Original Article

Proposal for a clinicopathological prognostic score for resected gastric cancer patients

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Abstract

Background: Factors other than pTNM stage have been associated with gastric cancer (GC) prognosis, and several alternative prognostic scores have been constructed. Our aims are to identify prognostic factors in western GC patients and to build clinicopathological prognostic models for overall survival (OS) and disease-free survival (DFS).

Methods: A Retrospective study of 204 cases of GC resected during the years 2000 to 2014 was conducted in our hospital. Clinicopathological features were assessed, univariate and multivariate analysis were performed and prognostic scores were constructed.

Results: Most patients were diagnosed at pTNM stages II and III (36.9% and 48.1%, respectively). According to Laurén classification, tumors were intestinal (55.8%), diffuse (35.2%) and mixed (9%). During follow-up, 43.5% of patients had tumor recurrence, and 28.6% died due to tumor. Univariate analysis showed that patient age, Laurén subtype, signet-ring cell morphology, pTNM stage, tumor grade, perineural invasion, growth pattern, intratumoral inflammation, adjuvant therapy, and desmoplasia were significantly related to tumor progression or death. Multivariate analysis showed that Laurén subtype, pT stage, and lymph node ratio (LNR) were significantly and independently associated with GC recurrence. Laurén subtype and LNR were significantly related to patient survival. Prognostic scores for tumor progression and death were developed and patients were classified into four prognostic groups which showed good prognostic performance.

Conclusion: A prognostic model comprising histological features such as Laurén subtype can be easily applied in clinical practice, and provides more prognostic information than pTNM stage alone. These models can further stratify resected GC patients and have the potential to aid in the individualization of patient management.

Keywords: Gastric cancer, histopathological score, prognosis, TNM classification

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INTRODUCTION

Gastric cancer (GC) is the fourth most frequent cancer and the second most cause of cancer-related deaths worldwide.[1] Its incidence depends on factors like patient gender, race, and geographical location.[2] 50% of all cases occur in Eastern Asia.[3] Histologically, more than

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90% of GC are adenocarcinomas. For this reason, in the present study we used GC as a synonym for gastric adenocarcinoma, therefore excluding squamous cell carcinoma of the gastroesophageal junction and rare histologic types of GC.

As previously mentioned, GC shows substantial geographic variation. In western countries, most cases are advanced at diagnosis[4] and 5-year survival rates are low (approximately 20%). In Japan and other Asian countries, where screening programs have been implemented, survival rates are higher.[2] Reported median overall survival (OS) of advanced disease is less than 1 year.[5,6] The best available tool for evaluating GC prognosis is TNM stage, which includes tumor depth, lymph node metastasis, and distant metastasis.[7] However, GC is a heterogeneous disease with varied clinicopathological and molecular features,[8,9] and factors other than anatomic spread have been identified as prognosticators.[10,11] Moreover, some authors have observed prognostic differences between patients with identical TNM stage tumors, and advanced GC remains a hard-to-predict disease.[5,12] Early recurrences in patients with early GC have also been reported.[9,12]An optimal stratification of GC is essential for determining patient prognosis and management. In addition, the limited benefit of chemotherapy (CT) in advanced GC and its potential harms, such as decreased quality of life or drug toxicity, make it necessary to individualize patient management.[5,13]

With this aim, several prognostic scores have been developed, including mainly clinical (preoperative and postoperative), immunohistochemical, and molecular features.[8,14,15] Clinicopathological scores based only on clinical and histological features have been reported less frequently. These scores are cheaper and easier to apply in clinical practice, but studies on histological features demand a consensual and standardized pathological evaluation. In our literature review, we have found that most studies on clinicopathological scores for GC have been performed in Korea, China, and Japan (46.7%). As far as we know, only five studies have developed clinicopathological scores for European patients with GC. Only one of them studied both OS and disease-free survival (DFS).

In this study, we have reviewed gastric carcinomas resected in our institution with the aim of (1) Identifying significant and independent prognostic factors for western patients with resected GC; (2) Building a clinicopathological prognostic model for the definition of the risk of recurrence and tumor death, after surgical treatment for advanced GC.

METHODS

Patients

We investigated all cases diagnosed with GC and surgically resected in a large tertiary hospital in Madrid (Spain), between the years 2000 and 2014. Ethical approval was obtained from the Ethics Committee at Hospital Clínico San Carlos on January 15, 2016. Two hundred and six resection specimens of patients with GC with or without adjuvant chemotherapy were included in our study. Patients were treated by total or subtotal gastrectomy with D1 or D2 lymphadenectomy. Specimens were formalin-fixed, paraffin-embedded, and stained with hematoxylin and eosin. All slides from these cases were retrospectively reviewed by two independent pathologists blinded to the outcome. A detailed protocol for histologic evaluation was followed, and discordant cases were conjointly reviewed. Histopathological features assessed are described below. Gross findings were retrieved from the database of Surgical Pathology Department (PatWin). Tumor morphology was classified according to Borrmann's classification into four types: Polypoid, flat or diffuse, ulcerative, and fungating.[16] Medical records (both electronic and paper-based) were reviewed and endoscopic and demographic data were collected for the study, including patient age, gender, familial history, presence of clinical symptoms, tumor location, and morphology. Tumor location was defined as the part of stomach which contained the bulk of the tumor, as described in endoscopy and/or pathology reports. Outcome measures were tumor progression (recurrence) and tumor death, after surgical resection with a curative intent.

