Individualized Adjuvant Chemotherapy Guided by Chemosensitivity Test Sequential to Extended Surgery for Advanced Gastric Cancer

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Abstract. *Background and Objectives: Various adjuvant chemotherapy regimens have been proposed for patients with advanced gastric cancer; however, the majority of these trials failed to show a clear survival benefit over surgery alone. In this study, the feasibility and efficacy of a strategy of extended surgery combined with individualized adjuvant chemotherapy for advanced gastric cancer with serosal invasion and nodal involvement was examined. Patients and Methods: Sixty-four patients with advanced gastric cancer underwent gastrectomy with extended lymph node dissection. After surgery, a chemosensitivity test by MTT assay, using highly purified tumor cells, was performed, and the patients received individualized adjuvant chemotherapy on the basis of the results of this chemosensitivity test. Results: Overall survival in the chemosensitivity-guided chemotherapy (CSC) group was significantly better than the standard chemotherapy (SC) and the no-chemotherapy (NC) group ($p<0.05$). In patients with stage IV disease, the 5-year survival rate was 38.1% in the CSC group and 0% in the SC + NC group, respectively, with a significant difference being observed in the two survival curves ($p<0.01$). In patients with paraaortic node involvement, survival in the CSC group was significantly better than that in the SC + NC group ($p<0.01$). On the other hand, in patients without paraaortic node involvement, no survival difference was observed between the two groups. Conclusion: The strategy of extended surgery combined with individualized adjuvant chemotherapy offers a favorable survival outcome for advanced gastric cancer patients with serosal invasion and nodal involvement.*

Gastric cancer is one of the leading causes of cancer-related death, especially in Asia, Africa and parts of Europe (1, 2). Extended lymph node dissection has been performed for gastric cancer in Japan, and the survival benefit of extended surgery has been demonstrated (3, 4). Neverthless, the prognosis of patients with advanced gastric cancer has not been sufficiently improved by extensive surgery (5). Therefore, various adjuvant chemotherapy regimens have been proposed to improve the postoperative survival. However, there are only a few reports which show a clear survival benefit of adjuvant chemotherapy over surgery alone (6).

It is important to select anticancer drugs which are effective against cancer cells in order to avoid the unnecessary use of these drugs which may cause adverse effects, especially after curative operation. In this respect, *in vitro* chemosensitivity testing is important (7). A rapid colorimetric assay was described by Mosmann (8) for determining the ability of viable cells to convert a soluble tetrazolium salt, 3-(4,5-di-methylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT), into an insoluble formazan precipitate. The MTT assay is a rapid and quantitative colorimetric system for determining the chemosensitivity of human tumor cells; however, the use of this assay for solid tumor tissues has been limited because of contamination by nonmalignant cells (9). In a previous study, we determined chemosensitivity in gastric cancer and colorectal cancer, using highly purified tumor cells, and showed a correlation between this sensitivity and clinical response (9-11). Since then, we have developed a treatment plan to improve the poor prognosis of patients with advanced gastric cancer. Gastrectomy, with extended lymph node dissection, was performed for patients with advanced gastric cancer showing serosal invasion and nodal involvement. After surgery, the MTT assay, using highly purified tumor cells, was performed,

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and patients received individualized adjuvant chemotherapy on the basis of the results of the chemosensitivity test.

In the present study, the feasibility and the efficacy of the strategy of extended surgery combined with individualized adjuvant chemotherapy for advanced gastric cancer with serosal invasion and nodal involvement is examined in a prospective non-randomized manner.

Patients and Methods

Patients. Sixty-four patients with advanced gastric cancer, admitted to Wakayama Medical University Hospital, Japan, between 1991 and 1996, underwent gastrectomy with extended lymph node dissection. This extended surgery was indicated for patients with advanced gastric carcinoma showing serosal invasion or N2 lymph node metastases. Total gastrectomy was performed in 49 patients, distal gastrectomy was performed in 14 patients and pancreaticoduodenectomy was performed in 1 patient. The lymph nodes, located perigastrically, around the gastric artery, the hepatic artery, the splenic artery and the celiac artery and paraaortic nodes were extensively dissected in all the patients.

The clinical stages of the 64 patients according to the TNM classification (4th edition) of malignant tumors by UICC were: 7 with stage Ib, 6 with stage II, 10 with stage IIIa, 12 with stage IIIb and 29 with stage IV. None of these patients had received any previous antitumor drugs. Surgical specimens were obtained from primary gastric lesions and the MTT assay was successfully performed in 38 patients.

Informed consent was obtained from the patient and/or the family twice, in advance of operation and of chemotherapy, in accordance with the guidelines of the Ethical Committee on Human Research, Wakayama Medical University, Japan.

Anticancer drugs. The antitumor drugs tested were cisplatin (CDDP), mitomycin C (MMC), doxorubicin (DOX) and 5-fluorouracil (5-FU). Each drug was diluted in complete medium at 10-fold therapeutic peak plasma concentration (Cmax x 10), achieved by intravenous administration of clinical doses (12), as described in our previous studies (10). The values were 10 μg/ml MMC, 100 μg/ml 5-FU, 4 μg/ml DOX and 20 μg/ml CDDP. The complete medium used consisted of RPMI-1640 (Nissui Co., Tokyo Japan) supplemented wlth 10% heat-inactivated fetal calf serum (GIBCO, New York, USA), 2 mM L-glutamine and antibiotics (100 units/ml of penicillin and 100 μg/ml of streptomycin).

Purification of fresh human gastric cancer cells. Freshly excised tumor tissues were processed using enzymatic digestion, as previously described (10). Briefly, tumor tissues were dissected into small pieces, which were immersed in complete medium containing collagenase (2 mg/ml, type V-S; Sigma), hyaluronidase (10 units/ml, type IV-S; Sigma), and DNase-I (0.4 mg/ml; Sigma). After a 40-min incubation at 37°C, the cells were harvested and were centrifuged on Ficoll-Hypaque (specific gravity 1.077; Pharmacia, Uppsala, Sweden) gradients at 400 xg for 30 min. The interface was collected, and suspended at a density of $1x10^6$/ml in complete medium. Then, the cell suspension was layered on discontinuous gradients consisting of 10 ml of 100% and 15 ml of 75% Ficoll-Hypaque. After centrifugation at 400 xg for 30 min, a tumor cell-rich fraction was collected from the 75% interface. The tumor cell-enriched suspension was then layered on discontinuous gradients containing 4 ml each of 25%, 15% and 10% Percoll (Pharmacia, Uppsala, Sweden) in complete medium. Centrifugation was performed at 15 xg for 7 min and tumor cells depleted of lymphoid cells were collected from the bottom and from the 25% interface. The cells thus prepared were primarily tumor cells, with less than 10% contamination by nonmalignant cells (9).

MTT assay. Chemosensitivity was assessed using the tetrazolium salt MTT (Sigma No. M2128) to measure the viability of tumor cells, as previously described (9, 10). Briefly, tumor cell suspensions ($1x10^6$ cells /ml) were added to each anticancer drug at a final concentration of Cmax x 10 in 96-well flat-bottomed microtiter plates (Corning No. 25860), and incubated at 37°C in a humidified 5% CO_2 atmosphere for 96 h. The chemosensitivity assay was assessed in triplicate. Microtiter wells containing tumor cells without anticancer drugs were used as controls for cell viability, while wells containing only complete medium were used as controls for nonspecific dye reduction. After incubation, the plates were centrifuged, the supernatants were removed and MTT solution with 10 μM of sodium succinate was added to all the wells. The plates were incubated for an additional 4 h, and dimethyl sulfoxide (DMSO) was then added to all the wells; the mixtures were pipetted thoroughly to dissolve the dark blue crystals. The plates were then read on a microplate reader (Corona Electric, MTP-32) using a test wavelength of 570 nm and a reference wavelength of 630 nm. The control wells without tumor cells had an optical density (OD) of less than 0.005, and the samples in which the OD was over 0.1 were accepted for the assay. The inhibition rate was calculated as follows:

Inhibition rate = (1 – OD drug-treated/OD control) x 100

The background of tumor cells (including dead cells) without addition of MTT had an OD of less than 0.012 after 96-h incubation, and the influence of dead tumor cells could therefore be ignored in the present study. The viability of tumor cells was maintained at 75-90%, during the 96-h incubation (10). The cut-offs were inhibition rates equal to or more than 74% (10).

Chemosensitivity test-oriented chemotherapy. The MTT assay was performed in 40 out of 64 patients, succeeding in 38. The patients received treatment according to the chemosensitivity guideline as follows: when sensitive drugs could be selected by the MTT assay, a single drug or combination of two or three drugs were chosen on the basis of these results; when no effective drugs were identified, patients primarily did not receive the adjuvant chemotherapy, or were treated with cisplatin and 5-fluorouracil (FP) at their request; when the chemosensitivity test could not be performed, the patients were treated with FP.

Six out of 38 patients did not receive chemosensitivity-guided chemotherapy after extended surgery of their own volition, although suitable drugs had been identified by the MTT assay.

Forty-two patients received adjuvant chemotherapy after surgery. Thirty-two patients were treated on the basis of the results of the MTT assay (chemosensitivity-guided chemotherapy group; CSC), while 17 patients received standard chemotherapy without any chemosensitivity information (standard chemotherapy group; SC). Patients were individually treated with the protocols shown in Figure 1. On the other hand, 15 patients did not receive any chemotherapy after surgery (no-chemotherapy group; NC).

Chemosensitivity-guided chemotherapy group (CSC)

Choose a single drug or combination therapy using two or three drugs as below on the basis of the results of chemosensitivity test (2 – 3 courses).

