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## Retrospective Cohort Study

## Prognosis factors of advanced gastric cancer according to sex and age

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## Abstract

## BACKGROUND

Gastric cancer has a relatively high prevalence and is one of the most common causes of cancer-related death worldwide. However, the prognosis for gastric cancer remains poor, especially in the advanced stages, despite many improvements in diagnosis and treatment.

## AIM

To evaluate the outcomes regarding advanced gastric cancer development according to sex and age.

## METHODS

We retrospectively reviewed 2005 patients who underwent curative gastrectomy for advanced gastric cancer between 2002 and 2007 at a single Korean centre. Prognosis and risk factors for nodal involvement were evaluated according to sex and age.

## RESULTS

In this retrospective cohort study, we examined the cases of 2005 patients [sex, 1384 men (69%), 621 women (31%)] with advanced gastric cancer. The patients' age range was 22-87 years (mean age:  $57.7 \pm 12.3$  years), with approximately 53.3% of the patients being  $\leq 60$  years old. Based on a Cox proportional hazards model, overall survival was independently predicted by older age, larger tumour size, lymphovascular invasion, lymph node metastasis, deeper tumour invasion, moderately-to-poorly differentiated tubular adenocarcinoma, and signet ring cell carcinoma. The same model revealed that relapse-free survival was independently predicted by advanced age, larger tumour size, lymphovascular invasion, deeper tumour invasion, poorly differentiated tubular adenocarcinoma,

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and signet ring cell carcinoma.

## CONCLUSION

Among patients with advanced gastric cancer, older age independently predicted poor overall survival and relapse-free survival. However, there were no significant sex-based differences in relapse-free and overall survival.

**Key words:** Carcinoma; Prognosis; Gastrectomy; Risk factors; Age; Adenocarcinoma

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**Core tip:** Understanding the association between age and the survival rate for gastric cancer might be helpful to clarify the prognostic value of age and potentially improve treatment efficacy. However, few studies have evaluated the effects of sex or age on gastric cancer outcomes, especially for advanced gastric cancer. Thus, we evaluated the relationships of age and sex with advanced gastric cancer outcomes in 2005 patients at our center.

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## INTRODUCTION

Gastric cancer (GC; cardia or non-cardia types) is an important disease worldwide, with up to 1000000 new diagnosed cases in 2018 and potentially more than 783000 deaths annually. Global estimates have suggested that GC is the fifth and third most frequently diagnosed and deadly cancer, respectively, with rates being approximately two-fold higher in men than in women<sup>[1]</sup>. The World Health Organization (WHO) and the Japanese Society of Gastroenterological Endoscopy define early gastric cancer as gastric tumours that are confined to the mucosal layer, regardless of lymph node metastasis, although the classification of advanced gastric cancer (AGC) remains a debatable issue<sup>[2]</sup>. Although most authors define AGC as tumours infiltrating beyond the submucosal layer, regardless of metastasis or N0 status, others consider T3-4 tumours to be AGC<sup>[3]</sup>. For example, AGC is considered any gastric tumour that is T2-4b/N0-3/M0-1 staged, according to the eighth edition of the American Joint Committee on Cancer TNM (AJCC TNM) system<sup>[4]</sup>. Thus, relative to early gastric cancer, AGC is defined as being locally advanced and metastatic. When curative treatment is not possible because of metastatic tumours, some patients may benefit from neoadjuvant therapy for locally advanced GC, which may allow a curative surgery performance in the future<sup>[5]</sup>.

The incidence and mortality rates for resectable AGC vary among East Asian countries, which have fewer complications and deaths, and better survival rates than the Western countries. For example, the 5-year survival rate is almost 70% in Japan<sup>[6]</sup>, higher to the corresponding rates of up to 25% in Europe and the United States<sup>[7]</sup>. Age is a prognostic factor for many cancers<sup>[8]</sup>, and the prevalence of GC increases with age, peaking at an age of 60-70 years<sup>[9]</sup>. Thus, understanding the association between age and the survival rate for GC might be helpful to clarify the prognostic value of age and potentially improve treatment efficacy<sup>[10]</sup>. Histopathological type, depth of invasion, and tumour size are known predictors of lymph node metastasis<sup>[11]</sup> and prognosis in patients with GC<sup>[12]</sup>. Kim *et al*<sup>[11]</sup> also recently stated that sex was a predictor for lymph node metastasis and that the histological subtype varied according to sex and age. However, few studies have evaluated the effects of sex or age on GC outcomes, especially for AGC. Thus, we evaluated the relationships of age and sex with AGC outcomes at our centre.

## MATERIALS AND METHODS

### Participants and study design

We retrospectively evaluated 2005 patients who had undergone curative gastrectomy for AGC between 2002 and 2007 at the Asan Medical Center (Seoul, South Korea). The study's retrospective protocol was approved by the institutional review board (protocol number S2019-1849-0001).

All patients had undergone extensive lymphadenectomy (D1 and greater) according to the 2018 Korean Gastric Cancer Association clinical management guidelines<sup>[12]</sup>. Macroscopic (endoscopic) findings were also analysed according to the Korean Gastric Cancer Association clinical management guidelines<sup>[13]</sup>. The WHO categorises gastric adenocarcinomas into four subtypes according to their histopathological pattern: Papillary, mucinous, tubular, and signet ring cell carcinoma (SRC)<sup>[14]</sup>. Tubular adenocarcinoma was classified as well-differentiated, moderately-differentiated, or poorly-differentiated according to the eighth edition of the AJCC TNM staging system<sup>[4]</sup>. According to the Japanese classification system, gastric adenocarcinoma was classified as differentiated (well-differentiated, moderately-differentiated, or papillary adenocarcinoma) or undifferentiated (poorly-differentiated adenocarcinoma or SRC)<sup>[15]</sup>. The patients' characteristics, lymph node metastasis statuses, and outcomes were reviewed to identify their relationships with sex and age. Relapse-free survival (RFS) was defined as the time from tumour resection until the first instance of disease recurrence, death that was unrelated to gastric cancer, or the last follow-up without evidence of recurrence. Overall survival (OS) was defined as the time from tumour resection until death by any cause or the last follow-up.

