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Establishment of the Standard Prophylactic Strategy for Peritoneal Recurrence and Proposal of the Optimal Therapeutic Protocol for Gastric Cancer

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1. Introduction

Advances in diagnosis and surgical techniques have improved the conditions of patients with gastric cancer. Peritoneal dissemination, however, is still the most frequent cause of death, and the prognosis of patients with peritoneal metastasis of gastric cancer is extremely poor (Balfour, 1973; Hioki et al.,2010; Maruyama, 1987; Makino et al., 2010; M. Yamamoto et al., 2009). In patients with serosal invasion, about half develop peritoneal recurrence and die from the disease within the first 2 years of follow-up, even if curative resection is performed (Abe et al., 1995; Ikeguchi et al., 1994; Kaibara et al., 1987; Moriguchi et al., 1992; Ribero et al., 1998). Furthermore, it has been reported that the survival span of the patients with cytology-positive peritoneal lavage fluid and without the macroscopic peritoneal dissemination (CY+/P-) of gastric cancer was almost the same as that of patients with P+ (Boku, et al., 1990; Shimada et al., 2003), and the 5-year survival rate of patients with CY+/P- is only 2% (Bando et al., 1999). Accordingly, the treatment recommendations for gastric cancer in the event of positive cytology range from palliative chemotherapy to attempts at neo-adjuvant therapies followed by surgical resection. However, the results of published randomized clinical trials of adjuvant perioperative intra-peritoneal chemotherapy have not fully demonstrated any significant improvement in survival as compared with surgery alone, especially in the cases with P+ (Cunliffe & Sugarbaker, 1989; Cheong et al., 2007; Hagiwara et al., 1992; Ikeguchi et al., 2005; Kunisaki et al., 2002; Sauter et al., 1994). Therefore, a reliable and appropriate standard prophylactic regimen for peritoneal recurrence in patients with gastric cancer needs be established.

Clinical and pathologic factors that have been found to correlate with the presence of positive cytology are usually at an advanced stage of the disease (Burke et al., 1998; Iitsuka et al., 1979; Koga et al., 1984; Ribeiro et al.,2006; Yawata et al.,1998). The most likely cause is the presence of intra-peritoneal free cancer cells from the serosal surface of the primary cancer and their implantation on the peritoneum. Furthermore, our previous study proved

that lymph node dissection opened the lymphatic channel and spread viable cancer cells into the peritoneal cavity (Marutsuka et al., 2003). This could explain the main reason for the peritoneal recurrence after curative surgery for patients with non serosa-invasive gastric cancer.

Peritoneal dissemination is probably completed by the implantation of peritoneal free cancer cells exfoliated from serosa-invasive tumors. Consequently, it is very important to prevent peritoneal metastasis prior to the fixation and progression of free cancer cells to the peritoneum in patients with advanced gastric cancer. This is because the presence of intra-peritoneal free cancer cells without macroscopic dissemination could possibly indicate a condition wherein the implantation of cancer cells on the intra-peritoneal wall has not yet occurred.

Based on this assumption, we have been advocating the adoption of 'extensive intra-operative peritoneal lavage' (EIPL) (Shimada et al., 2002; K. Yamamoto et al., 2005) as a reliable and practical intra-operative technique as an adjuvant therapy for preventing the implantation of cancer cells on the intra-peritoneal wall after a potentially curative resection combined with intra-peritoneal chemotherapy (EIPL-IPC). EIPL is very simple and can be performed anywhere and at anytime. It is a rather efficient method for reducing the number of intra-peritoneal free cancer cells to zero potentially, when the cancer cells are analyzed by a detection system using real-time reverse transcriptase-polymerase chain reaction (RT-PCR), and intra-peritoneal chemotherapy subsequent to EIPL could be effective for eradicating the remaining cancer cells. We have confirmed the clinical effectiveness of EIPL by ultra-rapid quantitative RT-PCR protocol (Marutsuka et al., 2003). Very few intra-peritoneal free cancer cells could be detected in the washing fluid after 6 to 8 washes. Finally, our recent prospective randomized controlled clinical trial clearly revealed that EIPL therapy significantly improved the 5-year survival rate of advanced gastric patients with intra-peritoneal free cancer cells (Kuramoto et al., 2009).

In this manuscript, the risk factors on peritoneal recurrence from clinicopathological features of gastric carcinoma and the contribution of EIPL method to the remarkable improvement in the 5-year survival for patients with CY+/P- on clinical trials is reviewed, and the optimal treatment protocol for patients with gastric cancer is proposed.

2. Clinicopathological features and risk factors on peritoneal recurrence for gastric carcinoma

Results of specific preoperative studies, intraoperative findings, postoperative pathologic staging, clinical management, and follow-up data from 2117 patients underwent gastric resection with D2 lymph nodes dissection for primary gastric carcinoma were registered prospectively (Shimada S, et al.). Preoperative diagnosis was made on the basis of endoscopic, radiologic, and endoscopic ultrasonographic (EUS) (Kida et al., 1998) findings. Pathologic diagnosis and classifications were based on the Japanese Classification of Gastric Carcinoma by the Japanese Research Society for Gastric Cancer (Japanese Research Society for Gastric Cancer, 1999).

