## Original Article

# Survival of metastatic gastric cancer: Significance of age, sex and race/ethnicity

Dongyun Yang[1*], Andrew Hendifar[2*], Cosima Lenz[1], Kayo Togawa[1], Felicitas Lenz[2], Georg Lurje[2], Alexandra Pohl[2], Thomas Winder[2], Yan Ning[2], Susan Groshen[1], Heinz-Josef Lenz[1,2]

[1]*Department of Preventive Medicine, University of Southern California/Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA;* [2]*Division of Medical Oncology, Sharon Carpenter Laboratory, University of Southern California/Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

**ABSTRACT**

**Background:** Despite the success of modern chemotherapy in the treatment of large bowel cancers, patients with metastatic gastric cancer continue to have a dismal outcome. Identifying predictive and prognostic markers is an important step to improving current treatment approaches and extending survival.

**Methods:** Extracting data from the US NCI's Surveillance, Epidemiology, and End Results (SEER) registries, we compared overall survival for patients with metastatic gastric cancer by gender, age, and ethnicity using Cox proportional hazards models. 13,840 patients (≥ 18 years) were identified from 1988-2004. Males and females were categorized by age grouping and ethnicity.

**Results:** 19% of Hispanic patients were diagnosed < 45 years of age as compared to 5.5% of Caucasians. Caucasian patients and men were more likely to be diagnosed with tumors in the gastric cardia ($P$<0.001). In our survival analysis, we found that women had a lower risk of dying as compared to men ($P$<0.001). Overall survival diminished with age ($P$<0.001). The median overall survival was 6 months in patients of ≤ 44 years old as compared to 3 months in patients 75 years and older. Gender differences in overall survival significantly varied by race and tumor grade/differentiation ($P$ for interaction = 0.003 and 0.005, respectively).

**Conclusion:** This is the largest study of metastatic gastric cancer patients from the SEER registry to show that age, gender, and tumor location are significant independent prognostic factors for overall survival in patients with metastatic gastric cancer.

**KEY WORDS** gastric cancer, gender, age, ethnicity, survival

J Gastrointest Oncol 2011; 2: 77-84. DOI: 10.3978/j.issn.2078-6891.2010.025

## Introduction

Although its incidence and mortality has declined over the last half-century, gastric cancer remains the fourth most common cancer and the second most frequent cause of cancer death in the world (1,2). The American Cancer Society estimates that in 2008, there were 21,500 new cases of gastric cancer and 10,880 deaths in the United States (3). As gastric cancer incidence declines, the frequency of proximal gastric and gastroesophageal junctional adenocarcinomas continues to rise and has become a significant clinical challenge (4,5). There is substantial geographic variation in the incidence and mortality of gastric cancer, with the highest rates in East Asia and the lowest in North America (2). H. pylori infection, dietary factors, and smoking patterns may contribute to these disparities (6-9).

The survival rates for gastric cancer are among the

* Both authors contributed equally to this work.

This work was funded by the NIH grant P30 CA 14089, supported by the San Pedro Guild and the Dhont Foundation.

Corresponding to: Heinz-Josef Lenz, MD, FACP. Sharon A. Carpenter Laboratory, Division of Medical Oncology, University of Southern California, Norris Comprehensive Cancer Center, Keck School of Medicine, 1441 Eastlake Avenue, Los Angeles, CA 90033. Tel: +1-323-865-3967, Fax: +1-323-865-0061. Email: lenz@usc.edu.

Submitted Nov 4, 2010. Accepted for publication Dec 17, 2010.
Available at www.thejgo.org

ISSN: 2078-6891

worst of any solid tumor. Despite the success of modern chemotherapy in the treatment of large bowel cancers, the 5-year survival of patients with advanced gastric cancer is 3.1% (1,4). The role of surgery is also limited as only 23% of stage IV gastric cancer patients receiving a palliative gastrectomy are alive one year after surgery (4). Progress was recently made as treating Her-2-Neu (H2N) over-expressing gastric cancers with Traztuzumab was found to significantly improve survival (10). Identifying additional predictive and prognostic markers is an important step to improving current treatment approaches and extending survival.

