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Prophylactic Strategy for Peritoneal Metastasis from Gastric Cancer

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Abstract

The prognosis of advanced gastric cancer patients with peritoneal metastasis is extremely poor.

We advocate extensive intraoperative peritoneal lavage (EIPL) as a useful and practical adjuvant surgical technique for gastric cancer patients who are likely to suffer from peritoneal recurrence.

In this article, we review the ability of EIPL to prevent peritoneal recurrence in patients with peritoneal free cancer cells, but not overt peritoneal metastasis (CY+/P-), and describe its potential as a prophylactic therapeutic strategy against peritoneal recurrence.

Introduction

Recently, the prognosis of advanced gastric cancer has improved markedly due to advances in surgical techniques and perioperative treatment, especially chemotherapy, including molecular targeted therapies. However, advanced gastric cancer patients with peritoneal metastases have an extremely poor prognosis [1-5].

The median survival time of patients with intraperitoneal free cancer cells without overt peritoneal metastasis (CY+/P-) is no more than 3-6 months [6-8]. In addition, there is no standard treatment for peritoneal metastasis from gastric cancer [9-12].

It has been established that peritoneal metastasis occurs due to the implantation of free cancer cells (derived from tumors involving the serosa) in the peritoneal cavity via adhesion to and invasion of the peritoneal surface. On the other hand, in CY+/P- the cancer cells have not yet become implanted on the peritoneal surface. We propose that there are marked differences between CY+/P- and peritoneal metastasis, and hence, these conditions require different management strategies.

We previously demonstrated that performing extensive intraoperative peritoneal lavage (EIPL) after curative surgery for advanced gastric or pancreatic cancer is a simple technique that helps to prevent peritoneal metastasis. Sometimes, we combine this technique with intraperitoneal chemotherapy (EIPL-IPC). This combined treatment significantly reduces the number of intraperitoneal free cancer cells and can sometimes completely eradicate them. Our prospective randomized control study demonstrated that this therapy significantly improved the survival rate of patients with CY+/P- advanced gastric cancer [13]. As we showed that this therapy was effective at reducing the number of free cancer cells in the abdominal cavity, we extended its indications to include advanced gastric cancer without CY+/P-.

In this article, we review the effectiveness of EIPL in terms of its ability to reduce the risk of peritoneal metastasis, and a treatment strategy for patients with advanced gastric cancer is proposed.

What is EIPL (Extensive Intraoperative Peritoneal Lavage) Therapy?

One of the principal causes of peritoneal metastasis is the seeding of free cancer cells (derived from a primary tumor) in the abdominal cavity. However, CY+/P- is different from peritoneal metastasis. For abdominal metastasis to occur, it is necessary for cancer cells to peel off from an advanced primary tumor and become attached and start proliferating on the peritoneal surface, which is called implantation. If we could reduce the number of free cancer cells in the abdominal cavity to zero, as is the case in the so-called "limiting dilution method", we could prevent abdominal metastasis.

On the basis of this strategy, we have demonstrated that EIPL and EIPL+IPC are effective intraoperative strategies for reducing the number of free cancer cells in the abdominal cavity [13].

In EIPL, the peritoneal cavity is extensively washed after curative surgery, and the peritoneal lavage fluid is stirred.

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Then, the fluid is completely aspirated. This process should be performed 10 times using 1 L of sterilized saline each time. Ten washes (1:10 dilution) result in just 1 in every 1010 cells in the abdominal cavity being cancerous (Figure 1). In addition, satisfactory stirring and washing of the abdominal cavity would remove any cancer cells that had the potential to adhere to the peritoneum.

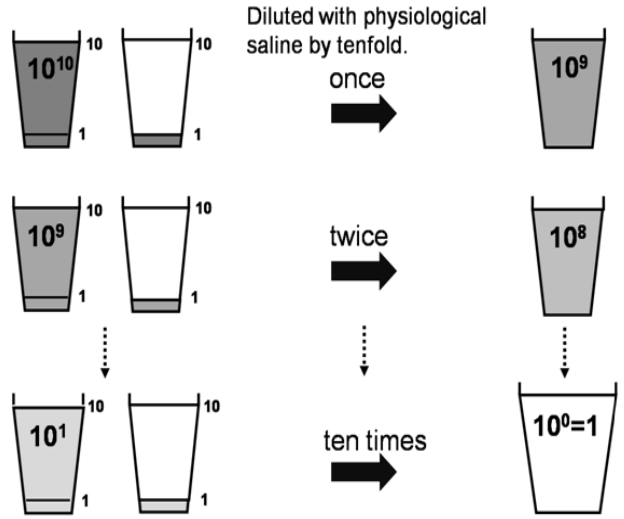

Figure 1: Changes in the numbers of intraperitoneal free cancer cells in five gastric cancer patients with CY+ that were treated with EIPL
The numbers of free cancer cells in 100-ml samples of lavage fluid collected using 1 L of saline were assessed using ultra-rapid RT-PCR. The free cancer cells were serially diluted with 8 L of saline and had disappeared from the lavage fluid after the 8th wash.

