mens: the results ranged from 10% to 35% in response rate, from 6 to 8 months in MST, and around 10% in 2-year survival.

## Results in Patients with Peritoneal Metastasis

Peritoneal metastasis is the major site developing from gastric cancer. However, these patients usually have poor general condition, impairment of oral intake, and complications such as bowel obstruction and hydronephrosis, which may prolong elimination of the agents. These patients with peritoneal dissemination are excluded from the phase II study because these studies usually require response evaluation as a primary endpoint whereas these patients usually have no measurable lesions. Thus, a specifically targeted study should be conducted. A phase II study of sequential combination of methotrexate (MTX) plus 5-FU (JCOG 9603) has been carried out in patients with malignant ascites [11]. A total of 37 patients were registered: remarkable decreases of ascites were observed in 13 (35%) patients, including 4 (11%) with disappearance of ascites, whereas 2 (5%) patients died of treatment-related toxicity. Results from retrospective analysis also showed similar efficacy for this population. Based on the results, a phase III study comparing 5-FU alone with MTX/5-FU (JCOG 0106) in patients with peritoneal dissemination has been initiated in the JCOG.

## Results in Patients with Bone Metastasis

Bone metastasis is a rare mode of cancer metastasis in patients with gastric cancer. However, if it occurs, it is usually associated with diffuse involvement and occasionally complicated with disseminated intravascular coagulation (DIC). Thus, the prognosis is very dismal. For such cases, we attempted palliative chemotherapy with sequential MTX/5-FU and have reported a retrospective analysis of 18 gastric cancer patients with bone metastasis who underwent this treatment [12]. Of the 18, 9 patients (50%) had the complication of DIC before initiation of chemotherapy, and 8 of them (89%) recovered from it. The median survival times for all patients and for the 9 with DIC were 186 and 113 days, respectively, and 2 patients (11%) survived longer than 1 year. Although grade 4 leukopenia was observed in 3 patients (17%), no treatment-related deaths occurred. Based on these results, this combination therapy may have palliative potential and be a feasible treatment for gastric cancer patients with bone metastasis, with or without DIC.

## Multivariate Analysis for Prognosis and Long-Term Results

Between 1985 and 1997, a total of 497 patients with advanced gastric cancer were enrolled onto four phase II studies and one phase III study in the Japan Clinical Oncology Group. Univariate and multivariate analysis for prognosis were carried out by log-rank test and by Cox's proportional hazard model, respectively [13]. Baseline patient background was median age of 61 years; 176, 238, and 86 patients with PS 0, 1, and 2, respectively; 84 patients with prior gastrectomy; and 315, 148, and 34 patients with one, two, or more metastatic sites, respectively. Thirty-nine (8%) and 11(2%) patients have survived longer than 2 and 5 years. Univariate analysis revealed that the 315 patients with a single metastatic site have survived longer than the remaining 182 patients ($P < 0.01$), and the 77 patients with only abdominal lymph node involvement

TABLE 2. Univariate and multivariate analysis for prognosis by each variable

| Variable | *n* | Univariate analysis MST (months) | Univariate analysis 2-year Survival (%) | Univariate analysis *P* value | Multivariate analysis Relative risk | Multivariate analysis 95% CI |
|---|---|---|---|---|---|---|
| Age | | | | | | |
| <60 years | 219 | 7.8 | 10.5 | 0.04 | — | |
| >60 years | 278 | 6.8 | 5.8 | | 1.16 | 0.97–1.40 |
| Sex | | | | | | |
| Male | 364 | 7.2 | 8.2 | 0.9 | — | |
| Female | 133 | 7.2 | 6.8 | | 0.93 | 0.75–1.14 |
| PS | | | | | | |
| 0 | 175 | 9.9 | 11.0 | <0.01 | — | |
| 1 | 236 | 6.8 | 8.5 | | 1.16 | 1.08–1.25 |
| 2 | 86 | 5.1 | 0 | | | |
| Histological types | | | | | | |
| Intestinal | 228 | 7.8 | 9.2 | 0.3 | — | |
| Diffuse | 266 | 6.5 | 6.8 | | 1.13 | 0.97–1.30 |
| Macroscopic types | | | | | | |
| Scirrhous | 137 | 6 | 4.4 | 0.04 | — | |
| Nonscirrhous | 360 | 7.6 | 9.2 | | 1.27 | 1.02–1.25 |
| History of gastrectomy | | | | | | |
| Yes | 84 | 8.3 | 14.3 | 0.02 | — | |
| No | 413 | 6.8 | 6.5 | | 1.01 | 0.92–1.10 |
| No. of metastatic sites | | | | | | |
| 1 | 315 | 8.3 | 9.5 | <0.01 | — | |
| 2 | 148 | 5.9 | 5.4 | | 1.32 | 1.14–1.53 |
| ≥3 | 34 | 5.4 | 2.9 | | | |

Multivariate analysis includes all the variables listed in the table
MST, mean survival time; CI, confidence interval; PS, performance status

have also survived longer than 117 patients with only liver metastasis ($P = 0.03$). In the multivariate analysis, better PS, small number of metastatic sites, and macroscopically nonscirrhous type were significantly associated with better prognosis (Table 2).

