Gastric Cancer (1998) 1: 125–133

Original article

Clinicopathologic characteristics and prognostic factors in 10783 patients with gastric cancer

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Abstract:
Background. **Although the results of gastric cancer treatment have markedly improved, this disease remains the most common cause of cancer death in Korea.**
Methods. **Clinicopathologic characteristics were analyzed for 10783 consecutive patients who underwent operation for gastric cancer at the Department of Surgery, Seoul National University Hospital, from 1970 to 1996. We also evaluated survival and prognostic factors for 9262 consecutive patients operated from 1981 to 1996. The clinicopathologic variables for evaluating prognostic values were classified as patient-, tumor-, and treatment-related factors. The prognostic significance of treatment modality [surgery alone, surgery + chemotherapy, surgery + immunotherapy + chemotherapy (immunochemosurgery)] was evaluated in patients with stage III gastric cancer (according to the International Union Against Cancer TNM classification of 1987). For the assessment of lymph node metastasis, both the number of involved lymph nodes and the ratio of involved to resected lymph nodes were analyzed, as a quantitative system.**
Results. **The mean age of the 10783 patients was 53.5 years and the male-to-female ratio was 2.07:1. Resection was performed in 9058 patients (84.0% resection rate). The 5-year survival rates were 55.9% for all patients and 64.8% for patients who received curative resection. Age, sex, preoperative hemoglobin and albumin levels, type of operation, curability of operation, tumor location, Borrmann type, tumor size, histologic differentiation, Lauren's classification, perineural invasion, lymphatic invasion, vascular invasion, depth of invasion, number of involved lymph nodes, ratio of involved to resected lymph nodes, and distant metastasis had prognostic significance on univariate analysis. Radical lymph node dissection, with more than 25 resected lymph nodes improved survival in patients with stage II and IIIa disease. As postoperative adjuvant therapy, immunochemotherapy was most effective in patients with stage III disease. Patients with identical numbers of lymph nodes -either the number of involved lymph nodes or the number of resected lymph nodes- were divided according to their ratios of involved-to-resected lymph nodes. In each numeric group, there were significant survival differences according to the ratio of involved-to-resected lymph nodes. However, patients who had the same involved-to-resected lymph node ratio did not show significant differences in survival rate according to either the number of involved or the number of resected lymph nodes. On multivariate analysis, curability of operation, depth of invasion, and ratio of involved to resected lymph nodes were independent significant prognostic factors.**
Conclusions. **Curative resection, depth of invasion, and lymph node metastasis were the most significant prognostic factors in gastric cancer. With regard to the status of lymph node metastasis, the ratio of involved to resected lymph nodes had a more precise and comprehensive prognostic value than only the number of involved or resected lymph nodes. Early detection and curative resection with radical lymph node dissection, followed by immunochemotherapy, particularly in patients with stage III gastric cancer should be the standard treatment in principle, for patients with gastric cancer.**

Key words: gastric cancer, prognostic factor, ratio of involved to resected lymph nodes

Introduction

The results of gastric cancer treatment have markedly improved as a result of early detection and extensive radical operation, reflecting the progress in diagnostic methods and surgical techniques. However, gastric carcinoma still remains a major cause of death from malignant disease worldwide and is the most common cause of cancer death in Korea. The identification of prognostic factors and determination of their relevance is an important aspect of oncological understanding of staging, and the establishment of therapeutic strategies. Of the many factors relevant to survival, depth of invasion, lymph node metastasis, and distant metastasis have

Offprint requests to: J.-P. Kim
Received for publication on Apr. 13, 1998; accepted on Oct. 22, 1998

been considered major prognostic factors [1–10]. We have previously reported that depth of invasion and lymph node metastasis were the most important prognostic factors in gastric cancer, and that for patients with advanced gastric cancer, immunochemosurgery (surgery plus immunotherapy plus chemotherapy) was the most effective treatment modality in patients with stage III gastric cancer according to UICC TNM classification of 1987 [11,12].

In this study, we analyzed the clinicopathologic characteristics and prognostic factors related to patient, tumor, and treatment in a large series of gastric cancer patients from one institute. We also analyzed quantitatively the number of involved lymph nodes and the ratio of involved to resected lymph nodes to determine the status of lymph node metastasis.

Patients and methods

We have experienced 10783 gastric cancer patients treated surgically at the Department of Surgery, Seoul National University Hospital from January 1970 to December 1996. The clinicopathologic characteristics of the 10783 patients were analyzed, and for prognostic factor analysis, we studied 9262 consecutive patients treated in the period 1981 to 1996 for whom there was a reliable computerized database. Follow-up was achieved in 8577 of the 9262 patients (92.6%), through the records of outpatient clinics, postcard replies, telephone interviews, and with the aid of the Korean National Statistical Office. The follow-up ended on August 1 1997 with the mean period of follow-up being 64.3 months. The precise causes of death could not be routinely ascertained in 8577 patients. The extent of resection was determined according to the location and extent of primary tumors. En-bloc resection with modified D3 (D2 + α) lymph node dissection, according to the Japanese classification, was the surgical procedure of choice.

Clinicopathologic variables

The clinicopathologic variables evaluated to determine prognostic factors were classified as patient, tumor, and treatment factors.