Two distinct histologic types of gastric cancer, the "intestinal type" and "diffuse type", have been described (11). The diffuse type of gastric cancer is undifferentiated and characterized by the loss of E-cadherin expression; an adhesion protein that helps maintains cellular organization (12). The well differentiated intestinal type is sporadic and highly associated with environmental exposures, especially H. pylori infection (13). There are also biologic differences between these subtypes of gastric cancer that may guide treatment approaches. H2N is over expressed more often in the intestinal *vs* the diffuse type, 30% *vs* 6% in one study (14). The Beta-catenin/Wnt signaling pathway is also recognized to play a large role in the molecular carcinogenesis of the intestinal type cancer (15).

Despite the genetic heterogeneity of gastric cancer, several biological determinants of risk and prognosis have been identified. Genetic polymorphisms of cytokines released with "oxidative stress" such as IL-Iβ, IL-10, and TNF-A have been associated with increased gastric cancer risk (16-18). Over expression of the oncogenes, tie-1, CMET and AKT have been found to confer a poor prognosis in both subtypes (19-21). Tumor expression of the isoenzyme COX-2 is an independent prognostic factor for gastric cancer survival (22). This benefit may be mediated by a reduction in lymphangiogenesis, another correlate of prognosis (22,23). Recently Her-2/Neu over expression, an important predictive and prognostic factor in breast cancer has been independently associated with a poor prognosis in gastric cancer (24,25).

The prognostic significance of age, gender, and ethnicity in metastatic gastric cancer is unclear. The prevailing belief that young patients with gastric cancer have a more aggressive disease has been recently called into question (26,27). Several prospective and population studies since 1996 have consistently shown that age is not a prognostic factor for survival, despite the higher prevalence of "diffuse type" cancer which typically has a worse outcome (28,29). However, according to a recent population-based study of gastric cancer, a significant impact of age on survival was found in patients with stage IV disease (30).

As compared to women, men are twice as likely to develop and die from gastric cancer, in the US (1). Although this may represent varying environmental exposures between genders, studies demonstrate that menstrual factors such as age of menopause and years of fertility are associated with gastric cancer incidence (31). Interestingly, woman may be more likely to have a "diffuse type histology" (32).

There are also significant ethnic and racial differences in gastric cancer incidence and survival. Asian patients consistently have increased survival rates compared to their western counterparts (33). Ethnic Asians living in the US share this benefit which suggests that these differences are not likely treatment related (34). Other racial differences in the US are notable as the incidence and mortality is 50% higher in African Americans than Caucasians (35).

Our study sought to evaluate the clinical correlates of survival in metastatic gastric cancer. Specifically we examined the influence of age, gender, ethnicity on survival. We also explored the interactions between patient characteristics and tumor histology, grade, size, and location (cardia *vs* non-cardia).

## Patients and methods

### *Data source*

Adult patients with metastatic gastric cancer were identified from the SEER registry 1988-2004 database, which collects information on all new cases of cancer from 17 population-based registries covering approximately 26% of the US population.

### *Study population*

The disease was defined by the following International Classification of Diseases for Oncology (ICD-O-2) codes: C16.0-C16.9. We identified patients (n=15,360) who had metastatic disease defined by SEER Extent of Disease code: 85. We restricted eligibility to adults (aged 18 years or older) who were diagnosed with metastatic gastric cancer (MGC) in 1988 and later (n=15,348); because the record of extent of disease was not available for accurate staging prior to 1988. We excluded cases (less than 10% of adult patients with metastatic gastric cancer) who were diagnosed at death certificate or autopsy, no follow-up records (survival time code of 0 months), as well as lacking documentation on race/ethnicity. A total of 13,840 MGC patients of 18 years and older were included in the final sample for the current analysis.

### *Variable definitions*

Information on age at diagnosis, sex, race, and ethnicity, marital status, treatment type, primary site, tumor grade and differentiation, histology, tumor size, and lymph node involvement, and overall survival were coded and available in SEER database. The primary endpoint in this study was overall survival that was defined as the months lapsing from diagnosis to death. For the patients who were still alive at last follow-up, overall survival was censored at the date of last follow-up or December 31, 2004, whichever came first.

