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Research Article

Resection Margins in Gastric Cancer: Risk Factor Analysis for Recurrence and Survival

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Abstract

Introduction: The association between resection margin status, resection margin distance and tumour recurrence and survival have been a matter of debate over the years.

Materials and Methods: This retrospective cohort study involves patients diagnosed with histologically confirmed gastric or esophagogastric junction cancer, who underwent curative surgery over a span of five years at a tertiary care center. All participants were followed for a minimum duration of five years.

Results: Ninety-six patients were included. 5% had R1 status: one with proximal positive margin, one with lymphatic invasion on the distal margin and three with distal margin invasion. No association was found between positive distal margin and distal margin distance (p=0.520). Recurrence rate was 34%, mainly presenting as peritoneal or locoregional disease. After using Cox Regression, tumour location, R1 status and perineural infiltration were associated with recurrence. Overall survival rate at 1- and 5-year were 80.1% and 54.2%, respectively. Increasing age (p=0.005; HR: 1,044 (95% CI: 1.01-1.08), positive margins (p=0.048; HR: 2.92 (95% CI: 1.01 - 8.44)) and recurrence (p=<0001; HR: 6,02 (95% CI: 2,87 - 12,6)) were associated with mortality. The 1- and 5-year recurrence free survival rate were 70.8% and 51.0%, respectively. Increasing age (p=0.018; HR: 1.032 (95% CI: 1.01-1.06)), positive margins (p=0.011; HR: 3.76 (95% CI: 1.36 - 10.41)) and advance stage (III-IV) (p=0.007; HR: 2.35 (95% CI: 1.26 - 4.35)) were associated with event occurrence.

Discussion and Conclusion: R0 resection is an important prognostic factor and should be achieved, although predicting this based only on the macroscopic resection margin distance seems difficult.

Keywords: Disease free survival; Gastric cancer; Overall survival; Recurrence; Resection margins

Introduction

Gastric cancer is the fifth most frequently diagnosed cancer and the 3rd leading cause of cancer-related deaths worldwide, contributing to over 768.000 deaths in 2020 [1]. Its incidence has a wide geographic variation, with a decreasing incidence over the years in Western Europe and the United States, and a high incidence in Japan and Korea, where it is the most diagnosed cancer in males [1].

Globally, gastric cancer has a poor prognosis since it's mostly diagnosed in an advanced stage.[1] Patients treated with curative intent have a 5-year survival rate of 70% for stage I resected disease but less than 30% for stage IIB and beyond [2]. Despite the improvement of outcomes in advanced gastric cancer related to the use of perioperative chemotherapy, surgical resection remains the only potentially curative treatment. [3] Surgical technique, Resection Margins (RM) and the extent of lymphadenectomy are important factors for patient outcomes [3]. Complete resection with negative margins (R0) is the primary goal of surgery in gastric cancer [1] Defining the minimum adequate RM to ensure negative margins has proven difficult, with several studies showing conflicting results [4-6]. The aim of this study was to determine the association between margin status and RM distance to the tumour and margin status and recurrence, Disease Free Survival (DFS) and Overall Survival (OS).

Material and Methods

This retrospective study included patients with histologically proven gastric or esophagogastric junction cancer, followed during a 10-year period (January 2011 - December 2020), who underwent surgery with curative intent between January 2011 and December 2015, in a tertiary center. Exclusion criteria were lymphadenectomy other than D2, R2 resection, histological diagnosis different from adenocarcinoma, Type I adenocarcinoma of the esophagogastric junction according to the Siewert classification [7] and follow up less than 5 years. The following demographic, clinical and pathological variables were recorded for each patient and inserted in a computerized database: age, sex, clinical TNM classification, neoadjuvant chemotherapy, type of gastrectomy, multivisceral resection, margin status, margin distance, tumour location, tumour diameter, tumour grade, T category, N category, Lauren pattern, WHO classification, lymphatic, vascular and perineural infiltration (LVI and PNI), pathological TNM classification, timing and site of recurrence, RFS and OS. Information was extracted from the clinical records. In addition, histological confirmation analysis of some of the specimens was performed to complete and standardize values. For this study, the minimum follow-up was 5 years or until death to determine RFS and OS.

