Port Site Recurrence following Laparoscopic Surgery

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Abstract: Laparoscopic surgery has rapidly spread since 1990, and laparoscopic cholecystectomies are currently being employed in the majority of cholelithiasis cases. The range of laparoscopic surgery application has now been extended to gastric cancer, colorectal cancer and other abdominal malignancies. However, laparoscopic surgery has a high risk of cancer cell seeding and port site recurrence (PSR), and the safety of the procedure has yet to be clearly established. The currently proposed causes of PSR include cancer cell seeding through laparoscopic instruments or aerosolization, local immunological and metabolic effects of CO₂ gas and peritoneal effects of pneumoperitoneum. A number of animal experiments have been conducted to elucidate the mechanism of PSR. In contrast, there have been only a few investigations regarding preventive measures against PSR. The reports by other researchers who experienced PSR, the causes of PSR and preventive measures for PSR were reviewed. Furthermore, we demonstrated that peritoneal defects tend to increases the frequency of PSR and peritoneal dissemination and thereby physically covering the peritoneal defect may possibly be an effective method for reducing the incidence of PSR.

Key words: port site recurrences (PSR), Laparoscopic surgery, Laparoscopic cholecystectomy, Seprafilm™

Introduction

Laparoscopic surgery has made great advances in recent years. This surgical procedure has been proven to be effective for the treatment of various diseases. However, laparoscopic surgery applied for the radical resection of cancer poses a risk of cancer cell seeding and port site recurrence (PSR), and the safety of this procedure remains to be established. These risks are a great obstacle to the further development of laparoscopic surgery. A number of hypothetical mechanisms of PSR have been proposed, but none of them are completely persuasive. There have been only a few investigations on the preventive measures used to avoid PSR. This paper discusses the possible causes of PSR and its preventive measures together with our findings.

Current Status of PSR in Clinical

Laparoscopic cholecystectomy (LC) is the standard surgical procedure for benign gallbladder diseases such as cholelithiasis and cholecystitis, although, it is still a contraindication for advanced gallbladder cancer. However, there are cases of unsuspected gallbladder cancer, which are incidentally found
during or after LC. According to the results of a questionnaire conducted by the Japan Society for Endoscopic Surgery in 1998, the frequency of unexpected gallbladder cancers was 452 of 92,255 (0.5%) in patients who underwent LC. Such patients are exposed to a risk of PSR. Actually, the incidence of PSR in these patients has been reported to range from 14% to 29%.\textsuperscript{2-5} It is possible that the further spread of LC will thus lead to more frequent encounters with unsuspected gallbladder cancer and PSR.

The first case of PSR was reported by Yamakawa et al.\textsuperscript{6} in 1983. In this case, PSR occurred following cholecystoscopy in a patient with obstructive jaundice. In the 1990's, the number of case reports of PSR that occurred following laparoscopic cholecystectomy applied to unsuspected gallbladder carcinoma increased, and PSR thus began to attract attention (Table 1). The majority of those cases were diagnosed as gallstones or acute cholecystitis pre-operatively. At the time of diagnosis as unsuspected gallbladder cancer, 18.4% of the cases turned out to be early cancer in Tis or T1 stage and the other cases were advanced stage. This was because differentiation between severe cholecystitis and advanced gallbladder cancer is difficult. The site of recurrence was not always the port site from which the specimen was taken. Nineteen point six percent of the patients had recurrence in more than one port site. It has been reported that PSR were observed even in patients from whom specimens were taken with a surgical pouch. At the time of PSR discovery, 37.3% of patients had peritoneal metastases, and 62.7% had a single recurrence in port sites. The mean time to recurrence was 33 months (range: 15 days to 3 years and 11 months), and the majority of the cases had a poor prognosis. Some of the cases of early stage cancer had peritoneal dissemination and PSR. This phenomenon unlikely to occur after an open cholecystectomy.

