Cancer Management and Research

Elevate Series

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REVIEW

Pathogenesis and Possible Consequences of Port-Site Metastasis in Gynecologic Oncology After Laparoscopic Procedures

Dominika Żyła[1], Maciej Dubaj[2], Katarzyna Słomczyńska[2], Krzysztof Kułak[3], Rafał Tarkowski[3], Marzena Furtak-Niczyporuk[4]

[1]1st Chair and Department of Oncological Gynecology and Gynecology, Students' Scientific Association, Medical University of Lublin, Lublin, Poland; [2]Chair and Department of Public Health, Students' Scientific Association, Medical University of Lublin, Lublin, Poland; [3]1st Chair and Department of Oncological Gynecology and Gynecology, Medical University of Lublin, Lublin, Poland; [4]Chair and Department of Public Health, Medical University of Lublin, Lublin, Poland

Correspondence: Dominika Żyła, Email dominika.zyla2211@gmail.com

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Abstract: Port-site metastasis (PSM) is an infrequent and serious complication of laparoscopic treatment. The incidence of PSM is 0.16–2.3% of patients undergoing laparoscopic surgery for gynecologic malignancies. Depending on the place of origin of the malignant tumor, PSM appears on average the earliest after ovarian cancer treatment and the latest after vaginal cancer surgery. To date, several important risk factors have been identified. Hypotheses such as wound contamination, hematogenous and lymphatic spread, immune response and CO2 pneumoperitoneum have been formulated as possible agents influencing the occurrence of PSM. Overall survival (OS) is a particularly important issue from the standpoint of the person performing the procedure and the patient. OS may be influenced by the histological type of cancer, its origin in the body, the method of treatment, as well as the type of PSM and the time of its occurrence after the end of therapy. Patients with PSM require local or systemic treatment, as well as consideration of complementary therapy. There are theories indicating that appropriate preoperative management in patients with gynecological malignancies can prevent the occurrence of PSM. Despite enormous laparoscopy development over the last 20 years, a complication such as PSM still leaves many unknowns and therefore causes difficulties in therapeutic procedures. Each patient should be closely monitored before and after the laparoscopic procedure to exclude potential factors for the occurrence of PSM and its possible post-procedure diagnosis. Moreover, it is the responsibility of the person performing laparoscopy to accomplish the procedure as precisely as possible to minimize the risk of this complication. The main aim of the following review is to present the phenomenon of PSM in gynecologic oncology, its epidemiology, pathogenesis and possible consequences for the prognosis of the patient.

Keywords: port-site metastasis, gynecological oncology, laparoscopy complication, metastasis prevention

Introduction

Oncological diseases are a growing problem of public health, becoming one of the leading causes of death. Gynecological cancers (ovarian, cervical and endometrial, vaginal, vulvar), if including breast cancer, are the most common type of cancer in women worldwide. They are characterized by a steady increase in incidence, currently at 3.6 million new cases and 1.3 million deaths per year worldwide in 2022 (not including breast cancer, 1.3 million and 680,000, respectively).[1–3] It is worth noting that gynecologic cancers account for up to 30–40% of all cancers in women and are responsible for 30% of cancer-related deaths in women worldwide.[4,5] In addition to an increased risk of death, they are associated with a significant reduction in quality of life. Therefore, it is essential to improve current therapeutic methods and develop new ones aimed at limiting tumor progression and metastasis.[1] Treatment methods for gynecologic cancers include surgery (classic open surgery as well as laparoscopic and robotic surgery), pharmacotherapy (chemotherapy, immunotherapy, hormone therapy, biological treatment), and radiation therapy (including local brachytherapy).[6] In many cases, the most appropriate method of management is laparoscopic surgery, which is a minimally invasive way of treatment for the patient, enabling faster recovery.[7] This surgical method does not apply to breast cancers, so these cancers will not be discussed in the following review. One of the rare but serious complications of laparoscopic surgery is

Received: 3 January 2025
Accepted: 10 July 2025
Published: 24 December 2025

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the formation of port-site-metastasis (PSM), which means the implantation of tumor cells at the site of trocar insertion after laparoscopic surgery for malignant tumors.[7,8] There are two types of PSM: isolated (iPSM), in which metastasis occurs only at the site of the scar after the surgery, and non-isolated - metastasis at the trocar site is part of a disseminated systemic process.[8] Metastases of this type mainly arise by direct implantation during surgery with an instrument, by transmission through gases used in surgical emphysema, or by dissemination through blood vessels.[7–14] Among both gynecologic and gastrointestinal cases, there is a better prognosis for patients with iPSM than with non-iPSM, both in terms of time to progression and overall survival.[7,15] There are also differences in treatment, with iPSM treated mostly with surgery and chemotherapy, and non-iPSM mostly with palliative chemotherapy.[7,15] The PSM affects 1–2% of cases after surgical treatment of cancers of the urinary (renal, prostate cancer), gastrointestinal (cancers of the gallbladder, stomach, pancreas, intestines) and reproductive systems.[7,9–14]

Abovementioned rate varies depending on the type of cancer - for gynecological cancers it is 0.16–2.3%, 0.71% for upper gastrointestinal cancers, 0.8–1.6% in oncology urology, and for gallbladder cancer even 10.3–14%.[7,15–17] The main methods of preventing PSM include: selection of appropriate surgical methods (smaller trocar, tight trocar fixation, reduced tissue trauma, exsufflate pneumoperitoneum through trocar rather than skin wound), flushing with iodopovidone, adjuvant chemotherapy.[7,15,18]

Gynecologic cancers account for a significant proportion of all cancers in women worldwide, and laparoscopic and robotic surgery have become the standard of care due to faster postoperative recovery and better avoidance of critical anatomical structures. Additionally, that ovarian cancer, especially serous cancer, has a predilection for spread through the peritoneal cavity and not through the blood or lymphatic system.[19] In uterine cancers, radical procedures are often performed, and during hysterectomy, cancer cells have a smaller chance of escaping into the abdominal cavity than in ovarian cancer, where the entire procedure is performed laparoscopically.

