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Prognostic factors and outcomes in Italian patients undergoing curative gastric cancer surgery

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Abstract

Background: Survival of patients after curative surgical resection for gastric cancer (GC) remains poor, thus emphasizing the need for better definition of prognostic factors to improve the long-term course of disease.
Methods: From 1999 to 2009, 110 patients had curative-intent gastrectomy for adenocarcinoma. Clinicopathological features, *Helicobacter pylori* infection, dietary habits and lifestyle, and the presence of proinflammatory gene polymorphisms were evaluated.
Results: At the end of follow-up, 55 deaths had occurred, 48 of them due to GC, whereas the median overall survival (OS) and disease-free survival (DFS) were 62 and 51 months, respectively. From the Kaplan–Meier analysis and log-rank test, statistically significant differences in OS and DFS were found for tumor site (only for DFS), tumor size, lymph node metastasis ratio (NR), and tumor-node-metastasis stage, but not for age, comorbidity, *H. pylori* infection, cigarette smoking, and *IL1B* or *TNFA* polymorphisms. Multivariable Cox regression analysis revealed NR was an independent prognostic factor for OS and DFS. Cardia tumor and patient age 65 years or older were also independent prognostic factors for OS and DFS.
Conclusions: Tumor-related factors remain strongest predictors of survival in GC patients after surgery. Particularly, NR was an effective feature in identifying patients at high risk for adverse outcome.

Keywords: Gastric adenocarcinoma; Tumor-related factors; Overall survival; Disease-free survival; Lymph node metastasis ratio

Introduction

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of death for cancer worldwide,[1] despite a decreasing global incidence and mortality.[2,3] Overall, GC has a poor prognosis,[4] with a 25% 5-year survival rate in both USA and Europe, being 10–15% in advanced disease.[2,5] A recently updated analysis of cancer mortality in European countries showed a constant decline in GC mortality[3] that, started worldwide several years ago,[6] may be partly attributed to improved dietary considerations,[7–9] to diminished prevalence of *Helicobacter pylori* infection,[10] and partly to better access to specialized diagnostics, staging, and treatment.[11]

Gastric adenocarcinoma accounts for more than 90% of GC cases and is a heterogeneous disease, with two main histologically identified variants, intestinal and diffuse.[12] While *H. pylori* is a well-established cause of gastric tumors of both histologic types,[10,13] intestinal adenocarcinoma seems to be more closely associated with the worldwide decline in GC rates, explaining the increased proportion of diffuse-type GCs in several countries.[12] However, it is the interaction between *H. pylori* infection and either environmental or host risk factors that mainly drives

Abbreviations: CI, confidence interval; GC, gastric cancer; DFS, disease-free survival; IL, interleukin; N, node; NR, node ratio; OS, overall survival; SD, standard deviation; T, tumor; TNF, tumor necrosis factor; TNM, tumor node metastasis.

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the initiation and progression of *H. pylori*-induced atrophic gastritis to adenocarcinoma.[14,15] Not surprisingly, *H. pylori* genotypes that cause more inflammation (i.e., *cagA*-positive *vacA* s1m1)[16] are more closely related to malignancy,[17,18] whereas polymorphisms in human genes encoding for interleukins (i.e., interleukin-1β, IL1β) or other proinflammatory cytokines (i.e., tumor necrosis factor-α, TNFα) may explain why some individuals infected with more virulent *H. pylori* develop GC while others do not.[12] Although a combination of smoking, alcohol, diet, and genetics are shown to modulate the risk for *H. pylori*-related carcinogenesis,[19,20] little is known as to whether any of these factors is associated with a worse prognosis and reduced long-term survival in patients with GC after complete surgical removal of the tumor,[21] which nowadays remains the only curative treatment option and the most important treatment-related prognostic factor.[22]

In this retrospective study, we examined the effects of host and environmental factors, which are shown to increase or predispose to the risk for development of GC, in comparison with known prognostic factors on the overall survival (OS) and disease free-survival (DFS) of patients undergoing surgery for potentially curable gastric adenocarcinoma in a large Italian University Hospital.