As explained above, the majority of the patients with unsuspected gallbladder carcinoma were diagnosed erroneously as having gallbladder wall thickening secondary to cholelithiasis or cholecystitis and thus underwent LC. These findings suggest that laparoscopy, due to its special surgical procedures or techniques, promotes the development of peritoneal dissemination and PSR, even in cases of early stage cancer. Accordingly, not only the selection of a laparotomic surgical procedure on the basis of accurate pre-operative diagnosis but also measures taken for unsuspected gallbladder carcinoma noticed after a laparoscopic cholecystectomy have been attracting attention as critical issues for the further development of laparoscopic surgery.\textsuperscript{7,8}

**Causes of PSR**

During a laparotomy, metastases to incisional wounds are very rare. In contrast, the incidence of metastases to trocar-site wounds has been reported to be higher in laparoscopic surgery than in laparotomy.\textsuperscript{9-11} The mechanism of PSR in laparoscopic surgery is considered to be different from that of metastases to incisional wounds after laparotomy.

The proposed causes of PSR include cancer cell seeding through laparoscopic instruments or aerosolization, local immunological or metabolic effects of CO\textsubscript{2} gas and peritoneal effects of pneumoperitoneal pressure. In order to elucidate the mechanism, many researchers have conducted numerous animal experiments.

**Identification of Mechanism of PSR by Animal Experiments** (Table 2)

1. **Direct Contamination**

It is hypothesized in some reports that port sites are contaminated with cancer cells when a removed tumor is taken out via a small surgical wound or when laparoscopic instruments contaminated with tumor cells are put in and taken out of the surgical wound.

Hewett PJ et al.\textsuperscript{12} counted cancer cells attached to the filters placed at the ports and the laparoscope and clamps put in and taken out of the surgical wound. Hewett PJ et al.\textsuperscript{12} counted cancer cells attached to the filters placed at the ports and the laparoscope and clamps put in and taken out of the surgical wound in a pig pneumoperitoneum model. They found numerous cancer cells attached to those instruments and thus suggested the cause of PSR to be direct contamination of laparoscopic instruments...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Procedure</th>
<th>Original Stage</th>
<th>N. of implant</th>
<th>Interval</th>
<th>Follow-up</th>
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<td>36</td>
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<td>53</td>
<td>M</td>
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<td>LC</td>
<td>T3</td>
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<td>58</td>
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<td>58</td>
<td>F</td>
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<td>T3</td>
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<td>67</td>
<td>F</td>
<td>Gallstones</td>
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<td>T3</td>
<td>1 + C</td>
<td>&lt;1mo</td>
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<td>T3</td>
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<td>Tis</td>
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<td>Tis</td>
<td>1</td>
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<td>T3</td>
<td>2</td>
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<td>T3</td>
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<td>T1</td>
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<td>T3</td>
<td>1</td>
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<td>T2</td>
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<td>T2</td>
<td>1</td>
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<td>T2</td>
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<td>T3</td>
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<td>Tis</td>
<td>1 + C</td>
<td>9mo</td>
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<td>T3</td>
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<td>T3</td>
<td>1 + C</td>
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<td>T3</td>
<td>1 + C</td>
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<td>60</td>
<td>F</td>
<td>Gallstones</td>
<td>LC</td>
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<td>3 + C</td>
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<td>59</td>
<td>F</td>
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<td>1 + C</td>
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<td>F</td>
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<td>1 + A</td>
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<td>T2</td>
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<td>T1b</td>
<td>1 + C</td>
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<td>12m, died</td>
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<td>Gallstones</td>
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<td>T2</td>
<td>1 + C</td>
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</tr>
</tbody>
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Abbreviations: LC, Laparoscopic cholecystectomy; Bx, biopsy; —, not stated.
such as clamps with cancer cells. Thomas WM et al. verified this hypothesis in their in vitro experiment.