Characteristics of the 11 five-year survivors are summarized in Table 3. The 11 patients consisted of 8 with paraaortic node metastases alone as an "unresectable factor," 1 with paraaortic and cervical node metastases, and the remaining 2 patients with only liver metastasis. Ten of the 11 patients achieved overall responses to the initial chemotherapy: 5 patients achieved complete response (CR) at the initial chemotherapy, and 1 patient achieved CR by the second-line chemotherapy. One patient, who had not achieved an objective response to the initial chemotherapy (FP), achieved CR in the third-line chemotherapy, consisting of 5-fluorouracil + doxorubicin + mitomycin C. Of the 11, 8 patients have received surgical resections: 4 patients had undergone gastrectomy before initiating the chemotherapy and the other 4 patients underwent surgical resection after achieving downstaging by the initial chemotherapy, including 2 with pathological CR in the surgically resected specimen. The remaining 3 patients have not received surgical resection during the follow-up

TABLE 3. Characteristics of 11 five-year survivors

| Age | Sex | PS | Macroscopy | Histology | Metastatic site | Gastrectomy | Initial regimen | Response, 1st/2nd | Survival (months) | Alive/dead |
|---|---|---|---|---|---|---|---|---|---|---|
| 75 | M | 0 | N | Diffuse | Liver | — | 5Fuci | CR/– | 60 | D |
| 65 | M | 0 | N | Intestinal | Abdominal LN | B | 5Fuci | PR/PR | 61 | A |
| 46 | M | 0 | N | Diffuse | Abdominal LN | B | 5Fuci | PR/– | 63 | A |
| 55 | M | 1 | N | Intestinal | Liver | — | UFTM | PR/CR | 65 | A |
| 47 | M | 0 | N | Intestinal | Abdominal LN | B | FP | CR/– | 85 | A |
| 52 | M | 1 | N | Intestinal | Abdominal LN | — | 5′FP | CR/– | 86 | D |
| 57 | M | 1 | N | Diffuse | Abdominal LN | A | EAP | PR/– | 87 | D |
| 53 | M | 0 | N | Diffuse | Abdominal LN | A | EAP | CR/– | 88 | A |
| 49 | F | 0 | N | Diffuse | Abdominal LN | B | FP | NC/CR | 90 | A |
| 58 | M | 0 | N | Intestinal | Abdominal and Cervical LN | A | EAP | CR/– | 103 | A |
| 62 | M | 1 | N | Intestinal | Abdominal LN | A | 5′FP | PR/– | 108 | A |

N, nonscirrhous type; LN, lymph node; A, after initial chemotherapy; B, before initial chemotherapy; UFTM, UFT+MMC; FP, 5-FU+CDDP; 5′FP, 5′FUDR+CDDP; EAP, etoposide+ADM+CDDP; CR, complete response; PR, partial response

period. Ten of the 11 5-year survivors presented no evidence of disease at 5 years, whereas 2 patients died after 5 years of recurrence of primary disease.

These results indicated that better PS, small number of metastatic sites, and macroscopically nonscirrhous type are independent favorable factors for survival. There was a small population of long-term survivors, particularly in patients with only paraaortic node metastasis as the "unresectable factor."

# New-Generation Regimens

## *Single-Agent and Combination Studies in Japan*

Recently, four promising agents, irinotecan (CPT-11), S-1, docetaxel, and paclitaxel, have become commercially available for treatment of gastric cancer in Japan. Results from single-agent registration studies for approval and their combinations are shown in Table 4.

CPT-11 is an inhibitor of DNA-topoisomerase I, which is a crucial enzyme involved in DNA replication and transcription. In the single-agent study, moderate activity of this agent was confirmed with a response rate of approximately 20% [14]. This agent was then investigated in combination with CDDP [15,16]. A phase II study of this combination achieved high response rate of 48% with MST of 9 months in all patients and of 59% with MST of 11 months in chemo-naive patients. The major toxicities were neutropenia and diarrhea: grade 4 neutropenia was observed in 57% and grade 3 or 4 diarrhea in 20% of the patients. This agent was then combined with MMC; the phase I/II study of this combination revealed similar efficacy results and less toxicity than the CPT-11 + CDDP regimen [17]. This regimen was evaluated in the phase II study as a second-line setting after failure of FU-based regimens [18]. Of the 45 patients registered, 13 patients achieved partial response (PR) with a response rate of 29%. Median progression-free survival was 4 months. Toxicities were moderate; grade 4 neutropenia was observed in 29% and grade 3 anorexia in 24% of the patients. This study concluded that this regimen could be a treatment option in patients resistant to FU-based regimen.