Histopathological features

All cases included in our study were gastric adenocarcinomas. Microscopical features such as tumor type, percentage of mucin pools and signet-ring cell morphology, tumor grade, presence of perineural infiltration, vascular invasion, necrosis, budding, peritumoral and intratumoral inflammatory infiltrates, desmoplasia, growth pattern at the tumor leading edge, T stage and N stage were assessed. Tumor type was evaluated according to Laurén classification (intestinal or diffuse). Tumor grade was reported as low (well and moderately differentiated, ≥50% gland formation) and high (poorly differentiated, <50% gland formation). Tumor budding was analyzed in hematoxylin and eosin stained slides (CK AE1-AE3 was not performed). It was considered positive when ≥5 single tumor cells or cell clusters of up to 4 tumor cells were seen at the leading edge in one ×20 visual field, as reported by Ueno *et al*.[17,18] Peritumoral and intratumoral inflammatory responses were scored as positive or negative following the

recommendations published by the Association of Directors of Anatomic and Surgical Pathology.[19] We also assessed the type of inflammatory infiltrates (lymphocytic-predominant, eosinophilic-predominant, or neutrophilic-predominant) and their density (mild, moderate, or intense).Tumor growth was scored as pushing and infiltrating, and pTNM stage was reported according to the 8th edition of the AJCC cancer staging manual.

Exclusion criteria

Patients with R1 or R2 resections and metastatic tumors at diagnosis were excluded from our study.

Statistical analysis

All information was stored in an anonymized Excel file and analyzed with the statistical package SPSS 20.0 for Windows. Quantitative data were summarized as mean and standard deviation (SD) after confirming Gaussian distribution or median and range for non-parametric variables. All qualitative data were represented with percentage and absolute numbers. For the analysis of association between variables, we employed either $\chi 2$ (Chi)-squared test (qualitative variables) or Student's *t*-test (to compare means between dichotomic quantitative variables). Statistical significance was settled at a P value <0.05. Multivariate Cox regression models for OS and DFS were calculated. Backward stepwise method was applied, and models were adjusted for potential confounders. Clinicopathological variables were considered categorical covariates.All variables such as age and sex, macroscopic type, tumor staging (T stage and LNR), lymphovascular invasion, perineural infiltration, Laurén subtype, presence of signet-ring cells and tumor grade, which are "classically" related to cancer progression and death, were included as covariates. All variables significantly associated to tumor death and recurrence were included in univariate analyses.

Two prognostic scores for tumor progression and death were developed based on hazard ratios.[20] Receiver-operating characteristic (ROC) analyses were performed and area under the curve (AUC) values were calculated. Kaplan–Meier curves were plotted.

A literature search was performed and our results were compared to those available in the literature.

RESULTS

Two hundred and four cases were included in our study. Clinicopathological features are summarized in Table 1. Males formed 44.6% of all cases. Mean age at diagnosis was 71.4 years, with no significant difference between genders (P = 0.781; male: 71.13, female 71.64). Smokers and former smokers formed 13.9% and 26.9% of all cases, respectively. A familial history of gastrointestinal cancer was reported in 20% of cases. 91% of tumors were symptomatic. 67.1% and 57.4% of all patients showed localized and systemic symptoms, respectively. Tumors were located in the gastric antrum or pylorus, body, fundus, and gastric cardia in 55.7%, 34.3%, 8.4%, and 1.7% of cases, respectively. As for macroscopic features, most tumors were fungoid (35.6%) or ulcerative (29.9%). Polypoid and flat lesions were described in 21.1% and 13.4% of cases. According to Laurén classification, tumors were intestinal (55.8%), diffuse (35.2%), and mixed (9%). Mucin pools, signet-ring cell morphology, tumor necrosis, budding and desmoplasia were seen in 19.1%, 41.7%, 26%, 25.6%, and 52% of cases, respectively. Marked intratumoral inflammatory infiltration was identified in 71.1% of tumors. Peritumoral Crohn-like lymphoid reaction was seen in 36.4% of cases. Lymphovascular and perineural invasion were identified in 44.2% and 50.2% of cases, respectively. All