(1) *Patient factors*: age in years (≤39, 40–64, ≥65), sex, duration of symptoms (≤6 months, >6 months), preoperative hemoglobin and albumin levels, T-cell percentage.
(2) *Tumor factors*: tumor location (upper third, middle third, lower third, entire stomach), Borrmann type, tumor size (≤2 cm, 2–5 cm, 5–10 cm, >10 cm), histologic type (well differentiated [WD], moderately differentiated [MD], poorly differentiated [PD], undifferentiated [UD], mucinous, signet ring cell), Lauren's classification (intestinal, mixed, diffuse), perineural invasion, lymphatic invasion, vascular invasion, depth of invasion (mucosa, submucosa, proper muscle, subserosa, serosa, adjacent organ), number of involved lymph nodes (0, 1–3, 4–6, ≥7), ratio of involved to resected lymph nodes (0, ≤0.1, ≤0.3, ≤0.5, >0.5), distant metastasis.
(3) *Treatment factors*: extent of resection (subtotal gastrectomy, total gastrectomy, combined resection of invaded adjacent organ, non-resection), residual tumor (R) category (R0, R1, R2; see below), intraoperative blood transfusion, operation time, number of resected lymph nodes (≤25, 26–35, 36–45, ≥46), postoperative complications, postoperative adjuvant therapy.

R0 was defined as a resection that resulted in complete macroscopic and microscopic tumor removal on intraoperative and histopathologic evaluation, done in accordance with the recommendations of the International Union Against Cancer (UICC) (1987) [13]. Histologic classification of the tumor was done in accordance with the grade of differentiation proposed by the World Health Organization. For evaluating postoperative adjuvant therapy, we allocated patients with stage III disease to an immunochemotherapy group, a chemotherapy group, and a surgery-alone group.

Protocol for immunochemotherapy (PMF)

Immunotherapy was started on postoperative day 4 or 5, with Picibanil (P), (a *Streptococcus pyogenes preparation*; Tokyo, Japan). Dose was 1.0 KE IM weekly.

Chemotherapy was started on postoperative day 8–10 with mitomycin-C, (M) 4 mg/50 kg and 5-fluorouracil, (F) 500 mg/50 kg given twice a week for 2 weeks, then weekly for 6 weeks. After 8 weeks, 5-fluorouracil was changed to oral form and continuously taken (800 mg/50 kg/day). Duration was 24 months (PMF, 2 months; PF, 22 months).

Protocol for chemotherapy (FAM)

Chemotherapy was started on postoperative days 25–30 with 5, fluorouracil 600 mg/m^2 on days 1, 8, 29, 36; adriamycin (A), 30 mg/m^2 on days 1, 29; and mitomycin-C 10 mg/m^2 on day 1. There was a 2-week interval between each cycle, with a total of six cycles.

Quantitative analysis of lymph node metastasis

The extent of lymph node dissection was categorized according to the number of resected lymph nodes,

based on previous anatomical studies [14]. We analyzed survival rates according to the ratio of involved to resected lymph nodes, as well as according to the numbers of involved and resected lymph nodes. To minimize the effect of the stage migration phenomenon and to obtain a creditable value for the number of involved lymph and the ratio of involved to resected nodes [15–16], patients with fewer than 15 isolated lymph nodes were excluded from the analysis of the relationship between number of involved lymph nodes and ratio of involved to resected lymph nodes.

Statistical analysis

Survival rates were calculated by the Kaplan-Meier method and differences in survival curves between the applicable variables were determined by the log-rank test on univariate analysis. Significant factors determined by univariate analysis were assessed by multiple stepwise regression analysis with a Cox proportional hazards model.

Results

The mean age of the 10783 patients was 53.5 years (range, 16–94 years), with peak incidence in the sixth decade. There was a male predominance of 2.07:1, but females were relatively predominant in patients younger than 40 years (1.12:1). Regarding the location of the primary tumor, 87.3% of lesions were located in the distal two-thirds of the stomach. However, upper-third lesions, particularly cardia cancer, increased in incidence from 5.8% in the 1970s and 1980s to 13.0% in the 1990s. Resection was performed in 9058 of these patients (resection rate, 84.0%). The operative procedures and residual tumor data are listed in Table 1.

According to the macroscopic classification, Borrmann type III was the most common (65.1%), followed by type II (19.1%), type IV (13.2%), and type I (2.5%), in advanced gastric cancers, while in early gastric cancers (EGCs), type IIc (53.8%) was the most frequently encountered, followed by types IIa + IIc (13.2%). The most common histologic classification was poorly differentiated adenocarcinoma (38.3%). The diffuse type of Lauren's classification accounted for 67.3% of cases. The overall incidence of EGC was 21.4%; its incidence showed a steady increase (7.7% in 1970–1980, 16.0% in 1981–1985, 21.2% in 1986–1990, 29.0% in 1991–1995, and 35.6% in 1996). Lymph node metastasis was found in 56.6% of the patients. The average number of resected and involved lymph nodes for each resected patient was 31.5 and 5.43, respectively.

According to the UICC TNM stage classification (1987) [13] 17.3% of patients were stage Ia; 11.6%, stage Ib; 15.0%, stage II; 20.0%, stage IIIa; 23.3%, stage IIIb; and 13.2%, stage IV.