Proximal and distal Resection Margin (RM) were defined as the shortest distance between the tumour, at the most proximal or distal end, to each resection line macroscopically, measured on formalin-fixed surgical specimens by pathologists. A negative RM (R0 resection) was defined as the complete absence of both macroscopic and microscopic tumour involvement at the resection line on histopathology assessment. A microscopically positive RM (R1 resection) was defined as the presence of viable singular tumour cells or cell aggregates at the line of resection on histopathology assessment, in the absence of visible tumour involvement of the resection line. Cancer staging was based on the American Joint Committee on Cancer TNM classification, 8th edition. [8] Time to recurrence was calculated from the date of surgery to the date of recurrence diagnosis. Recurrence was classified as locoregional (anastomosis site, remaining stomach, gastric bed, regional lymph nodes, adjacent organ or paraaortic lymph node), hematogenous (distant organs), peritoneal (peritoneal seeding or Krukenberg's tumour) and mixed. OS rate was computed as the percentage of patients in the study who were alive at the 1-, 3- and 5 year-mark after surgery. RFS rate was calculated as the percentage of patients in the study who were alive and without recurrence at the 1-, 3- and 5 year-mark.

Statistical Analysis

Categorical data are presented as the percent proportion; continuous data are presented as the mean ± Standard Deviation (SD) or median ± Interquartile Range (IQR) depending on its distribution. To compare differences in categorical data between two groups, Fisher's exact test or the Chi-Square test was used, as appropriated. The Unpaired T Student t-test for independent samples was used to compare continuous data between two groups. Survival and recurrence analysis was made using the Kaplan-Meier Method (LogRank test) for categorical data and Univariate Cox Regression for continuous data. All variables found to be statistically significant were subsequently included in a multivariate Cox regression model to determine their weight predicting recurrence or survival. When both N category and pTNM classification were statistically significant, only pTNM classification was maintained. Hazard Ratio (HR) and 95% confidence intervals (95% CI) were presented. All analyses were two-sided, and statistical significance was defined as $p<0.05$. Statistical analyses were performed with the IBM SPSS Advance Statistics 28.0 package.

Results

Ninety-six patients were included in the study, 56 (58.3%) of which were male, with a mean age of 70±12 years old. Most patients (n=45 (46.9%)) had stage III disease, 18 (18.8%) were treated with neoadjuvant chemotherapy, 55 (57.2%) patients had

tumours located at the antrum and 54 (56.3%) underwent subtotal gastrectomy. Positive margins (R1) were present in 5 (5.2%) of the patients: 1 with proximal margin invasion (a patient with a tumour located on the cardia who underwent total gastrectomy), 3 with distal margin invasion (1 patient with a tumour located on the antrum who underwent total gastrectomy, 1 patient with an antrum tumour who underwent subtotal gastrectomy with multivisceral resection and 1 patient with a tumour located on the gastric body who underwent total gastrectomy) and 1 with lymphatic invasion on the distal margin. Since only one patient presented R1 due to proximal positive margin (distance: 3mm), it was not possible to test the association between proximal margin distance and margin status. Mean proximal R0 distance was 41±40mm. Mean distal margin distance in R0 patients was 41±29mm and in R1 due to distal margin involvement was 27±12mm. No statistical difference was found between the medians of R0 and R1 patients (p=0,520). Table 1 resumes demographic, clinical and histopathological characteristics of positive and negative margin groups. The distribution is homogeneous for most characteristics except for Lauren pattern, WHO classification, pTNM classification and recurrence.