Table 1: Clinicopathological features of our series

FEATURE			*n* (valid %)
Age [mean (SD)]			71.4 (12.4)
Male			90 (44.6%)
Smoking habit		Ex-smoker	54 (26.9%)
		Active smoker	28 (13.9%)
Drinking habit		Ex-drinker	9 (4.5%)
		Active drinker	22 (11.1%)
Symptoms		Localized	104 (67.1%)
		Systemic	89 (57.4%)
		Total	142 (91%)
Location		Cardias	3 (1.7%)
		Fundus	15 (8.4%)
		Body	61 (34.3%)
		Antrum	99 (55.7%)
Macroscopic type		Polypoid	41 (21.1%)
		Flat	26 (13.4%)
		Ulcerative	58 (29.9%)
		Fungoid	69 (35.6%)
Laurén type		Intestinal	111 (55.8%)
		Diffuse	70 (35.2%)
		Mixed	18 (9%)
Mucin pools			38 (19.1%)
Signet-ring cell morphology			83 (41.7%)
High grade			107 (53.8%)
Tumor necrosis			52 (26%)
Infiltrative pattern			124 (62.6%)
Budding			34 (25.6%)
Desmoplasia			102 (52%)
Lymphovascular invasion			88 (44.2%)
Perineural invasion			100 (50.2%)
Intrat. II[a]	Density	None	11 (5.6%)
		Mild/moderate	46 (23.3%)
		Marked	140 (71.1%)
	Type	Lymphocytic	178 (94.6%)
		Neutrophilic	3 (1.6%)
		Eosinophilic	7 (3.7%)
Peritumoral inflammatory infiltrate			54 (36.4%)

[a]Intra. II: Intratumoral inflammatory infiltrate

tumors were surgically resected, and 22% of patients received adjuvant therapy. Neoadjuvant therapy and immunotherapy were not administered. GC treatment, staging, and patient outcomes are presented in Table 2. As for pTNM stage, most tumors were T3 (61.9%) and 68.8% showed lymph node metastasis. 15% of GC were stage I, 36.9% stage II, and 48.1% stage III. During follow-up, 43.5% of patients showed recurrences and 28.6% of patients died due to the GC. Median OS and DFS were 29 and 14.5 months, respectively. Tumor recurrences were locoregional in 35.2% and distant in 64.8% of cases.

Univariate analysis (Chi-squared test) results are summarized in Table 3. Patient age, Laurén subtype, perineural invasion, intratumoral inflammatory infiltration, pT, pN, LNR, pTNM stage and adjuvant therapy were significantly associated to tumor recurrence. Presence of signet-ring cells approached significance ($P = 0.056$). Younger patients and patients with diffuse GC, perineural invasion, no inflammatory infiltration and higher pT, pN, LNR or pTNM stage showed more recurrences. When considering tumor death, patient age, Laurén subtype, presence of signet-ring cells, tumor grade, tumor desmoplasia, pN, LNR, pTNM stage, adjuvant therapy and tumor recurrence were significant prognostic factors. Growth pattern and lymphovascular invasion were significant. ($P = 0.069$ and 0.059, respectively). Younger patients and patients with diffuse GC, presence of signet-ring cells, high-grade, non-desmoplastic tumors and higher pN, LNR and pTNM stage showed higher death rates.

Table 2: Tumor treatment, staging and patient outcomes

Feature			*n* (valid %)
Gastrectomy	Subtotal		141 (69.5%)
	Total		62 (30.5%)
Adjuvant therapy			36 (22%)
pT	T1		10 (5.1%)
	T2		41 (20.8%)
	T3		122 (61.9%)
	T4		24 (12.2%)
pN	N0		59 (31.2%)
	N1		37 (19.6%)
	N2		50 (26.5%)
	N3		43 (22.8%)
TNM stage	I		28 (15%)
	II		69 (36.9%)
	III		90 (48.1%)
LNM[a] [mm, mean (SD)]			10.5 (7.33)
LNR[b][mean (SD)]			0.24 (0.28)
Extracapsular extension			69 (52.3%)
Tumor death			48 (28.6%)
Recurrence	Total		87 (43.5%)
	Type	Locor[c]	31 (35.2%)
		Distant	57 (64.8%)
OS[d] [months, median (range)]			29 (0-205)
DFS[e] [months, median (range)]			14.5 (0-186)

[a]LNM: Lymph node metastases. [b]LNR: Lymph node ratio. [c]Locor: Locoregional. [d]OS: Overall survival. [e]DFS: Disease-free survival

Patients treated by adjuvant therapy showed significantly more recurrences and deaths. A separate univariate analysis was performed and adjuvant therapy was significantly associated with pTNM stage ($P = 0.018$). Patients receiving adjuvant therapy were stage I (0%), stage II (33.3%), and stage III (66.7%).