### Statistical analysis

Continuous data were presented as means  $\pm$  SD and analysed using the Student's *t*-test. Risk factors were analysed using the logistic regression model (multivariate analysis) or the Chi-squared test (univariate analysis). Survival outcomes were compared using the Kaplan-Meier method with the log-rank test (univariate analysis) or the Cox proportional hazards regression model (multivariate analysis). All analyses were performed using the IBM SPSS software (version 25.0; IBM Corp., Armonk, NY, United States), and differences were considered statistically significant when  $P < 0.05$ .

## RESULTS

The patients' clinicopathological characteristics are summarised in **Table 1**. The patients' age range was 22-87 years (mean:  $57.7 \pm 12.3$  years), with approximately 53.3% of the patients being  $\leq 60$  years old. The participants were 1384 men (69%) and 621 women (31%) (total, 2005). The mean body mass index (BMI) was  $23.3 \pm 3.2$  kg/m<sup>2</sup> (range: 12.3-57.8 kg/m<sup>2</sup>). Approximately 30.7% of patients had comorbidities, including hypertension (22%), diabetes mellitus (10.6%), and other conditions (5.6%).

The mean tumour size was  $6.3 \pm 3.5$  cm (range: 1-48 cm), with 55.3% and 44.7% of the tumours being  $> 5$  cm and  $\leq 5$  cm, respectively. The tumour locations were the lower-third (59.7%), middle-third (23.1%), and upper-third (17.2%). The depths of invasion were the subserosal layer (43.1%), exposed or invading the serosa (30.4%), the muscularis propria (25.1%), and the submucosal layers (1.4%). The histopathological findings were tubular adenocarcinomas (poorly-differentiated: 49.5%, moderately-differentiated: 31.1%, and well-differentiated: 3.1%), SRC (10.9%), mucinous adenocarcinoma (3.5%), papillary adenocarcinoma (0.3%), neuroendocrine tumours (0.2%), and other histopathological abnormalities (1.3%). The surgical procedures were subtotal (55.2%) and total gastrectomy (44.8%), with a mean number of  $28.4 \pm 12$  retrieved lymph nodes (LNs) (range: 12-106 lymph nodes) and 53.8% of these cases involving LN metastasis. Lymphovascular and perineural invasions was observed in 51% and 46.1% of cases, respectively. Adjuvant chemotherapy was provided to 66.8% of patients, with the recurrence and mortality rates being 33.5% and 43.6%, respectively. The mean OS duration was  $55.3 \pm 32.2$  mo (range: 0.5-129.7 mo) and the mean RFS was  $51.1 \pm 33.6$  mo (range: 0.5-129.7 mo).

### Prognostic factors

Based on the Cox proportional hazards model, OS was independently predicted by advanced age, larger tumour size, lymphovascular invasion, LN metastasis, moderately-to-poorly differentiated tubular adenocarcinoma, and SRC (**Table 2**). The independent predictors of RFS in this model were advanced age, larger tumour size, lymphovascular invasion, poorly differentiated tubular adenocarcinoma, and SRC

**Table 1 Clinicopathologic characteristics of all patients**

| Characteristic                                     |             |
|--|-------------|
| Age (yr)   |             |
| Range  | 22-87       |
| mean ± SD  | 57.7 ± 12.3 |
| Age grouping, <i>n</i> (%)                         |             |
| ≤ 60 yr  | 1069 (53.3) |
| > 60 yr  | 936 (46.7)  |
| Sex, <i>n</i> (%)                                  |             |
| Male   | 1384 (69)   |
| Female   | 621 (31)    |
| Body mass index (kg/m <sup>2</sup> )               |             |
| Range  | 12.3–57.8   |
| mean ± SD  | 23.3 ± 3.2  |
| Comorbidities, <i>n</i> (%)                        |             |
| Hypertension                                       | 441 (22)    |
| Diabetes mellitus                                  | 212 (10.6)  |
| Others   | 112 (5.6)   |
| Tumour size (cm)                                   |             |
| Range  | 1-48        |
| mean ± SD  | 6.3 ± 3.5   |
| Location, <i>n</i> (%)                             |             |
| Upper third  | 345 (17.2)  |
| Middle third                                       | 463 (23.1)  |
| Lower third  | 1197 (59.7) |
| Depth of invasion, <i>n</i> (%)                    |             |
| Muscularis propria                                 | 504 (25.1)  |
| Subserosal   | 865 (43.1)  |
| Serosa exposed or invaded                          | 608 (30.4)  |
| Histology, <i>n</i> (%)                            |             |
| Papillary adenocarcinoma                           | 7 (0.3)     |
| Tubular adenocarcinoma (well differentiated)       | 62 (3.1)    |
| Tubular adenocarcinoma (moderately differentiated) | 624 (31.1)  |
| Tubular adenocarcinoma (poorly differentiated)     | 992 (49.5)  |
| Signet ring cell carcinoma                         | 219 (10.9)  |
| Others   | 101 (5)     |
| Gastrectomy, <i>n</i> (%)                          |             |
| Subtotal   | 1127 (56.2) |
| Total  | 878 (43.8)  |
| Retrieved lymph nodes, <i>n</i>                    |             |
| Range  | 12-106      |
| mean ± SD  | 28.4 ± 12   |
| Lymph node metastasis, <i>n</i> (%)                |             |
| Yes  | 1079 (53.8) |
| No   | 926 (46.2)  |
| Lymphovascular invasion, <i>n</i> (%)              |             |
| Yes  | 1023 (51)   |
| No   | 982 (49)    |
| Perineural invasion, <i>n</i> (%)                  |             |
| Yes  | 925 (46.1)  |
| No   | 1080 (53.9) |
| Adjuvant chemotherapy, <i>n</i> (%)                |             |
| Yes  | 1340 (66.8) |
| No   | 665 (33.2)  |

