Surgical Resection of Stage IV Gastric Cancer and Prognosis

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Abstract. *The aim of this study was to determine risk factors for prognosis in stage IV gastric cancer after gastrectomy. Surgical resection of stage IV gastric cancer has recently been proposed as the treatment of optimal choice; however treatment results, including prognosis, remain elusive. Patients included 128 resected patients of stage IV gastric cancer. The average survival time was 14.6 months with a 5-year survival rate of 4.7%. The most robust univariate predictors for poor prognosis were lymph node metastasis ratio (LNMR) over 50%, preoperative high value of CA19-9, preoperative high value of CEA and P factor as tumor factors, and LN dissection extent (LNDE) and operative curability as treatment factors. Among these univariate prognostic factors, LNMR, preoperative CA19-9 and P factor were independent on multivariate analysis (relative risk: RR=1.71, 1.47 and 1.6, respectively), and the combination can clearly classify the patients into the definite prognostic groups as group A (0 factor, average survival 22.8 months), B (1 factor, 14.0 months), and C (more than 2 factors, 5.5 months). On the other hand, LNDE likely affects prognosis in all the 3 groups. Our results suggested that stage IV gastric cancer is subdivided into the definite prognostic group by tumor factors and rigorous surgical treatment might have the potential to prolong survival.*

In 2004, approximately 50,000 people died from gastric cancer, the second leading cause of cancer death in Japan (1). Complete surgical resection remains the only potentially curative modality for gastric adenocarcinoma, contributing to the recent improvement of outcome in operable gastric cancer (2). On the other hand, for stage IV gastric cancer, only a marginal improvement has been reached for the 5-year survival rate (5-10%) in the last three decades worldwide (2-5), because both biological behavior and optimal treatment strategy have not been well established so far.

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In both the UICC (Union International Contre Le Cancer) and JCGC (Japanese Classification of Gastric Cancer) staging system, stage IV contains not only those patients with distant metastasis but also those with far-advanced T and N status without distant metastasis. Hence, patients with stage IV gastric cancer are likely composed of heterogeneous groups with clinicopathological predictors that identify subgroups with significantly different prognosis. Previous studies proposed that the prognostic factors for stage IV gastric cancer were tumor factors such as lymph node metastasis ratio (LNMR) (6-8), lymphatic invasion (9), vascular invasion (10), liver metastasis (10) and peritoneal metastasis (9), and treatment factors such as lymph node dissection extent (LNDE) (10), curability (11) and postoperative chemotherapy (12). In this current study, we validated all such currently feasible clinical parameters as well as tumor markers (CEA and CA19-9) as prognostic predictors and extracted the excellent combination of bona fide predictors of prognosis with resected stage IV gastric cancer using a multivariate modality.

Patients and Methods

Registration of patients. A total of 1,039 patients underwent gastrectomy at Kitasato University Higashi Hospital between January 1, 1990 and January 31, 2000, and were entered into a prospective database. From this patient cohort, 160 patients were identified with stage IV gastric cancer. Four cases with double cancers (gastric cancer or colorectal cancer) and 1 case with operative death were excluded from this analysis. For the remaining 155 cases, we preliminarily performed prognostic analysis. Univariate analysis revealed five prognostic factors: lymph node metastasis ratio (LNMR), preoperative CEA, preoperative CA19-9, LNDE and curability (data not shown). For these five factors, 132 cases were all informative, among which four were not documented for the number of resected lymph nodes. The final confirmative analysis was performed for 128 cases.

Patient demographics, tumor characteristics, treatment related factors and postoperative course were recorded and analyzed. Perioperative transfusion was defined as allogeneic blood transfusion during operation or the first 2 postoperative days. Transfusion was performed at the discretion of the treating surgeon and anesthesiologist. Tumor stage and grade were classified according to the 13th edition of the JCGC staging system.