Allardyce R et al. and Hewett PJ et al. demonstrated a large number of cancer cells attached to instruments used for laparoscopic surgery or ports of which the instruments were put in and taken out after laparoscopic manipulation following intraperitoneal administration of radio-labeled cancer cells. Ishihara H and Wilkinson NW et al. compared the incidences of cancer cell implantation in incisional wounds and port sites of which the laparoscopic instruments were put in and taken out by video ports and then median incisions. All these experiments suggest that cancer cell implantation is clearly promoted by laparoscopic instruments.

2. Influence of Pneumoperitoneal Pressure

Some reports have suggested that PSR is influenced by CO₂ pneumoperitoneum and the difference in pneumoperitoneal pressure.

Watson DI and Mathew G et al. compared the incidence of cancer cell implantation to surgical wounds in CO₂ pneumoperitoneum, gasless laparoscopic surgery and laparotomy in a rat model. The incidence of cancer cell implantation was higher under CO₂ pneumoperitoneum in both reports. Bouvy ND et al. compared the incidences of cancer cell implantation to ports after gasless laparoscopy, CO₂ pneumoperitoneum and air pneumoperitoneum in rats with a renal capsule containing injected cancer cells and demonstrated high incidences of cancer cell implantation for both CO₂ and air pneumoperitoneum. Wittich Ph and Moreira H Jr. et al. demonstrated that the incidence of cancer cell implantation increases with increasing pneumoperitoneal pressure in animal models.

3. Aerosolization

In 1995, Kazemier G attributed the cause of PSR in all previously reported PSR cases to the "chimney effect" for the first time. Later, Hubens G et al. demonstrated in rat models that the incidence of cancer cell implantation was higher for pneumoperitoneum in combination with port insertion than for pneumoperitoneum only, and supported the theory of the "chimney effect." Similarly, Tseng LN et al. demonstrated that the incidence of cancer cell implantation increased in a model of pneumoperitoneum with air leakage in comparison to the control animals.

Champault G et al. placed a filter on each port before laparoscopic surgery in humans and examined cells collected on the filters. They reported that the collected cells included a large number of mesothelial cells and blood cells, and concluded that this finding suggests that PSR is attributable to cancer cell aerosolization.

However, there have been some reports against the theory of aerosolization. Whelan RL et al. demonstrated that there was no
difference in the number of cancer cells attached to the filter with and without pneumoperitoneum in both a rat model and an in vitro experiment with cultured cells and balloons.

4. Metabolic and Immunological Effects of Pneumoperitoneum

The induction of acidosis and increased intraperitoneal hyaluronic acid (HA) under CO₂ pneumoperitoneum have been suggested. Jacobi CA et al.²⁸ demonstrated in rat models that the incidence of cancer cell implantation was higher in pneumoperitoneum with CO₂ and helium than in pneumoperitoneum with CO₂ only, and suggested a possible causal relationship of the systemic effect of increased CO₂ in blood and acidosis to PSR.

Brundell S et al.²⁹ suggested that hematogenous spread is a possible mechanism in the development of PSR in rat models, which underwent laparoscopic insufflation followed by mammary adenocarcinoma cells into the internal jugular vein.

Yamaguchi K et al.³⁰ demonstrated that the intraperitoneal hyaluronic acid (HA) level increased by CO₂ pneumoperitoneum and that intraperitoneal HA administration increased the incidence of PSR in a murine model. HA is a high-molecular acid mucopolysaccharide consisting of a chain structure of N-acetylglucosamine and D-glucuronic acid. HA physiologically exists in the peritoneum. It is contained by mesothelial cells and combines cells with the extracellular matrix.³¹ HA plays a critical role in wound healing and angiogenesis³²,³³ which is believed to promote mesothelial healing in patients under peritoneal dialysis.³⁴ On the other hand, in recent years, HA has also been reported to occasionally enhance cancer cell motility to a slight degree through CD44 on the surface of cancer cells.³⁵,³⁶,³⁷

In contrast, cytokines such as TNF-α and IL-1 in serum have been reported to increase more in laparotomy than in CO₂ pneumoperitoneum and concerned with recurrence.³⁸,³⁹

5. Effects on Peritoneal and Mesothelial Injury

Some reports have also suggested the possibility that PSR results from cancer cell infiltration promoted by peritoneal injury due to port removal and peeling of peritoneal mesothelial cells.