Age. We chose the cut points for age groups based on the previous studies (18-44, 45-54, 55-64, 65-74, and 75 and older).

Ethnicity. Patients were divided into five ethnic groups, "Caucasian" (Race/Ethnicity code, 1), "African American" (Race/Ethnicity code, 2), "Asian" (Race/Ethnicity code, 4-97), "Hispanic" (Spanish/Hispanic Origin code, 1-8), and Native American (Race/Ethnicity code, 3).

Primary site. According to the latest guidelines for gastric cancer classification[a], the stomach is anatomically delineated into the upper, middle, and lower thirds by dividing the lesser and greater curvatures at two equidistant points and joining these points. The sites were defined by the following codes from ICD-O-2: Cardia, (C16.0), Body (C16.1-2, C16.5-6), Lower (C16.3-4), and Overlapping lesion of stomach (C16.8). For the ones that are not specified, they were categorized together as Stomach, NOS (C16.9).

Marital status. Subjects were categorized into "Not married" (including never married, separated, divorced, widowed, and unknowns) and "Married" (including common law).

Treatment type. SEER variables, RX Summ-radiation and RX summ-surg prim site were used to define treatment types: "Surgery" for patients who had surgery (local tumor destruction and excision, and gastrectomy) and/no radiation, "Radiation therapy only" for patients who only had radiation therapy, "Untreated" for patients who did not have surgery nor radiation therapy, and "Unknown". Information on chemotherapy was not available in SEER.

Grade. Grade was defined by the following ICD-O-2 codes; well/moderately differentiated (Code 1-2), poorly differentiated/undifferentiated (Code 3-4), and others (Code 5-9).

Histological type. Histological types were defined by the following ICD-O-3 codes: 8140- for adenocarcinoma, 8490 for Signet ring cell carcinoma, and the rest of the types were categorized as 'Others'.

The size of the primary tumor and the presence of lymph node involvement were not of interest in the current analysis. Our cohort consisted entirely of patients with metastatic disease.

### *Statistical analysis*

Subjects were grouped by age to 18-44, 45-54, 55-64, 65-74, and 75 and older. We stratified them by sex, race, marital status, treatment type, grade, histological type, and primary site. Descriptive statistics were calculated for categorical variables using frequencies and proportions. Sex, race, tumor grade, marital status, primary site, histological type, and treatment type were independent variables. Differences among age groups in each subgroup were evaluated using the chi-square test.

We constructed Cox proportional hazards models to examine the association between age and survival in men and female separately. We compared survival across age groups adjusting for potential confounders including geographic region and year of diagnosis. By conducting this analysis separately by gender, we were able to determine pattern differences between genders. The Cox proportional hazards model included year of diagnosis and participating SEER registry site as stratification variables. Marital status, treatment, primary site, histology, tumor grade and differentiation, size of primary tumor, and lymph node involvement were used as covariates. Hazard Ratios (HRs) and 95% confidence intervals were generated, with hazard ratios less than 1.0 indicating survival benefit (or reduced mortality). Pairwise interactions (age and sex, age and race, and sex and race) were checked using stratified models and were tested by comparing corresponding likelihood ratio statistics between the baseline and nested Cox proportional hazards models that included the multiplicative product terms (36). Departure of the proportional hazard assumption of Cox models will be examined graphically such as log-log survival curves or smoothed plots of weighted Schoenfeld residuals (37) and by including a time-dependent component individually for each predictor.

All analyses were conducted using $P<0.05$ as the significance level and statistical analyses were performed with the use of SAS software (version 9.1; SAS Institute, Cary, NC).

## Results

### *Patient baseline characteristics*

The final cohort for analysis consisted of 13,840 patients, 8710 men (63%), and 5130 women (37%). Their age distribution is as follows: 1,207 (9%) aged 18–44; 1,698 (12%) aged 45–54; 2,701 (20%) aged 55–64; 3,901 (28%) aged 65–74; and 4,333 (31%) aged 75 years and older. The

median age was 68 years (range: 18–104). 60% of the MGC cohort were White, 13% African American, 13% Asian, 14 % Hispanic, and 1% Native American. Tumor characteristics and treatment received are shown in Table 1.