Clinical Evaluation of EIPL and EIPL-IPC Therapy

As a primary study, we performed EIPL in 5 patients with gastric cancer involving the serosa combined with CY+/P- and then examined the number of free cancer cells in the abdominal cavity using the ultra-rapid quantitative reverse transcription polymerase chain reaction (RT-PCR) protocol. Continuous stirring and washing of the abdominal cavity 6 to 8 times reduced the number of free cancer cells from 3.8 × 105 ± 1.4×105/100 ml to 2.8 ± 1.5/100 ml. In contrast, 2.8 × 104 ± 4.5×104/100 ml of free cancer cells remained after the abdominal cavity was washed three times using 1 L saline each time [14].

Based on the above pilot study, we developed EIPL-IPC therapy. In this treatment, cisplatin (CDDP) is infused into the abdominal cavity at a dose of 100 mg/body after the EIPL, and the solution is suctioned at 1 hour after its injection. Even if a few cancer cells remained in the abdominal cavity, they would be extremely unlikely to survive or disseminate [13].

To verify the effects of EIPL-IPC therapy on survival, we designed a prospective randomized multicenter trial examining the use of this therapy in advanced gastric cancer patients with CY+/P-. Eighty-eight advanced gastric cancer patients with CY+/P- were enrolled in this study and were allocated to three groups: the surgery alone group, surgery plus IPC group, and surgery plus EIPL and IPC (EIPL-IPC) group. The overall 5-year survival rate of the EIPL-IPC group was 43.8%, which was significantly higher than those of the IPC group (4.6%, *P < 0.0001*) and the surgery alone group (0%, *P < 0.0001*), as shown in Figure 2. Univariate and multivariate analyses demonstrated that of all of the examined factors EIPL had the greatest impact on survival. These results clearly demonstrated that EIPL-IPC therapy is effective [13].

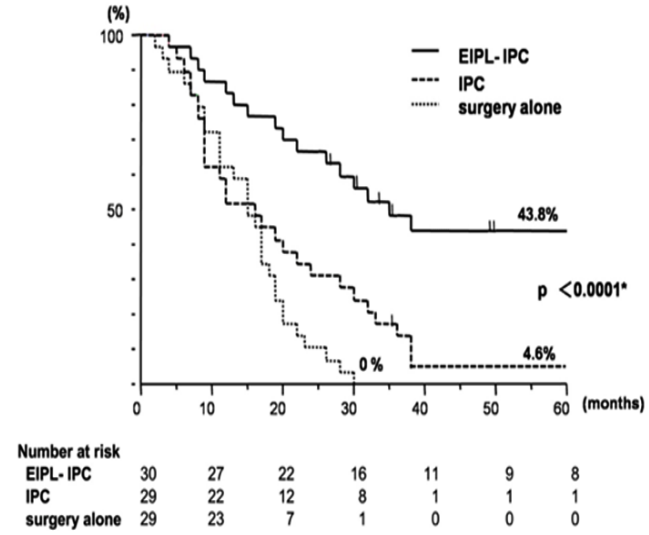

Figure 2: The survival curves for 88 patients stratified according to treatment *according to the log-rank test

Expanding Applications of EIPL

Even when no free cancer cells or overt peritoneal metastasis is detected in the abdominal cavity, half of patients with gastric cancer involving the serosa have been reported to develop peritoneal recurrence after curative surgery [15]. We studied the mechanisms responsible for peritoneal recurrence after curative surgery for gastric cancer that did not involve the serosa.

