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Port-Site Metastasis in Gynecological Malignancies

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ABSTRACT

Background: Minimally invasive oncologic surgery has become the standard of care in many gynecologic cancers. While laparoscopic surgery provides many benefits to patients, such as faster recovery, there are unique challenges associated with minimally invasive techniques. Port-site metastasis is a rare complication after laparoscopic oncologic surgery in management of gynecologic malignancies.

Methods: We present the case of a 44-year-old female with isolated port-site recurrence following laparoscopic radical hysterectomy with node-negative, clinical stage IB1 cervical adenocarcinoma. In addition, we provide an updated review of the literature on management and oncologic outcomes of port-site metastasis.

Conclusion: Port-site metastasis prevention necessitates a better understanding of underlying risk factors and pathophysiology in order to optimize outcomes. Future studies are needed on risk-reducing strategies and standardization of management for port-site metastasis.

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INTRODUCTION

Surgical oncology has been revolutionized in the last two decades by minimally invasive surgery techniques and enhanced recovery after surgery protocols, conferring reduced morbidity and faster recovery time for patients undergoing oncologic treatment. Although laparoscopic treatment of cancer has become the standard of care in many circumstances, there are unique complications associated with minimally invasive techniques. In particular port-site metastasis (PSM) is a rare phenomenon, occurring in up to 20.3% of oncologic laparoscopic surgeries, and is defined as tumor growth at the site of a port incision after laparoscopic resection of malignant tumor.[1–4]

Previous case reports of PSM in patients with cervical cancer have demonstrated advanced stage disease at the time of surgery as a risk factor.[5,6] Here, we present a case report of an isolated PSM occurring after robotic-assisted laparoscopic surgery in a patient with early stage, node-negative cervical adenocarcinoma and provide review of recent literature on management as well as oncologic outcomes of PSM.[7]

CASE REPORT

The patient is a 44-year-old nulliparous female, non-smoker with cerebral palsy, initially presented with a 1.5 cm polypoid ectocervical mass. Cervical biopsy was performed showing moderately-differentiated invasive adenocarcinoma of the cervix. Pre-operative imaging revealed no evidence of any other lesions concerning for metastatic disease.

Examination under anesthesia, cystoscopy, proctoscopy, and cervical biopsies were performed. Intra-operative findings included necrotic cervical mass measuring approximately 1.5 cm. There was no evidence of disease in the parametria or vagina. Cystoscopy and proctoscopy were unremarkable. She was clinically staged with invasive

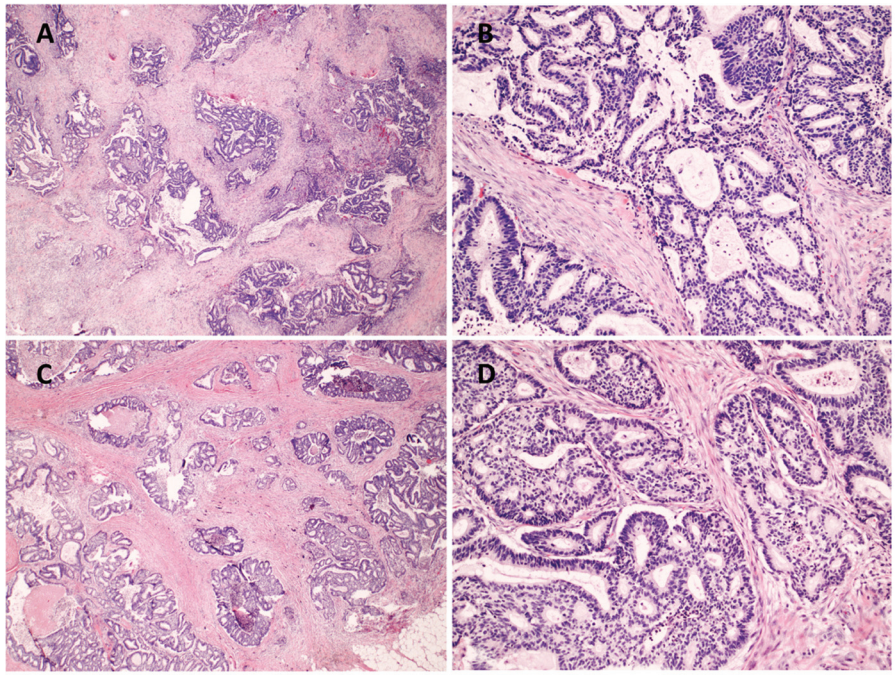

Figure 1. Histological features of the primary and recurrent tumors. A: Low-power view of the primary cervical adenocarcinoma of usual type, deeply invading the uterine stroma (hematoxylin and eosin 20x). B: High-power view of the carcinoma showing typical cribriform adenocarcinoma glands (hematoxylin and eosin 100x). C: Recurrent tumor at Low-power magnification showing similar growth patterns (hematoxylin and eosin 20x). D: High-power view of the recurrent tumor showing similar histological features to the primary cervical tumor (hematoxylin and eosin 100x).