Multivariate analysis results are shown in Table 4. We found that Laurén subtype, pT stage, and lymph node ratio were factors independently associated with tumor recurrence. When analyzing OS as the dependent variable, only Laurén subtype and LNR were significant prognostic predictors. DFS curves at mean of covariates and depending on Laurén subtypes and T stage are presented in Figure 1. OS functions at mean of covariates and depending on Laurén subtypes are included in Figure 2.

Two simple prognostic scores based on the hazard ratios from the Cox regression analyses were constructed, as seen in other studies [Table 5].[20,21]

In respect of tumor recurrence, total score ranged from 0 to 13. ROC analyses were performed. Area under the curve (AUC) for TNM stage (I–III) was 0.615 (95% CI: 0.534-0.696, *P*: 0.007). AUC for recurrence score was 0.659 (0.581–0.738, $P < 0.001$). Cut-off points were defined and patients were classified into four prognostic categories: SC1 (≤3), SC2 (>3–6), SC3 (>6–10), SC4 (>10–13). 11.3%, 23.1%, 52.7%, and 12.9% of patients were SC1, SC2, SC3, and SC4, respectively. Kaplan–Meier curves [Figure 3] showed a good patient stratification into four groups with evenly spaced curves.

Regarding tumor death, total score ranged from 0 to 11. ROC analyses were performed, and AUC for TNM stage (I–III) was 0.594 (95% CI: 0.498–0.690, $P = 0.071$). AUC for death score was 0.685 (0.593–0.778, $P < 0.001$). Cut-off points were defined and patients were classified into four prognostic groups: SC1 (<1), SC2 (1-<5), SC3 (5-<8), and SC4 (8–11). 28.2%, 48.9%, 13.8%, and 9% of patients were SC1, SC2, SC3, and SC4, respectively. Kaplan–Meier curves [Figure 4] showed good stratification into four categories with evenly spaced curves.

DISCUSSION

Incidence of GC and GC-related mortality have slightly decreased in the last decades, probably due to the emergence of new surgical techniques and management options. However, GC is still diagnosed at advanced stages and shows high mortality rates.[22] In fact, recurrence rates of almost 70% have been reported in patients

Table 3: Univariate analysis (Chi-squared test/T-student test). Variables associated with recurrence and tumor death

Event	Feature	*p*		OR (95% CI)
Recurrence	Age [mean dif. (SD)]	0.017		4.47 (1.86)
	Laurén subtype	0.017	Intestinal	1
			Diffuse	2.32 (1.25-4.3)
			Mixed	0.86 (0.3-2.48)
	Signet-ring cells	0.056		1.69 (0.95-3.03)
	Perineural invasion	0.035		1.98 (1.11-3.52)
	Intrat. II[a]	0.035	None	1
			Mild-mod	0.09 (0.01-0.76)
			Severe	0.08 (0.01-0.65)
	pT	0.06	T1	1
			T2	1.71 (0.32-9.29)
			T3	4 (0.82-19.62)
			T4	3.67 (0.64-21.15)
	pN	0.038	N0	1
			N1	1.75 (0.74.4,15)
			N2	1.95 (0.88-4.33)
			N3	3.37 (1.46-7.81)
	pTNM stage	0.007	I	1
			II	3.16 (1.07-9.35)
			III	4.92 (1.71-14.16)
	LNR [mean dif. (SD)]	0.006		0.11 (0.41)
	Adjuvant therapy	<0.001		4.52 (2-10.21)
Tumor death	Age [mean dif. (SD)]	0.027		4.92 (2.21)
	Laurén subtype	0.003	Intestinal	1
			Diffuse	3.59 (1.7-7.58)
			Mixed	1.66 (0.47-5.88)
	Signet-ring cells	0.006		2.68 (1.32-5.43)
	High grade	0.008		2.67 (1.28-5.58)
	LV[b] invasion	0.059		1.94 (0.97-3.86)
	Infiltrative front	0.069		2 (0.94-4.25)
	Desmoplasia	0.035		0.48 (0.24-0.95)
	pN	0.001	N0	1
			N1	1.4 (0.5-3.94)
			N2	0.53 (0.18-1.59)
			N3	3.93 (1.5-10.28)
	pTNM	0.072	I	1
			II	4 (0.84-10.13)
			III	5.21 (1.16-24.1)
	LNR [mean dif. (SD)]	0.007		0.16 (0.048)
	Recurrence	<0.001		20.9 (7.64-57.13)
	Adjuvant therapy	0.005		3.12 (1.38-7.07)

[a]Intrat. II: Intratumoral inflammatory infiltrate. [b]LV: Lymphovascular

with advanced disease.[13] Histologically, according to Laurén's criteria, GC can be classified into three types: Intestinal, diffuse, and mixed.[23] The WHO classification of gastrointestinal neoplasms establishes four histologic patterns: Tubular, discohesive, mucinous, and papillary.[24] Mixed GC accounts for approximately 25% of all tumors, a fact which could reflect the heterogeneity of GC. As for its molecular features, GC is a polygenic disease, which results from the combined interaction of multiple genes and tumor microenvironment.[8]

