



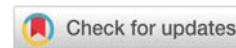
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## Review Article

# Port-Site Metastasis (PSM): Definition, clinical contexts and possible preventive actions to reduce risk

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## Abstract

The "port-site metastasis" represents a tumor recurrence that develops in the abdominal wall within the scar tissue of the insertion site of one or more trocars, after laparoscopic surgery, not associated with peritoneal carcinomatosis. This last aspect is central because in the literature some isolated cases are reported, but most cases are associated with peritoneal carcinomatosis. The first case in the literature dates back to 1978 and in the literature, the incidence varies from 1% to 21%, although most published research reports a very small number of patients. Currently, the incidence in a specialized cancer center is consistent with the incidence of recurrence on a laparotomy scar. Possible mechanisms for cell implantation at the port site are direct implantation into the wound during forced, unprotected tissue retrieval or from contaminated instruments during tumor dissection; the effect of gas turbulence in lengthy laparoscopic procedures, and embolization of exfoliated cells during tumor dissection or hematogenous spread. Probably, however, the triggering mechanism is necessarily multifactorial. To date, the only significant prognostic factor in patients diagnosed with port-site metastasis is the interval between laparoscopy and the diagnosis of the port site: in fact, patients who develop the port site within 7 months after surgery have a generally worse prognosis, as well as port-site metastasis are more frequent in advanced cancers and the presence of ascites. To reduce the risk, the following measures are proposed in the literature: 1) Select the patient who does not have a metastatic oncologic condition or friable cancerous masses or lymph node spread or attached external or intracystic vegetations, preferring well-localized, benign or low-malignant or otherwise intact tumors; 2) Use wound protectors and use of protective bags (or endo bag) for tissue retrieval; 3) Peritoneal washing with heparin, to prevent free cell adhesion, or washing with cytotoxic solutions. Evaluate the utility of using Povidone-iodine, Taurolidine (which has anti-adhesion activity and decreases proangiogenic factors), and chemotherapy products; 4) Avoid removing pneumoperitoneum with trocars in place; 5) Avoiding direct contact between the solid tumor and the port site; 6) Prefer laparoscopy to laparotomy, if possible; 7) Avoid the use of gas or direct CO<sub>2</sub> insufflation, although in literature the point is controversial and deserves more attention and study, as the initial hypothesis that CO<sub>2</sub> increased the invasion capacity of tumor cells (in vitro and in vivo) has been refuted several times. Insufflation of hyperthermic CO<sub>2</sub> and humidified CO<sub>2</sub> leads to a better outcome in patients with a malignant tumor who undergo a laparoscopic procedure compared with normal CO<sub>2</sub> pneumoperitoneum; 8) Comply with surgical protocols and techniques by updating one's surgical skills, as it has been demonstrated, as already reported here, the presence of cancerous cells on instruments, washing systems and trocars (in particular, on the trocars of the first operator). Suturing all layers of the abdominal wall decreases the risk of the port site; 9) Avoid excessive manipulation of the tumor mass during the surgical/operative procedure.

## Contents of the manuscript

### Introduction. General profiles

Video-laparo-surgery or laparoscopy is a surgical technique that involves performing abdominal surgery without opening the wall; it consists, therefore, in performing surgery without performing a laparotomy but using (as in endoscopy) a camera connected to a monitor and thin surgical instruments (such as

forceps, scissors, suture, electrocoagulation and needle holders) that are introduced through small holes made in the abdominal wall. To do this, it is necessary, first of all, to introduce a gas (CO<sub>2</sub> or carbon dioxide) into the abdominal cavity to create enough space to be able to maneuver the instruments, through a small incision around the navel, semicircular or longitudinal, of a little more than one centimeter [1].

In the past, without the current radiological diagnostic

capabilities, most diagnoses requiring surgery were made by laparotomy, i.e. open surgery, with the risk of negative outcomes in terms of complications, hospital stay, and post-operative recovery. The idea of minimizing the invasiveness of a diagnostic assessment, although it seems rather recent, has never been "foreign" to medicine. Already in 1902 Georg Kelling, a surgeon from Dresden performed the first laparoscopic procedure on a small dog. In 1910, Hans Christian Jacobaeus, of Swedish origin, performed the first laparoscopy on a human being. Subsequently, numerous surgeons perfected the technique and made it popular, but almost always limited to gynecologic applications. The first publication with an enlarged object was by Raoul Palmer in the 1950s, followed by those of Frangenheim and Semm. In 1968, Philippe Mouret used laparoscopy for differential diagnosis of appendicitis, while Hans Lindermann and Kurt Semm used CO<sub>2</sub> insufflation around the early 1970s [2].