Table I. *Distribution of clinical, pathologic, and treatment factors and univariate analysis of prognostic factors in 128 patients undergoing gastrectomy of stage IV gastric cancer.*

Parameters	No. of patients	%	DSS		Parameters	No. of patients	%	DSS	
			Average survival (months)	*P**				Average survival (months)	*P**
Gender					Dissemination (P+CY)				
Male	86	67	18	NS	Yes	67	52	15	0.04
Female	42	33	17		No	61	48	20	
Age, years					preoperative CEA				
<60	63	49	20	NS	≥2.5	26	20	11	$p=0.0007$
≥60	65	51	16		<2.5	102	80	19	
Tumor position					preoperative CA19-9				
Upper	64	50	18	NS	≥37	24	19	10	<0.0001
Middle	30	23	20		<37	104	81	20	
Lower	34	27	15		Preoperative therapy				
Differentiation					Yes	13	10	19	NS
Poor	92	72	18	NS	No	115	90	18	
Other	36	28	18		Postoperative therapy				
Vascular invasion					Yes	49	38	18	NS
Present	126	98	18	NS	No	79	62	16	
Absent	2	2	22		Surgical procedure				
Lymphatic invasion					TGR	96	75	17	NS
Present	126	98	18	NS	DGR	32	25	19	
Absent	2	2	22		LNDE				
T factor					D0, D1	44	34	12	0.0003
T1, T2	43	34	21	NS	D2, D3, or D4	84	66	20	
T3, T4	85	66	16		Curability				
N factor					B	38	30	23	0.0049
n0	8	6	17	NS	C	90	70	15	
n1	21	16	16		Splenectomy				
n2	32	25	16		Yes	20	16	21	NS
n3 or M	67	52	19		No	108	84	17	
M category					Perioperative transfusion				
M0	121	95	18	NS	Yes	95	74	17	NS
M1	7	5	18		No	33	26	19	
P category									
P0	114	89	8	<0.0001					
P1, P2, P3	14	11	19						

DSS, disease-specific survival; NS: not significant; TGR: total gastrectomy. DGR: distal gastrectomy; P: peritoneal dissemination; LNDE: lymph node dissection extent. *Log-rank test.

Statistical analysis. Statistical computations were performed using the SAS software package (SAS Institute, Cary, NC, USA), StatView version 5.0. A result was considered statistically significant when the *p*-value was <5% ($p<0.05$). The time of follow-up was calculated from the date of first operation. Disease-specific survival (DSS) was estimated according to the Kaplan-Meier method and compared using the log-rank test (13, 14). A multivariate logistic model was built using the variables that had prognostic potential suggested by the univariate analysis ($p<0.1$). Multivariate logistic regression analysis was performed for the strongest prognostic predictor of LNMR.

Results

Patient characteristics. The characteristics of the 128 patients included in this study are displayed in Table I. The average age of patients was 59 years (range, 21 to 86 years). Thirteen patients received preoperative chemotherapy and 79 patients postoperative chemotherapy, either as standard of care or as part of different clinical trials. All patients were informative for prognosis, namely, death within 5 years or alive at 5 years, and there was no censored case among the 128 patients. Table I shows the univariate analysis of the different factors of disease-specific survival. LNMR, P factor, preoperative CEA, preoperative CA19-9, LNDE and curability were associated with a poor outcome (Figure 1).

Multivariate characterization of prognostic factors. The first attempt at building a multivariate model for DSS was made using logistic analysis. All factors that had prognostic potential as suggested by the univariate analysis ($p<0.1$).

Table II. *Multivariate analyisis of factors associated with diease-specific survival taken into account the dissociation of tumor factors from treatment factors.*

Variable	Tumor factor			Treatment factor			Whole analysis		
	RR	95% CI	*P*-value	RR	95% CI	*P*-value	RR	95% CI	*P*-value
LNMR	1.66	1.25-2.21	0.0005	-	-	-	1.71	1.29-2.26	0.0002
preoperative CA19-9	1.46	1.08-1.98	0.01	-	-	-	1.47	1.09-1.97	0.01
P factor	1.66	1.09-2.52	0.02	-	-	-	1.6	1.07-2.39	0.02
Age	1.12	0.87-1.45	NS	-	-	-	1.15	0.9-1.46	NS
preoperative CEA	1.27	0.93-1.75	NS	-	-	-	1.11	0.81-1.52	NS
T factor	1.13	0.86-1.48	NS	-	-	-	1.08	0.83-1.41	NS
CY	1.1	0.85-1.44	NS	-	-	-	0.9	0.66-1.22	NS
LNDE	-	-	-	0.61	0.44-0.83	0.002	0.77	0.58-1.03	NS
Curability	-	-	-	1.25	0.90-1.75	NS	1.37	0.97-1.93	NS

RR: relative risk; CI: confidence interval; LNMR: lymph node metastatic ratio; P: peritoneal dissemination; CY: intraperitoneal cytology; LNDE: lymph node dissection extent; NS: not significant.