S-1 is a new oral fluoropyrimidine that consists of three components: tegafur; which is a prodrug of 5-FU, CDHP, which competes with dihydropyrimidine dehydrogenase, and oxonic acid, which suppresses the gastrointestinal toxicity of tegafur. This agent is highly active with a response rate of 45% (45/101) in the two registration phase II studies and is widely used in Japan [19,20]. Various attempts in combination with other agents such as CDDP, CPT-11, and taxanes have been conducted. First, this agent

TABLE 4. Results of the single-agent study in Japan

| Agents | No. of patients | Response rate | MST (months) |
|---|---|---|---|
| CPT-11 | 76 (20) | 18% (25%) | NS (NS) |
| S-1 | 101 (101) | 45% (45%) | 8.3 (8.3) |
| Docetaxel | 129 (51) | 17% (18%) | 7.5 (NS) |
| Paclitaxel | 60 (28) | 23% (21%) | 11.5 (11.4) |

Numbers in parentheses are results in chemonaive patients
CPT-11, irinotecan; NS, not stated

was combined with CDDP. This combination phase I/II study was scheduled as S-1 40 mg/m$^2$ twice daily for consecutive 21 days and 2-h infusion of CDDP at 60–70 mg/m$^2$ on day 8, which was repeated every 5 weeks [21]. This study revealed an excellent response rate of 76% with MST of 12.6 months. Toxicities were moderate but easily manageable; grade 3 or 4 hematological and nonhematological toxicities were 15.8% and 26.3%, respectively. Another combination, S-1 + CPT-11, is also promising. A phase I/II study of this combination revealed similar response rates of around 50% with a MST of 14 months [22].

The taxanes docetaxel and paclitaxel inhibit microtubule depolymerization and have moderate activity for gastric cancer with a response rate of around 20% in their single-agent studies [23–26]. Taxanes also have promising activity as a second-line treatment, and their combinations are now being investigated as a frontline treatment. The Swiss Group for Clinical Cancer Research has reported a phase II study of docetaxel 85 mg/m$^2$ with CDDP 75 mg/m$^2$ administered once every 3 weeks for advanced gastric cancer and observed a response rate of 52% and median time to progression of 6.6 months [27].

## *Randomized Controlled Trials Including Newer-Generation Regimens*

There are three randomized trials under investigation including the above new-generation regimens in Japan. In JCOG, three-arm randomizations were designed. This study (JCOG 9912) compares 5-FU alone, as a control arm based on the results from the previous study (JCOG 9205), with a combination of CPT-11 + CDDP and with S-1 alone. This study requires a sample size of 450, and final accrual will be completed in 2005. The second study is a randomized trial comparing S-1 alone with S-1 + CDDP (sponsored by Taiho) with a sample size of 300, and the third study (sponsored by Wyeth) is comparing S-1 alone with 5-FU/leucovorin with a sample size of 200. Final results of the JCOG 9912 and the Taiho study will appear in 2006–2007.

An international randomized controlled trial (V-325) comparing CDDP + 5-FU (CF) with docetaxel + CDDP + 5-FU (DCF) was conducted outside of Japan, and the interim results were reported at the Annual Meeting of the American Society of Clinical Oncology in 2003 [28]. The doses and schedule of the DCF arm were docetaxel 75 mg/m$^2$ on day 1, CDDP 75 mg/m$^2$ on day 1, and 5-FU 750 mg/m$^2$/day as continuous infusion on days 1–5, repeated every 3 weeks; the dose and schedule of CF arm were CDDP 100 mg/m$^2$ on day 1 and 5-FU 1000 mg/m$^2$/day as continuous infusion on days 1–5 given every 4 weeks. At the interim analysis on 232 patients, time to progression was superior ($P = 0.0008$) for DCF (5.2 months compared to 3.7 months for CF). MST was also longer for patients receiving DCF (10.2 months) than those receiving CF (8.5 months, $P = 0.0064$). Neutropenic fever, infections, diarrhea, and mucositis were also higher for DCF than CF. These results indicated the superiority of DCF to CF for advanced gastric cancer.

