Prognostic factors and recurrence pattern in node-negative advanced gastric cancer


Department of Surgery, Ulsan University College of Medicine and Asan Medical Centre, 388-1, Pungnap 2-dong, Songpa-ku, Seoul 138-736, Republic of Korea

Accepted 5 October 2012
Available online 11 November 2012

Abstract

Aims: Despite better overall survival in node-negative advanced gastric cancer (AGC), a significant proportion of patients develop recurrence and they may benefit from adjuvant therapy. The aim of this study was to evaluate the prognostic factors and recurrence pattern of node-negative AGC.

Methods: A total of 424 patients who underwent curative gastrectomy with extended lymphadenectomy for node-negative AGC between 2003 and 2005 were retrospectively reviewed. Patients with tumor involvement of adjacent organs (T4b), gastric cancer recurrence, tumor in the remnant stomach, less than 15 harvested lymph nodes, and those who received neoadjuvant chemotherapy were excluded.

Results: Invasion to deeper layers, undifferentiated histology, signet ring cell type compared with tubular adenocarcinoma, and tumor size larger than 6.3 cm correlated with poorer prognosis in univariate analysis. In multivariate analysis, however, only differentiation and depth of invasion, especially the presence of serosa involvement were significant. The 5-year survival rates of the four groups classified by differentiation and depth of invasion [T2/3 (differentiated type), T2/3 (undifferentiated type), T4a (differentiated type), and T4a (undifferentiated type)] were 98%, 92%, 80%, and 72%, respectively (P < 0.01). In terms of recurrence pattern, Lauren’s type and depth of invasion were significant. Recurrence with peritoneal seeding was associated with the diffuse type and invasion into the subserosa or serosa, while hematogenous metastasis was related to the intestinal type and invasion to the proper muscle or subserosa layer.

Conclusions: Differentiation and serosa involvement should be considered to stratify patients with node-negative AGC for adjuvant treatment.

© 2012 Elsevier Ltd. All rights reserved.

Keywords: Node-negative advanced gastric cancer; Prognosis; Recurrence; Differentiation; Serosa involvement

Introduction

Nodal metastasis is the most important prognostic factor for survival after curative resection in gastric adenocarcinoma.1,2 Importantly, many patients have node-negative disease on their pathologic examination. Although node-negative advanced gastric cancer (AGC) shows a better overall survival than node-positive AGC, a significant number of patients still develop recurrence. Patients without node metastasis are theoretically free of locoregional micrometastasis and can potentially benefit from adjuvant therapy.

Several reports demonstrate that the depth of invasion is an independent prognostic indicator in node-negative gastric cancer including early gastric cancer (EGC).3−5 However, there is still controversy on the prognostic significance of other factors, including patient age, tumor size, histology, differentiation, and the presence of lymphovascular invasion. Moreover, most studies include a significant proportion of patients with EGC, which has a very low risk of recurrence,3−7 as well as patients with understaged disease due to limited lymphadenectomy and the subsequent small number of retrieved lymph nodes on pathology.4,5,8,9

In this study, by only investigating patients with node-negative AGC, we aimed to evaluate the prognostic factors and their relation to survival. In addition, we analyzed the pattern and indicators of recurrence.

Methods

Patient population

Patients who underwent curative gastrectomy with extended lymphadenectomy (R0) for node-negative AGC at the Asan Medical Centre from 2003 to 2005 were...
identified. Among them, patients with pathologically confirmed tumor involvement of adjacent organs (T4b), recurring gastric cancer, tumor in the remnant stomach, <15 harvested lymph nodes, and those who received neoadjuvant chemotherapy were excluded.

Data collection

The medical records of the resulting 424 patients were retrospectively analyzed to determine their clinicopathologic characteristics, including age at operation, sex, tumor location, tumor size, gross appearance of lesion, number of harvested lymph nodes, depth of tumor invasion, histological type and differentiation by World Health Organization (WHO) classifications, Lauren’s classifications, the presence of lymphovascular and/or perineural invasion, and oncological outcome (recurrence and survival).

Pathologic classification

Tumor location was classified as upper, middle, and lower third of the stomach based on the criteria from the Japanese Gastric Cancer Association. The depth of invasion was divided into the proper muscle (T2), subserosa (T3), and serosa exposure (T4a) according to the American Joint Committee on Cancer staging manual 7th edition. With regards to differentiation, differentiated type tumors included well/moderately-differentiated adenocarcinomas and papillary adenocarcinoma, while poorly-differentiated adenocarcinoma, signet ring cell carcinoma, mucinous adenocarcinoma, and other types of carcinoma were classified as undifferentiated types.