The 5-year overall survival rate for patients treated in the period 1981–1996 was 55.8%, and that of patients who received curative resection was 64.8%. The 5-year survival rates according to TNM stage were 92.9% for Ia, 84.2% for Ib, 69.3% for II, 45.8% for IIIa, 29.6% for IIIb, and 9.2% for IV (Fig. 1). The 5-year survival rate was 91.7% for EGC and 45.7% for advanced gastric cancer.

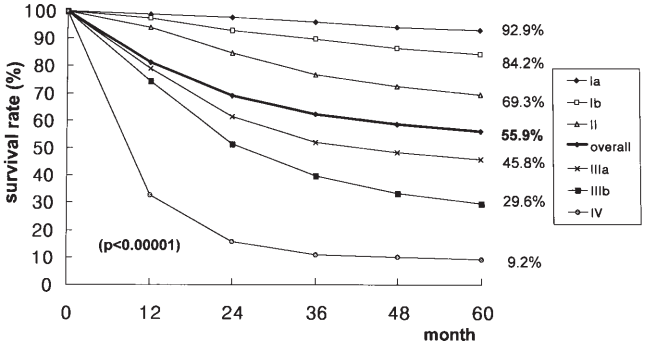

Fig. 1. Survival curves in gastric cancer patients according to TNM stage (International Union Against Cancer classification (1987)[13])

Table 1. Type of operation (op.) and residual tumor data in 10783 patients with gastric cancer treated between 1970 and 1996 at Seoul National University Hospital

Type of op./Residual tumor	R0	R1	R2	Total (%)
Subtotal gastrectomy	6837	81	137	7055 (65.5)
Total gastrectomy	1543	63	95	1701 (15.7)
Combined resection	262	13	27	302 (2.8)
Bypass			499	499 (4.6)
Feeding tube insertion			527	527 (4.9)
Vessel ligation			161	161 (1.5)
Explo ratory laparotomy only			538	538 (5.0)
Total (%)	8642 (80.2)	157 (1.5)	1984 (18.3)	10783 (100)

For definitions of residual tumor (R) categories R0, R1, R2, see text

Table 2. Univariate analysis of clinicopathologic variables in patients with gastric cancer in this series

Variable	5-YSR (%)	*P* value	Variable	5-YSR (%)	*P* value
Age (years)		<0.0001	Lauren classification		<0.0001
<40	57.9		Intestinal	72.9	
40–64	58.2		Mixed	70.4	
≥65	44.9		Diffuse	57.2	
Sex		0.0175	Lymphatic invasion		<0.0001
Male	54.6		(−)	60.3	
Female	57.8		(+)	42.2	
Symptom duration		0.1478	Perineural invasion		<0.0001
T-cell percentage		0.2929	(−)	58.9	
Hemoglobin		0.0017	(+)	38.5	
<12 mg%	47.3		Vascular invasion		<0.0001
≥12 mg%	62.4		(−)	31.3	
Albumin		0.0021	(+)	57.8	
<3.5 mg%	45.4		Depth of invasion		<0.0001
≥3.5 mg%	64.8		Mucosa	93.4	
Location		<0.0001	Submucosa	89.8	
Lower 1/3	59.6		Muscle	77.2	
Mid 1/3	57.8		Subserosa	60.5	
Upper 1/3	49.4		Serosa	39.7	
Whole	15.8		Adj. organ	8.7	
Extent of op.		<0.0001	No. of res. LN		0.0569
STG	68.7		≤25	62.4	
TG	45.4		26–35	63.0	
Combined	19.6		36–45	63.6	
Resection (−)	6.8 (3-YSR)		≥46	59.0	
Postop. complication		0.0581	No. of inv. LN		<0.0001
R category		<0.0001	0	85.4	
R0	64.8		1–3	65.6	
R1	9.9		4–6	33.9	
R2	8.2		>7	27.4	
Tumor size (cm)		<0.0001	Ratio of inv. to res. LN		<0.0001
≤2	87.6		0	85.4	
2–5	63.7		≤0.1	70.1	
5–10	35.2		≤0.3	49.4	
>10	25.2		≤0.5	27.8	
Borrmann type		<0.0001	>0.5	14.1	
I	60.7		Distant metastasis		<0.0001
II	59.7		(−)	60.7	
III	47.5		(+)	9.4	
IV	16.7		Adjuvant therapy[a]		0.0012
Histology		<0.0001	No. adj. tx.	27.2	
W/D	72.4		Chemotx.	36.8	
M/D	64.2		Immunochemotx.	44.8	
P/D	52.6				
U/D	30.3				
Mucinous	47.4				
Signet ring	63.4				

STG, Subtotal gastrectomy; TG, total gastrectomy; R, residual; W/D, well differentiated; M/D, moderately differentiated; P/D, poorly differentiated; U/D, undifferentiated; adj., adjacent; tx, therapy; inv., involved; res., resected; 5-YSR, 5-year survival rate; LN, lymph nodes

[a] Analysis in patients with stage III gastric cancer according to International Union Against Cancer classification (1987) [13]

Univariate analysis

The results of univariate analysis are summarized in Table 2. Age, sex, preoperative status (hemoglobin and albumin levels), type of operation, R-category, tumor location, Borrmann type, tumor size, histologic differentiation, Lauren's classification, perineural invasion, lymphatic invasion and vascular invasion, depth of invasion, number of involved lymph nodes, ratio of involved to resected lymph nodes, and distant metastasis had prognostic significance on univariate analysis. The number of resected lymph nodes had prognostic significance in patients with stage II and IIIa disease ($P < 0.05$). The postoperative adjuvant treatment was significant in patients with stage III gastric cancer ($P < 0.05$).

