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Port-Site Metastasis Following Laparoscopic Surgery

Terence C. Chua[1], Tristan D. Yan[1],
David L. Morris[1] and Paul H. Sugarbaker[2]
[1]*Hepatobiliary and Surgical Oncology Unit, UNSW Department of Surgery, St George Hospital, Sydney*
[2]*Washington Cancer Institute, Washington*
[1]*Australia*
[2]*USA*

1. Introduction

In the 1990s, laparoscopic surgery became accepted as a standard approach for general surgical operations including cholecystectomy (Barkun et al., 1992) and appendectomy (Attwood, Hill, Murphy, Thornton, & Stephens, 1992). In these randomized studies, the laparoscopic compared to the open approach resulted in decreased length of hospital stay, fewer postoperative complications, more rapid return to normal activities with reduced analgesic requirements. This was associated with decreased cost of care and also achieved superior cosmetic results leading to increased patient satisfaction. Following this, the frontier of laparoscopic surgery was pushed further forward through experimentation of other complex intraabdominal surgery including colorectal surgery (Milsom, Lavery, Church, Stolfi, & Fazio, 1994), bariatric surgery (Cowan, 1992) and more recently hepatopancreaticobiliary surgery (Gigot et al., 2002). The growth and expanded role of laparoscopic surgery in abdominal operations meant that cancer surgery may now be performed using laparoscopy.

Despite the perioperative advantages, laparoscopic cancer surgery has been highly debated and its oncological appropriateness has been questioned. Doubts over the technique concerned compromising oncologic principles through loss of the surgeon's ability to perform tactile assessment which could otherwise have been performed in an open surgery. It was also thought that with laparoscopic approach may limit the extent of resections. For example, in the setting of laparoscopic colon resection, reduced lymph nodes harvested from insufficient mesentery may make disease staging inaccurate. Further, there are concerns regarding the development of port-site metastasis.

Port site metastasis was first described by Dobronte and colleagues (Döbrönte, Wittmann, & Karácsony, 1978) who described the case of a patient developing local tumor metastases in the abdominal wall two weeks after laparoscopy for malignancy and explained that this occurred due to infiltration of malignant ascites during needle and trocar insertion into the abdominal cavity at the port site. Since this report, there has been extensive publication of case reports in the literature, describing this phenomenon in gastrointestinal (Cook & Dehn, 1996), urological (Chueh, Tsai, & Lai, 2004) and gynaecological malignancies (Sanjuán et al.,

2005). This chapter identifies through a literature search the risk of port-site metastasis in laparoscopic surgery for cancer and discusses the current understanding to guide practice and management.

2. Incidence of port site metastasis

It was initially thought that port-site metastasis was associated with advanced malignancy. Cook and Dehn reported a rate of five of 46 patients (11%) developing port-site metastasis after undergoing laparoscopy and identified that advanced disease with serosal involvement of the tumor was associated with the occurrence of this phenomenon (Cook & Dehn, 1996). However, port-site metastasis has also been reported in patients undergoing colectomy for Duke A tumors (Prasad, Avery, & Foley, 1994). This may have been a result of soilage of tumor into the peritoneal cavity during surgery, implantation of circulating tumor cells present in the lymphatics and haematogenous system that are transacted as part of surgery or trauma during the process of specimen retrieval.

To ascertain the incidence of port-site metastasis, we undertook a literature review of large clinical trials that reported results after an adequate follow-up time to determine the risks of its occurrence. As shown in table 1, from the 17 studies reviewed that included 11,027 cancer patients undergoing laparoscopic surgery or diagnostic laparoscopy, it appears that the port-site metastasis is a rare phenomenon, occurring in less than 2% of patients (COLOR, 2009; Fleshman et al., 2007; Jayne et al., 2010; Kaiser, Kang, Chan, Vukasin, & Beart, 2004; Kim, Park, Joh, & Hahn, 2006; Koffron, Auffenberg, Kung, & Abecassis, 2007; Lacy et al., 2008; Liang, Huang, Lai, Lee, & Jeng, 2007; Lujan et al., 2009; Martinez, Querleu, Leblanc, Narducci, & Ferron, 2010; Miyajima et al., 2009; K. H. Ng et al., 2009; S. M. Ng et al., 2008; Rassweiler et al., 2003; Shoup et al., 2002; Song et al., 2010; Zivanovic et al., 2008). In eight randomized clinical trials comparing laparoscopic surgery to open surgery for cancer, there was no statistical difference in the development of port-site metastasis or wound metastasis (COLOR, 2009; Fleshman et al., 2007; Jayne et al., 2010; Kaiser et al., 2004; Lacy et al., 2008; Liang et al., 2007; Lujan et al., 2009; S. M. Ng et al., 2008).

