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Port site metastasis after minimally invasive surgery of cervical carcinoma: case report and review of the literature

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Summary

Port site metastasis after minimally invasive surgery in cervical cancer is rare. The authors report a case of port site metastasis in a 45-year-old woman with Stage Ib2 squamous caner of the cervix, together with an update of past 15-year published 12 cases in the literature. It occurred at the port site 18 months after laparoscopic surgery and completion of radiation and chemotherapy. Local excision of the mass was performed and histopathologic examination revealed metastasis of the squamous cell carcinoma of the cervix. The patient was still alive without recurrence and still participating in the follow-up. The authors searched the Medline database to evaluate the incidence, mechanism, relevant factors, preventive measures, treatment, and prognosis of port site metastasis in cervical cancer.

Key words: Port site metastasis; Cervical cancer; Minimally invasive surgery.

Introduction

Laparoscopic surgery is widely used for gynecological tumor and robotic surgery is increasingly developing nowadays. Port site metastasis following minimally invasive surgery for gynecological cancer has been recognized as a potential problem over the last two decades. The authors report a case of port site metastasis following laparoscopic surgery to treat early Stage Ib2 cervical squamous cell carcinoma (SCC), accompanied by a review of port site metastasis after minimally invasive surgery for the treatment of uterine cervical cancer.

Case Report

A 45-year-old woman was referred to the authors for postcoital bleeding. On examination, a 6-cm mass was visualized at the cevical anterior lip. A punch biopsy revealed an invasive squamous cell carcinoma of the cervix (G1-G2). The patient was diagnosed with Stage Ib2 cervical caner. The treatment strategy was chemotherapy of BIP (bleomycin, ifosfamide, platinum) followed by laparoscopic radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. Histopathological examination revealed a moderately and poorly differentiated 3×2-cm squamous carcinoma of cervix with deep muscle infiltration. The tumor was confined within the uterine cervix and all of the resection margins were negative. There was one metastatic lymph node of 21 lymph nodes dissected. Postoperative chemotherapy and radiotherapy were performed. She received three cycles of BIP and external radiation therapy of the pelvis at a dose of 46 Gy and vaginal cuff at a dose of 14 Gy.

Eighteen months after surgery, a mass approximately 0. 5 cm in diameter was detected at the site of the laparoscopic port at the left lower abdomen. The patient did not pay attention to it until the mass enlarged to 2 cm. The SCC was 1. 16 ng/ml (normal < 1.5 ng/ml), CEA was 2.75 ng/ml (normal < 5 ng/ml), CA199 was 16.52 U/ml (normal < 39 U/ml), CA125 was 13.46 U/ml (normal < 35 U/ml). Ultrasonography showed a hypoechoic lesion ranging 1.4×1.9×0.8 cm at the left port site with a distance of 0.7 cm from the skin (Figure 1). 18F-FDG PET/CT scans revealed a hypermetabolic mass in the left lower abdominal wall at the port site (Figure 2). Biopsy showed SCC of the cervix. Local excision of the mass was performed and the mass was in the subcutaneous tissue and did not involve fascia (Figure 3). Histopathological examination revealed metastasis of the SCC of the cervix, which was showing positive immunohistochemistry for p63, p40, and

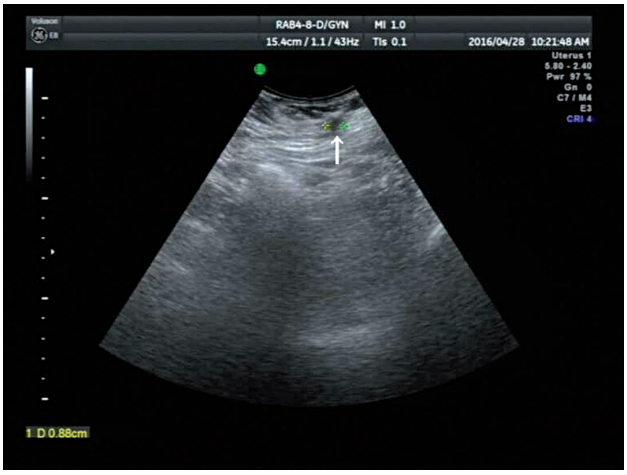

Figure 1. — Ultrasonography showing a hypoechoic lesion ranging 1.4×1.9×0.8 cm at the left port site with a distance of 0.7 cm from the skin. The arrow indicates the hypoechoic lesion.