Patient-related factors. Patients over 64 years old had a significantly lower survival rate than patients in the

Table 3. Five-year survival rates according to the ratio of involved to resected lymph nodes (LNs) in relation to the numbers of involved and resected LNs

	Ratio of inv. to res LN					
	0	≤0.1	≤0.3	≤0.5	≥0.5	*P* value
No. of inv. LN						
0	85.8	—	—	—	—	
1–3	—	70.3	53.5	—	—	0.0001
4–6	—	65.4	53.7	23.9	—	0.0013
≥7	—	75.0	43.4	27.2	13.7	0.0001
P value		0.877	0.003	0.560		
NO. of res. LN						
15–25	85.8	69.7	48.9	30.0	9.9	<0.0001
26–35	85.1	64.9	52.9	21.9	14.6	<0.0001
36–45	86.3	71.4	46.2	32.3	14.2	<0.0001
≥46	84.7	72.1	46.9	21.3	10.2	<0.0001
P value	0.371	0.426	0.148	0.131	0.600	

other two age groups (<40 and 40–64 years) ($P < 0.0001$). Survival rates in those aged less than 40 years and those in the 40- to 64-year group showed no significant difference. There were no significant differences in stage of disease among the three age groups, but elderly patients (more than 64 years) had a significantly lower proportion of EGC than the other two age groups. The proportions of EGC in the young (<40 years), intermediate (40–64 years), and elderly (>64 years) patients were 26.2%, 23.5%, and 19.4%, respectively. Women had a slightly better prognosis than men (5-year survival rates 54.6% and 57.8%, respectively). Preoperative hemoglobin and albumin levels had prognostic significance ($P < 0.05$), but preoperative T-cell percentage and symptom duration had no significant prognostic value.

Tumor-related factors. Most of the carcinomas were found in the distal two-thirds of the stomach. Patients with tumor arising in the distal two-thirds showed significantly better survival than patients with tumor arising in the upper-third or entire stomach ($P < 0.0001$). The size of tumors was directly correlated with survival ($P < 0.0001$). Patients with Borrmann type I had the best survival rate, while those with Borrmann type IV (linitis plastica) had the worst. There were no significant differences in survival rate according to macroscopic type in EGC. Patients with more differentiated tumors had a better prognosis ($P < 0.0001$). Signet ring cell carcinoma is regarded as a poor prognostic histology. In this study it was predominant in EGC and consequently indicated a good prognosis, comparable to that of moderately differentiated carcinoma.

Survival curves in relation to depth of invasion revealed that the deeper the invasion, the lower the survival rate ($P < 0.0001$). The 5-year survival rates of patients with invasion of the mucosa, submucosa, proper muscle, subserosa, serosa, and extension to adjacent organ were 93.4%, 89.8%, 77.2%, 60.5%, 39.7%, and 8.7%, respectively.

Survival rates were markedly decreased in relation to increased numbers of metastatic lymph nodes ($P < 0.0001$). The 5-year survivals were 85.4% for patients without nodal involvement, 65.6% for patients with one to three metastatic nodes, 49.9% for patients with four to six metastatic nodes, and 27.4% for patients with more than six metastatic nodes. Patients were divided into five groups according to the ratio of involved to resected lymph nodes (0, ≤0.1, ≤0.3, ≤0.5, >0.5). The 5-year survival rates were 85.4% for patients with a ratio of 0, 70.1% for those patients with a ratio of up to 0.1, 49.4% for those with a ratio of up to 0.3, 27.8% for those with a ratio of up to 0.5, and 14.1% for patients with a ratio of more than 0.5. Patients in identical numeric groups — either the number of involved or of resected lymph nodes — were classified according to the ratio of involved-to-resected lymph nodes ($P < 0.0001$). In each numeric group, there were significant survival differences according to the ratio of involved-to-resected lymph nodes ($P < 0.0001$). In patients grouped according to the ratio of involved-to-resected lymph nodes the number of involved and resected lymph nodes had no significant prognostic value, except for patients with more than six involved lymph nodes who had a ratio of up to 0.3, who had a poor survival rate (Table 3). Lymphatic invasion, perineural invasion, and vascular invasion also had prognostic significance on univariate analysis. (all, $P < 0.0001$).

Treatment-related factors. The 5-year survival rates according to extent of resection were 68.7% for subtotal gastrectomy, 45.4% for total gastrectomy, and 19.6% for combined resection. There were no 5-year survivors in the non-resection group. According to curability of

Table 4. 5-year survival rates according to number of resected lymph nodes at different TNM stages

Stage	No. of resected LNs ≤25	26–35	36–45	≥46	*P* value
	Five-year survival rates (%)				
Ia and Ib	89.0	89.2	92.7	88.2	0.1448
II	64.4	70.1	71.9	75.4	0.0352*
IIIa	43.1	52.9	55.9	61.4	0.0052*
IIIb	27.5	30.0	31.3	30.1	0.3826
Overall	62.4	63.0	63.6	59.0	0.0569