CDDP:	10 - 15 mg / m²	day 1 –day 5	
MMC:	8 - 10 mg / m²	day 1	
5-FU:	500 - 750 mg / m²	day 1 –day 5	(continuous infusion)
ADR:	20 mg / m²	day 1	

Chemotherapy without chemosensitivity group (standard chemotherapy group; SC).

Combination therapy using two drugs as below (2 – 3 courses)

CDDP:	10 - 15 mg / m²	day 1 –day 5	
5-FU:	500 - 750 mg / m²	day 1 –day 5	(continuous infusion)

Figure 1. *Treatment protocol of adjuvant chemotherapy. Patients were individually treated with different protocols. In cases where the sensitive drugs could be selected by MTT assay, either a single drug or combination of two or three drugs was chosen on the basis of the results of the chemosensitivity test. In cases where there were no sensitive drugs, patients did not receive the adjuvant chemotherapy, or were treated with cisplatin and 5-fluorouracil (FP) as self-requested. In cases where the chemosensitivity test could not be performed, patients were treated with FP.*

Statistical analysis. Quantitative results were expressed as mean±standard deviation of the mean. Statistical analysis was performed by ANOVA and Fisher's test. Background factors were compared using the Student's *t*-test, the Mann-Whitney *U*-test and the χ^2 test. The survival rates were estimated using the Kaplan-Meier method, and the differences were analyzed by using the log-rank test, to compare the resulting curves of the treatment groups. Multivariate analysis was examined according to Cox's proportional hazard model. A *p*-value of <0.05 was considered to be statistically significant. StatView 5.0 software (Abacus Concepts, Inc., Berkeley, CA, USA) was used for all statistical analyses.

Results

Patient characteristics. The clinicopathological characteristics of the patients were shown in Table I. There were no significant differences in background factors which were considered to be related to prognosis between the CSC group and the SC + NC group.

Chemosensitivity of patients with advanced gastric carcinoma. The MTT assay was performed in 40 out of 64 patients who received extended surgery, succeeding in 38, but failing in 2 patients because of low OD. The success rate of this assay was 95%. The chemosensitivity of the patients with advanced gastric carcinoma is shown in Table II. At a drug concentration of Cmax x 10, the inhibition rates of tumor cells for each of the four drugs was around 65%. There was no significant difference in chemosensitivity between differentiated and undifferentiated types.

Table I. *Clinicopathological characteristics.*

Clinicopathological characteristics	CSC group (n=32)	SC + NC group (n=32)	*p*
Age (yrs; average±SD)	57.8±13.0	57.2±11.3	NS
Gender(male/ female)	26/ 6	22/10	NS
Stage			
I	2	5	NS
II	3	3	
III	12	10	
IV	15	14	
Depth of tumor invasion			
t1	2	2	NS
t2	10	11	
t3	15	12	
Lymph node metastases			
n0	6	7	NS
n1	0	0	
n2	26	25	
Tumor type			
type 0	2	0	NS
type 1	1	1	
type 2	5	7	
type 3	18	20	
type 4	6	4	
Histological type			
differentiated	17	14	NS
undifferentiated	15	18	
Operation			
distal gastrectomy	7	7	NS
total gastrectomy	25	24	
pancreaticoduodenectomy	0	1	
Curability of surgery			
Curative	27	24	NS
Noncuratiive	5	8	

There were no significant differences in background factors which were considered to be related to the prognosis of gastric cancer patients between the CSC group and the SC + NC group.

Effect of chemosensitivity-guided adjuvant chemotherapy on survival of gastric cancer patients. The 5-year survival rate was 56.3% in the CSC group and 28.1% in the SC + NC group, respectively, presenting a significant difference in the two survival curves ($p<0.05$) (Figure 2A). The difference between the two groups was remarkable in patients with advanced stage. In patients with stage III disease, the 5-year survival rate was 66.7% in the CSC group and 30.0% in the SC + NC group, respectively, although there was no statistically

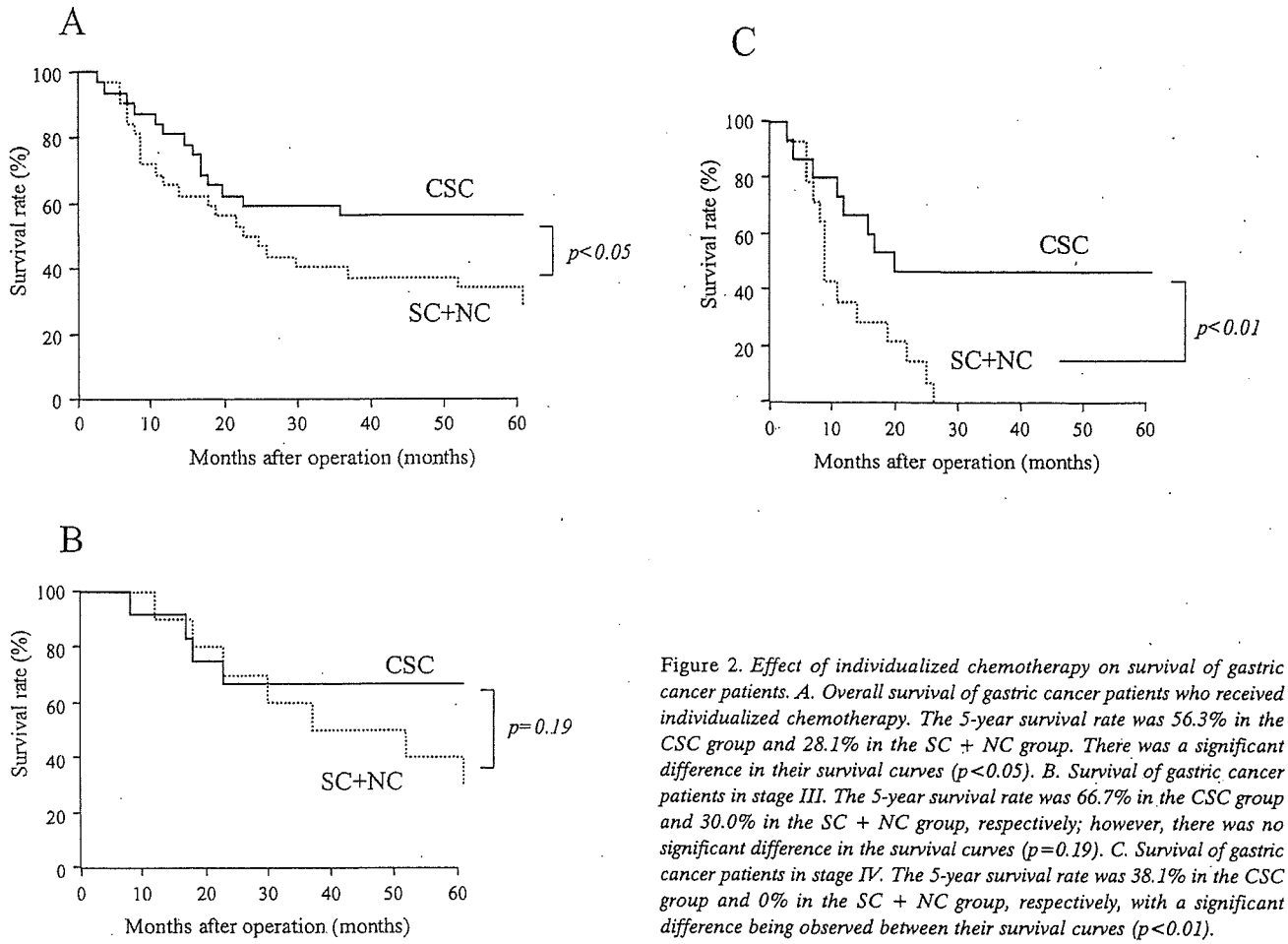

Figure 2. *Effect of individualized chemotherapy on survival of gastric cancer patients. A. Overall survival of gastric cancer patients who received individualized chemotherapy. The 5-year survival rate was 56.3% in the CSC group and 28.1% in the SC + NC group. There was a significant difference in their survival curves ($p<0.05$). B. Survival of gastric cancer patients in stage III. The 5-year survival rate was 66.7% in the CSC group and 30.0% in the SC + NC group, respectively; however, there was no significant difference in the survival curves ($p=0.19$). C. Survival of gastric cancer patients in stage IV. The 5-year survival rate was 38.1% in the CSC group and 0% in the SC + NC group, respectively, with a significant difference being observed between their survival curves ($p<0.01$).*

Table II. *Chemosensitivity of patients who received extended surgery.*

(n=38)

	Inhibition rates (%)			
	CDDP	MMC	ADR	5-FU
All cases	66±23	66±21	64±23	69±25
Differentiated type	68±19	66±21	65±21	68±25
Undifferentiated type	64±28	67±22	62±25	70±25

Data are expressed as mean + standard deviation (SD).
Differentiated type: well- or moderately- differentiated tubular adenocarcinoma, papillary adenocarcinoma.
Undifferentiated type: poorly-differentiated adenocarcinoma, signet-ring cell carcinoma.

significant difference in survival ($p=0.19$) (Figure 2B). In patients with stage IV disease, the 5-year survival rate was 38.1% in the CSC group and 0% in the SC + NC group, respectively, with a significant difference being observed between the survival curves ($p<0.01$) (Figure 2C). To analyze the characteristics of patients who benefited from the adjuvant chemotherapy, patients with stage IV were divided into two groups according to the existence of paraaortic lymph nodes metastases. In patients with paraaortic lymph node metastases, the 5-year survival rate was 42.9% in the CSC group and 0% in the SC + NC group, respectively, and there was significant difference in the survival curves ($p<0.01$) (Figure 3A). On the other hand, in patients without paraaortic lymph node metastases, no survival difference was observed between the two groups (Figure 3B).