Variable		Positive margin	Negative margin	p value	With Recurrence	Without recurrence	p value
Age (mean ± SD)		77 ± 14	71 ± 12	0.21	72 ± 13	69 ± 12	0.088*
Sex (n)	Male	4	52	0.397	20	36	0.222
	Female	1	39		13	27	
BMI (mean ± SD) (kg/m^2)		21 ± 3	24 ± 4	0.074	23 ± 4	24 ± 3	0.719*
Neoadjuvant treatment (n)	Yes	0	18	0.58	6	12	0.739
	No	5	73		27	51	
Type of gastrectomy (n)	Subtotal	2	52	0.715	17	37	0.744
	Total	3	39		16	26	
With multivisceral resection (n)		6	1	0.201	4	3	0.102
Tumour location (n)	Cardia	1	2	0.434	3	0	**0.007**
	Fundus	0	5		1	4	
	Body	1	16		13	18	
	Antrum	2	53		16	39	
	Multicentric	0	2		0	2	
Proximal margin distance (mean ± SD) (mm)		-	40±35		41 ± 25	41 ± 26	0.907*
Distal margin distance (mean ± SD) (mm)		27±12	40±29	0.52	25 ± 38	35 ± 43	0.819*
Tumour diameter (mean ± SD) (mm)		59 ± 24	41 ± 26	0.093	43 ± 27	44 ± 43	0.966*
Margin Status (n)	R0	-	.	-	29	62	**<0.001**
	R1	-	-		4	1	
Tumour grade (n)	G1	0	19	0.181	2	17	**0.031**
	G2	0	33		11	22	
	G3	5	35		19	21	
	Gx	0	3		1	3	

pT category (n)	T0 / Tis	0	2	0.221	1	1	0.172
	T1	0	21		6	15	
	T2	0	22		5	17	
	T3	2	35		13	24	
	T4	3	11		8	6	
N category (n)	N0	1	44	0.365	7	38	**<0.001**
	N+	4	46		26	24	
Lauren pattern (n)	Intestinal	0	55	**0.013**	15	40	**<0.001**
	Diffuse	4	19		16	7	
	Mixed	0	5		0	5	
	Indetermined	1	12		2	11	
WHO classification (n)	Tubular	0	50	**0.033**	11	39	**<0.001**
	Papillary	0	6		5	1	
	Mucinous	0	3		0	3	
	Poorly cohesive	4	21		16	9	
	Uncommon variants	1	11		1	11	
LVI (n)	Yes	5	54	0.153	25	34	**0.032**
	No	0	37		8	29	
PNI (n)	Yes	5	45	0.058	7	38	**<0.001**
	No	0	45		7	38	
pTNM classification (n)	Stage I-II	1	67	**0.024**	16	52	**<0.001**
	Stage III-IV	4	24		17	11	
With recurrence (n)		4	29	**0.046**			
Timing of recurrence (months)		7 ± 3	18 ± 13	**0.029**			
Site of recurrence (n)	Locoregional	3	8	0.426			
	Hematogenous	0	7				
	Peritoneal	1	11				
	Mixed	0	3				

*Significance value of the model; BMI: Body Mass Index; LVI: Lymphovascular invasion; PNI: Perineural infiltration; WHO: World Health Organization.

Table 1: Demographic, clinical and histopathological characteristics of positive and negative margin groups and associated with recurrence.

Recurrence Analysis

The median follow-up was 56.5 months (IQR: 18-63.5 months); during this period, 44 deaths (45.8%) and 33 recurrences (34%) were registered, presenting mainly as peritoneal (36%) or locoregional (33%) disease. Table 1 summarizes the univariate analysis of demographic, clinical and histopathological associations with recurrence.

Mean proximal margin distance was 41±26mm in patients without recurrence and 41±25mm in patients with recurrence. There was no statistical difference between recurrence depending on proximal margin distance (p=0.907). Patients were also divided in 4 groups depending on proximal margin distance (<2cm, ≥2cm and <3cm, ≥3cm and <5cm and ≥5cm); no statistical difference between groups was found relating to recurrence (p=0.387).

Median distal margin distance was 35±43mm in patients without recurrence and 25±38mm in patients with recurrence. There was no statistical difference between median distal margin distance between patients with or without recurrence (p=0.819). Tumour location (p=0.007), margin status (p=<0.001), pN (p<0.001), pTNM classification (p<0.001), OMS classification (p<0.001), Lauren classification (p<0.001), tumour grade (p=0.031), PNI (p=<0.001) and LVI (p=0.032) had a statistically significant association with recurrence.