The incidences of lymph node metastasis from tumors with mucosal (M), submucosal (SM), and advanced gastric cancer were 2.5%, 20.2%, and 71.2%, respectively. The detailed pathological analysis revealed that all M tumors with lymph node metastasis (n=14) had ulceration or ulceration scar (UL+) in the lesions even if the lesion was smaller than 1.5 cm in diameter. On the other hand, no M tumor without ulceration or ulceration scar (UL-)

(n=328) had any lymph node metastasis. In advanced gastric cancer, approximately 57% of the metastatic tumors had distant lymph nodes metastasis. Serosal invasion was also popular in advanced gastric cancer; approximately 50% of the advanced tumors had serosal invasion.

Fig 1 showed cancer-specific 5-year survival rates of gastric cancer according to the tumor depth. Gastric resection with D2 lymph nodes dissection for primary gastric carcinoma yielded good prognosis in M and SM tumors; 98% and 95% of the cancer-specific 5-year survival rates, respectively. There were no apparent prognostic factors in patients with M tumors. In patients with SM tumors, the cancer-specific 5-year survival of those with lymph node metastasis was significantly lower than that of those without such metastasis (77.6% vs 98.2%; $P < 0.001$). An sharp decrease in survival was seen between patients with two positive nodes and those with three positive nodes, and the cancer-specific 5-year survival rate of patients with three or more metastatic lymph nodes was significantly lower than that of those with one or two nodes ($P = 0.041$). Multivariate analyses revealed that the involvement of three or more lymph nodes was the sole independent prognostic determinant ($P = 0.016$); the level of nodal metastasis was not an independent prognostic factor ($P = 0.384$). In advanced gastric cancer, serosal invasion was the strong prognostic factor as well as the factor of more than three lymph nodes metastasis. These results suggest that gastric cancer patients with lymph nodes metastasis and serosal invasion should be given special weight of additional therapy after surgery (Fig. 1).

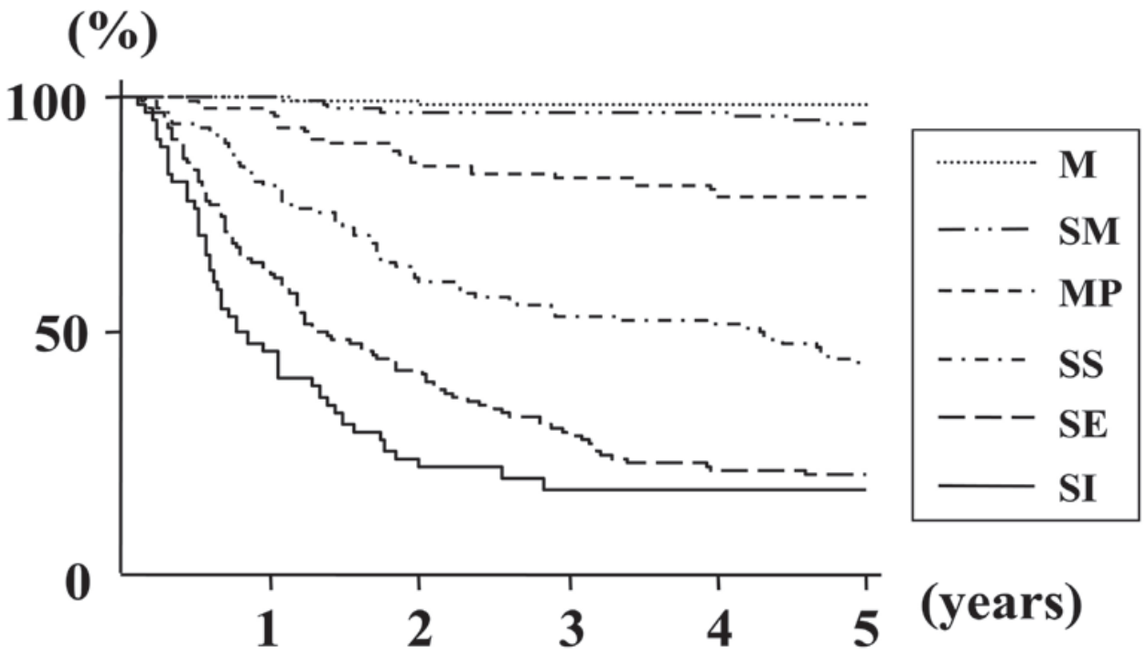

Fig. 1. Cancer-specific 5-year survival rates of gastric cancer according to the tumor depth. M: mucosal tumor, SM: submucosal tumor, MP: tumor with muscularis proprial invasion, SS: tumor with subserosal invasion, SE: tumor with serosal invasion, SI: tumor invasion of adjacent structures (Shimada et al., 2003)

3. Real-time detection system for Intra-peritoneal free cancer cells

An ultra-rapid quantitative RT-PCR protocol, which is a combined system of an ultra-rapid RT-PCR, using a fully automated mRNA extractor and a real-time one-step RT-PCR system with a hybridization probe format, has been established to diagnose intra-peritoneal cancer cells spread during a surgical operation (Marutsuka et al., 2003). This new method enabled us to obtain the results of RT-PCR within approximately 70 minutes after sampling. Furthermore, we carried out multiple-marker RT-PCR assays in a combination of carcinoembryonic antigen (CEA) and cytokeratin 20 (CK20) to eliminate false positive results and to improve specificity. This assay system was able to detect at least 10 cancer cells in 1×10^7 of leukocytes, indicating comparable sensitivity to conventional nested-RT-PCR. Accordingly, the accurate diagnosis of the spread of intra-peritoneal cancer cells was done during the actual operation (Fig. 2).