For patients with stage IV disease, a significant difference in the survival curves was observed between the CSC group and either the SC group or the NC group ($p<0.05$), although the survival difference between the SC group and the NC group was not significant (Figure 4).

Multivariate analysis of risk factors for prolonged overall survival. Multivariate analysis of risk factors for prolonged overall survival was examined according to Cox's proportional hazard model. The risk ratio of each factor is

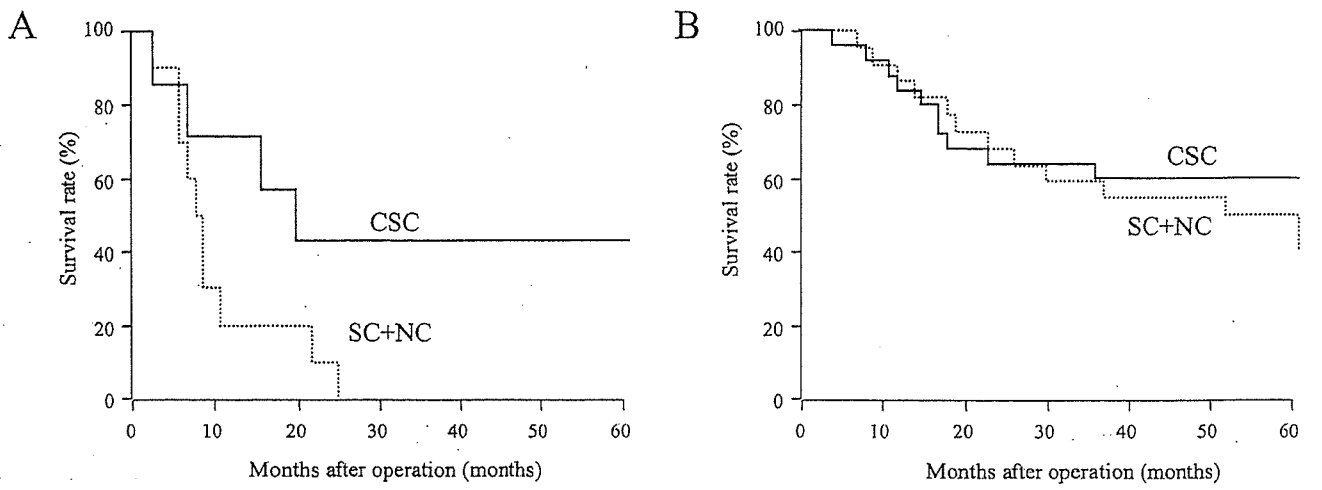

Figure 3. *Effect of individualized chemotherapy on survival of patients with and without paraaortic lymph node involvement. A. Survival of gastric cancer patients with paraaortic lymph node involvement. The 5-year survival rate was 42.9% in the CSC group and 0% in the SC + NC group, respectively, with a significant difference in the survival curves ($p<0.01$). B. Survival of gastric cancer patients without paraaortic lymph node involvement. No significant survival difference was observed between the CSC group and the SC + NC group.*

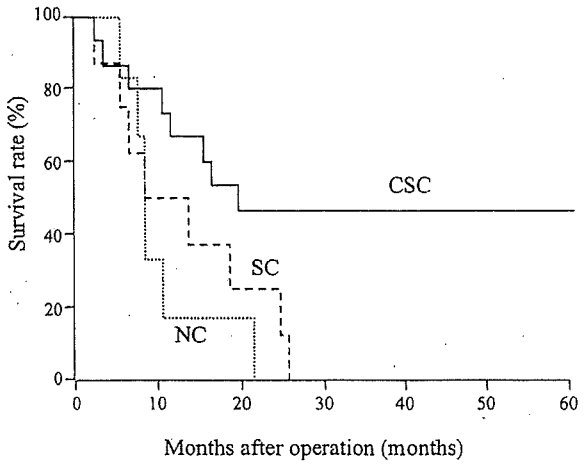

Figure 4. *Effect of individualized chemotherapy on the survival of gastric cancer patients in stage IV. When the SC + NC group was divided into the SC group and the NC group, a significant difference was observed between the survival curves of the CSC group and the SC group or the NC group ($p<0.05$). On the other hand, there was no significant difference in the survival between the SC group and the NC group.*

shown in Table III. Chemosensitivity-guided chemotherapy was an independent risk factor for overall survival.

Discussion

Surgical resection is the most common approach for the treatment of patients with advanced gastric carcinoma. Although, the benefit of D2 lymphadenectomy is yet to be clarified (13, 14), Japanese surgeons have established D2 lymph node dissection (15), and some specialized centers in other countries have shown the benefits of D2 lymph node dissection (16-22). Furthermore, some Japanese specialists have performed a pilot study of extended D4 lymph node dissection (removal of paraaortic nodes in addition to D2 dissecton) for patients with advanced gastric carcinoma (23, 24). Nevertheless, the prognosis of the patients who have paraaortic node involvement is still poor (23, 24). Therefore, we attempted to improve the postoperative survival of such patients by the combination of extensive surgery with adequate adjuvant chemotherapy.

To date, various adjuvant chemotherapy regimens have been proposed; however, the majority of trials have failed to show a clear survival benefit over surgery alone (25, 26), although several meta-analyses have shown the survival benefit of adjuvant chemotherapy after curative surgery compared with surgery alone (27-29). The most recent study conducted by the Japanese Clinical Oncology Group (JCOG) also could not show the efficacy of adjuvant chemotherapy (30).

Bearing the problem of drug resistance in mind, the MTT assay has proven to be a rapid and quantitative colorimetric system for the determination of the chemosensitivity of tumor cells, correlating with clinical response (9-11, 31, 32). This strategy was employed in choosing the regimen of adjuvant chemotherapy for advanced gastric cancer patients who underwent gastrectomy.

In this study, survival of the patients in the CSC group was significantly better than that in the SC + NC group. The difference between the two groups was more remarkable in patients with advanced stage, especially in patients with stage IV disease (5-year survival rate: 38.1%). This result is

Table III. *Multivariate analysis of risk factors for prolonged overall survival.*

Risk factors	Hazard ratio	*p*	95%CI
Chemosensitivity-guided chemotherapy	3.636	0.0045	1.491 ~ 8.863
Peritoneal metastases	2.684	0.0416	1.038 ~ 6.940
Histological type	2.344	0.0670	0.942 ~ 5.830
Depth of tumor invasion	1.289	0.4197	0.696 ~ 2.387
Lymph node metastases	1.981	0.0151	1.141 ~ 3.437
Curability of surgery	2.894	0.1386	0.709 ~ 11.816

Multivariate analysis of risk factors for prolonged overall survival was examined according to Cox's proportional hazard model. Chemosensitivity-guided chemotherapy was an independent risk factor for overall survival.

consistent with previous reports (7, 33, 34). In stage IV, it was patients with paraaortic node involvement who benefited from the adjuvant chemotherapy. These results suggest that adjuvant chemotherapy after extended surgery might prolong the survival of patients who possibly have micrometastatic lesions which were not resected during operation. Noteworthily, when the SC + NC group was divided into its two counterparts, a significant difference in the survival curves of stage IV patients was observed not only between the CSC group and the NC group, but also between the CSC group and the SC group. Adjuvant chemotherapy in the SC group failed to show a survival advantage over surgery alone, although cisplatin and 5-fluorouracil (FP) were used in most of this group. Therefore, it is suggested that the chemosensitivity test based on the MTT assay using highly purified tumor cells would be useful for planning individualized adjuvant chemotherapy, resulting in a favorable survival outcome.

Several studies are in agreement with our viewpoint. Kubota *et al.* have reported that prediction of chemosensitivity using a histoculture drug-response assay would potentially contribute to patient survival in gastric cancer (33). The collagen gel droplet embedded culture-drug sensitivity test (CD-DST) has been recently developed, and it has been reported that CD-DST can predict the response to chemotherapy with a high accuracy in breast cancer patients (35). Each method of chemosensitivity testing, including our method, has merits and demerits. Quite recently, so-called tailor-made chemotherapy has been developed using biomarkers such as multiple drug-resistant protein (MRP)-1 (36) and dihydropyrimidine dehydrogenase (DPD) (37), but superiority to bioassays are yet to be established (35).

New anticancer drugs have been recently developed, and some of them, such as TS-1, CPT-11, paclitaxel and docetaxel, are already available for gastric cancer. TS-1, in particular, is a novel oral anticancer drug and has been reported to be very effective in a phase II clinical trial (38). These new drugs, as single or combined regimens, will surely play major roles in chemotherapy against gastric cancer. However, with efficacy rates less than 50%, potential adverse effects and high costs, correct selection by chemosensitivity testing is obviously desirable.

In conclusion, chemosensitivity testing of individual gastric cancer with highly purified tumor cells using the MTT assay was useful in choosing effective anticancer drugs for adjuvant chemotherapy. The strategy of extended surgery combined with individualized adjuvant chemotherapy offers a favorable survival outcome for advanced gastric cancer with serosal invasion and nodal involvement.

