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CASE SERIES

Port Site Metastasis After Minimally Invasive Surgery in Gynecologic Malignancies: Two Case Reports and a Review of the Literature

Nan Yu*, Ting Zhou*, Haiying Sun, Peiying Fu, Ronghua Liu

Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ronghua Liu, Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Anv., Wuhan, Hubei, 430030, People's Republic of China, Tel +86-27-63639807, Fax +86 (27) 83663078, Email liuzhu38@126.com

Abstract: Port site metastasis (PSM) is considered an uncommon and rare complication in gynecologic malignancies with unclear treatment recommendations or guidelines. Thus, we report the treatment strategies and outcomes of two cases of PSMs following gynecologic malignancies and a review of the literature to provide much information about the most frequent sites of PSMs and the incidence of PSMs in different gynecological tumors. A 57-year-old woman underwent laparoscopic radical surgery for right ovarian serous carcinoma in June 2016 followed by postoperative chemotherapy. Because PSMs were present near the port site of the bilateral iliac fossa, the tumors were completely removed on August 4, 2020, and the patient received chemotherapy. She has shown no signs of relapse. During the same period, a 39-year-old woman underwent laparoscopic type II radical hysterectomy for endometrial adenocarcinoma involving the endometrium and cervix on May 4, 2014, without adjuvant treatment. In July 2020, a subcutaneous mass under her abdominal incision was removed, and chemotherapy plus radiotherapy was administered. Metastasis was found in the left lung in September 2022, but there was no abnormality in the abdominal incision. We showed the two cases of PSMs, reviewed articles to provide some new insights about the incidences of PSMs in the gynecologic tumors, and discussed the proper preventive strategies.

Keywords: ovarian cancer, endometrial cancer, port site, metastasis

Introduction

Port site metastasis (PSM) is defined as cancer growth at the site of a port incision after minimally invasive surgery.[1–3] Patients with PSM may have other synchronous metastases,[4] and it is uncertain whether PSM will affect the prognosis of patients. The results of some studies indicate that it is generally considered a poor prognostic factor when recurrence occurs.[5,6] The overall incidence of PSM in gynecologic malignancies has been reported to be 1–2%.[7–9] For primary gynecologic tumors with surgical indications, primary surgery is important, and thorough surgery is closely related to patient survival. However, the surgical indications vary among different types of gynecologic malignancies. There is enough evidence to support that laparoscopic surgery is not beneficial to ovarian cancer patients, and the incidence of PSM in ovarian cancer after diagnostic laparoscopy in advanced ovarian cancer prior to surgery varies significantly from 17% to 47%.[10,11] At present, the standard and recommended approach for ovarian cancer and cervical cancer is the open abdominal approach according to the National Comprehensive Cancer Network (NCCN) guidelines.[12,13] For early-stage endometrial carcinoma, minimally invasive surgery is still recommended,[14] and PSM is rare in patients with endometrial cancer, occurring in approximately 0.1% of such patients.[15] There are a few reports on PSM after robot-assisted surgery, and the overall incidence is <2%.[16,17] Metastases related to the incisional recurrence of PSM in gynecological carcinomas are scarce, and there are no general recommendations for their treatment, probably due to the heterogeneity

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and rarity of such cases.[18] Here, we report two cases concerning PSM after laparoscopic surgery and review the literature, aiming to provide the reliable incidence of PSM in the three major gynecological tumors, offer support for proposed treatment in the clinic and assess prognosis.