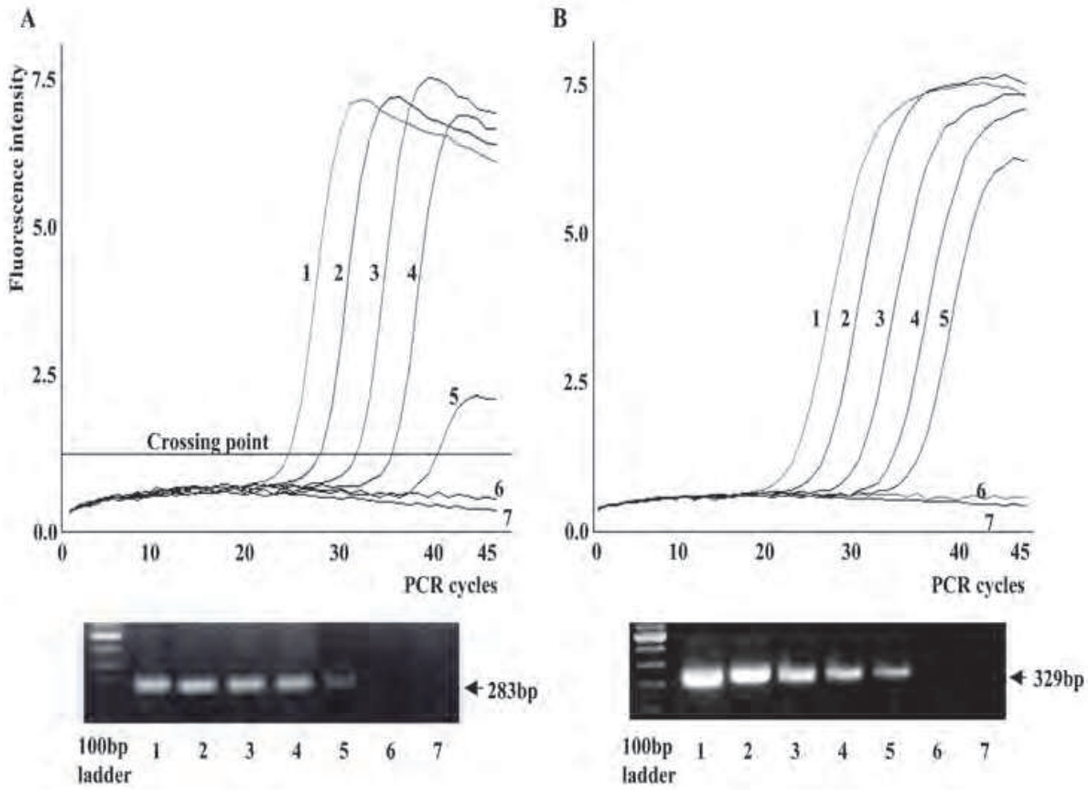

Fig. 2. Sensitivity of ultra-rapid quantitative RT-PCR assay by LightCycler™ using CEA (A) and CK20 (B) mRNA marker. Curves and lanes 1-5 were serially diluted 10^5 cells to 10^1 cells of WiDr colon carcinoma cell in 10^7 leukocytes from healthy volunteer, respectively; curve and lane 6: 10^7 leukocytes from healthy volunteer; curve and lane 7: no template. This assay system could detect at least 10 WiDr colon carcinoma cells in 10^7 leukocytes. The PCR products were analyzed by 2% agarose gel electrophresis, and they were matched to the expected sizes of CEA and CK20. 'Crossing points' were used to establish an external standard curve for quantification. Forty-five rounds of amplification were completed within 30min. (Marutsuka et al., 2003)

4. Mechanisms of peritoneal recurrence after operation for non-serosa-invasive gastric cancer

Even though curative surgery has been performed for patients with non- serosa-invasive gastric cancer, some patients die of peritoneal recurrence (Abe et al., 1995; Bozzetti et al., 1986; Fink & Longmire, 1991; Shimada et al., 2001a; Yoo et al., 2000). As shown in Table 1, even in patients with early gastric cancer, three out of 420 died of peritoneal recurrence.

