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The Diversity of Gastric Carcinoma

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Chemotherapy for Advanced Unresectable Gastric Cancer

Atsushi Ohtsu

Introduction

Gastric cancer is a major health problem in many regions of the world. Despite remarkable improvement in survival as a result of early detection and curative surgery, approximately 50 000 deaths were observed in Japan in 2001 [1]. Unresectable advanced or recurrent gastric cancer still has a poor prognosis, with a median survival of less than 9 months. Randomized trials have demonstrated that the 5-fluorouracil (5-FU)-based regimen provides superior survival and quality of life in patients with advanced gastric cancer when compared to best supportive care [2–4]. However, this survival advantage appears to be marginal, and no standard regimens worldwide have yet been established, although various challenges have been conducted.

Recently developed new agents, such as irinotecan, S-1, and taxanes, may have potential to break through this status. Newer-generation regimens with these agents are being investigated in randomized trials worldwide. A molecular targeting agent is another new topic in the field of chemotherapy and is also under development for gastric cancer. This review focuses on the results of newer-generation regimens, particularly in Japan, after a brief summary of older-generation regimens.

Overview of the Older-Generation Regimens

Results from Randomized Controlled Trials

During the past two decades, various randomized trials (Table 1) have been carried out. In Europe, a combination of flurorouracil, doxorubicin, and high-dose methotrexate (FAMTX) used to be a standard regimen based on the European Organization for Research and Treatment of Cancer (EORTC) trials [5]. However, this regimen failed to demonstrate any superiority to other combination regimens, 5-FU plus cisplatin or etoposide plus 5-FU/leucovorin, in the subsequent EORTC randomized study [6].

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TABLE 1. Results of randomized trials using older-generation regimens

Study	Treatment	No. of patients	Response rate (%)	Median survival (months)	*P* value
Wils et al. (1991) [5]	5-FU + ADM + MMC	103	7	6.7	0.004
	5-FU + ADM + MTX	105	33	9.6	
Kim et al. (1993) [9]	5-FU	94	26	6.9	ns
	5-FU + ADM + MMC	98	25	6.6	
	5-FU + CDDP	103	51	8.5	
Webb et al. (1997) [7]	5-FU + ADM + MTX	130	21	5.7	0.0009
	Epirubicin + CDDP + 5-FU	126	45	8.9	
Vanhoefer et al. (2000) [6]	5-FU + CDDP	134	20	7.2	ns
	Etoposide + LV/5-FU	132	9	7.2	
	5-FU + ADM + MTX	133	12	6.7	
Ohtsu et al. (2003) [10]	5-FU	106	11	7.1	ns
	5-FU + CDDP	104	34	7.3	
	UFT + MMC	70	9	6.0	

5-FU, 5-fluorouracil; ADM, adriamycin; MMC, mitomycin C; MTX, methotrexate; CDDP, cisplatin; LV, leucovorin; UFT, ftorafur and uracil

Another randomized study in the United Kingdom revealed the superiority of a combination of epirubicin, cisplatin (CDDP), and 5-FU (ECF) to FAMTX in terms of survival [7], although survival results of these studies were limited, with a median survival time (MST) ranging from 6 to 8 months. Other trials including 5-FU alone as a control arm and in comparision with FU-based regimens also failed to demonstrate survival prolongation of combination regimens [8,9].

The Japan Clinical Oncology Group (JCOG) has carried out a randomized controlled trial comparing 5-FU alone with UFT (ftorafur and uraeil) + mitomycin C (UFTM) and with 5-FU + CDDP (FP) for advanced gastric cancer (JCOG 9205) [10]. A total of 280 patients with advanced gastric cancer were randomly allocated and analyzed for survival, response, and toxicity. At the interim analysis, the UFTM arm showed a significantly inferior survival with higher incidences of hematological toxicities than control arm 5-FU alone, and the registration to UFTM was terminated. Both investigational regimens, FP and UFTM, had a significantly higher incidence of hematological toxicities than 5-FU alone, although they were feasible. The overall response rates of 5-FU alone, FP, and UFTM arms were 11%, 34%, and 9%, respectively. The median progression-free survival was 1.9 months with 5-FU alone, 3.9 months with FP, and 2.4 months with UFTM, respectively. Although FP demonstrated a higher response rate ($P < 0.001$) and longer progression-free survival than 5-FU alone ($P < 0.001$), no differences in overall survival were observed between the arms; the median survival times and 1-year survival rates were 7.1 months and 28% with 5-FU, 7.3 months and 29% with FP, and 6.0 months and 16% with UFTM, respectively. This study concluded that both investigational regimens, FP and UFTM, showed no survival advantages as compared to 5-FU alone, and 5-FU alone still remains a reference arm in future trials for advanced gastric cancer.