Case Description

Case 1

A 57-year-old woman was admitted due to a pelvic mass in June 2016. Computed tomography (CT) evaluation showed a low-density tumor (13.0 cm × 6.0 cm × 3.8 cm) in the right adnexa (Figure 1A, red arrow). The serum tumor marker tests showed a CA125 level of 208.5 U/mL (<35.0 U/mL), and normal levels of alpha-fetoprotein (AFP), human epididymis protein 4 (HE4), CA19-9 and carcinoembryonic antigen (CEA). She underwent laparoscopic hysterectomy, bilateral adnexectomy, pelvic lymph node dissection, paraaortic lymphadenectomy, omental excision, appendectomy, debulking surgery, with lysis of the pelvic adhesions. The operation was successful, and complete resection (R0) was achieved. The postoperative pathology diagnosed high-grade serous ovarian carcinoma (HGSC) considered stage IIIB. The immunohistochemical results showed CK7 (+), WT-1 (+), ER (+), PAX-8 (+), CA125 (partial +), P16 (scattered +), CK20 (-), Villin (-), CDX-2 (-), PR (-), VIM (-), CEA (-), P53 (-), and Ki-67 labeling index (LI) of approximately 60%. The patient was given eight cycles of paclitaxel (175 mg/m^2) and carboplatin (AUC 5) for chemotherapy. Three weeks after the second cycle of chemotherapy, the CA125 value dropped to a normal level. After chemotherapy, the patient was regularly followed up every 3 months.

On June 31, 2020, CT revealed a nodule (3.2 cm × 3.2 cm) in the left inguinal region (Figure 1B, red arrow) during regular follow-up. Three-dimensional color Doppler ultrasound showed a mixed mass (6.1 cm × 3.1 cm × 5.6 cm) in the left iliac fossa and solid masses (1.5 cm × 1.0 cm, 1.9 cm × 1.4 cm) before the right iliac fossa, with no blood flow signal on either side. Chest and abdominal CT showed no metastasis in other organs of the patient. The CA19-9 and HE4 levels were 44.5 IU/mL and 160.97 pmol/L, respectively. Transabdominal resection of the bilateral inguinal metastases and cytoreductive surgery were performed on August 4, 2020. During the operation, an approximately 6 cm mass was found in the left inguinal area, along with two masses of approximately 1.5 cm and 2.5 cm in the right inguinal area. The majority of the left-sided mass was located in the tendon and ligament between the fascia and rectus abdominis, and its lower boundary was the peritoneum; the mass had a clear boundary and obvious capsule. The right-sided masses were fused into one mass, similar in appearance to the mass on the left (Figure 2A). The lesions on both sides were located near the port site. The postoperative histopathologic examination revealed poorly differentiated adenocarcinoma, which was consistent with the recurrence of ovarian cancer (Figure 2B and C). The immunohistochemical results showed CK7 (+), PAX-8 (+), WT1 (+), ER (SP1) (+), ER (positive control) (+), PR (1E2) (-), PR (positive control) (+), VIM (-), P16 (partial +), CK20 (-), Villin (-), CDX-2 (-), SATB2 (-), TTF-1 (-), P53 (-), and a Ki-67 LI approximately 40%. The patient received four cycles of PLD (30 mg/m^2) and carboplatin (AUC 5). At present, this patient is still being followed up, and there have been no signs of recurrence.

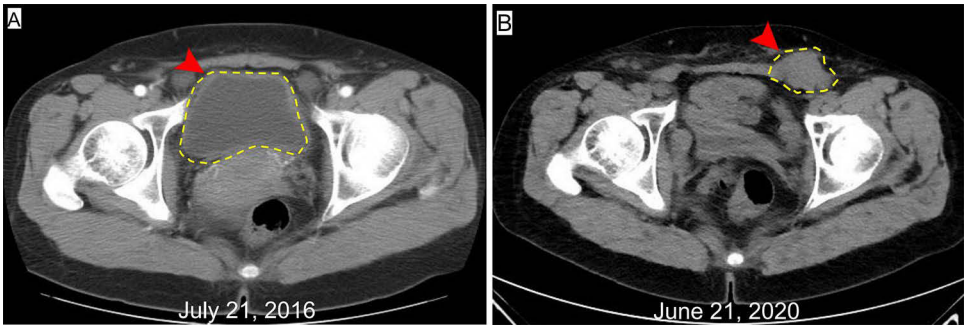

Figure 1 Pelvic computed tomography (CT) results of the patient in Case 1 at the time of initial treatment and recurrence. (**A**) CT revealed a mass (13.0 cm × 6.0 cm × 3.8 cm) in the right adnexa (red arrow and yellow outline) on July 21, 2016. The boundary between the mass and uterus was clear. A liquid density shadow could be seen in the pelvic cavity. No enlarged lymph node shadow was found in the retroperitoneum or pelvic wall; (**B**) CT showed a nodule (3.2 cm × 3.2 cm) in the left inguinal region (red arrow and yellow outline) on June 31, 2022.