	Mucosal tumor	Submucosal tumor
No. of patients	621	430
Lymph node metastasis (%)	14 (2.3)	84 (19.5)
Cancer death (5-year survival rate: %)	6 (99.0)	26 (94.0)
Recurrence		
Hematogenous	6	19
Lymphatic	0	4
Peritoneal	0	3

Table 1. Lymph node metastasis and cancer death in early gastric carcinoma treated by D2 gastrectomy

Our investigations based on the intraoperative ultra-rapid RT-PCR system elucidated the cause (Marutsuka et al., 2003). Peritoneal lavage samples from 63 patients with non-serosa-invasive gastric carcinoma were obtained at laparotomy and immediately after lymph node dissection. To identify the free cancer cells in the samples, CEA and CK20 specific RT-PCR were performed using LightCycler™ method in combination with an automated mRNA extractor. In the peritoneal lavage samples from non-serosa-invasive cases after lymph node dissection, a CEA mRNA product was detected in 15 of 63 patients (23.8%) (Fig. 3). This was not evident in the mucosal (M) tumors, but was identified in three (14.3%), five (33.3%), and seven (53.8%) patients with submucosal (SM), muscularis propria (MP), and subserosal (SS) tumor, respectively. As regards CK20 mRNA, the product was identified in 14 of 63 patients (22.2%). Just like CEA mRNA, CK20 mRNA was not detected in the mucosal tumors, but was identified in three (14.3%), five (33.3%), and six patients (46.2%) with SM, MP, and SS tumor, respectively. Both CEA mRNA and CK20 mRNA were detected in three (14.3%), four (26.7%), and six (46.2%) with SM, MP, and SS tumor, respectively. In consequence, the number of free cancer cells, calculated by the standard curve for cancerous cells, were 3.5 ± 3.7 (mean ± SD), 12.1 ± 9.6, and 124.8 ± 224.0 cells/100ml in the lavage after lymph node dissection from SM, MP, and SS tumor, respectively.

This study using the intraoperative ultra-rapid RT-PCR system revealed that free cancer cells were found in 14.3% and 26.7% of the lavage fluid after lymph node dissection from patients with SM and MP tumors, respectively. Statistical analysis demonstrated that lymph node metastasis was the independent predictor for the existence of intra-peritoneal free cancer cells after lymph node dissection.

From our previous study on 1272 cases of gastric carcinoma, 1/257 cases (0.4%) of SM and 6/136 cases (4.4%) of MP cases developed peritoneal metastasis after potentially curative operation (Shimada et al., 2001a, 2003). Among them, 86% of the patients had lymph node metastasis and/or lymphatic invasion. Our results determined that lymph node dissection is the main factor for spreading viable free cancer cells into the peritoneal cavity. Thus, it was proved that lymph node dissection opens the lymphatic channel and spreads viable cancer cells into the peritoneal cavity.

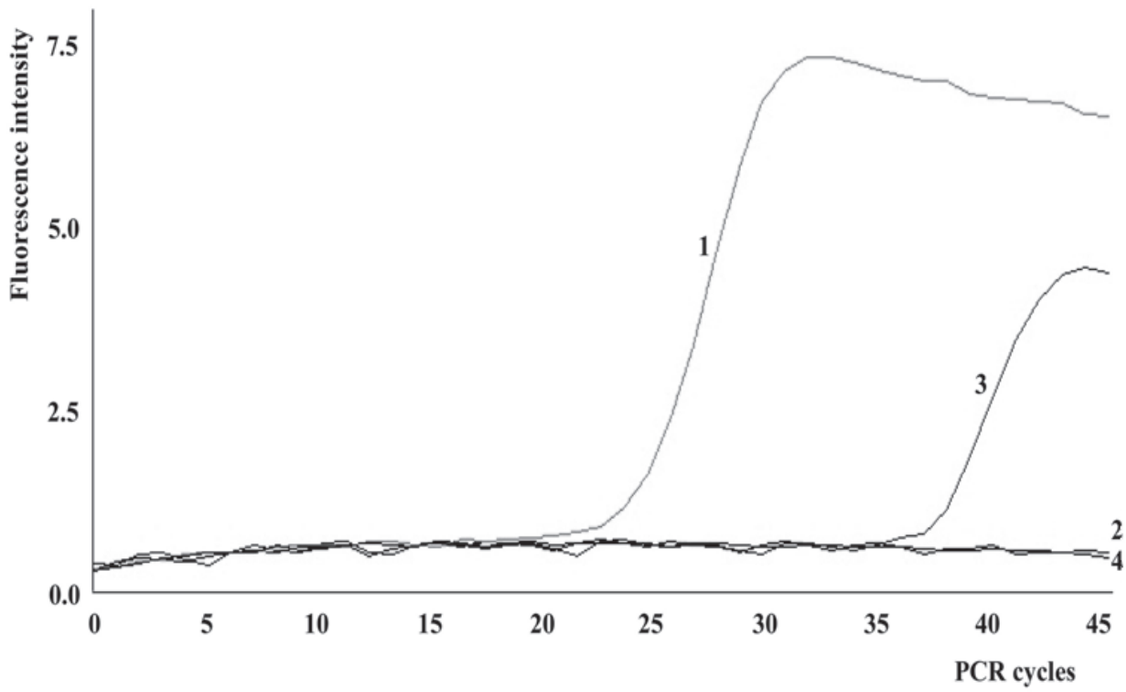

Fig. 3. Representative results of ultra-rapid RT-PCR by LightCycler™ in a patient with SM tumor of well-differentiated adenocarcinoma with lymph node metastasis and lymphatic invasion. Curve 1: WiDr colon cancer cells as positive control; curve 2: intraperitoneal lavage sample at laparotomy; curve 3: intraperitoneal lavage sample immediately after lymph nodes dissection; curve 4: no template as negative control. (Marutsuka et al., 2003)

5. EIPL therapy

To date, there are no definitive effective therapies for peritoneal carcinomatosis. Therefore, attention has been paid to detecting peritoneal free cancer cells in patients with advanced gastric carcinoma without overt peritoneal metastasis, and attempts to prevent peritoneal metastasis (S. Fujimoto et al.,1999; T. Fujimoto et al., 2002; Hamazoe et al., 1994; Hayes et al., 1999; Rosen et al, 1998; C.C. Wu et al., 1997, Yonemura et al., 1995; Yu et al., 1998).