* Difference in survival between patients with ≤25 resected LNs and those with 26 to 35 resected LNs. TNM stages according to reference [13]

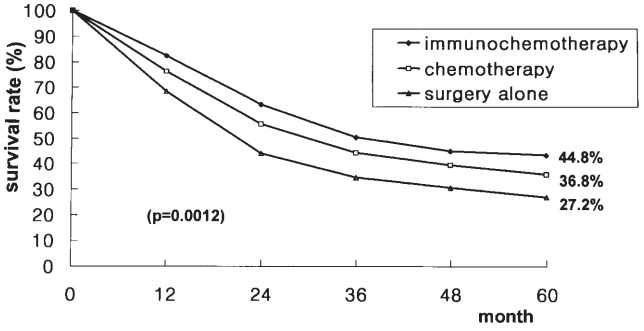

Fig. 2. Survival curves according to adjuvant therapy in stage III gastric cancer patients

operation, patients with curative resection (UICC R0 resection) had a significantly better survival rate than patients with noncurative surgery ($P < 0.0001$). Patients with stage II and IIIa gastric cancer in whom 26 or more lymph nodes were removed had a better survival rate than patients with fewer than 26 removed lymph nodes ($P < 0.05$), while the number of resected lymph nodes had no significant survival impact on patients with stage Ia, Ib, IIIb, IV gastric cancer, or overall (Table 4). Transfusion, operation time, and postoperative complications didn't show any impact on survival rates. Regarding adjuvant treatment modality, there were significant differences in survival in stage III patients ($P = 0.0012$); the 5-year survival rates were 44.8% for the immunochemosurgery group, 36.8% for the surgery + chemotherapy group, and 27.1% for the surgery-alone group (Fig. 2).

Multivariate analysis

Table 5 shows the independent prognostic factors identified by the multivariate analysis performed with significant factors identified by univariate analysis. Independent prognostic factors were curability of operation (Fig. 3), depth of invasion (Fig. 4), and ratio of involved to resected lymph nodes (Fig. 5). The number

Table 5. Independent progrostic factors in gastric cancer identified by multivariate analysis

Factor	Relative risk	*P* value
Curability of operation	3.6735	0.0147
Depth of invasion	2.1835	0.0056
LN ratio (no. of inv. LN/no. of. res. LN)	2.0576	0.0076

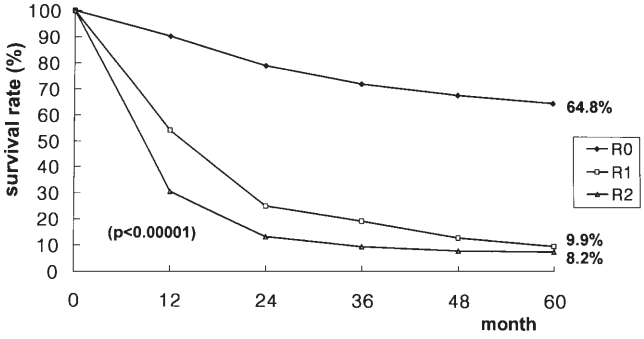

Fig. 3. Survival curves according to R-category, i.e., curability of operation. See text for explanation of R0, R1, R2

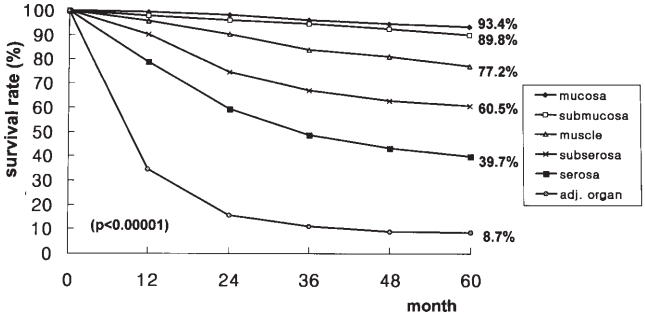

Fig. 4. Survival curves according to depth of invasion

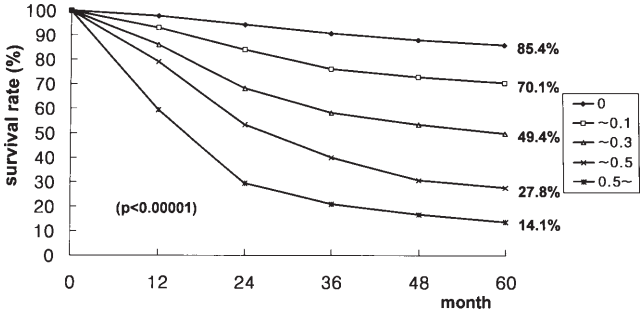

Fig. 5. Survival curves according to ratio of involved to resected lymph nodes

of involved or resected lymph nodes was not a prognostic factor on multivariate analysis.

Discussion

The prognosis of gastric cancer has improved in recent years, with the 5-year survival rate being 50%–60% in Eastern series [5,7,11,17], in contrast to the still grim results in most Western series [18–20]. The present study showed that curability of operation, depth of invasion, and lymph node metastasis (ratio of involved to resected lymph nodes) were the most significant prognostic factors in gastric cancer.