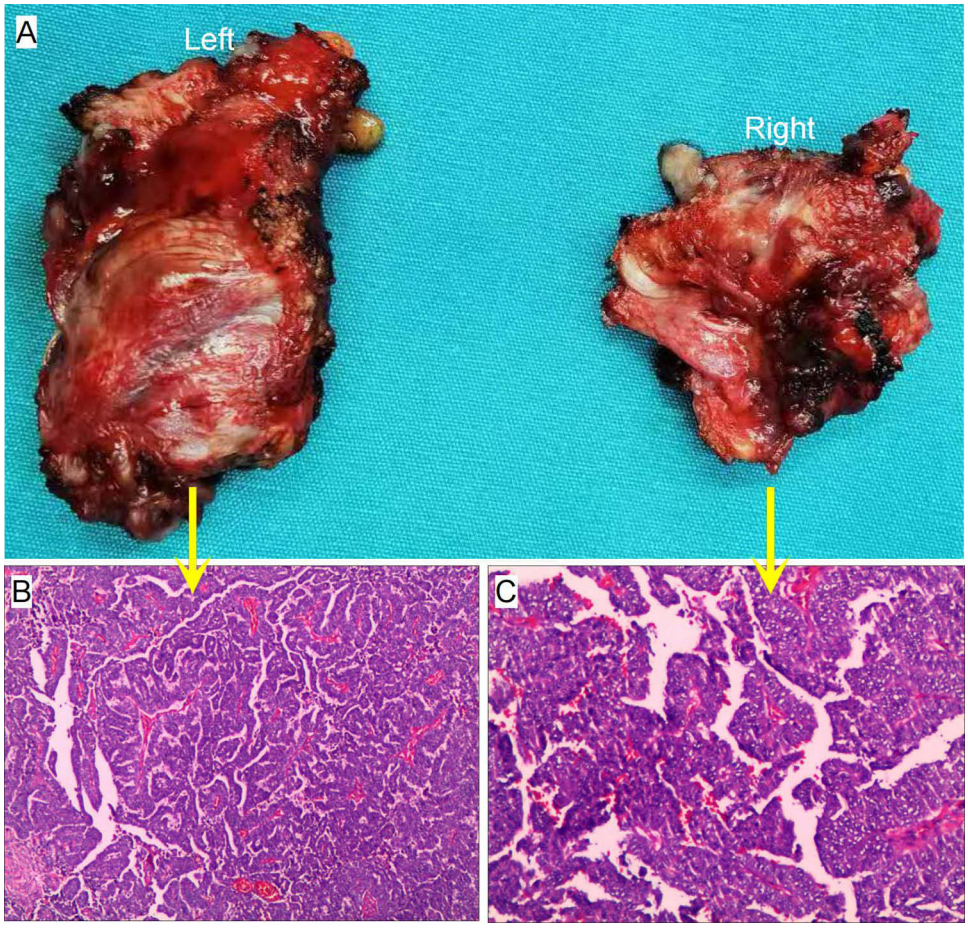

Figure 2 Gross tissue and pathological examination of the surgical samples from both sides. Two masses with irregular surfaces and slightly hard textures are shown (**A**). Hematoxylin–eosin (HE) staining confirmed that these specimens were tumor tissues, 20 × ((**B**), left side; (**C**), right side).

