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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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).
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.

**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: \( p = 0.0005 \); 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.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tumor factor</th>
<th>Treatment factor</th>
<th>Whole analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>LNMR</td>
<td>1.66</td>
<td>1.25-2.21</td>
<td>0.0005</td>
</tr>
<tr>
<td>preoperative CA19-9</td>
<td>1.46</td>
<td>1.08-1.98</td>
<td>0.01</td>
</tr>
<tr>
<td>P factor</td>
<td>1.66</td>
<td>1.09-2.52</td>
<td>0.02</td>
</tr>
<tr>
<td>Age</td>
<td>1.12</td>
<td>0.87-1.45</td>
<td>NS</td>
</tr>
<tr>
<td>preoperative CEA</td>
<td>1.27</td>
<td>0.93-1.75</td>
<td>NS</td>
</tr>
<tr>
<td>T factor</td>
<td>1.13</td>
<td>0.86-1.48</td>
<td>NS</td>
</tr>
<tr>
<td>CY</td>
<td>1.1</td>
<td>0.85-1.44</td>
<td>NS</td>
</tr>
</tbody>
</table>

LNDE: lymph node dissection extent; NS: not significant.

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

<table>
<thead>
<tr>
<th>RR</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>T factor (T1,2 vs. T3,4)</td>
<td>4.53</td>
</tr>
<tr>
<td>P factor</td>
<td>4.42</td>
</tr>
<tr>
<td>CEA</td>
<td>2.52</td>
</tr>
<tr>
<td>CA19-9</td>
<td>1.99</td>
</tr>
<tr>
<td>Dissemination</td>
<td>1.79</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
</tr>
</tbody>
</table>

RR: relative risk.
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 effector to promote lymph node spreading of cancer cells. CEA was demonstrated to be taken
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 Le⁴ 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.

References


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