Ten-year survival outcomes of patients with potentially resectable gastric cancer: impact of clinicopathologic and treatment-related risk factors

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Abstract	**Background** Despite therapeutic advancements, gastric cancer (GC) remains a leading cause of death worldwide.

Methods This retrospective cohort study statistically analyzed the clinicopathologic characteristics, treatments and outcomes of patients with potentially resectable GC managed at our institution between 2006 and 2010. The STROBE checklist was applied.

Results Preoperative assessment of 164 GC patients (male: female ratio 1.87, median age 65 years) assigned 132 (80.5%) to total (56; 42.4%) or subtotal (76; 57.6%) gastrectomy. Resection margins were microscopically tumor-free (R0) in 100 (75.8%), microscopically infiltrated (R1) in 25 (18.9%) and macroscopically infiltrated (R2) in 7 (5.3%) patients. Nodal plane dissection was D0 in 34 (25.8%), D1 in 62 (47.0%) and D2 in 36 (27.3%) patients. Early GC was diagnosed in 19 patients (14.4%). Fluorouracil-based chemotherapy was administered in 69.7% and chemoradiation in 18.2% of patients. The 5- and 10-year survival rates of patients with R0 resection were 74% and 65.4%, respectively. The 2-year survival rates for R1 and R2 resection were 28.9% and 0% respectively. The 5- and 10-year survival rates according to nodal plane dissection were 55.6% and 41.4% for D2, and 53.2% and 49.7% for D1, respectively. On multivariate analysis, T4, N3 and R1/R2 remained independent negative prognostic factors for overall survival. Microscopic or macroscopic infiltration of surgical margins was the worst adverse prognostic factor for survival.

Conclusion These results are equivalent to those from centers of excellence and indicate the urgent need for improvements in the field, particularly in the development of predictive models to guide personalized therapy.

Keywords Gastric adenocarcinoma, D2 gastrectomy, resection, radiotherapy, multidisciplinary, survival, chemotherapy

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Introduction

Gastric cancer (GC) remains the fifth most frequent cancer and the third cause of cancer-related deaths worldwide [1,2]. In 2012, an estimated 951,600 new cases of GC were diagnosed, while 723,100 deaths due to GC occurred globally [1,2]. Gastric cancer affects twice as many men as women and its incidence presents heterogeneity among different countries: the highest rates are encountered in eastern and western Asia, Latin America, and some former Soviet European countries, and the lowest in Northern America and many parts of Africa [1,2]. In Greece, 1357 deaths from GC were recorded in 2015 (www.statistics.gr). Differences in these rates partly reflect regional discrepancies in several factors, including consumption of fresh products, salt-preserved foods, obesity, alcohol intake, smoking, and incidence of *Helicobacter pylori*

(*H. pylori*) infection, as well as genetic predisposition such as *cadherin 1* gene mutation [2-4]. During the recent decades, the incidence of GC has gradually decreased because of primary prevention programs associated with smoking reduction, *H. pylori* infection control and reducing reliance on salt-preserved foods [2]. However, despite the additional introduction of specialized multidisciplinary team (MDT) meetings, the optimization of surgical procedures, advances in systemic chemotherapy, targeted treatments and immunotherapies in the metastatic setting, the overall 5-year survival rates remain low at 20-29%, whereas the median survival of patients with metastatic disease is 9-10 months [3,5]. An exception is the improved 5-year survival rate of more than 50% documented in Japan and Korea, due to secondary prevention programs, including endoscopic procedures [5].

Treatment options for patients with GC primarily depend on tumor staging and resectability and derive from a detailed and precise evaluation of imaging and pathology in the context of MDT meetings [6]. Oncologic resection remains the cornerstone of the therapeutic management of GC, but 15-year survival is 21% for the D1 group and 29% for the D2 group (P=0.34) [7]. Aiming to improve these poor results, combination strategies, including chemotherapy, radiotherapy (RT), targeted therapy and immunotherapy, are under intense investigation in the adjuvant, neoadjuvant and metastatic settings. Moreover, following a SWOG-directed Intergroup study, chemoradiation with 5-fluorouracil (5FU) has gained a lot of attention in the United States after curative surgery; nonetheless, concern has been raised about the associated toxicity and benefit of such strategy after optimally performed surgery [8].