adenocarcinoma of the endocervix, International Federation of Gynecologists and Obstetricians (FIGO) stage IB1.

The patient underwent a robotic-assisted type III radical hysterectomy with bilateral pelvic sentinel lymphadenectomy and ovarian preservation. Pelvic sentinel lymph nodes were negative with intra-operative frozen pathology. The specimens including abdominopelvic washings, uterus, cervix, upper vagina, as well as bilateral fallopian tubes were removed intact vaginally, contained in a laparoscopic bag. Uterine manipulator was avoided in order to prevent fracturing of cervical tumor. Fascial closure was performed by utilizing 0 Vicryl™ suture with a fascial closure device in the umbilical and 12-mm assistant ports. The port sites were irrigated with sterile saline prior to skin closure. There were no intra-operative complications. Pre- and postoperative hemoglobin values were 12.7 g/dL and 12.0 g/dL, respectively. Patient was discharged on postoperative day 1 and her postoperative course was uneventful. Final pathology showed negative washings, surgical margins, parametria, and lymph nodes. The tumor size measured 1.5 cm with no lymphovascular space invasion (LVSI) and 83% of stromal invasion (**Figure 1**). Briefly, in a prospective study performed by Sedlis et al., intermediate-risk factors were identified in patients with node-negative stage IB disease, including tumor diameter greater than 4 cm, deep cervical stromal invasion and positive LVSI. In the presence of two of these factors, adjuvant radiation therapy has been shown to provide statistical benefit in progression-free survival (Sedlis criteria).[8,9] Concurrent chemotherapy and radiation may be considered when the following pathology is present: positive margins, parametrial involvement, and positive lymph nodes (Peters criteria).[9] Given the fact that neither of the aforementioned criteria were met, the decision was made for the patient to undergo surveillance.[8,9]

Postoperatively, she was monitored with physical exams and vaginal cytology every 3 to 6 months per National Comprehensive Cancer Network (NCCN) guidelines, without evidence of recurrence. Approximately 4 years after her initial diagnosis, she returned to care with worsening right periumbilical pain. She underwent abdominal and pelvic imaging, which showed a new hyperdense 4.4 cm mass within the right rectus sheath (**Figure 2**). The area of concern was near the prior assistant port site, which was used for removal of lymph nodes in a containment bag as well as assistance with surgical instruments. Subsequent computed tomography-guided core needle

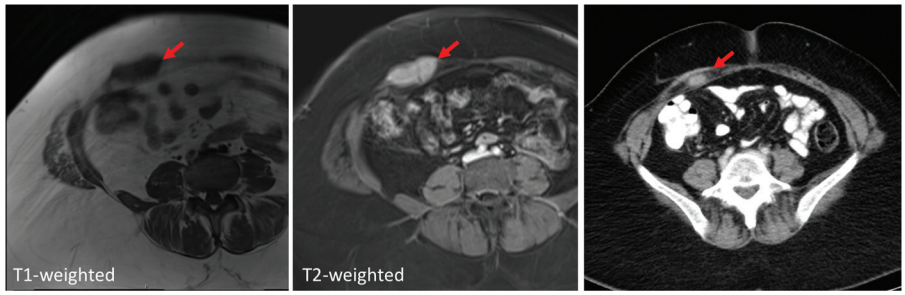

Figure 2. Pre-operative radiographic studies of port-site metastasis. A: Magnetic resonance imaging of abdomen and pelvis with and without intravenous contrast in 2016. T1- and T2-Weighted axial images demonstrating diffusely enhancing mass measuring 2.0 × 4.1 × 3.1 centimeters, involving the right rectus sheath. B: computed tomography of abdomen and pelvic with intravenous contrast and oral contrast showing 1.7 centimeter right abdominal wall metastatic implant.

biopsy of the abdominal wall mass suggested metastatic adenocarcinoma of endocervical origin.

