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Comparison of Survival Curves of Gastric Cancer Patients After Surgery According to the UICC Stage Classification and the General Rules for Gastric Cancer Study by the Japanese Research Society for Gastric Cancer

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Objective

This study compared the UICC classification with the General Rules for Gastric Cancer Study (GRGCS) of the Japanese Research Society by analyzing recent results of gastric cancer surgery in Japan.

Summary Background Data

The present UICC stage classification for gastric cancer was published in 1987 and the Japanese GRGCS were published in 1985. Both are based on the results of surveys conducted in the early 1970s.

Methods

The survival curves of 926 patients, who underwent gastric cancer surgery between 1982 and 1985 at Kyoto University Hospital and its 31 associated hospitals, were analyzed according to the UICC classification and the GRGCS using SAS computer software.

Results

There was no difference in survival rate between UICC stages IA and IB. GRGCS stage III was found to include UICC stages II, IIIA, and IIIB, and GRGCS stage IV included UICC stages IIIA, IIIB, and IV, with significantly different survival rates. In contrast, each UICC stage included different GRGCS stages with no significant differences in survival rates. The survival rate of stage IV patients of both classifications who underwent gastrectomy was significantly higher than that of stage IV patients receiving bypass or exploratory surgeries.

Conclusions

The UICC classification is better than the GRGCS for classifying gastric cancer in Japan. However, UICC stage I does not need to be subdivided into stages IA and IB, and stage IV should be further subdivided into stages IVA and IVB according to the surgery performed: IVA, gastrectomy, and IVB, bypass or exploratory surgery.

The stage classifications of malignant diseases are important for prospective prognosis as well as for precise analysis of the results of treatment. Such classifications may contribute to improvement in therapy. Accordingly, the stage should reflect exactly the prognosis of the patients, and it should change with improvement in therapeutic results.

The prognosis of gastric cancer has been widely surveyed in Japan. The Japanese Research Society for Gastric Cancer (JRSGC) has conducted this survey and their General Rules for Gastric Cancer Study (GRGCS) has been extensively used to classify the stages of gastric cancer.[1,2] However the GRGCS was modified in 1985 to accommodate contemporary therapeutic approaches, especially those of surgery which have improved significantly.[1-4] In 1987 the UICC proposed a new stage classification to accommodate the development in surgical procedures according to the surveys in Japan and USA.[5] However, these new classifications have already become dated, because they were developed based on the results of surveys conducted approximately 20 years ago. This study assesses whether these classification procedures can accommodate the recent results of gastric cancer surgery in Japan. The patients, who were enrolled in a multi-institutional study, were treated postoperatively with adjuvant chemoimmunotherapy using mitomycin-C, fluoropyrimidines, and oral or intradermal streptococcal preparation OK-432,[6] which are standard regimens for gastric cancer after surgery in Japan and Korea.[7,8] In the present study, we used Akaike's information criterion (AIC) to analyze and evaluate the value of individual prognostic factors for gastric cancer after surgery.[9,10] The patients were classified into substaging groups and their survival curves were compared.

PATIENTS AND METHODS

Patients

One thousand and eleven patients with gastric cancer were enrolled into a multi-institutional study on postoperative adjuvant immunotherapy with oral OK-432.[6] For 926 of these patients, the cancer stages were precisely defined. All the patients received 10–20 mg of mitomycin-C intravenously during the surgery and afterwards they received oral fluoropyrimidines (futraful at 12 mg/kg/day, 5-FU at 5 mg/kg/day, or carmofur at 15 mg/kg/day) daily for 2 years. One third of the patients received intradermal OK-432 at 0.5 mg weekly (intradermal OK-432 group) and another one third of the patients received oral OK-432 at 0.5 mg weekly (oral OK-432 group). The remaining one third of the patients received oral placebo (control group). The survival rate of the oral OK-432 group, was significantly greater than those of the other two groups of patients. There were no differences in survival rates between the control group and the intradermal OK-432 group.

Stage Classification

Both stage classification, the GRGCS[1,2] and UICC,[5] are summarized in Table 1.