In an international survey of port-site metastasis involving members of the German Society of Surgery, Swiss Association for Laparoscopic and Thoracoscopic Surgery and Austrian Society of Minimal Invasive Surgery, participants reported 70 of 409 cases (17.1%) of port-site metastasis in patients undergoing laparoscopic cholecystectomy for gallbladder cancer and 19 of 412 cases (4.6%) of port-site metastasis in patients undergoing laparoscopic surgery for colorectal cancer (Paolucci, Schaeff, Schneider, & Gutt, 1999). These authors further alluded to the association of port-site metastasis and the propensity for intraperitoneal spread of cancer. The incidence data reported in this study appears to be high when compared to the tabulated studies. It is likely that the high incidence may be an effect of the learning curve of laparoscopic cancer surgery during the 1990s era as modern data seems to suggest otherwise.

In summary, it appears from current data that port-site metastasis is a rare occurrence and its incidence is unlikely to be more common than wound metastasis when oncologic principles are adhered to in the technical performance of laparoscopic surgery.

3. Hypotheses for port-site metastasis

There are several mechanisms that have been proposed and studied in an experimental setting to investigate the development of port-site metastasis in animal models. Although

these in-vivo experiments has provided some mechanisms to explain its occurrence, the limitations in the homology of animal models where human cancer cell lines are used due to the lack of available native tumor cells and the immunodeficient state of these animal models (de Jong & Maina, 2010). Nevertheless, animal models remain a unique opportunity to provide in vivo information in translation research. The most commonly discussed hypotheses include hematogenous dissemination, wound contamination, effects of pneumoperitoneum that including the type of insufflating gas, chimney effect, aerosolization, surgical technique and the local immune response. Experiments investigating these hypotheses have yielded both positive and negative results and it is likely the occurrence of port-site metastasis is multifactorial stemming from a combination of these various hypotheses.

3.1 Hematogenous dissemination

The concept of hematogenous dissemination goes against the concept of direct spread of cancer cells to explain port-site metastasis. The establishment of port-sites for access results in tissue trauma and during the healing process, its hyperaemic state, provide a nutrient rich environment for tumor growth and may become a sanctuary site of tumor metastasis in patients with free circulating tumor cells within the systemic circulation. It has been previously shown that tumor cells establish themselves in sites with increased blood supply at a greater rate than normal tissues (Murphy et al., 1988). Two studies specifically compared the rates of port-site metastasis in a group undergoing intravenous cancer cell injection versus intraperitoneal injection in a mice model. Iwanaka et al reported an incidence of 0% compared to 63% of port-site metastasis in immature A/J mice undergoing intravenous compared to intraperitoneal injection of TBJ-neuroblastoma cells (Iwanaka, Arya, & Ziegler, 1998). Brundell et al used male Dark Agouti rats and injected a suspension of 10^5 Dark Agouti mammary adenocarcinoma cells into the internal jugular vein and stimulated laparoscopic conditions by a 15 minute period of insufflations and compared the port-site metastasis rate in rats who had routine closure of port-sites or in another group whom they performed a mid-line laparotomy prior to closure. These authors reported one case of port-site metastasis in the laparoscopic group and no wound metastasis in the laparotomy group (Brundell, Ellis, Dodd, Watson, & Hewett, 2002). Both these studies demonstrate that port-site metastasis occurring through hematogenous dissemination is rare, even in the presence of a hyperaemic wound state induced by the mid-line laparotomy as performed in the second study.