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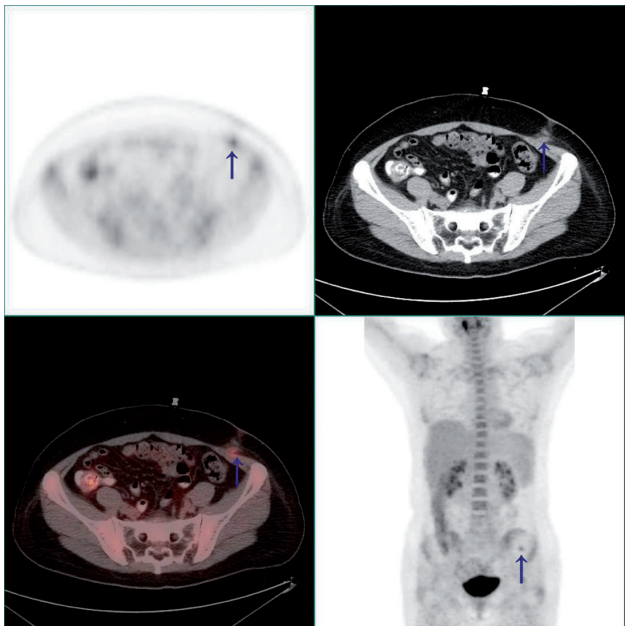

Figure 2. — PEC-CT showing a hypermetabolic mass in the left lower abdominal wall at the port site. The arrows indicate the hypermetabolic lesion.

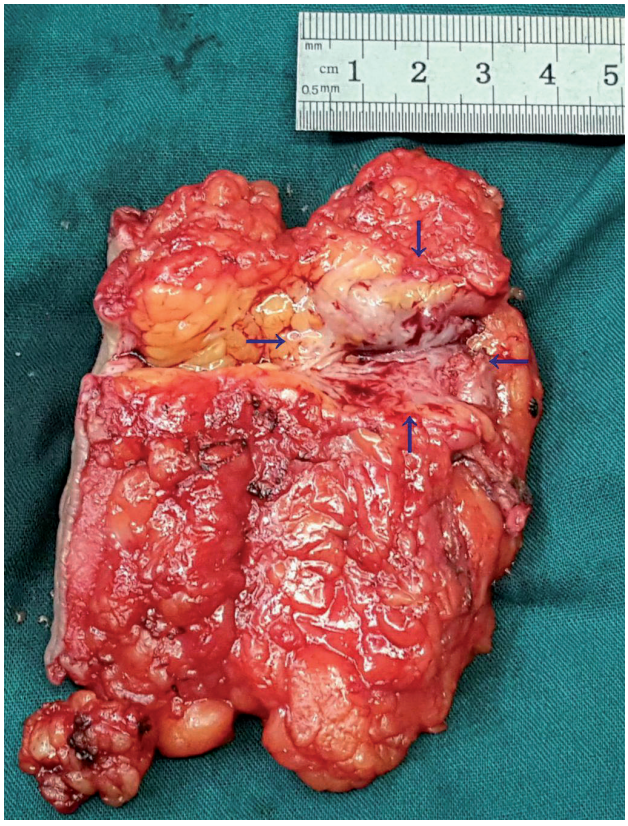

Figure 3. — The mass is in the subcutaneous tissue and does not involve fascia. The arrows indicate the lesion.