Additionally, some gynecological cancers show high expression of adhesion molecules (eg, integrin), which helps them "stick" to damaged tissues, such as the port site.[20] This is associated with a higher incidence of complications such PSM in gynecologic malignancies compared to other types of cancer.

The main aim of the following review is to present the phenomenon of PSM in gynecologic oncology, its epidemiology, pathogenesis and possible consequences for the prognosis of the patient.

Material and Methods

A literature review was conducted by PubMed, Scopus, Web of Science and Google Scholar. The following search terms and their combinations in English were used when reviewing the aforementioned databases: "PORT-SITE METASTASIS", "TROCAR SITE METASTASIS", "GYNAECOLOGY", "LAPAROSCOPY", "GYNECOLOGIC ONCOLOGY" and the operator "AND". The analyzed publications about Port-Site Metastasis were dated from 2003 to 2024. Two of the studies with the publication date of 1978 were accepted as the first reports of port-site metastasis. The mentioned papers met all the inclusion criteria, except for the time frame, and due to their high merit and relevance to the topic at hand, they were included in the review. The review process began on February 14, 2024, and continued for 2 weeks, until March 2024. At that time, the review was conducted by two independent reviewers, and the results of the reviews were compared. During the mentioned period, all relevant papers were analyzed.

Inclusion criteria of papers were: period 2003–2024, nature of the work (original work, review, case report, editorial), subject matter of the work (PSM in gynecologic cancers), English language. The exclusion criteria were: nature of the paper (abstract, poster), inappropriate time frame (except for the two papers mentioned earlier), language of the paper other than English. Initially, 82 works were obtained. Then, after applying the interval, 57 works remained. An analysis was then made first of the titles and abstracts, papers not relevant to the topic of port site metastasis in gynecologic oncology were rejected, and then the entirety of the remaining articles was analyzed. In the end, 36 papers were included in the analysis. Chosen papers were investigated regarding to epidemiology, pathogenesis, oncological outcomes and prevention of port-site metastasis. A non-systematic approach was used to analyze the included publications. It was decided to choose a non-systematic method because of the wide range of topics covered and the desire for a comprehensive presentation of the issues discussed, rather than a thorough review of all available literature.

Epidemiology

The first reported data on PSM in gynecologic oncology dates back to 1978. Döbrönte et al described a case of the growth of metastases in a trocar scar in the second week after treatment of ovarian cancer. The authors suggested the cause as ascites and the presence of tumor cells in the peritoneal fluid.[21] Since then, case reports of a similar phenomenon have been published, but there are few studies defining the epidemiology of PSM. Gao et al and Benabou et al report that PSM occurs in 0.16–2.3% of patients undergoing laparoscopic surgery for gynecologic malignancies.[7,8] The incidence of iPSM is 0.2–0.5% of surgeries.[8] The incidence rate of PSMs in robotic surgery is similar to laparoscopic surgery, with a rate of 0.9–1.9%[8] Rindos et al in a study in a group of 142 patients undergoing laparoscopic robotic surgery observed that PSM occurred in only 2 of them (1.41%). Both patients were diagnosed with endometrioid adenocarcinoma.[22] Yu et al indicated that PSM incidence in robotic surgeries does not exceed 2%.[23] PSM was most common in patients after diagnostic laparoscopy with high-grade ovarian cancer (17–47%).[23] Ataseven et al in a study in a group of 214 women with epithelial ovarian cancer observed that this phenomenon affected as many as 46.7% of them.[24] However, clinically diagnosed ovarian cancer cases have a PSM rate of only 5% due to the earlier surgery.[8] Interestingly, in this type of cancer, PSM is most common in incisions of the lower abdomen, rectus abdominis muscle, both inguinal regions and pubic conjunctiva, and is rare in the umbilical region or epigastrium.[23] This is primarily related to surgical techniques and the disruption of the continuity of these anatomical structures during the procedure.[23,24] Such a high rate in ovarian cancers is primarily related to their high degree of malignancy, anatomical conditions (intraperitoneal location, vascularization, presence of ascites) and the frequency of laparoscopic versus open surgery.[7,8,23,24] In other types of gynecologic cancers, PSM is much less common. The percentage of this type of metastasis in patients with cervical cancer is 0.43%, and with endometrial cancer is 0.1–0.33%.[8,23,25] Reports on PSM after surgery for fallopian tube cancer (distinguished by some authors, actually being an ovarian cancer), vaginal cancer and teratomas are casuistic.[26,27]

Ramirez et al in the largest study to date (n=58) on this issue in patients with gynecologic cancers, indicated that PSM for ovarian cancer occurs on average 17 days after surgery (min-max: 4–730 days), cervical cancer - 5 months (min-max: 1.5–19 months), endometrial cancer - 13.5 months (min-max: 6–21 months), fallopian tube cancer - 7 months (n=1) and vaginal cancer - 20 months (n=1).[28] The above epidemiological data are shown in Figure 1.