***Age and ethnicity in MGC***

5.5 % of Whites with MGC were between 18-44 years of ages as compared to 10% of African Americans, 11% of Asians, and 19% of Hispanic patients. 36% of White gastric cancer patients were diagnosed over 75 years of age; 29% of

**Table 1 Overall survival of patients with metastatic gastric cancer by demographic and clinicopathologic characteristics and treatment, SEER data 1988-2004**

| Characteristics | *N* | Median OS (95% CI), months | Hazard Ratio (95% CI)* | *P* value* |
|---|---|---|---|---|
| Sex | | | | |
| Male | 8710 | 4 (4, 4) | 1 (Reference) | |
| Female | 5130 | 4 (4, 4) | 0.916 (0.881, 0.952) | <.001 |
| Age, years | | | | |
| 18-44 | 1207 | 6 (5, 6) | 0.806 (0.748, 0.868) | |
| 45-54 | 1698 | 5 (5, 6) | 0.920 (0.862, 0.981) | |
| 55-64 | 2701 | 5 (4, 5) | 1 (Reference) | <.001 |
| 65-74 | 3901 | 4 (4, 4) | 1.119 (1.062, 1.179) | |
| ≥75 | 4333 | 3 (3, 3) | 1.395 (1.325, 1.470) | |
| Race | | | | |
| White | 8281 | 4 (4, 4) | 1 (Reference) | |
| African American | 1781 | 4 (3, 4) | 1.040 (0.982, 1.102) | |
| Asian | 1770 | 4 (4, 5) | 0.966 (0.905, 1.031) | 0.16 |
| Hispanic | 1880 | 4 (4, 5) | 1.024 (0.965, 1.087) | |
| Native American | 128 | 3 (2, 4) | 1.222 (0.959, 1.556) | |
| Site | | | | |
| Cardia | 3383 | 5 (4, 5) | 0.969 (0.919, 1.021) | |
| Body | 3402 | 4 (4, 4) | 1 (Reference) | |
| Lower | 2417 | 4 (4, 4) | 0.996 (0.942, 1.053) | .003 |
| Overlapping lesion of stomach | 1635 | 4 (4, 4) | 1.086 (1.020, 1.157) | |
| NOS | 3003 | 3 (3, 4) | 1.048 (0.994, 1.105) | |
| Treatment | | | | |
| Surgery | 1573 | 8 (7, 8) | 0.600 (0.561, 0.643) | |
| Radiation alone | 1779 | 5 (5, 5) | 0.802 (0.746, 0.862) | <.001 |
| Untreated | 4774 | 3 (3, 3) | 1 (Reference) | |
| Unknown | 5714 | 4 (3, 4) | 0.922 (0.843, 1.009) | |
| Grade/differentiation | | | | |
| Well/moderately differentiated | 2874 | 5 (4, 5) | 1 (Reference) | |
| Poorly differentiated or undifferentiated | 7917 | 4 (4, 4) | 1.193 (1.139, 1.250) | <.001 |
| Unknown | 3049 | 4 (3, 4) | 1.040 (0.982, 1.101) | |
| Histology | | | | |
| Adenocarcinoma | 8041 | 4 (4, 4) | 1 (Reference) | |
| Signet ring cell carcinoma | 2485 | 4 (4, 4) | 0.985 (0.936, 1.037) | <.001 |
| Other | 3314 | 4 (4, 4) | 0.883 (0.843, 0.925) | |

* Based on Cox proportional hazards model included all variables in the table, tumor size, lymph node involvement, and marital status.

Asian, 27% of AA, and 20% of Hispanic.

***Tumor location: cardia vs non-cardia***

The incidence of cardia and non-cardia tumors varied significantly depending on gender and ethnic background. 30% of men and 14% of women had gastric ca arising from the cardia. The incidence of cardia cancers also varied significantly across ethnicities. 32% of Whites had cardia primaries, 13% of AA's, 11% of Asians, and 14% of Hispanics.

***Survival analysis***

The median overall survival (OS) in patients with MGC was only 4 months. The prognostic significance of several clinical and tumor characteristics were limited as the median OS varied little when stratified by sex, race, tumor site, grade/ differentiation, and histology (Table 1).

