Microscopic Positive Margins in Gastric Adenocarcinoma Following Oncological Resection: Prognostic Factors and Long-Term Survival

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Background: In the context of gastric cancer, surgical resection stands as the sole curative treatment. Central to influencing overall survival are the resection margins. This research aims to identify the factors influential in determining microscopically positive resection margins (R1) and to evaluate overall survival.
Methods: Our study encompassed 549 patients diagnosed with adenocarcinoma of the stomach who underwent curative-intent surgery between January 2011 and December 2021 in our Surgery Department. We investigated the incidence of positive margins (R1) and their impact on survival rates, as well as the determinants of R1. The standardization of R1 involved ensuring a margin distance of less than 1 mm from the tumor line to the margin.
Results: The incidence of R1 margins was 13.29% (73 patients). Among these, proximal R1 margins were observed in 29 patients (39.72%), while 49 cases (67.12%) presented circumferentially positive margins, with 20 cases (27.39%) exhibiting distally positive margins. Nineteen patients (26.02%) had two R1 margins, and 3 patients had all resection margins microscopically positive (4.10%). Factors such as tumor dimension, invasion of other organs, pT stage, pN stage, pL1 stage, pV1 stage, pPn stage, Lauren type, and tumoral grading demonstrated significance ($p < 0.01$) in the occurrence of positive R1 margins.
Conclusion: Tumor dimension, invasion of other organs, pT stage, pN stage, pL1 stage, pV1 stage, pPn stage, Lauren type, and tumoral grading could be regarded as factors for predicting microscopically positive margins. Moreover, positive resection margins have a detrimental impact on overall survival.

Keywords: gastric adenocarcinoma; overall survival; R1 margins; prognostic factors

Introduction

Gastric cancer ranks as the fifth most common cancer globally in terms of incidence. Cancer-related mortality stands as the fourth leading cause of death worldwide, claiming 800,000 lives in 2020 alone. Gastric cancer remains among the deadliest cancers, with a mere 20% overall survival rate at five years [1]. The highest incidence is documented in East Asia, South America, and Eastern Europe, with a male-to-female ratio of 3:1 for those affected by stomach cancer [2]. Adenocarcinoma accounts for over 90% of gastric malignant tumors, while gastrointestinal stromal tumors, lymphomas, and neuroendocrine tumors make up the remaining 10% [3].

Resectional surgery remains the sole curative treatment for gastric malignant tumors, with a few exceptions such as a highly select group of stage IA patients who may benefit from endoscopic resection. For other patients with resectable gastric cancer (stage IB-III), radical gastrectomy with perioperative oncological therapy is the established standard of care. The surgical approach may involve total gastrectomy or subtotal gastrectomy, coupled with omentectomy and D2 lymphadenectomy. The decision regarding the extent of radical gastrectomy considers factors such as tumor location, Tumor Node Metastasis (TNM) classification, and histological subtype [3].

The final anatomopathological report must include details such as pTNM staging, tumor grade differentiation, cancer staging, and resection margin assessment [4]. According to the 2nd edition of "A standardized pathology report for gas-

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tric cancer", a resection margin of less than 0.2 cm should be documented in the pathology report and is classified as an R1 resection [4].

In patients undergoing gastrectomy for gastric cancer, the reported prevalence of R1 resections exhibited wide variability, ranging from 0.8% to 20.0%. Numerous studies, including those incorporated into a systematic review by Raziee *et al*. [5] published in 2012, have suggested an impact on survival. In a review from 2014, Aurello *et al*. [6] reported an R1 rate of 5.2%, while Bickenbach *et al*. [7] identified a rate of 4.5% R1 in 2013, specifically in patients who underwent gastrectomy for curative intent. Various studies have demonstrated that positive microscopic resection is linked with advanced locoregional disease, typically T3–T4 stage [8,9].

