Tumor differentiation is not a risk factor for lymph node metastasis in elderly patients with early gastric cancer


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Accepted 29 July 2014
Available online 23 August 2014

Abstract

Background: The aim of this study was to identify risk factors for lymph node metastasis in elderly patients (70 years or more) with early gastric cancer.

Methods: We reviewed the prospectively collected database of 6893 patients with early gastric cancer who had undergone curative gastrectomy in 3 tertiary cancer centers between January 2003 and December 2009 in Korea. Patients were sorted into 4 groups according to age: less than 50, fifties, sixties, and 70 years or more. Risk factors for lymph node metastasis in early gastric cancer were analyzed.

Results: One thousand and thirty five patients (15.0%) were 70 years or more. As age increased, the frequency of large differentiated tumor, lymphatic and submucosa invasion increased. Old age was associated with a lower risk for lymph node metastasis in patients with early gastric cancer (Odds ratio [OR], OR, 0.622; 95% CI, 0.546–0.830, P = 0.010). Ulceration or differentiation of tumor was not associated with lymph node metastasis in elderly patients with early gastric cancer.

Conclusions: Elderly patients with undifferentiated type histology early gastric cancer without other risk factors for lymph node metastasis may be candidates for endoscopic resection.

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Keywords: Gastric cancer; Elderly; Endoscopic procedure

Introduction

Gastric cancer is a common cancer worldwide.1 Gastric cancer surgery in the elderly is increasing because of the rise in the numbers of elderly people in the population and the increased incidence of cancer with age.2

Although surgical and postoperative care techniques have improved, age is still an important risk factor for morbidity and mortality after surgery.3,4 As age increases, the frequency of comorbid diseases increases, functional status decreases, mental status is frequently altered, and tolerance for surgical treatment decreases.5

Endoscopic resection (ER), including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is an alternative treatment option for a subset of patients with early gastric cancer.6 Currently, ER is considered as a standard treatment for early gastric cancer (EGC) that meets the criteria for absolute indication: an intramucosal differentiated-type adenocarcinoma ≤2 cm in size and without ulcerative findings or lymphatic-vascular involvement. Recent studies have shown that long-term results after ER are comparable to those after surgery.7,8

Characteristics of elderly patients with gastric cancer include frequent combination with comorbid diseases,
Patients and methods

Study cohort and data sources

The study cohort was composed of 7111 patients with early gastric cancer who were treated by open or laparoscopy-assisted gastric cancer surgery between January 2003 and December 2009 at one of three institutions in Korea: Chonnam National University Hwasoon Hospital, National Cancer Center, and Samsung Medical Center. Patients who (i) had a histologically confirmed gastric adenocarcinoma, (ii) had a tumor with a depth confined to the mucosa or submucosa, and (iii) had newly diagnosed cancer without previous treatment were included in the analysis. Two hundred and eighteen patients with less than 15 lymph nodes retrieved for proper nodal staging were excluded after the primary surgery were excluded to avoid incorrect staging. Finally, 6893 patients with early gastric cancer were analyzed in this study. All information was obtained with appropriate Institutional Review Board waivers and data were collected without revealing any personal information.

Operative procedures

The surgical procedures and reconstruction methods were as follows. Gastrectomy was performed for a tumor-free margin of 2 cm. Extent of lymph node dissection was determined using the recommendations of the Japanese Research Society for Gastric Carcinoma. After open or laparoscopic laparotomy, surgeons examined the intra-abdominal cavity and inspected the peritoneum, diaphragm, liver capsule, and pelvic cavity. All patients enrolled in the present study underwent gastrectomy with D1 + β or more lymph node dissection. Tumors were staged in accordance with the 6th UICC tumor node metastasis (TNM) classification.

Statistical methods and analyses

Patients were grouped according to their ages: less than 50, fifties, sixties, and 70 or more. Continuous variables were expressed as medians with ranges. Statistical significance was estimated by using the appropriate statistical methods for matched data. Continuous variables were compared by using the Student’s t test, and categorical variables were compared by using the Chi-square test or Fisher’s exact test. Categorical variables were compared by conditional logistic regression.

Results

Patient characteristics

Clinical and pathological characteristics are shown in Table 1. The median age of the 6893 patients was 58 years (range: 21–88 years). One thousand and thirty five patients (15.0%) were 70 years old or older. With increasing age, the frequency of large differentiated tumor, lymphatic invasion, and submucosa invasion was significantly increased whereas the frequency of ulceration was decreased.