Cox regression analysis was employed to study the weight of each variable when predicting recurrence. Table 2 shows the Cox regression coefficient, Wald test, HR and 95% CI for each predictor. Tumor location, positive margins and PNI were associated with recurrence. Tumours located in the fundus (p=0.017; HR: 0.017 (95% CI: 0.001-0.49)), body (p=0.030; HR: 0.056 (95% CI: 0.004-0.75)) and antrum (p=0.026; HR: 0.050 (95% CI: 0.004-0.70)) were less associated with recurrence than tumours located in the cardia. Patients with positive margins (p=0.035; HR: 3.85 (95% CI: 1.10 - 13.45)), had four times more recurrence than the remaining patients. Perineural infiltration (p=0.013; HR: 5.43 (95% CI: 1.43-2062)) was five times more associated with recurrence than patients without PNI.

Predictor		B	Wald χ^2	p	Hazard ratio	95% CI
Tumour location	Cardia	Ref.	6.05	0.109	Ref.	Ref.
	Fundus	-4.08	5.65	**0.017**	**0.02**	**0.001-0.49**
	Body	-2.88	4.73	**0.030**	**0.06**	**0.004-0.75**
	Antrum	-2.99	4.93	**0.026**	**0.05**	**0.004-0.70**
	Multicentric	-	-	-	-	-
Margin status (R1)		1.35	4.45	**0.035**	3.85	1.10-13.45
Advanced stage (Stage III-IV)		0.66	1.60	0.207	1.93	0.70-5.35
WHO classification	Tubular	Ref.	1.09	0.896	Ref.	Ref.
	Papillary	0.10	0.02	0.892	1.11	0.26-4.77
	Mucinous	-8.43	0.01	0.938	0	-
	Poorly cohesive	-7.56	0.01	0.932	0.01	-
	Uncommon variants	-1.64	0.99	0.319	0.20	0-4.87
Lauren classification	Intestinal	Ref.	0.08	0.994	Ref.	Ref.
	Diffuse	9.34	0.01	0.916	-	-
	Mixed	-7.59	0.02	0.898	0	-
	Indetermined	0.38	0.05	0.819	1.46	0.06-39.23
Tumour grade	G1	Ref.	4.82	0.090	Ref.	Ref.
	G2	1.47	2.77	0.096	4.37	0.77-24.75
	G3	-0.72	0.47	0.492	0.49	0.06-3.82
LVI (yes)		-0.41	0.44	0.505	0.66	0.19-2.25
PNI (yes)		1.69	6.18	**0.013**	**5.43**	**1.43-20.62**

LVI: Lymphovascular invasion; PNI: Perineural infiltration; WHO: World Health Organization

Table 2: Cox regression predicting recurrence using tumour location, margin status, tumour stage, WHO classification, Lauren classification, tumour grade, LVI and PNI.

Survival Analysis

The 1-, 3-, and 5-year OS rate of the entire series were 80.1%, 59.4% and 54.2% (Figure 1), respectively, while the 1-, 3- and 5-year were RFS 70.8%, 54.2% and 51.0% (Figure 2). Table 3 resumes the univariate analysis of demographic, clinical and histopathological associations with OS. Mean proximal margin distance was 40±26mm in alive patients in 5-years OS and 41±25mm in deceased patients in OS. There was no statistical difference between proximal margin distance between both groups (p=0.969). After further division in 4 groups depending on proximal margin distance as previously described, proximal margin distance remained without statistically significant difference between groups (p=0.401). Median distal margin distance was 40±37mm in alive patients in OS and 40±44mm in deceased patients. There was no statistical difference between median distal margin distance in patients with or without recurrence (p=0,935). Age (p=0.002), Margin status (p=<0.001), pN (p=0.007), pTNM stage (p=<0.001), PNI (p=0.024) and recurrence (p=<0.001) were associated with OS. Cox regression analysis was employed to study the weight of each variable when predicting OS.