However, age, use of local treatment, tumor differentiation, and tumor site were found to have a clinically significant effect. The youngest group of patients had an improved OS when compared to their older counterparts (Table 1), as the median OS for patients 44 years or younger was 6 months compared to 3 months in patients 75 years or older. Survival was significantly worse in every successive age decile. Patients who had received any treatment had significantly improved survival. Gastrectomy or local surgery had a median OS of 8 months compared to a median OS of 3 months in patients who were not treated with surgery or radiation [HR = 0.600 (0.561, 0.643)] (Table 1). Similarly, patients receiving radiation treatment had a survival benefit [HR = 0.802 (0.746, 0.862)].

Tumor characteristics had a significant impact on survival. As expected, patients with poorly differentiated tumors had a worse survival than those with moderately or well differentiated tumors [HR 1.19, $P < 0.001$ (1.139, 1.250)]. We also found that tumors located in the gastric cardia conferred a survival benefit when compared to non-proximal tumors [HR=0.945, $P < 0.001$ (0.904, 0.989)].

In multivariate analysis, sex, age, treatment, and tumor characteristics were significantly associated with overall survival. Females had lower risk of dying compared to males (HR=0.916, 95%CI: 0.881–0.952) and mortality increased with age at diagnosis ($P<0.001$, Table 1). There was no significant difference in OS across race/ethnicity groups ($P=0.16$, Table 1).

***Sex, race, grade/differentiation and MGC***

The effect of sex on OS was significantly varied by race and tumor differentiation in patients with MGC ($P_{\text{for interaction}}=0.003$ and 0.005, respectively, Table 2). White and African American woman had significantly lower risk of dying compared to their male counterparts. In Asian, Hispanic, and Native American populations, men and women had equivalent survival (Table 2.) Women also had a significantly lower risk of dying compared to males in patients whose tumors were poorly differentiated or undifferentiated or had unknown tumor grade (Table 2).

## Discussion

This cohort of metastatic gastric cancer patients from the SEER database represents a wide cross-section of patients with variable socioeconomic and ethnic backgrounds. Our analysis also included a robust variety of pathology and is likely a more generalizable representation than can be found in clinical trials or case series.

As expected, we found tumor characteristics such as grade, differentiation, and histology were associated with survival in advanced gastric cancer. Notably, there was a survival advantage attributable to gastric cardia lesions when compared to non-cardia lesions. This survival advantage persisted after controlling for the increased prevalence of cardia lesions in Caucasians and men.

Survival differences between cardia and non-cardia lesions may reflect differences in pathogenesis and tumor biology. H. pylori infection is recognized as a unique risk factor for non-cardia lesions while gastroesophageal reflux disease plays a role in the development of proximal lesions (38,39). Interestingly, there is growing evidence that H2N expression is variably expressed in proximal and distal gastric cancer lesions (40). The proto-oncogene Her-2/neu (H2N) is located on chromosome 17q21 and encodes a transmembrane tyrosine kinase growth factor receptor featuring substantial homology with the EGFR (41,42). Over-expression of the H2N protein has been identified in from 10 to 34% of breast cancers and is associated with a poor prognosis (43). Over-expression of H2N has been reported in gastric and gastro-esophageal tumors (24). Additionally, there are studies describing H2N as a poor prognostic factor in gastric cancer (40). Further studies are needed to investigate its role in the development of proximal and distal gastric lesions.

In addition to tumor characteristics, patient features, such as age and sex, also had significant prognostic impact. Ethnicity – often described in gastric cancer literature as having a prominent prognostic role – had no effect on survival. We could not confirm previous reports that Asian and Hispanic patients with gastric cancer have an improved outcome. We did find that a higher percentage of Hispanic patients present at a younger age. 36% of our Hispanic patients presented at ages less than 54 yo *vs* 16% of white patients. These findings are consistent with a

