Review

Intraabdominal Continuous Hyperthermic Peritoneal Perfusion for Patients with Advanced Gastric Cancer — Present and Future

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Abstract: Reasonable extent of lymphadenectomy in combination with perioperative reliable adjuvant countermeasure to prevent postoperative peritoneal metastasis, as a prophylactic therapy is indispensable to improve the results of surgical treatment of gastric cancer with serosal invasion. Further therapeutic modality should be improved to obtain life prolongation for patients with gastric cancer with disseminating peritoneal metastasis or for gastrectomized patients with postoperative peritoneal metastasis. We believe that intraoperative continuous hyperthermic peritoneal perfusion (CHPP) combined with intraabdominal chemotherapy would be a candidate for the most reliable adjuvant therapy as both prophylactic and therapeutic modalities against peritoneal metastasis from gastric cancer.

Key words: continuous hyperthermic peritoneal perfusion (CHPP), gastric cancer, peritoneal metastasis

Introduction and Background

The results in the treatment of gastric cancer have improved in recent years. This improvement is primarily due to an increase in the number of patients treated for early gastric cancer, as well as to extensive lymph node dissection and positive accomplishment of concurrent resection of the surrounding organs that are involved1-3). However, in patients with advanced gastric cancer with serosal invasion, it is unclear whether extensive lymph node dissection significantly contributes to improvements in the results of treatment of gastric cancer, since the most likely pattern of recurrence is by means of peritoneal metastasis under these clinical conditions.

Scanning electron microscopy of a macroscopically normal peritoneum of patients with gastric cancer that had invaded the gastric serosa occasionally reveals that a few malignant cells have become lodged in the naked area of the submesothelial connective tissue, providing a picture of incipient peritoneal metastasis4). Moreover, on cytologic examination of peritoneal lavage immediately after a laparotomy, intraperitoneal free cancer cells have been detected in approximately 20% of patients who underwent potentially curative resection of tumors5-8). These patients have been shown to have a very poor prognosis and a close relationship has been indicated between our results of cytologic examination on the appearance of intraperitoneal free cancer cells in patients with advanced gastric cancer and the development of postoperative peritoneal metastasis9). To improve therapeutic results of advanced gastric
cancer, a reasonable extent of lymphadenectomy and other appropriate countermeasures should be performed concurrently to prevent postoperative peritoneal recurrence. Furthermore, therapeutic countermeasures should be devised for patients with advanced gastric cancer and disseminating peritoneal metastasis at the time of the diagnosis of primary gastric lesion, and for patients with postoperative recurrent peritoneal metastasis.

**Continuous Hyperthermic Peritoneal Perfusion (CHPP) as Prophylactic and Therapeutic Modalities of Peritoneal Metastasis from Gastric Cancer**

Despite recent advances in anticancer chemotherapy, no satisfactory treatment is available for peritoneal metastasis. Thermotherapy has been employed clinically as one of a variety of multimodal therapies for cancer. Hyperthermia has been applied locally, regionally, and systemically to various tumors. However, it is not easy to heat an extensive peritoneal surface sufficiently and homogeneously to the desired temperature. During CHPP, the entire peritoneal surface can be heated with a large volume of hyperthermic perfusate. Hyperthermic treatment for peritoneally disseminated metastasis was first reported by Euler et al., experimentally, in 1974. Shiu and Fortner reported in 1980 that intraperitoneal hyperthermic treatment was feasible and effective using rats with implanted peritoneal cancers. We also reported an experimental study of the feasibility of CHPP for peritoneal carcinoma.

In a clinical setting, a successful outcome after intracavitary CHPP in one patient with pseudomyxoma peritonei was reported by Spratt. We introduced this system as prophylactic and therapeutic modalities of peritoneal metastasis, and it is probably the first trial of CHPP in combination with an anticancer drug after gastric surgery. After our reports, many surgeons have introduced CHPP not only for prophylactic therapy but also for the treatment of peritoneal metastasis with their own modification in the hyperthermic induction system.

**CHPP as a Prophylactic Therapy for Postoperative Peritoneal Metastasis for Gastrectomized Patients with Gastric Cancer**

Results of CHPP as a prophylactic therapy of postoperative peritoneal metastasis have only been reported by us; we summarize them, as follows.

Under general anesthesia in the operating room, after a gastrectomy, three silicon tubes were placed in the pelvic, and right and left subphrenic cavities, respectively. After closure of the abdominal wall, physiologic saline containing 10 μg/ml mitomycin C, which had been heated to 48-50°C by passage through a tubular coil in a water bath, was infused into the peritoneal cavity through an intrapelvic tube attached to a pump at a rate of 200 ml/min for 50-60 min. The inflow and outflow temperatures were maintained at 44-45°C and 40-42°C, respectively. After the retained perfusate fluid had been drained spontaneously over the 24 hours that followed CHPP, the three tubes were removed.