Given isolated port-site recurrence, the patient underwent radical abdominal wall excision of the mass with a 2 cm circumferential margin. Exploration of the abdomen and pelvis did not reveal any additional masses. Peritoneal washings were performed. Fascial defect measuring approximately 9 cm was repaired with mesh. Final pathology showed metastatic carcinoma consistent with primary cervical cancer, as well as negative margins and washings. Radiation therapy to the anterior abdominal wall was recommended postoperatively; however, the patient declined it and opted for ongoing surveillance.

Follow-up imaging after resection of her anterior abdominal wall mass, was obtained as per NCCN guidelines. Nearly 7 years after her initial diagnosis and 3 years after resection of port-site metastasis, she was diagnosed with a second port-site recurrence on abdominal imaging, which revealed a 1.7 cm right abdominal wall metastatic implant (**Figure 2**). Pre-operative imaging did not show any other metastatic site and she was taken to the operating room for needle-localized resection of abdominal wall mass. Exploratory laparoscopy did not reveal any lesions concerning for recurrence in the peritoneal cavity. The abdominal wall mass was resected and fascial defect was repaired with composite mesh. Peritoneal washings were negative for malignancy and final pathology was consistent with primary cervical cancer with negative margins (**Figure 1**). As per tumor board recommendations, she was counseled to undergo anterior abdominal wall radiation. However, she opted for close surveillance after extensive discussion and did not pursue chemoradiation. Follow-up imaging performed 6 months after second resection of PSM did not show any evidence of metastasis.

METHODS

We searched PubMed, Google Scholar, and Ovid Medline through June 2020 using the following key words: port-site metastasis, gynecologic malignancy, cervical cancer. Case reports as well as comparative retrospective and prospective studies were reviewed. Five publications were compared by histologic subtype, PSM treatment, and oncologic outcomes (**Table 1**).

EPIDEMIOLOGY

The overall incidence rate of incisional metastases is 1 – 2% and is equivalent in laparoscopy as well as laparotomy.[10] In gynecologic cancer, the incidence of PSM after laparoscopic surgery has been reported ranging between 0.16 – 2.3%.[2–4] In robotic-assisted surgery for gynecologic malignancies, the PSM incidence is comparable to laparoscopic surgery at 1.41% or 0.28% per port site.[11] The differences in reported PSM incidence rates are at least partly attributable to the initial stage of disease at time of surgery. Higher incidence rates are seen in case series where patients with peritoneal carcinomatosis have been included.[4,12]

In most reported cases, PSM developed within 12 months of the antecedent surgical procedure and was usually associated with synchronous metastasis.[13] Isolated PSM is a very rare condition, where cancer growth occurs only at a port site without any other site of metastasis.[14] Among patients with cervical cancer, PSM has been reported in the literature to have an estimated incidence of 1.25%.[3] Most patients with PSM have locally advanced squamous cell cervical carcinoma and the surgical approach is conventional laparoscopy.[3] A review of PSM in cervical cancer patients from

1980 to 2002, revealed 13 published case reports with port-site recurrence after laparoscopy.[15] Our group published the first report of isolated PSM occurring 4 years after robotic-assisted laparoscopic surgery in a patient with early stage, node-negative cervical adenocarcinoma.[7] Our aim in this review is to shed some light on the likely mechanism of PSM, risk factors, and preventive measures as well as propose management strategies and summarize the impact on the oncological outcomes of patients, who experience this rare complication.

MECHANISM OF RECURRENCE

The exact pathophysiology of PSM is unknown, though several mechanisms have been proposed. At the molecular level, abdominal wound hypoxia and subsequent acidosis have been shown to induce expression of interleukin-8 (IL-8), which is implicated in regulation of angiogenesis via vascular endothelial growth factor.[16,17] Martinez-Palones et al. reported increased microvessel density in a patient with advanced cervical cancer and subsequent PSM.[17] Immunohistochemistry of PSM tissue revealed strong expression of CD31, which is found in endothelial tissue. This finding suggested increased angiogenesis at site of recurrence, likely contributing to tumor progression.[17]