Ataseven et al found that risk factors for PSM in ovarian cancers include high tumor grade - pT3 (OR=13.5; 95% CI=2.93–62.0; p=0.041), lymph node involvement - pN1 (OR=2.97; 95% CI=1.31–6.72; p=0.009) and the presence of ascites ≥500mL (OR=3.90; 95% CI=1.52–11.0; p=0.005).[24] Chen et al following Ramirez et al additionally mention

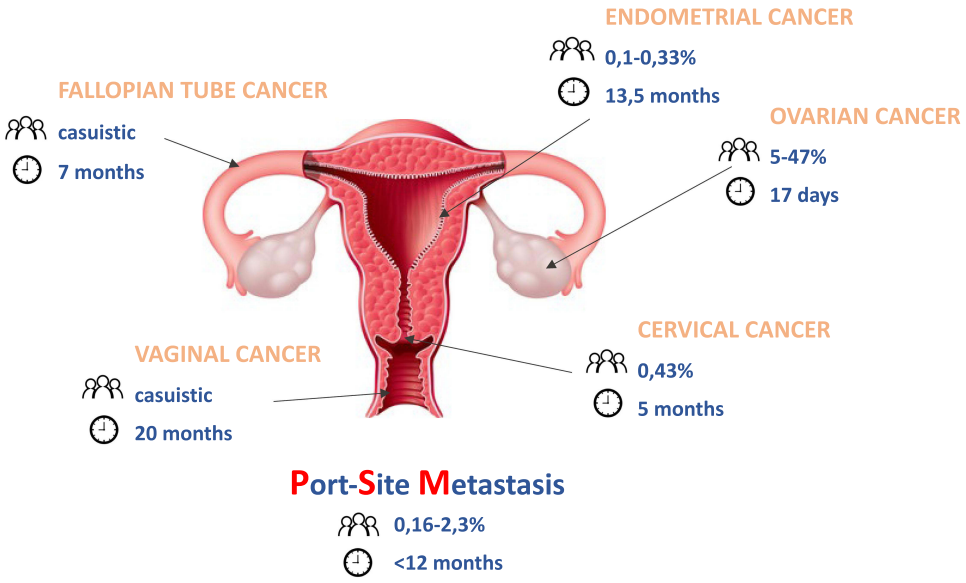

Figure 1 Epidemiology of PSM in particular types of gynecologic cancers. Included are the percentage of incidence in patients and the median time to development of metastases after surgery.[8,23–28]

https://doi.org/10.2147/CMAR.S515514

carbon dioxide (CO2)-generated pneumoperitoneum, lack of adequate surgeon skills (expressed by a flat learning curve and a small number of operations performed), and inflammatory and immunologic factors.[26,28] Risk factors for PSM are summarized in Box 1.

The risk of PSM in ovarian cancer increases in the presence of several factors related to tumor aggressiveness, the patient's immune status, and surgical technique. High-grade tumors (pT3) and lymph node involvement (pN1) are markers of advanced disease and indicate a high potential for peritoneal dissemination of cancer cells.[29]

The presence of ascites exceeding 500 mL facilitates the mechanical spread of tumor cells within the abdominal cavity during surgical manipulation.[30]

Immunosuppression reduces the body's ability to eliminate tumor cells that may implant at surgical wound sites. A lack of surgical experience may lead to improper handling of the tumor or malignant fluid, increasing the risk of cellular dissemination. Additionally, the use of carbon dioxide (CO_2) for pneumoperitoneum may promote local tissue damage, spread of cancer cells, and the creation of conditions favorable to tumor implantation at port sites.[31]

Pathogenesis

The pathogenesis of PSM remains unclear to this day. Its understanding would enable the introduction of effective mechanisms to prevent or at least reduce the risk of developing this type of metastasis. The most likely pathogenetic mechanisms for the development of PSM are discussed below.

Wound Contamination

One of the first described potential mechanisms of PSM is the theory by DerHagopian et al (1978), the so-called oncotaxis.[32] The authors suggested that micrometastases persist at "rest" in the wound. Under the influence of proper factors, such as injuries, mechanical stress or immunosuppression (diabetes mellitus, chemotherapy, release of corticosteroids), the metastases are "activated," proliferate and increase angiogenesis and evade the immune response by secreting cytokines and growth factors.[32,33] Key in this process is the activation of nuclear factor-kappa B (NFkB).[34] Micrometastases can reach the surgical wound directly through contact with the tumor or contaminated instruments (tumor cells are found on trocars and in instrument washings) or through intraperitoneal spread.[7,33,35] This is confirmed by studies on animals, where the accumulation of tumor cells in extraction wounds has been proven in 70% of cases. Moreover, it has been observed that 55% of PSM cases are specifically related to extraction ports, while the second most common site of occurrence is working ports. During surgery, the tissue to which tumor cells most often attach is the damaged peritoneal surface. This is facilitated by the small wound area and frequent manipulation and movement of equipment during the procedure.[35] Furthermore, it was observed that a flat learning curve and the lack of experience possessed by the operator influenced the increased incidence of PSM. The lack of skills is considered by most researchers as a low number of surgeries performed or a lack of experience in laparoscopic surgery. The use of appropriate precautions and atraumatic intraoperative manipulation indicated a lower chance of developing metastases in in vivo studies compared to excessive manipulation, with an incidence of 13.8% vs 63.8%, respectively.[25] In addition, in a study in a rat model, it was observed that manipulation of tumor tissue was a major factor in the dissemination of cancer,

Box 1 Risk Factors for PSM

High-grade ovarian cancer (pt3)
Lymph node involvement (pn1)
Ascites >500mL
Lack of surgeon skills
Immunosuppression (diabetes, stress resulting from mechanical trauma, steroids)
Use of CO_2 to generate pneumoperitoneum

Notes: Footnotes[24–28].

regardless of the type of procedure - laparoscopy or laparotomy.[35] Interestingly, in some studies no significant differences in recurrence rate and length of disease-free survival (DFS) have been demonstrated between laparoscopic and open surgery techniques for endometrial and cervical cancers.[36,37] However, many researchers have observed an effect on patient prognosis, as described later in this paper.