|                               |             |
|-------------------------------|-------------|
| Recurrence, <i>n</i> (%)      |             |
| Yes                           | 671 (33.5)  |
| No                            | 1334 (66.5) |
| Mortality, <i>n</i> (%)       |             |
| Yes                           | 874 (43.6)  |
| No                            | 1131 (56.4) |
| Overall survival (mo)         |             |
| Range                         | 0.5-129.7   |
| mean ± SD                     | 55.3 ± 32.2 |
| Recurrence-free survival (mo) |             |
| Range                         | 0.5-129.7   |
| mean ± SD                     | 51.1 ± 33.6 |

SD: Standard deviation.

(Table 2).

We also found that the prognostic factors varied according to sex and age (Tables 3 and 4). For example, among men the prognostic factors were age, tumour size, lymphovascular invasion, depth of invasion, moderately-to-poorly differentiated tubular adenocarcinoma, and SRC (Table 3), while among women the prognostic factors were tumour size, and lymphovascular invasion. Among ≤ 60-year-old patients the prognostic factors were tumour size, and lymphovascular invasion (Table 4), while among > 60-year-old patients the prognostic factors were lymphovascular invasion, any tubular adenocarcinoma, SRC, and mucinous adenocarcinoma.

#### **Risk factors for lymph node metastasis according to sex and age**

Based on the logistic regression model, the independent risk factors for LN metastasis were larger tumour size and lymphovascular invasion (Table 5). Among men, the risk of LN metastasis was related to tumour size, lymphovascular invasion, tubular adenocarcinoma classification, and mucinous adenocarcinoma (Table 6), while among women the risk factors for LN metastasis were tumour size, and lymphovascular invasion. Among ≤ 60-year-old patients, the independent risk factors for LN metastasis were larger tumour size, and lymphovascular invasion (Table 7), while among > 60-year-old patients, the independent risk factors were larger tumour size, lymphovascular invasion, and poorly differentiated tubular adenocarcinoma.

#### **Evaluation of survival according to sex and age**

We did not detect significant differences according to sex in the OS (Figure 1A) and RFS (Figure 1B) outcomes of Korean patients with AGC (both  $P > 0.05$ ). However, the different age groups exhibited significant differences in OS (Figure 2A) and RFS (Figure 2B). We also evaluated whether sex might be associated with different outcomes in each age group, although we did not detect significant differences in OS (Figure 3A) and RFS (Figure 3B) among ≤ 60-year-old or > 60-year-old patients (Figure 4).

## **DISCUSSION**

Although East Asian countries (including Japan) have survival rates reaching up to 70% for GC<sup>[6]</sup>, the outcomes remain poor in Western countries despite their advances in diagnosis and treatment, as depicted by the 5-year OS rates of < 30%<sup>[7]</sup>. Thus, a better understanding of the prognostic factors for GC might provide new insights and enhance the treatment of advanced-stage cases. We evaluated the outcomes of 2,005 patients who had been diagnosed with AGC during 2002 and 2007 according to age, which is an independent risk factor for several cancers, including AGC<sup>[8]</sup>. However, previous studies have used age cut-offs of 50, 30, or 45 years, respectively<sup>[8,9]</sup>. In our study, we used an age cut-off at 60 years based on recent studies and the new age subdivision suggested by the WHO<sup>[9]</sup>. Likewise, other studies have compared outcomes among elderly and younger patients with GC; however, they yielded inconclusive results<sup>[16,17]</sup>.

Younger patients may experience poorer survival rates because of their characteristics and different tumour behaviours<sup>[18]</sup>. For example, Chen *et al*<sup>[19]</sup> reported that 56-65-year-old patients exhibited better clinicopathological features and gastric cancer-specific survival rates than other age groups of patients with operable GC.

