Clinical Area: Intraperitoneal hyperthermic chemotherapy (IPHC)

Study Type: Randomized controlled trial.
Study Aim: To evaluate the survival benefit of intraoperative chemohyperthermic peritoneal perfusion (CHPP) combined with surgery for patients with advanced gastric cancer.

Outcomes
- **Primary:** Survival.
- **Secondary:** Peritoneal recurrence; perioperative factors; adverse effects.

Design
- **Number of subjects:** N=139
- **Description of study population:** Single center study in Japan. Group 1: 26 males/22 females, mean age=58.3 years; Group 2: 25 males/19 females, mean age=59.2 years; Group 3: 32 males/15 females, mean age=61.1 years.
- **Inclusion criteria:** Preoperative finding of T3 or T4 tumor; intraoperative findings of serosal involvement; white blood cell count ≥3000 u/L; platelet count ≥150,000 u/L.
- **Exclusion criteria:** >75 years old; active liver disease, renal dysfunction or severe metabolic disease such as diabetes mellitus.
- **Intervention:** One of three groups: 1) surgery + CHPP (n=48); 2) surgery + chemonormothermic peritoneal perfusion (CNPP) (n=44); 3) surgery alone (n=47). Surgery consisted of extended gastrectomy with D2- or D4-dissection according to the Japanese Classification of gastric cancer, and routine Roux-en-Y reconstruction. For groups 1 and 2, after reconstruction, the peritoneal cavity was expanded using a peritoneal cavity expander. For CHPP, the abdominal cavity was filled with 8-10 mL of heated saline at 42°C containing 30 mg of mitomycin C and 300 mg of cisplatin. The saline was circulated for 60 min and the temperature was maintained at 43-43.5°C. For CNPP, 8L of 37°C saline was introduced with the same doses of mitomycin C and cisplatin.
- **Source of outcome data:** Clinical examination, laboratory tests, CT scan, X-ray.
- **Length of follow-up:** Median follow-up=5.5 years (range=2.4 to 10.8 years).

Validity
- **Blinding?** Does not appear to be blinded.
- **Appropriate randomization procedures?** Procedures not discussed, authors indicated patients were randomized.
- **Appropriate comparison intervention (placebo or adequate dose of accepted intervention)?** Yes.
- **Treatment/control groups comparable at baseline?** Yes.
- **Other than intervention, was care/follow-up similar in each group?** Yes.
• *Adequate compliance with intervention?* Yes.
• *Sufficient statistical power?* Not reported.
• *Intention to treat analysis?* Appears to be.
• *Completeness of follow-up:* Some follow-up on all patients, minimum of 2.4 years.
• *Industry funding?* None disclosed.
• **Conclusions regarding validity of methods:** Reasonably valid. Study may be underpowered, and method of randomization was not discussed. More consistent long-term follow-up would be preferable.

**Results**

**5-year survival rate**

<table>
<thead>
<tr>
<th></th>
<th>CHPP</th>
<th>CNPP</th>
<th>Surgery-alone</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-year survival</td>
<td>61</td>
<td>44</td>
<td>42</td>
<td>0.021¹</td>
</tr>
</tbody>
</table>

¹Significantly better survival in CHPP group; no significant difference between the CNPP and surgery groups.

**Peritoneal recurrence, No.**

<table>
<thead>
<tr>
<th></th>
<th>CHPP</th>
<th>CNPP</th>
<th>Surgery-alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal</td>
<td>6</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

*Note:* Numbers too small for statistical comparison

**Adverse effects, No.**

<table>
<thead>
<tr>
<th></th>
<th>CHPP</th>
<th>CNPP</th>
<th>Surgery-alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Major post-operative complications</td>
<td>9</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Anastomamotic leakage</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatic fistula</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Authors’ Conclusions**

“…These results indicate that intraoperative hyperthermia combined with chemotherapy using high dose of CDDP and MMC has a great role in the prophylaxis of intraperitoneal recurrence after curative resection of advanced gastric cancer….”

**Reviewer’s Conclusions**

Estimated 5-year survival was higher in the group receiving surgery plus CHPP, compared to the groups receiving surgery plus CNPP or surgery alone.

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