Case 2

A 39-year-old woman was referred to local hospital for cervical myoma and underwent transabdominal surgery (she underwent cesarean section in 2003) on April 5, 2014. During the operation, a 5 cm × 4 cm mass was found at the scar of the lower segment of the uterus. The serous layer on the surface of the mass was cut, and a pseudocapsule was found between the mass and myometrium of the uterus. Forceps were used to clamp the tumor, revealing that the tumor tissue was fragile and that the tissue had broken through the endometrium and entered the uterine cavity. Postoperative pathological results showed that endometrial adenocarcinoma involved the cervical involvement. On May 4, 2014, laparoscopic type II radical hysterectomy, bilateral adnexectomy and pelvic lymph node dissection were performed. Intraoperative tests of the ascitic fluid suggested that some cells had heterogeneous nuclei. No tumor cells were found in the bilateral appendages or pelvic lymph nodes after the second operation. The presence of lymphovascular space invasion (LVSI) and tumor cell differentiation status remained unknown. This patient has at least one risk factor for deep myometrial invasion, but we cannot know why there is no any adjuvant treatment after the second operation.

On February 21, 2019, hypoechoic nodules examined by ultrasound (2.81 cm × 1.24 cm) were found at the right abdominal wall incision in the same hospital. However, it was not processed additional treatment. The woman was referred to our hospital on May 10, 2020. Color Doppler ultrasound examination in our hospital showed one subcutaneous solid mass in the abdominal wall (4.1 cm × 2.2 cm), showing obvious enlargement from the year prior. Color Doppler ultrasound examination on May 21, 2020, showed that the solid mass (4.6 cm × 2.2 cm × 4.0 cm) was still growing (Figure 3A). CT on July 22, 2020, revealed an abnormal nodule (3.1 cm × 2.3 cm) in the right rectus abdominis (Figure 3B), with the supplying artery to the mass originating from the right external iliac artery. No metastasis was

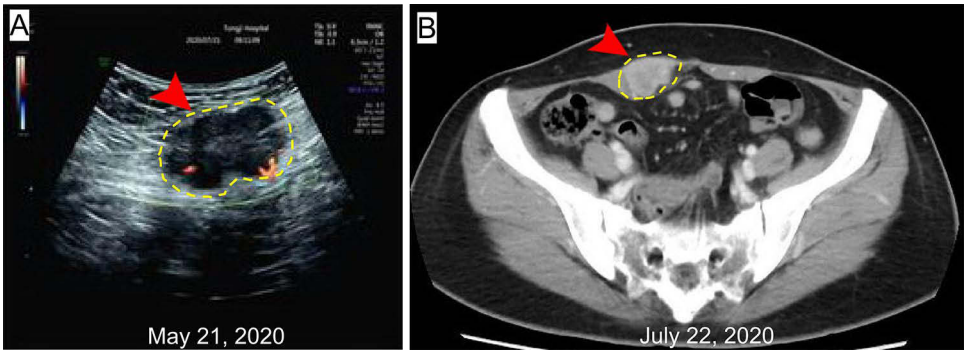

Figure 3 Imaging results of the patient in Case 2. (**A**) Ultrasound showed subcutaneous mass in the abdominal wall (4.1 cm × 2.2 cm) on May 21, 2020 (red arrow and yellow outline); (**B**) CT indicted abnormal enhanced nodule of right rectus abdominis (3.1 cm × 2.3 cm) on July 22, 2020 (red arrow and yellow outline).

found in any other organs. The serum tumor marker tests showed an AFP level of 9.56 ng/mL (<7.0 ng/mL) and normal levels of CEA, CA125, CA19-9, squamous cell carcinoma antigen (SCCA) and human epididymis protein 4 (HE4). On July 23, 2020, the patient underwent resection of the abdominal wall lesion. A hard mass with clear boundaries measuring approximately 5 cm × 5 cm was found in the rectus abdominis during the operation (Figure 4A and B). The postoperative pathological examination showed that the abdominal wall mass was an endometrial adenocarcinoma metastasis (Figure 4C and D). At the same time, tumor metastases were found in the muscles and nerves. There was no LVSI in the tumor tissue. The immunohistochemical results showed CK7 (+), VIM (+), PAX-8 (+), P16 (partial +), ER (SP1) (approximately 2% weak +), ER (positive control) (+), PR (1E2) (-), PR (positive control) (+), P53 (wild type), WT1 (-), Napsin A (-), P504S (-), CEA (-), and an Ki-67 LI of approximately 60%. The patient four cycles of received PLD 30 mg/m^2 and carboplatin AUC 5 followed by external beam radiotherapy. Unfortunately, when the patient was