**Table 2 Overall survival of patients with gastric cancer by sex, SEER data 1988-2004**

| | Males | | | Females | | | |
|---|---|---|---|---|---|---|---|
| | *N* | MS (95% CI), ms | Hazard Ratio (95% CI)* | *N* | MS (95% CI), ms | Hazard Ratio (95% CI)* | Hazard Ratio (95% CI)† |
| Race | | | | | | | |
| White | 5373 | 4 (4, 4) | 1 (Reference) | 2908 | 4 (3, 4) | 1 (Reference) | 0.907 (0.862, 0.956) |
| African American | 1129 | 3 (3, 4) | 1.082 (1.006, 1.165) | 652 | 4 (4, 5) | 0.977 (0.884, 1.079) | 0.818 (0.729, 0.918) |
| Asian | 1039 | 4 (4, 5) | 0.892 (0.819, 0.972) | 731 | 4 (4, 5) | 1.077 (0.968, 1.199) | 1.027 (0.918, 1.150) |
| Hispanic | 1095 | 4 (4, 4) | 1.031 (0.955, 1.114) | 785 | 5 (4, 5) | 1.052 (0.953, 1.161) | 0.925 (0.827, 1.034) |
| Native American | 74 | 3 (2, 4) | 1.036 (0.749, 1.433) | 54 | 3 (2, 5) | 1.304 (0.866, 1.963) | 1.016 (0.536, 1.927) |
| *P* value for interaction* | | | | 0.003 | | | |
| Grade/differentiation | | | | | | | |
| Well/moderately differentiated | 1990 | 5 (4, 5) | 1 (Reference) | 884 | 4 (4, 4) | 1 (Reference) | 1.009 (0.917, 1.112) |
| Poorly differentiated or undifferentiated | 4965 | 4 (4, 4) | 1.231 (1.162, 1.303) | 2952 | 4 (4, 4) | 1.130 (1.037, 1.231) | 0.913 (0.867, 0.961) |
| Unknown | 1755 | 4 (3, 4) | 1.105 (1.028, 1.187) | 1294 | 4 (3, 4) | 0.956 (0.864, 1.057) | 0.870 (0.797, 0.950) |
| *P* value for interaction* | | | | 0.005 | | | |

* Based on Cox proportional hazards model in males and females, separately, adjusted for age, marital status, site of primary tumor, treatment, histology, grade, tumor size, and lymph node involvement.

† Hazard ratios compared overall survival in females to males (reference group) across race or grade/differentiation based on Cox model adjusted for age, marital status, site of primary tumor, treatment, histology, grade, tumor size, and lymph node involvement.

single institution study, which found that Hispanics present at a younger age when compared to other ethnicities (44).

After adjusting for sex, race, marital status, treatment type, primary site, histology, the year of diagnosis and SEER site, we found significant increased cancer-specific mortality among men and older age groups. The survival for our youngest age group was 2 fold higher than the oldest age group. Our findings do not confirm previous reports that younger patients with metastatic gastric cancer have poorer survival. Outside of treatment with surgery, young age was the best prognostic marker. We could not address the role of systemic chemotherapy on overall survival in the current study due to lack of information in SEER. This likely reflects the higher rate of treatment we found in the younger patients and unlikely represents differences in tumor biology or kinetics.

Consistent with previous reports, we found that women with MGC lived longer than men. We did not find any association between gender disparities and age. Women of every age group, pre-and post-menopausal, had an equivalent survival advantage. When examined more closely, we found that this difference was limited to African American and White patients. There were no gender differences in the Hispanic and Asian patients. These differences were not attributable to the presence of cardia or non-cardia lesions. Although there have been no reports of variable expression of H2N by gender, there are gender differences in expression of estrogen receptor (ER) and ER messenger RNA in gastric cancer (45). A possible explanation for the survival advantages in women may be found in a recent study addressing the interactions between the estrogen receptor and her-2neu receptor pathways in breast cancer development and treatment response. Hurtado and colleagues found her-2-neu up regulation following the silencing of PAX-2 in cell lines treated with tamoxifen, which suggests that tamoxifen-estrogen receptor and estradiol-estrogen receptor complexes inhibits transcription of Her-2-Neu via

Pax-2 (46).