The objective of our study was to evaluate the impact of clinical, pathologic and treatment-related risk factors in the survival outcomes of patients with GC from our institution during the period 2006-2010.

Patients and methods

We conducted a retrospective review of patients assessed for potentially resectable GC at Attikon University General Hospital from 2006-2010. All patients were discussed in our institution's MDT meeting, as per hospital policy, and after thorough clinicopathologic and imaging evaluation, decisions were taken about personalized treatment. As this was a general hospital with two departments of surgery, neither of which was a specialized center for GC, most surgeons had a training background in general surgery. The present study was approved by the institutional review board and written informed consent to the treatment was obtained from all patients, whose data were anonymized and transferred to a dedicated database. The STROBE checklist was applied in this observational study.

Patient data

Patients were staged using chest/abdominal computed tomography (CT), magnetic resonance imaging and, in selected cases, positron emission tomography-CT prior to surgery to exclude metastatic or locally advanced/unresectable disease. Patients with adenocarcinoma of the esophagogastric junction or stage IV GC (including liver and peritoneal metastasis, extra-regional lymph nodal involvement including the para-aortic and iliac chain) and patients treated with neoadjuvant chemotherapy were excluded from this study. Total gastrectomy was performed for proximal and middle gastric lesions, whereas subtotal gastrectomy was performed for tumors of the distal body, antrum and pylorus, with a minimum surgical resection margin of at least 5 cm. D1 or D2 lymphadenectomy was performed according to the clinical staging: i.e., patients with an anticipated T1N0 or T2N0 tumor underwent a D1 lymphadenectomy, whereas patients with more advanced clinical staging (>T3 or N+) were offered a D2 lymphadenectomy. D1 lymphadenectomy includes dissection of all perigastric lymph nodes plus the left gastric artery lymph nodes; D2 lymphadenectomy includes dissection of perigastric, celiac artery branches and hepatoduodenal ligament lymph nodes; while D0 lymphadenectomy includes anything less than D1 lymphadenectomy. Histopathologic examination of the resected specimens was performed using the GC classification staging system of the American Joint Committee on Cancer, 7th edition. Surgical margins were defined as R0 (no cancer cells identified microscopically at the circular or linear, proximal or distal resection margin); R1 (cancer cells present microscopically at the linear or circular, proximal or distal resection margin); or R2 (tumor tissue seen at the circular or linear, proximal or distal resection margin on gross examination by the naked eye). According to the national clinical recommendations available at the time, adjuvant postoperative chemoradiation was offered to all patients with T3-T4/N0 and T1-T2/N+ tumors, except for patients treated with D2 lymph node dissection, who received only postoperative chemotherapy without RT.

Statistical analysis

For the purposes of this study, all available patients were included in the analysis. All patients were followed up until death or the final analysis of data. Categorical variables were summarized as absolute and relative (%) frequencies, whereas median and interquartile range (IQR) were used to summarize the distributions of continuous variables. Survival analysis techniques were used to summarize the time from diagnosis to death and to explore potential associations with demographic and clinical characteristics. More specifically, Kaplan-Meier survival curves and estimated cumulative probabilities of death were used for descriptive purposes, whereas the main analyses were based on univariable and multivariable Cox proportional hazards models and log-rank tests. Survival analyses were performed overall, as well as separately for individuals who underwent surgery and those who did not. No multivariable model was fitted to the subgroup of individuals who did not undergo surgery because of the small size of this group. Poisson modeling was used to explore the association between the number of lymph nodes excised and the year of diagnosis,

while adjusting for potential confounders. Differences in various clinical characteristics in relation to age (as a categorical variable with three groups) and sex were assessed through chi-square tests. All analyses were performed using Stata 10 (Stata Corp., TX USA).