**Table 2** Multivariate analysis of factors influencing survival using a Cox proportional hazards model

| Characteristic                    | Overall survival |       |             | Recurrence-free survival |       |             |
|-----------------------------------|------------------|-------|-------------|--------------------------|-------|-------------|
|                                   | P value          | HR    | 95%CI       | P value                  | HR    | 95%CI       |
| Sex                               |                  |       |             |                          |       |             |
| Male                              |                  | 1.000 |             |                          | 1.000 |             |
| Female                            | 0.434            | 0.943 | 0.813-1.093 | 0.292                    | 0.925 | 0.801-1.069 |
| Age                               |                  |       |             |                          |       |             |
| ≤ 60 yr                           |                  | 1.000 |             |                          | 1.000 |             |
| > 60 yr                           | 0.001            | 1.723 | 1.502-1.978 | 0.001                    | 1.658 | 1.451-1.895 |
| Tumour size                       |                  |       |             |                          |       |             |
| ≤ 5 cm                            |                  | 1.000 |             |                          | 1.000 |             |
| > 5 cm                            | 0.001            | 1.455 | 1.252-1.690 | 0.001                    | 1.505 | 1.302-1.740 |
| Lymphovascular invasion           |                  |       |             |                          |       |             |
| No                                |                  | 1.000 |             |                          | 1.000 |             |
| Yes                               | 0.001            | 1.678 | 1.450-1.943 | 0.001                    | 1.676 | 1.455-1.931 |
| Lymph node metastasis             |                  |       |             |                          |       |             |
| No                                |                  | 1.000 |             |                          | 1.000 |             |
| Yes                               | 0.047            | 0.866 | 0.752-0.998 | 0.111                    | 0.894 | 0.780-1.026 |
| Depth of invasion                 |                  |       |             |                          |       |             |
| Muscularis propria                | 0.102            | 0.654 | 0.394-1.088 | 0.160                    | 0.696 | 0.419-1.155 |
| Sub-serosal                       | 0.125            | 0.676 | 0.410-1.115 | 0.200                    | 0.721 | 0.437-1.189 |
| Serosal exposed                   | 0.080            | 0.636 | 0.383-1.055 | 0.142                    | 0.685 | 0.413-1.135 |
| Serosal invasion                  | 0.287            | 0.705 | 0.370-1.342 | 0.272                    | 0.697 | 0.366-1.189 |
| Histology                         |                  |       |             |                          |       |             |
| Tubular adenocarcinoma (well)     |                  | 1.000 |             |                          | 1.000 |             |
| Tubular adenocarcinoma (moderate) | 0.036            | 1.783 | 1.038-3.061 | 0.069                    | 1.562 | 0.967-2.523 |
| Tubular adenocarcinoma (poorly)   | 0.008            | 2.070 | 1.211-3.538 | 0.026                    | 1.716 | 1.067-2.759 |
| Signet ring cell carcinoma        | 0.001            | 2.689 | 1.535-4.707 | 0.001                    | 2.290 | 1.387-3.781 |
| Mucinous adenocarcinoma           | 0.156            | 1.601 | 0.836-3.066 | 0.236                    | 1.431 | 0.791-2.588 |

HR: Hazard ratio; CI: Confidence interval.

Similarly, Song *et al*<sup>[9]</sup> reported that age is related to the prognosis of GC, although younger patients had a higher survival rate after surgery, relative to elderly patients. Our study revealed that OS was independently predicted by advanced age, larger tumour size, lymphovascular invasion, LN metastasis, deeper tumour invasion, moderately-to-poorly differentiated tubular adenocarcinoma, and SRC. These findings may be related to younger patients typically presenting with more advanced disease<sup>[18,20]</sup>. The better outcomes among older patients may also be related to two factors: (1) The poor tolerance of extensive lymphadenectomy and standardised chemotherapy in older adults<sup>[21]</sup>, which lead clinicians to provide only remedial options to younger patients, as they are generally in better condition and more able to tolerate chemotherapy<sup>[22]</sup>; and (2) Younger patients have better tolerance of surgery and recovery<sup>[23]</sup>.

Moreover, our study revealed that approximately two-thirds of the patients with AGC were male, which suggests that they may have been more frequently exposed to GC risk factors that are associated with male sex, such as increased alcohol intake and smoking. These factors might contribute to an increased GC incidence later in life<sup>[24]</sup>. We also found that RFS and OS were independently predicted by advanced age, larger tumour size, lymphovascular invasion, deeper tumour invasion, poorly-differentiated tubular adenocarcinoma, and SRC. These findings conflict with those of Suh *et al*<sup>[25]</sup>, who reported that age was an independent risk factor for RFS, but not for OS. Several studies have also revealed that a diffuse histological subtype is commonly detected in younger individuals<sup>[26,27]</sup>. Our study revealed that the histological subtype was significantly associated with GC outcomes among older patients with available histological information.

To the best of our knowledge, there are few studies that have evaluated the

**Table 3 Multivariate analysis of factors influencing survival according to sex using a Cox proportional hazards model**

| Characteristic                    | Male    |       |             | Female  |       |             |
|-----------------------------------|---------|-------|-------------|---------|-------|-------------|
|                                   | P value | HR    | 95%CI       | P value | HR    | 95%CI       |
| Age                               |         |       |             |         |       |             |
| ≤ 60 yr                           |         | 1.000 |             |         | 1.000 |             |
| > 60 yr                           | 0.001   | 1.882 | 1.601-2.213 | 0.136   | 1.204 | 0.943-1.536 |
| Tumour size                       |         |       |             |         |       |             |
| ≤ 5 cm                            |         | 1.000 |             |         | 1.000 |             |
| > 5 cm                            | 0.001   | 1.443 | 1.212-1.718 | 0.001   | 1.610 | 1.239-2.090 |
| Lymphovascular invasion           |         |       |             |         |       |             |
| No                                |         | 1.000 |             |         | 1.000 |             |
| Yes                               | 0.001   | 1.697 | 1.428-2.017 | 0.001   | 1.587 | 1.238-2.035 |
| Lymph node metastasis             |         |       |             |         |       |             |
| No                                |         | 1.000 |             |         | 1.000 |             |
| Yes                               | 0.166   | 0.890 | 0.754-1.050 | 0.437   | 0.907 | 0.709-1.161 |
| Depth of invasion                 |         |       |             |         |       |             |
| Muscularis propria                | 0.025   | 0.521 | 0.295-0.920 | 0.736   | 1.220 | 0.385-3.866 |
| Sub-serosal                       | 0.044   | 0.565 | 0.324-0.986 | 0.824   | 1.139 | 0.362-3.587 |
| Serosal exposed                   | 0.039   | 0.551 | 0.314-0.970 | 0.986   | 0.990 | 0.311-3.147 |
| Serosal invasion                  | 0.264   | 0.669 | 0.330-1.354 | 0.653   | 0.693 | 0.140-3.434 |
| Histology                         |         |       |             |         |       |             |
| Tubular adenocarcinoma (well)     |         | 1.000 |             |         | 1.000 |             |
| Tubular adenocarcinoma (moderate) | 0.043   | 1.754 | 1.017-3.026 | 0.886   | 0.929 | 0.337-2.559 |
| Tubular adenocarcinoma (poor)     | 0.010   | 2.029 | 1.181-3.486 | 0.739   | 0.844 | 0.312-2.282 |
| Signet ring cell carcinoma        | 0.001   | 3.153 | 1.769-5.619 | 0.812   | 0.883 | 0.317-2.459 |
| Mucinous adenocarcinoma           | 0.359   | 1.390 | 0.688-2.810 | 0.896   | 1.080 | 0.342-3.409 |