Morbidity, mortality and postoperative follow-up

Twenty four patients experienced postoperative complications, but there was no operation-related mortality case. Follow-up was conducted until November 30, 2011 or until death. The median follow-up period was 63 months (range: 7–107 months).

Statistical analysis

SPSS statistical software (version 12.0 for Windows, Chicago IL, USA) was used for all statistical analyses. Mean survival rates were calculated using the Kaplan–Meier method, and prognostic factors were analyzed using the Cox proportional hazards model. Analysis of indicators affecting recurrence pattern was performed using the Fisher–McNemar test. Statistical significance was set at $P < 0.05$.

Results

Clinicopathologic characteristics

The median age at operation was 58 and the ratio of men to women was 2. The median tumor size and number of harvested lymph nodes were 5 cm and 27, respectively. Most patients had malignant lesions on the lower third of the stomach and received distal gastrectomy. In addition, most tumors were Borrmann type 3 on gross appearance, had undifferentiated histology, and involved the proper muscle or subserosal layer (Table 1).

Recurrence and survival

At the time of analysis, 40 patients had recurrence, of which 25 had seeded peritoneal nodules, six had liver

| Table 1 Clinicopathologic findings in patients with node-negative advanced gastric cancer. |
|-----------------|-----------------|-----------------|-----------------|
| Variables       | Age (years)     | Sex             | Tumor location  |
| Age (years)     | 58 (23–82)      | Male            | Upper           |
| Sex             | 283             | Female          | Middle          |
| Tumor location  | 112             |                 | Lower           |
|                |                 |                 | Entire          |
| Tumor size (cm) | 4.8 (0.8–25.5)  |                 |                 |
| Gross appearance (Borrmann type) | 27 (15–82) | Type 1          |
|                |                 | Type 2          |
|                |                 | Type 3          |
|                |                 | Type 4          |
|                |                 | Type 5          |
| Depth of invasion |                 | Total gastrectomy | 138            |
| Proper muscle (T2) |                 | Proximal gastrectomy | 1              |
| Subserosa (T3)  |                 |                 |                 |
| Serosa exposed (T4a) |             |                 |                 |
| Lymphovascular invasion | Positive | 103             |
| Perineural invasion | Positive | 104             |
|                 | Negative        | 245             |
|                 |                 |                 |

Some values were absent from the pathology reports; therefore, these numbers are not equal to total number of patients. T stage was based on the American Joint Committee on Cancer staging manual 7th edition.
metastases, three had lung metastases, and six had locoregional metastases such as at the anastomosis site and adjacent lymph nodes. Among all patients, 35 died due to gastric cancer during the follow-up period, and the overall 5-year survival rate was 92%.

**Prognostic factor analysis**

Several factors were significantly associated with prognosis (Table 2). Invasion to deeper layers \( (P < 0.01) \), undifferentiated histology \( (P < 0.01) \), signet ring cell type compared with tubular adenocarcinoma \( (P < 0.02) \), and tumor size larger than 6.3 cm \( (P < 0.02) \) showed poorer prognosis in univariate analysis. In multivariate analysis, however, only differentiation \( (P < 0.05) \) and depth of invasion, especially the presence of serosa involvement \( (P < 0.01) \), was significantly related with prognosis. On the other hand, sex \( (P = 0.20) \), tumor location \( (P = 0.23) \), Lauren’s type \( (P = 0.64) \), and the presence of lymphovascular invasion \( (P = 0.25) \) and/or perineural invasion \( (P = 0.96) \) were not significantly related.

**Subgroup survival analysis according to depth of invasion and differentiation**

According to these two factors, we divided patients into four groups: T2/3 (differentiated type), T2/3 (undifferentiated type), T4a (differentiated type), and T4a (undifferentiated type), with 5-year survival rates of 98%, 93%, 80%, and 72%, respectively \( (P < 0.01) \) (Fig. 1).

**Table 2**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio</th>
<th>Univariate analysis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular adenoca. vs. signet ring cell ca.</td>
<td>2.65</td>
<td>1.24–5.66</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiated vs. undifferentiated</td>
<td>3.60</td>
<td>1.40–9.27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 6.3 ) cm vs. &gt;6.3 cm</td>
<td>2.27</td>
<td>1.17–4.40</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Depth of invasion(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2/T3 vs. T4a</td>
<td>5.68</td>
<td>2.45–13.17</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\(^a\) T stage was based on the American Joint Committee on Cancer staging manual 7th edition.