3.2 Wound contamination

The effect of direct wound contamination stems from a variety of reasons. The extraction of tumor through a small port-site together with the leakage of CO2 that occurs may induce movement of free tumor cells that have an increased propensity to implant in the traumatised tissue of the wound (Tseng et al., 1998). During the surgical procedure, ongoing passage and extrication of instruments that are contaminated by tumor material due to the dissection process, may also explain its occurrence. Bundell et al studied the mechanism of wound contamination through detecting an increased deposition of radiolabeled human colon cancer cells that were injected intraperitoneally in trocar site due to contamination, demonstrated increased movement of tumor cells with increase in volumes of gas insufflations and decreased insufflations pressures leading to an increased contamination of trocar and port-sites (S. M. Brundell et al., 2002).

3.3 Pneumoperitoneum

Carbon dioxide is the most commonly used gas for insufflations during laparoscopic surgery. It is non-flammable, inexpensive, colourless, readily available and readily absorbed (Menes & Spivak, 2000). The effect of insufflating gas to distend the abdomen creates a high pneumperitoneal pressure and consequentially stimulate movement of free peritoneal tumor cells or may result in sloughing or shedding of tumor cells from viscera into the peritoneal cavity (Moreira et al., 2001). Hirabayashi et al further elucidated the effect of pneumoperitoneum by using a scanning electron microscope to study the effects of how tumor cells disseminate to form port-site metastases after pneumoperitoneum in a nude mice model injected with human gastric cancer cells. They found that pneumoperitoneum immediately results in peeling and destruction of the muscular layer of the abdominal peritoneum, increasing the propensity of tumor cell adhesion at port-sites and subsequently healing process occurs leading to scar formation with presence of entrapped tumor cells (Hirabayashi et al., 2002). A "chimney effect" that occurs when gas leaks out along the trocar has been thought to be implicated in the development of port-site metastases. In an experiment to examine this hypothesis, tumor cells at trocar sites were found to be higher compared to the control when leakage of carbon dioxide gas along the trocar was permitted during a rat animal model injected with CC-531 tumor cells intraperitoneally (Tseng et al., 1998). However, this may be related to the concentration of the amount of injected intraperitoneal tumor cells in the animal model as some other authors have not yielded similar results in their experiments to support this theory. Brundell et al demonstrated that increasing the tumor cell inoculums resulted in increased deposition of tumor cells on both ports and port-sites in a swine model, and further showed that displacement of the ports (removing and reinserting) increased the number of tumors cells deposited at port-sites (Brundell et al., 2003). Whelan et al failed to show that aerosolization of viable tumor cells in either in vivo or in vitro experiments with pressures up to 30 mmHg (Whelan et al., 1996). Pneumoperitoneum increases intraabdominal pressure and results in an increased in blood flow in the anterior abdominal wall. This has also been thought to increase the risk of port-site metastasis as the increased circulation provides a favourable medium for growth of tumor cells (Yavuz, Rønning, Lyng, Grønbech, & Mårvik, 2003). In addition, the type of gas has also been shown to influence the rates of port-site metastasis with helium insufflations being the least likely compared to argon and nitrogen that were more likely to be associated with port-site metastasis (Gupta, Watson, Ellis, & Jamieson, 2002).

3.4 Immune response

Carbon dioxide has been thought to be toxic to lymphocytes in vitro and hence its insufflations into the peritoneal cavity may potentially affect the peritoneal cell-mediated immunity. Mathew et al demonstrate this in an experiment where adenocarcinoma cells were injected in the left upper quadrant of the peritoneal cavity in syngeneic tumor-bearing rats and subjected to laparotomy, laparoscopy with carbon dioxide or gasless laparoscopy. The authors obtained peritoneal macrophage levels and showed that tumor-bearing rats produced significantly less TNG-alpha in vitro during laparoscopy with carbon dioxide compared to gasless laparoscopy or laparotomy (Mathew, Watson, Ellis, Jamieson, & Rofe, 1999). The results of this experiment was replicated by Ost et al who measured TNF-alpha levels from peritoneal macrophage in mice subjected to either carbon dioxide pneumoperitoneum or laparotomy and showed that peritoneal macrophage TNF-alpha secretion was significantly inhibited in mice subjected to carbon dioxide pneumoperitoneum