Adjuvant chemoradiation may be considered for patients who haven't received benefit from neoadjuvant chemotherapy and have not undergone optimal D2 lymphadenectomy. Additionally, in highly selective cases where R1 resection margins are present, adjuvant radiotherapy or chemoradiation may be considered [3]. Most studies indicate that tumor size, T stage, N stage, tumor grade, vascular invasion, lymphatic invasion, and histological type are correlated with tumoral invasion and can predict positive resection margins.

The primary objective of our study is to identify predictive factors associated with the occurrence of positive microscopic margins following gastrectomy for oncological purposes. We deem significant the surgical technique, extent of resection, pTNM staging, tumoral grading, and Lauren type. As a secondary aim, we investigate the impact of R1 resection on overall survival.

Materials and Methods

This retrospective study involved cases of gastric adenocarcinoma that underwent surgery with curative oncological intent at the Institute of Gastroenterology and Hepatology Octavian Fodor in Cluj-Napoca between January 2011 and December 2017. We utilized the electronic database to gather information on eligible patients for the study. Following the application of inclusion and exclusion criteria, 549 patients who underwent curative surgery for malignant gastric tumors were included. Patients excluded from the study had distant metastasis, underwent palliative surgery, or had an undetermined resection status. Histopathological results were documented by our pathology department according to the eighth edition of the American Joint Committee on Cancer (AJCC) guidelines. All patients included in the study provided informed consent, and the study received approval from the Ethics Committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy.

From the electronic database, we recorded variables pertaining to demographic aspects (age, gender, setting), surgical factors (type of surgery, intraoperative tumor location, type of anastomosis, macroscopic invasion, complication rate), and histopathological findings (TNM status, vascular, lymphatic, and perineural invasion, resection margin, Lauren type, tumor differentiation grade). Consensus defines a resection margin within 1 mm from tumoral cells as an R1 resection margin.

Patients underwent annual check-ups, including gastroscopy and contrast thoraco-abdomino-pelvic computed tomography. Overall survival was analyzed from the time of gastric resection to either death or December 31, 2022, the last day of data collection. Statistical analysis was performed using SPSS 19 (IBM Corp., Armonk, NY, USA). Association between qualitative variables was assessed using Pearson Chi-Squared Test and Fisher Test. Correlation between quantitative variables was determined using Spearman-Rho tests with consideration for Kendall coefficients. Normality of continuous variables was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests.

For differences between mean values of two groups, *T*-test for independent variables was employed, while Mann-Whitney U test addressed differences in median values rank between two groups. Survival analysis was performed using Kaplan-Meier curves and the Log-Rank test, with Breslow and Tarone-Ware analyses assessing significance. Significant variables from binary logistic regression were selected for multivariate analysis. A *p*-value less than 0.05 adjusted for Bonferroni correction in multivariate analysis was considered statistically significant.

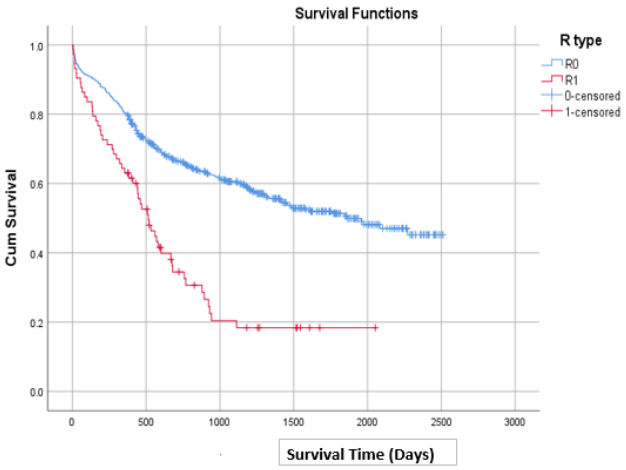

Fig. 1. Kaplan-Meier curve compare the overall survival after gastrectomy, considering the presence of R1 margins. In R0 group, there was a 56.1% survival rate, whereas in the R1 group we encountered a 27.4% survival rate. The difference was statistically significant (p value < 0.0001).