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Surgical Management of Small Gastrointestinal Stromal Tumors of the Stomach

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Abstract
Small gastrointestinal stromal tumors (GISTs) (<3 cm) occasionally are found in the stomach during endoscopy. There is no consensus about the surgical management of these small tumors, although this clinical issue is crucial because some of the tumors show unexpected malignant behavior. In this study, we evaluated the clinical management of patients with gastric GISTs who underwent surgical resection. Altogether, 31 patients with gastric GISTs were examined retrospectively. Surgical resection was fundamentally indicated for the patients with gastric GISTs suspected to be malignant by endoscopy or endoscopic ultrasonography (EUS). The malignant grade of the GISTs was evaluated by the mitotic rate, tumor size, and MIB-1 index. EUS was useful for differentiating benign from malignant GISTs; but by limiting the study to patients with small tumors (<3 cm), the diagnostic value of EUS was not satisfactory for defining the surgical indication. Tumors that were <50 mm were successfully treated by laparoscopic surgery. Of the 31 patients, 4 had a relapse of the disease, and 1 of those 4 patients had a small tumor (30 mm). All of the recurrences were classified in the high risk category. Surgery is indicated for gastric GISTs that are ≥20 mm or are suspected to be malignant based on EUS findings. Laparoscopic resection is feasible and is recommended as the treatment of choice for patients with tumors < 50 mm. Risk assessment can be most useful for predicting recurrence.

Gastrointestinal stromal tumors (GISTs) are the most common nonepithelial, mesenchymal neoplasms of the gastrointestinal tract.[1,2] Grossly, they appear to arise from the muscular layer, and their presumed origin from smooth muscle cells has led to the use of such terms as "leiomyoma," "leiomyosarcoma," and "leiomyoblastoma".[3] However, it has been recognized that there are a group of sarcomas arising from the gastrointestinal tract that do not have the typical features of leiomyosarcoma. Recent immunohistochemical studies have shown that up to 94% of GISTs express CD117, a KIT protein,[1,3,4] and 60% to 70% of GISTs stain for CD34.[1,5,6] Therefore, the GIST is now considered a completely separate entity from leiomyoma and leiomyosarcoma, which were previously thought to be the most common soft tissue neoplasms in the gastrointestinal tract.[6]

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GISTs occur mainly in the stomach (40–70%),[6] and small GISTs of <3 cm are occasionally found in the stomach during endoscopy because of improvements in the upper gastrointestinal endoscopic examination. However, there is no consensus about the surgical management of such small tumors. This clinical issue is crucial because some of these small tumors exhibit unexpected malignant behavior.[5] Moreover, small tumors can be resected by a laparoscopic surgical procedure in most cases,[7–9] and tumor size has been previously reported to be one of the most important prognostic factors for GISTs.[3,5,6]

In the present study, we analyzed the clinicopathologic features and evaluated clinical management in 31 patients with gastric GISTs. We also examined the feasibility of the preoperative diagnosis of GISTs using endoscopic ultrasonography (EUS). We have tried to formulate guidelines for the surgical management of GISTs, especially of tumors <3 cm.

PATIENTS AND METHODS

Patients

A series of 33 patients with submucosal tumors (SMTs) of the stomach were admitted to Wakayama Medical University Hospital between 1998 and 2003 and underwent surgical treatment. Altogether, 31 of those patients had histologically proven GISTs and were retrospectively examined in this study. Surgical resection was fundamentally indicated for the patients with gastric SMTs suspected to be malignant.

Methods

The clinical diagnosis before treating the patients was obtained via gastrointestinal endoscopy, EUS, and computed tomography (CT). EUS was mainly used for diagnosing the SMTs in 30 patients; one patient did not undergo EUS. Our criteria for endoscopic or EUS findings being interpreted as possibly malignant were as follows: ulcer formation, tumors >30 mm, asymmetric margin, heterogeneous US pattern, existence of an echo-free area, and rapid growth.

The histologic diagnosis of all tumors was obtained by microscopy with conventional hematoxylin and eosin (H&E) staining. Immunohistochemical staining for CD117, CD34, s-100 protein, vimentine, and αSMA was also carried out; and CD117- andCD34-positive tumors were diagnosed as GISTs. The malignant grades of the tumors were evaluated using the mitotic rate and tumor diameter. We used the determination that tumors <5 cm in diameter with 0 to 4 mitoses/50 high-power fields (HPFs) were considered benign, and tumors >5 cm in diameter with 0 to 4 mitoses/50 HPF were considered low-grade malignant. Tumors with >5 mitoses/50 HPF were considered malignant.[6,10]

We also evaluated each tumor using the risk categories proposed by Fletcher and colleagues.[5] Tumors <2 cm in diameter with 0 to 4 mitoses/50 HPF were considered very low risk, and tumors 2 to 5 cm in diameter with 0 to 4 mitoses/50 HPFs were low risk. Tumors <5 cm in diameter with 6 to 10 mitoses/50 HPF or tumors 5 to 10 cm in diameter with 0 to 4 mitoses/50 HPF were considered intermediate risk. Tumors >5 cm in diameter with a mitotic count higher than 5/50 HPF, those >10 cm, and those with >10 mitoses/50 HPF were classified as high risk tumors.[5]

Statistical Analysis

Quantitative results were expressed as the mean ± standard deviation of the mean (SEM). The statistical significance of the difference between the two groups was determined by Student's *t*-test. StatView 5.0 software (Abacus Concepts, Berkeley, CA, USA) was used for all statistical analyses.

RESULTS

Clinicopathologic Characteristics

The clinicopathologic characteristics of the patients are shown in Table 1. Seven patients who had symptoms (*e.g.*, epigastric pain) came to Wakayama Medical University Hospital for further examination; the other 24 patients with no symptoms underwent an ordinary checkup, at which time an abnormality of the stomach was detected. No particular differences were observed in tumor growth patterns. EUS findings showed a malignant pattern in 71% and a benign pattern in 26%. The mean tumor size was 40.2 ± 26.2 mm (range 10–120 mm). Pathologic examinations showed that 64% of the tumors were malignant, 13% were low-grade malignant, and 23% were benign based on the classifications of Amin *et al.*[10]

Risk categories were also used for the prediction of clinical behavior. Altogether, 8 cases were in the high risk group, 15 were in the intermediate risk group, 4 were in the low risk group, and 4 were in the very low risk group. Most of the cases (74%) were in the high and intermediate groups.

Surgical treatment was performed in all cases, with laparoscopic partial gastrectomy being performed in al-

Table 1.
Clinicopathologic characteristics of 31 patients

Age (years), mean ± SD	63.1 ± 13.2
Gender	
Male	13 (42%)
Female	18 (58%)
Clinical symptoms	
Anemia/bleeding	3 (10%)
Abdominal pain	4 (13%)
None	24 (77%)
Tumor location	
Upper third	23 (74%)
Middle third	8 (26%)
Lower third	0
Growth pattern	
Intragastric	8 (26%)
Intramural	11 (35%)
Extragastric	12 (39%)
EUS pattern	
Malignant	22 (71%)
Benign	8 (26%)
Not done	1 (3%)
Tumor size (mm), average ± SD	40.2 ± 26.2
Pathologic malignancy grade	
Malignant	20 (64%)
Low-grade malignant	4 (13%)
Benign	7 (23%)
Risk category	
High	8 (26%)
Intermediate	15 (48%)
Low	4 (13%)
Very low	4 (13%)
Operation	
Laparoscopic partial resection	15 (48%)
Intragastric tumor resection	7 (23%)
Open partial resection	6 (19%)
Open gastrectomy	3 (10%)

EUS: endoscopic ultrasonography.

most half of the cases (48%). Intragastric tumor resection was performed in 23% of the cases and open partial gastrectomy in 19%. Open gastrectomy was performed in only three cases (10%): one proximal gastrectomy and two total gastrectomies).

The clinical characteristics of patients with benign tumors were compared to those of patients with malignant/low grade malignant tumors. There were no significant differences (Table 2).

Correlation between EUS Findings and Pathologic Malignancy Grade

To assess whether EUS was valuable for differentiating benign from malignant gastric GISTs, a correlation between EUS findings and the pathologic diagnosis was examined. Of the 24 cases of malignant or low-grade malignant GISTs, 21 were diagnosed as malignant tumors, and 4 of the 6 benign GISTs were diagnosed as benign based on EUS findings. There was a significant correlation between EUS findings and the pathologic diagnosis ($P < 0.05$). The sensitivity and specificity were 83.3% and 66.7%, respectively, and the accuracy was 80.0% (Table 3). Clearly, limiting the results to patients with tumors <3 cm caused the diagnostic value of EUS to decline. No significant correlation between EUS and the pathologic diagnosis was recognized. More importantly, the sensitivity fell to 70.0%, and the specificity was 80.0%; therefore, the accuracy was only 73.3% (Table 4).

Correlation of Tumor Size with Pathologic Malignancy Grade and Risk Category

The size of the tumor in malignant or low-grade malignant cases ranged from 17 to 120 mm (mean 46.8 mm), which was larger than that in benign cases (mean 19.6 mm, range 11–80 mm) ($P < 0.05$) (Fig. 1A). Regarding the risk categories, the risk similarly tended to increase in proportion to tumor size. Tumor size ranged from 30 to 120 mm (mean 58.3 mm) in the high risk group, from 17 to 80 mm (mean 41.9 mm) in the intermediate risk group, from 24 to 40 mm (mean 31.3 mm) in the low risk group, and from 10 to 15 mm (mean 12 mm) in the very low risk category (Fig. 1B). However, it should be noted that some of the malignant tumors and those in the intermediate risk category were <30 mm.