Dissemination Through Blood and Lymphatic Vessels

The onset of PSM by this way seems to be extremely rare. It is particularly taken into consideration in the high-grade cancers, when PSM accompanies the systemic dissemination of the disease and distant metastases. However, it should be remembered that only 0.1% of cancer cells are able to survive in the circulatory system and give metastases.[7,8] The main factor for this is anoikis, which is cell death when the cell loses its connection to the extracellular matrix (ECM). The signaling pathways responsible for anoikis are among others integrin signaling, PI3K-Akt, DAPK1 and Fas.[38] However, some cells are able to develop resistance to this cell death, including through the activity of norepinephrine, signaling pathways (TGF-β and SOX2), proteins (CASC4, NOTCH 3, CBX2, CPT1A) or an increase in receptor activity of tyrosine kinase.[39–42] The phenomenon of resistance primarily affects gynecological cancers, including high-grade epithelial ovarian, endometrial or cervical cancer.[43]

Immune Response

There are numerous reports available that speak to the influence of the role of the immune system on the formation of PSM. The impaired function of this system as a result of surgery is associated with mechanical trauma of tissues. It leads to over-activation of inflammatory cells, and thus faster depletion of their resources. This may contribute to increased tolerance to the development of metastasis and recurrence. The immune system definitely returns to its primary function faster after laparoscopic surgery than open surgery.[35] However, the use of pneumoperitoneum with CO_2 causes suppression of the intraperitoneal cellular response. One of the reasons for this is the decreased release of tumor necrosis factor α (TNF-α) by peritoneal macrophages, which impairs the cellular immune response and facilitates the formation of metastases.[35] In addition to the suppression of TNF-alpha secretion by peritoneal macrophages might be seen as a negative factor leading to the progression of transitional-cell carcinoma PSM, particularly if surgical oncological practices are compromised.[35] Moreover, local hypoxia across the post-surgical wound and acidosis as a consequence of mechanical tissue damage induce the expression of hypoxia-inducible factor 1 (HIF-1) and interleukin-8 (IL-8). They enhance angiogenesis by stimulating vascular endothelial growth factor (VEGF), which also promotes the formation of PSM.[7,8] Sylla showed the effect of surgical trauma on immune surveillance in tumor resistance. Surgical injury triggered the activation of inflammatory cells. This inflammatory reaction may drain immune resources and worsen tumor-associated changes to the immune system. Invasive treatment of tumor tissue during surgery may lead to the subsequent discharge of freed tumor cells. At the same time, a change in the ratio of growth factors to inhibitory factors due to surgical trauma promotes the growth and establishment of freed tumor cells.[8]

However, the researchers unanimously emphasize that the status of the immune response during laparoscopic procedures and its influence on the future development of the PSMs needs to be further investigated.[35]

Pneumoperitoneum

One of the most interesting theories in the development of PSM in gynecologic oncology is the effect of peritoneal emphysema using CO_2. In addition to the previously described effect of this gas on disrupting the immune microenvironment inside the peritoneal cavity, emphysema causes near-instant exfoliation and destruction of the outer layers of the peritoneum and muscles of the abdominal wall. This increases the chances of implantation of tumor cells present in the ascitic fluid at the port sites and their subsequent entrapment by the superstructured tissues during their healing.[35] Furthermore, high pressure in the peritoneal cavity during surgery results in increased migration of cells, including tumor cells. The pressure may also lead to increased blood flow in the vessels of the front of the abdominal wall, also contributing to the implantation and formation of PSM.[35] Another theory involving the contribution of pneumoperitoneum during ovarian cancer surgery was made by Sugarbaker. The author suggested that a small amount of peritoneal fluid with tumor cells in it is pushed outward under the influence of high pressure during CO_2 infusion. Then, they are

settled on the surfaces of the instruments under the influence of their movements during the operation, and adhere to the wound after their removal.[44] A similar theory is the "chimney effect," which posits that cancer cells enter the port with the constant microleakage of gas along the trocars.[7,8,35] Another postulated mechanism of PSM is the stimulation of tumor growth by the high pressure in the peritoneal cavity during surgery. In vivo studies have shown increased growth of tumor tissue with rising gas pressures of 5, 10 and 15 mmHg.[35] This was confirmed by Zheng et al who reported an increased proliferation of gastrointestinal stromal tumor (GIST) cells when exposed to CO_2 at 8 mmHg for 1 hour, and cell migration increased with longer (3 hours) exposure to this gas or at higher (15 mmHg) pressure.[45] The above observations were not confirmed in a meta-analysis conducted by Mo et al. The authors showed that the use of CO_2-induced pneumoperitoneum did not increase the risk of PSM compared to laparoscopy without gas (OR=2.23; 95% CI=0.90–5.55; p=0.08) or laparotomy (OR=0.97; 95% CI, 0.031–3.00; p=0.08).[46] Similarly, Asthana et al conducting a study on canine transitional cell carcinoma cell lines found no effect on proliferation up to 7 days after surgery with reduced cell survival at a pressure of 10 mmHg.[47]

During gynecological laparoscopy, various attempts have been made to reduce the risk of PSM. Studies have investigated the use of alternative gases for insufflation (such as helium or N_2O) that may reduce tumor cell deposition, but their use is not yet standard. Scientists Neuhaus SJ et al emphasize that the presence of tumor at port sites was considerably lower following helium insufflation compared to air, CO_2, or N_2O ($p < 0.0001$).[48]

N_2O has been considered for its anesthetic properties but is less commonly used due to concerns about its flammability and potential to promote combustion. However, despite promising results in animal studies, the use of helium and other gases in clinical practice is not common.[49]

Despite these findings, there is no consensus on the optimal gas and further research is needed to establish definitive guidelines.