Results

Patient characteristics and type of surgery performed

A total of 164 patients, 59 women and 105 men, were considered for GC resection at our institution between 2006 and 2010. The median age was 65 years (range 56-73). Surgical resection was performed as front-line treatment in 132 patients; 56 (42%) underwent total gastrectomy and 76 (58%) subtotal gastrectomy. Although at initial imaging all patients were considered eligible, further evaluation at the MDT meeting indicated metastatic disease in 32 patients (19.5%) with peritoneal (55%), lymph nodal (25%) or liver disease (20%), diverted from surgery. D0 gastrectomy was performed in 31 (23.5%), D1 in 62 (47%), D2 in 36 (27.3%), while 3 (2.3%) patients had a palliative operation.

Pathology data

T and N stages for all patients are shown in Table 1. Of the 132 patients operated, 92 (70%) had intestinal and 40 (30%) diffuse adenocarcinoma; 33 (25%) had proximal and 99 (75%) distal location; and 52 (39%) had vascular infiltration and 39 (29%) perineural invasion. An R0 resection was identified in 100 patients (75.8%), whereas R1 and R2 resection were recognized in 25 (18.9%) and 7 (5.3%) patients, respectively.

Adjuvant chemotherapy and RT data

Ninety-two of the 132 patients (70%) received adjuvant therapy (chemotherapy or chemoradiotherapy) based on the stage and according to the European Society of Medical Oncology's guidelines available at the time. Chemotherapy was offered to all but 1 patient, who did not undergo surgery because of advanced disease and significant comorbidities. There was a range of chemotherapy treatments applied in the adjuvant and metastatic setting, mainly 5FU, platinum and taxane-based as previously reported [9,10]. Postoperative RT was offered to 2 (6.3%) patients who did not receive surgical treatment for symptom palliation and to 24 (18.2%) patients who underwent resection and fulfilled the predefined criteria.

Survival outcomes

At the time of analysis, the median follow-up time was 114.8 months (range 4.4-195) and the median survival time

Table 1 Description of clinicopathologic characteristics of patients according to whether surgery was performed or not

Clinicopathologic characteristics	Surgery performed		
	No N (%)	Yes N (%)	Total N (%)
	32 (100.0)	132 (100.0)	164 (100.0)
Sex			
Female	13 (40.6)	46 (34.8)	59 (36.0)
Male	19 (59.4)	86 (65.2)	105 (64.0)
Age			
<50	3 (9.4)	17 (12.9)	20 (12.2)
50+	29 (90.6)	115 (87.1)	144 (87.8)
Type of surgery			
Total gastrectomy	0 (0.0)	56 (42.4)	56 (34.1)
Subtotal gastrectomy	0 (0.0)	76 (57.6)	76 (46.3)
Not performed	32 (100.0)	0 (0.0)	32 (19.5)
T stage			
T1	0 (0.0)	19 (14.4)	19 (11.6)
T2	0 (0.0)	19 (14.4)	19 (11.6)
T3	0 (0.0)	47 (35.6)	47 (28.7)
T4	32 (100.0)	47 (35.6)	79 (48.2)
N stage			
N0	0 (0.0)	40 (30.3)	40 (24.4)
N1	0 (0.0)	16 (12.1)	16 (9.8)
N2	0 (0.0)	23 (17.4)	23 (14.0)
N3a	0 (0.0)	27 (20.5)	27 (16.5)
N3b	0 (0.0)	26 (19.7)	26 (15.9)
Nx	32 (100.0)	0 (0.0)	32 (19.5)
Perineural infiltration			
No	0 (0.0)	93 (70.5)	93 (56.7)
Yes	0 (0.0)	39 (29.5)	39 (23.8)
NA	32 (100.0)	0 (0.0)	32 (19.5)
Vascular invasion			
No	0 (0.0)	80 (60.6)	80 (48.8)
Yes	0 (0.0)	52 (39.4)	52 (31.7)
NA	32 (100.0)	0 (0.0)	32 (19.5)
Resection margins			
R0	0 (0.0)	100 (75.8)	100 (61.0)
R1	0 (0.0)	25 (18.9)	25 (15.2)
R2	0 (0.0)	7 (5.3)	7 (4.3)
Surgery not done	32 (100.0)	0 (0.0)	32 (19.5)
Plane of nodal dissection			
D0	0 (0.0)	31 (23.5)	31 (18.9)
D1	0 (0.0)	62 (47.0)	62 (37.8)

(Contd...)