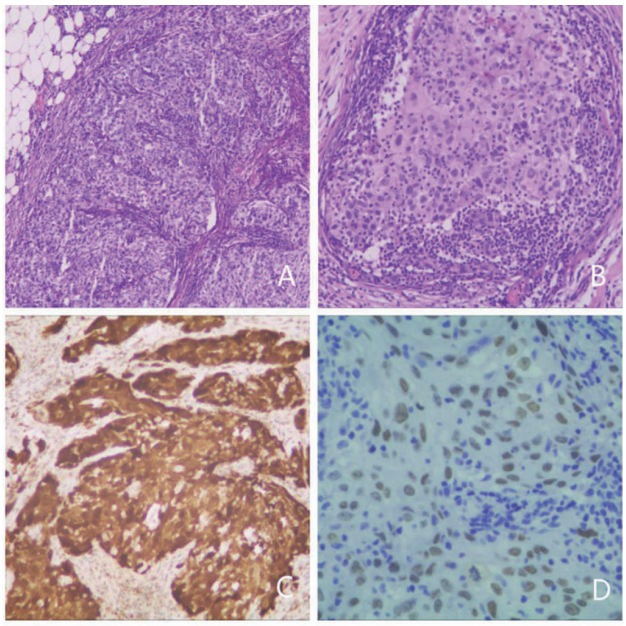

Figure 4. — (A and B) Histopathological examination of the port site metastasis is showing squamous cell carcinoma of the cervix with positive immunohistochemistry for p16 (C), p63, and p40 (D) protein.

p16 protein (Figure 4). At the three months' follow-up, there was no evidence of locoregional recurrence or distant metastasis.

Discussion

With the development of minimally invasive surgery (both laparoscopy and robot) for treating cancer, a new complication of port site metastasis arises. There are 12 cases published of port site metastasis after laparoscopic or robotic surgery for cervical cancer (Table 1) [1–12]. Nine cases reported of port site metastasis after traditional laparoscopic surgery (9/12, 75%) and three after robotic surgeries (3/12, 25%) for cervical carcinoma in the recent 15 years. The FIGO stage was various from Ib1 to IVb. The majority of them were squamous carcinoma (7/12, 58. 3%) and initial staging of disease was IIb (5/12, 41. 7%). Eight cases (8/10, 80%) were identified as poor differentiation of cervical cancer. Ten patients underwent lymphadenectomy, six patients' lymph nodes (60%) were positive. In six cases (50%), laparoscopy was performed for lymphadenectomy to assess the stage of the cervical cancer and to determine the field of radiotherapy. The time interval from laparoscopic surgery to port-site metastasis ranged 1–18 months. Patients died of disease in four cases (33. 3%). The present authors reported an additional case in this article. Reymond *et al.* proposed the following definition for port site recurrence: early tumor recurrences that develop locally in the abdominal wall, within the scar tissue of one or more trocar

Table 1. — *Characteristics of cases of port site metastasis in cervical cancer in recent 15 years.*

Author (Published)	Histology	Stage	Adjuvant therapy before surgery	Treatment	Differentiation	LN status	Metastasis (months)	Location	Treatment after metastasis	Follow up (months)
Tjalma *et al,* 2001 [1]	Squam	IIIb	No	LAL+RT	Poor	Neg	15	Umbilical port site	Sur+CT	DOD (24)
Gregor *et al,* 2001 [2]	Squam	IIb	No	LL+RT	Poor	Pos	3	Port site	Sur	AWD (3)
Agostini *et al,* 2001[3]	Squam	IIb	No	LAL+RT+CT	-	Pos	7	Port site	Sur	DOD (6)
Picone *et al,* 2003 [4]	Tubular mucin-secreting Adno	IIb	RT	CH+BSO+LPL +LOT+RT	Well	Pos	5	Port site	CT	DOD (2)
Martínez-Palones *et al,* 2005 [5]	Adno	IIIb	No	LAL+RT+CT	Poor	Pos	7	Umbilical port site	none	-
PARK *et al,* 2008 [6]	Adno	IIb	No	LL+RT+CT	-	Pos	1	Three port sites+liver	CT	-
Yenen *et al,* 2009 [7]	Squam	IIb	No	LAL (extraperitoneal) +RT+CT	Poor	Pos	12	Port site	Sur	-
Sert *et al,* 2010 [8]	Adno	Ib1	No	RLRH+BSO +LPL	M&W	Neg	18	Port site+ bladder+ sigmoideum+ abdominal and pelvic wall+LN	Sur+RT +CT	AWD (15)
Bolles *et al,* 2012 [9]	Squam	Ib2	No	RLRH+BS +LPAL+LOT +RT+CT	Poor	Neg	5	Umbilical port site +LN	Sur (include BO)	-
Kim *et al,* 2013 [10]	Mucinous adno	Ib1	No	RLRH+RO +LPL	Poor	Neg	4	Port site +peritoneal cavities+LN	RT+CT	AWD (17)
Ota T e*t al,* 2013 [11]	Squam	IIa	RT+RH +BSO +PL	HLS+RT+CT	Poor	-	12	Hand-assisted port site	Sur	DOD (7)
Kharod *et al,* 2015 [12]	Squam	IVb	No	LC	Poor	None	18	Umbilical (after LC)	RT+CT port site	-
Present	Squam	Ib2	CT	LRH+BSO +LPL+RT+CT	M&P	Pos	18	Port site	Sur	NED (2)