The aforementioned postulated theories of PSM formation are shown in Figure 2. None of them has been fully confirmed and accepted by researchers. Therefore, further research is needed to fully understand the pathogenesis of this phenomenon.

Impact on Oncological Prognosis

The phenomenon of PSM and its influence on an impact of the prognosis is not completely clarified. To date, it has been noticed that the prognosis depends on the histological type of cancer and its place of origin in the human body. Attention was also paid to differences in prognosis due to the occurrence of PSM as an isolated form (iPSM) and disseminated

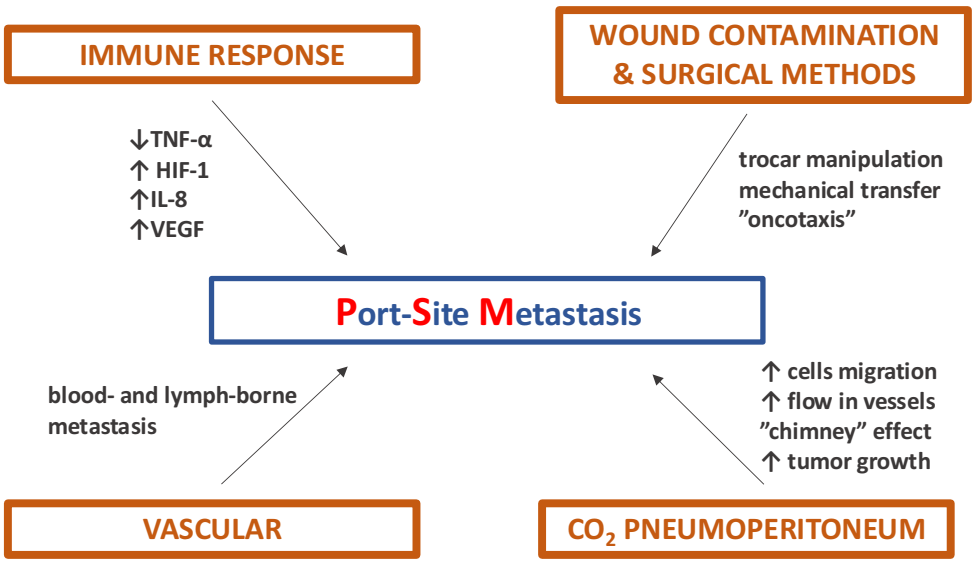

Figure 2 Postulated pathways of PSM formation.[7,8,32–47]
Abbreviations: TNF-α, tumor necrosis factor α; HIF-1, hypoxia-inducible factor 1; IL-8, interleukin 8; VEGF, vascular endothelial growth factor; CO_2, carbon dioxide.

form (non-iPSM).[50] Moreover, an important issue affecting the overall survival (OS) of patients is the form of therapy used to treat cancer and its metastases, as well as the time interval between subsequent stages of the therapeutic process. The prolonged time between surgery and the use of chemotherapy or cytoreduction results in a more frequent occurrence of PSM.[7,42,43] The limited number of studies and, consequently, the availability of data do not allow for an accurate estimation of the prognosis and prognostic factors.

As one of the first, Van Dam et al performed a retrospective study comparing serous and non-serous ovarian cancer occurring in 104 women who underwent laparoscopic removal of the adnexa with subsequent cytoreduction. Unfortunately, the lack of impact of PSM on the prognosis was observed. It was associated with the development of PSM in only 9 of all patients. Nonetheless, the researchers noticed a prolonged time (median, 6 days vs 17 days; $P<0.01$) from the start of chemotherapy and cytoreduction in patients with PSM compared to those in whom this phenomenon did not occur.[51] Compared to Van Dam et al, Huang et al found no temporal relation between PSM and therapy. They described 31 patients with ovarian cancer who underwent laparoscopic removal of the adnexa with subsequent chemotherapy or observation only. Out of 31 women, 8 of them developed PSM.[50] However, in the mentioned studies, the results regarding the prognosis of patients were similar. According to the authors, iPSM has a considerably more promising prognosis compared to non-iPSM. Additionally, a worse prognosis is associated with the use of chemotherapy in patients diagnosed with PSM. Due to the studies, patients with advanced stages of cancer who were treated with chemotherapy had shorter survival times.[50,51]

Some references assess the correlation between PSM and OS in patients with gynecological cancers. According to the univariate analysis by Ataseven et al, the occurrence of PSM in women with epithelial ovarian cancer after laparoscopy and cytoreduction is associated with shortened OS. On the other hand, in the multivariate analysis of the mentioned authors, the phenomenon of PSM was not among the factors of worse OS.[24] Similar results were obtained by Heitz et al, who, in their cohort study observed no significant effect of PSM on OS in patients with ovarian cancer after laparoscopy.[52] However, in several of the analyses performed, a correlation of negative OS with the occurrence of PSM was observed. Bogani et al, in their retrospective study of 2,636 patients with endometrial cancer treated with various methods (open surgery, laparoscopy, robotic surgery), diagnosed only 3 of them with the appearance of PSM. All cases occurred after open surgery. The time from the primary surgery to the occurrence of PSM was 11, 13 and 24 months, respectively. Importantly, they indicated that the presence of non-iPSM after surgical treatment is associated with significantly worse OS compared to iPSM.[53] The association of PSM with unfavorable OS was also demonstrated by Nunez et al, who considered this phenomenon as an independent factor. The study compared the OS of patients with PSM, which was 73, 35 and 23% appropriately with OS of 95, 82 and 82% in patients without PSM. Moreover, it was suggested this condition was associated with a more aggressive disease.[54] Prior, Zivanovic et al, in their cohort study identified the interval between laparoscopy and detection of PSM as the only factor for OS. According to the authors, the occurrence of PMS up to 7 months after laparoscopy is associated with shorter OS (median, 12 months) compared to PMS appearing 7 months after the procedure (median, 37 months).[55] Vergote et al assessed the impact of PSM on both OS and progression-free survival. However, despite the occurrence of PSM in 30 of 173 patients with ovarian cancer, there was no statistical correlation with the time after laparoscopy. Surprisingly, women with PSM had an extended 3-year survival compared to those without port-site metastases, despite the lack of statistical significance of the study.[56]