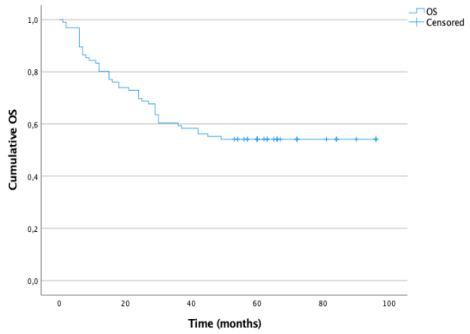

Figure 1: Overall Survival (Kaplan-Meier curves).

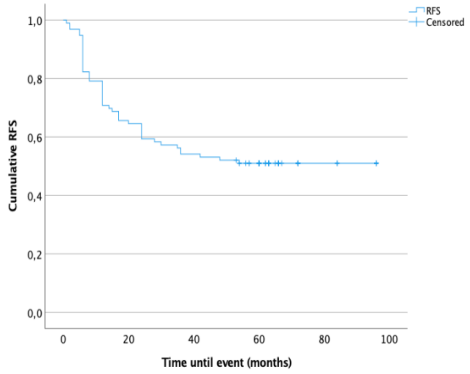

Figure 2: Recurrence Free Survival (Kaplan-Meier curves).

Variable		1 yr-OS rate (%)	3 yr-OS rate (%)	5 yr-OS rate (%)	p value
Age		-	-	-	0.002*
Neoadjuvant treatment	Yes	83.3	72.2	72.2	0.134
	No	79.5	56.4	50. 0	
Type of gastrectomy	Subtotal	77.8	59.3	55.6	0.668
	Total	85.7	59.5	53.4	
Multivisceral resection	Yes	57.1	42.9	42.9	0.341
	No	82.0	60.7	55.1	

Tumour location	Cardia	33.3	33.3	33.3	0.127
	Fundus	80.0	60.0	60.0	
	Body	60.6	51.6	45.2	
	Antrum	81.8	65.5	61.8	
	Multicentric	50.0	50.0	0	
Proximal margin distance (mm)		-	-	-	0.969*
Distal margin distance (mm)		-	-	-	0.935*
Tumour diameter (mm)		-	-	-	0.800*
Margin status	R0	83.5	62.6	57.1	<0.0001
	R1	20.0	0	0	
Tumour grade	G1	84.2	78.9	78.9	0.082
	G2	78.8	51.5	45.5	
	G3	77.5	55.0	47.5	
pT category	T0 / Tis	100	100	100	0.189
	T1	90.5	66.7	66.7	
	T2	68.2	54.5	45.5	
	T3	86.5	59.5	56.8	
	T4	64.3	50.0	35.7	
N category	N0	84.4	71.1	68.9	0.007
	N+	76.0	48.0	40.0	
Lauren pattern	Intestinal	83.6	60.0	56.4	0.159
	Diffuse	73.9	47.8	34.8	
	Mixed	80.0	80.0	80.0	
	Indetermined	76.9	69.2	69.2	
WHO classification	Tubular	80.0	60.0	56.0	0.220
	Papillary	100	33.3	33.3	
	Mucinous	66.7	66.7	66.7	
	Poorly cohesive	76.0	52.0	40.0	
	Uncommon variants	83.3	83.3	83.3	
LVI	No	83.8	67.6	64.9	0.105
	Yes	78.0	54.2	47.5	
PNI	No	84.4	68.9	66.7	0.024
	Yes	76.0	50.0	44.0	
pTNM classification	Stage I-II	83.8	67.6	64.7	<0.001
	Stage III-IV	71.4	39.3	28.6	
Recurrence	No	85.7	79.4	77.8	<0.001
	Yes	69.7	21.2	9.1	

* Significance value of the model; LVI: Lymphovascular invasion; PNI: Perineural infiltration; WHO: World Health Organization.

Table 3: Demographic, clinical and histopathological associations with OS.