To date, the interpretation of V-325 study results appears to be controversial. Although this study confirmed the superiority of DCF compared to CF in terms of efficacy, MST of the DCF arm was 10.2 months, which does not seem to be a definite improvement. The latest combination studies in Japan, although the numbers of the patients were small, yielded 12 months or longer MST (Table 5). According to the ret-

TABLE 5. Treatment results of newer-generation regimens in Japan and V325 study

| Regimen | Phase | No. of patients | Response rate | MST (months) |
|---|---|---|---|---|
| CPT-11 + CDDP | II | 44 (29) | 48% (59%) | 9.0 (10.8) |
| CPT-11 + MMC | I/II | 30 (16) | 50% (63%) | 8.5 (NS) |
| S-1 + CDDP | I/II | 25 (25) | 75% (76%) | 12.5 (12.5%) |
| S-1 + CPT-11 | I/II | 40 (40) | 55% (55%) | 14.0 (14.0) |
| Docetaxel + CDDP + 5-FU (V325 study)s | III | 111 (111) | 39% (39%) | 10.2 (10.2) |

Number in parentheses are results in chemonaive patients; NS, not stated

rospective analysis of National Cancer Center Hospital East, the MST of 111 patients treated with chemotherapy for advanced unresectable gastric cancer in daily practice was improved to 11 months after application of the newer-generation regimens. Whether the superiority of DCF can be accepted should await obtaining the results of ongoing randomized trials in Japan.

## Molecular Targeting Agents Under Investigation

Recently developed molecular targeting agents may provide a significant impact in this field, as successful results of bevacizumab and cetuximab have been observed in colorectal cancer [29,30].

Gefitinib is an orally active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that has shown single-agent activity against non-small cell lung cancer. A Japan–Europe joint phase II study was conducted to investigate the efficacy, tolerability, and pharmacokinetics of gefitinib in patients with metastatic gastric adenocarcinoma [31]. Seventy-five patients (32 Japanese, 43 non-Japanese) were randomized to receive 250 mg/day or 500 mg/day gefitinib orally. Disease control was achieved in 13 patients: 1 (250 mg/day) had a partial response and 12 had stable disease (4 at 250 mg/day, 8 at 500 mg/day), with a disease control rate of 18%. The most common drug-related adverse events were diarrhea (45.9%), rash (35.1%), and anorexia (12.2%). Drug-related grade 3/4 adverse events were experienced by 11.1% and 23.7% of patients given 250 mg/day and 500 mg/day gefitinib, respectively. Gefitinib exposure appeared to be unaffected by ethnicity or previous gastric surgery. Furthermore, there was no marked difference in plasma concentration in patients with disease control (partial response plus stable disease) versus progressive disease. In conclusion, gefitinib monotherapy was generally well tolerated, but its activity seemed to be limited.

Investigations of two other molecular targeting agents are now being planned. EMD72000 is a 95% humanized monoclonal antibody against EGFR that showed promising activity for colorectal adenocarcinoma in the phase I study [32]. This agent has less toxicity, particularly in allergic reaction and skin rash, than cetuximub, which is a chimeric antibody against EGFR. The single-agent phase II study is going to begin in patients with EGFR-positive gastric tumors. Another planned agent is trastuzumab, a monoclonal antibody to Her2 protein, which is widely used in patients with Her2-overexpressing breast cancer. We have evaluated the frequency of Her2 overexpression and the concordance between protein expression and gene amplification in 200

surgical and endoscopic biopsy specimens using two commercial immunohistochemical (IHC) kits and fluorescence in situ hybridization (FISH) [33]. Among these 200 cases, 46 (23%) of the patients were found to exhibit Her2 protein overexpression. The following IHC scores were obtained: 0, 126 (63%); 1+, 28 (14%); 2+, 12 (6%); and 3+, 34 (17%). Gene amplification examined with FISH was observed in 54 cases (27.1%). Among the 200 biopsy specimens, Her2 protein overexpression was observed in 21.5% of the specimens (2+, 7.5%, and 3+, 14%). The concordance rate between the surgically resected materials and the biopsy specimens was 88.7%. From these background results, trastuzumab can be applied for clinical trial in patients with Her 2 overexpressed gastric cancer.

## Conclusions

Older-generation regimens against advanced gastric cancer have limited efficacy. No standard regimens worldwide, as well as in Japan, have been established yet, and a limited number of patients have achieved objective response and long-term survival. However, some of the new-generation regimens improved response rate more than 50% and suggested survival prolongation in the preliminary studies. These treatments are being investigated in ongoing randomized studies in Japan, and we should wait for the results to confirm these improvements. Recent development of molecular technology has produced various types of molecular targeting agents. These agents are the other new hopes for improving efficacy results with less toxicity than classic cytotoxic agents. Understanding the biology of gastric cancer may result in better targets or cellular pathways to be modified or blocked by therapeutic interventions. Additionally, improvement of the clinical trial design and molecular surrogate in clinical research will lead to the development of better treatments. Both clinical and biology research will be more important.

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## The Diversity of Gastric Carcinoma

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ISBN 4-431-21139-X

9 784431 211396

springeronline.com

Reprint from

M. Kaminishi, K. Takubo, K. Mafune (Eds.)
The Diversity of Gastric Carcinoma
Pathogenesis, Diagnosis, and Therapy



Springer

# The Gastric Cancer Treatment Guideline

Mitsuru Sasako

## Introduction

The Japan Gastric Cancer Association issued the first edition of the *Gastric Cancer Treatment Guideline* in March 2001 [1]. Based on new evidence, the second edition was issued in April 2004 [2]. In this chapter, the content of this guideline is introduced.