There are some reports that young patients with gastric cancer have a poorer prognosis than older patients because they include a higher proportion with advanced stage tumors, due to less suspicion of malignant disease and aggressive tumor biology [21]. However, in the present study, young patients (less than 40 years) showed no significant difference in stage of disease, although Lauren's diffuse type was predominant. In contrast, the proportion of patients with EGC was significantly lower in elderly patients (>64 years) than in the intermediate (40–64 years) and young (<40 years) patients, and the survival of the young patients was significantly better than that of the elderly patients, possibly because of the higher proportion with EGC. This may be explained by the young patients having better nutritional and immune status, which may lead to a better prognosis, provided early detection and reasonable treatment is employed.

Gastric cancer is most common in the distal two-thirds of the stomach, but upper-third lesions, particularly cardia cancer, have been increasing in incidence; patients with these lesions have a poorer survival than those with lesions in the distal two-thirds, because of detection at a more advanced stage and extensive lymphatic spread [22–24]. We [25] have reported that because the poorer prognosis of cardia gastric cancer was due to a more advanced stage at the time of detection, better means for early diagnosis should be developed, and curative resection with at least 2-cm cancer-free resection margins should be performed. In the present study, results were similar, in that the incidence of upper-third lesions increased from 5.8% in the 1970s and 1980s to 13.0% in the 1990s, and the survival rate was poorer than that of patients with distal two-thirds lesions, while patients with lesions involving the entire stomach had the worst prognosis.

Depth of invasion was one of the independent prognostic factors on multivariate analysis. The increase in incidence of EGC has contributed greatly to the improvement in survival of gastric cancer patients. Our data also showed an increase in the incidence of EGC. The proportion of early gastric cancers was 7.7% in the 1970s, 19.1% in the 1980s, 29.0% in the 1990s, and 35.6% in the 1996, with these results lower than those in Japanese reports of the same periods. We [26,27] have reported that proper muscular and subserosal lesions should be considered as different T stages, because they have significantly different survival rates. In the present study, results were similar in that 5-year survivals in patients with proper muscular and subserosal lesions were 77.2% and 60.5%, respectively ($P < 0.05$). With regard to locally advanced gastric cancer which directly invades pancreas, duodenum, or liver, without distant metastasis, we [28] have previous data showing that combined curative resection, such as the Whipple operation, increases survival.

Generally, curative resection is defined as a complete tumor removal with adequate margins of clearance and lymphatic drainage. There have been controversies over the value of extended lymph node dissection for the treatment of gastric cancer [16,29–38]. We believe that curative gastric resection with extended lymphadenectomy, along with early detection of cancer, markedly contributed to improved survival. The German Gastric Cancer Study Group reported that the relevance of lymph node metastasis did not depend on the number of resected lymph nodes, provided 15 or more nodes were resected, as stage migration played a rather small role. They found that extirpation of more than 25 lymph nodes (defined as radical lymph node dissection) had a prognostic impact on survival in patients with stage II and IIIa disease [16]. In the present study we had a similar result, which may explain findings that radical lymph node dissection contributes to locorerional control and improved survival in patients with stage II and IIIa gastric cancer.

With regard to the status of lymph node metastasis, the patterns of lymphatic spread through lymph nodes at various anatomical locations have provided valuable information about prognosis. But nodal staging by anatomical location is a somewhat artificial classification that is poorly reproducible, and it is sometimes difficult to classify certain lymph nodes into the correct anatomical levels. Neither the number of nodes involved nor the ratio of resected to involved nodes is an artificial classification, and either emerges as a simple, objective assessment tool. Therefore we performed a quantitative analysis to determine the status of lymph node metastasis as a prognostic factor in gastric cancer. Previously, we had suggested that the staging of lymph node metastasis should be based on the number of involved lymph nodes [26], and several reports agreed with our suggestion [39–41]. The UICC TNM classification revised in 1997 [42] ultimately adopted the number of involved lymph nodes as a parameter for the assessment of lymph node metastatic status, although the cat-

egories were rather different from ours. Verification of the cut-off value for number of involved lymph nodes may be necessary. We believe that gastric cancer patients with more than seven metastatic lymph nodes will not show a significant survival difference according to the number of involved lymph nodes. Therefore in the present study, we assessed the number of involved lymph nodes as nil, one to three, four to six, and more than six. There was a linear trend showing decreasing survival rate associated with an increasing number of involved lymph nodes. The ratio of involved to resected lymph nodes has been identified as an another independent prognostic factor in centers where D2 lymphadenectomy is already established as a standard procedure [43–47]. This ratio and the number of involved lymph nodes depend on the extent of lymphadenectomy; therefore, this ratio or the number of involved nodes is expected to be a more comprehensive factor that includes surgical and pathologic values. We classified the involved-to-resected lymph node ratio as nil, ≤ 0.1, ≤ 0.3, ≤ 0.5 and > 0.5, and this showed a linear trend for decreasing survival rate associated with an increasing ratio of involved-to-resected lymph nodes**.** The ratio of involved-to-resected lymph nodes was an independent prognostic factor on multivariate analysis, while the number of involved or resected lymph nodes was not. Thus, when radical lymph node dissection is the standard operation for gastric cancer, the ratio of involved-to-resected lymph nodes has a more comprehensive and precise prognostic value than the number of involved or resected lymph nodes.