HR: Hazard ratio; CI: Confidence interval.

survival rates and prognostic factors among patients with AGC. Our study revealed that OS among patients with AGC was independently predicted by older age, larger tumour size, lymphovascular invasion, LN metastasis, deeper tumour invasion, moderately-to-poorly differentiated tubular adenocarcinoma, and SRC. However, LN metastasis and moderately differentiated tubular adenocarcinoma were not risk factors for poor RFS in these patients. Furthermore, there were no significant differences according to sex in the RFS and OS outcomes. Nevertheless, there were significant differences in RFS and OS according to patient age using a cut-off value of 60 years.

**Limits of the study**

However, our study was limited by the small sample size and the lack of a control group. Nevertheless, we provided new data regarding a disease with an increasing incidence in younger patients and adults, which has considerable psychological and social effects. Increased awareness of AGC is needed to ensure that GC is diagnosed at a potentially curable stage.

**Table 4** Multivariate analysis of factors influencing survival according to age using a Cox proportional hazards model

| Characteristic                    | ≤ 60 yr old |       |             | > 60 yr old |       |             |
|-----------------------------------|-------------|-------|-------------|-------------|-------|-------------|
|                                   | P value     | HR    | 95%CI       | P value     | HR    | 95%CI       |
| Sex                               |             |       |             |             |       |             |
| Male                              |             | 1.000 |             |             | 1.000 |             |
| Female                            | 0.300       | 1.116 | 0.907-1.373 | 0.017       | 0.780 | 0.636-0.957 |
| Tumour size                       |             |       |             |             |       |             |
| ≤ 5 cm                            |             | 1.000 |             |             | 1.000 |             |
| > 5 cm                            | 0.001       | 1.973 | 1.586-2.454 | 0.086       | 1.187 | 0.976-1.444 |
| Lymphovascular invasion           |             |       |             |             |       |             |
| No                                |             | 1.000 |             |             | 1.000 |             |
| Yes                               | 0.001       | 1.783 | 1.441-2.206 | 0.001       | 1.580 | 1.307-1.910 |
| Lymph node metastasis             |             |       |             |             |       |             |
| No                                |             | 1.000 |             |             | 1.000 |             |
| Yes                               | 0.485       | 0.929 | 0.756-1.142 | 0.147       | 0.872 | 0.725-1.049 |
| Depth of invasion                 |             |       |             |             |       |             |
| Muscularis propria                | 0.185       | 0.570 | 0.249-1.308 | 0.371       | 0.746 | 0.392-1.418 |
| Sub-serosal                       | 0.280       | 0.638 | 0.283-1.441 | 0.472       | 0.792 | 0.420-1.495 |
| Serosal exposed                   | 0.214       | 0.594 | 0.262-1.350 | 0.465       | 0.786 | 0.412-1.500 |
| Serosal invasion                  | 0.518       | 0.724 | 0.272-1.929 | 0.549       | 0.765 | 0.318-1.839 |
| Histology                         |             |       |             |             |       |             |
| Tubular adenocarcinoma (well)     |             | 1.000 |             |             | 1.000 |             |
| Tubular adenocarcinoma (moderate) | 0.731       | 0.891 | 0.463-1.718 | 0.010       | 2.547 | 1.246-5.205 |
| Tubular adenocarcinoma (poorly)   | 0.929       | 0.972 | 0.514-1.837 | 0.004       | 2.812 | 1.380-5.730 |
| Signet ring cell carcinoma        | 0.427       | 1.309 | 0.674-2.543 | 0.001       | 3.652 | 1.700-7.843 |
| Mucinous adenocarcinoma           | 0.134       | 0.525 | 0.226-1.220 | 0.002       | 3.847 | 1.648-8.979 |

HR: Hazard ratio; CI: Confidence interval.