Some of the studies performed to date describe patients with primary endometrial or cervical cancer in whom the PSM process had a later onset. The authors of the works mentioned in the previous paragraph report on the relation between the occurrence of PSM and its treatment and relative survival.[57–59] Palomba et al focused on 12 patients with endometrial cancer. They underwent laparoscopic staging followed by adjuvant therapy. Within 25 months after the procedure, 4 patients developed iPSM and the remaining 8 patients developed non-iPSM. Some of the women underwent resection followed by chemoradiotherapy, while the rest of them received only chemotherapy without excision of the lesion. An increased survival of at least 5 months was observed in women who underwent resection combined with chemotherapy for the treatment of iPSM. However, all patients with non-iPSM died due to the histological type and high stage.[57] Conterminously, Grant et al described 7 cases of endometrial cancer with subsequent development of PSM. 6 of 7 patients underwent surgical resection combined with postoperative chemotherapy. According to the study, disease-free survival rates were 100%, 1 year and 44%, 2 years after the therapeutic intervention for PSM.[59] Referring to the review

of patients with cervical cancer performed by Zhong et al, the research collected therein reports 13 cases of post-laparoscopic or robotic PSM. The phenomenon occurred 1–18 months after the procedure and a death rate of 33.3%. In all patients, surgical resection of PSM and chemotherapy were performed. However, only one of them showed no symptoms of the disease after treatment.[58]

The studies mentioned above are summarized in Table 1. It includes the histological type of cancer, its origin and the impact on OS associated with PSM.

The occurrence of PSM requires treatment in gynecological patients. One study examined iPSM treatments in 13 of 18 women undergoing various therapies. Local treatment as a first method (surgery and/or radiotherapy) combined with systemic treatment as a second method (chemotherapy and/or hormone therapy), was compared with local or systemic treatment alone. Patients undergoing the first method showed a lower recurrence rate (2/8, 25%) than those treated with the second method (4/5, 80%), although statistical significance was not achieved (odds ratio, 12.0; 95% Cl= 0.79–181; p=0.10). Moreover, there were no deaths due to the disease using combined therapy compared to single-modality treatment with death 2 of 5 treated patients.[50] Additionally, reviewing the literature related to PSM allows us to find numerous clinical cases of patients undergoing post-PSM treatment.[25,26,60–66] Various therapeutic techniques have been described, ranging from a wait-and-see approach[65] through the use of radiotherapy and chemotherapy (CCRT)[25] to surgical excision alone[26,64] or surgery combined with chemotherapy or postoperative chemotherapy and radiotherapy.[60–63,66] According to the studies mentioned above, the patients had no evidence of PSM recurrence and therefore remained disease-free. Rindos et al, upon identifying PSM in 2 of 142 patients with endometrial cancer, initiated appropriate treatment in each of them. The first one received chemotherapy and radiotherapy, while the second one underwent surgical excision of the lesion and subsequent radiotherapy. No recurrence was observed in any of these cases.[22]

Prevention

Although the mechanism of PSM is still not fully understood to date, many surgeons are trying to find proper ways to prevent PSM in order to reduce recurrence.

A very important element in the prevention of PMS is the proper selection of the candidate patient. In a major report on PSM in patients with gynecologic cancer, Ramirez et al showed that of 58 patients with ovarian, cervical, uterine or vaginal cancer, 83% of patients had advanced (stage III or IV) disease.[28] Other risk factors associated with PMS were ascites (occurred in 71% of patients) and residual disease after primary excision of the mass (97% of patients).[28] Ataseven et al have reached similar conclusions by analyzing patients with epithelial ovarian cancer undergoing diagnostic laparoscopy. They found that risk factors for PSM were higher tumor stage, involvement of lymph nodes and ascites[24] Their observations suggest that gynecologists should perform a very careful analysis of the risk factors for PSM in patients with tumors of high grade.[11,23,28] Optionally, they may consider laparotomy in patients with suspected high-grade and stage gynecologic cancer.[8]

An important element of prevention is the appropriate choice of surgical method - laparoscopic or classical. According to a study in a group of 83 women with primary advanced ovarian cancer and 21 women with recurrent ovarian cancer, metastasis at the trocar site occurred in 58% of patients undergoing laparoscopy in which only the skin was sutured at the end of the procedure, and in 2% of patients undergoing laparoscopy with closure of all layers.[51] Moreover, none of the patients who underwent laparoscopy with complete closure of the peritoneum, rectal sheath and skin, followed by cytoreductive surgery or chemotherapy within 1 week after laparoscopy, had metastases in the abdominal wall.[51] This confirms the safety of this method in patients with disseminated ovarian cancer.