Also in those years, in 1972, Clarke published the first laparoscopic film [3], while Mouret dissolved an adhesion bridge in a case of intestinal occlusion laparoscopically [4]. In 1975, Tarasconi performed the first laparoscopic organ resection reported in the literature [5]. In 1981, Semm performed the first laparoscopic appendectomy [6], but was ostracized by his professional environment and even suspended by the German Surgical Society from medical-surgical practice for performing an unethical surgical manoeuvre. Since those years, the indications for the use of surgical scoping have progressively extended not only to various pathologies but also to other districts, such as, for example, inguinal hernias, thorax or arthroscopies [2] up to much more serious and compromising pathological conditions, such as the colorectal district, in which Jacobs performed the first laparoscopy in history [7], also criticized and challenged.

However, despite the ostracism of certain circles, over the years the validity, efficacy, efficiency and cost-effectiveness of the laparoscopic surgical technique compared to open surgery (and/or laparotomy) has been demonstrated; however, this enthusiasm, again during the first half of the 1990 decade, was partially diluted when single cases or case studies on the risk of metastasis at the trocar port site began to emerge in the literature [8]. Therefore, while the video laparoscopic approach to pathology has demonstrated undoubted advantages such as a reduction in the extent of the surgical wound and therefore in-wall complications, a reduction in manual traction and tissue manipulation, limitation of blood loss, as well as a decrease in immune activation and catabolic response to surgical trauma, reduction of postoperative pain and reduction of hospitalization time, resulting in a more rapid resumption of work; on the other hand, the issue under consideration is concrete, although statistically rare, and therefore deserves special attention, especially when the morbid condition is referred to cancer [9].

### Clinical contexts

If we were to define the object of study of "port site metastasis", it would be a tumor recurrence that develops in the abdominal wall within the scar tissue of the insertion site of one or more trocars, after laparoscopic surgery, not

associated with peritoneal carcinomatosis [10]. Precisely this last aspect is central since a few isolated cases are reported in the literature but most cases are associated precisely with peritoneal carcinomatosis.

The first case in the literature dates back to 1978 [11] and in the literature, the incidence varies from 1% to 21%, although most published research reports a very small number of patients [12,13]. Currently, the incidence in a specialized cancer center is consistent with the incidence of recurrence on a laparotomy scar [12].

Possible mechanisms for cell implantation at the port site are direct implantation into the wound during forced, unprotected tissue retrieval or from contaminated instruments during tumor dissection; the effect of gas turbulence in lengthy laparoscopic procedures, and embolization of exfoliated cells during tumor dissection or hematogenous spread. Probably, however, the triggering mechanism is necessarily multifactorial [14].

Another publication [15] attempted to concretely identify potential circumstances favoring metastatic spread at the portal site:

1. Direct contact between the solid tumor and the portal site increases local tumor growth;
2. Laparoscopy is associated with less intraperitoneal tumor growth than laparotomy;
3. CO<sub>2</sub> insufflation promotes tumor growth to the peritoneum and is associated with more abdominal wall metastasis than gasless laparoscopy.

However, this latter aspect has been repeatedly challenged and excluded or at least reduced to a secondary risk that is not perfectly relevant, instead emphasizing other factors: local trauma, tumor manipulation, biological properties of the tumor mass, and individual surgical skills [16,17].

Another study [18] focused on the technical comparison between laparoscopy and laparotomy, claiming that:

1. Tumor growth after laparotomy is greater than after endoscopy;
2. Tumor spread is worse after laparoscopy CO<sub>2</sub> than after laparotomy;
3. Some of the disadvantages of CO<sub>2</sub> laparoscopy can be treated by using local treatments or gasless laparoscopy.

The risk of dissemination appears high when large numbers of malignant cells are present. Adnexal tumors with external vegetation and bulky lymph nodes should be considered as contraindications to CO<sub>2</sub> laparoscopy [18].