The status of CY+/P- includes the condition where peritoneal implantation has not occurred yet. We have proposed that EIPL is a quite formidable method for reducing the number of cells to potentially zero, just like the so-called 'limiting dilution' approach. EIPL was performed in five cases of serosa-invasive (SE) gastric carcinoma with CY+/P-, and its efficacy was evaluated by the ultra-rapid quantitative RT-PCR protocol (Shimada et al., 2002). Sequential washing of intra-peritoneal free cancer cells of $3.8 \times 10^5 \pm 1.4 \times 10^5$/100ml of lavage decreased the number to 2.8 ± 1.5 cells by 6 to 8 washes. Free cancer cells were not detected in the washing fluid after that (Fig. 4).

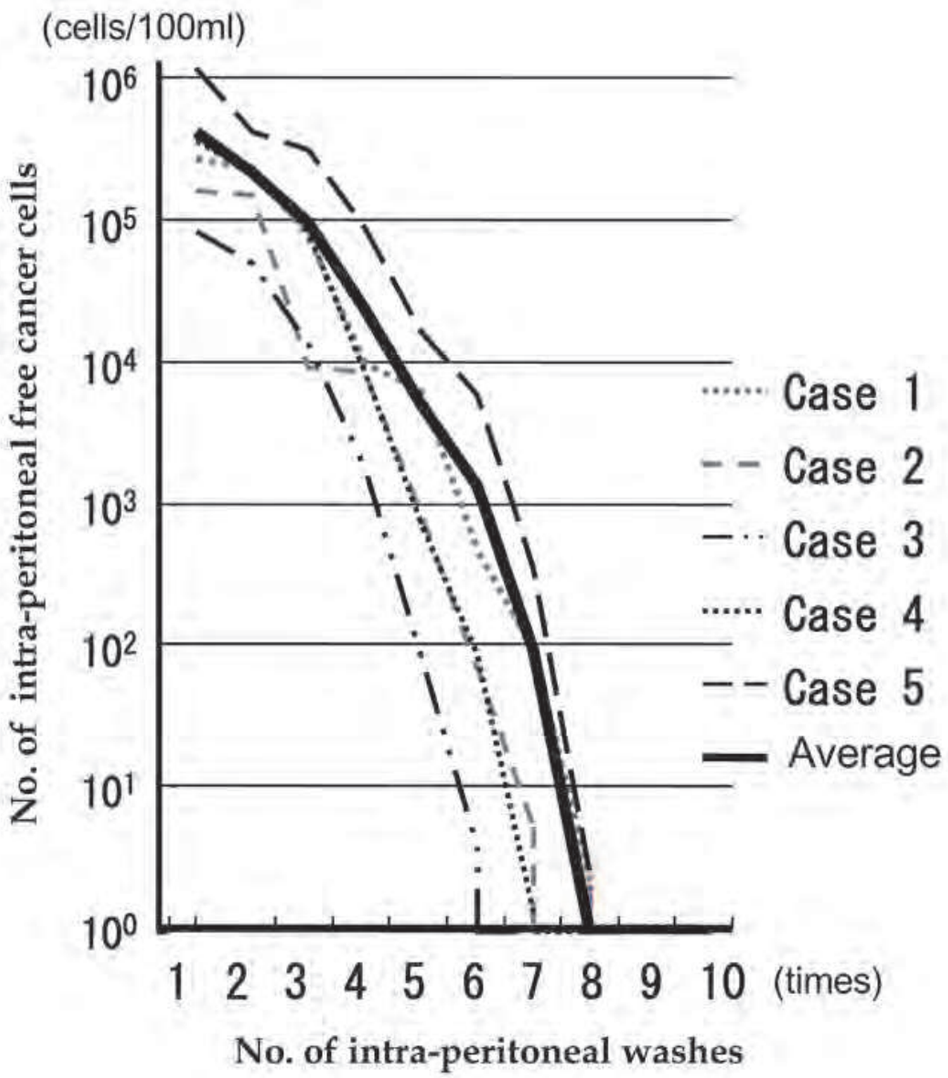

Fig. 4. Changes in numbers of intra-peritoneal free cancer cells in five gastric cancer patients with CY+ treated by EIPL therapy. The numbers of free cancer cells in 100 ml of samples from the first to the 10th wash using each 1 litter of saline were quantitated by ultra-rapid RT-PCR. The free cancer cells in the lavage fluids were serially diluted by 8 litters of saline and disappeared in washing fluids after the 8th wash.

On the other hand, $2.8 \times 10^4 \pm 4.5 \times 10^4$ of intra-peritoneal free cancer cells still remained in 100ml of the lavage when not treated with EIPL. Our preliminary subset analysis based on 24 consecutive patients with CY+/P- who underwent curative surgical treatment for advanced gastric cancer, and were followed up for 2 years or until death, has shown a statistically significant ($P = 0.017$) improvement of a two-year survival rate when treated with EIPL as compared with when not treated with EIPL (Shimada et al., 2002).