Our results come from two trials; one is a historical controlled study (1980-1983), and other is a randomized controlled study (1983-1986).

The subjects were all primary gastric cancer patients with macroscopic serosal invasion by the cancer and no macroscopic peritoneal metastasis. They all had had a curative gastrectomy in our clinic.
As shown in Table 1, in the historical controlled study, the postoperative 3-year survival rate of patients (74%) in the treated group was significantly higher than the survival rate (53%) of those in the control group (p < 0.04). In the randomized controlled study, the 5-year survival rate (64%) of patients in the CHPP group was higher than that of patients in the control group (53%) although there was no statistically significant difference (p = 0.2427) between the rates. Median survival time was prolonged to 77 months in the CHPP group compared with 66 months in the control group.

Peritoneal recurrence was more frequent in the control group than in the CHPP group in both studies. The mortality rate as a result of peritoneal metastasis for patients in the CHPP group tended to be lower than that for patients in the control group.

In treating patients with CHPP, the incidence of anastomotic leakage and adhesive ileus as a result of the heat and the anti-cancer drug are the most important concerns. However, there was no difference in the incidence of such complications between treated and untreated patients in both studies. Shimizu et al. reported that intraperitoneal hyperthermia at temperatures up to 44.0°C for 30 minutes, applied using saline supplemented with mitomycin C, had no adverse effects in healing intestinal anastomoses when assessed in terms of breaking strength and histologic examination. However, it has been reported that CHPP at higher temperatures can cause a leakage of intestinal anastomosis or intestinal perforation. CHPP did not induce postoperative prolonged intestinal paresis or chemical peritonitis. Although thrombocytopenia and elevated serum GOT and GPT levels were observed in the CHPP group, they returned to normal range within 2 weeks of CHPP.

The first aim of our CHPP is to wash out intraperitoneal free cancer cells by irrigation with a massive volume of perfusate, and the second aim is to damage cancer cells and peritoneal micrometastases directly by heat and exposure to an anticancer drug. Our results indicate that CHPP is a simple, safe, and readily available prophylactic therapy for postoperative peritoneal metastasis of gastric cancer with serosal invasion, which is highly likely to appear in the peritoneum after gastric surgery.

### Table 1. Postoperative Survival Rates and Patterns of Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Survival rates</th>
<th>Patients deceased</th>
<th>Cause of death *</th>
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<tbody>
<tr>
<td></td>
<td>3-year</td>
<td>5-year</td>
<td></td>
</tr>
<tr>
<td>Historical controlled study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHPP group (n = 38)</td>
<td>74%**</td>
<td>63%</td>
<td>11</td>
</tr>
<tr>
<td>Control group (n = 55)</td>
<td>53%</td>
<td>43%</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Randomized controlled study</td>
<td></td>
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</tr>
<tr>
<td>CHPP group (n = 42)</td>
<td>78%</td>
<td>64%</td>
<td>18</td>
</tr>
<tr>
<td>Control group (n = 40)</td>
<td>68%</td>
<td>53%</td>
<td>22</td>
</tr>
</tbody>
</table>

*P, peritoneal metastasis; H, hematogeneous metastasis; O, other metastasis

**p < 0.04.

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**CHPP as a Therapeutic Modality for Peritoneal Metastasis in Patients with Gastric Cancer**

The first clinical evaluation of the effects of CHPP on the antitumor activity in patients with gastric cancer and disseminating peritoneal metastasis as a therapeutic modality was first reported in 1981 by Maeta et al. A total of
39 hyperthermic treatments (CHPP) were performed on 11 patients. The heating methodology, including the temperature of the perfused saline, duration and intraabdominal anticancer chemotherapy (mitomycin C), was almost the same as that of single CHPP which was performed as a prophylactic therapy for postoperative peritoneal metastasis for patients who underwent curative gastrectomy. As an antitumor activity, peritoneal tumor regression was observed in 2 of the 11 patients. However, life-prolongation was not sufficient; only one of the 11 survived more than one year.

However, Yonemura et al. applied intraperitoneal thermochemotherapy (CHPP) to patients with gastric cancer with peritoneal metastasis, and they reported that second-look surgery after the hyperthermic treatment revealed a remarkable diminution in the degree of peritoneal metastasis in 7 of the 14 patients. Moreover, long-term 3-year survival was noted in 4 of 41 patients with peritoneally disseminated gastric cancer.

Fujimoto et al. reported that CHPP resulted in complete destruction of cancer cells in the abdominal effusion, as well as on and just beneath the peritoneum. Further remarkable life-prolongation by CHPP was reconfirmed by them, as follows.