The final model defined LNMR, preoperative CA19-9, and P factor as independent factors (Table II). Because univariate analysis included both tumor factors and treatment factors, the dissociative analysis was performed. Among tumor factors, LNMR, preoperative CA19-9 and P factor were associated with prognosis, while LNDE was the only treatment factor independently involved in patient prognosis. Preoperative CEA and curability were eliminated after multivariate analysis. Multivariate logistic regression analyses were also performed for LNMR (Table III). T factor, P factor and CEA were predictors for LNMR, suggesting that CEA is involved in LNMR.

Table III. *Tumor factors affecting LNMR by logistic regression analysis.*

	RR	*P*
T factor (T1,2 *vs.* T3,4)	4.53	0.002
P factor	4.42	0.01
CEA	2.52	0.04
CA19-9	1.99	NS
Dissemination	1.79	NS
Age	1	NS

RR: relative risk.

Combination of tumor factors and prognosis in resected stage IV gastric cancer. We next validated whether a combination of independent prognostic factors can actually predict the definite patient prognosis as staging (Figure 2A). We assigned positivity of 0 factor, 1 factor and more than 2 factors among the 3 tumor factors of LNMR, preoperative CA19-9 and P factor to the staging groups A, B and C, respectively. Group A showed the best prognosis, followed by group B and subsequently group C (A *vs.* B: $p=0.0001$; B *vs.* C: $p<0.0001$). We then substituted LNMR with preoperative CEA as a surrogate trial marker of LNMR (see Table III) and similarly assigned positivity of 0 factor, 1 factor and more than 2 factors among preoperative CEA, preoperative CA19-9 and P factor to the 3 staging groups of A', B', and C', respectively. Group A' still showed the best prognosis, followed by group B and C, but groups B and C were not significantly different (Figure 2B).

LNDE affects patient prognosis for stage IV gastric cancer after gastrectomy. As treatment factor, LNDE is the only independent factor to affect patient prognosis (Table II). We then validated the 3 staging groups for LNDE effect against patient prognosis. Figure 3A shows the significant difference of prognosis of stage IV gastric cancer after gastrectomy according to LNDE ($p=0.0003$). LNDE likely affects all 3 staging groups (Figure 3B-D), but statistical significance was only found in group C, probably due to the small number tested in each group. Intriguingly, rigorous LNDE affects patients who survived for more than 10 months, which may suggest that operative reduction of tumors could be effective for patients who are anticipated for longer survival.

Discussion

Cancer patient survival is affected by both tumor factors (malignant degree and disease extent) and treatment factors. Our multivariate analysis revealed high relative risks for LNMR (1.71), CA19-9 (1.47) and P factor (1.6) which were identified as potent independent prognostic factors in resected stage IV gastric cancer (Table II), and the combination of these factors proved to be an excellent predictor of survival (Figure 2A). Previous multivariate analysis of stage IV gastric cancer revealed higher relative hazards for treatment factors