Several studies have hypothesized different mechanisms promoting the development of PSM.[10] One of the most accepted hypotheses implicated in PSM is the use of CO_2 gas and the "chimney effect" created by rapid desufflation through the port sites. The main concern with rapid desufflation is related to the theoretical increase in number of tumor cells at the port site caused by leakage of gas. This theory has been challenged by studies, which showed no difference in PSM between gasless versus conventional laparoscopy.[17–20] In 2014, a meta-analysis including 20 randomized control trials using animal models found that wound recurrence was not significantly higher in laparoscopic surgery compared to gasless laparoscopy (odds ratio [OR] 2.23; 95% confidence interval [CI], 0.90 – 5.55; $P = .08$) or laparotomy (OR, 0.97; 95% CI, 0.031 – 3.00; $P = .08$).[21]

Furthermore, surgical technique and repeated reintroduction of trocars have also been proposed in the development of PSM.[10,17] The latter may lead to trauma and exposure to malignant cells, rendering the surrounding tissue susceptible to tumor implantation. Additional mechanisms suggested in PSM include hematogenous spread, direct wound implantation by malignant cells, and aerosolization of tumor cells.[10,17] The theory of hematogenous spread is less favored given only 0.1% of malignant cells survive in the circulation and could theoretically induce metastasis.[10,17] Direct wound implantation caused by malignant cells from contaminated instruments and trocars could explain development of PSM. This is supported by a previous study, which demonstrated presence of tumor cells in trocars and instrument washings during 12 staging laparoscopies for pancreatic cancer.[17,22]

RISK FACTORS AND PREVENTIVE MEASURES

Ramirez et al. have published the largest series in gynecologic cancer, detailing the risk factors associated with PSM in a report of 58 patients with ovarian, cervical, uterine, or vaginal cancer.[23] The median age of patients in the aforementioned study ranged from 44 – 63 years, depending on the primary cancer.[23] Higher grade and advanced stage of disease were strongly associated with PSM in ovarian cancer.[23] For instance, 83% of patients with ovarian malignancy, who developed PSM had advanced stage disease (FIGO stage III or IV).[23] In cervical cancer patients, 80% of PSM was associated with squamous cell carcinoma.[23] Other risk factors associated with PSM included ascites and residual disease after primary debulking.[10,23]

Although many risk factors and proposed mechanisms associated with PSM remain controversial, it is essential to develop preventative strategies to minimize recurrence. Patient selection is likely one of the most important factors in minimizing the risk of PSM. Based on prior data suggesting higher rates of PSM in patients with higher grade and progression of disease, surgeons should always consider obtaining imaging studies and tumor markers prior to performing surgery. This may allow for better risk stratification and pre-operative planning.

Additionally, adequate use of laparoscopic instruments, avoiding tissue trauma and repeated replacement of laparoscopic trocars, is crucial in prevention of PSM.[10,23,24] Surgeons may consider fixing trocars to the anterior abdominal wall to minimize dislocation. Other techniques suggested to reduce the risk of PSM include desufflating the abdomen with trocars in place in order to avoid the "chimney effect" and closing fascia with peritoneum at port sites for 10- to 12-mm trocars.[10] Rinsing trocars, laparoscopic instruments, and incisions with povidone-iodine solution has been associated with decreased risk of PSM.[2,10,23,25] The aforementioned protective measures were studied using an animal model.[25] Schneider et al. performed a randomized trial in 18 pigs injected with

Table 1.
Management and Oncologic Outcomes of Patients with Port-Site Metastasis in Gynecologic Cancer

Study	Primary	Histology	Figo Stage	Treatment	Metastasis Diagnosis and Treatment	Oncologic Outcomes
van Dam et al. (1999)	Ovarian (n = 104)	Serous vs. Non-serous	IIIC-IV	LSC resection of adnexal mass followed by: -NACT -> LPT-> ACT -LPT -> ACT -chemo alone	9/104 patients developed PSM, all with delay > 7 days from diagnosis to chemo or tumor debulking. −1/9 with poor prognosis received palliative care −6/8 underwent resection and chemotherapy with complete resolution	Kaplan-Meier survival analysis showed survival outcomes equivalent in patients with PSM versus no PSM.
Huang et al. (2003)	Ovarian (n = 31)	Epithelial or Borderline	IC-IIIC	LSC resection of adnexal mass +/− SO +/− LND followed by: -surveillance -chemo	8/31 patients developed PSM ranging from 11 days to 13 months from surgery. −6/8 underwent resection +/− chemo +/ RT -no association between interval to subsequent treatment and PSM	5/8 patients died of disease ranging from 8 – 48 months. Worse prognosis if PSM diagnosed during chemo or after adequate chemo regimen.
Palomba et al. (2012)	Endometrial (n = 12)	Endometrioid or Serous	IA-IV	TLH/LAVH + BSO +/− LND followed by: -surveillance -BT +/− pelvic RT -chemo/HT	4/12 patients with PSM had isolated disease on average 25 months from surgery. −3/4 underwent excision followed by RT and chemo −1/4 palliative RT and HT	Patients who underwent resection of PSM followed by adjuvant therapy had increased survival > 5 months.
Grant et al. (2015)	Endometrial (n = 7)	Endometrioid or Serous	IA-IIIA	TLH/BSO +/− LND followed by: -surveillance -BT +/− pelvic RT -chemo	Patients selected for study with PSM on average 15 months from TLH. −6/7 underwent resection −7/7 received RT	DFS at 1 and 2 years after PSM treatment were 100% and 44%, respectively. 3/7 patients developed additional recurrences in lung, abdominal and pelvic LN, perihepatic.
Zhong et al. (2018)	Cervical (n = 13)	Squamous, Mucinous, Adenocarcinoma	IB1-IVB	Laparoscopy, +/− RH, +/−LND, +/− BSO followed by: -surveillance -RT -chemo	Patients selected for study with PSM on average 9 months from surgery. −8/13 underwent resection −2/8 also received chemo +/− RT	Only 1 patient without evidence of disease after PSM resection.