Table 1 *(Continued)*

Clinicopathologic characteristics	Surgery performed		
	No N (%)	Yes N (%)	Total N (%)
	32 (100.0)	132 (100.0)	164 (100.0)
D2	0 (0.0)	36 (27.3)	36 (22.0)
Not done	32 (100.0)	3 (2.3)	35 (21.3)
Chemotherapy			
No	1 (3.1)	40 (30.3)	41 (25.0)
Yes	31 (96.9)	92 (69.7)	123 (75.0)
Radiotherapy			
No	30 (93.8)	108 (81.8)	138 (84.1)
Yes	2 (6.3)	24 (18.2)	26 (15.9)

N, number of patients

was 47.6 months (95% confidence interval [CI] 27.5-70.5). For patients who underwent surgery, the median follow-up and survival times were 114.8 (range 5.1-195.0) and 100.3 (95%CI 54.0-195.0+) months, respectively. In contrast, the median follow-up and survival times in patients who did not undergo surgery were 27 (range 4.4-37.0) and 13 (95%CI 10.0-17.1) months, respectively. The survival time since diagnosis and by surgical margins, plane of nodal dissection and TNM, are shown in Table 2. The Kaplan-Meier survival curve in relation to surgical margin involvement is shown in Fig. 1A. The mean (95%CI) survival rates at 5 years post diagnosis for T3 and T4 were 57.4 (42.1-70.1) and 25.5 (14.2-38.5), whereas for N2, N3a and N3b they were 56.5 (34.3-73.8), 37.0 (19.6-54.6) and 15.4 (4.8-31.5), respectively. The mean (95%CI) survival at 5 years post diagnosis was 85.0 (69.6, 93.0), 81.3 (52.5-93.5), 56.5 (34.3-73.8), 37.0 (19.6-54.6) and 15.4 (4.8-31.5) according to the presence of 0, 1-2, 3-6, 7-15 and >16 infiltrated lymph nodes (Fig. 1B).

The mean (95%CI) survival at 5-years post diagnosis in relation to the absence or presence of vascular infiltration was 61.3 (49.7-70.9) and 48.1 (34.1-60.8), whereas for absence or presence of perineural invasion it was 61.3 (50.6-70.3) and 43.6 (27.9-58.3), respectively. The Kaplan-Meier survival curve according to TNM stage is shown in Fig. 1C.

The association of the surgical margin status with N stage revealed that there was a statistically significant difference (P<0.001) in the mean (95%CI) survival at 2 years post diagnosis between patients in the subgroup including R1/R2 & N0/N1/N2 [11.1 (0.6-38.8)] and those with R0 & N3 [83.3 (64.5-92.7)] disease. The respective Kaplan-Meier survival curves are shown in Fig. 1D.

On univariate Cox regression analysis of patients treated with surgery, T3 and T4 tumors, N2/N3 tumors, perineural infiltration, R1 and R2 resection, chemotherapy and RT were associated adversely with survival to a degree that reached statistical significance (Table 3). Radiotherapy was associated with increased risk of death but this finding was not confirmed in the multivariate analysis. On multivariate Cox regression

analysis, patients treated with surgery, T3 and T4 tumors, N3 stage, R1 and R2 resection reached statistical significance and remained independent negative prognostic factors for overall survival (Table 4).

Discussion

Data on the long-term survival of patients with GC initially considered to be resectable are important and provide a reference point for the evaluation of advanced therapeutic strategies. Our study provides findings concerning the epidemiologic, clinicopathologic and 10-year survival data of patients with potentially resectable GC. This is the first real-world data reporting on patient outcomes from Greece.