Table 1. COMPARISON OF UICC STAGE CLASSIFICATION AND THE GRGCS OF THE JAPANESE RESEARCH SOCIETY FOR GASTRIC CANCER

Categories	UICC (Stage)	GRGCS (Stage)
pT1, n0, M0	IA	I
pT1, n1, M0	IB	II
pT2, n0, M0	IB	I
pT1, n2, M0	II	III
pT2, n1, M0	II	II
pT3, n0, M0	II	II
pT2, n2, M0	IIIA	III
pT3, n1, M0	IIIA	III
pT4, n0, M0	IIIA	IV
pT3, n2, M0	IIIB	III
pT4, n1, M0	IIIB	IV
pT4, n2, M0	IV	IV
Any pT, any n, M1	IV	IV

pT1, tumor invades lamina propria or submucosa; pT2, tumor invades muscularis propria or subserosa (ss; IN GRGCS); pT3, tumor penetrates the serose (visceral peritoneum) without invasion of adjacent structures; pT4, tumor invades adjacent structures; n0, no regional lymph node metastasis; n1, metastasis in perigastric lymph node(s) within 3 cm of the edge of the primary tumor; n2, metastasis in perigastric lymph node(s) more than 3 cm from the edge of the primary tumor or in lymph nodes along the left gastric, common hepatic, splenic, or celiac arteries; M0, no distant metastasis; M1, distant metastasis.

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Statistical Analysis

Survival curves were obtained by using the Kaplan-Meier method and compared with the generalized Wilcoxon and Cox-Mantel tests. The results were analyzed using the SAS software package. The prognostic values of the various background factors on survival after surgery were analyzed according to Akaike's information criterion (AIC). AIC was proposed to find the optimal mathematical model among many possible ones, and AIC was calculated as follows:[9,10]

$$AIC = -2\sum_{i=0}^{1}\sum_{j=0}^{c} n(i,j)\cdot\log(n(i,j)\cdot n/n(i^*)\cdot n(:^*j) + 2(c-1)$$

where n(i,j) : number of cases with the i-th outcome in the j-th category

n(i,*) : total number of cases with the i-th outcome

n(*j) : total number of cases in the j-th category

n : total number of cases

c : total number of categories

The categories of background factors include the depth of invasion (pT1–pT4), nodal involvement (n0–4), venous invasion (v0–2), lymphatic invasion (ly0–2), arterial invasion (a0–2), the infiltrating pattern (INFα, β, γ), histological grade (grade 1–3), etc. These predictor variables were fixed to the original gradings, and the survival time was dichotomized by moving the cutoff point from 6 months to 5 years. The smaller the AIC value, the greater the prognostic information.

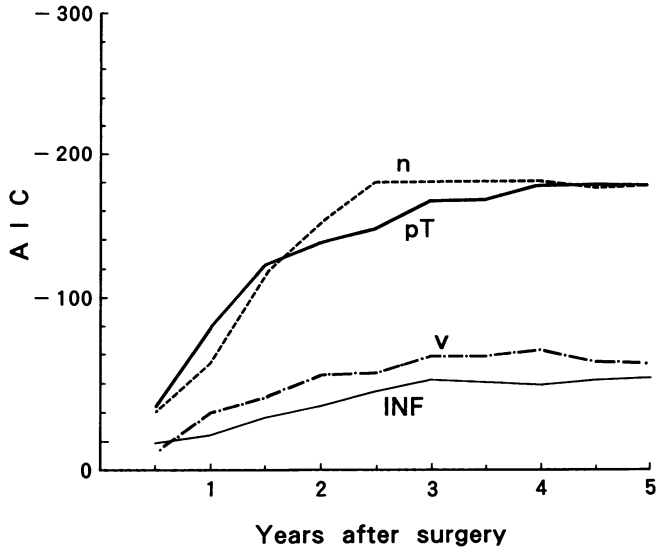

Figure 1. Changes in AIC for several predictor variables as survival time is dichotomized at different cutoff points. pT, histological (postsurgical) depth of invasion; n, nodal involvement; v, venous invasion; INF, intra-and extra-mural growth pattern.