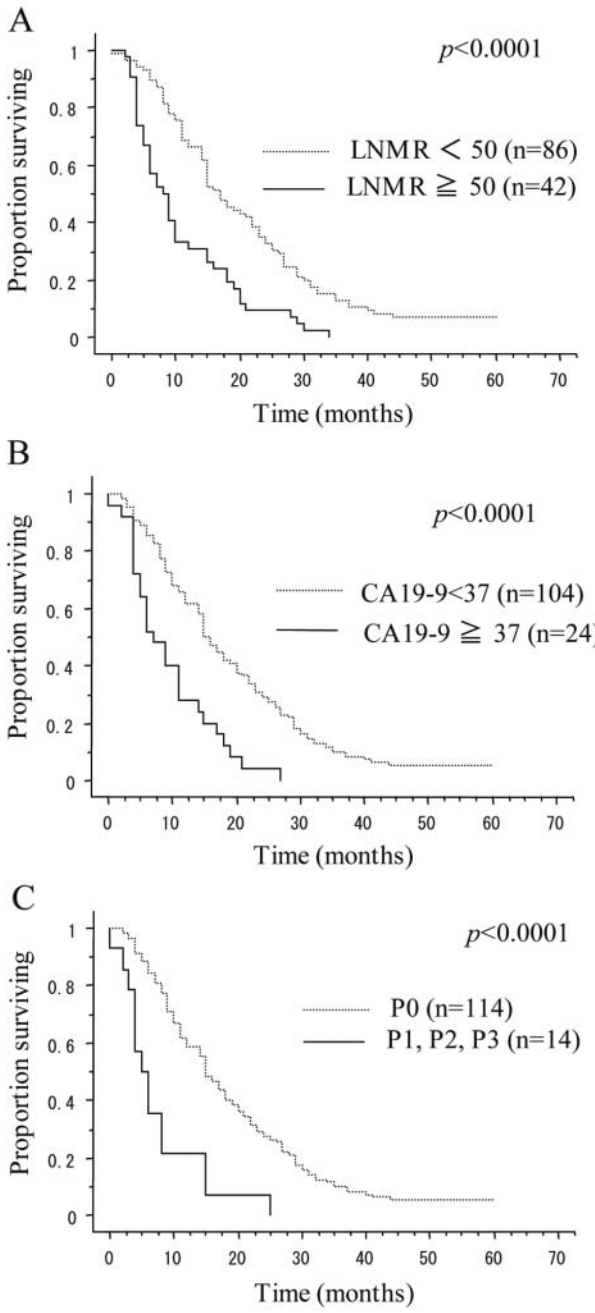

Figure 1. *Disease-specific survival of stage IV gastric cancer patients after gastrectomy by Kaplan-Meier analysis. (A) LNMR, (B) preoperative CA19-9 and (C) P factor.*

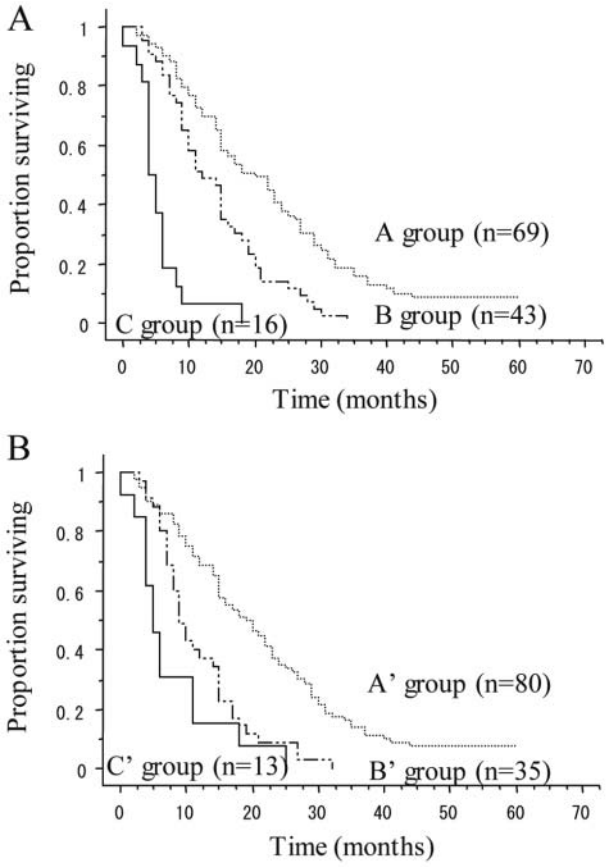

Figure 2. *Combination of independent prognostic factors extracted from multivariate analysis. (A) LNMR, preoperative CA19-9 and P factor were combined to predict survival of resected stage IV gastric cancer patients. Definitions of group A, B, and C are described in Patients and Methods. A statistical difference was found between groups A and B (HR=3.8: p=0.0001), and between group B and C (HR=5.0: p<0.0001). (B) CEA, preoperative CA19-9 and P factor were combined to predict survival of resected stage IV gastric cancer patients. Definitions of group A', B', and C' are described in Patients and Methods. A statistical difference was found between groups A' and B' (HR=4.4: p<0.0001), but not between groups B' and C'. Note that CEA could not be replaced with LNMR.*