Despite the clinical and genetic variability of advanced gastric cancer, we were able to identify clinical correlates for improved outcomes, which included gender and age. We did not find an association between ethnicity and survival. This is thought provoking as there are clear differences in the age of presentation and the prevalence of cardiac tumors. Hispanic patients were twice as likely to develop gastric cancer at < 45 years old than Caucasians. Conversely Caucasians were twice as likely to develop gastric cardia lesions *vs* non-proximal cancers. Further research into biological basis for these differences is warranted.

## References


1. Brenner H, Rothenbacher D, Arndt V. Epidemiology of stomach cancer. Methods Mol Biol 2009;472:467-77.
2. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24:2137-50.
3. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71-96.
4. Karpeh M, Kelsen D, Tepper J. Cancer of the stomach. In: DeVita V, Hellman S, Rosenberg S, editors. Cancer Principles & Practice of Oncology. Philadelphia: Lippincot, Williams & Wilkins; 2001. p. 1092-126.
5. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998;83:2049-53.
6. Kamangar F, Qiao Y, Blaser MJ, Sun XD, Katki H, Fan JH, et al. Helicobacter pylori and oesophageal and gastric cancers in a prospective study in China. Br J Cancer 2007;96:172-6.
7. Bertuccio P, Praud D, Chatenoud L, Lucenteforte E, Bosetti C, Pelucchi C, et al. Dietary glycemic load and gastric cancer risk in Italy. Br J Cancer 2009;100:558-61.
8. Abnet CC, Freedman ND, Kamangar F, Leitzmann M, Hollenbeck AR, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. Br J Cancer 2009;100:551-7.
9. Shikata K, Doi Y, Yonemoto K, Arima H, Ninomiya T, Kubo M, et al. Population-based prospective study of the combined influence of cigarette smoking and Helicobacter pylori infection on gastric cancer incidence: the Hisayama Study. Am J Epidemiol 2008;168:1409-15.
10. Van Custem E, Kang Y, Chung H, Shen L, Sawaki A, Lordick F, et al. Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC) [abstract]. J Clin Oncol 2009;s27:LBA4509.
11. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965;64:31-49.
12. Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, et al. E-cadherin germline mutations in familial gastric cancer. Nature 1998;392:402-5.
13. Takenaka R, Okada H, Kato J, Makidono C, Hori S, Kawahara Y, et al. Helicobacter pylori eradication reduced the incidence of gastric cancer, especially of the intestinal type. Aliment Pharmacol Ther 2007;25:805-12.
14. Vergara R, Torrazza I, Castillo Fernandez O. Her-2/Neu overexpression in gastric cancer. J Clin Oncol 2009;s27:e15679.
15. Clements W, Wang J, Sarnaik A, Kim OJ, MacDonald J, Fenoglio-Preiser C, et al. beta-Catenin mutation is a frequent cause of Wnt pathway activation in gastric cancer. Cancer Res 2002;62:3503-6.
16. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 2000;404:398-402.
17. El-Omar EM, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology 2003;124:1193-201.
18. Gorouhi F, Islami F, Bahrami H, Kamangar F. Tumour-necrosis factor-A polymorphisms and gastric cancer risk: a meta-analysis. Br J Cancer 2008;98:1443-51.
19. Amemiya H, Kono K, Itakura J, Tang RF, Takahashi A, An FQ, et al. c-Met expression in gastric cancer with liver metastasis. Oncology 2002;63:286-96.
20. Cinti C, Vindigni C, Zamparelli A, La Sala D, Epistolato MC, Marrelli D, et al. Activated Akt as an indicator of prognosis in gastric cancer. Virchows Arch 2008;453:449-55.
21. Lin WC, Li AF, Chi CW, Chung WW, Huang CL, Lui WY, et al. tie-1 protein tyrosine kinase: a novel independent prognostic marker for gastric cancer. Clin Cancer Res 1999;5:1745-51.
22. Mrena J, Wiksten JP, Thiel A, Kokkola A, Pohjola L, Lundin J, et al. Cyclooxygenase-2 is an independent prognostic factor in gastric cancer and its expression is regulated by the messenger RNA stability factor HuR. Clin Cancer Res 2005;11:7362-8.
23. Iwata C, Kano MR, Komuro A, Oka M, Kiyono K, Johansson E, et al. Inhibition of cyclooxygenase-2 suppresses lymph node metastasis via reduction of lymphangiogenesis. Cancer Res 2007;67:10181-9.
24. Tanner M, Hollmén M, Junttila T, Kapanen A, Tommola S, Soini Y, et al. Amplification of HER-2 in gastric carcinoma: association with Topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol 2005;16:273-8.
25. Park DI, Yun JW, Park JH, Oh SJ, Kim HJ, Cho YK, et al. HER-2/neu amplification is an independent prognostic factor in gastric cancer. Dig Dis Sci 2006;51:1371-9.
26. Holburt E, Freedman SI. Gastric carcinoma in patients younger than age 36 years. Cancer 1987;60:1395-9.
27. Wang JY, Hsieh JS, Huang CJ, Huang YS, Huang TJ. Clinicopathologic study of advanced gastric cancer without serosal invasion in young and old patients. J Surg Oncol 1996;63:36-40.