Table 2. FIVE-YEAR SURVIVAL RATES OF SUBGROUPS ACCORDING TO THE DEPTH OF INVASION AND NODAL INVOLVEMENT

Distant Metastasis	Depth of Invasion	Nodal Involvement n0	n1	n2
M0	pT1	91.1% (n = 203)	93.3% (n = 31)	68.4% (n = 13)
M0	pT2	86.3% (n = 152)	72.6% (n = 127)	38.6% (n = 83)
M0	pT3	64.8% (n = 34)	43.8% (n = 54)	24.4% (n = 51)
M0	pT4	100.0% (n = 5)	16.7% (n = 15)	6.9% (n = 16)
M1	Any pT		Any n 6.6% (n = 142)	

RESULTS

The values of various background factors on the prognosis of the patients after gastric cancer surgery were analyzed by using AIC. Figure 1 shows how the AIC value changed with recategorization of survival time. The predictor variables were fixed to the original gradings, and the survival time was dichotomized by moving the cutoff point from 6 months to 5 years. M-factor (distant metastasis) was excluded from this analysis. Only four factors (pT, n, v, INF) were found to show the significant prognostic values. Below a cutoff point of 20 months, the classification according to the depth of invasion (pT) showed the lowest value of AIC. Between 20 and 50 months the classification according to the nodal involvement (n-factor) showed lower (more negative) AIC value than the classification according to pT. Thus pT- and n-factors were found to be the most important prognostic factors after gastric cancer surgery. The 5-year survival rates of subgroups according to the pT- and n-factors, the UICC classification, and the GRGCS classification are summarized in Table 2.

The breakdown by UICC stage was as follows: IA, 203; IB, 183; II, 174; IIIA, 142; IIIB, 66; and IV, 158 patients. The same breakdown by GRGCS stage showed I, 311; II, 185; III, 236; and IV, 194 patients. The patients received a variety of surgeries: curative surgery (C-surgery), noncurative gastrectomy (NC-gastrectomy), and bypass or exploratory surgery (BE-surgery). Most patients in stages I and II of both classifications received C-surgery, but 1–5% patients underwent NC-gastrectomy. The percentage of NC-gastrectomy performed increased with the stage, and 19.0% and 16.7% of the patients that were classified as UICC stage IIIA and IIIB underwent NC-

gastrectomy, respectively. Of the stage IV patients, 9.5% underwent BE-surgery, 81% NC-gastrectomy and 9.5% C-surgery. Using the GRGCS classification, 11.4% of the stage III patients underwent NC-gastrectomy, and of the stage IV patients, 7.7% experienced BE-surgery, 74.2%, NC-gastrectomy and 18%, C-surgery.

The overall survival rates according to the postsurgical (microscopic) stage classifications are shown in Figure 2. The 5-year survival rates corresponding to the new UICC postsurgical classification were as follows: I, 89.5% (n = 386) [IA, 91.1% (n = 203); IB, 87.6% (n = 183)]; II, 70.8% (n = 174); III, 36.5% [IIIA, 43.0% (n = 142); IIIB, 22.8% (n = 66)]; and IV, 6.3% (n = 158). There were no differences in the cumulative survival rates between stage IA and IB patients. The overall survival rates according to GRGCS postsurgical classification were as follows: I, 89.8% (n = 311); II, 78.6% (n = 185); III, 44.8% (n = 236); and IV, 12.6% (n = 194).