Materials and methods

Patients and specimens

The study population consisted of consecutive patients, with a histologically confirmed diagnosis of primary gastric adenocarcinoma, who received curative-intent surgical therapy between the years 1999 and 2009 at the Università Cattolica del Sacro Cuore (UCSC).[23] All patients who underwent subtotal or total gastrectomy with D2 lymph node dissection aimed at complete tumor resection (i.e., R0) as defined by absence of residual disease (microscopic or macroscopic tumor) after intervention,[24] were eligible. Patients were identified from a prospective surgical database, maintained at the UCSC, that included demographics and clinicopathological parameters (age, sex, presence of comorbidity, date of surgery, anatomic subsite, size, tumor stage, Lauren's classification, status of lymph node metastasis, (neo)adjuvant chemotherapy, date of relapse, and date of last follow-up). Tumor-node-metastasis (TNM) staging was performed according to the American Joint Committee on Cancer 7th edition.[25] Lymph node involvement was classified as N0 (no metastasis), N1 (1–2 metastatic nodes), N2 (3–6 metastatic nodes), or N3 (7 or more metastatic nodes),[26] whereas the ratio between metastatic and examined lymph nodes was classified as NR0 (0%), NR1 (<15%), NR2 (15–40%), or NR3 (>40%).[27] Additional baseline data were recorded from each patient at the first medical or surgical oncology visit, by using a lifestyle and diet questionnaire which included items on tobacco smoking, alcohol consumption, and dietary habits. All patients were seen postoperatively at intervals ranging from 3 (for the first 2 years) to 6 (thereafter) months (last follow-up in 2012), and the mean (SD) follow-up period for the entire cohort was 52.9 (44.8) months (range, 1–158 months).

Surgical resection specimens, one sample from the tumor tissue and one sample from the adjacent nonneoplastic mucosal tissue, were obtained from each patient after gastrectomy, frozen in liquid nitrogen, and stored at −80 °C until processing. For histopathological evaluation, the tissue specimens were fixed in 10% buffered formalin, embedded in paraffin, and cut into sequential 4-μm sections. DNA was extracted from frozen gastric mucosal samples using a commercially available kit (Qiagen), and *H. pylori* infection status was assessed through amplification of the genes *glmM* (*ureaseC*), *cagA*, and *vacA* (s1 and m1 alleles) by PCR of specific fragments.[28,29] DNA was also isolated from each patient's peripheral blood lymphocytes and used to determine the presence of allelic polymorphisms in the genes encoding TNF-α (*TNFA-308A*) and IL1β (*IL1B-511T* and *IL1B-31C*), and the IL1 receptor antagonist variant*2 (*IL1-RN*2*) carrier status.[30,31] Written informed consent was obtained before sample collection from the all patients, and this study was approved by the Ethics Committee of UCSC.

Statistical analysis

Differences between patients' characteristics according to tumor site (noncardia or cardia) or *H. pylori* infection status (positive or negative) were analyzed by the Student's *t* test for continuous variables and by the Pearson's χ^2 test for categorical variables. Overall survival was defined as the time from date of surgery until death from any cause (event) or alive at last follow-up (censored). Disease-free survival was defined as the time from surgery until occurrence of local or distant relapse (event) or alive without documented relapse at last follow-up (censored). The OS and DFS at 1 and 5 years of follow-up were chosen as long-term outcomes, and the Kaplan–Meier method with the log-rank test was used to assess the effect of variables on survival. Variables showing a significant trend for association with survival in the univariable Cox regression analysis, as well as variables with known prognostic value were included into subsequent multivariable Cox proportional hazards regression models for OS and DFS. All tests were two-sided and considered statistically significant at $P < 0.05$. Statistical analyses were performed by STATA software package version 12.0.

Results

Patient characteristics

Of the original cohort of 156 patients,[23] 10 were excluded from the analysis because they were lost to follow-up, as well