**Table 5** Analysis of lymph node metastasis using the chi-squared test and a logistic regression model

| Characteristic                    | Lymph node metastasis |            | Univariate | Multivariate |             |         |
|-----------------------------------|-----------------------|------------|------------|--------------|-------------|---------|
|                                   | Yes                   | No         | P value    | OR           | 95%CI       | P value |
| Sex                               |                       |            |            |              |             |         |
| Male                              | 766 (71)              | 618 (66.7) | 0.040      | 1.000        |             |         |
| Female                            | 313 (29)              | 308 (33.3) |            | 0.840        | 0.682-1.034 | 0.099   |
| Age                               |                       |            |            |              |             |         |
| ≤ 60 yr                           | 573 (53.1)            | 496 (53.6) | 0.837      | 1.000        |             |         |
| > 60 yr                           | 506 (46.9)            | 430 (46.4) |            | 1.035        | 0.854-1.255 | 0.726   |
| Tumour size                       |                       |            |            |              |             |         |
| ≤ 5 cm                            | 580 (53.8)            | 316 (34.1) | 0.001      | 1.000        |             |         |
| > 5 cm                            | 499 (46.2)            | 610 (65.9) |            | 0.552        | 0.453-0.674 | 0.001   |
| Lymphovascular invasion           |                       |            |            |              |             |         |
| Yes                               | 415 (38.5)            | 608 (65.7) | 0.001      | 0.356        | 0.294-0.431 | 0.001   |
| No                                | 664 (61.5)            | 318 (34.3) |            | 1.000        |             |         |
| Depth of invasion                 |                       |            |            |              |             |         |
| Muscularis propria                | 252 (23.4)            | 252 (27.2) |            | 0.647        | 0.297-1.409 | 0.273   |
| Sub-serosal                       | 453 (42)              | 412 (44.5) |            | 0.711        | 0.329-1.537 | 0.386   |
| Serosal exposed                   | 327 (30.3)            | 233 (25.2) |            | 0.908        | 0.418-1.975 | 0.808   |
| Serosal invasion                  | 30 (2.8)              | 18 (1.9)   |            | 1.078        | 0.414-2.809 | 0.877   |
| Histology                         |                       |            |            |              |             |         |
| Tubular adenocarcinoma (well)     | 46 (4.3)              | 16 (1.8)   | 0.011      | 1.000        |             |         |
| Tubular adenocarcinoma (moderate) | 342 (32.3)            | 282 (31)   |            | 0.560        | 0.301-1.043 | 0.068   |

|                                 |            |          |       |             |       |
|---------------------------------|------------|----------|-------|-------------|-------|
| Tubular adenocarcinoma (poorly) | 519 (49)   | 473 (52) | 0.583 | 0.315-1.080 | 0.086 |
| Signet ring cell carcinoma      | 119 (11.2) | 100 (11) | 0.676 | 0.347-1.318 | 0.251 |
| Mucinous adenocarcinoma         | 33 (3.1)   | 38 (4.2) | 0.474 | 0.218-1.029 | 0.059 |

OR: Odds ratio; CI: Confidence interval.

**Table 6 Analysis of lymph node metastasis according to sex using a logistic regression model**

| Characteristic                    | Male    |       |             | Female  |       |             |
|-----------------------------------|---------|-------|-------------|---------|-------|-------------|
|                                   | P value | OR    | 95%CI       | P value | OR    | 95%CI       |
| Age                               |         |       |             |         |       |             |
| ≤ 60 yr                           |         | 1.000 |             |         | 1.000 |             |
| > 60 yr                           | 0.919   | 1.012 | 0.804-1.274 | 0.512   | 1.127 | 0.789-1.610 |
| Tumour size                       |         |       |             |         |       |             |
| ≤ 5 cm                            |         | 1.000 |             |         | 1.000 |             |
| > 5 cm                            | 0.001   | 0.532 | 0.418-0.677 | 0.006   | 0.605 | 0.425-0.863 |
| Lymphovascular invasion           |         |       |             |         |       |             |
| No                                |         | 1.000 |             |         | 1.000 |             |
| Yes                               | 0.001   | 0.359 | 0.284-0.453 | 0.001   | 0.357 | 0.254-0.501 |
| Depth of invasion                 |         |       |             |         |       |             |
| Muscularis propria                | 0.684   | 0.823 | 0.323-2.098 | 0.190   | 0.387 | 0.094-1.601 |
| Sub-serosal                       | 0.735   | 0.852 | 0.338-2.149 | 0.298   | 0.474 | 0.116-1.035 |
| Serosal exposed                   | 0.934   | 1.040 | 0.409-2.645 | 0.585   | 0.673 | 0.163-2.779 |
| Serosal invasion                  | 0.817   | 1.143 | 0.369-3.540 | 1.000   | 1.000 | 0.160-6.255 |
| Histology                         |         |       |             |         |       |             |
| Tubular adenocarcinoma (well)     |         | 1.000 |             |         | 1.000 |             |
| Tubular adenocarcinoma (moderate) | 0.044   | 0.489 | 0.244-0.980 | 0.853   | 1.157 | 0.247-5.405 |
| Tubular adenocarcinoma (poor)     | 0.047   | 0.497 | 0.249-0.992 | 0.726   | 1.312 | 0.288-5.979 |
| Signet ring cell carcinoma        | 0.122   | 0.543 | 0.251-1.177 | 0.520   | 1.673 | 0.349-8.015 |
| Mucinous adenocarcinoma           | 0.048   | 0.411 | 0.170-0.992 | 0.945   | 1.065 | 0.178-6.387 |

OR: Odds ratio; CI: Confidence interval.