Table 4 shows the COX regression coefficient, Wald test, OR and 95% CI for each predictor. Age, positive margins, and recurrence were associated with OS. Increasing age (p=0.005; HR: 1,044 (95% CI: 1.01-1.08)) was associated with more mortality. Positive margins (p=0.048; HR: 2.92 (95% CI: 1.01 - 8.44)) and recurrence (p=<0001; HR: 6,02 (95% CI: 2,87 - 12,6)) had an almost 3-fold and 6-fold increase of mortality, respectively. Table 5 resumes the univariate analysis of demographic, clinical and histopathological associations with RFS. Mean proximal margin distance was 41±26mm in RFS patients and 41±25mm in patients with recurrence or deceased. There was no statistical difference between proximal margin distance between groups (p=0.977). After division in 4 groups depending on proximal margin distance (same as previously explained), the variable remained without statistical significance (p=0.394). Median distal margin distance was 30±31mm in event-free patients and 30±47mm in patients with recurrence or deceased. There was no statistical difference between median distal margin distance in patients with or without recurrence (p=0.795). Age (p=0.015), positive margins (p=<0.001), pTNM stage (p=<0.001), tumour location (p=0.012), OMS classification (p=0.033), Lauren classification (p=0.026), LVI (p=0.040), PNI (p=0.004) and pN (p=<0.001) were associated with RFS.

Predictor	B	Wald χ^2	p	Hazard ratio	95% CI
Age	0.04	7.87	**0.005**	**1.04**	**1.01 - 1.08**
Margin status (R1)	1.07	3.90	**0.048**	**2.92**	**1.01 - 8.44**
Advanced stage (Stage III-IV)	0.44	1.72	0.190	1.56	0.80 - 3.03
PNI	0.00	0.00	0.995	1.00	0.50 - 2.02
Recurrence	1.80	22.53	**<0.001**	**6.02**	**2.87 - 12.64**

Table 4: Cox regression predicting overall survival from recurrence, PNI, margin status, pTNM stage and Lauren classification.

Variable		1 yr-RFS rate (%)	3 yr-RFS rate (%)	5 yr-RFS rate (%)	p value
Age		-	-	-	0.015*
Neoadjuvant treatment	Yes	72.2	72.2	60.6	0.323
	No	70.5	50.0	48.7	
Type of gastrectomy	Subtotal	72.2	57.4	55.6	0.583
	Total	69.0	50.0	42.9	
Multivisceral resection	Yes	42.9	42.9	42.9	0.417
	No	73.0	55.1	51.7	
Tumour location	Cardia	33.3	33.3	0	0.012
	Fundus	100	60.0	60.0	
	Body	64.5	41.9	38.7	
	Antrum	74.5	61.8	61.8	
	Multicentric	100	100	0	
Proximal margin distance (mm)		-	-	-	0.977*
Distal margin distance (mm)		-	-	-	0.795*
Tumour diameter (mm)		-	-	-	0.904*
Margin status	R0	74.7	57.1	53.8	0.001
	R1	0	0	0	

Tumour grade	G1	78.9	73.7	73.7	0.119
	G2	72.7	48.5	45.5	
	G3	65.0	47.5	42.5	
pT category	T0 / Tis	50.0	50.0	50.0	0.317
	T1	85.7	66.7	66.7	
	T2	63.6	50.0	45.5	
	T3	73.0	56.8	51.4	
	T4	57.1	35.7	35.7	
N category	N0	80.0	68.9	68.9	<0.001
	N+	62.0	40.0	33.9	
Lauren pattern	Intestinal	78.2	58.2	54.5	0.026
	Diffuse	52.2	30.4	26.1	
	Mixed	80.0	80.0	80.0	
	Indetermined	69.2	69.2	69.2	
WHO classification	Tubular	76.0	58.0	56.0	0.033
	Papillary	66.7	33.3	16.7	
	Mucinous	66.7	66.7	66.7	
	Poorly cohesive	56.0	36.0	32.0	
	Uncommon variants	83.3	83.3	83.3	
LVI	No	78.4	64.9	64.9	0.040
	Yes	66.1	47.5	42.4	
PNI	No	82.2	66.7	66.7	0.004
	Yes	60.0	42.0	38.0	
pTNM classification	Stage I-II	80.9	64.7	60.3	<0.001
	Stage III-IV	46.4	28.6	28.6	

* Significance value of the model; LVI: Lymphovascular invasion; PNI: Perineural infiltration; WHO: World Health Organization.