## Background of the Japanese Guideline

Gastric cancer remains the most common cancer in Japan, although it surrendered first place of the high annual mortality rate to lung cancer. The mortality rate of gastric cancer is seven times higher in Japan than in the United States and three times higher than in the UK [3]. Consequently, gastric cancer patients are treated not only in cancer specialist hospitals but also in most university hospitals and general hospitals, even in rural areas. In more than 100 Japanese hospitals, more than 100 patients undergo gastrectomy for gastric cancer every year. Even in other hospitals, the hospital volume is much higher than in most European hospitals.

The second unique situation in Japan is that more than half the patients have T1 tumors, that is, early gastric cancer. This result is partly due to the mass screening system, which covers actually as little as 10% of the entire population over 40 years old [4]. On the whole, the knowledge of the high risk of gastric cancer among general practitioners and even among the common citizen seems more important for early detection of this disease. Most Japanese tend to undergo endoscopy when they have even minimum symptoms of the upper gastrointestinal tract. We have accumulated an enormous database using the common rule, The General Rules for the Gastric Cancer Study issued by the Japanese Research Society for Gastric Cancer in 1962. According to the large database, the incidence of lymph node metastasis increases by

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tumor depth, and the deeper the tumor invasion, the more distant regional lymph nodes become metastatic. The incidence of nodal metastasis was just 2%–3% in T1 mucosal cancer and 15%–20% in T1 submucosal cancer [5]. Using this database, it was possible to select patients with T1 tumors who have negligible risk of lymph node metastasis. Together with the development of the instruments and technique of endoscopic mucosal resection (EMR), many of these mucosal cancers with minimal risk of nodal metastasis are now treated endoscopically [6]. In the year 2003, approximately 350 patients with T1 tumor underwent an EMR as definitive treatment, whereas about 300 underwent open surgery at National Cancer Center Hospital, Tokyo.

One of the reasons for this high incidence of early gastric cancer (EGC) is that the diagnostic criteria of gastric carcinoma are slightly different in Japan from those in the West [7]. Many Western pathologists diagnose the lesions without definite invasion as dysplasia, whereas they are diagnosed as well-differentiated adenocarcinoma in Japan if they have cellular and structural atypia compatible with adenocarcinoma. As biopsy specimens are usually taken from the surface of the lesions, they cannot prove deeper invasion of the lesions. Therefore, many of these "dyplasia" actually invade into the submucosal layer or even deeper when they are resected and histologically examined [8].

The most common type of surgery for curable gastric cancer in Japan is a gastrectomy with D2 lymph node dissection. In many Western countries, surgeons refrain from this procedure due to higher mortality than limited surgery (D0/1) and uncertain efficacy [9]. This contrast is partly explained by the high incidence of the disease and subsequent high hospital and surgeon volume in Japan, but also by the relatively low body mass index of the average Japanese. Difficulty and efficacy of abdominal surgery are somewhat affected by the volume of intraabdominal adipose tissue. In obese patients, generally speaking, a complicated surgery is much more difficult than in slim patients. Less than 1% of patients have body mass index over 30 in Japan, whereas more than 20% are obese in the United States. This fact makes surgeons more conservative in use of an aggressive type of surgery in the West.

## Principles: Basic Structure of the Guideline

This guideline shows the standard treatments and reasonable options for each stage. They are clearly separated into two groups, the standard treatments or the treatments under investigation (Tables 1, 2). As treatment strategy varies widely in EGCs, the standard treatment is indicated with detailed conditions in stage Ia and Ib tumors. Unlike many other guidelines, the algorithm system is not used.

## Treatment of Early Gastric Cancer

A wide resection with lymphadenectomy remains the gold standard treatment for gastric cancer, even for T1 gastric cancers, 10% of which have lymph node metastasis. In the guideline, standard radical gastrectomy is defined as a gastrectomy of more than two-thirds of the stomach with D2 lymph node dissection. However, patients with negligible risk of having nodal metastasis can be treated by a mere wide resection, avoiding a gastrectomy, which makes a serious change of eating habits obligatory.