ACT, adjuvant chemotherapy; BT, brachytherapy; BSO, bilateral salpingo-oophorectomy; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; HT, hormone therapy; LAVH, laparoscopic-assisted vaginal hysterectomy; LSC, laparoscopic; LND, lymph node dissection; LPT, laparotomy; NACT, neoadjuvant chemotherapy; RT, radiation therapy; SO, salpingo-oophorectomy; TLH, total laparoscopic hysterectomy.

HeLa cells intraperitoneally, creating a xenogeneic tumor, followed by laparoscopic sigmoid resection.[25] Pigs that were randomized to laparoscopy using preventative measures, including trocar fixation, prevention of gas leaks, rinsing of instruments with povidone-iodine, mini-laparotomy protection, rinsing of trocars before removal, peritoneal closure, and rinsing of all wounds with povidone-iodine, had significantly less tumor recurrence at port sites compared to the control group ($P = .002$).[25]

Furthermore, the use of containment bag for tissue extraction is commonly employed by contemporary surgeons as a way to prevent contamination of port sites with malignant cells. This change in practice was at least partly due

to several case reports of patients, who developed PSM after uncontained extraction of malignant tissue.[26,27]

Current practices by oncologic surgeons was recently reviewed by Baptiste et al.[28] In a survey of 132 members of the Society of Gynecologic Oncology, the authors studied the association between preventative measures and PSM.[28] Moreover, the study compared surgeons with PSM cases versus no prior cases in regards to pneumoinsufflation pressure, mode of delivery of the specimen, use of local anesthesia at port site incisions, and method of desufflation.[28] Interestingly, there were no statistically significant differences found in practice patterns except for increased cases of PSM in surgeons performing greater than 75% of oncologic surgeries applying minimally invasive technique.[28]

MANAGEMENT OF PORT-SITE METASTASIS

While the presentation and risk factors for PSM after laparoscopic surgery for gynecologic malignancies have been reported, the management and prognosis of isolated port-site metastases have not been fully elucidated.[29] Known risk factors for PSM, such as disease burden, positive washings, peritoneal carcinomatosis, and tissue manipulation play an important role and deserve serious consideration in guiding treatment options.[30] The management of PSM is individualized based on the distribution and burden of disease. Treatment options have included excision with or without adjuvant chemotherapy and abdominal wall radiation.

Chemoradiotherapy has been shown to have both curative and palliative effects, including reduction of tumor size and relief of abdominal pain associated with abdominal wall metastases.[31]

When PSM is diagnosed along with widespread recurrent disease, the recurrence should be treated with the accepted course of treatment for the primary malignancy. Palliative radiation therapy can be considered in patients with subcutaneous metastases that are painful or at risk for skin erosion.[13]

IMPACT ON ONCOLOGIC OUTCOMES

The prognosis of patients with port-site metastasis can vary widely depending on site of origin and histology of cancer, as well as whether the PSM is an isolated presentation or as part of a disseminated state.[32] Given the limited number of cases and respective follow-up, the true associated prognosis of PSM is still not clear. A limited number of studies, which included follow-up and oncologic outcomes in patients with PSM, are summarized in **Table 1**.