Stage III gastric cancer is already considered to be a systemic disease. To improve the prognosis, systemic treatment, such as immunotherapy or chemotherapy, is needed in the early postoperative period to kill the micrometastatic or remaining cancer cells after curative resection. We [11,12,48] have already reported the effectiveness of immunochemosurgery, that is, radical surgery followed by early postoperative adjuvant immunochemotherapy, in randomized prospective trials with stage III gastric cancer patients. Since the present study was carried out retrospectively and randomization was incomplete, the differences in survival rates according to modality of postoperative adjuvant therapy are not as conclusive as those in our previous study.

Apart from the clinical and pathologic prognostic factors in gastric cancer, recent molecular biological studies have indicated new prognostic factors that are now being extensively investigated. These are: growth factors and receptors (such as epithelial growth factor and receptors, and transforming growth factor T-β1 receptor); oncogene and suppressor genes (such as c-*erbB2*, *ras*, *HST-1*, K-*sam*, c-*met*, *p53*, *DCC*, *Rb P21*, and *nm23*); cell adhesion molecules (such as integrins, cadherin, the immunoglobulin superfamily, and CD44); chromosome deletion of 1q, 5q, 7p 17p; tissue inhibitor of metalloproteinase, matrix metalloproteinases and urokinase plasminogen activator and microsatellite instability. We are also investigating some of these factors and expect to find new prognostic factors.

In conclusion, curative resection, depth of invasion, and lymph node metastasis were the most significant prognostic factors in gastric cancer. With regard to the status of lymph node metastasis, the ratio of involved-to-resected lymph nodes had a more precise and comprehensive prognostic value than the number of involved nodes. Consequently, early detection and curative resection with radical lymph node dissection, followed by immunochemotherapy, particularly in patients with stage III gastric cancer, should be the treatment strategy of choice for patients with gastric cancer.

References

1. Harrison JD, Fielding JWL. Prognostic factors for gastric cancer influencing clinical practice. World J Surg 1995;19:496–500.
2. Soreide O, Lillestol J, Viste A, Bjerkeset T. Factors influencing survival in patients with cancer of the stomach. Acta Chir Scand 1982;148:367–72.
3. Haugstvedt TK, Viste A, Eide GE, Soreide O and Members of the Norwegian stomach cancer trial. Norwegian multicentre study of survival and prognostic factors in patients undergoing curative resection for gastric carcinoma. Br J Surg 1993;80:475–8.
4. Hermanek P. Prognostic factors in stomach cancer surgery. Eur J Surg Oncol 1986;12:241–6.
5. Maruyama K. The most important prognostic factors for gastric cancer patients. A study using univariate and multivariate analysis. Scand J Gastroenterol 1987;22:63–8.
6. Yu CCW, Levison DA, Dunn JA, Ward LC, Demonakou M, Allum WH, et al. Pathological prognostic factors in the second British Stomach Cancer Group trial of adjuvant therapy in resectable gastric cancer. Br J Cancer 1995;71:1106–10.
7. Nakamura K, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y, et al. Pathology and prognosis of gastric carcinoma. Findings in 10000 patients who underwent primary gastrectomy. Cancer 1992;70:1030–7.
8. Andrus A, Karl K. Factors influencing survival of patients after radical surgery for gastric cancer. Acta Oncol 1994;33:913–20.
9. Msika S, Chastang C, Houry S, Lacaine F, Huguier M. Lymph node involvement as the only prognostic factor in curative resected gastric carcinoma: A multivariate analysis. World J Surg 1989;13:118–23.
10. Boku T, Nakane Y, Minoura T. Prognostic significance of serosal invasion and free intraperitoneal cancer cells in gastric cancer. Br J Surg 1990;77:436–9.
11. Kim JP, Kim YW, Yang HK, Noh DY. Significant prognostic factors by multivariate analysis of 3926 gastric cancer patients. World J Surg 1994;18:872–8.
12. Kim JP, Kwon OJ, Oh ST, Yang HK. Result of surgery on 6589 gastric cancer patients and immunochemosurgery as the best treatment of advanced gastric cancer. Ann Surg 1992;216:269–79.
13. Hermaneck P, Sobin LH. UICC TNM classification of malignant tumors. 4th ed. Berlin: Springer; 1987:39–46.
14. Wagner PK, Ramaswamy A, Ruschoff J, Schmitz-Moormann P, Rothmund M. Lymph node counts in the upper abdomen: Ana-