TABLE 1. Stage-specific standards of care by the Japanese Guideline

| | N0 | N1 | N2 | N3 |
|---|---|---|---|---|
| T1(M) | EMR, ModA | ModB | STD | Ext<br>Palliative surgery<br>CTX |
| T1(SM) | ModA<br>ModB | STD | | |
| T2 | STD | STD | STD | Radiation therapy |
| T3 | STD | STD | STD | Palliative care |
| T4 | Ext (C.R) | Ext (C.R) | | |
| M1 | | | | |

MER, endoscopic mucosal resection; ModA, modified gastrectomy A; ModB, modified gastrectomy B; STD, standard gastrectomy; Ext (C.R), extended gastrectomy with combined resection of involved organs; EXT, extended gastrectomy including extended lymphadenectomy, combined organ resection for lymphadenectomy; CTX, chemotherapy

TABLE 2. Treatments in clinical research by the Japanese Guideline

| | N0 | N1 | N2 | N3 |
|---|---|---|---|---|
| T1(M) | EMR* | LADG | | Ext<br>Reduction surgery<br>CTX<br>HTCTX |
| T1(SM) | LADG<br>LR, SG | | | |
| T2 | LADG | ACTX | ACTX | |
| T3 | ACTX | D3<br>ACTX | D3<br>ACTX | |
| T4 | CTX, ACTX<br><br>Rad | Ext<br>CTX<br>ACTX | | |
| M1 | | | | |

EMR*, extended indication for EMR; LADG, laparoscopy-assisted distal gastrectomy; LR, local resection wedge resection; SG, segmental gastrectomy; ACTX, adjuvant chemotherapy; D3, D3 lymphadenectomy; HTCTX, hyperthermochemotherapy

The endoscopic mucosal resection (EMR) is the most beneficial method for patients because they do not have to undergo laparotomy or general anesthesia [6]. Theoretically, several groups of patients have very limited probability of nodal metastasis [10]. If the lesion is a mucosal cancer of differentiated histology without either lymphatic or vascular involvement, and without ulcerative change, the probability of lymph nodal metastasis is less than 0.3%. If the lesions fulfill the criteria, except that there is ulcerative change inside the lesion, only those that are 3 cm or less in size can be regarded as node negative (less than 0.8%). For lesions showing minimal submucosal invasion, less than 500 μm in depth, without lymphatic or vascular involvement, with

size 3 cm or less, the upper limit of 95% confidence interval of the probability of nodal metastasis is 2.5%.

However, EMR for a large lesion is technically demanding and it is not easy to remove lesions larger than 2 cm in one piece by the strip biopsy method. In this regard, EMR using a specially invented knife or hook to dissect the entire submucosal layer from the surface of the proper muscle layer is becoming more and more popular because it enables one-piece resection with full mucosal and submucosal layers of large size, up to even 10 cm. The term endoscopic submucosal dissection (ESD) is recently being used for this technique with the intention of discriminating it from EMR by strip biopsy technique using a snare [6]. At the moment, ESD is not for every gastroenterologist or surgeon. Therefore, the indication for EMR is described as follows in the Japanese Guideline: mucosal cancer, differentiated-type histology, smaller than 2 cm, without ulcer or ulcer scar in the lesion. These criteria should be confirmed by histological evaluation of the endoscopically resected specimen. To be accurate in evaluating the whole specimen, it is strongly advised to carry out a one-piece resection. For this meaning, EMR for T1 tumors other than those described in the guideline are regarded as treatment under investigation.

T1 tumors that do not meet the criteria for EMR or ESD should be treated by surgery. Two types of modification of D2 gastrectomy are recommended in the Japanese Guideline, because of low incidence of lymph node metastasis to the second tier nodal stations [11]. The area of resection is the same as the standard gastrectomy, but with D1 (including all perigastric lymph nodes of the relevant part of the stomach) plus the left gastric artery nodes is one option for clinically T1 (mucosal) and pN0 cancer of differentiated type larger than 2 cm or of undifferentiated histology of any size. For clinically T1 (submucosal) and pN0 cancer or clinically T1 (mucosal) and pN1 cancer, two-thirds or wider gastrectomy with D1 plus the left gastric, the common hepatic, and the celiac artery nodes is the recommended option. The indication of the modified procedures is based on the clinical and surgical diagnosis and therefore contains some risk of underestimation. The guideline gives caution of this risk. Other T1 tumors should be treated by the standard D2 gastrectomy. Laparoscopic gastrectomy with D1 or D2 lymph node dissection is nominated as a treatment under investigation.

## Treatment of Curable Advanced Gastric Cancer

For sT2 and sN0–2 tumors and sT3 and sN0–2 tumors, the standard D2 gastrectomy is the gold standard in the Japanese Guideline. For sT4 and sN0–2 tumors, the standard D2 gastrectomy with additional resection of the involved organ is regarded as the standard [13]. If published results of clinical studies evaluating the efficacy of D2 dissection are reviewed, the majority of them showed negative results [12–14]. However, all these negative studies were heavily criticized regarding the quality of surgery given in the D2 arm [15,16]. These results were understandable if the concepts of hospital volume and learning curve are incorporated.

The clinical trial (phase III) carried out by the Japan Clinical Oncology Group (JCOG) to evaluate the efficacy of paraaortic lymph node dissection has been closed and the survival results are awaited [17].