such as both LNDE (2.6) and curability (1.9) than those for tumor factors including peritoneal metastasis (1.9), lymphatic invasion (1.7) and venous invasion (1.5) (9). Our current study, thus, for the first time, identified tumor factors as robust independent parameters as being far superior to treatment factors in resected stage IV gastric cancer. Because stage IV gastric cancer is basically incurable and there has not been any treatment proven to prolong survival, prognostic separation of stage IV disease by tumor factors can represent the definitive biological classification of human gastric cancer, which would lead to identification of molecular targets for tailor-made therapy. LNMR with stage IV is the most dismal phenotype of gastric cancer clinically.

Among the reported prognostic factors of stage IV gastric cancer as tumor factors (6-10), only LNMR was a strong predictor for survival of stage IV gastric cancer after gastrectomy in our study (Table I, Figure 1A). Multivariate logistic regression analysis for LNMR revealed CEA contribution ($p=0.04$, see Table III), indicating that CEA could be a significant effecter to promote lymph node spreading of cancer cells. CEA was demonstrated to be taken

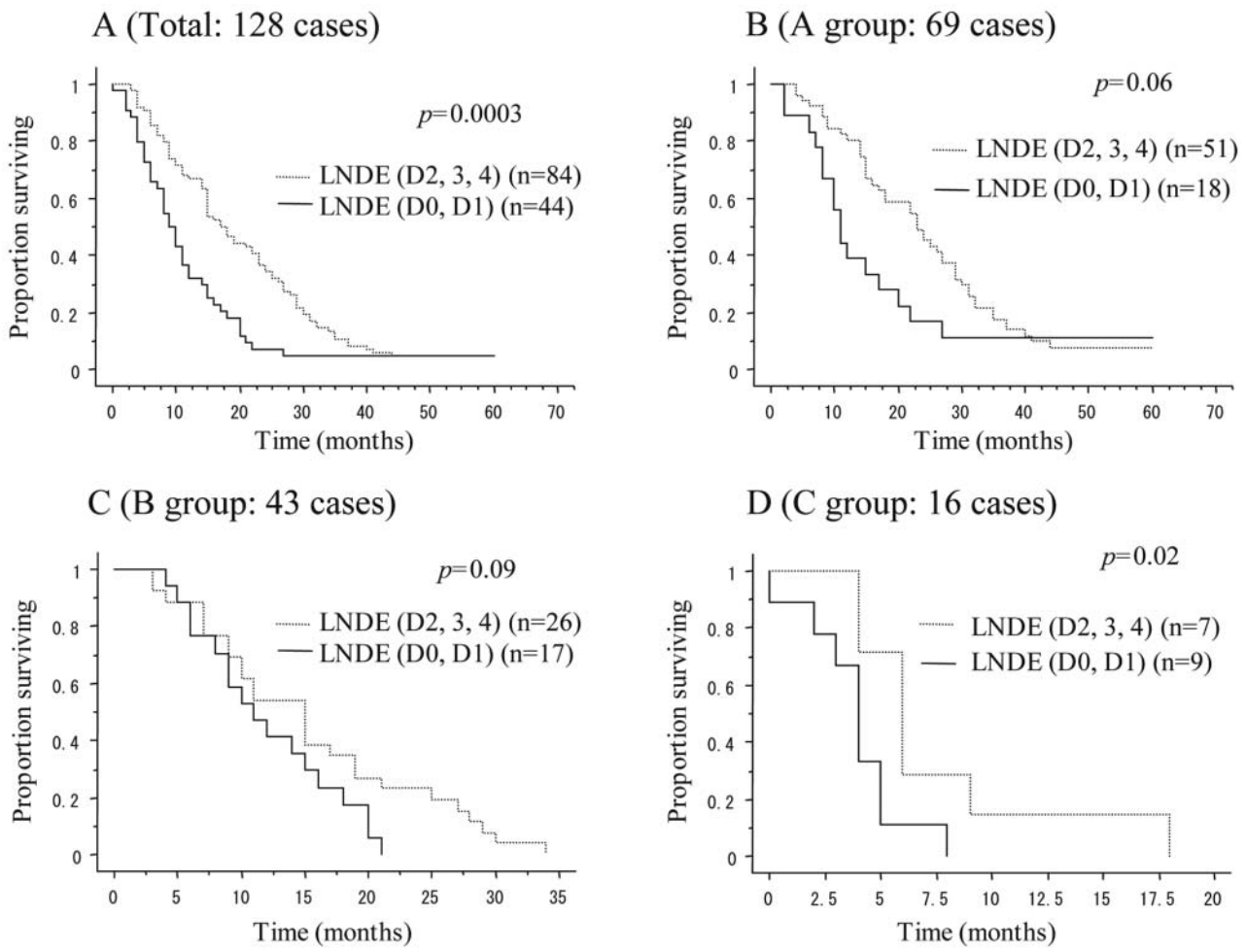

Figure 3. *LNDE, which was divided into D0, D1 group and D2, D3, D4 group, contributed to patients survival in resected stage IV gastric cancer. (A) The survival curves of a total of 128 cases were calculated using Kaplan Meier method, and compared using log-rank analysis (p=0.0003). (B) Survival curve of group A (n=69). (C) Survival curve of group B (n=43). (D) Survival curve of group C (n=16).*

up by macrophages, leading to activation and subsequent release of various cytokines for the implantation of cancer cells (15-18). Hence, CEA could be a suitable molecular target to regulate lymph node spreading of cancer cells. On the other hand, LNMR was not informative until operation had been carried out, and CEA might have been used as a surrogate marker of LNMR preoperatively, which regretfully failed (Figure 2B). This failure represents the much stronger contribution of LNMR than CEA to patient prognosis of resected stage IV gastric cancer.