Surgical Treatment

Complete resection with a macroscopic safety margin of >2 cm was accomplished in all cases. Most of the tumors that were <50 mm were treated by laparoscopic surgery. In cases treated by laparoscopic surgery, tumors with an intragastric growth pattern were treated by laparoscopic intragastric surgery,[11] and tumors showing intramural or extragastric growth patterns were treated by laparoscopic partial resection of the stomach. On the other hand, most of the tumors >50 mm were treated by open partial resection or gastrectomy. Two of the tumors <50 mm were treated by open surgery because they were accompanied by other disease, such as gastric carcinoma (Fig. 2). None of the tumors ruptured during the operation. Histologic surgical margins of resected tumors measured >15 mm in all cases. Among the 31 patients, one who also had gastric cancer underwent a regional lymph node dissection, and four patients with large tu-

Table 2.
Comparison of clinical factors between patients with benign and low-grade malignant/malignant tumors

Clinical factor	Benign (n = 7)	Low-grade/malignant (n = 24)	*P*
Age (years), mean ± SD	62.4 ± 14.5	63.3 ± 13.1	0.8819
Gender			
Male	5	8	
Female	2	16	0.0723
Clinical symptoms			
Symptomatic	2	6	
Asymptomatic	5	18	0.8493
Tumor location			
Upper third	5	18	
Middle third	2	6	0.8493
Growth pattern			
Intragastric	2	6	
Intramural	4	7	
Extragastric	1	11	0.2704
Microscopic findings			
Ulcer formation	0	7	
No ulcers	7	17	0.1044

Table 3.
Diagnostics value of EUS for the gastric GIST

	Pathologic diagnosis (n = 30)	
EUS diagnosis	Malignant/low-grade malignant	Benign
Malignant	20	2
Benign	4	4

To assess whether EUS was valuable in the diagnosis of the malignancy grade of gastric gastrointestinal stromal tumors (GISTs), a correlation between EUS findings and the pathologic diagnosis was examined. There was a significant correlation between EUS findings and pathologic diagnosis ($P < 0.05$). The sensitivity and specificity were 83.3% and 66.7%, respectively, and the accuracy was 80.0%.

Table 4.
Diagnostics value of EUS for small gastric GISTs (<3.0 cm)

	Pathologic diagnosis (n = 15)	
EUS diagnosis	Malignant/low-grade malignant	Benign
Malignant	7	1
Benign	3	4

To assess whether EUS was valuable in the diagnosis of the malignancy grade of small gastric GISTs (< 3.0 cm), a correlation between EUS findings and pathologic diagnosis was examined. No significant correlation between EUS and pathologic diagnosis was recognized. The sensitivity and specificity were 70.0% and 80.0, respectively, and the accuracy was 73.3%.

mors underwent sampling of lymph nodes adjacent to the tumors. Although most of these five patients had large tumors that were pathologically malignant and were defined as high risk, the histological examination revealed no lymph node involvement in any of them (data not shown).

Correlation of Recurrence with Malignant Grade or Risk Classification

Among 20 malignant tumors, 8 (40%) were defined as high risk, 11(55%) as intermediate risk, and just 1 (5%) as low risk in the risk categories. All of the low-grade

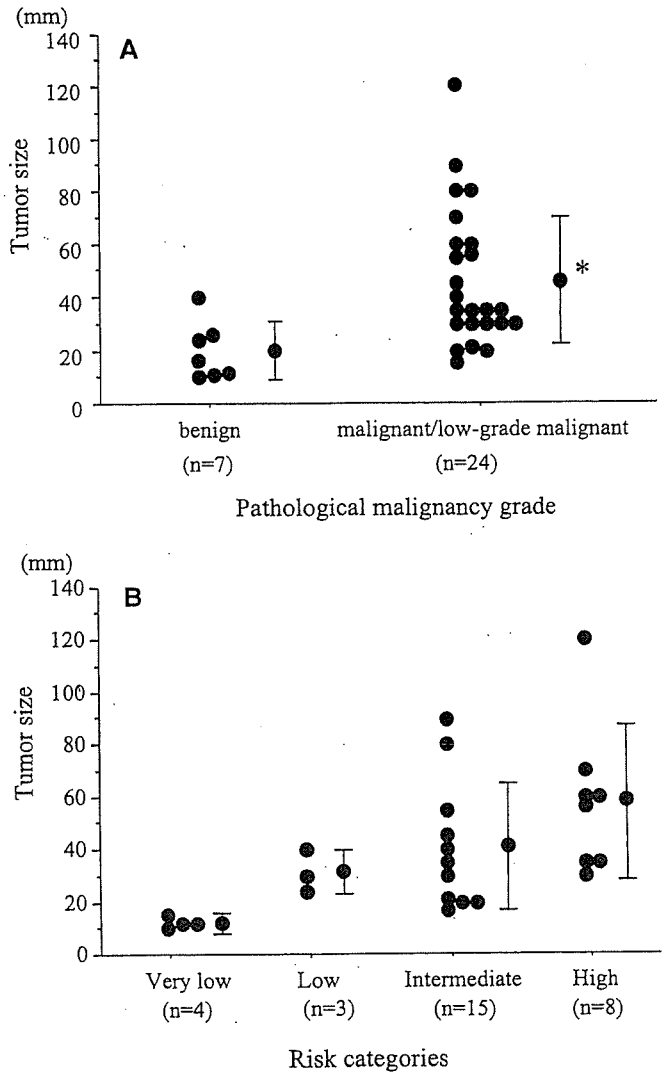

Figure 1. A. Correlation of tumor size with pathologic malignancy grade. Tumors <5 cm in diameter and with 0 to 4 mitoses/50 high-power fields (HPF) were considered benign, and tumors >5 cm in diameter and with 0 to 4 mitoses/50 HPF were low-grade malignant. Tumors with more than 5 mitoses/50 HPF were considered malignant. **B.** Correlation of tumor size with risk categories. Tumors <2 cm in diameter and with 0 to 4 mitoses/50 HPF were considered very low risk, and tumors 2 to 5 cm in diameter and with 0 to 4 mitoses/50 HPF were low risk. Tumors <5 cm in diameter and with 6 to 10 mitoses/50 HPF or tumors 5 to 10 cm in diameter and with 0 to 4 mitoses/50 HPF were intermediate risk. Tumors >5 cm in diameter and a mitotic count higher than 5 mitoses/50 HPF, tumors >10 cm, or tumors with >10 mitoses/50 HPF were classified as high risk.

malignant tumors were classified into the intermediate risk category, and all of the benign tumors were classified into the low or very low risk category (Fig. 3).

The median follow-up time was 32 months (9–68 months). No patients received adjuvant or neoadjuvant therapy with imatinib mesylate. Among the 31 patients, 4 (13%) experience a relapse, and 1 died of a recurrent

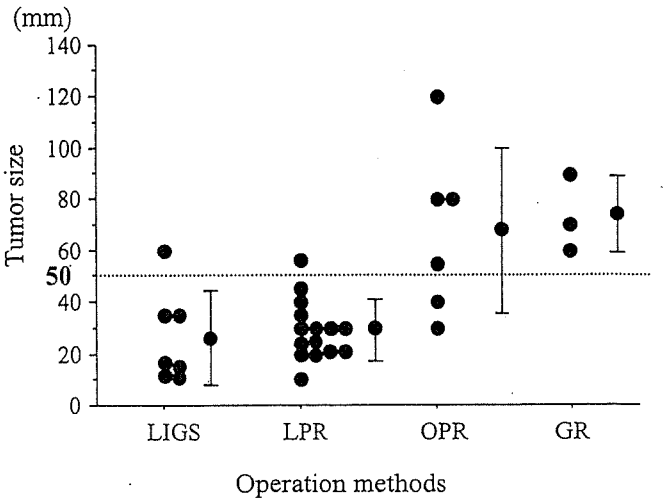

Figure 2. Surgical treatment and tumor size. Laparoscopic partial gastrectomy was performed in almost half of the cases (48%). Intragastric tumor resections were performed in 23% of cases and open partial gastrectomy in 19%. Open gastrectomy was performed in only 10% of cases. Correlation of tumor size and operative methods was evaluated. LIGS: intragastric tumor resection; LPR: laparoscopic partial resection; OPR: open partial gastrectomy; GR: open gastrectomy.

tumor. The site of recurrence was the liver in all cases. Neither lymph node recurrence nor local recurrence was observed. These recurrent cases were defined as malignant by a pathology examination and were classified in the high risk category (Table 5); moreover, the MIB-1 index of the tumors in recurrent cases was 9.2 ± 6.8 (2.4–18.1), which was significantly higher than that in the cases without recurrence 2.1 ± 1.1 (0.7–4.5) ($P < 0.0001$) (data not shown).

DISCUSSION

Endoscopic ultrasonography is considered one of the most useful tools for preoperative management of GISTs along with CT and magnetic resonance imaging (MRI).[6,12] EUS is more useful than those examinations for assessing small tumors. First, it is superior to other imaging modalities for measuring tumor size accurately. Moreover, it is a valuable method not only in the differential diagnosis of a submucosal tumor[13,14] but also for differentiating benign from malignant tumors. Yamada and colleagues reported of the usefulness of EUS for defining malignant myogenic tumors and identifying tumor diameter, shape, ulceration depth, heterogeneity, and anechoic spaces as predictors of malignancy.[15] It has been reported that the EUS findings associated with malignancy in the stromal cell tumors were tumor size (diameter >4 cm), irregular extraluminal border, echo-

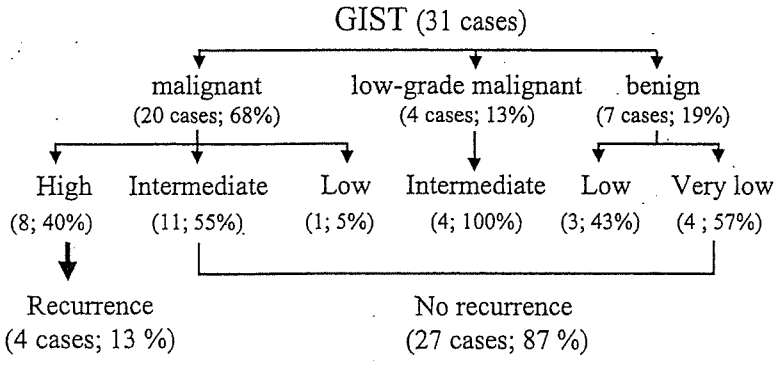

Figure 3. Correlation of recurrence with malignancy grade and with risk classification.