6. Five-year survival rates of patients who had EIPL therapy through a prospective randomized clinical trial

Following a pioneering study (Shimada et al., 2002; K. Yamamoto et al., 2005), we performed the EIPL therapy for advanced gastric cancer patients with CY+/P- in order to clearly clarify the distinct 5-year survival effects through a prospective randomized multicenter trial (Kuramoto et al., 2009). A total of 88 gastric cancer cases with CY+/P- 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, 100mg of cisplatin (CDDP) was administered into the peritoneal cavity, after the EIPL treatment. Peritoneal lavage for the surgery alone group and the IPC group was done with 3 liters (1 liter, three times) before the closure of the abdominal wall or intra-peritoneal chemotherapy, respectively.

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 %, $P < 0.0001$) (Fig. 5). 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.

The results of the present prospective randomized multicenter study far exceeded our expectations and showed a remarkably much better prognosis than previous studies on gastric cancer patients with CY+/P-. For example, a study on the median survival time (MST) of 91 patients with CY+/P- who had potentially curative resection stated survival to be only 386 days (Kodera et al., 1999), and the 5-year overall survival rate has been 13% (Rosenberg et al., 2006). In this study, the surgery alone group as well as the IPC group also showed similar results to the reports just cited. Surprisingly, however, in the CY+/P- group the overall five-year survival rate and MST were 42.1% and 35 months, respectively, and showed remarkably significant ($P < 0.0001$) improvement of both survival and MST. The results appeared so convincing and promising to us as to serve as a solid basis for employing the EIPL-IPC therapy with a great degree of confidence and high expectations.

7. Proposal of the optimal and practical therapeutic strategy for gastric cancer

Based on the data presented in this review, the authors propose the following treatment protocol for gastric cancer (Fig. 6). Accurate diagnosis of mucosal or submucosal cancer is made macroscopically including an EUS examination. Mucosal and submucosal invasion is correctly diagnosed in 75 to 85% of patients using EUS. All mucosal lesions with UL- should be treated by endoscopic submucosal dissection (ESD). If histologic examination of the ESD

specimen reveals complete resection, the treatment is considered to be perfect and the patient only needs follow-up. If histologic examination reveals an incomplete resection, laparoscopic local resection is required. For a mucosal tumor with UL+, laparoscopic gastrectomy with D1 is indicated. All macroscopic SM and advanced cancer cancer (MP, SS, SE and SI) should be treated by gastrectomy with D2 (Shimada et al., 2001a).

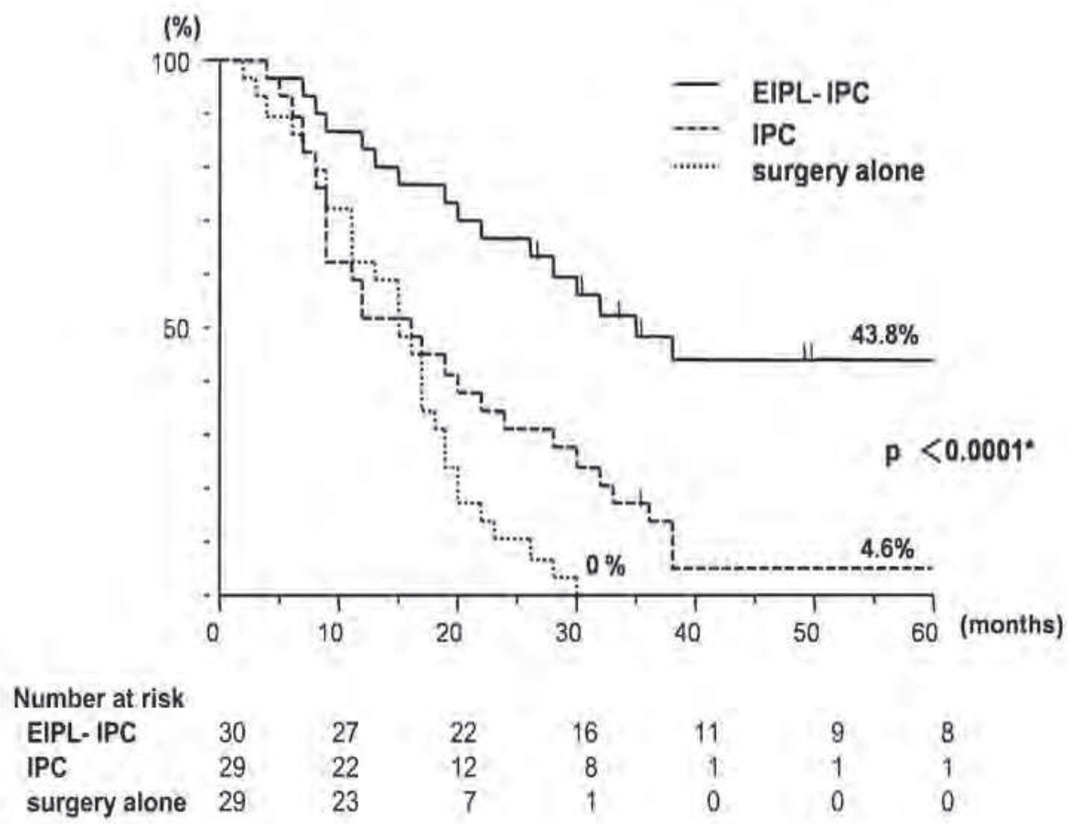

Fig. 5. The survival curves for 88 patients stratified according to the treatment. *By log-rank test. (Kuramoto et al., 2009)