**Table 7 Analysis of lymph node metastasis according to age using a logistic regression model**

| Characteristic                | ≤ 60 yr old |       |             | > 60 yr old |       |             |
|-------------------------------|-------------|-------|-------------|-------------|-------|-------------|
|                               | P value     | OR    | 95%CI       | P value     | OR    | 95%CI       |
| Sex                           |             |       |             |             |       |             |
| Male                          |             | 1.000 |             |             | 1.000 |             |
| Female                        | 0.066       | 0.762 | 0.571-1.018 | 0.543       | 0.910 | 0.670-1.235 |
| Tumour size                   |             |       |             |             |       |             |
| ≤ 5 cm                        |             | 1.000 |             |             | 1.000 |             |
| > 5 cm                        | 0.001       | 0.452 | 0.344-0.594 | 0.020       | 0.707 | 0.528-0.947 |
| Lymphovascular invasion       |             |       |             |             |       |             |
| No                            |             | 1.000 |             |             | 1.000 |             |
| Yes                           | 0.001       | 0.312 | 0.239-0.407 | 0.001       | 0.406 | 0.307-0.536 |
| Depth of invasion             |             |       |             |             |       |             |
| Muscularis propria            | 0.024       | 0.169 | 0.036-0.790 | 0.452       | 1.477 | 0.535-4.077 |
| Sub-serosal                   | 0.046       | 0.211 | 0.046-0.975 | 0.444       | 1.481 | 0.541-4.056 |
| Serosal exposed               | 0.122       | 0.298 | 0.064-1.381 | 0.332       | 1.659 | 0.597-4.607 |
| Serosal invasion              | 0.324       | 0.422 | 0.076-2.341 | 0.503       | 1.571 | 0.418-5.903 |
| Histology                     |             |       |             |             |       |             |
| Tubular adenocarcinoma (well) |             | 1.000 |             |             | 1.000 |             |

|                                   |       |       |             |       |       |             |
|-----------------------------------|-------|-------|-------------|-------|-------|-------------|
| Tubular adenocarcinoma (moderate) | 0.340 | 0.644 | 0.261-1.589 | 0.088 | 0.465 | 0.193-1.121 |
| Tubular adenocarcinoma (poor)     | 0.788 | 0.885 | 0.364-2.151 | 0.031 | 0.381 | 0.158-0.918 |
| Signet ring cell carcinoma        | 0.909 | 0.947 | 0.370-2.424 | 0.166 | 0.496 | 0.184-1.339 |
| Mucinous adenocarcinoma           | 0.483 | 0.677 | 0.228-2.014 | 0.068 | 0.346 | 0.111-1.080 |

OR: Odds ratio; CI: Confidence interval.

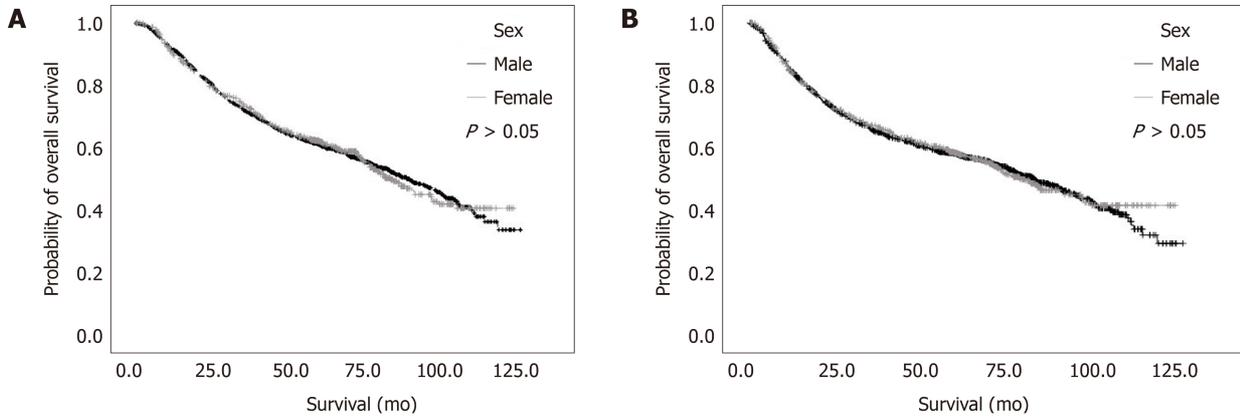


Figure 1 Kaplan-Meier curves. A: Overall survival; B: Relapse-free survival according to sex.

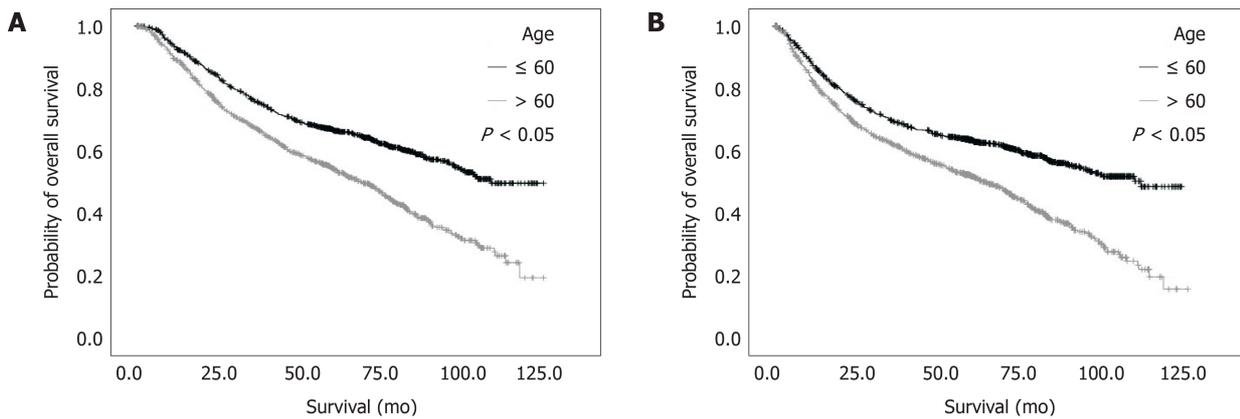


Figure 2 Kaplan-Meier curves. A: Overall survival; B: Relapse-free survival according to age.