**Predictors for recurrence pattern**

In terms of recurrence pattern, Lauren’s type \( (P < 0.01) \) and depth of invasion \( (P < 0.03) \) were of significant value. Recurrence with peritoneal seeding was associated with diffuse type and infiltration to the subserosa or serosa. Hematogenous metastasis was related with intestinal type and invasion to the proper muscle or subserosa layer. Locoregional recurrence occurred equally regardless of Lauren’s type and level of invasion (Fig. 2).

**Discussion**

**Importance of the study**

Previously, several studies investigated the prognostic factors for node-negative gastric adenocarcinoma with R0 resection. In contrast to previous studies, we excluded patients with node-negative EGC to lessen their confounding effect and patients with less than 15 harvested lymph nodes to eliminate possible understaging. In addition, to the best of our knowledge, our study is the largest scaled one assessing prognostic factors in node-negative AGC.

In other studies, the 5-year survival rate in node-negative gastric cancer including EGC patients ranged from 72% to 92%,\(^3\)–\(^5\) and was found to be 86% in a recent multicentric European study that included only AGC patients.\(^13\) Despite the more positive outcome found in our study, we demonstrated that a significant proportion of patients had recurrence, many of which died from their disease. It is therefore important to determine groups of patients with high-risk of recurrence that may benefit from adjuvant chemotherapy.

**Prognostic value of several factors and comparison with other studies**

The median age and sex ratio of our patients were similar to those of other Eastern studies.\(^3\)–\(^8\) Advanced T stage
is consistently reported as an adverse prognostic factor in node-negative cancer. The present study was in agreement with this trend in that the presence of serosa involvement was the most powerful predictor of recurrence and survival. Secondly, differentiated histology showed better oncologic outcome, which is in accordance with previous reports. One European study indicated that Lauren’s type was a prognostic factor in node-negative gastric cancer. However, this finding was not reproduced in our study; rather, Lauren’s type was a strong predictor of recurrence pattern. This may be because the proportion of the intestinal type in that study (75%) was significantly higher than in our study (49%).

Unlike in breast cancer, the prognostic significance of tumor size has yet to be determined in gastric cancer. Our study demonstrated that tumor size was not significant in node-negative AGC in multivariate analysis. Two previous studies reported the importance of tumor size, but both studies included EGC patients. Considering that EGC patients usually have small tumors and excellent outcome after curative gastrectomy, there is possibility that enrollment of EGC patients may influence the results of two studies.

Lymphovascular invasion is related to lymph node metastasis and poorer outcome in gastric cancer. While this parameter was reported as prognostically significant in node-negative AGC in some studies, no such prognostic value was observed in both univariate and multivariate analysis of our study. Rather, lymph node micrometastasis might affect the prognosis of node-negative gastric cancer patients. Kim et al. reported that lymph node micrometastasis was related to the lymphovascular invasion resulting in a poor prognosis for node-negative gastric cancer. Moreover, Yonemura, et al. demonstrated that isolated tumor cells in lymph nodes in patients with T1-T4N0 gastric cancer could be an adverse prognostic factor.
In general, it is reported that the diffuse type is related with peritoneal recurrence and the intestinal type with hematogenous metastasis in gastric adenocarcinoma.\textsuperscript{17,18} However, few studies discuss the predictors of recurrence patterns in node-negative gastric adenocarcinoma. We demonstrated that peritoneal seeding was the predominant route for recurrence in our patients, and that it was related with the diffuse type and invasion to the subserosa/serosa layer in node-negative AGC. By contrast, hematogenous metastasis was associated with the intestinal type and invasion to more superficial layers. Serosal invasion increases the probability of dissemination of cancer cells into peritoneal cavity and induce stromal reaction around tumor which contribute in tumor progression as well as carcinogenesis.\textsuperscript{19,20}

Conclusion

In conclusion, serosal invasion and undifferentiated histology are two predictors of poor prognosis in node-negative AGC patients. Moreover, Lauren’s type and depth of invasion may be helpful to predict the recurrence pattern of node-negative AGC. Such parameters should be considered to stratify patients for adjuvant treatment. Further studies are needed to confirm that adjuvant therapy can improve survival in such patients.

Conflict of interest statement

The authors have no conflicts of interest or financial support to declare.

References