Our patients had a male-to-female ratio of 1.87. This is in agreement with a retrospective analysis of 534 patients with stage III GC from Taiwan [11]. The patients' median age and location rates (proximal vs. distal) were similar to those in previously reported prospective and retrospective studies of patients with resectable GC [12,13].

Adenocarcinoma subtypes were assessed according to the Lauren classification and the intestinal-to-diffuse rate was found to be similar to that in a recent study reporting on 534 patients from Taiwan [11]. Our study was not designed to identify survival benefit in relation to chemotherapy, but a recent report on a GC registry indicated that tumor classification according to Lauren predicted not only survival, but also response to chemotherapy, as docetaxel was associated with improved progression-free survival and overall survival in patients with intestinal adenocarcinoma [14]. The optimal combination and sequence of chemotherapy in the treatment algorithm is under intense investigation, but perioperative chemotherapy is currently gaining ground, particularly for T3/T4a and/or regional lymph node positive tumors [15]. In this context, preoperative FLOT, a docetaxel-based triplet chemotherapy, was compared to ECF/ECX anthracycline-based triplet chemotherapy and was found to be superior, as it was associated with significantly higher proportions of pathologic complete regression [15].

In the univariate analysis of our study, vascular and perineural invasion were found to be associated with an increased risk of death. This effect was not maintained in the multivariate analysis, most probably because of the small numbers of patients, but a previous study including 734 patients who underwent surgery indicated that both vascular and perineural invasion were independent prognostic factors for disease-free and overall survival [16].

Another important pathological aspect influencing the clinical outcome of GC patients was found to be microscopic and macroscopic tumoral infiltration of surgical margins. In the univariate analysis, both R1 and R2 resection were associated with a statistically significantly higher risk of death, an effect also maintained in the multivariate analysis as one of the most important predictors of relapse and death. It is well established that the effectiveness of surgery depends on the adequacy of the surgical procedures and on a cancer-free surgical margin

Table 2 Long-term survival outcomes of patients according to TNM stage, plane of nodal dissection and status of surgical resection margins

Clinicopathologic characteristics	% of patients alive (95% confidence interval)		
	36 months	60 months	120 months
pTNM stage			
IIA	93.8 (63.2, 99.1)	93.8 (63.2, 99.1)	93.8 (63.2, 99.1)
IIB	83.3 (48.2, 95.6)	66.7 (33.7, 86.0)	66.7 (33.7, 86.0)
IIIA	72.2 (45.6, 87.4)	44.4 (21.6, 65.1)	38.1 (16.6, 59.5)
IIIB	57.1 (39.3, 71.5)	34.3 (19.3, 49.8)	17.6 (6.6, 32.9)
IIIC	20.8 (7.6, 38.5)	16.7 (5.2, 33.7)	12.5 (3.1, 28.7)
Nodal dissection			
D0	71.0 (51.6, 83.7)	64.5 (45.2, 78.5)	60.2 (40.4, 75.3)
D1	67.7 (54.6, 77.8)	53.2 (40.1, 64.7)	49.7 (36.7, 61.4)
D2	69.4 (51.7, 81.8)	55.6 (38.1, 69.9)	41.4 (24.3, 57.7)
Not done	33.3 (0.9, 77.4)	0 (0, 0)	0 (0, 0)
Resection margins			
R0	90.0 (82.2, 94.5)	74.0 (64.2, 81.5)	65.4 (54.8, 74.2)
	12 months	18 months	24 months
R1	68.0 (46.1, 82.5)	32.0 (15.2, 50.2)	12.0 (3.0, 27.7)
R2	85.7 (33.4, 97.9)	42.9 (9.8, 73.4)	0.0 (0.0, 0.0)