Another crucial element in preventing PMS is the proper use of laparoscopic instruments.[27] Several methods have been proposed to reduce the probability of occurrence of PMS, including the use of trocars with smaller diameters, proper placement of trocars with minimal tissue trauma, rinsing trocars in 5% povidone-iodine before insertion and when replacing instruments, and using a wound protector at the site of trocar insertion.[7,8,23,62,65] An effective preventive measure is the use of a protective bag to remove the lesions to avoid the spread of tumor tissue inside the abdominal cavity.[27,65] The effectiveness of the above preventive methods has been confirmed in a study using an animal model by Schneider et al and therefore surgeons are advised to follow them scrupulously.[7]

Table 1 Prognostic Factors of PSM and OS Outcomes

Study	Primary Cancer	Histological Type	FIGO Stage	Treatment	PSM Diagnosis	OS Outcomes
van Dam et al (1999)[51]	Ovarian (n=104)	Serous vs Non-serous	IIIC-IV	LSC resection followed by NACT, LPT, ACT-LPT, ACT-chemo alone	9 of 104 patients	No statistical impact of PSM on prognosis.
Huang et al (2003)[50]	Ovarian (n=31)	Epithelial or Borderline	IC-IIIC	LSC resection ± SO ± LND followed by surveillance chemo	8 of 31 patients	5 of 8 patients died. Worse prognosis in PSM patients with chemotherapy treatment.
Ataseven et al (2016)[24]	Ovarian (n=250)	Epithelial	IIIC-IV	LSC followed by PDS	100 of 250 patients	No statistical impact of PSM on prognosis.
Heitz et al (2010)[52]	Ovarian (n=66)	Epithelial	IIB-IV	LSC, LPT	31 of 66 patients	No significant impact of LSC in PSM on OS.
Bogani et al (2015)[53]	Endometrial (n=2636)	No data available	IVE	LSC followed by TLH/LPT/ robotically-assisted surgery	3 of 2636 patients	The presence of non-iPSM after surgery is related to worse OS than iPSM.
Nunez et al (2015)[54]	Ovarian or Fallopian tube (n=4)	No data available	No data available	LSC followed by CRS/ HIPEC	3 of 4 patients	PSM is a negative OS prognostic factor.
Zivanovic et al (2008)[55]	Ovarian, Fallopian tube, Cervical, Uterine (n=1474)	Ovarian-serous or endometrioid; Fallopian tube-serous; Cervical-squamous; Uterine-serous	Ovarian-IIIC; Fallopian tube-IIIC; Cervical-IB; Uterine-IIIC	LSC/SO/second-look LSC/ TLH/LAVH±LND±SO	18 of 1474 patients	OS in patients who developed PSM <7 months from the LSC is worse than in patients with PSM >7 months after LSC.
Vergote et al (2005)[56]	Ovarian (n=173)	Serous, Mucinous, Endometrioid, Clear cell, Undifferentiated, Mixed	IIIA-IV	LSC followed by NACT/ PDS+ID	30 of 173 patients	No statistical impact of PSM on prognosis.
Palomba et al (2012)[57]	Endometrial (n=12)	Endometrioid or Serous	IA-IV	TLH/AVH, BSO ± LND followed by surveillance BT ± pelvic RT chemo/HT	12 of 12 patients	Treatment of PSM with resection followed by ACT increases OS >5 months. All patients with non-iPSM died.
Grant et al (2015)[59]	Endometrial (n=7)	Endometrioid or Serous	IA-IIIA	TLH/BSO ± LND followed by surveillance BT ± pelvic RT chemo	7 of 7 patients	Disease-free survival at 1 and 2 years after PSM therapy was 100% and 44%.
Zhong et al (2018)[58]	Cervical (n=13)	Squamous, Mucinous, Adenocarcinoma	IB1-IVB	LSC ± RH ± LND ± BSO followed by surveillance RT chemo	13 of 13 patients	No evidence of PSM in only one patient after treatment.

Notes: Footnotes[24,50–59].

Abbreviations: LSC-laparoscopic; NACT-neoadjuvant chemotherapy; LPT-laparotomy; ACT-adjuvant chemotherapy; TLH-total laparoscopic hysterectomy; SO-salpingo-oophorectomy; BSO-bilateral salpingo-oophorectomy; LND-lymph node dissection; BT-brachytherapy; RT-radiation therapy; HT-hormone therapy; PDS-primary debulking surgery; ID-interval debulking; CRS-cytoreductive surgery; HIPEC-hyperthermic intraperitoneal chemotherapy; LAVH-laparoscopic-assisted vaginal hysterectomy.

https://doi.org/10.2147/CMAR.S515514

The use of adjuvant therapy in patients with PSM is still controversial. In a study by Lönnerfors et al, 9 of 475 women (1.9%) were diagnosed with PSM after robotic surgery. All nine women received adjuvant therapy for a median time of 33 days after surgery (min-max: 8–46 days). Four women had their PSM surgically removed: three of them radically (including a woman who had presented i-PSM) and one - nonradically. Five women received chemotherapy for recurrent disease. In addition, one underwent radiotherapy. In all patients, the disease progressed despite treatment. The exception was one woman with i-PSM, who had no further progression. The median survival time after recurrence was 4 months (min-max: 2–16 months).[66] No correlation or effect of adjuvant therapy on PMS was found.[8] Similar conclusions were reached by Vergote et al. They reported that adjuvant chemotherapy had no significant effect on treatment outcomes.[26,66]

Tips for surgeons

1. Individual choice of surgical method (laparoscopy vs classic) with consideration of PSM risk factors present in patients, especially highly malignant ovarian cancer and ascites.