Table 5.
Characteristics of the recurrent cases

Patient (years/gender	Tumor size (%)	Recurrent site (mm)	Time of recurrence	Pathologic (months)	Risk category malignancy grade	MIB-1 index
78/M	70	Liver	15	Malignant	High	5.7
49/M	30	Liver	18	Malignant	High	10.7
62/M	60	Liver	24	Malignant	High	18.1
72/F	56	Liver	24	Malignant	High	2.4

The median follow-up time was 32 months (9 to 68 months). Altogether, 4 (1%) of 31 patients and were classified in a high risk category.

genic foci, and cystic spaces.[12] We have reported the differential diagnosis of myogenic tumors of the gastrointestinal tract,[16] and our data were similar to those in the two reports mentioned above. Most of the myogenic tumors previously diagnosed as smooth muscle tumors are thought to have been GISTs,[17] and therefore the predictive criteria of EUS findings could be applied.

In the present study, the preoperative differential diagnosis of EUS for gastric GISTs according to our criteria showed that the sensitivity and specificity were 83.3% and 66.7%, respectively, and the accuracy 80.0%. When limiting the results to patients with tumors <3 cm, the sensitivity was as low as 70.0% and the accuracy was only 73.3%, suggesting that the preoperative diagnostic value of EUS was not satisfactory for defining the surgical indication.

Recently, EUS-guided fine-needle aspiration (FNA) biopsy has been reported to be efficient in the diagnosis of GIST,[18,19] although it is not satisfactory in terms of differentiating benign from malignant GISTs at this time. Therefore, we did not use EUS-guided FNA as a routine examination in this study. However, we do think that the technique will be useful in the near future for differentiating benign from malignant tumors by improving the molecular diagnosis.

During the surgical management of gastric GISTs, the decision to operate is an important issue, especially for small, asymptomatic tumors that are found incidentally. There have been no reports clearly mentioning surgical indications for gastric GISTs. In this study, we established operative indications prospectively in the cases suspected to be malignant based on endoscopic or EUS findings. This is consistent with a previous report of gastric myogenic tumor.[20] However, we should keep in mind that the false-negative rate for a preoperative EUS diagnosis was fairly high (16.7% for all tumors) and 30.0% for small tumors. In fact, 10 tumors were <30 mm, and 4 of them were classified in malignant/borderline risk or intermediate risk categories; two of those four tumors (the sizes of which were 20 mm) were diagnosed as benign by EUS. Therefore, we cannot say definitively that tumors diagnosed as benign by EUS are not candidates for surgical intervention. It has been reported that even in patients with small tumors (20–50 mm) with a low mitotic rate who underwent complete resection there have been recurrences.[21,22]

The overall 5-year survival rate for patients with primary gastric GISTs who underwent complete resection ranges from 20% to 63%, with a recurrence rate of around 50% (19–76%).[23,24] In addition, the median survival times for patients whose tumors recur after complete resection are short, typically only 9 to 16 months.[23,25] Therefore, we propose that tumors that are ≥20 mm should undergo surgery, regardless of the EUS findings.

Complete surgical resection with an adequate margin remains the definitive treatment for gastric GISTs. Few reports have mentioned adequate surgical margins of gastric GISTs. It has been reported that a 2 cm margin seems sufficient for gastric GISTs.[25] Although the optimum width of the safety margin has not been defined, several investigators support the idea that it is enough for complete resection to resect a tumor with a tumor-free margin.[20,26] It has also been reported that an extended operation has no advantage over local excision for gastric leiomyosarcoma.[27]

Based on these points of view, laparoscopic wedge resection would be the most appropriate operative method for gastric GISTs.[20,24,26] Laparoscopic intragastric surgery[11] is also a suitable method for tumors exhibiting an intragastric growth pattern. These methods are thought to be minimally invasive because of a satisfactory postoperative course and a good quality of life after surgery.[7–9,11,26] However, it is important to avoid accidental rupture of tumors during laparoscopic procedures because tumor rupture before or during surgery is a statistically significant prognostic factor indicating a poor outcome.[28] As large tumors tend to rupture, inadequate laparoscopic handling could cause unexpected rupture of a tumor. Hence we should not insist on using laparoscopic resection, especially for large tumors.

In the present study, all patients with tumors <50 mm that were not accompanied by other diseases, such as gastric carcinoma, were treated successfully by laparoscopic surgery. On the other hand, most of the tumors >50 mm were treated by open surgery. There were no tumor ruptures during operation, and neither lymph node recurrence nor local recurrence was observed. We propose that laparoscopic resection be considered the treatment of choice for gastric GISTs that are <50 mm.

The malignancy grade is usually evaluated by the mitotic rate and tumor diameter. In the present study, the method proposed by Amin and colleagues[10] was used. Therefore, large tumors were mostly categorized as borderline malignant or malignant. Recently, Fletcher and colleagues have devised a classification of patients with GIST based on the risk of metastasis. All GISTs should be considered as having some low malignant potential, and they should be described in terms of risk assessment, rather than using distinct benign and malignant categories.[5,6] We classified each tumor according to these risk categories and compared the conventional malignancy grade to the risk category. The results showed a good correlation between those two classifications: 40% of the malignant tumors were defined as high risk, and all of the benign tumors were classified into low or very low risk categories. It is noteworthy that all of the recurrent cases were defined as malignant by the pathology examination and were also classified in the high risk category. Four of the eight high risk cases (50%) experienced a relapse; and, according to the risk category, we could predict that the small tumor (3 cm diameter), as shown in Table 4, metastasized to the liver within 2 years. Therefore, risk assessment can be considered to be most useful for predicting disease recurrence in the present circumstances.

During the past several years, many investigators have attempted to define more objective indicators. Although several studies have shown that the MIB-1 index is an independent factor of a poor outcome,[29–31] it does not provide better prognostication than the conventional mitosis count.[32] In the present study, although the MIB-1 index of the tumors in recurrent cases was significantly higher than that in the cases without recurrence, one patient with a tumor (with the MIB-1 index as low as 2.4) developed liver metastases within 2 years. Therefore, the MIB-1 index is not a better indicator than the mitosis count or the tumor size at this stage. Recently, it was reported that c-*kit* mutation is an independent prognostic factor.[33] However, it has not yet been proven clinically useful on an individual-case basis.

CONCLUSIONS

Gastric GISTs ≥20 mm or that are suspected to be malignant based on EUS findings are candidates for surgery. Laparoscopic resection is feasible and is recommended as the treatment of choice for gastric GISTs. However, for tumors >50 mm, the suggested treatment is open surgery to avoid an accidental rupture. Risk assessment is thought to be most useful for predicting recurrence of disease in the present circumstances.

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Review article

Follow-up of gastric cancer: a review

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Abstract
Although there is broad agreement in the staging, classification, and surgery for gastric cancer, there is no consensus regarding follow-up after gastrectomy. Follow-up varies from investigations on clinical suspicion of relapse to intensive investigations to detect recurrences early, assuming that this improves survival and quality of life. Advanced gastric cancers recur mainly by locoregional recurrence or distant metastasis. Local recurrences detected at endoscopy or on computed tomography (CT) are invariably incurable. For early gastric cancers, endoscopy can detect new primaries, but the incidence of these tumors is low, and many thousands of procedures are required to detect each operable case. CT is much better at detecting liver metastasis and, although these are usually multiple and unresectable, there are several reports of good survival following liver resection for isolated metastasis. Tumor markers have been used with some success to detect subclinical recurrences and could be used to target more invasive or expensive procedures. In chemotherapy, many newer agents are promising significantly improved survival, but again, the evidence for greater benefit when administered prior to the patient becoming symptomatic is lacking. Overall, it appears that follow-up policy is as much decided by the wealth and facilities of the institution as by any significant evidence base. Although the early detection of recurrent cancer is an emotive issue for both patients and surgeons, considering the amount of time and money invested in follow-up, and the lack of evidence of efficacy, a randomized controlled trial of intensive follow-up is required.

Key words Stomach neoplasms · Gastrectomy · Follow up · Recurrence

Introduction

Surgery for gastric cancer is becoming more successful. In the West, units with special interests in gastric cancer have improved the proportion of cancers that are diagnosed at a potentially curative stage to 63% and are reporting 5-year survival rates of 70% for R0 resections [1,2]. The centralization of services, earlier diagnosis, and more successful surgery has greatly increased the number of patients requiring follow-up. In a unit performing 50 R0 resections a year, approximately 150 patients will be undergoing follow-up at 5 years, and 200 at 10 years. In Japan and other countries in Eastern Asia where large units perform over 500 gastrectomies per year, with the majority for early-stage disease, the problems of follow-up are increased by at least an order of magnitude.

There are three main reasons for follow-up: to detect problems associated with the operation, to collect outcome data, and to detect recurrent disease. Many units actively investigate patients in order to detect recurrences at an earlier and asymptomatic stage, in the hope that this will lead to improved outcomes. The evidence for this, however, is weak and several surgeons have questioned the use of scarce resources in intensive follow-up.