Stage IA and IB are not shown as there were no deaths, HR was 0 and upper limit of confidence interval could not be estimated
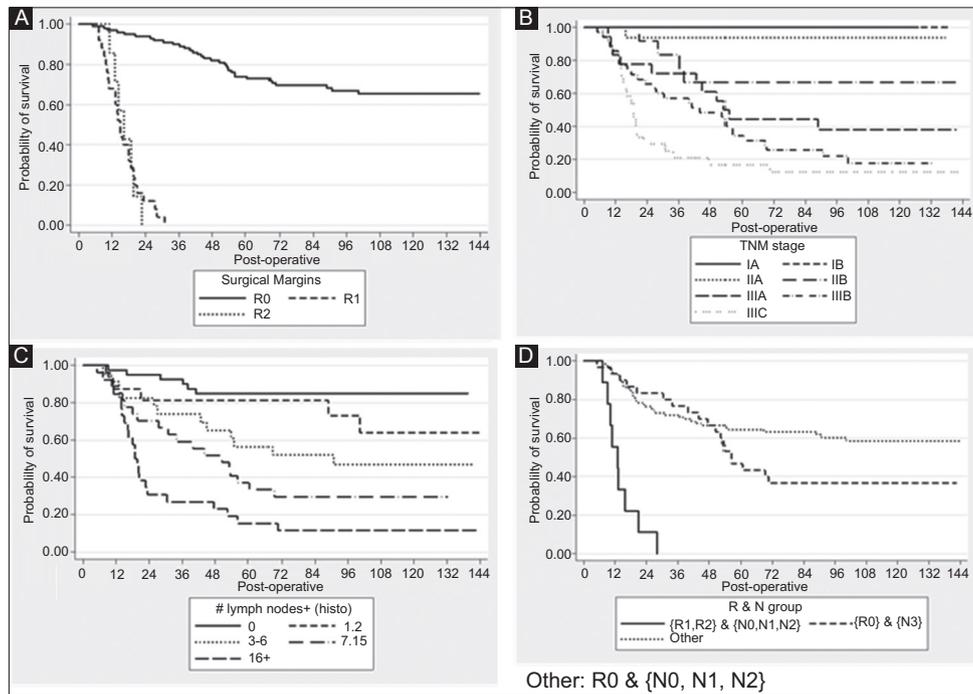

Figure 1 Kaplan-Meier survival curves according to: (A) infiltration of surgical margins; (B) number of involved lymph nodes; (C) TNM stages (7th AJCC edition); (D) resection margin (R0, R1, R2) and nodal (N0, N1, N2, N3) infiltration

specimen (R0), as patients with R1 or R2 resection have a mean survival of 8.7 months [17]. More importantly, the analysis of patients according to N stage and margin infiltration indicated that patients with margin infiltration had far worse survival

when compared to patients with N2 disease. Similarly to our study, achieving R0 resection was also found to be significant in a recent study including 82 patients with gastric cardia cancer and R1/R2 resection was found to be associated with

Table 3 Univariate cox regression analysis of prognostic factors in patients treated with surgery

Factor	Hazard ratio	95% confidence interval	P-value
Sex			
Female	0.98	(0.58, 1.63)	0.925
Male*	1		
Age			
<50*	1		
50+	1.05	(0.52, 2.12)	0.901
Type of surgery			
Total gastrectomy*	1		
Subtotal gastrectomy	0.63	(0.39, 1.03)	0.064
T stage			
T2*	1		
T3	3.77	(1.13, 12.61)	0.031
T4	10.39	(3.20, 33.76)	<0.001
N stage			
N0*	1		
N1	2.24	(0.68, 7.33)	0.184
N2	4.26	(1.60, 11.35)	0.004
N3a	6.85	(2.73, 17.20)	<0.001
N3b	13.24	(5.33, 32.89)	<0.001
Perineural infiltration			
No*	1		
Yes	1.76	(1.07, 2.91)	0.026
Vascular invasion			
No*	1		
Yes	1.59	(0.98, 2.59)	0.062
Resection margins			
R0*	1		
R1	35.01	(15.37, 79.75)	<0.001
R2	35.48	(12.11, 103.95)	<0.001
Plane of nodal dissection			
D0	1		
D1	1.36	(0.70, 2.66)	0.363
D2	1.49	(0.73, 3.05)	0.278
Not done	2.61	(0.58, 11.69)	0.210
Chemotherapy			
No*	1		
Yes	21.17	(5.17, 86.69)	<0.001
Radiotherapy			
No*	1		
Yes	1.84	(1.04, 3.23)	0.035