tomic basis for lymphadenectomy in gastric cancer. Br J Surg 1991;78:825–7.
15. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 1985;312:1604–8.
16. Siewert JR, Bottcher K, Roder JD, Busch R, Hermanek P, Meyer HJ, et al. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. Br J Surg 1993;80:1015–8.
17. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. World J Surg 1987;11:418–25.
18. Allum WH, Powell DJ, McConkey CC. Gastric cancer: A 25-year review. Br J Surg 1989;76:535–40.
19. Akoh JA, MacIntyre IMC. Improving survival in gastric cancer: Review of 5-year survival rates in English language publications from 1970. Br J Surg 1992;79:293–9.
20. Wanebo HJ, Kennedy BJ, Steele G, Winchester D, Osteen R. Cancer of the stomach: A patient care study by the American College of Surgeons. Ann Surg 1993;218:583–92.
21. Tso P, Bringaze W, Dauterive A, Correa P, Cohn I. Gastric carcinoma in the young. Cancer 1987;59:1362–5.
22. Park JG, Gazdar AF, Kim YI, Choi BI, Song IS, Kim JP. Gastric cancer in Korea: Experience at the Seoul National University Hospital. In: Sugarbaker P. Management of gastric cancer. Boston: Kluwer Academic; 1991:285–305.
23. Webb JN, Busuttil A. Adenocarcinoma of the esophagus and of the esophago-gastric junction. Br J Surg 1978;65:475–9.
24. Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. Br J Cancer 1990;62:440–3.
25. Kim JP, Yoo HY, Kim SC, Yang HK. Clinical analysis of gastric cardia cancer. J Korean Cancer Assoc 1994;26:361–8.
26. Kim JP, Jung SE. Patients with gastric cancer and their prognosis in accordance with number of lymph node metastases. Scand J Gastroenterol 1987;22 (Suppl 133):33–5.
27. Kim JP, Yang HK, Oh ST. Is the new UICC staging system of gastric cancer reasonable? (Comparison of 5-year survival rate of gastric cancer by old and new UICC stage classification.) Surg Oncol 1992;1:209–13.
28. Byun JC, Lee JH, Kim SJ, Yu HJ, Lee KU, Kim JP. Pancreatoduodenectomy for gastric cancer. J Korean Cancer Assoc 1998;30:72–9.
29. Roder JD, Bonenkamp JJ, Craven J, van de Velde CJH, Sasako M, Bottcher K, et al. Lymphadenectomy for gastric cancer in clinical trial: Update. World J Surg 1995;19:546–53.
30. Lee WJ, Lee WC, Houng SJ, Shun CT, Houng RL, Lee PH, et al. Survival after resection of gastric cancer and prognostic relevance of systematic lymph node dissection: 20 years' experience in Taiwan. World J Surg 1995;19:707–13.
31. Yang HK, Kang SB, Lee KU, Choe KJ, Kim YI, Kim JP. Prognostic significance of the extent of lymph node dissection in gastric cancer. J Korean Cancer Assoc 1997;29:198–203.
32. Paceli F, Doglietto GB. Extensive versus limited lymph node dissection for gastric cancer. A comparative study of 320 patients. Br J Surg 1993;80:1153–6.
33. Viste A, Svanes K. Prognostic importance of radical lymphadenectomy in curative resection for gastric cancer. Eur J Surg 1994;160:497–502.
34. Siewert JR, Kestlmeier R, Busch R, Bottcher K, Roder JD, Muller J, et al. Benefit of D2 lymph node dissection for patients with gastric cancer and pN0 and pN1 lymph node metastases. Br J Surg 1996;83:1144–7.
35. Dent DM, Madden MV, Price SK. Randomized comparison of R1 and R2 gastrectomy for gastric cancer. Br J Surg 1988;75:110–2.
36. Robertson CS, Chung SCS, Woods SDS. A prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. Ann Surg 1994;220:176–82.
37. Bonenkamp JJ, van de Velde CJH, Sasako M, Hermans J. R2 compared with R1 resection for gastric cancer: Morbidity and mortality in a prospective, randomized trial. Eur J Surg 1992;158:413–8.
38. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JTM. Randomized comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995;345:745–8.
39. Ichikura T, Tomimatsu S, Okusa Y, Uefuji K, Tamakuma S. Comparison of the prognostic significance between the number of metastatic lymph nodes and nodal stage based on their location in patients with gastric cancer. J Clin Oncol 1993;11:1984–1990.
40. Isozaki H, Okajima K, Kawashima Y, Yamada S, Nakata E, Nishimura J. Prognostic value of the number of metastatic lymph nodes in gastric cancer with radical surgery. J Surg Oncol 1993;53:247–51.
41. Adachi Y, Kamakura M, Mori H, Baba Y, Maehara Y, Sugimachi K. Prognostic significance of the number of positive lymph nodes in gastric carcinoma. Br J Surg 1994;81:414–6.
42. Sobin LH, Wittekind Ch, editors. International Union Against Cancer: TNM classification of malignant tumors. 5th ed. New York: Wiley-Liss; 1997.
43. Yu W, Choi GS, Whang I, Suh IS. Comparison of five systems for staging lymph node metastasis in gastric cancer. Br J Surg 1997;84:1305–9.
44. Okusa T, Nakane Y, Boku T, Dakada H, Yamamura M, Hioki K. Quantitative analysis of nodal involvement with respect to survival rate after curative gastrectomy for carcinoma. Surg Gynecol Obstet 1990;170:488–94.
45. Roder JD, Bottcher K, Siewert JR, Busch R, Hermaneck P, Meyer HJ, et al. Prognostic factors in gastric carcinoma. Results of the German gastric carcinoma study 1992. Cancer 1993;72:2089–97.
46. Liu CL, Yang TL. Percentage of dissected lymph nodes and number of lymph nodes with metastasis as a prognostic factor after resection of gastric cancer. First international gastric cancer congress, 1995; Tokyo: Monduzzi: 1995;1005–8.
47. Juvan R, Repse S, Omejc M, Jelenc F, Lamovec J. Prognostic value of lymph node metastasis ratio in gastric cancer. Second international gastric cancer congress, 1997; Munich: Monduzzi: 1997;223–7.
48. Kim JP. The concept of immunochemosurgery in gastric cancer. World J Surg 1987;11:465–72.