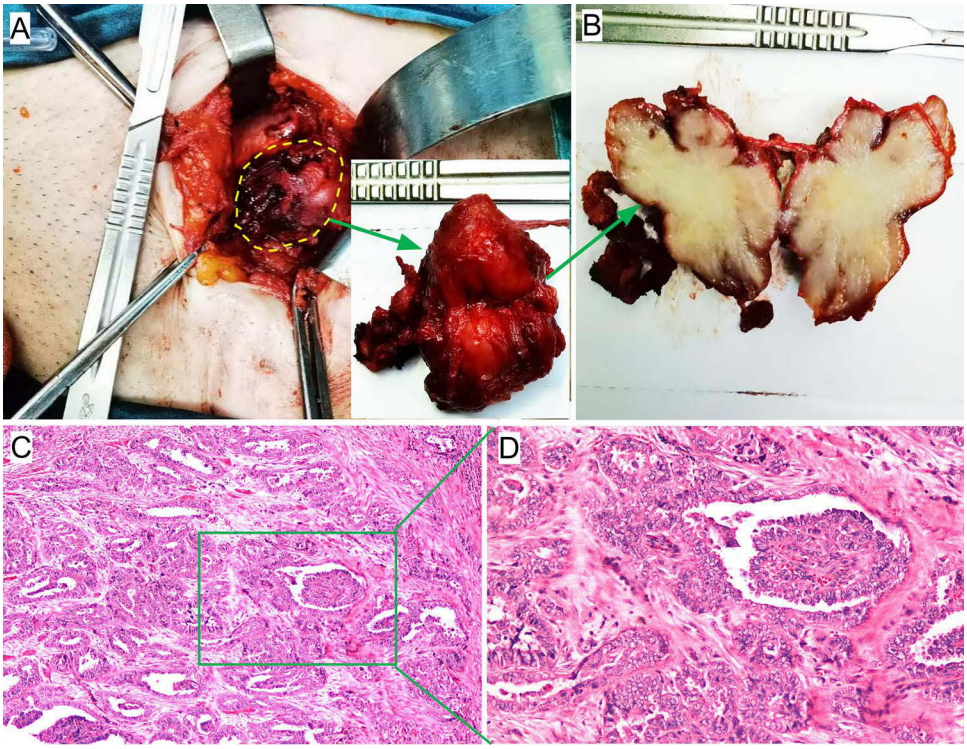

Figure 4 Intraoperative photograph of abdominal wall lesions and HE staining. (**A**) the gross mass in the abdominal wall had a hard texture. (**B**) sectioning the mass confirmed that it was yellow solid tissue. (**C** and **D**) HE staining confirmed that these specimens were tumor tissues (**C**, 20 ×; D, 100×).

followed up in September 2022, although the abdominal incision was normal, CT revealed metastasis in the right lung. She is currently undergoing chemotherapy.

Discussion

The Influence of Laparoscopic/Open Surgery in PSM

Incisional recurrence may occur in both laparoscopy and laparotomy, which is a rare and potentially avoidable complication.[19] The etiology of PSM remains unknown. Some mechanisms related to incisional implantation after open surgery have been proposed in other studies. The most likely reason is due to hematogenous spread to the surgical incision, which could occur in cases of advanced-stage cancer.[20] In addition, neoplastic cells are seeded after direct contact between the tumor and the surgical wound, and tumor cells spread intraperitoneally.[5,20] Chandra et al thought residual viable cells exfoliated from the tumor or by contamination of surgical instruments or equipment.[21] The other proposes that the cancer cells implanted in incisional sites during the primary surgery can remain dormant for several years and become activated later by some factors. The second patient in our report underwent surgery via an open abdominal approach one month before laparoscopic surgery. This may have represented a high-risk factor for incision implantation metastasis. We recommend that the incision be strictly protected and fully flushed before suturing for treating similar cases in the future.