(Ost et al., 2008). In a human experiment, Evard et al sampled blood and peritoneal fluid before and after pneumoperitoneum from 16 patients undergoing laparoscopic cholecystectomy and measured cytokine levels, lymphocyte vitality and showed that there were significant decrease in absolute lymphocyte and cytokine counts during the early postoperatively before returning to normal levels (Evrard et al., 1997). This transient immunosuppression may facilitate implantation of tumor cells during laparoscopic surgery.

3.5 Surgical technique

Arguably, the strongest risk for port-site metastasis would be the surgical technique. Anecdotal case series reporting port-site metastasis after laparoscopic surgery have shown a decrease in rates of port-site metastasis with experience. In a large animal study of mice established with splenic tumors (n=128) who underwent either an open splenectomy or laparoscopic -assisted splenectomy, it was shown that the incidence of port-site tumor recurrence in the laparoscopic-assisted group decreased significantly with time (Lee, Gleason, Bessler, & Whelan, 2000). This was likely the experience in human laparoscopic surgery. During the 1990s, there were a large number of case reports describing the occurrence of port-site metastasis after laparoscopic surgery. This occurred during the initial learning curve of surgeons. However, in contemporary series such as the rates of port-site metastasis reported in the trials shown in table 1, port-site metastasis is a rare occurrence due to improved handling of tumor laparoscopically, meticulous resection, rinsing of instruments and the application of protective measures. Other factors that include suture closing of the peritoneum (Agostini et al., 2002) and the type of instruments have also been investigated (Nduka, Poland, Kennedy, Dye, & Darzi, 1998).

4. Clinical significance of port-site metastasis

The clinical significance of port-site metastasis should be regarded as a sign of locoregional recurrence. Although this could manifest as a "drop metastasis" during specimen retrieval, it is more compatible that the entry into the peritoneal cavity during laparoscopic surgery with insufflations of gas, repeated instrument cannulation of port-sites and tumor dissection process that leads to spillage of lymph and blood containing circulating tumor cells makes port-site metastasis a condition with high risk for peritoneal carcinomatosis. Z'graggen et al in a series of 37 patients undergoing laparoscopic cholecystectomy for unsuspected gallbladder cancer reported that all patients developed port -site metastasis as recurrence that was associated with peritoneal metastases (Z'graggen et al., 1998). The rate at which port-site metastasis develop is likely a factor of the tumor biology. Zivanovic et al reported 20 of 1694 patients developing port-site metastasis after laparoscopic procedures for gynaecologic malignancies and showed that in patients who developed port-site metastasis 7 months from the laparoscopic procedure had a median survival of 12 months compared to 37 months for patients who develop port-site metastasis after 7 months (P=0.004) (Zivanovic et al., 2008). Therefore, port-site metastasis should be regarded a strong risk factor for peritoneal dissemination in addition to other previously described factors that include full thickness penetration of tumor through the bowel wall, spillage of tumor from lymphatic channels by surgical trauma or free perforation of the tumor (Sugarbaker, 1988).

Peritoneal dissemination of cancer cells in the peritoneal cavity circulate with peritoneal fluid as a transport vector along with gravitational forces and fluid hydrodynamics driving the peritoneal circulation resulting in the pelvis and subphrenic spaces being a