Based on the results of these randomized trials, no regimens have exceeded 5-FU alone, and there still remain limitations on efficacy results in older-generation regi-

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. EMD72 000 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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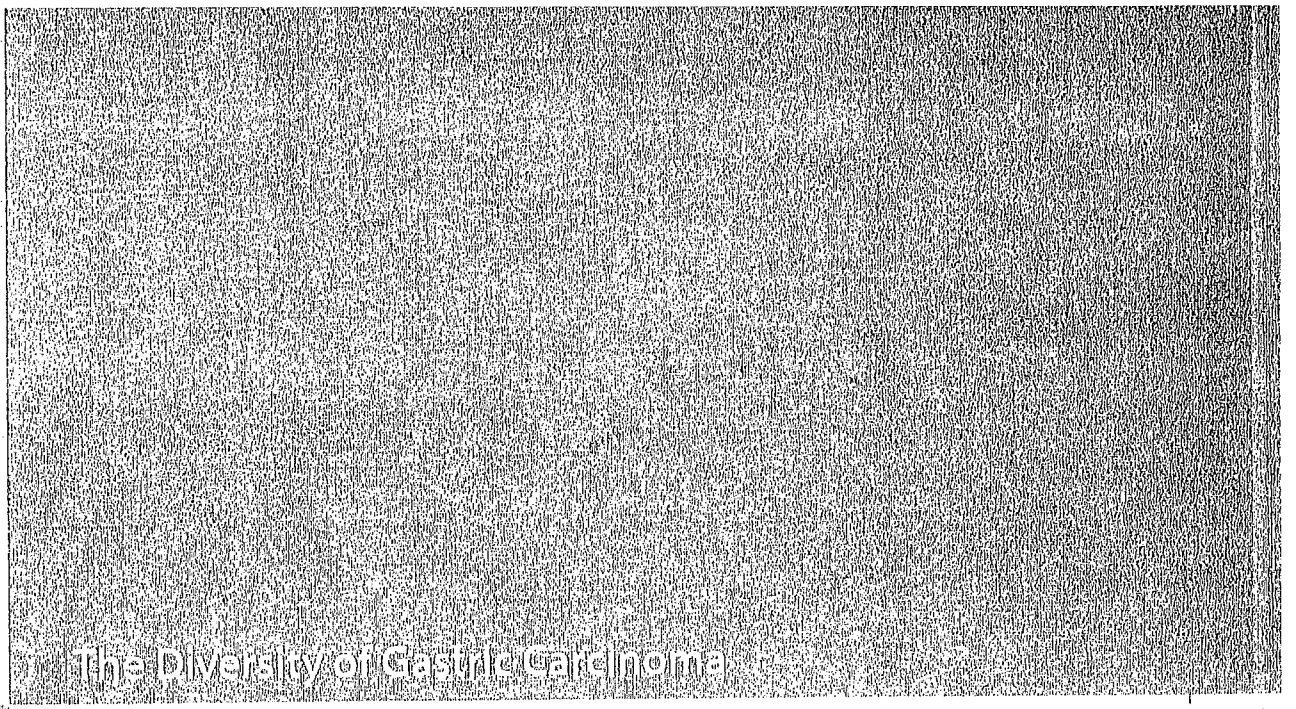

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ISBN 4-431-21139-X

springeronline.com

Reprint from

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

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