In 1999, Van Dam et al. conducted a retrospective study of 104 women with serous versus non-serous ovarian cancer at various stages who underwent laparoscopic removal of adnexal mass followed by cytoreductive surgery.[24] Nine out of 104 patients developed PSM, which did not yield a significant impact on oncologic outcomes and survival.[24] However, the authors did find a longer time interval between the start of systemic chemotherapy or cytoreductive surgery in patients with PSM compared to no abdominal wall recurrence.[24] In a subsequent study conducted in 2003, Huang et al. reviewed 31 patients with ovarian cancer undergoing laparoscopic resection followed by surveillance or chemotherapy and reported eight patients, who developed PSM.[32] Contrary to Van Dam et al., the authors did not find a significant association between interval to subsequent treatment and PSM.[32] Both studies revealed that patients with isolated PSM have improved prognosis compared to patient with multiple sites of metastasis.[24,32] Also, PSM diagnosed in patients who have undergone adequate treatment with chemotherapy is associated with worse prognosis.[24,32]

More recently, studies of patients with primary endometrial or cervical carcinoma and subsequent PSM, supported surgical resection along with adjuvant chemotherapy and/or radiation for treatment of PSM.[12,15,33] Palomba et al. investigated PSM in 12 patients with endometrial cancer who had undergone staging procedure followed by adjuvant therapy.[12] Four out of 12 patients developed isolated PSM on average 25 months after surgery. Seventy-five percent of patients with PSM underwent surgical resection of recurrence followed by chemoradiotherapy.[12] The remaining patients received chemoradiotherapy without surgical resection of PSM. Patients who underwent surgical resection combined with chemoradiotherapy for treatment of PSM had increased survival of at least 5 months.[12]

Similarly, Grant et al. reported on seven patients with endometrial cancer and subsequent diagnosis of PSM.[33] Six out of seven patients were treated with surgical resection of PSM followed by chemoradiotherapy. Disease-free survival at 1 and 2 years after PSM treatment were 100% and 44%, respectively.[33] In patients with cervical cancer, Zhong et al. reviewed 13 case reports of PSM and found only one patient with no evidence of disease after surgical resection and chemoradiotherapy.[15] Overall, these studies reported improved outcomes in patients undergoing surgical resection of PSM followed by chemoradiotherapy. However, there were several limitations including small sample size, lack of control group, and generalizability of results.

Ultimately, the determination of oncologic outcomes for patients with PSM is multifactorial and includes timing of

disease, described as length of time from most recent surgery or systemic therapy to diagnosis of PSM, as well as spread of disease. Continued efforts to obtain long-term data in larger patient cohorts will be beneficial in establishing the impact of PSM on progression-free and overall survival. Furthermore, this will allow for standardization of treatment and effective management of PSM.

CONCLUSION

Advances in minimally invasive cytoreductive surgery have revolutionized the field of oncology since the 1990s. Surgeons have embraced the many advantages of minimally invasive techniques in oncologic care, including faster postoperative recovery time. In 2017, Stewart et al. provided a comprehensive review of oncologic outcomes in laparotomy versus minimally invasive approaches in cervical, uterine, and ovarian malignancies.[34] There is overwhelming evidence in favor of a minimally invasive approach in most patients with the exception of advanced cancer where more extensive tumor debulking may be required including bowel resection.[34]

Although PSM is a rare complication associated with laparoscopic and robotic oncologic surgery, it is crucial to understand its risk factors and pathophysiology in order to prevent recurrence and optimize outcomes. Surgeons should anticipate tumor burden based on pre-operative workup and consider laparotomy in patients with suspected high grade and stage of gynecologic cancer. When a minimally invasive approach is chosen, certain measures may further decrease the risk of recurrence including removal of specimen in a controlled fashion using containment bag and use of povidone-iodine solution. Many of these strategies were utilized during our case, including use of laparoscopic retrieval bags and rinsing of port sites. Furthermore, there was no evidence of ascites or intraperitoneal disease, and surgical margins as well as lymph nodes were both negative. Given ovarian preservation in our case, one possibility leading to PSM is the presence of microscopic ovarian metastasis. Although rare, ovarian metastases have been previously reported in patients with cervical adenocarcinoma.[35–39] However, our patient did not have advanced stage disease and is less likely to have had ovarian involvement. In summary, prompt diagnosis and treatment of PSM with resection alone or followed by chemoradiotherapy has been associated with improved oncologic outcomes. Future studies should focus on long-term data evaluating risk-reducing methods and standardization of PSM treatments.

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