First Author	Year Published	Type of Study	Number of Patients		Tumor Origin	Duration of Follow-up (Months)	Risk of Recurrence [Lap / Open] (%)	Disease-Free Survival [Lap / Open] (% at X-Years)	Incidence of Port-Site Metastasis [Lap / Open] (%)
			Laparoscopic	Open					
Jayne (Jayne et al., 2010)	2010	Randomized	526	268	Colorectal	56	NR	55 / 58 (P=0.48) at 5-years	1.7 / 0.4 (P=NR)
Lujan (Lujan et al., 2009)	2009	Randomized	97	96	Rectal	34	NR	85 / 81 (P=0.895) at 5-years	0 / 0 (P=NR)
COLOR (COLOR, 2009)	2009	Randomized	534	542	Colon	53	31 / 29 (P=0.24)	74 / 76 (P=0.70) at 3-years	1.3 / 0.4 (P=0.09)
Lacy (Lacy et al., 2008)	2008	Randomized	111	108	Colon	95	18 / 29 (P=0.07)	84 / 61 (P=0.0015) at 5-years	1 / 0 (P=0.65)
Ng (S. M. Ng et al., 2008)	2008	Randomized	51	48	Rectal	90	NR	78 / 74 (P=0.55) at 5-years	0 / 2 (P=NR)
Fleshman (Fleshman et al., 2007)	2007	Randomized	435	428	Colon	60	19 / 22 (P=0.25)	69 / 68 (P=0.94) at 5-years	0.9 / 0.5 (P=0.43)
Liang (Liang et al., 2007)	2007	Randomized	135	134	Colon	40	NR	72 / 68 (P=0.362) at 5-years	0.7 / 0.7 (P=NR)
Kaiser (Kaiser et al., 2004)	2004	Randomized	15	20	Colon	35	0 / 5 (P=NR)	NR	0 / 0 (P=NR)
Martinez (Martinez et al., 2010)	2010	Retrospective	1216	-	Uterine / Cervical	49	NR	NR	0.4 / -
Song (Song et al., 2010)	2010	Retrospective	1417	-	Gastric	41	3.5 / -	94 / -	0 / -
Ng (K. H. Ng et al., 2009)	2009	Retrospective	579	-	Rectal	56	23 / -	76 / -	0.7 / -
Miyajima (Miyajima et al., 2009)	2009	Retrospective	1057	-	Rectal	30	7 / -	NR	0 / -
Zivanovic (Zivanovic et al., 2008)	2008	Retrospective	1694	-	Gynaeco-logical	NR	NR	NR	1.2 / -
Koffron (Koffron et al., 2007)	2007	Retrospective Matched Analysis	300	100	Liver	69	2 / 3 (P>0.05)	NR	0 / NR
Kim (Kim et al., 2006)	2006	Retrospective	312	-	Rectal	30	NR	NR	0 / -
Rassweiler (Rassweiler et al., 2003)	2003	Retrospective	1000	-	Urological	58	NR	NR	0.2 / -
Shoup (Shoup et al., 2002)	2002	Retrospective	1548	-	Diagnostic Upper GI Cancers	8	NR	NR	0.8 / -

Table 1. Literature review of major clinical trials reporting the risk of port-site metastasis

common site for cancer cell implantation (Carmignani, Sugarbaker, Bromley, & Sugarbaker, 2003). Peritoneal carcinomatosis when managed with chemotherapy alone is

a rapidly progressive disease state characterised by a symptomatic clinical course that occurs as a result of the peritoneal tumor masses that leads to abdominal pain and sub-acute bowel obstruction. In a single centre experience of 349 patients with peritoneal carcinomatosis from colorectal cancer, the median survival was 7 months (Jayne, Fook, Loi, & Seow-Choen, 2002). A combined modality approach of cytoreductive surgery and perioperative intraperitoneal chemotherapy introduced by Dr. Paul Sugarbaker from the Washington Cancer Centre has been shown to be effective in managing this locoregional recurrence and alter the fulminant natural history of this disease (Sugarbaker, Schellinx, Chang, Koslowe, & von Meyerfeldt, 1996). Current results of cytoreductive surgery with perioperative intraperitoneal chemotherapy for non-gynaecologic malignancies showed a potential for a median survival of 34 months with a corresponding 5-year survival rate of 37% (Olivier Glehen et al., 2010).