As previously mentioned, prognostic stratification systems of GC need to be refined to provide accurate and individualized information. The pTNM staging system is still the main tool for patient stratification.[7] However, several issues have arisen. First of all, pTNM system only assesses the anatomic extension of GC, taking into account tumor depth and lymph node or distant metastasis.[25] A marked prognostic heterogeneity has been reported among patients with advanced GC, and some authors have observed early recurrences in early GC cases.[5,12] Several prognostic factors other than pTNM stage have been identified, including clinical (age, gender, nutritional status, blood test findings),[6,20,26] pathological (tumor depth, lymphovascular invasion, histologic type, histologic grade),[27-29] immunohistochemical and molecular features.[30] These factors have been repeatedly reported in the literature and have demonstrated significant prognostic value in multiple studies. Based on these findings, some authors have built new prognostic models which have shown better prognostic performance than TNM stage.[22] The clinicopathological scoring system proposed by Qian *et al*. identified high risk patients in stage II or III, and they observed that low-risk stage III

Table 4: Multivariate analysis (Cox regression). Features independently associated with overall survival and disease-free survival

Recurrence	Feature		*p*	Exp (B), 95% CI[a]
	LNR		<0.001	4.97, 2.17-11.37
	Laurén	Intestinal	0.046	1
		Diffuse	0.041	1.66, 1.02-2.72
		Mixed	0.450	0.71, 0.29-1.72
	T	T1	0.133	1
		T2	0.257	3.297, 0.42-25.92
		T3	0.078	5.954, 0.82-43.25
		T4	0.09	6.01, 0.76-47.80
Tumor death	Laurén	Intestinal	0.014	1
		Diffuse	0.004	2.74, 1.39-5.41
		Mixed	0.506	1.46, 0.48-4.46
	LNR		<0.001	8.33, 2.85-24.34

[a]CI: Confidence interval

patients had higher survival probabilities than stage II patients.[13] Costa *et al*. suggested that the epidemiological discrepancy between Asian and western countries cannot be explained solely by differences in screening interventions, because this discrepancy persists even when patients are stratified according to their TNM stage.[22] In our opinion, the prognostic role of the TNM staging system should not be underestimated, and new prognostic scores could be used as an adjunct to pTNM stage, in order to individualize management decisions. Specific prognostic scores could also be applied to different populations and patient subgroups.

An optimal prognostic score should be objective, reliable, and practical.[12] Variables included in the score should be standardized and easy to assess.[24] Most published prognostic scores include clinical (preoperative and postoperative) and molecular features.[8,14,15] Immunohistochemical or molecular techniques may be difficult to introduce in certain centers, but models including clinical and histological features are cheap and easy-to-implement in clinical practice.[31,32] Thus, they may be useful to refine the existing TNM classification. Previously published histopathological models have been summarized in Table 6. Almost half of these studies have been performed in Chinese, Korean, or Japanese

Table 5: Prognostic scores

Dependent variable	Prognostic score			Total score
Tumor progression	Laurén subtype	Intestinal	0	Range: 0-13
		Diffuse	2	SC1: ≤3
		Mixed	0	SC2: >3-6
	T stage	T1	0	SC3: >6-10
		T2	3	SC4: >10-13
		T3-T4	6	
	LNR	LNR x5		
Tumor death	Laurén subtype	Intestinal	0	Range: 0-11
		Diffuse	3	SC1: <1
		Mixed	1	SC2: 1-<5
	LNR	LNR x8		SC3: 5-<8
				SC4: 8-11