There is no doubt that laparoscopic surgery is being used more frequently in the treatment of benign diseases and malignancies. The mechanism whereby PSM occurs after laparoscopic surgery has never been explained clearly, although improper surgical techniques and contamination have been considered.[4] One animal tumor model suggested that surgical technique skill, but not the establishment of a CO_2 pneumoperitoneum, was an important factor for inducing PSM.[22] Sugarbaker indicated that the ascites fluid may drain from the peritoneal cavity through the port site tunnel and then seed in traumatized tissues after the operation.[23] In addition, peritoneal fluid contaminated by cancer cells may enter the peritoneal aspect of the port site and infiltrate these tissues. Furthermore, "the aerosol effect" has also been taken into account.[16] The location of the laparoscopic port site is also important. Nguyen et al reported one patient with endometrial adenocarcinoma who underwent robotic-assisted laparoscopic hysterectomy, recurrent abdominal wall masses imbedded within the fascia were close to the primary port sites.[24] The metastatic masses at the puncture points were located in both groins and muscles in the ovarian cancer patients we reported. The causes of tumor metastasis in these two locations were related to the above factors. In our retrospective analysis, we found that PSM in most case reports occurred more frequently in the incision lower abdomen rectus abdominus of bilateral inguinal regions and pubic symphysis.[25–28] PSM around the umbilicus or epigastrium is rare.[29,30] Whether the puncture point near the tumor is more likely to cause implant metastasis remains unknown and needs further study.

Clinicians have further found that there was no difference in incisional metastasis rates between laparoscopic and open surgery. A study compared the two surgical methods in 475 Singaporean patients with endometrial carcinoma (229 underwent laparotomy and 145 underwent laparoscopy) and showed no significant differences in the recurrence rate and disease-free intervals.[31] Another meta-analysis of cervical cancer revealed similar outcomes.[32] Laparoscopy is supported for the management of early endometrial cancer with low- to moderate-certainty evidence and has similar overall survival (OS) and disease-free survival (DFS) in presumed early-stage primary endometrioid adenocarcinoma of the endometrium with lower operative morbidity and hospital stay.[33] Compared with open surgeries, laparoscopic surgeries are less invasive and associated with decreased recovery time and prolonged quality of life.[34] However, any benefits over the open technique still need more clinical data and prospective randomized trials.

Treatment of PSM

Local recurrence in surgical incisions can affect all layers of the abdominal wall and involves the entire incision or port site.[35] There is no effective standard treatment regimen for incisional metastasis. Doctors should exclude whether other organs have metastatic lesions. On the premise that the patient's physical condition can tolerate surgery, complete resection of metastasis is recommended.[36] If the defect at the incision of the abdominal wall is too wide after the removal of the metastasis, a mesh is needed to fill in the defect. A systematic review and meta-analysis showed that hernia rates

after stoma reversal can decrease significantly with the use of prophylactic mesh. Chemotherapy is one of the treatment strategies for advanced and recurrent disease.[37] For ovarian cancer, the current National Comprehensive Cancer Network guidelines recommend intravenous paclitaxel/carboplatin and liposomal doxorubicin/carboplatin regimens as adjuvant and neoadjuvant therapy after debulking surgery.[38,39] PD-1 and/or bevacizumab may benefit patients with endometrial cancer. After chemotherapy, we suggested that the ovarian cancer patient (case 1) undergo homologous recombination repair (HRR) or homologous recombination repair deficient (HRD) tests and take PARPi (poly ADP ribose polymerase inhibitors) orally, but the patient did follow this recommendation because of economic reasons. Similarly, we recommended biomarker analysis for the endometrial carcinoma sample to the patient (case 2) and immunotherapy based on the analysis results. However, the patient refused this recommendation. The two patients did not receive follow-up testing and treatment due to various reasons, which may adversely affect the prognosis.

Prognosis of PSM

The timing of tumor metastasis at the port site is irregular and varies (2 weeks to 10 years). Reports have shown incisional recurrence in less than 1 year in cervical cancer[40] and endometrial carcinoma.[41] Early endometrial cancer patients (Stage IA Grade 1) can also develop PSM after laparoscopic surgery.[42] However, most cases have shown that PSM tends to occur in advanced cancer, and patients at risk for recurrence may have a poor prognosis because of their advanced cancer status. However, this theory may not apply to early-stage ovarian cancer.[43] It remains unclear if PSM affects the prognosis of patients with gynecological tumors.

