Recent Advances in Gastric Cancer Treatment

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Introduction

We have developed successful gastric cancer treatment modalities during recent 40 years. The results have been reported not only in surgical treatment but also in recent chemotherapies. Since, however, various regional disparities in treatment outcomes were reported in Japan, the Ministry of Health, Labour and Welfare (MHLW) expressed requirements to reformulate appropriate guidelines. The Japanese Gastric Cancer Association (JGCA) promptly published “JGCA Gastric Cancer Treatment Guidelines”1 and “Digests of JGCA Gastric Cancer Treatment Guidelines”;2 JGCA and its forerunner The Japanese Research Society for Gastric Cancer have been publishing “Japanese Classification of Gastric Carcinoma”,3 which is considered to present the standard treatment for gastric cancer. Physicians should refer to this book, which has comprehensive coverage including clinical anatomy. With the recent emphasis on evidence-based medicine (EBM), guidelines should be described good treatment methods with evidence. However, high-quality evidence is difficult to obtain.

Morbidity and Outcomes of Gastric Cancer Treatment

In Osaka, there is an excellent regional cancer registration system which is operated by Osaka Medical Association, Osaka Prefectural Government, and Osaka Medical Center for Cancer and Cardiovascular Diseases. This system has been specially exempted from the recently enforced “Personal Information Protection Law”. There is a figure called “cancer incidence” (the proportion of patients who developed cancer during a given year per 100,000 population) reported in this system. At present, the incidence of gastric cancer is 50 for males and 25 for females. Since the figure reported 20 years ago was approximately 100 for males, there has been a 50% reduction during the past 20 years (Fig. 1).

According to the report of Fujimoto, et al.4 in 2003, 40% of all patients had localized cancer including early cancer, and 6.3% of these patients were diagnosed by mass screening. The overall 5-year survival rate was approximately 48%. Although early gastric cancer is detected more and more, there still are many advanced cancers. The overall survival rate is not satisfactory (Fig. 2).

Gastric Cancer Treatment Guidelines

After the Japanese Research Society for Gastric Cancer was reorganized to the Japanese Gastric Cancer Association in 1998, “JGCA Gastric Cancer Treatment Guidelines” was published. The JGCA published the 1st edition of the guidelines in 2001 and the 2nd edition in 2004. A book for patients titled “Digests of Gastric...
Cancer Treatment Guidelines” was published in December 2001.

The introductory part of the guidelines states that all of guidelines are evidence based in principle. However, even the extensive description concerning surgical treatment is rarely guaranteed by the data from clinical trials. The “standard treatment in the guidelines is subtotal/total gastrectomy + D2 dissection. Surgical operations that are less extensive than the standard treatment are referred to as limited operation, while more extensive operations are referred to as extended operation.

The following sections outline ongoing clinical trials and the methods of attractive treatment.

EMR/ESD

The method to resect cancer using an endoscopic technique was developed over 20 years ago. With subsequent development of instruments for this procedure, endoscopic mucosal resection (EMR) has now become a technique performed almost routinely by endoscopists. However, there has been no study proving the safety and good outcome in a large population. A surveillance program of EMR involving the cooperation of member physicians has just started.

On the other hand, endoscopic submucosal dissection (ESD) intended to remove a wider area of the mucosa has been introduced. Since the use of this procedure is in the stage of skill acquisition, it will take some time before clinical studies start.

Sentinel Lymph Nodes

The sentinel lymph node is the first lymph node to which cancer is expected to spread. There have been several attempts to identify the sentinel lymph node associated with gastric cancer. If we know which lymph node would be the first station of the metastasis of early cancer and if we could be sure that the absence of metastasis in the biopsy of this lymph node indicates the absence of metastasis in other sites, the need for lymph node dissection would be eliminated. Reports from overseas have demonstrated the significance of sentinel lymph nodes in malignant melanoma and breast cancer. Similar studies concerning gastric cancer are mostly conducted in Japan, and clinical trials to evaluate the effectiveness are ongoing.

At present, clinical studies are ongoing to verify the applicability of the sentinel lymph node theory to gastric cancer. One is the study conducted by the Japanese Society for Sentinel Node Navigation Surgery. In this study, isotope and dye tracers are injected, hot nodes or blue-stained nodes are excised intraoperatively, and histological examination is performed using rapid methods and permanent preparations. D2 dissection is performed later whether metastasis is detected or not. Another study is conducted.
A dye (indocyanine green) is injected, stained lymph nodes are excised, and histological examination is performed using rapid methods and permanent preparations. D2 dissection is performed later to verify whether or not the stained lymph nodes are the ones where metastasis takes place. Both studies are intended to confirm the absence or low occurrence of false negative results.