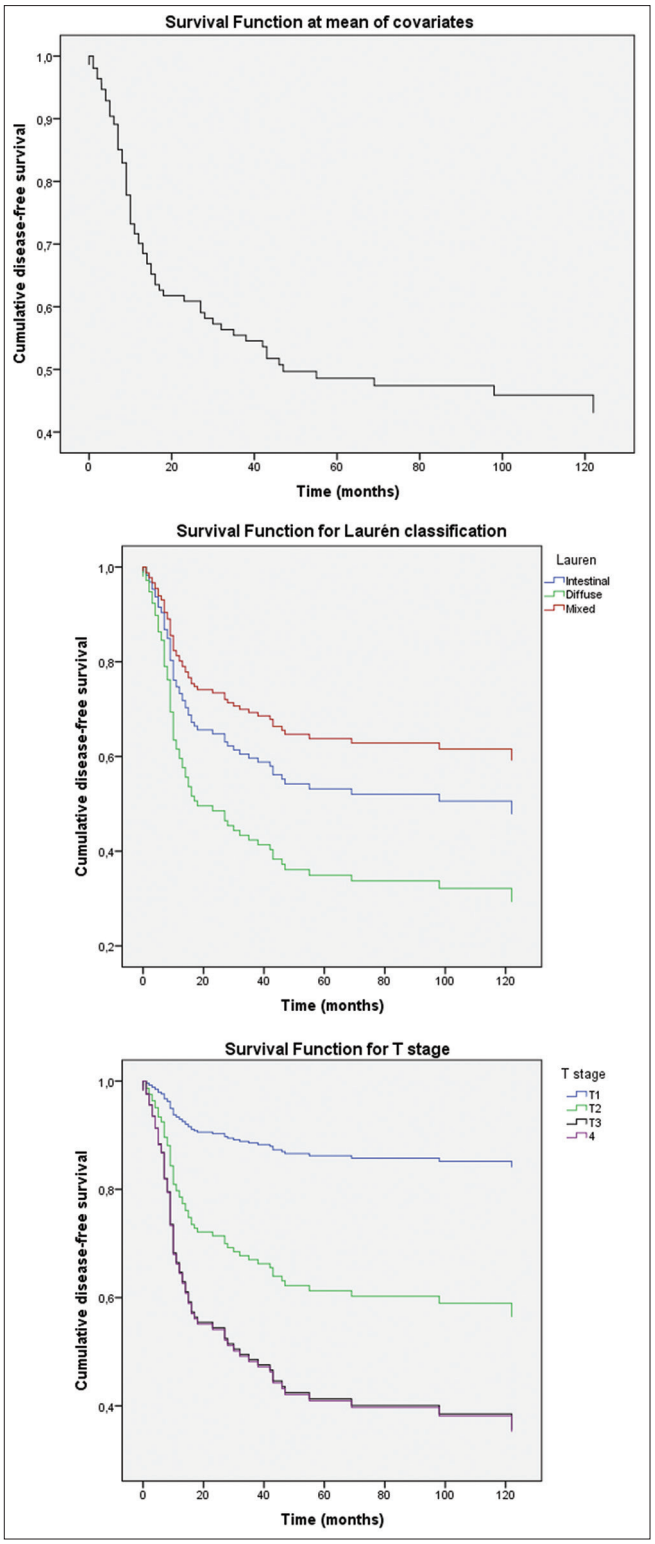


Figure 1: Disease-free survival plots: Disease-free survival function at mean of covariates (top). Survival function for Laurén subtypes (center). Intestinal and diffuse subtypes were independently related to DFS. Survival function for T stage (bottom). T1, T2 and T3-4 tumors showed decreasing DFS rates

population. Due to the geographical variations of GC, more studies should be performed in other populations

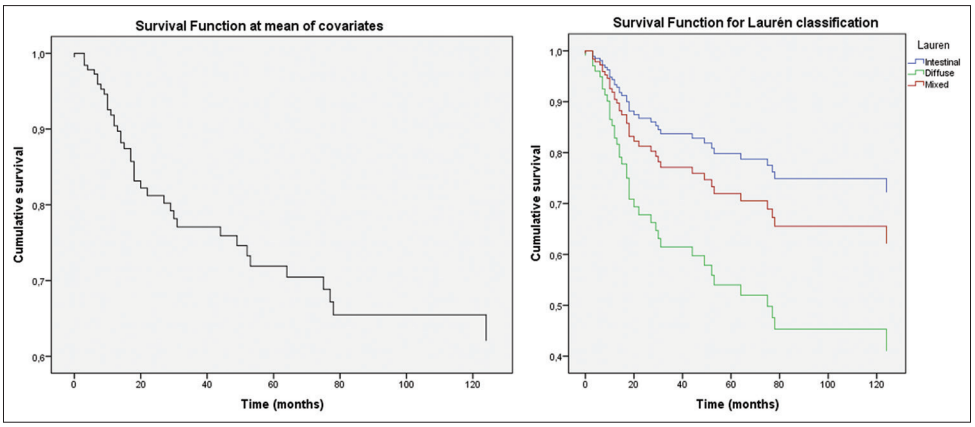


Figure 2: Overall survival plots: Survival function at mean of covariates (left). Survival function for Laurén subtypes (right). Intestinal and diffuse subtypes were independently related to OS

to identify risk factors and to develop and validate specific prognostic equations.

Previous clinical prognostic scores included mainly nutritional and inflammatory variables, such as neutrophil/lymphocyte ratio, circulating concentrations of C-reactive protein, albumin or bilirubin.[5,6,12,25] Nutritional or performance status variables like EGOC or PG-SGA could be more subjective.[20,26,33] As for clinicopathological scores, most reported features are gender, age, pTNM stage, Laurén classification, tumor depth, lymphovascular invasion, and lymph node involvement [Table 6]. Some clinicopathological nomograms for predicting survival of patients with GC have also been created.[34-36] In our univariate analyses, we have found that patient age, Laurén subtype, presence of signet-ring cells, perineural invasion, intratumoral inflammatory infiltration, pT, pN, pTNM stage, LNR and adjuvant therapy were significantly associated with tumor progression. Histological grade and desmoplasia were associated with death due to GC.