* Reference group

T1 stage is not shown as there were no deaths, HR was 0 and upper limit of confidence interval could not be estimated

Table 4 Multivariate cox regression analysis of prognostic factors in patients treated with surgery

Factor	Hazard ratio	95% confidence interval	P-value
Age			
per 10 years	0.98	(0.79, 1.22)	0.854
Sex			
Female	0.92	(0.50, 1.68)	0.781
Male*	1		
T stage			
T2*	1		
T3	1.91	(0.53, 6.85)	0.322
T4	3.32	(0.93, 11.86)	0.064
N stage			
N0*	1		
N1	1.80	(0.51, 6.32)	0.357
N2	2.51	(0.83, 7.53)	0.102
N3	2.95	(1.11, 7.85)	0.030
Resection margins			
R0*	1		
R1	20.98	(8.37, 52.60)	<0.001
R2	15.39	(4.57, 51.82)	<0.001
Plane of nodal dissection			
D0	1		
D1	0.77	(0.35, 1.73)	0.532
D2	0.82	(0.33, 2.01)	0.660
Not done	1.36	(0.25, 7.45)	0.726

* Reference group

T1 stage is not shown as there were no deaths, HR was 0 and upper limit of confidence interval could not be estimated

a 5-year survival rate of 13% [18]. Achieving an R0 resection is of the utmost importance, but is not always feasible. Twelve studies included in a systematic review, reporting on a total of 15,008 patients, indicated that intraoperative frozen sections should be performed to achieve a negative margin with intraoperative re-excision and that surgical re-excision of an R1 resection should be considered for patients with fewer than three disease-positive nodes, because survival is more likely to be governed by positive margins than by nodal status [19]. However, although management of the surgical margin seems to be of paramount importance in the early stage, at a later stage of the disease, when additional adverse pathologic characteristics (such as N3 disease) are present and ultimately determine patients' outcomes, the decision to extend a resection to achieve a cancer-free resection margin should be considered carefully and personalized [20].

The univariate analysis of this study found signs of a possible negative association of RT with survival. This is somewhat misleading, as most patients receiving RT had positive lymph nodes or infiltrated surgical margins and thus a more

unfavorable disease prognosis. Despite several clinical studies, the role of RT in resected GC remains controversial [8,9,21]. A previous study from Europe that randomized patients with histologically proven, radically resected GC, stage ≥T3 and ≥N1, to receive 6 cycles of docetaxel with cisplatin, both at 75 mg/m^2 every 3 weeks (arm A), or the same treatment with RT (45 Gy; arm B) showed no differences in overall and disease-free survival between the two arms. [9]. Similarly no survival benefit was found in the ARTIST trial from Korea, which randomized patients with resected GC to receive 6 cycles of capecitabine 1000 mg/m^2 twice a day on days 1 to 14 and cisplatin 60 mg/m^2 on day 1 every 3 weeks (arm A), or two cycles of the same chemotherapy followed by RT 45 Gy concurrently with capecitabine 825 mg/m^2 twice a day, followed by two additional cycles of chemotherapy (arm B) [21]. The USA 0116 SWOG-directed intergroup trial randomized patients to surgery alone (arm A) or postoperative chemoradiotherapy, including bolus 5FU 425 mg/m^2/d and leucovorin 20 mg/m^2/d on days 1 through 5 before, during, and after RT to a total of 45 Gy (1.8 Gy/d 5 d/wk for 5 weeks), targeting common locoregional failure sites such as the tumor bed, regional nodes, and anastomoses [8]. Two major differences between the later study and the previous ones were the administration of 5FU-based chemotherapy and the inclusion of 85% of patients with N1-N3 disease (only 10% of patients had D2 dissection). An important randomized study, which aims to compare TS-1 (40-60 mg b.i.d.; 4 weeks - 2 weeks off; 8 cycles), TS-1 (40-60 mg b.i.d.; 2 weeks - 1 week off) + oxaliplatin (130 mg/m^2 q 3 weeks) both for 8 cycles, with or without RT (45 Gy in 5 weeks) in D2 resected GC, is currently underway to shed light on the need for RT in optimally resected patients (ClinicalTrials.gov Identifier: NCT01761461).