Using the 5-year survival rates of substaging groups (Table 1), the relationship between the UICC stage and the GRGCS stage was analyzed. GRGCS stage II includes UICC stages IB (pT1, n1; pT2, n0) and II (pT2, n1), which had similiar survival rates (Fig. 3a). GRGCS stage III also includes UICC stages II (pT1, n2; pT3, n0), IIIA (pT2, n2; pT3, n1), and IIIB (pT3, n2), which had significantly different survival rates (Fig. 3b). GRGCS stage IV includes UICC stages IIIA (pT4, n0), IIIB (pT4, n1), and IV (any T, any n, M1), which also showed significantly different survival rates (Fig. 3c). By contrast, UICC stage II includes GRGCS stages II (pT2, n1) and III (pT1, n2; pT3, n1), UICC stage IIIA includes GRGCS stages III (pT2, n2; pT3, n1) and IV (pT4, n0), and UICC stage IIIB includes GRGCS stages III (pT3, n2) and IV (pT4, n1). No significant differences were observed between the survival rates in the various GRGCS subgroups (Fig. 4a–c).

Most stage I and II cancers of both classifications can be curatively resected by surgery. Stage III may include 10–20% NC-gastrectomy, due to the incomplete removal of involved nodes. Because a variety of surgeries can be applied to stage IV gastric cancer, this stage may include various categories of advancing factors, such that different prognoses may suggest different surgical methods. This is particularly evident for GRGCS stage IV cancers, which includes a larger number of curatively resected patients (18%) than UICC stage IV (9%). C-surgery for GRGCS stage IV was performed on 21 UICC stage IIIA-IIIB and 14 UICC stage IV cancers. In contrast, C-surgery for UICC stage IV was done on 14 GRGCS stage IV and only 1 GRGCS stage III cancers. Furthermore, no significant differences were seen in survival rates of the UICC stage IV patients undergoing C-surgery and NC-gastrectomy (Fig. 5), although there were significant differences in survival rates of the GRGCS stage IV patients experiencing these two forms of surgery. For both classification systems, significant differences in survival rates were observed between stage IV patients who had undergone NC-gastrectomy and BE surgery.

The overall agreement rates between macroscopic stages and microscopic stages were 63.2% for GRGCS and 64.6% for UICC (Table 3). The agreement rates were

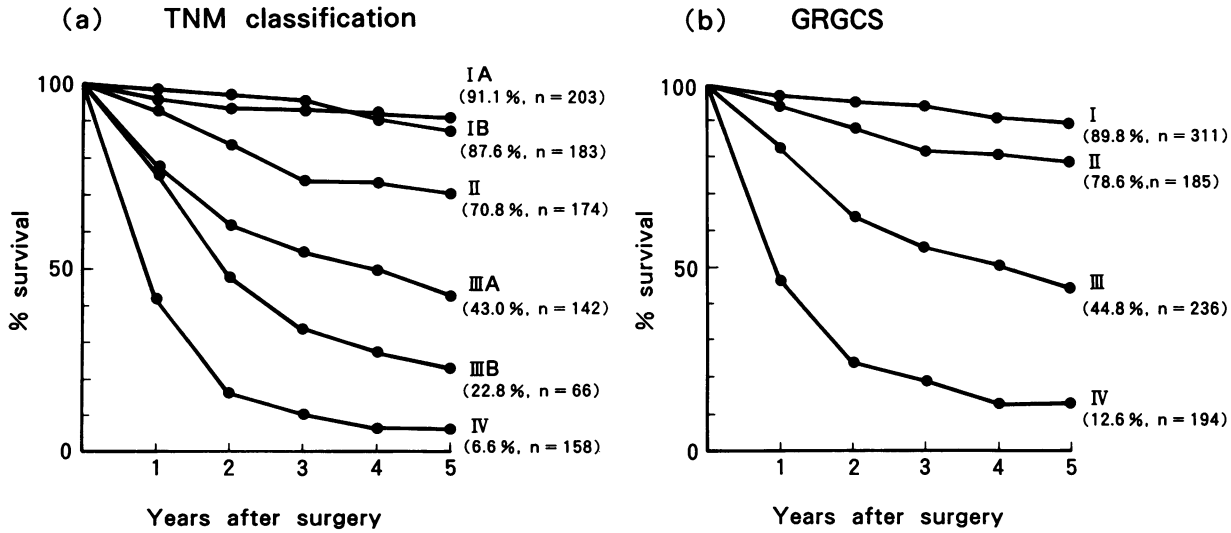

Figure 2. The survival curves of patients after gastric cancer surgery according to the UICC stage classification and the General Rules for Gastric Cancer Study (GRGCS) by the Japanese Research Society for Gastric Cancer. The numbers in parentheses indicate 5-year survival rates and the number of patients.