Lymph node metastasis and risk factors for lymph node metastasis in all patients

The overall rate of lymph node metastasis was 10.3%. The median number of invaded nodes was 0 (range: 0–64). There was no significant difference in the rate of lymph node metastasis among different age groups (Table 1). Univariate and multivariate analyses showed that ulceration (OR, 1.191; 95% CI, 1.003–1.416, $P = 0.047$), tumor differentiation (OR, 1.840; 95% CI, 1.535–2.206, $P < 0.001$), lymphatic invasion (OR, 5.478; 95% CI, 4.536–6.615, $P < 0.001$), tumor size (OR, 2.207; 95% CI, 1.723–2.826, $P < 0.001$), and tumor depth (OR, 3.664; 95% CI, 2.947–4.556, $P < 0.001$) were significantly associated with lymph node metastasis (Table 2).

When elderly patients were compared with other patients, multivariate analysis showed that old age
was associated with a lower risk for lymph node metastasis in patients with early gastric cancer (OR, 0.622; 95% CI, 0.546–0.830, \( P = 0.010 \)).

Comparison of risk factors for lymph node metastasis among different age groups

Univariate and multivariate analyses showed that tumor size, lymphatic invasion, and tumor depth were significantly associated with lymph node metastasis in all age groups (Table 3). However, tumor differentiation was not associated with lymph node metastasis in elderly patients (70 years or more) with early gastric cancer, and ulceration was not associated with lymph node metastasis in any age group. When we analyze the signet ring cell type histology as a subtype of tumor differentiation, tumor differentiation was not associated with lymph node metastasis in elderly patients (70 years or more) with early gastric cancer.

Undifferentiated tumor without the other risk factors for lymph node metastasis did not exhibit lymph node metastasis in elderly patients (0/17), while the other patients had lymph node metastasis [less than 50; 1.9% (2/106) versus fifties; 1.4% (1/72) versus sixties; 2.1% (1/48), respectively].

**Discussion**

The main findings of this study regarding risk factors for lymph node metastasis in elderly patients with early gastric cancer are: 1) Increasing age is associated with a lower risk for lymph node metastasis in patients with early gastric cancer; 2) early gastric cancer in elderly patients shows a
The presence of an ulcer is not easily defined and even the definition of an ulcer is not clear. Ulcers do not always present with the same features when endoscopy is performed. Data regarding the presence of ulcers have been formed. The presence or absence of lymph node metastasis is the most important factor in deciding on a treatment modality for patients with early gastric cancer. Endoscopic resection is an alternative treatment option for a subset of patients with early gastric cancer. ER has been reported as a safer method to cure patients with early gastric cancer. Although surgical and postoperative care techniques have recently improved, age is still an important risk factor for morbidity and mortality after surgery.

### Table 3
Hazard ratio for lymph node metastasis in elderly patients.

<table>
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<td>1.436</td>
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<td>1.521</td>
<td>1.379</td>
<td>1.486</td>
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<td>(1.077–1.914)</td>
<td>(0.874–1.710)</td>
<td>(0.817–1.726)</td>
<td>(0.892–1.650)</td>
<td>(0.894–2.097)</td>
<td>(0.837–2.101)</td>
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<td>(0.889–1.701)</td>
<td>(0.926–1.730)</td>
<td>(0.958–1.935)</td>
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<td>Present</td>
<td>1.168</td>
<td>1.230</td>
<td>1.265</td>
<td>1.361</td>
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<td>(0.889–1.701)</td>
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<td>3.126</td>
<td>6.542</td>
<td>3.681</td>
<td>6.906</td>
<td>3.320</td>
<td>5.409</td>
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<td>(1.072–1.633)</td>
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<td>(1.381–2.394)</td>
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<tr>
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<tr>
<td>Macosa</td>
<td>4.726</td>
<td>2.476</td>
<td>8.750</td>
<td>4.500</td>
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<td>1</td>
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</table>