In colorectal cancer, several randomized controlled trials (RCTs) and metaanalyses have demonstrated improved survival in patients undergoing intensive follow-up [3], and national bodies such as the American Society of Clinical Oncology (ASCO) and the Association of Coloproctology of Great Britain and Ireland have issued guidelines on the follow-up of colorectal cancer [4,5]. ASCO guidelines are also available for other cancers, such as breast [6] and lung [7], but for gastric cancer they are notable by their absence. Even the Japanese Gastric Cancer Association (JGCA) guidelines, which are proscriptive in the diagnosis and surgical treatment of gastric cancer, offer no guidance on follow-up [8]. This lack of guidance is unsurprising, given the paucity of high-quality evidence and the complete lack of RCTs. In the absence of national protocols, surgical units have adopted widely disparate regimes,

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and in a discussion of gastric cancer follow-up involving centers from the United States (Memorial Sloan-Kettering [MSK], Roswell Park, and University of Washington), United Kingdom (Royal Liverpool), and Japan (National Cancer Center [NCC]) the only constant was visits to the outpatient department [9]. Routine endoscopy is performed by all centers, but not by MSK, on high-risk (pT3, pT4) patients, as recurrent disease in this group is rarely curable. Recommendations for routine computed tomography (CT) scanning ranged from not at all to biannually for 5 years, and there was little agreement on what tests were useful, how frequently they should be performed, or for how many years they should continue. Overall there is little consensus on an appropriate follow-up regime, and the efficacies of such programs remain ill documented. Although articles quote recurrence rates or patterns, most reveal little if anything about how recurrences are treated, and with what success [10–14].

This article aims to examine the literature and to present the evidence for the efficacy of follow-up protocols and investigations after gastrectomy, from the dual viewpoints of detecting and treating asymptomatic recurrent disease. It does not address follow-up of patients after endoscopic mucosal resection (EMR), as cancers treated by EMR have different recurrence patterns and outcomes [15,16].

Recurrence patterns of gastric cancer

Gastric cancer has four broad patterns of recurrence: local recurrence either in the gastric bed or regional lymph nodes, peritoneal dissemination, liver metastasis and distant metastasis. In the West, the pattern of recurrence tends to be local. In the 1982, article by Gunderson and Sosin,[17] examining recurrence patterns discovered at planned re-laparotomy following curative resection, 86 of 107 patients had recurrences, with 82 evaluated. Distant metastasis alone accounted for 21 (26%) failures, but local failure was more frequent, present in 72 (88%) patients. In 44 (54%) patients, this was the only failure modality. In an Italian series with 215 recurrences from 441 gastrectomies, 96 (45%) suffered local recurrence, 57 (27%) hepatic, 77 (36%) peritoneal, and 20 (9%) distant metastases [10]. In the East, the pattern is different, with fewer local recurrences. In a series from Japan, of 939 operated patients, there were 207 recurrences, of which 130 had complete records. Recurrence was local in 29 (22%), 56 (43%) were peritoneal, 43 (33%) hepatic, and 27 (21%) distant; and 25% had recurrences at multiple sites [11]. In a large series from Korea examining 508 patients with recurrent cancer from an initial 2328 operated patients, 425 had recurrence at only one site, 98 (23%) had local recurrence, 172 (40%) had peritoneal recurrence, 75 (18%) had hepatic secondaries, and 80 (19%) had distant metastasis [18]. The lower local recurrence rates in the East appear to be related to the routine performance of D2 lymphadenectomy, as use of this technique in the West leads to similarly low local recurrence rates [14]. Risk factors for recurrence include greater stage of disease, undifferentiated (Lauren diffuse) type, and proximal tumors [18,19].

Early gastric cancer (EGC) carries a very favorable prognosis, and, in a report from the NCC Tokyo following up 1475 patients with EGC, only 1.4% were found to have recurrent disease. Of the 20 recurrences, 11 were at multiple sites, 1 was peritoneal, 4 were local, and 4 were hematogenous [20]. A similarly low rate was reported from 1452 patients with EGC from Korea, with only 4 local recurrences and 2 recurrences confined to the liver [21].

It is worthwhile to be aware of the time scale over which disease recurs. The consensus appears to be that over two-thirds of recurrences occur in the first 3 years and that fewer than 10% occur after 5 years [12,19,22]. In EGC, there is a difference in the reported literature regarding recurrence times, with Lee et al. [21] reporting the majority (62%) of recurrences detected at less than 2 years and fewer than 10% occurring after 5 years, while Sano et al. [20] reported deaths from recurrences occurring later: 23% occurring after 5 years and only 40% occurring within the first 3 years.

Adjuvant treatments after gastrectomy may alter patterns of recurrence. In the adjuvant chemoradiation study of MacDonald et al. [23], adjuvant treatment reduced the proportion of patients recorded as having local and regional recurrences as the first site of relapse from 29% and 72%, respectively, in the surgery alone group to 19% and 65% in the chemoradiation group.

There is evidence that specific pathological features of the resected tumor can provide insights into the likely modalities of recurrence, allowing follow-up plans to be modified. For example, for T1/2 N0 tumors with histological evidence of venous capillary infiltration, recurrence is invariably by hepatic metastasis. Although bone secondaries are relatively uncommon, in poorly differentiated or signet-ring cell carcinomas with very extensive nodal involvement, they are more likely, and some may respond to chemotherapy [24].

Second primaries

Second primary cancers can arise in the remnant stomach and they can occasionally be difficult to differentiate

from recurrence. Much of the literature relates to gastrectomies for peptic ulcer disease, and it was thought that the bile reflux that was common after Billroth I and II type operations caused an increase risk of gastric cancer after decades, and a meta-analysis, published in *Cancer Research*, estimated a relative risk of 1.48 after 15 years [25]. However, in a study of 6459 patients over 25 to 33 years, the rate of second primaries was not different from that in the general population [26]. After partial gastrectomy for cancer, the risk of second primaries appears small; in one Korean series of 1452 patients followed for EGC, only 5 such tumors were discovered, representing an approximate annual incidence of 70 per 100000 [21]. In the study of Kikuchi et al. [27], of follow-up endoscopy in 210 patients who underwent gastrectomy for EGC, after 6 years, 2 were found to have further gastric cancers, representing an annual incidence of 160 per 100000. In addition, one esophageal cancer and one duodenal cancer were found, and importantly, all of these new cancers were treatable by endoscopic mucosal resection (EMR). Like primary gastric cancers, second primaries are amenable to surgery if detected early. In cases not suitable for EMR , R0 resection rates of up to 85% have been reported [28], with 5-year survival of approximately 40% [29–31].

Detection of recurrent disease

There are many investigations that may be used to detect recurrent gastric cancer, and these can broadly be divided into endoscopy, imaging, and blood tests. Endoscopy has the ability to detect intraluminal recurrences with a high degree of accuracy and it also has the ability to detect new cancers at a treatable stage.

The use of tumor markers has become more commonplace. Carcinoembryonic antigen (CEA) and Carbohydrate antigen (CA) 19-9 levels are easily determined by a simple blood test and have reported sensitivities of between 16% and 65% for individual markers, increasing to up to 85% if both were used [32–34]. Increases in markers are commonly seen prior to the clinical detection of recurrences, and in a prospective study, both tumor markers were useful indicators of recurrence, even in patients whose original tumors did not express them [34, 35]. Other tumor markers, such as CA 72-4 and CA 125, have been investigated, but sensitivities are significantly lower than those for CEA and CA19-9 [33].

Reports on the use of imaging in detecting recurrent gastric cancer are few, and are often limited to descriptions of typical findings [35,36]. The ability of imaging to detect recurrence is poor and this has been recognized in the design of trials of chemotherapy. For many cancers, disease-free survival, as documented by imaging, is a primary endpoint, but in an ongoing trial in gastric cancer, this endpoint has not been used because of poor accuracy [37]. The ability to detect hepatic metastases is probably also overestimated, and has been examined in a recent metaanalysis of trials comparing the accuracy of several imaging methods. When the required specificity was set at greater than 85%, the most sensitive method was 18F-fluorodeoxyglucose positron emission tomography (PET) with a sensitivity of 90%, followed by magnetic resonance imaging (MRI; 76%), CT (72%), and ultrasonography (US; 55%) [38]. In gastric cancer, the great majority of patients under follow-up will not have hepatic metastases, and even with high specificities, there are likely to be many false-positive results. The ability of CT to primarily diagnose a primary carcinoma of the stomach is not as good as its ability to stage a known cancer, and there is a direct tradeoff between sensitivity and specificity. In one report, when the criterion for diagnosis was a gastric wall thickness of 2 cm or more, sensitivity was only 50% and specificity 88%. When the criterion was reduced to 1 cm, sensitivity was 100%, but specificity dropped to only 36% [39].

As well as inaccuracies in detecting local recurrences and hepatic metastasis, conventional imaging is poor at detecting peritoneal disease, which accounts for around 40% of recurrences. Barium enema has been described as useful in the diagnosis of such recurrence in colorectal cancer [40], and this method has been used at some Japanese institutes to confirm the presence of peritoneal disease suspected clinically (Fig. 1).