On the other hand, we also revealed in this study that a preoperative high value of CA19-9 was an alternate independent prognostic predictor. Most surprisingly, serum CA19-9 is a predictor with almost a similar potency to P factor in resected stage IV gastric cancer. The serum level of CA19-9 is different from CA19-9 on cancer cells in that the molecular species carrying the sialyl Le^a epitope would be involved in the metastatic process rather than the epitope on the cancer cells. Mucin-bound CA19-9, the usual form in the serum, can ligate with E-selectin in endothelial cells, which may elicit E-selectin production systemically (19). Moreover cancer-associated carbohydrate antigens bound to mucin can augment macrophage induction of COX-2 and various cytokines (20). These findings could support the interesting hypothesis that CA19-9 makes the disease more systemic, thus making it a promising therapeutic target, allowing for the classical hypothesis that CA19-9 is presumed to enhance extravasation and metastasis by interaction with E-selectin expressed on endothelium (21).

Treatment related factors (10-12, 22-25) have also been reported to be associated with the outcome of patients with advanced gastric cancer. Nevertheless, no such factor was an independent prognostic factor in our multivariate

analysis, and LNDE and curability were eliminated by the three relevant tumor factors after multivariate analysis. These results may suggest that LNDE was particularly affected by the intraoperative status of lymph node metastasis and P factor. As stated earlier, we classified stage IV gastric cancers into three groups with different prognosis according to tumor factors, and LNDE seemed to affect the patients who survived more than 10 months in all three groups of patients (Figure 3). These findings may encourage surgeons to perform rigorous lymphadenectomy for given patients with stage IV gastric cancer, because it means that the operation could be effective in prolonging the survival of such patients.

In conclusion, our current study revealed that survival of patients with resected stage IV gastric cancer was properly predicted by a combination of several tumor factors and gastrectomy with rigorous lymphadenectomy may affect survival. A randomized controlled trial could be meaningful to validate whether gastrectomy with rigorous lymphade-nectomy actually does prolong the survival of stage IV gastric cancer patients, if both morbidity and mortality are permitted. Moreover, from our current result, we presumed mechanistic relevance of lymph node spread of cancer cells and involvement of serum epitope of CA19-9 in systemic metastasis, which would lead to the promising challenge for a novel strategy of advanced gastric cancer.

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