Although a Dutch report has described the high post-operative morbidity and hospital mortality after gastrectomy with D2 lymph node dissection (Bonenkamp et al., 1995), D2 resections appear to be feasible and safe in Japanese (Japanese Research Society for Gastric Cancer, 1999; Kuramoto et al., 2009; Maruyama, 1987; Nakamura et al., 1992; Ohgaki et al., 1999; Sano et al., 2004; Shimada et al., 2001b; C.W. Wu et al., 2008) and certain Western patients (Harrison et al., 1998; Lim et al., 2007). In our study, operative morbidity and hospital mortality was 1.5% (16 of 1051) and 0.5% (5 of 1051) respectively. Certain factors in the Dutch patients such as a more advanced tumor stage or larger physical build to the Japanese patients in this study might have influenced the high morbidity and mortality. The present study on patients with gastric cancer suggested that the potential benefits of D2 operation outweigh the risk of increased postoperative morbidity and mortality. Therefore, advanced gastric cancer should be treated by gastrectomy with D2, and D2+α may be

necessary for patients with apparent N2 and/or N3 lymph nodes metastasis. Complete extirpation of gastric cancer with a sufficient resection margin from the tumor and the removal of metastatic lymph nodes is the only treatment that offers hope of cure for patients with gastric cancer (Balfour, 1973; Harrison et al., 1998; Japanese Research Society for Gastric Cancer, 1999; Maruyama, 1987; Shimada et al., 2003; Zhang et al., 2010). However, as a matter of course, excessive gastrectomy and lymph node dissection have to be avoided for the adverse effects they have on a patient's subsequent quality of life.

From the viewpoint of prophylactic strategy against peritoneal recurrence, the findings presented in this paper should greatly transform the surgical treatment for gastric cancer, including non-serosa-involved tumors. The authors strongly advocate for the adoption of the new treatment protocol for gastric cancer as shown in Fig. 6.

After the appropriate tumor resection and lymph node dissection, our novel EIPL regimen serves an extremely important role for gastric patients with high peritoneal recurrent risks such as serosal invasion and lymph node metastasis. The innovative EIPL method is very practical and the theoretical basis creates high expectation as to the effects of cyto-reduction, potentially to nil. Furthermore, the EIPL therapy is simple, very little time-consuming, inexpensive, it is not curtailed by place or time, and does not need any special techniques or devices in order to be applied. In addition, even if a few cancer cells were to remain after EIPL therapy, these cells might find it difficult to survive and/or to disseminate due to the effects of IPC or postoperative systemic chemotherapy with S1 (Ishizoe et al., 2006; Shirasaka et al., 2000; Sugimachi et al., 1999) .

Conventional cytological examination with Papanicolou staining (Papanicolaou, 1963) has been reported to lack sensitivity, and it is suggested that occult free cancer cells are present at the time of the operation in such cases. Therefore, improvements have been made by many investigators using immunological methods with selected monoclonal antibodies or real-time RT-PCR for the detection of free cancer cells in the peritoneal washes (Benevolo et al., 1998; Broll et al., 2001; Dicken et al., 2006; Kodera et al., 2002; Saito et al., 2007; P. Vogel et al., 1999; I. Vogel & Kalthoff, 2001). These methods have allowed the identification of cytology false-negative cases in gastric cancer. However, because these means are not generally available at the actual time of the operation, a cytological examination is commonly performed to detect the existence of free cancer cells in the peritoneal cavity. From these cautionary points of view, it is only prudent that the EIPL-IPC therapy would be employed for all patients with serosa-involved gastric cancer and regardless of CY+/P-.

On the other hand, although curative surgery has been used for patients with non-serosa-involved gastric cancer, some die of peritoneal recurrence. One of the reasons postulated for peritoneal dissemination in non-serosa-involved gastric cancer is that the lymph node dissection might open lymphatic channels and spread viable cancer cells to the peritoneal cavity (Fink & Longmire, 1991). We have demonstrated that free cancer cells were found in the lavage fluid after the lymph node dissection in 26.7% of patients with muscle-involved tumors, suggesting that the surgical operation itself causes the peritoneal dissemination of the these cancer cells (Marutsuka et al., 2003). Therefore, EIPL therapy is also strongly recommended for non-serosa-involved gastric carcinomas suspected of lymphatic invasion through surgery, or positive real-time RT-PCR for detection of free cancer cells in the peritoneal washes after D2 operation for non-serosa-involved tumor, including early gastric carcinoma (Fig. 6).