Another JCOG clinical trial on gastric cancer invading the lower esophagus proved that the abdominal-only approach should be used for these tumors whose esophageal invasion is 3 cm or less. Therefore, the majority of patients with type II or III tumors of the Siewert classification should be treated through laparotomy and the transdiaphragmatic approach [18]. Thorough mediastinal node dissection by thoracotomy is not needed to treat these tumors.

Just as in Europe, any kind of adjuvant treatment is regarded as a treatment under investigation. Although many meta-analyses of adjuvant chemotherapy show a small but significant benefit of adjuvant chemotherapy over surgery alone, treatment regimens of these analyses are widely heterogeneous. Similar to the conclusions of all these meta-analyses, adjuvant chemotherapy after curative surgery is regarded as under investigation and should be evaluated exclusively in clinical trials with surgery alone as the control [19–21]. Also, the guideline advocates RCT on adjuvant chemotherapy for curable gastric cancer, both pre- and postoperatively.

In the United States, an adjuvant chemoradiotherapy (CRT) after curative surgery is now regarded as the standard treatment [22]. However, in the clinical trial that proved the benefit of CRT over surgery alone, the type of lymph node dissection was just D0 (almost without nodal dissection) for 54% of patients, D1 for 36%, and D2 dissection for 10% of the patients. This finding means that 90% of the patients underwent surgery with insufficient local control in terms of lymph node dissection. Together with the fact that adjuvant chemotherapy alone could not prove a benefit over surgery alone, this trial proved the efficacy and importance of local control for the treatment of gastric cancer. Because the standard surgery for curable tumors in Japan includes much wider lymph node dissection and the stage-specific survival results of this trial were still worse than those of Japanese data, these results supporting the efficacy of CRT cannot be applied to Japanese patients. The effect of CRT after D2 dissection remains uncertain. In the Japanese guideline, the standard treatment for curable advanced gastric cancer is still D2 gastrectomy alone. Any kind of adjuvant treatment is regarded as investigational.

## Treatment of Incurable Gastric Cancer

Only those who can undergo R0 resection have a possibility of cure depending on the tumor stage, that is, T factor and N factor. Patients with nonresectable disease or with distant metastasis are incurable and are primarily treated by chemotherapy if they do not have serious symptoms such as massive bleeding or stenosis hindering oral intake. In the guideline, resection of primary gastric tumor in patients with distant metastasis is defined as reduction surgery and is regarded as investigational treatment. This reduction surgery has often been carried out in Japan without any evidence of advantage for the patients.

Similarly, the majority of recurrences are nonresectable and are treated by chemotherapy. However, at the moment, there is no standard chemotherapy regimen for nonresectable or recurrent gastric cancer. In the United States, the combination chemotherapy using fluorouracil and cisplatin plus docetaxel (5-FU + CDDP + docetaxel) is now regarded as the standard [23]. In Europe, on the other hand, epirubicin

+ CDDP + 5FU is recommended as the standard regimen [24]. These two newly developed regimens are highly toxic, and their efficacy and safety are not yet confirmed in Japanese patients. Actually, combination chemotherapy including TS-1, CPT-11, paclitaxel, 5-Fu, or CDDP is under investigation with the expectation of a longer survival period than with 5-FU alone.

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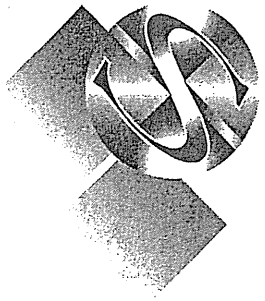

# Surgical Resection of the Stomach with Lymph Node Dissection

Mitsuru Sasako, Takeo Fukagawa, Hitoshi Katai and Kateshi Sano

## Aims

- To describe the techniques of radical lymph node clearance in gastric cancer surgery.
- To identifiy the aspects of surgery associated with significant morbidity.
- To define the use of pancreatic and splenic resection in gastric cancer surgery.

## Type of Gastric Resection

### Commonly Used Types of Resection

As gastrectomy is now rarely indicated for benign disease of the stomach, this chapter focusses on gastrectomy for gastric malignancies. For gastric cancers, several types of resection are commonly used. For proximal advanced tumours or large tumours, a total gastrectomy (TG) is usually used. For a distally located tumour which does not involve the proximal third of the stomach, a distal (DG) or distal subtotal gastrectomy (DSG) is the preferred type of gastric resection. In the 1980s, proximal gastrectomy (PG) was for a while abandoned because of the high incidence of reflux oesophagitis and in pursuit of radical surgery. However, with the identification of an increasing number of small T1/2 tumours located near the cardia, interest in the role of proximal gastrectomy has been renewed. For similar tumours in the middle of the stomach, pylorus preserving distal gastrectomy (PPG) is being undertaken in an attempt to improve quality of life after surgery [1].