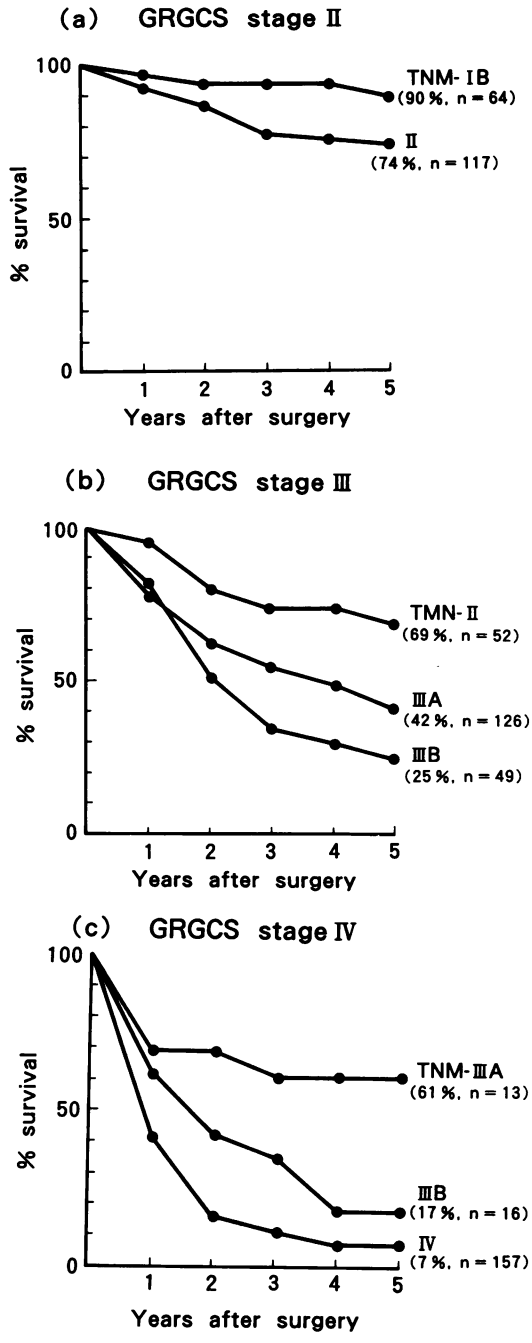

Figure 3. Relationship between the survival curves of patients grouped according to the UICC stage classification and those classified according to GRGCS—(I). The numbers in parentheses indicate 5-year survival rates and the number of patients. a: TNM-IB vs. II, $p < 0.01$ by generalized Wilcoxon test; $p < 0.01$ by Cox-Mantel test. b: TNM-II vs. IIIA, $p < 0.001$ by generalized Wilcoxon test; $p < 0.001$ by Cox-Mantel test, IIIA vs. IIIB, $p < 0.05$ by Cox-Mantel test. c: TNM-IIIA vs. IIIB, $p < 0.05$ by Cox-Mantel test, IIIB vs. IV, $p < 0.05$ by Cox-Mantel test

high in stage IV, and low in stage II for both classification systems. In UICC stages I and III, agreement rates became lower in respective substages IA, IB, IIIA, and IIIB.