Our study has some limitations, as it included only a small number of patients in each subgroup. In our analysis, we identified 34 patients with stage I-II GC who were not treated with nodal dissection. This D0 subgroup had a 10-year survival benefit of 60%, significantly greater than the D1 and D2 survival values achieved. This result is misleading and should be interpreted with caution, as the subgroup of patients with stage I-II and lymph node negative disease had a better natural history and survival [22]. Based on the patient's performance status and clinical evidence, D1 or D2 resection represents the recommended surgical procedure [23]. Likewise, as our analysis included patients with T1-T2 and node-negative disease who did not receive chemotherapy or RT, overall patient survival was better among those not treated with chemotherapy or RT than in those who were treated, a misleading effect due to the better prognosis of this subgroup of patients.

Notwithstanding the evolution of endoscopic and surgical techniques, improved molecular targeted therapies and chemoradiation, GC remains a leading cause of death worldwide. Multimodal planning of GC management, including surgeons, medical and radiation oncologists, radiologists and pathologists, is imperative and of cardinal importance. Despite improvements in radical resection with tumor-free margins and extended lymph node dissection, patients' survival prospects remain poor. The prognosis of GC is influenced by a variety of additional tumor-, patient- and

therapy-related factors, such as involvement of the surgical margins, lymphovascular invasion, number of lymph nodes involved and molecular signature, regardless of the type of lymphadenectomy [3]. Molecular studies have yielded a vast quantity of new information for the potential exploitation of novel molecules targeting the different GC subtypes [24,25]. Three randomized studies (the Dutch, the FLOT4/AIO and the CRITICS studies) have provided proof of the superiority of perioperative administration of FLOT regimen and gastrectomy with D2 lymphadenectomy over adjuvant postoperative chemoradiotherapy [7,15,26]. These findings offer new therapeutic options expected to supersede the 0116 SWOG trial protocol, the previous standard of care, including adjuvant chemoradiotherapy [8]. Finally, as detailed immune profiling of GC is yielding promising results, early studies with immune checkpoint inhibitors in advanced disease suggest that GC may be amenable to immune modulation [27,28].

Our study provides additional information about the survival of patients with GC, treated in a real-world environment, and confirms the importance of TNM staging for survival, as more advanced tumors (T4, N2 and N3) were

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Summary Box

What is already known:

- Gastric cancer (GC) remains the fifth most frequent cancer and the third cause of cancer-related deaths worldwide
- The heterogeneity in the incidence of GC among countries is due to differences in fresh product consumption, salt-preserved foods, obesity, alcohol intake, smoking, incidence of *Helicobacter pylori* infection and genetic predisposition, such as *cadherin 1* gene mutation
- Since 1991, the cornerstone of treatment in GC has been gastrectomy with lymphadenectomy, followed by adjuvant chemoradiotherapy, according to the USA 0116 SWOG-directed intergroup trial
- The identification of GC molecular subtypes defines sets of patients (Epstein-Barr Virus positive, microsatellite unstable, genomically stable and chromosomally unstable) for targeted therapy trials

What the new findings are:

- Gastrectomy with D1 or D2 lymphadenectomy, significantly improves the survival of patients with GC and is the optimal surgery for patients with resectable GC
- Microscopic and macroscopic infiltration of surgical margins are the worst negative prognostic factors for survival. Achieving R0 surgical resection is of the utmost importance

found to be associated with worse outcomes on multivariate analysis. Inclusion criteria and analyses of future clinical trials must reevaluate the role of surgery, RT and chemotherapy in relation to tumor location, Lauren histology and the newly developed molecular profiling, as reported in the seminal Cancer Genome Atlas Study.

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