Abbreviations:Adno: adenocarcinoma; AWD: alive with disease; BSO: bilateral salpingo-oophorectomy; BS: bilateral salpingectomy; BO: bilateral oophorectomy; CH: colpohysterectomy; CT: chemotherapy; DOD: dead of disease; HLS: hand-assisted laparoscopic splenectomy; LAL: laparoscopic aortic lymphadenectomy; LC: laparoscopic cholecystectomy; LL: laparoscopic lymphadenectomy; LN: lymph node; LOT: laparoscopic ovarian transposition; LPAL: laparoscopic pelvic and aortic lymphadenectomy; LPL: laparoscopic pelvic lymphadenectomy; LRH: laparoscopic radical hysterectomy; M&P: moderately and poorly-differentiated; M&W: moderately and well-differentiated; NED: no evidence of disease; Neg: negative; PL: pelvic lymphadenectomy; Pos: positive; RH: radical hysterectomy; RLRH: robotic-assisted laparoscopic radical hysterectomy; RO: right oophorectomy; RT: radiotherapy; Squam: squamous carcinoma; Sur: surgery.

sites or an incision wound, after laparoscopy or thoracoscopy for cancer, which are not associated with peritoneal carcinomatosis [13]. The incidence of port site metastasis is low. Ramirez *et al.* performed a Medline search and reported the estimated incidence of port site metastases in all patients undergoing laparoscopic surgery for malignant disease is approximately 1–2% [14]. Another analysis of a prospective database of all patients undergoing transperitoneal laparoscopic procedures for malignant conditions found port site metastases documented in 20 of 1,694 patients (1.18%) [15]. Nagarsheth *et al.* reported the overall incidence of port site metastases after laparoscopic procedures in gynecologic cancers was 2.3% [16]. Ndofor *et al.* concluded the rate of port site metastasis after robotic surgery in women with gynecologic cancer to be low and similar to the rate for laparoscopic procedures through a prospective database [17]. A retrospective cohort analysis of women with gynecologic malignancies who underwent robotic-assisted surgery from 2007 to 2011 found that two of 142 patients each had a single port site metastasis, for an overall rate of 1.41%, or 0.28% per port site. Another two patients (1.41%) both with port site metastases had concurrent sites of pelvic recurrence [18]. A

prospective study reported the occurrent rate of port site metastases in the first 475 women undergoing robotic surgery for gynecological cancer was 1.9%.

The mechanism of port site metastasis has not been defined. Several possible mechanisms have been postulated, including hematogeneous spread, direct wound implantation during extraction of the malignant specimen or through a contaminated instrument, chimney effect, aerosolization of tumor cells, surgical techniques such as excessive tumor manipulation and a lack of surgical experience, pressure due to pneumoperitoneum, the effect of carbon dioxide on tumor cell biology, and impairment of local immune response after laparoscopic surgery [19]. Review of reports of animal or human studies revealed no evidence that hematogenous spread plays a major role in the etiology of port site metastases. The most common proposed etiologies are the wound implantations caused by the surgical technique and instrumentation; the leakage of insufflation gas through the ports, known as the "chimney effect", and the impact of pneumoperitoneum on local immune reactions [14]. However, Mo *et al.* used a meta-regression to analyze 20 randomized control studies involving 1,229 animals, which showed that wound recurrence was not significant in the laparoscopic surgery *vs.* gasless laparoscopic surgery subgroups [odds ratio (OR), 2.23; 95% confidence interval (CI), 0.90–5. 55; $p = 0.08$) or the laparoscopic surgery vs. laparotomy subgroups (OR, 0. 97; 95% CI, 0. 31–3. 00; $p = 0.08$), suggesting that carbon dioxide pneumoperitoneum does not enhance wound metastases following laparoscopic abdominal tumor surgery [20]. A histological examination of the excised umbilical mass showed the peritumoral increase in microvessel density and strong CD31 positivity, which suggests angiogenesis as a potential factor leading to seeding of tumor cells at the umbilical port [5].