5. Diagnostic laparoscopy in patients at high risk for port-site metastasis

Data cited in this manuscript strongly suggests that the benefits of laparoscopic oncologic surgery outweigh the risk of port-site metastasis. However, there is a subgroup of patients who may profit greatly from diagnostic laparoscopy but who are at increased risk for cancer implantation at the trochar site. These are patients with ascites in whom there is a high index of suspicion for peritoneal carcinomatosis or peritoneal mesothelioma. Patients to be included in this group are those who may have mucinous ascites from a colorectal or appendiceal adenocarcinoma, ascites from ovarian cancer, ascites associated with a diagnosis of gastric cancer, or ascites from peritoneal mesothelioma. In these high risk patients a modification of the diagnostic laparascopic technique should be considered. The port-sites should be limited to the midline or limited to sites that can be included as part of the abdominal incision. Lateral ports should be avoided except under unusual circumstances and are rarely mandatory in this clinical setting – diagnostic laparascopy in patients with suspect carcinomatosis.

6. Management of port-site metastasis

A simple subcutaneous wide excision of port-site metastasis would constitute a failure of the understanding of the mechanism that underlies its occurrence. Owing to the high risk for peritoneal carcinomatosis, an extensive clinical work-up comprising of positron emission tomography scans and contrast enhanced computed tomography scan should be performed to identify for other sites of metastasis. In the absence of distant metastasis, a wide excision of the port site together with a laparotomy to survey the peritoneal cavity should be performed. If there are evidence of peritoneal seeding, a cytoreductive surgery combined with perioperative intraperitoneal chemotherapy should be performed in patients whose demographic and disease factors fulfil the selection criteria for treatment. For pseudomyxoma peritonei, a complete cytoreduction may achieve 5- and 10-year survival of 87% and 74% respectively (Youssef et al., 2011), a median survival of 53 months and 5-year survival of 47%may be achieved in patients with diffuse malignant peritoneal mesothelioma (Yan et al., 2009), a median survival of 30 months and 5-year survival of 27% for colorectal carcinomatosis (Elias et al., 2010), a median survival of 30 months and 5-year survival of 25% for ovarian carcinomatosis (Helm et al., 2010) and a median survival of 15 months and 5-year survival of 23% in the setting of a complete cytoreduction for gastric carcinomatosis (O. Glehen et al., 2010).

7. Conclusion

Previous reports of an increased clinical incidence of port-site metastasis needs to be re-evaluated. It appears from current data that the incidence of port-site metastasis is rare and is unlikely difference from that of wound metastasis, hence does not negate the benefits of laparoscopic cancer surgery. The reduction in incidence may in part be due to adherence to oncologic principles during laparoscopic surgery and prevention strategies that include port-site protective applications (Seow-Choen, Wan, & Tan, 2009). There may be a preponderance for the occurrence of port-site metastasis in malignancies that have a propensity for peritoneal dissemination, for example, ovarian cancer, colorectal cancer, pancreatic cancer, gastric cancer and appendiceal cancer. Port-site metastasis is a strong risk factor for peritoneal dissemination. An accurate diagnostic work-up should include imaging and exploration of the peritoneal cavity to identify peritoneal metastases. In the setting of peritoneal disease, referral to specialized peritoneal surface malignancy centres for treatment should be mandatory.

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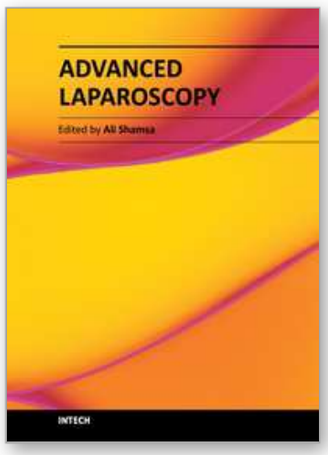
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The present book, published by InTech, has been written by a number of highly outstanding authors from all over the world. Every author provides information concerning treatment of different diseases based on his or her knowledge, experience and skills. The chapters are very useful and innovative. This book is not merely devoted to urology sciences. There are also clear results and conclusions on the treatment of many diseases, for example well-differentiated papillary mesothelioma. We should not forget nor neglect that laparoscopy is in use more extensively than before, and in the future new subjects such as use of laparascopy in treatment of kidney cysts, simple nephrectomy, pyeloplasty, donor nephrectomy and even robotic laparoscopy will be researched further.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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