With regard to age of the patient, younger patients showed more recurrences and decreased survival rates. However, the effect of age on GC survival is contradictory. Some studies support our results, but others have observed that younger patients show better survival rates.[37] pTNM stage (including tumor depth and lymph node involvement), tumor grade, and perineural invasion are well-known prognostic factors, which can be extrapolated to almost all tumor types. Intratumoral immune response has gained attention in the last decades, and lymphocytic infiltration has been shown to be a factor of better prognosis in several tumor types.[38,39] In our study, only 5.6% of GC showed no intratumoral inflammation, and these patients developed significantly more recurrences. In 94.6% of tumors, the inflammation was predominantly

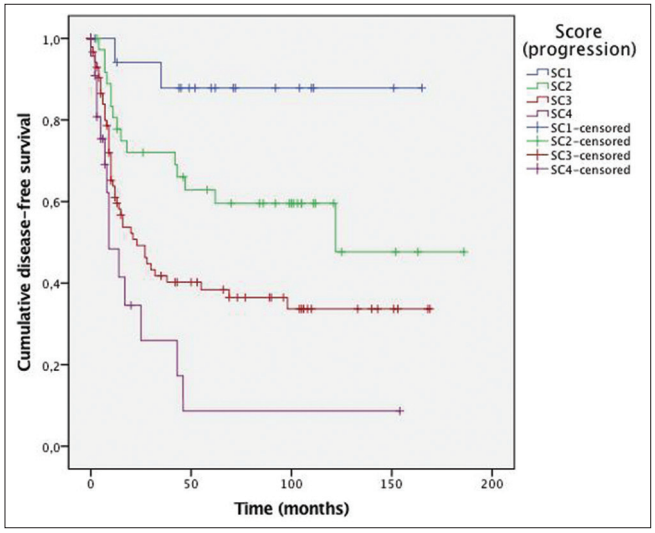
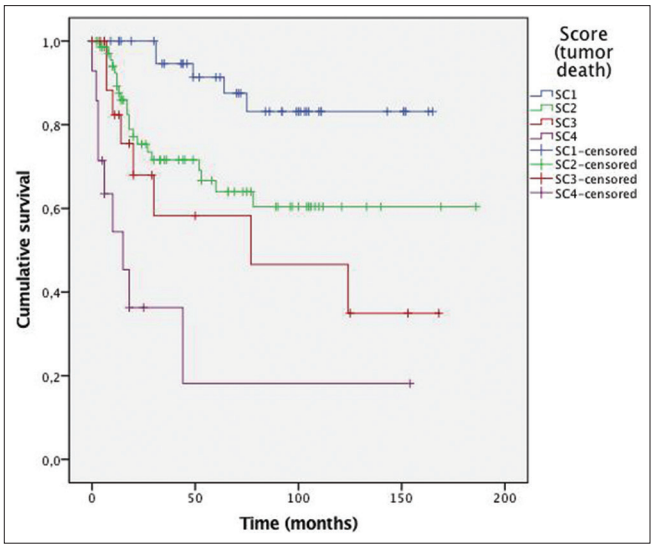


Figure 3: Disease-free survival curves depending on our prognostic score. *P* value by log-rank test was $P < 0.001$



Figures 4: Overall survival curves depending on our prognostic score. *P* value by log-rank test was $P < 0.001$

Table 6: Prognostic scores including histopathological factors reported in the literature