   As it was previously noted in our work, the patient's risk factors for PSM should be considered before selecting a surgical method. These include high-grade ovarian cancer, ascites above 500 mL, and lymph node involvement. In addition, patient-dependent factors that increase the risk of PSM through immunosuppression include diabetes or steroid use.[24–28] Patients with risk factors are not candidates for minimally invasive procedures.[29] In patients with suspected advanced neoplastic processes, laparotomy may be considered.[8]
2. Using smaller trocars (if possible), applying as minimal manipulation of utensils as possible during surgery, trocar immobilization, reducing removal and reinsertion of trocars.

   It was observed that the use of trocars with a diameter of 15 mm compared to those with a diameter of 20 mm reduced the occurrence of PSM.[67] Additionally, optimal attachment of trocars to the abdominal wall prevents their displacement during the procedure and thus reduces tissue trauma. This reduces the amount of damaged tissue to which cancer cells could easily adhere.[35]
3. Rinsing the instrument tip in 5% iodopovidone before insertion and after removal from the abdominal cavity.

   In a study conducted by C. Schneider et al, two groups of peritoneal cavities of pigs with implanted cancer cells were compared. In the first group, protective measures against PSM were used, including lavage of trocars in 5% iodopovidone. The control group, on the other hand, was deprived of additional preventive methods. Both groups survived the tumor resection. PSM was observed in 23 of 36 port sites (63.8%) in the control group, while in the protected group only 5 of 36 port sites (13.8%). Moreover, in the described 5 cases of PSM in the protected group, 2 cases occurred due to a deviation from the protective protocol.[68] In the available literature, the use of 5% iodopovidone is also cited by Q. Gao et al and K. Benabou et al.[7,8]
4. Applying bags for holding tissue fragments during their removal from the abdominal cavity.

   Researchers J. B. Song et al emphasize the importance of using a bag in every case of suspected malignancy. The tumor is extracted in its entirety, preventing its disintegration and contact with the surface of the port insertion, as well as the further spread of tumor cells. In their work, they also cite cases of PSM development due to failure to use a bag to extract the removed tissue.[69] Each procedure maintains a risk of disintegration of the evacuated lesion. Therefore, the use of a retrieval bag seems to be a good preventive method.[70]
5. Extraction of all gas from the pneumoperitoneum before extending the trocars.

   If gas is not sufficiently removed from the peritoneal cavity, there is a risk of airflow along with peritoneal fluid contaminated with tumor cells. This results in a potential risk of dissemination and implantation of tumor cells at the port site. Increased movement of tumor cells tends to attach to the wound tissue.[35,71]
6. Layered suturing of trocar wounds with a diameter of 10–20mm.

   Based on information regarding the size of port sites for which layered suturing is indicated, it is said to be 10 mm in diameter and larger. This is indicated by a study conducted by A. Lambertz et al. The researchers concluded that intraabdominal pressure in combination with a port site not sutured in layers affects the movement of intraabdominal contents outward. At the same time, peritoneal fluids that may contain cancer cells come into contact with the unprotected edges of the wound[72] ultimately leading to the formation of PSM.

7. Consider introducing adjuvant chemotherapy soon after surgery in patients at risk for PSM.

   Adjuvant chemotherapy should be considered in patients who did not undergo the methods of preventing PSM discussed in this article during laparoscopy. Notably, the use of additional therapy after the procedure has a significant impact on OS.[73]

Conclusion

Laparoscopy, as a minimally invasive technique, is commonly used as a treatment in gynecological patients. Despite its enormous development over the last 20 years, a complication such as PSM still leaves many unknowns and therefore causes difficulties in therapeutic procedures. It may happen because even if PSM is known as a severe complication, it is rare. Nevertheless, PSM is a phenomenon that definitely requires further in-depth analysis. To date, the research conducted does not indicate any unequivocal certainty regarding the pathogenesis, factors influencing the prognosis of patients or precise methods of preventing this process. An important issue seems to be the molecular analysis of *anoikis* and the deepening of knowledge on the number and frequency of cancer cells releasing from the primary tumor mass. The results of most research works do not have statistical significance, which allows only hypothetical assumptions about PSM. Moreover, there is a lack of detailed, new studies conducted in recent years. Our knowledge of PSM is based on analyses and experiences from the 1990s. Only short case series and isolated reports are available. Additionally, when analyzing studies conducted on animals or cancer cell suspensions, research limitations should be taken into consideration. The use of different animal cancer cell lines may affect the experiment due to the biological specificity of the cells. On the other hand, studies using cancer cell suspensions only allow assessing how cells reach the port, but not how often PSM happens. Until the results of large, multicenter prospective randomized clinical trials appear, the prevention and treatment of PSM will be subject to many discussions. What is more, each patient should be closely monitored before and after the laparoscopic procedure to exclude potential factors for the occurrence of PSM and its possible post-procedure diagnosis. It is the responsibility of the person performing laparoscopy to accomplish the procedure as precisely as possible, to adjust the laparoscopic instruments to a given procedure and to the patient, to exactly close all layers of integument in the surgical field, and, if necessary, to apply additional therapy after the procedure. Key areas for improvement include proper placement of trocars with minimal trauma to surrounding tissues and suturing of the peritoneum before wound closure. Furthermore, postoperative monitoring of the patient is an important point in order to detect PSM.

Acknowledgment

Manuscript preparation was supported during Harvard Medical School's Polish Clinical Scholars Research Training Program, organised by the Agencja Badan Medycznych (ABM, English: Medical Research Agency, Warsaw, Poland.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by research grant DS125 of the Medical University of Lublin.

Disclosure

The authors report no conflicts of interest in this work.

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