DISCUSSION

The UICC stage classification system for various cancers is the most popular in the world. However, in

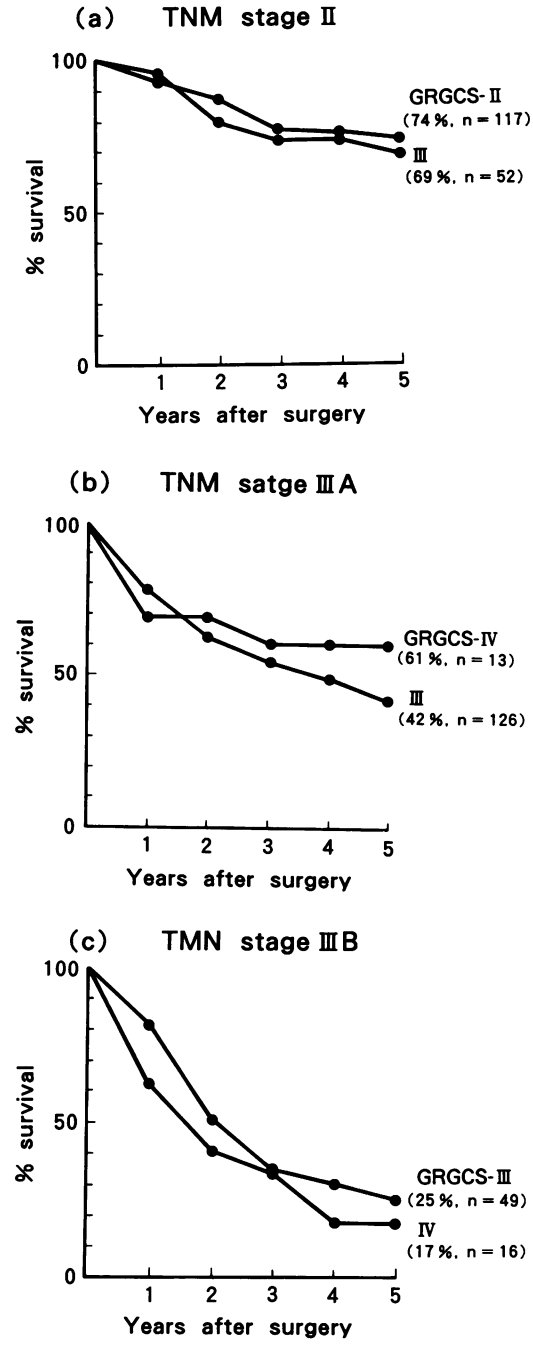

Figure 4. Relationship between the survival curves of patients grouped according to the UICC stage classification and those classified according to GRGCS—(II). The numbers in parentheses indicate 5-year survival rates and the number of patients. a: There were no significant differences between the survival curves of GRGCS-stage II and III in TNM stage II. b: There were no significant differences between the survival curves of GRGCS-stage III and IV in TNM stage IIIA. c: There were no significant differences between the survival curves of GRGCS-stage III and IV in TNM stage IIIB.

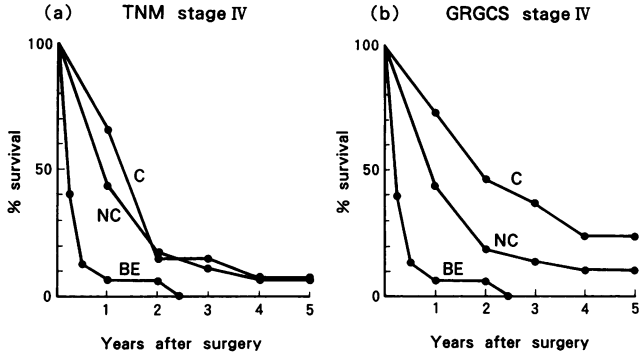

Figure 5. Survival curves of patients after surgery for stage IV gastric cancer. C, curative surgery; NC, non-curative gastrectomy; BE, bypass or exploratory surgery. 5-year survival rates were as follows. a: TNM stage IV: C-surgery, 7.3% (n = 15); NC-gastrectomy, 7.3% (n = 128); BE-surgery, 0% (n = 15). b: GRGCS stage IV: C-surgery, 23.6% (n = 35); NC-gastrectomy, 10.5% (n = 144); BE-surgery, 0% (n = 15).

