50%) in patients with recurrence of ovarian or primary peritoneal malignancies undergoing procedures in the presence of ascites.[28] Along with this, the study by Obermair et al[66] is also noteworthy. The given study is a retrospective review of patients presenting with stages 1–4 endometrial cancer, who had a hysterectomy, bilateral salpingo-oophorectomy with or without surgical staging. The surgical intent was total laparoscopic hysterectomy (TLH) in 226 patients (44.3%) and total abdominal hysterectomy (TAH) in 284 patients (55.7%). The conclusion was that the incidence of PSM in early-stage endometrial cancer treated by TLH is low.[66]

Surgical technique

One of the primary reasons for PSM occurrence is the surgical technique used. In the development of PSM, spillage or liberation of cells from the primary tumor has one of the key roles; therefore, handling of tumor during laparoscopy is rather important.[67–69]

There are several interesting studies performed by Lee et al[70] at different times. One of the studies involved female mice that underwent crushing of a subcapsular splenic tumor during laparoscopic exploration. The scope of port site involvement in these mice was very high in comparison with those that did not undergo tumor crashing. In the same animal model, the authors found that surgical technique may be a possible factor in port tumor formation. They also noted that PSMs decreased with surgeon experience,[71] and wound recurrence may actually be the result of an unfortunate learning curve.[72]

Polat et al,[73] in their experimental study in rats, referred to the effect of types of resection and manipulation on trocar site contamination after laparoscopic colectomy. The investigators detected and quantified the amount of contamination at the port-site by means of a method utilizing radiolabeled colloid particles following extra- or intracorporeal laporoscopic resection of cecum. Prior to the experimental surgery, they obtained a high concentration of luminal colonic radiotracer activity by per anum application of sulfur colloid molecules labeled with Tc-99m pertechnetate. In three main groups of rats, they either resected a portion of cecum extracorporeally or intracorporeally, or did no resection at all. Each main group was further divided into two subgroups, in which the manipulations were either atraumatic or traumatic. They excised trocar sites as 2-cm doughnuts after completion of the surgical procedure. Gamma camera imaging to quantify the amount of radioactive contamination at trocar sites was used. We detected an overall incidence of contamination in 44% of rats. This rate was 71% and 17% in traumatic and atraumatic subgroups. The resection itself increased the rate and intensity of contamination as well ($p = 0.04$). The most intensive contamination was detected in the intracorporeal resection with traumatic manipulation subgroup.[73] This study proves the significance of tumor manipulation. PSM formation can be a result of tumor extraction without the use of an entrapment sac or by direct dissemination of tumor by contaminated instruments.[30,67,74,75]

The significance of tumor manipulation during surgery in PSMs is also proved by other studies. In a rat model study, Mathew et al[76] presented an increased level of metastases due to tumor manipulation in open and laparoscopic surgery. The randomized controlled trial performed by Mutter et al[77] on rats also pointed out that tumor manipulation is the main factor acting on tumor dissemination in both laparoscopy and laparotomy. In the conclusion, the investigators also highlighted that the laparoscopic surgery had a beneficial effect on local tumor growth compared with laparotomy in the case of tumor manipulation. This beneficial effect of laparoscopic surgery may be related to a better preservation of immune function in the early postoperative period.[77] Oncological safety of the accurately implemented marcellation of the surgical specimen referred to by many authors should be especially underlined.[78–81]

In addition, some literature review exists regarding the surgical technique decreasing the risk of PSMs. In particular, Agostini et al[82] showed in their investigation in rat models that peritoneal closure decreases the risk of PSMs. Schneider et al,[83] in their experimental, prospective, randomized, single-blind study, investigated the influence of quality surgery on the incidence of port-site recurrences and concluded that trocar fixation, prevention of gas leaks, rinsing of instruments with povidone–iodine, minilaparotomy protection, rinsing of trocars prior to removal, peritoneal closure, and rinsing of all wounds with povidone–iodine during surgery decrease the risk of PSMs.[83]

Conclusion

PSMs are seldom encountered. The etiology of PSMs is multifunctional. Recurrence of PSMs is quite rare in endometrial and cervical cancers treated laparoscopically. Nevertheless, a tangible role in PSM incidence is attributed to ovarian cancer, primary peritoneal cancer, presence of ascites and biologically aggressive diseases, surgery-related factors including tumor manipulation and wound contamination. Unquestionable advantages of laparoscopic oncologic surgery should be highlighted. The following key factors may decrease the incidence of PSMs: a surgeon's experience, correct and maximally atraumatical tumor manipulation and marcellation, tumor removal from the vagina, use of an impermeable bag, povidone–iodine irrigation of the laparoscopic instruments, trocar, and port site wounds, and suturing of 10 mm and larger trocar wounds. In our opinion, further investigations of the mechanisms of PSM would contribute to the prevention of this insidious pathology.

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