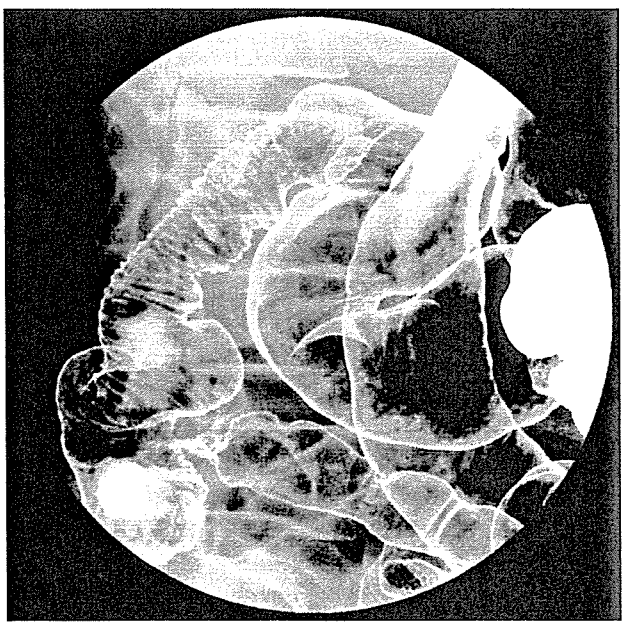

Fig. 1. Barium enema showing a typical "bellows" appearance caused by peritoneal dissemination

From the previous discussion it can be appreciated that imaging in the search for asymptomatic recurrence is fraught with difficulties, missing many recurrences and producing a number of false-positive results. Imaging is perhaps more useful when a clinical recurrence is suspected, such as in the face of rising tumor markers. In this role, PET can be especially useful in cases where conventional imaging results are equivocal, as it can confirm or refute the presence of recurrence in most cases [41]. Overall, the ability to detect asymptomatic recurrences — despite intensive follow-up — is poor, with the proportion of such recurrence detected varying from only 22% to 45% [22,42].

Treatment options

Surgery

Peritoneal disease and distant metastases are not amenable to surgery with curative intent. Theoretically, local recurrence, if detected at an early stage, could be amenable to surgery, but this is not borne out in the literature, with only occasional reports of longer-term survival [43,44]. In a study of 197 recurrences, both symptomatic and asymptomatic, 41 surgical procedures resulted in no cures [22].

The treatment of liver metastasis has undergone a revolution. Traditionally seen as indicative of advanced, incurable disease, in colorectal cancer, hepatic resections for metastases are now routine, and 5-year survival rates of 40% are achieved [45,46]. The treatment of liver metastasis from upper gastrointestinal cancers is still seen by most surgeons as fuftile, but some evidence is now available that challenges this notion. In 1994, Ochiai et al. [47] reported on a retrospective series of 21 patients who had undergone liver resection for synchronous or metachronous gastric cancers, where 4 patients were alive 5 years post-resection. In 1997, Miyazaki et al. [48] reported on 21 similar patients, and although 16 died (mean survival, 5 months), 5 were still alive at the time the paper was submitted, with the two longest survivors having survived for 10 years. In the past 2 years, five small retrospective reports have reported on a total of 102 patients undergoing hepatectomy, with 5-year survivals between 20% and 38% [49–53], suggesting that liver resection could be considered in patients in whom this could result in an R0 resection.

Although the proportion of recurrences that are hepatic is considerable (14% to 33%) [11,19], the proportion of the total number of patients undergoing curative resection who develop hepatic secondaries is small, and even fewer are suitable for resection. Okano et al. [53] reported that, between 1986 and 1999, of 807 patients undergoing surgery for gastric cancer, only 12 cases (1.5%) of hepatic recurrences were found, and only 6 (0.7%) of these were suitable for resection. Likewise, Sakamoto et al. [50] reported that, of 4730 patients undergoing gastrectomy between 1985 and 2001, 122 (3%) were found to have hepatic recurrence, but only 10 (0.2%) were suitable for resection. Although the number of patients in each series is small, several of the studies reported more favorable survival in patients with single metastatic lesions [48–50,53] and poorer survival where venous or lymphatic invasion was a feature of the original tumor [47,49].

With the possible exception of a few hepatic metastases, the vast majority of recurrences are not curable, and any resection is likely to be palliative. In advanced primary gastric cancer such resections are associated with a high mortality and little survival benefit [54,55]. It is unlikely that patients with recurrence will fare any better, and most surgeons would reserve palliative surgery for the relief of obstructive symptoms.

Chemotherapy

The history of the development of chemotherapy for advanced gastric cancer is one of small phase II studies with promising response rates and large phase III studies demonstrating no improvement in survival [56–60]. Standing out among these negative trials are three RCTs that do demonstrate a significant survival benefit. The first, in 1984, demonstrated a benefit for 5-fluorouracil (5-FU) and adriamycin plus mitomycin C (FAM) [61]. The second, in 1991, with 213 patients, demonstrated a benefit of methotrexate and 5-FU plus adriamycin (FAMTX) compared with FAM [56]. In the third trial, in 1997, epirubicin, cisplatin, and 5-FU (ECF) was shown to be superior to FAMTX [62]. Although these trials are encouraging, they should be taken in context, as the best median survival was in the 1991 trial with FAMTX, and this was only 42 weeks. In a subsequent RCT including FAMTX, it did not fare as well, with a median survival of only 30 weeks and a response rate of only 12% compared with 41% in the earlier trial [58]. Although the improvements in survival reported in these three trials were statistically significant, they were small, and the potential benefit appears in the improvement in 1- and 2-year survivals [61,63].

In many centers, chemotherapy has become the standard of care for advanced and recurrent gastric cancer and it is offered in the hope of improving survival and quality of life. It is not, however, universally seen to be beneficial, and its detractors point out that the number of negative RCTs far exceeds the number of positive trials. In the context of aggressive follow-up to detect asymptomatic disease, there is no evidence that treatment at an earlier stage improves outcomes, and in two studies of intensive follow-up, chemotherapy did not

improve survival in the group with recurrences detected prior to their becoming symptomatic [22,42].

For the alleviation of symptoms, response rates can — and do — translate into lessening symptoms and improved quality of life, but these patients, by their very nature, are not asymptomatic and are not helped by protocols designed to detect asymptomatic disease.

Results of follow-up

The literature regarding the benefits of intensive follow-up for gastric cancer is scarce. There are no RCTs and most reports are retrospective or observational. Very few report anything other than the detection of recurrences or death as the primary endpoints, and the implication is that recurrence equates to death. We discovered two studies on the efficacy of intensive follow-up, and both reported negatively. In the study by Kodera et al. [22], there were 88 patients detected with asymptomatic disease and 109 who presented symptomatically. Recurrences that were asymptomatic were more likely to be liver or distant metastases. More patients with asymptomatic disease underwent chemotherapy (88% vs 72%) and resection of metastasis (10 vs 5), but neither of these differences was significant. No patients were cured and there was no improvement in overall survival from the time of the original operation [22]. Bohner et al. [42] also found no benefit to intensive follow-up, although in their group, only 15 of the 67 recurrences were detected at an asymptomatic stage. Examining the observational studies, in the review of Sano et al. [20], of 1475 patients with EGC, all 20 patients with recurrence died. In the study of Yoo et al. [18], of 508 patients with recurrences, 48 (9%) underwent further resection, but only 19 (3.7%) were with curative intent. Of the 19, only 5 (1%) remained disease-free at the time of publication, and it is possible that they will suffer further recurrence [18].

Discussion

All surgeons follow up their patients, and some go to great efforts to detect recurrent disease, with the perceived benefit of increasing their patients' prospects of further curative treatment or at least an extension of life. Efforts at detecting recurrences early are fraught with difficulties. Imaging has relatively low sensitivity and the reports on the sensitivity of tumor markers vary. Even with intensive follow up, most recurrences are not detected until they become symptomatic [22,42]. The evidence that early detection of recurrent disease will lead to improved survival is also lacking. The nature of gastric cancer is that most recurrences are incurable by surgery at whatever stage they present [11,18], and the survival benefits of chemotherapy are small [58,62,64]. Despite theoretical advantages, there are no reports in the literature demonstrating benefit for earlier delivery of chemotherapy, but there are studies that demonstrate no survival benefit in patients treated for asymptomatic recurrences [22,42].

There are, fortunately, some developments in the treatment of recurrent disease that may make a difference in future. New chemotherapeutic agents such as paclitaxel, CPT-11, and S-1 are yielding higher response rates and these may translate to improved survival. The results of three large ongoing Japanese RCTs of S-1, perhaps the most promising agent, are expected to be reported in 2006. On the surgical front, liver resection might become as acceptable for gastric cancer as it is for colorectal cancer. Between 1.5% and 3% of gastrectomy patients will develop hepatic metastasis, and of these, between 8% and 50% are potentially resectable, with reported 5-year survival rates of between 20% and 38% [50,52,53]. However, the nature of early reports is that they invariably overestimate survival advantages, and until a large prospective study has demonstrated benefit, liver resection cannot be assumed to be a standard form of treatment.

Intensive follow-up has the potential to detect new gastric cancers in the remnant stomach, and these cancers are often amenable to treatment [28–30]. However, after gastrectomy for benign disease, the incidence of second primaries is low, comparable to that of primary gastric cancers [26,29], and at least one nonrandomized trial has demonstrated no benefit from endoscopic surveillance in this group [65].

In two large studies of EGC, the death rates from nongastric cancers were significantly higher than those for recurrent or new gastric cancers [20,21]. The validity of what is effectively screening patients for other cancers is dependent on national priorities. In wealthy countries where population screening is the norm it may be justified, but in less wealthy countries without such programs, follow-up for these reasons might appear inappropriate.

It has been argued that follow-up may benefit patients' psychological wellbeing. While it is true that negative investigations can be reassuring, there is no evidence that complex investigations have any more psychological benefit than simple tests. Patients believe that negative tests mean that they are cancer-free and that that the detection of early recurrence, like early detection of their original cancer, will give them a chance of curative treatment. Intensive investigations by physicians reinforce these false beliefs. A patient's psychological wellbeing can be shattered by positive tests. If truly indicative of a recurrence, the knowledge that a cure is not possible leaves a permanent shadow