Table 5: Demographic, clinical and histopathological associations with RFS.

Cox regression analysis was used to study the weight of each variable when predicting RFS. The model including these variables had no statistical significance (p=1). After testing several models, the most significant model contained age, margin status and pTNM stage. Increasing age (p=0.018; HR: 1.032 (95% CI: 1.01-1.06)) was associated with more mortality. Positive margins (p=0.011; HR: 3.76 (95% CI: 1.36 - 10.41)) and advance stage (III-IV) (p=0.007; HR: 2.35 (95% CI: 1.26 - 4.35)) had an almost 4-fold and 2-fold decrease of RFS, respectively.

Discussion

The adequate resection margin has been a question of debate for years. A margin of at least 6cm was firstly believed to be necessary [4], but recent studies have showed that shorter margins can achieve similar prognostic results. The 2018 Japanese Guidelines recommend a proximal margin of 2, 3 or 5 cm depending on tumour location, growth pattern and depth of invasion [9]. NCCN Guidelines are less clear about the ideal margin, stating that the primary goal of surgery is complete resection with negative microscopic margins (R0) along with lymphadenectomy, with T4b tumours requiring en bloc resection of involved structures [1]. ESMO Guidelines recommend a proximal margin of ≥3cm for tumours with an expansive growth pattern (including intestinal histotypes) and ≥5cm for those with an infiltrative growth pattern (including poorly cohesive/diffuse histotypes); if this margin cannot be assured, frozen section is recommended [10]. These differences between recommendations show the heterogeneous results described in literature. Disparities between the association of positive margins and survival have been reported, with some studies claiming no association [11-13] while others report worst survival if positive margins. [5,14-18] Articles reporting that this relation depends on the tumour stage can also be found, with reports maintaining this association only in advanced gastric cancer (≥T3 or N+) [19-21] or the opposite, claiming that margin status only affects prognosis in early disease with negative nodes [22-26]. The results obtained in this study are concordant with some of the literature, with positive margins remaining an independent risk factor for recurrence, OS and RFS, while distal and proximal margin distance per se has no association with neither of those.

The impact of positive margins in OS remains even when we add recurrence to our model, maintaining its independent weight, decreasing the OS almost 3-fold and RFS almost 4-fold. As such, the effort to assure negative margins whenever possible must be made. Although our results fail to corroborate the association between margin distance and negative margins, some authors have proposed a secure margin distance. [3-5] Whenever possible, frozen section should also be used to confirm negative margins [27]. Although it has some limitations, such as not being routinely available and being time and resource consuming, it still represents the safest way to ensure negative margins. [5] Intraoperative frozen section also aids decision making during the surgical procedure. If margins are positive, resection may be extended, or the procedure altered from a subtotal to a total gastrectomy.

Although authors differ in opinions regarding the advantage of extending the resection during surgery [12], or even which patients benefit from re-excision [15,28,29], the evidence is piling towards avoiding positive margins.

The association between cardia tumours and recurrence found in this study has also been previously found, [30,31] with some authors describing a worse OS and RFS for upper third tumours [32,33]. Several limitations can be pointed to this study. It is a retrospective, single-center observational study, that considers a period of 10 years, during which changes in the clinical management of gastric cancer and in surgical technique occurred. The advances in perioperative treatment due to the MAGIC [34] and then FLOT [35] trials aren't reflected by our population, as demonstrated by the low number of patients submitted to perioperative treatment. Our limited sample size and the low number of R1 patients can also compromise some of the conclusions of this study. The main advantage is the 5-year minimum follow-up, permitting a survival analysis of both OS and RFS. Still, more studies are needed with larger, multicentric samples, to validate the findings presented in this paper.

Conclusion

R0 resection is an important prognostic factor and should be achieved during gastric cancer surgery with curative intent, but it is difficult to predict this R0 resection based solely on the macroscopic resection margin distance.

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