### Total Versus Subtotal Gastrectomy

The concept of total gastrectomy as the appropriate radical surgical management of gastric cancer was promoted by some enthusiasts in the West during the 1970s. This concept has been described as "gastrectomie totale en principe". In Japan, however, TG was carried out only when it was required to allow an R0 resection to be achieved while DG was carried out for many antral tumours, with satisfactory results. To establish the role of the extent of gastric resection, several trials have been carried out to evaluate TG in principle.

There have been two randomised controlled trials comparing TG with DG for antral tumours. In France between 1980 and 1985, 201 patients were randomized between TG and DSG to test if TG could increase 5-year survival rate from 30% after DSG to 50%. After excluding 32 ineligible cases, 84% of randomised patients were included in the analysis; no differences in postoperative morbidity and mortality or in 5-year survival rates were demonstrated [2]. A

similar trial was carried out in Italy enrolling 648 patients between 1982 and 1993 [3]. This trial was set up to test the equivalence of DSG and TG, i.e. DSG should show 5-year survival rates no worse than −10% of the results of TG (50%). There was no significant difference in postoperative death (1.2% after DSG and 2.3% after TG) and 5-year survival rate after DSG was better than after TG (65% versus 62%), confirming the equivalence of the two methods for antral tumours. A further trial has compared DSG with D1 nodal dissection versus TG with D3 dissection [4]. The sample size was small (55 patients) and hypothesis tested included both the extent of gastric resection and extent of lymphadenectomy; as a result the trial is difficult to evaluate. The results demonstrated no significant differences in outcome though the survival curve after DSG was better than after TG.

Theoretically, the oncological gain provided by TG over DSG lies in the reduction in the risk of positive resection margins, the removal of missed second primaries and increasing the extent of lymphatic clearance. The extent of nodal dissection increases the dissection of the left cardiac nodes, short gastric artery nodes, splenic hilum nodes and distal splenic artery nodes. The pattern of lymphatic spread in antral cancers would indicate that removal of these node groups is unlikely to improve outcome. The problem of positive margins is mainly due to inaccurate diagnosis of proximal extension of tumours. For cancers in the mid body on the greater curve, the risk of lymphatic involvement of the splenic hilar and distal splenic artery nodes might support a need for total gastrectomy. For such cases, negative sampling of the nodes at the root of the left gastroepiploic artery or the sentinel nodes may safely allow surgeons to avoid TG.

## Indications for Proximal Gastrectomy (PG)

In 1970s, PG was abandoned for two reasons: a high incidence of local failure in the remnant stomach and frequent and severe reflux oesophagitis due to bile reflux when reconstruction was by oesophagogastrostomy. A dramatic increase in junctional tumours small cancers at the cardia, has been observed in the West. For small tumours located at the cardia as well as T1 tumours in the proximal third of the stomach, PG has been revived in both hemispheres during the 1990s. For T1 tumours of the proximal stomach, PG with extended D1 (D1 plus proximal splenic, coeliac and common hepatic artery nodes) is carried out, followed by a reconstruction with short segment jejunal interposition (modified Merendino's operation: Figure 25.1). For large tumours involving the cardia, because of intramural distal extension to the antrum and the significant incidence of nodal metastasis to the lower lesser curvature and infrapyloric nodes, a TG should be carried out. Harrison et al [5] claimed that TG is not necessary for proximal gastric cancer but the average size of the tumours treated by PG in their series was just 4 cm, much smaller than those treated by TG. Their method of reconstruction was traditional oesophagogastrostomy. As they did not evaluate the quality of life (QOL) of patients, especially in terms of reflux oesophagitis, their technique cannot be justified.

## Pylorus Preserving Gastrectomy (PPG)

Due to the increasing recognition of early gastric cancer in Japan, several surgical techniques have been recently tested to reduce

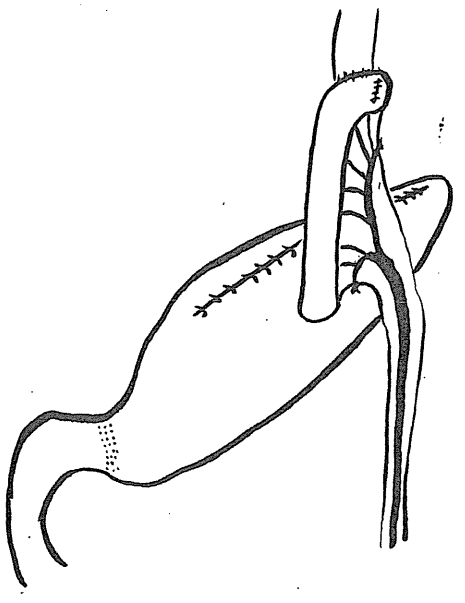

**Figure 25.1.** Modified Merendino's operation of proximal partial gastrectomy with jejunal interposition.