Wang *et al.* found that the majority of recurrences were in patients with adenocarcinoma cell type, advanced stage (far-advanced disease), and often with diffuse peritoneal carcinomatosis, suggesting that port site metastasis may contribute to the highly aggressive nature of the disease. Risk factor that contributed to early occurrence of port site metastasis were ovarian cancer, presence of ascites, and diagnostic or palliative procedures for malignancy ($p < 0.001$, $p = 0.08$, and $p < 0.001$, respectively) [21]. Agostini *et al.* designed an animal experiment and showed the risk of port-site metastases was 58% when the peritoneum was not closed compared with 14% when the peritoneum was sutured closed [22]. Patients with advanced stage are more likely to have port site metastasis. The risk of port site metastases is highest (5%) in patients with recurrence of ovarian or primary peritoneal malignancies undergoing procedures in the presence of ascites [16]. High-risk histology and/or advanced stage of disease at surgery seem to be contributing factors [23]. This further supports the concept that patients with advanced disease are not ideal candidates for minimally invasive procedures. A Medline computer database search from January 1980 to September 2002 reported 13 cases published with port site recurrence after laparoscopy for cervical carcinoma. The majority of them were squamous carcinoma (9/13 at least, 69%) and initial staging of disease was Ib (7/13 (54%)). Of ten cases of laparoscopy with lymphadenectomy, in three cases (30%) nodes were not involved. In eight cases (61.5%), laparoscopy was performed for lymphadenectomy (pelvic in three cases, aorticopelvic in two cases, and aortic in three cases) [24].

Several preventive measures, have been suggested, including careful patient selection, proper placement of trocars with minimal tissue trauma, rinsing the tip of instruments in 5% povidine-iodine when changing instruments, minimal handling of the tumor, deflating the pneumoperitoneum with trocars in place, the use of protective bags to retrieve the tumor, removing all intra-abdominal fluid before trocar removal, lavage of the peritoneal cavity as well as of the port wounds with cytotoxic agents, closure of 10-12-mm trocar sites and modifications of surgical technique [10, 14]. Ziprin *et al.* considered locoregional administration of tumor static agents (heparin, taurolidine, iodine, 5-fluorouracil, doxorubicin, and matrix metalloprotease inhibitors) might have a role in diminishing the biologic effects of the pneumoperitoneum on tumor cells [19]. Curet *et al*. suggested to avoid liquid spillage when closing the trocar site and use closed suction drain [25]. Zivanovic *et al*. advised the closure of the peritoneum and fascia of all port sites > 5mm and closure of all sites in the setting of advanced disease or malignant ascites [15]. However, there are no general recommendations for treatment of port site metastasis, perhaps due to the heterogeneity and rarity of port site metastasis. If it is surgically resectable, excision of the port site metastasis is generally recommended. If the mass is not resectable, the patient might be treated with supportive care, chemotherapy, and/or radiotherapy [10]. In selected cases with isolated recurrences, well controlled status of the primary lesion, good performance status, and long progression free survival, a surgical resection with negative margins in a multidisciplinary approach may provide a long term complete remission alleviating the need for systemic chemotherapy (thus sparing organ function and chemotherapeutic options for future relapses) and a survival advantage in recurrent cervical cancer patients [26]. All patients undergoing minimally invasive surgery for malignancies should be followed closely, with special attention to the port sites, preferably with a CT scan of the abdomen every six months over the first three years [8].

For patients with extrapelvic recurrent cervical cancer, hence not treatable with radiation or resectable with an exenteration, palliative chemotherapy is the mainstay of treatment with a median overall survival of 12 months [27]. Zivanovic *et al.* reported patients who developed port site metastases within seven months from the laparoscopic pro-

cedure had a median survival of 12 months, whereas patients who developed port-site metastasis seven months had a median survival of 37 months ($p = 0.004$)[15]. As minimally invasive surgery (both laparoscopy and robot) for treating cervical cancer has developed, it has become the preferred surgical route for this procedure. The port site metastasis is not a reason to restrict the development of minimally invasive surgery. On the contrary, more researches should be done to understand the mechanism and prevention of port site metastasis.

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