Clinical Trials of Extended Surgery

Clinical trial on the meaning of D3 dissection

Ohashi et al. reported that a few patients with paraaortic node metastasis who underwent curative gastrectomy including para-aortic node dissection could survive over five years. This extended nodes dissection became popular about 15 years ago. Since the technique is a little bit complicated and it takes additional time, we felt a need to evaluate this technique and the outcome.

In 1995, JCOG started a clinical study to examine the value of this extended surgery. The phase III study is to compare the extended lymph node dissection (D2 plus para-aortic node dissection) to standard dissection (D2) for advanced gastric cancer in terms of the adverse events and survival rates.

During the registration period of approximately 5 years, 520 cases were enrolled from 24 facilities. The study is now in the followup period, and results will become visible in several years.

Extended surgery for schirrhous gastric cancer

The treatment results for schirrhous gastric cancer are notoriously poor. The 5-year survival rate after curative surgical is reported to be approximately 15%. A report from western Europe claims that schirrhous gastric cancer is not an indication for surgical operation. A characteristic feature of schirrhous gastric cancer is retroperitoneal recurrence, in which cancer cells invade the retro-peritoneum and, spreading downwards, cause stenosis of the intestines and the ureters.

A procedure of extended surgery for schirrhous gastric cancer resecting whole stomach and adjacent organs to prevent retroperitoneal recurrence was introduced approximately 20 years ago. The extended operation, Left Upper Abdominal Exenteration, includes en bloc removal of the whole stomach, transverse colon, transverse mesocolon, body and tail of pancreas, and spleen. This method provided good results in patients up to stage III, but the results in stage IV disease were not better than those of conventional treatment. Although anticancer chemotherapy was used simultaneously, this study failed to show the effectiveness of chemotherapy on the survival rate. A randomized phase III study has yet to be planned (Fig. 3).
Chemotherapy

Only reports from overseas have demonstrated the effectiveness of chemotherapy on survival period of patients. The most basic chemotherapeutic agent is believed currently 5-FU. The next step is to identify the chemotherapeutic modality that is more effective than 5-FU (Table 1).

5-FU vs. CPT-11 + CDDP vs. TS-1
At present, JCOG is conducting a phase III study designed to prove that CPT-11+CDDP or TS-1 is more effective than 5-FU. Patient registration has just been completed, and at least 3 years will be needed before results can be obtained after the followup period. In future, we should look for a therapeutic method that is more effective than these options, using whichever is better as the reference therapy.

Table 1 Phase III trials comparing best supportive care and chemotherapy

<table>
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<tr>
<th>Authors</th>
<th>No. of Pts</th>
<th>RR (%)</th>
<th>MST (m)</th>
<th>P</th>
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<td>30</td>
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<td>9</td>
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<td></td>
<td>BSC</td>
<td>10</td>
<td>3</td>
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<tr>
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<td>21</td>
<td>29</td>
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<tr>
<td></td>
<td>BSC</td>
<td>20</td>
<td>3.1</td>
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<tr>
<td>Glimelius</td>
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<td>30</td>
<td>10</td>
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<td>BSC</td>
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BSC: best supportive care

Postoperative UFT therapy
Various postoperative chemotherapies have been carried out, but few were found to be effective. A recent study proved the effectiveness of postoperative UFT therapy as compared with no chemotherapy. However, the subjects of this study were limited to patients with T2 N1-2 disease, rather than the more common T3 disease. The result of this study shines as the first successful evidence that postoperative chemotherapy can be effective for patients with T2 N1-2 disease (Fig. 4).10

Postoperative TS-1 therapy
A study designed to prove the effectiveness of postoperative oral administration of TS-1 started 3 years ago. The registration of more than 1,000 patients has been completed, and the study is now in the follow-up period. While expectations...
are high for the effectiveness of TS-1, the actual results are not obtained yet. Another phase III study using TS-1 as the reference treatment has already begun, but such an attempt is premature.

**Conclusion**

Following the issuance of the guidelines for gastric cancer treatment, there has been much discussion concerning the level of evidence qualifying the guidelines. Clinical trials will be providing evidences to the future guidelines. Clinical trials are not conducted in a special case, but supported by the participation of many facilities and many patients. Participating in a clinical trial which has promising better effectiveness is a far better option than continuing convenient treatment without evidence.

**References**