Peritoneal lavage samples were obtained from 63 patients with gastric cancer that did not involve the serosa just after laparotomy and after lymph node dissection, and the levels of carcinoembryonic antigen (CEA) and cytokeratin (CK) 20 mRNA in these samples were examined. CEA or CK20 mRNA was detected after lymph node dissection in 16 of 63 patients (25.4%), despite no CEA or CK20 mRNA being detected just after laparotomy. These molecules were not evident in patients with mucosal (M) tumors, but were detected in 3 (14.3%), 6 (46.2%), and 7 (53.8%) patients with tumors of the submucosa (SM), muscularis propria (MP), and subserosa (SS), respectively. These findings showed that free cancer cells were present in the peritoneal cavities of patients with gastric cancer that did not involve the serosa after lymph node dissection. Moreover, our previous study of 1272 gastric cancer patients revealed that 1/257 patients (0.4%) with tumors of the SM and 6/136 patients (4.4%) with tumors of the MP developed peritoneal recurrence after undergoing a potentially

curative resection [16]. These results suggest that lymph node dissection is a major factor in the spread of cancer cells into the peritoneal cavity. As patients with gastric cancer that does not involve the serosa should be at low risk of metastasis, EIPL can be used to prevent peritoneal recurrence after curative surgery.

We performed EIPL in patients with advanced pancreatic cancer, in which peritoneal recurrence often occurs and has a high mortality rate [17]. EIPL was applied to 15 of 39 consecutive patients with pancreatic cancer who underwent curative surgery. The peritoneal recurrence rate of the EIPL group was significantly lower than that of the non-EIPL group (6.7% vs. 45.8%, p = 0.013), and EIPL was found to be an independent negative risk factor for peritoneal recurrence. On the basis of these findings, EIPL is considered to be applicable to various types of abdominal cancer that involve seeding in the abdominal cavity.

Prospects for EIPL in the Future

Peritoneal metastasis often arises in patients with advanced gastric cancer, even after curative resection, and it is considered to be a life-threatening condition. Patients with gastric cancer combined with CY+/P- are classified as having stage IV disease, and their 5-year survival rates range from 0-35% [18]. Once peritoneal metastasis forms, it is difficult to eradicate. Although many researchers have attempted to find a cure for this obstinate disease, they have not yet been successful. For this reason, we propose that more effective treatments that can be administered before peritoneal metastasis develops are needed.

CY+/P- denote that metastatic cells have not yet become implanted on the peritoneal surface. We hypothesize there might be marked differences between CY+/P- and peritoneal metastasis, and hence, that these conditions require different management strategies. Accordingly, it is considered reasonable to focus on devising effective intraoperative techniques for preventing peritoneal recurrence that can be used in combination with appropriate radical resection. Practically, radical resection combined with D2 lymph node dissection appears to be feasible and safe [19-21]. The curative resection of gastric cancer together with a sufficient resection margin and the removal of metastatic lymph nodes is the only treatment that can cure gastric cancer [1,22]. Therefore, advanced gastric cancer should be treated with radical resection, even if it is accompanied by CY+/P- because our novel EIPL-IPC regimen is able to eradicate CY+. In a small retrospective study, we reported that CY+ is not a prognostic factor for advanced gastric cancer patients with CY+/P- that are treated with EIPL [23]. These results suggest that EIPL might have a down-staging effect on the category of CY+/P- gastric cancer from IV to III.

On the basis of our experience in a series of studies and clinical observations, we have decided that EIPL should be applied not only to CY+/P- gastric cancer, but also to other types of CY- advanced gastric cancer, as it might prevent lymphatic invasion and the development of peritoneal metastasis.

Proposal for a Practical Therapeutic Strategy for Gastric Cancer

Based on the findings described in our review, we propose the following treatment protocol for gastric cancer (Figure 3). A correct diagnosis of mucosal or submucosal cancer can be made macroscopically using endoscopic ultrasonography (correct diagnosis rate: 75-80%). All mucosal lesions without ulceration (UL) should be treated with endoscopic submucosal dissection (ESD). If a pathological examination of the ESD specimen shows that a complete resection has been achieved, the patient only needs to undergo follow-up. However, if the pathological examination shows that the resection was incomplete, laparoscopic partial resection will be required. For mucosal tumors with ulceration (UL+), laparoscopic gastrectomy with D1 lymph node dissection is indicated. All macroscopic tumors of the SM and other types of advanced gastric cancer, including tumors of the MP, SS, SE and SI, should be treated with standard gastrectomy combined with lymph node D2 dissection. Standard gastrectomy combined with D2 lymph node dissection appears to be feasible and safe. The complete resection of gastric cancer together with a sufficient resection margin and the removal of metastatic lymph nodes is the only treatment that is able to cure gastric cancer.

From the viewpoint of a prophylactic strategy against peritoneal recurrence, the findings presented in this review greatly transform the surgical treatment for gastric cancer, including tumors that do not involve the serosa [24]. We strongly advocate the adoption of the treatment protocol for gastric cancer shown in Figure 3.