PSM is considered a poor prognostic factor and may be associated with a worse prognosis.[44,45] PSM had no impact on survival in one study, but PSM was associated with more postoperative complications and a higher surgical burden.[11] Grant et al reported disease-free survival rates 1 and 2 years after PSM of 100% and 44%, respectively, with a median follow-up of 2 years from the time of PSM of endometrial cancer.[16] Previous studies showed that the prognosis of patients with advanced ovarian cancer and endometrial adenocarcinoma was not impacted by the development of PSM.[46,47] Some doctors even found that patients who all had stage III or IV ovarian cancer with PSM actually had a longer 3-year survival than those without PSM, although this difference did not reach statistical significance.[48] However, because surgery and postoperative adjuvant therapy are often not involved in the long-term follow-up of patients who undergo resection of the incisional metastases, it is difficult to assess the impact of PSM on prognosis.

Prevention of PSM

We also investigated the specific situation of PSM in different types of gynecological tumors through a review of the literature. A total of 182 articles related to PSM of different gynecological tumors were screened from the databases. Among them, 20 English studies (prospective or retrospective case studies) met the inclusion criteria (Table 1).[49–61] The incidences of PSM in the three most common gynecologic tumors (ovarian cancer, uterine tumors and cervical cancer) were 23%, 3.5% and 2.4%, respectively. The incidence of PSM was approximately 4% in patients with unspecified types of gynecologic tumors. When all the gynecological malignancy patients were combined, the incidence of PSM was 7% (Figure 5). Our results show that the incidence of PSM is highest in ovarian cancer patients. This is consistent with the results reported in the literature.[62] Therefore, in terms of preventing PSM, doctors should strictly grasp the indications for surgery. Except for certain early ovarian cancer patients, laparoscopic surgery should be avoided in most ovarian cancer patients because of the known contraindications to laparoscopic surgery for ovarian cancer.

Direct implantation of cancer cells into port sites during minimally invasive approaches may be the most intuitive mechanism of PSM. Some doctors believe that surgical error is a major risk factor that results in PSM.[19] Some measures have been put forward to reduce the chances of PSM, including using trocars with smaller diameters as much as possible, proper placement of trocars with minimal tissue trauma, rinsing trocars in 5% povidone-iodine before insertion, trocar fixation and prevention of gas leakage, decreasing the removal and reintroduction of trocars, and rinsing the tip of instruments in 5% povidone–iodine when changing instruments.[63,64] In addition, doctors should use retrieval bags to retrieve the tumor, and the outer surface of the bag should be washed repeatedly with normal saline before removal, and all abdominal fluid and gas should be removed before trocar removal. Thus, we recommend that in similar cases in our