High frequency of lymphatic vessel, submucosa invasion, and differentiated tumor, and 3) ulceration and tumor differentiation are not associated with lymph node metastasis. The presence of an ulcer is not easily defined and even the definition of an ulcer is not clear. Ulcers do not always present with the same features when endoscopy is performed. Data regarding the presence of ulcers have been formed. The presence or absence of lymph node metastasis is the most important factor in deciding on a treatment modality for patients with early gastric cancer. Endoscopic resection is an alternative treatment option for a subset of patients with early gastric cancer. ER has been reported as a safer method to cure patients with early gastric cancer. Although surgical and postoperative care techniques have recently improved, age is still an important risk factor for morbidity and mortality after surgery. The rates of mortalities after gastric cancer surgery have been reported as 0.2%—10% and those of elderly patients have been reported as 2.7%—7.9%. There has been no report comparing the characteristics of patients with early gastric cancer in terms of lymph node metastasis according to age. Most studies regarding characteristics of elderly patients with gastric cancer have reported that the prognosis of those patients does not differ from that of the other patients. Although there was no difference in the frequency of lymph node metastasis among different age groups, multivariable analysis proved to be that old age (70 years or more) was associated with a lower risk for lymph node metastasis in patients with early gastric cancer. This might result in part from the higher frequency of differentiated tumors in elderly patients than in the other age groups. Irrespective of tumor progression, differentiated tumors were commonly found in elderly patients with gastric cancer. The high frequency of differentiated tumors in elderly patients with early gastric cancer might be due to different carcinogenic steps compared to that in patients of other age groups. High frequency of lymphatic and submucosa invasion in elderly patients might be overestimated in this study because this study is not a randomized study. Lymphatic and submucosa invasion have been known to be the most powerful predictor for lymph node metastasis in early gastric cancer. Therefore, surgery tends to be recommended for elderly patients with early gastric cancer more strongly than younger patients with early gastric cancer, even those who have severe comorbid diseases. Tumor size, tumor depth, and lymphatic invasion were closely associated with lymph node metastasis regardless of age. Hazard ratios of tumor and lymphatic invasion for lymph node metastasis in elderly patients were higher than in all patients in this study. Therefore, surgery should be recommended even in elderly patients with high risk of morbidity or mortality after considering of life expectancy of those patients. The presence of an ulcer is not easily defined and even the definition of an ulcer is not clear. Ulcers do not always present with the same features when endoscopy is performed. Data regarding the presence of ulcers have been quite different in reports (10.2%—74.7%). This study was a type of multicenter study, and the definition of ulcer...
was somewhat different among the three centers. Only one institution defined ulcer according to the pathological findings. Therefore, we could not find an association between ulcer and lymph node metastasis in age groups. Moreover, ER is not always possible when a deep ulcer is present or the presence of submucosal invasion is obscure. Unlikely other well-known risk factors for lymph node metastasis, tumor differentiation was not associated with lymph node metastasis in elderly patients with early gastric cancer. Hirasawa et al. has reported that no lymph node metastasis in elderly patients with early gastric cancer. Therefore, we could not find an association between tumor differentiation was not associated with lymph node metastasis was found if undifferentiated tumors met the other absolute indication of ER. Recent small studies have reported that survival of patients who underwent ER for undifferentiated gastric cancers was not inferior to that of patients after surgery. However, there have been reports that even those tumors metastasized to lymph nodes and there have been no large studies to be generalized. We found that no tumors metastasized to lymph node in elderly patients with early gastric cancer and undifferentiated tumors without the other risk factors for lymph node metastasis.

It has been reported that signet ring cell histology is an unfavorable risk factor for lymph node metastasis in patients with early gastric cancer. When we analyzed the signet ring cell histology as a subtype of tumor differentiation, there was no association of tumor differentiation and lymph node metastasis in elderly patients (70 years or more) with early gastric cancer. Therefore, if other risk factors are not present, the undifferentiated tumor might be removed by ER in elderly patients with early gastric cancer.

The major limitation of this study is that it is a retrospective study, so elderly patients with a high risk of operative mortality might not be included. In other words, there might be selection bias for choosing treatment modality. Another limitation of this study is that pathological data was assessed on surgical specimens not on biopsy specimens. In spite of that, this study included more than six thousand patients and data from three cancer centers. This large series might be helpful to minimize the selection bias.

In summary, tumor differentiation is not associated with lymph node metastasis in elderly patients (more than 70 years) with early gastric cancer. Therefore, those patients with early gastric cancer meet the criteria; an intramucosal adenocarcinoma ≤2 cm in size and without ulcerative findings or lymphatic-vascular involvement except undifferentiated histology may be candidates for endoscopic resection.

**Author contributions**

JHL had full access to all of the data in the study and JHL had final responsibility for the decision to submit the study for publication.

**Study concept and design:** LJH, NBH, SK.

**Acquisition of data:** LJH.

**Drafting and manuscript:** LJH, SK.

**Critical revision of the manuscript for important intellectual content:** SK, YWK, YKP.

**Administrative, technical or material support:** SYR, KWR.

**Supervision:** BHN.

**Conflict of interest statement**

The authors have no conflicts of interest, financial or otherwise.

**References**