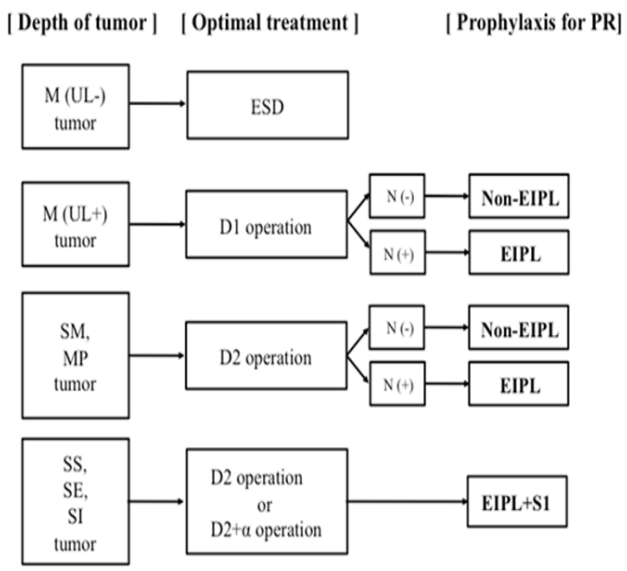

Figure 3: A practical treatment protocol for gastric cancer
PR: Peritoneal recurrence; M: Mucosal tumors; SM: Submucosal tumors; MP: Tumors exhibiting invasion into the Muscularis Propria; SS: tumors displaying Subserosal Invasion; SE: tumors demonstrating Serosal Invasion; SI: tumor invasion of adjacent structures; UL+: tumors with ulceration or Ulceration Scars; UL-: tumors without ulceration or ulceration scars; ESD: Endoscopic Submucosal Dissection; D1 operation: gastrectomy combined with the dissection of the group 1 lymph nodes; D2 operation: gastrectomy combined with the dissection of the group 1 and 2 lymph nodes; N(+): surgery-induced lymph node metastasis; N(-): no evidence of lymph node metastasis; EIPL: Extensive Intraoperative Peritoneal Lavage

The use of our novel EIPL technique after adequate tumor resection and lymph node dissection could make an extremely important contribution to the survival of patients with advanced gastric cancer that are at high risk of peritoneal recurrence, including serosal invasion and lymph node metastasis. Our innovative EIPL method is very practical, and its theoretical basis creates high expectations regarding its cytoreductive effects. In addition, EIPL is simple and inexpensive, does not take very long, is not restricted to a particular place or time, and does not require any special techniques or devices. Furthermore, even if a few cancer cells were to remain after EIPL they would be unlikely to survive or disseminate due to the effects of postoperative systemic chemotherapy with S1.

Many investigators have used immunological methods involving selected monoclonal antibodies or real-time RT-PCR to detect free cancer cells in peritoneal lavage fluid during cytological examinations; however, these techniques are not generally available at the time of surgery [24]. Despite this, cytological examinations are still commonly used to detect the existence of free cancer cells in the peritoneal cavity. From these points of view, it is only prudent that EIPL should be performed in all patients with gastric cancer involving the serosa, regardless of the presence/absence of CY+/P-.

On the other hand, although curative surgery has been used to treat patients with gastric cancer that does not involve the serosa, some die of peritoneal recurrence. We previously reported that free cancer cells were found in the lavage fluid collected after lymph node dissection in 26.7% of patients with tumors involving muscle tissue, suggesting that the surgery itself caused the peritoneal dissemination of cancer cells. Therefore, EIPL is also strongly recommended for cases of gastric carcinoma that do not involve the serosa On the other hand, although curative surgery has been used to treat patients with gastric cancer that does not involve the serosa, some die of peritoneal recurrence. We previously reported that free cancer cells were found in the lavage fluid collected after lymph node dissection in 26.7% of patients with tumors involving muscle tissue, suggesting that the surgery itself caused the peritoneal dissemination of cancer cells. Therefore, EIPL is also strongly recommended for cases of gastric carcinoma that do not involve the serosa (including early stage gastric carcinoma), but in which surgery-induced lymphatic invasion is suspected to have occurred or a positive result is obtained during a cytological examination performed after D2 lymph node dissection (Figure 3).

Conclusion

We reviewed clinical studies concerning EIPL, which demonstrated the ability of this technique to improve the survival of gastric cancer patients with peritoneal free cancer cells. These findings convinced us to recommend EIPL as the optimal treatment for gastric cancer patients who are likely to suffer from peritoneal metastasis, which is a life-threatening disease. It is our earnest wish that many surgeons around the world will adopt EIPL as a prophylactic strategy for peritoneal metastasis.

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