However, in the literature, there are many contrary cases, where the hypothesis of dissemination by laparoscopy tends to be excluded. This is the case of malignant tumors of the gallbladder [19] or the urinary tract [20]; while in the

hypothesis of uterine cancer [21] specific precautions are suggested to keep the risk around 0–1%:

1. Abdominal wall protection;
2. Avoidance of morcellation of the tumor;
3. Adequacy of surgical technique.

However, morcellation of suspected solid tumors, treatment of adnexal tumors with external vegetation but without peritoneal spread, and bulky lymph nodes should be considered as contraindications to CO<sub>2</sub> laparoscopy (so-called Chimney Effect) [21].

Another work [22] focuses attention on the main pathophysiological factors attached to the risk of metastatic spread:

1. Direct contact implantation;
2. Pneumoperitoneum;
3. Gas used;
4. Trocar placement and related tissue trauma;
5. Visceral manipulation;
6. Frequent instrumental reintroduction.

Yet another work [23] instead emphasizes more pointedly the conditions for developing recurrences at the site of the port:

1. Viable tumor cells must be freed from the primary tumor; they must be transported to a wound and find there a favorable environment for growth;
2. Traumatic manipulation of the tumor;
3. Trocar slippage;
4. Fluid projection, as well as poor extraction techniques, can cause the implantation of malignant cells into the subcutaneous tissue.

The recent literature of the last five years confirms what has been stated so far, suggesting however to differentiate the investigation based on the type of district involved, morbid condition, and general and specific conditions of the patient. To date, the only significant prognostic factor in patients diagnosed with port site metastasis is the interval between laparoscopy and the diagnosis of the port site: in fact, patients who develop the port site within 7 months after surgery have a generally worse prognosis, as well as port-site metastasis are more frequent in advanced cancers and the presence of ascites [24–28].

### Possible preventive actions to reduce risk. Conclusions

The central question is, therefore: is it possible to prevent the risk of port-site metastasis? The answer cannot, at present, be completely affirmative but it is possible to reduce the risk by remaining around 1% of cases by implementing

these precautions derived from surgical experience and the literature:

1. Select the patient who does not have a metastatic oncologic condition or friable cancerous masses or lymph node spread or attached external or intracystic vegetation, preferring well-localized, benign or low-malignant or otherwise intact tumors.
2. Use wound protectors and use of protective bags (or endo bags) for tissue retrieval.
3. Peritoneal washing with heparin, to prevent free cell adhesion or washing with cytotoxic solutions. Evaluate the utility of using Povidone-iodine, Taurolidine (which has anti-adhesion activity and decreases proangiogenic factors), and chemotherapy products [29].
4. Avoid removing pneumoperitoneum with trocars in place.
5. Avoid direct contact between the solid tumor and the port site.
6. Prefer laparoscopy to laparotomy, if possible and if it does not diminish the opportunities to preserve the patient from clinical risk and danger.
7. Avoid the use of gas or direct CO<sub>2</sub> insufflation, although in literature the point is controversial and deserves more attention and study, as the initial hypothesis that CO<sub>2</sub> increased the invasion capacity of tumor cells (in vitro and in vivo) has been refuted several times. Insufflation of hyperthermic CO<sub>2</sub> and humidified CO<sub>2</sub> leads to a better outcome in patients with a malignant tumor who undergo a laparoscopic procedure compared with normal CO<sub>2</sub> pneumoperitoneum [30].
8. Comply with surgical protocols and techniques by updating one's surgical skills, as it has been demonstrated, as already reported here, the presence of cancerous cells on instruments, washing systems, and trocars (in particular, on the trocars of the first operator). Suturing all layers of the abdominal wall decreases the risk of the port site [31].
9. Avoid excessive manipulation of the tumor mass during the surgical/operative procedure.

Future research on this object of investigation should focus on prospective randomized trials, paying particular attention to the psychological profiles of patient management [32–43] and the links with the immune system, since it has been demonstrated in non-recent studies that laparoscopy implies less systemic immunosuppression after surgery compared to laparotomy (noting lower IL6 levels and a lower increase in CD4 and CD8 subpopulations) [44]; furthermore, CO<sub>2</sub> has been shown to induce in vitro a worsening in peritoneal macrophage function, with lower cytokine and TNF $\alpha$  release and a negative effect on peritoneal defense mechanisms [45].



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