Table 1 Characteristics of PSM Patients in the Included Studies

Author	Year	Tumor Types	Stage	Surgical Approaches	Time to PSM, Months	Total Patients	Patients with PSM	Rate (%)
Childers JM et al[49]	1994	Ovarian serous papillary adenocarcinoma	IIa	Laparoscopy	2	88	1	1.14
Kruitwagen RF et al[50]	1996	Ovarian Ccancer	IIIC or IV	Laparoscopy	–	43	7	16.27
Kadar N et al[2]	1997	Gynecological malignancies	–	Laparoscopy	–	25	4	16
Huang KG et al[51]	2003	Ovarian cancer	–	Laparoscopy	2/11/13/0.36/13/0.5	31	6	19.35
Nagarsheth NP et al[52]	2004	Ovarian cancer/ primary peritoneal cancer	IIIB/IIIC	Laparoscopy	0.43/1.53	83	2	2.41
Vergote I et al[10]	2005	Ovarian carcinoma	III or IV	Laparoscopy	–	173	30	17.34
Park JY et al[40]	2008	Cervical adenocarcinoma	IIB	Laparoscopy	1	75	1	1.33
Polterauer S et al[53]	2008	Cervical cancer	IB2-IIIB	Laparoscopy	-	65	3	4.62
Zivanovic O et al[54]	2008	Gynecological Mmalignancies	-	Laparoscopy	-	1499	18	1.20
Jung US et al[55]	2009	Ovary transitional cell carcinoma	-	Laparoscopy	3	24	1	4.17
Martínez A et al[56]	2010	Cervical cancer	IB-IVA	Laparoscopy	12	921	4	0.43
		Endometrial cancer	IC		6	295	1	0.33
Ndofor BT et al[57]	2011	Gynecological Malignancies	-	Robot-assisted opertaion	0.7/11	181	2	1.10
Lönnerfors C et al[9]	2013	Cervical cancer	-	Robot-assisted	6 (range 2–19)	191	5	2.62
		Endometrial cancer	-	opertaion		222	4	1.80
		Ovarian cancer	-			58	0	0
Manchana T et al[58]	2014	Endometrial cancer	III	Robot-assisted opertaion	5/13	30	2	6.67
Rindos N et al[59]	2014	Gynecologic malignancies	IA/IIA	Robot-assisted opertaion	25/14	142	2	1.41
Grant JD et al[16]	2015	Endometrial cancer	IA-IIIA	Laparoscopy	15	214	7	3.27
Barraez D et al[60]	2015	Endometrioid cancer	IA, IB, IIIA	Robot-assisted opertaion	9/6/37/19	446	4	0.90
Nunez MF et al[45]	2015	Peritoneal carcinomatosis	-	Laparoscopy	-	65	22	33.85
Ataseven B et al[11]	2016	Epithelial ovarian cancer	-	Laparoscopy	-	214	100	46.73
Lakhi N et al[61]	2018	Uterine papillary serous cancer	IIIC	Laparoscopy	0.23	22	1	4.54

Abbreviation: PSM, port site metastasis.

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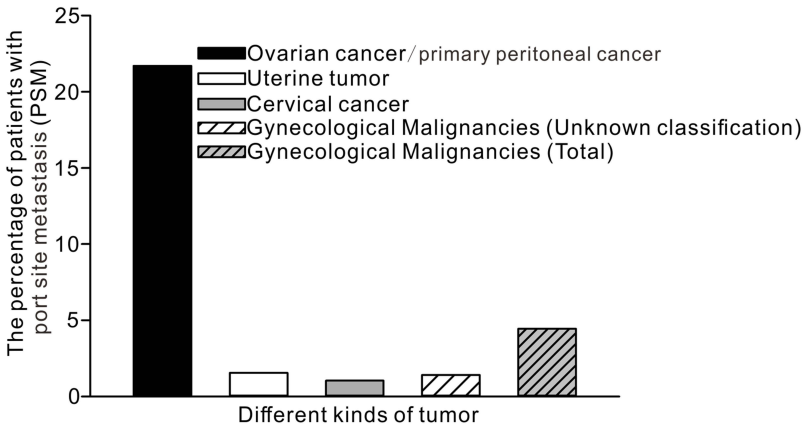

Figure 5 The percentage of patients with gynecological malignancies and PSM.

report, the doctors should clearly understand the surgical indications, pay attention to the details mentioned above during the operation, and conduct postoperative treatment according to different tumor types after the operation.

Conclusion

PSM after laparoscopic surgeries is rare but has been reported, although the causes are unknown. Without unified treatment standards, resection of metastatic tissue has been previously considered. To decrease the rate of PSM, we should be careful in the primary excision of tumors, avoiding tumor cell implantation during surgery. Laparoscopic surgery is no longer recommended for intermediate and advanced ovarian and cervical cancer. Instead, open surgery should be performed. Whether laparoscopic surgery for endometrial carcinoma has a negative impact on the prognosis of patients remains to be determined. However, we cannot avoid the occurrence of metastasis of the puncture hole with a low recurrence rate and deny the operation method of laparoscopy. Doctors must strictly grasp these surgical indications and take the best possible measures to avoid tumor implantation at the port sites during the operation.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the corresponding author without undue reservation.

Ethics Statement

The Ethics Committee of the Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology approved the study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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