28. Lee JH, Ryu KW, Lee JS, Lee JR, Kim CG, Choi IJ, et al. Decisions for extent of gastric surgery in gastric cancer patients: younger patients require more attention than the elderly. J Surg Oncol 2007;95:485-90.
29. Tso PL, Bringaze WL 3rd, Dauterive AH, Correa P, Cohn I Jr. Gastric carcinoma in the young. Cancer 1987;59:1362-5.
30. Al-Refaie WB, Pisters PW, Chang GJ. Gastric adenocarcinoma in young patients: A population-based appraisal [abstract]. J Clin Oncol 2007;s25:4547.
31. Freedman ND, Chow WH, Gao YT, Shu XO, Ji BT, Yang G, et al. Menstrual and reproductive factors and gastric cancer risk in a large prospective study of women. Gut 2007;56:1671-7.
32. Dicken BJ, Bigam DL, Cass C, Mackey JR, Joy AA, Hamilton SM. Gastric adenocarcinoma: review and considerations for future directions. Ann Surg 2005;241:27-39.
33. Bollschweiler E, Boettcher K, Hoelscher AH, Sasako M, Kinoshita T, Maruyama K, et al. Is the prognosis for Japanese and German patients with gastric cancer really different? Cancer 1993;71:2918-25.
34. Theuer CP, Kurosaki T, Ziogas A, Butler J, Anton-Culver H. Asian patients with gastric carcinoma in the United States exhibit unique clinical features and superior overall and cancer specific survival rates. Cancer 2000;89:1883-92.
35. Ries LA, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, et al. The annual report to the nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. Cancer 2000;88:2398-424.
36. Rothman K. Modern epidemiologyed. 2nd ed. Philadelphia: Lippincott-Raven; 1998.
37. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:512-26.
38. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825-31.
39. Helicobacter and Cancer Collaborative Group. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut 2001;49:347-53.
40. Ross JS, McKenna BJ. The HER-2/neu oncogene in tumors of the gastrointestinal tract. Cancer Invest 2001;19:554-68.
41. Akiyama T, Sudo C, Ogawara H, Toyoshima K, Yamamoto T. The product of the human c-erbB-2 gene: a 185-kilodalton glycoprotein with tyrosine kinase activity. Science 1986;232:1644-6.
42. Coussens L, Yang-Feng TL, Liao YC, Chen E, Gray A, McGrath J, et al. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. Science 1985;230:1132-9.
43. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177-82.
44. Yao JC, Tseng JF, Worah S, Hess KR, Mansfield PF, Crane CH, et al. Clinicopathologic behavior of gastric adenocarcinoma in Hispanic patients: analysis of a single institution's experience over 15 years. J Clin Oncol 2005;23:3094-103.
45. Zhao XH, Gu SZ, Liu SX, Pan BR. Expression of estrogen receptor and estrogen receptor messenger RNA in gastric carcinoma tissues. World J Gastroenterol 2003;9:665-9.
46. Hurtado A, Holmes KA, Geistlinger TR, Hutcheson IR, Nicholson RI, Brown M,et al. Regulation of ERBB2 by oestrogen receptor-PAX2 determines response to tamoxifen. Nature 2008;456:663-6.