Knolmayer TJ et al.⁴₀ intraperitoneally injected saline into a swine model after pneumoperitoneum and counted the epithelial cells in the saline collected later. They reported that the number of deciduous epithelial cells collected increased with increasing intraperitoneal pressure, thus suggesting more severe peritoneal injury with higher intraperitoneal pressure. Volz J et al.⁴¹ performed CO₂ pneumoperitoneum at 6 mmHg for 30 minutes and observed the peritoneum electron microscopically. They found impaired peritoneal mesothelial cells, which had partially peeled off and been replaced with infiltrating inflammatory cells, thus suggesting that mesothelial cells were damaged by pneumoperitoneum. Hirabayashi Y et al.⁴² examined the abdominal wall with the port sites under both light and scanning electron microscopy after intraperitoneal injection of gastric cancer cells and CO₂ pneumoperitoneum in a murine model. They reported that free cancer cells appear to attach themselves to the injured port sites immediately after CO₂ pneumoperitoneum, and such cells are associated with the development of PSR after laparoscopic surgery.

The authors previously showed that peritoneal injury increased the frequencies of port site metastasis and peritoneal dissemination. In addition, the healing period for the peritoneal injury (0-5 days post operation) demonstrates a high-risk for port site metastasis, and the frequency of port site metastasis has been shown to decrease if the injured peritoneum has been completely repaired (Table 3). It is believed that the disseminated cancer cells can come in contact with the injured peritoneum even after surgery and thus form metastatic lesions, leading to PSR.

Discussion of Clinical Cases

There have been a number of reports postulating that cancer cells were implanted when the gallbladder was pulled out of the peritoneum or via surgical instruments in
cases of advanced gallbladder carcinoma in the SE or SI stage, and this is highly likely. However, PSR has been reported even in patients with more superficial gallbladder carcinoma than that in the SS or intramucosal stage or in situ cancer. In a number of reports, the PSR in these cases is attributed to the dissemination of cancer cells in bile leaked due to intraoperative gallbladder perforation to the trocar sites, and all of these cases are related to laparoscopic manipulation: The diagnostic precision for carcinoma is lowered by indirect visual observation through TV monitors or by the use of cramps in palpation. Intrapерitoneal or incisional wound ligation is performed less accurately in laparoscopic surgery than in a laparotomy. PSR is thus attributable to surgical procedures of laparoscopic surgery.

However, the cases of PSR reported also include those in which recurrence was observed in port sites other than those used for gallbladder removal or in which PSR occurred despite the use of a bag for gallbladder removal. The types of recurrence vary, thus suggesting the possible involvement of local or systemic effects attributable to laparoscopic manipulation, and the used of special surgical procedures.

**Prevention of PSR**

The primary preventive measure for PSR is an accurate preoperative diagnosis. In particular, care should be exercised in patients with a gallbladder filled with gallstones or severe cholecystitis because it is difficult in those patients to make an accurate diagnosis of gallbladder cancer preoperatively. Accordingly, if gallbladder wall thickness and mass-like lesions are observed on the diagnostic imaging findings, then the possibility of cancer should be considered and a laparotomy should be selected instead of laparoscopic surgery depending on the age or course of the individual patients.

If the diagnosis of gallbladder cancer is unfortunately made intraoperatively, then preventive measures against PSR should be taken. In this case, the surgical procedure is often converted to laparotomy followed by intraperitoneal irrigation, the injection of anticancer drugs and port-site removal.