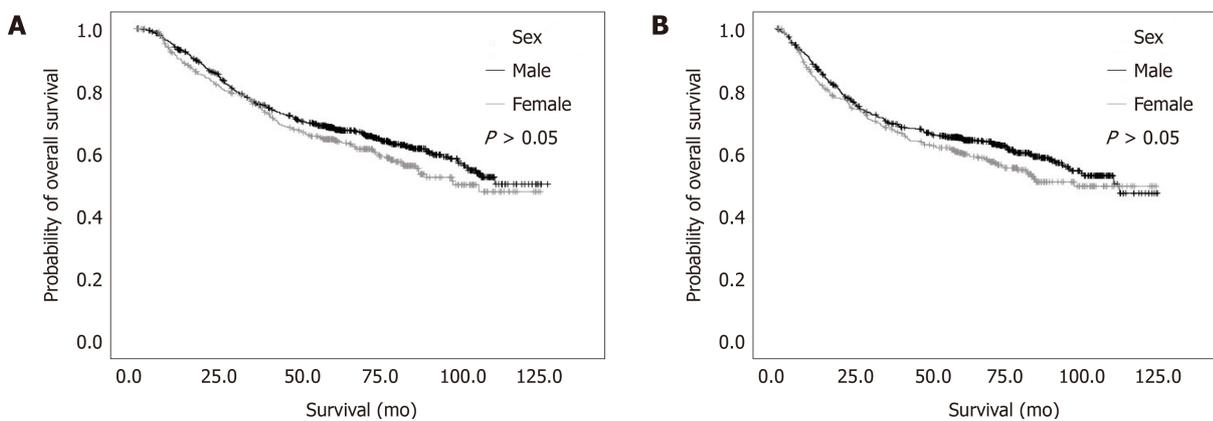


Figure 3 Kaplan-Meier curves. A: Overall survival; B: Relapse-free survival according to sex among younger patients ( $\leq 60$  years old).

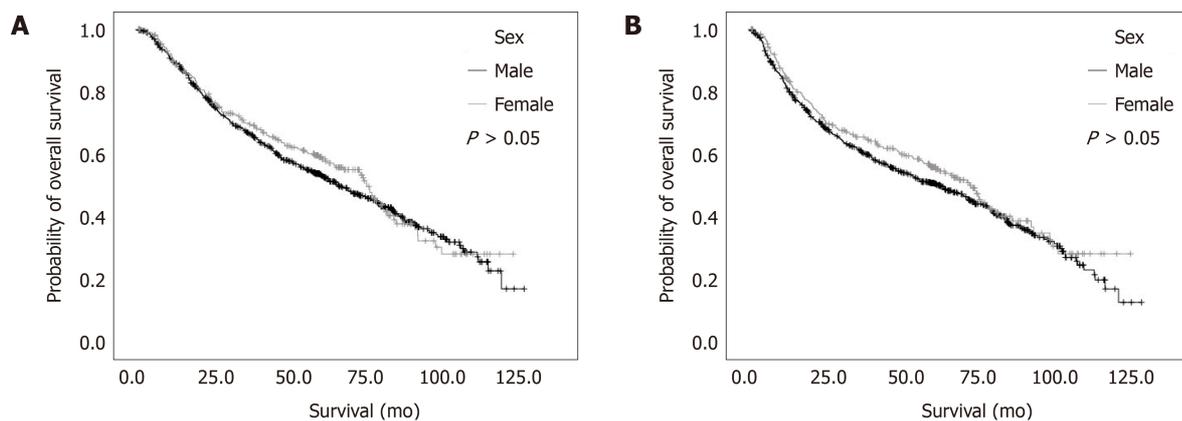


Figure 4 Kaplan-Meier curves. A: Overall survival; B: Relapse-free survival according to sex among older patients (> 60 years old).

## ARTICLE HIGHLIGHTS

### Research background

Gastric cancer has a relatively high prevalence specially in east countries. However the prognosis still poor with those advanced cases. Despite the improvement in diagnostic and treatment.

### Research motivation

Although outcomes of advanced gastric cancer is not satisfied. Searching for factors may improve the result and outcomes of treatment may help to improve the prognosis.

### Research objectives

This study aimed to see the prognosis factors in advanced gastric cancer according to patient's age and gender.

### Research methods

2005 patients with advanced gastric cancer who underwent surgical treatment at one Korean single centre between 2002-2007. Retrospectively, data collected and analyzed. Possible prognosis factors were evaluated.

### Research results

A total of 2005 patients [sex, 1384 men (69%), 621 women (31%)] with advanced gastric cancer. Cox proportional hazards model, overall survival was independently predicted by older age, larger tumour size, lymphovascular invasion, lymph node metastasis, deeper tumour invasion, moderately-to-poorly differentiated tubular adenocarcinoma, and signet ring cell carcinoma. The same model revealed that relapse-free survival was independently predicted by advanced age, larger tumour size, lymphovascular invasion, deeper tumour invasion, poorly differentiated tubular adenocarcinoma, and signet ring cell carcinoma.

### Research conclusions

Older age was independently predicted factor for poor overall survival and relapse-free survival. However, there were no significant difference found according to gender in relapse-free and overall survival.

### Research perspectives

Study was limited by the small sample size and the lack of a control group. Nevertheless, we provided new data regarding a disease with an increasing incidence in younger patients and adults, which has considerable psychological and social effects. Increased awareness of advanced gastric cancer is needed to ensure that gastric cancer is diagnosed at a potentially curable stage.

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