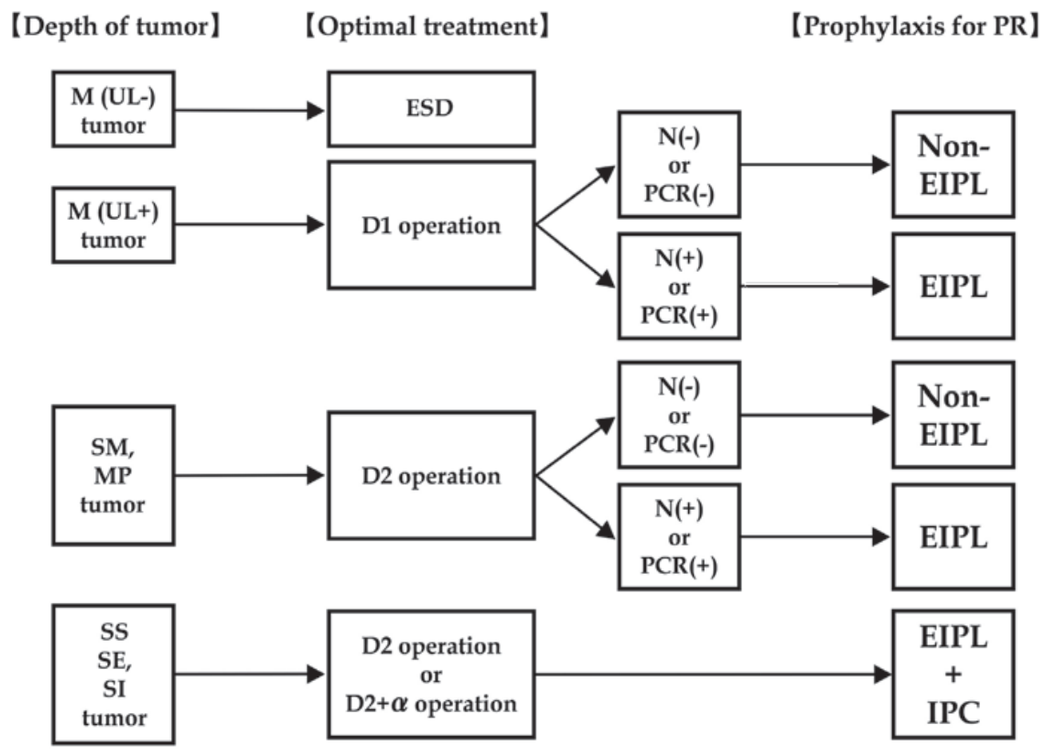

Fig. 6. A practical and optimal treatment protocol for gastric cancer. PR: peritoneal recurrence, M: mucosal tumor, SM: submucosal tumor, MP: tumor with muscularis proprial invasion, SS: tumor with subserosal invasion, SE: tumor with serosal invasion, SI: tumor invasion of adjacent structures, UL+: tumor with ulceration or ulceration scar, UL-: tumor without ulceration or ulceration scar, ESD: endoscopic submucosal dissection, D1 operation: gastrectomy with dissection of group 1 lymph node, D2 operation: gastrectomy with dissection of group 1 and 2 lymph node, N(+): positive lymph node metastasis through surgery, N(-): no evidence of lymph node metastasis, PCR: real-time reverse transcriptase-polymerase chain reaction, EIPL: extensive intraoperative peritoneal lavage, IPC: intra-peritoneal chemotherapy

8. Conclusion

EIPL therapy was developed as a prophylactic strategy for peritoneal recurrence, with the goal of improving the prognosis for patients with gastric cancer. In the present article, the risk factors on peritoneal recurrence from clinicopathological features of gastric carcinoma and the therapy's contribution to a remarkable improvement in the 5-year survival for gastric cancer patients with positive lavage cytology on prospective randomized controlled clinical trials was reviewed. From the viewpoint of prophylactic strategy against peritoneal recurrence, we propose the optimal and practical treatment protocol for gastric cancer.

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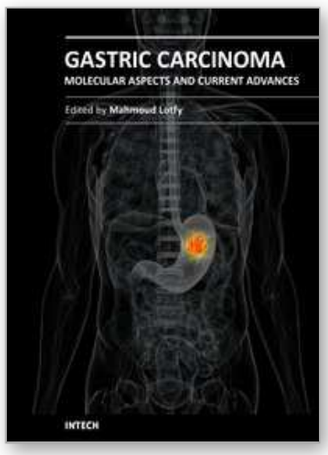

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Gastric cancer is one of the most common tumors worldwide. It has a heterogeneous milieu, where the genetic background, tumor immunology, oxidative stress, and microbial infections are key players in the multiple stages of tumorigenesis. These diverse factors are linked to the prognosis of the gastric cancer and the survival of gastric cancer patients. This book is appropriate for scientists and students in the field of oncology, gastroenterology, molecular biology, immunology, cell biology, biology, biochemistry, and pathology. This authoritative text carefully explains the fundamentals, providing a general overview of the principles followed by more detailed explanations of these recent topics efficiently. The topics presented herein contain the most recent knowledge in gastric cancer concerning the oncogenic signaling, genetic instability, the epigenetic aspect, molecular features and their clinical implications, miRNAs, integrin and E-cadherin, carbohydrate-associated-transferases, free radicals, immune cell responses, mucins, Helicobacter-pylori, neoadjuvant and adjuvant therapy, prophylactic strategy for peritoneal recurrence, and hepatic metastasis.

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