Some experiments for PSR prevention have been performed with animal models of laparoscopic surgery. Neuhaus SJ et al. reported that they decreased the incidence of PSR by the intraperitoneal injection of heparin. Eshraghi N et al. reported that the incidence of PSR decreased after port-site irrigation with an anticancer drug (5-FU).

Based on the thesis that PSR is attributable to peritoneal injury caused by ports, PSR prevention experiments were performed with sodium hyaluronate/carboxymethylcellulose film (Seprafilm™), whose preventive efficacy against postoperative adhesion after a laparotomy has been highly evaluated in recent years, in a nude mice model. As a
result, when the peritoneal injury at port sites was covered with Seprafilm, cancer cell fixation and infiltration were prevented until the injured peritoneum was repaired and cancer cell implantation to the port sites was remarkably prevented (Figure 1). Therefore, if Seprafilm could be placed on the injured peritoneum after laparoscopic surgery for such cancers as gallbladder cancer, it may reduce the frequency of PSR. However, some problems still exist in clinical application because it is difficult to introduce a sufficient sized Seprafilm into the peritoneal cavity through the trocar. It is therefore necessary to improve the technique for covering the peritoneum with Seprafilm laparoscopically.

In general, laparoscopic surgery is regarded as a surgical procedure that causes less injury to the peritoneum. It is characterized by the lack of any need to hold the intestine, less frequent insertion of foreign matter such as gauze, less blood loss and a highly maintained intraperitoneal humidity. Because of these characteristics, laparoscopic surgery is considered to be a more gentle surgical procedure than a laparotomy. However, it has the following disadvantages: Intraperitoneal irrigation is not sufficient and trocar-site wounds are left unclosed.

Based on the above factors, it is necessary to take the following measures to prevent

![Image](image.png)

**Fig. 1.** The protective effect of Seprafilm against PSR in a murine model.

The nude mouse model, which brings on PSR, was used to examine protection of PSR. A 2-cm median incision was made with surgical scissors and the port sites were created by an ear puncher which was used to penetrate the abdominal wall at four sites including the upper right, lower right, upper left and lower left sides. Only the skin of the penetration wounds was closed with 5.0 nylon, but no wound of the muscle or peritoneum was repaired. Seprafilm pieces measuring 10×15 mm in size were overlayed at two sites on the peritoneal defects of the right abdomen, and GBdj cells (a human gallbladder cancer cell line; 10⁶ cells) were injected into the abdominal cavity. The other two peritoneal defect sites on the left abdomen were used as a control without any treatment (Left side figure). All mice were sacrificed after seven days, and the abdominal wall with the port sites was excised. All wounds were examined macroscopically and microscopically, and the frequencies of implantation into the port site were evaluated at the following four grades: Grade 1: No tumor was observed; Grade 2: A small tumor was observed microscopically; Grade 3: A large tumor was observed microscopically; Grade 4: Tumor nodes were observed macroscopically.

As a result, Seprafilm group showed an effective protection against wound implantation than control group (Seprafilm group: ■, Control group: ○○○○ (Figure on the right)
PSR: 1) Avoid any unnecessary organ holding; 2) maintain the pneumoperitoneal pressure at as low a level as possible; 3) be careful not to allow any cancer cells to come in contact with ports by the use of a pouch during tumor removal; 4) irrigate the peritoneal cavity with adequate saline; 5) irrigate trocar-site wounds and reduce peritoneal injury by peritoneal repair; and 6) when a complication of gallbladder carcinoma is found, sufficient port-site and peritoneal irrigation should be performed while a re-operation including a partial hepatectomy should also be considered. In addition, port-site removal should be considered (Table 3).

Conclusions

Owing to the spread of laparoscopic cholecystectomies, the number of cases of gallbladder carcinoma diagnosed intra- or post-operatively is increasing. Due to advances in laparoscopic surgery, the frequency of laparoscopic surgery for gastrointestinal malignancies is also increasing. It is therefore important to identify the causes of PSR and develop effective measures to prevent it in order to enhance the further development of laparoscopic surgery.

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