Author, year pub	Type of patients included	Predicted end point	Variables included
Becker Germany 2012 Ann Surg	NA[a] + S[b]	OS[c]	yT yN Histopathological tumor regression
Bria[32] Italy 2012 Ann Oncol	S	CSS[d]	Sex Stage Margins Tumor location Lymph node involvement APC IHC[e] expression Fhit IHC expression
		OS	Age Sex Stage Margins Tumor location Lymph node involvement APC IHC expression HER2 expression
Kologlu[25] Turkey 2000 Am J Surg	S	OS and DFS[f]	pT pN (AJCC[g] 1992, UICC[h] 1997) pM Metastatic lymph node ratio Resectability Tumor location Lymph node dissection (D1 or D2) Borrman classification Lauren classification
Vieira Costa[22] Brazil 2006 Ann Surg Oncol	S	OS	Sex Weight loss Pre-operative lymphocyte count Lymph node ratio Lymph node dissection TNM stage
Zhu[29] China 2014 BMJ Cancer	S	OS	Histological grading stage
Marrelli[27] Italy 2005 Ann Surg	S	DFS	pN pT Lymph node dissection (D1 vs D2-3) Tumor location Age
Sekiguchi[28] Japan 2016 J Gastroenterol	S Early tumors	Lymph node metastasis	Tumor size Tumor depth Histologic type Ulcerative features Lymphovascular invasion
Haraguchi[26] Japan 2018 Oncotarget	S	OS Tumor progression	Tumor depth and size
Qian[13] China 2016 Drug Des Devel Ther	S + A[i]	OS Treatment response	Lymph node rate Lymphovascular invasion pTNM (I-IV) Preoperative CEA level Preoperative hemoglobin
Park[42] Korea 2015 Gastric cancer	S in early GC[j] (stage I)	DFS	Age Sex pTNM (stage) Lymphovascular invasion Perineural invasion CEA level
Marubini[43] Italy 1993 Eur J Cancer	S±A	OS	Age Tumor depth Tumor location Lymph node involvement
Ichikura[41] Japan 1993 Surg Today	S±A with serosal invasion	DFS	Lymph node involvement Macroscopic type Serosal invasion (macroscopic) Interstitial conective tissue
	S±A without serosal invasion	DFS	Lymph node involvement Serosal invasion (macroscopic) Venous invasion
Kattan[44] US 2003 J Clin Oncol	S	Nomogram for CSS	Age Sex Tumor location Laurén classification Number of positive lymph nodes Number of negative lymph nodes Tumor depth
Dikken[34] US / Holland 2013 Ann Surg Oncol	S±A	Nomogram for conditional probability of survival	Sex Age Tumor location Laurén classification Tumor diameter Positive lymph nodes Negative lymph nodes Tumor depth
Han[35] Korea 2012 J Clin Oncol	S±A	Nomogram for OS	Sex Age Tumor location Tumor depth Number of metastatic lymph nodes Number of negative lymph nodes

[a]NA: Neoadjuvanttherapy. bS: Surgery. cOS: Overall survival. [d]CSS: Cancer-specific survival. [e]IHC: Immunohistochemistry. [f]DFS: Disease-free survival. [g]AJCC: American Joint Committee on Cancer. [h]UICC: Union for International Cancer Control. [i]A: Adjuvant therapy. wjGC: Gastric cancer

However, lymph node ratio retained prognostic significance. This could be explained by the fact that the extent of lymph node dissection and lymph node positivity in our series was highly variable, and N ratio shows significant advantages in this circumstance.

Based on these results, we developed prognostic scores for tumor progression and death, and our patients were classified into four prognostic groups which showed good prognostic performance in Kaplan–Meier curves.

In respect of GC management, surgery is the only curative treatment and resectable tumors are treated by total or subtotal gastrectomy.[22,27] Early disease could be treated by endoscopic submucosal dissection or endoscopic mucosal resection.[40] The role of adjuvant therapy in advanced GC depends on patient or tumor features,[6] and neoadjuvant therapy is being increasingly used.[15] In our series, patients with adjuvant therapy showed more recurrences and tumor death than patients without postoperative chemotherapy. In a separate analysis, and we found that adjuvant therapy was significantly associated only with pTNM stage ($P = 0.018$). Patients receiving adjuvant therapy were stage I (0%), stage II (33.3%), and stage III (66.7%). So, association between adjuvant therapy and tumor death or recurrence seems to be a reflection of pTNM stage, because it was administered in patients with more advanced tumors, and those patients showed higher progression and death rates despite this therapy. Finally, metastatic tumors are treated by palliative chemotherapy regimens.[36]

CONCLUSIONS

In western countries, GC is commonly diagnosed in advanced stages and shows low survival rates. pTNM staging is currently the best prognostic tool available, but factors other than pTNM stage have been consistently reported to be associated with GC prognosis, and patients with the same pTNM stage may show different outcomes. Several clinicopathological models including molecular or immunohistochemical features have been proposed, but models based on clinical and histological features only, are scarce, and most of them were developed in China, Japan, or Korea. We have analyzed patients with resected GC. Univariate analyses showed that patient age, Laurén subtype, presence of signet-ring cells, perineural invasion, intratumoral inflammatory infiltration, pT, pN, pTNM stage, LNR and adjuvant therapy were significantly associated with tumor progression. Histological grade and desmoplasia were associated with death due to tumor. In our multivariate analysis, factors independently related to OS and DFS were lymph node ratio, Laurén subtype, and T-stage. Prognostic scores for tumor progression and death were developed and patients were classified into four prognostic groups for each outcome. Kaplan–Meier curves showed good patient stratification with evenly spaced curves.The development of prognostic scores including other histopathological features, such as Laurén subtype, can improve the prognostic value of pTNM stage and has the potential to aid in the individualization of patient management.

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Conflicts of interest
There are no conflicts of interest.

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