Intraperitoneal hyperthermic chemoperfusion (CHPP) combined with aggressive surgery was performed in 48 gastric carcinoma patients with peritoneal carcinomatosis; 18 gastric carcinoma patients with peritoneal carcinomatosis serving as controls were treated with surgery alone. The survival period was extended for the 48 patients who underwent surgery plus CHPP compared with the control patients (P = 0.00167), as shown in Table 2.

<table>
<thead>
<tr>
<th>Survival rates</th>
<th>1-year</th>
<th>3-year</th>
<th>5-year</th>
<th>8-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHCP (CHPP) group (n = 48)</td>
<td>54.0%</td>
<td>41.5%</td>
<td>31.0%</td>
<td>25.4%</td>
</tr>
<tr>
<td>Control group (n = 18)</td>
<td>18.9%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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Of the 29 patients with peritoneal carcinomatosis in the upper abdominal cavity, the 21 patients treated with CHPP and surgery had survival periods superior to those of the 8 patients treated by surgery alone. The 5-year survival rate of the 18 CHPP patients with countable metastasis in the entire cavity was 41.6%, whereas the 50% survival duration of the control group was 110 days. Nineteen patients with numerous metastasis in the entire cavity died within 673 days, regardless of whether or not CHPP was used. Based on these results, Fujimoto et al. concluded that peritoneal carcinomatosis is not a disease beyond treatment. CHPP treatment combined with extensive surgery provides an effective and practical method of treating this disease entity.

To our knowledge, attempts to cure peritoneal metastasis from gastric cancer have not been successful in the past. Palliative treatments to remove the primary lesion of the peritoneal metastasis have always resulted in rapidly recurring tumor growth within the abdominal cavity. Sugarbaker et al. and Fujimoto et al. reported that intraperitoneal chemotherapy had limited drug penetration through the subperitoneal layer and consequently...
produced no antitumor effect on the deeply invasive microfoci. They proposed that to supplement this limited penetration, every effort must be made to surgically remove residual foci on the peritoneoserosal surface, as well as to extirpate the intraabdominal metastatic and/or infiltrated organs.

Based on these reports, CHPP combined with aggressive surgery is currently performed in many hospitals in Japan and in Western countries as an adjuvant treatment in patients with advanced gastrointestinal and ovarian cancers.

**Prospects in Future**

The intraabdominal (i.p.) administration of cisplatin is one of the most effective therapies for peritoneal metastasis and cisplatin is widely used for not only CHPP but also conventional i.p. chemotherapy. However, the effect of fluid osmolarity on the therapeutic efficacy of i.p. administration of cisplatin has not been well established. Recently, we attempted to clarify the effect of fluid osmolarity on i.p. cisplatin chemotherapy. After i.p. administration of cisplatin, uptake of cisplatin in vivo by tumor cells in hypotonic solution (154 mOsM) was significantly greater than in isotonic (308 mOsM) or hypertonic (616 mOsM) solution. The LD₅₀ value of cisplatin in hypotonic solution was lower than that in isotonic and than that in hypertonic solution. However, when a dose equal to one-half of the LD₅₀ was administered in each solution to mice with i.p. tumors, survival of mice given cisplatin in hypotonic solution was significantly prolonged as compared with the survival of the other mice. These results demonstrated that the therapeutic efficacy of i.p. cisplatin was augmented when the drug was administered in hypotonic solution. There are no reports with respect to the combined use of the hypotonic i.p. cisplatin chemotherapy with CHPP. We now expect synergistic improvement in both anti-cancer activity and life-prolongation through the use of such combination therapy.

Recently, Sugarbaker et al. and Yonemura et al. have stressed the importance of a combined therapy of both cytoreductive surgery (peritonectomy procedures) and CHPP for peritoneal metastasis. They intended to remove all metastatic peritoneal lesions (peritonectomy) to the greatest extent, including gastrectomy. They reported that such intensive cytoreductive surgery combined with CHPP resulted in the markedly enhanced life prolongation. In the near future, peritonectomy combined with followed CHPP may become one of the most common aggressive treatment modalities for patients with gastric cancer with disseminating peritoneal metastasis.

**References**

進行胃癌症例に対する腹腔内持続温熱灌流——現状と将来

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要 旨：胃の臓器に浸潤した進行胃癌に対する外科治療の成績向上のためには、合理的な系統的リンパ節郭清範囲の検討とともに、術後の腹膜転移に対する信頼しうる予防的対策の導入が重要である。更に、診断時に腹膜転移を有する胃癌症例、また胃切除後に発症した腹膜転移症例などの治療成績向上（生存期間延長）のためには、腹膜転移そのものに対する治療方法の改善も重要である。これらの対応の一つとして、術中の腹腔内化学療法を併用した腹腔内持続温熱灌流療法（CHPP）は、腹膜転移の予防、あるいは治療対策として有用である事が既に示されている。今後、CHPPはperitonectomyや低浸透圧化学療法など他治療法との併用により、更に、腹膜転移の予防、治療対策として意義が高まる事が予測される。