EDITORIAL OPEN ACCESS

Can the peritoneal recurrence be prevented after curative surgery?

Shinya Shimada, Masafumi Kuramoto, Takashi Marutsuka, Satoshi Ikeshima, Kenichiro Yamamoto, Hideo Baba

Although advances in diagnosis and surgical techniques have improved the conditions of patients with gastric cancer, peritoneal recurrence is still the most frequent cause of death, and the prognosis of patients with peritoneal metastasis of gastric cancer is extremely poor [1, 2]. In patients with pancreatic cancer, besides, one of the major features is its early peritoneal recurrence as well as liver metastasis after curative surgical treatment [3].

The most likely cause of peritoneal recurrence in patients with serosa-invasive gastric cancer is the presence of intra-peritoneal free cancer cells from the serosal surface of the primary cancer and their implantation on the peritoneum. Furthermore, it has been proved that lymph node dissection opened the lymphatic channel and spread viable cancer cells into the peritoneal cavity, using CEA and CK20 specific ultra-rapid quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) in combination with an automated mRNA extractor [4]. This CEA and CK20 specific RT-PCR study demonstrated that free cancer cells were found in 0.0%, 14.3% and 26.7% of the lavage fluid after lymph node dissection from patients with mucosal (M), sub mucosal (SM) and muscularis propria (MP) tumors, respectively, and that the number of free cancer cells, calculated by the standard, were 0.0 (M), 3.5±3.7 (SM, mean ± SD) and 12.1 ± 9.6 (MP) cells per 100 ml in the lavage. Yu et al. [5] also verified that lymphadenectomy can disseminate cancer cells into the cavity which leads to increased risk of peritoneal recurrence using cytological analysis by smearing and immunohistochemistry. These data could explain the main cause of the peritoneal recurrence after curative surgery for patients with non serosa-invasive gastric cancer. Consequently, it is very important to prevent peritoneal metastasis prior to the fixation and progression of free cancer cells to the peritoneum.

We have developed a powerful method for reducing the number of free cancer cells in peritoneal cavity to potentially zero, based on the law of "limiting dilution", namely EIPL (Extensive Intraoperative Peritoneal Lavage) [4, 6, 7]. The EIPL is a very simple, little time-consuming, inexpensive and practical intra-operative technique. This therapy can easily be performed anywhere and anytime, and it does not require any special techniques or devices. After the potentially curative operation, the peritoneal cavity was extensively shaken and washed, which was then followed by the complete aspiration of the fluid. This procedure was done 10 times using 1 liter of physiological saline. For example, ten washes of a 1:10 dilution resulted in just one cancerous cell from 10^{10} cells in the container based on the 'limiting dilution theory'. Furthermore, sufficient shaking and washing of the peritoneal cavity could remove the cancer cells which merely adhere to the peritoneum. Actually, the effectiveness of the EIPL has been confirmed in patients with peritoneal cytology-positive free cancer cells without macroscopic peritoneal dissemination (CY1/P0) by the ultra-rapid quantitative RT-PCR, that is, sequential washing of intraperitoneal free cancer cells of $3.8 \times 10^5 \pm 1.4 \times 10^5$/100 ml of lavage decreased the number to 2.8 ± 1.5 cells by 6 to 8 washes. Free cancer cells were not detected in washing fluid after that.

Our prospective randomized controlled clinical trial clearly revealed that EIPL therapy significantly improved

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the five-year survival rate of advanced gastric patients with CY1/P0 [7]. Briefly, a total of 88 gastric cancer cases with CY1/P0 from 1522 patients with advanced gastric cancer at multicenter were enrolled in this study, and were randomly allocated to three groups: surgery alone group, surgery plus intra-peritoneal chemotherapy (IPC) group, and surgery plus EIPL and IPC (EIPL-IPC) group. In EIPL-IPC group, 100 mg of cisplatin (CDDP) was administered into the peritoneal cavity after the EIPL treatment. The overall five-year survival rate of the patients with EIPL-IPC was 43.8%, and this data was significantly higher than that of the IPC group (4.6%, $p < 0.0001$) and the surgery alone group (0 %, $p < 0.0001$). Among various recurrent patterns, the EIPL-IPC group had a significantly lower incidence of peritoneal recurrence than either of the other groups ($p < 0.0001$). Univariate and multivariate analyses clearly revealed that EIPL was the most significant impact factor. In addition, based on 39 consecutive patients with invasive ductal adenocarcinoma of the pancreas who underwent curative surgical treatment, peritoneal, hepatic, lymphatic, local, and extra-abdominal recurrent rates in EIPL and non-EIPL groups were 6.7%, 40.0%, 26.7%, 13.3%, 13.3%, and 45.8%, 50.0%, 20.8%, 29.2%, and 20.8%, respectively. Among these recurrent patterns, peritoneal recurrent rate of EIPL group were significantly lower than those of non-EIPL ($p = 0.013$) [8].

Finally, exploring the innovative EIPL method as a prophylactic strategy for peritoneal recurrence after curative operation, in Asian and non-Asian countries, phase II and phase III studies were planned [9, 10]. Especially, Japanese CCOG 1102 phase III study [10]; a total of 300 patients will be accrued from 20 institutions, has registered from November 2013. The promising EIPL results will be validated in such larger multi-institutional prospective randomized trials.

Keywords: Cancer cells, Lymph node dissection, Lymphadenectomy, Peritoneal metastasis, Peritoneal recurrence

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Author Contributions

Shinya Shimada – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Masafumi Kuramoto – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Takashi Marutsuka – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
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Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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