Japan and other Asian countries such as Korea, China, and Chinese Taipei, where the incidence of gastric cancer is high, the GRGCS stage classification also has been widely accepted. This new UICC classification was designed by The Japanese Joint Committee (JJC) and The American Joint Committee on Cancer (AJCC) and is based on the results of a survey conducted by JRSGC between 1969 and 1973 of 15,589 patients with gastric cancer in Japan and by NCI of 4785 patients with gastric cancer in the US.

The stage classification should reflect the treatment results and should be modified according to major advances in diagnosis and treatment. Since the UICC and the GRGCS classifications were established from the results of treatments obtained more than two decades ago, the present study was designed to determine if these classification procedures accommodate the current status of gastric cancer in Japan.

The results of this study demonstrate that the UICC classification reflects the treatment results better than the GRGCS classification, which includes subgroups with significantly different prognoses. This is particularly evident for GRGCS stages III and IV. In contrast, each UICC stage consisted of patients with almost identical prognoses. The GRGCS classification has the disadvantage that nodal involvement and depth of invasion are treated separately. Our AIC analysis demonstrates that nodal involvement and depth of invasion have almost the same influence on prognosis after surgery (Fig. 1). Furthermore, the present study demonstrates that the influences of these two factors may be additive, which means that the prognosis of patients with n1 plus pT1 is inferior to that of patients with n1 alone or pT1 alone. From this viewpoint, the UICC classification can predict the prognosis after gastric cancer surgery more accurately than the GRGCS classification. In classification using the GRGCS criteria this is most obvious for GRGCS stage III and stage IV cancers. GRGCS stage IV cancers include UICC stage IIIA, IIIB, and IV. Relevant to this point is the observation that the prognosis of IIIA patients was much better than for the other two groups (Fig. 3). In addition, the results of surgery also demonstrate this problem. Whereas we noted a significant difference in survival rate of GRGCS stage IV patients undergoing C-surgery and NC-gastrectomy, no difference was seen for UICC stage IV patients (Fig. 4). This observation also suggests that the UICC stage classification is more beneficial than the GRGCS classification. However, a problem is apparent with the current stage IV classification. The prognosis of stage IV patients who

Table 3. CORRELATION BETWEEN MACROSCOPIC AND POSTSURGICAL HISTOPATHOLOGICAL STAGES

	Agreement Rate (Postsurgical Stage/Macroscopic Stage)				
UICC stage	I	II	III	IV	overall
	80.0% (276/345)*	35.3% (48/136)	53.4% (135/253)	72.4% (139/192)	64.6% (598/926)
	IA 64.6% (128/198)	IB 36.1% (53/147)		IIIA 38.6% (51/132)	IIIB 25.6% (31/121)
GRGCS stage	I	II	III	IV	overall
	83.7% (169/202)	37.3% (84/225)	56.5% (161/285)	79.9% (171/214)	63.2% (585/926)

*The numbers in parentheses indicate the number of patients with respective stages.

received BE-surgery was significantly worse than that of patients who underwent gastrectomy. Accordingly, we propose that the stage IV patients who undergo BE-surgery should be classified as stage IVB, and those who undergo gastrectomy should be classified as stage IVA. This may clinically well reflect the differences in advancing factors in stage IV.

Furthermore, UICC classification subdivides stage I into IA and IB. In the present study, there were no significant differences in survival rates between stage IA and IB (only 3.5% difference in 5-year survival rate). However, in other Japanese reports, there were 10~15% differences in 5-year survival rates between stage IA and IB.[11,12] The reason for this discrepancy may be that they included the patients who underwent surgery from the 1960s to 1980s. In contrast the present study includes the patients between 1985 and 1987. The technical improvement in removing lymph node (especially of n_1 nodes) may be the major reason for this result. Accordingly, it may not be necessary to subdivide stage I into IA and IB in the present Japan.

The results of this study demonstrate that the UICC classification is better than the GRGCS classification, and the two should be unified. We propose two changes to the modified classification scheme. The UICC stage I does not need to be subdivided into stages IA and IB, and stage IV should be further subdivided into stages IVA and IVB according to the surgery performed: IVA, gastrectomy; IVB, BE-surgery.

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