Results

The cohort comprised 549 patients, with 374 males (68.12%) and 175 females (31.87%). The age range was between 30 and 89 years old. Subtotal gastrectomy was performed for 311 patients (56.64%), while total gastrec-

Table 1. Comparison of different variables between R0 and R1 group.

		R0	R1	*p*-value
Age		65.15 (±10.30)	62.89 (±11.26)	0.08
Tumor dimension (mm)		40 (26.25–65)	60 (40–90)	0.001
Gender	Male	322 (86.1%)	52 (13.9%)	0.54
	Female	154 (88%)	21 (12%)	
Surgery	Subtotal gastrectomy	280 (90%)	31 (10%)	0.009
	Total gastrectomy	196 (82.4%)	42 (17.6%)	
Mortality	No	381 (89.0%)	47 (11.0%)	0.003
	Yes	95 (78.5%)	26 (21.5%)	
Anastomosis	Manual	381 (88.4%)	50 (11.6%)	0.02
	Mechanical	95 (80.5%)	23 (19.5%)	
Setting	Rural	198 (86.1%)	32 (13.9%)	0.8
	Urban	278 (87.2%)	41 (12.8%)	
Complications	No	443 (87.2%)	65 (12.8%)	0.22
	Yes	33 (80.5%)	8 (19.5%)	
Invasion	No	464 (88.2%)	62 (11.8%)	0.001
	Yes	12 (52.2%)	11 (47.8%)	
Macro-invasion	No	436 (89.7%)	50 (10.3%)	0.001
	Yes	40 (63.5%)	23 (36.5%)	
Lymphatic invasion	No	162 (94.7%)	9 (5.3%)	0.001
	Yes	314 (83.1%)	64 (16.9%)	
Perineural invasion	No	236 (94.4%)	14 (5.6%)	0.001
	Yes	240 (80.3%)	59 (19.7%)	
Vascular invasion	No	330 (90.2%)	36 (9.8%)	0.001
	Yes	146 (79.8%)	37 (20.2%)	
T stage	1	71 (98.6%)	1 (1.4%)	0.001
	2	55 (96.5%)	2 (3.5%)	
	3	123 (93.9%)	8 (6.1%)	
	4	227 (78.5%)	62 (21.5%)	
N stage	0	152 (96.2%)	6 (3.8%)	0.001
	1	78 (90.7%)	8 (9.3%)	
	2	100 (90.9%)	10 (9.1%)	
	3	146 (74.9%)	49 (25.1%)	
Grading	1	82 (93.2%)	6 (6.8%)	0.02
	2	186 (89.0%)	23 (11.0%)	
	3	208 (82.5%)	44 (17.5%)	
Lauren type	Diffuse	84 (83.2%)	17 (16.8%)	0.01
	Intestinal	244 (91.0%)	24 (9.0%)	
	Mixed	148 (82.2%)	32 (17.8%)	

Different variables were analyzed in order to establish ones which influence R1 resection margin. The significance level was *p* lower than 0.05. Qualitative variables were represented as no. (%), with the exception of age (years) and tumor dimension (mm) represented as mean ± SD.

tomy was conducted for 238 patients (43.35%). All patients underwent at least a D1.5 lymphadenectomy. Tumor localization was distal in 226 cases (41.16%) and proximal in 323 cases (58.83%). Adenocarcinoma was confirmed in all cases. Regarding staging, there were 289 cases classified as pT4 (52.64%), 131 as pT3 (23.86%), 57 as pT2 (10.38%), and 72 as pT1 (13.11%). The AJCC 8th edition staging classes of the cohort are presented in Table 1. Of the total, 158 patients (28.77%) were classified as pN0, 86 (15.66%) as pN1, 110 (20.03%) as pN2, and 195 (35.51%) as pN3. Lymphatic invasion was present in 378 patients (68.85%), while vascular invasion was observed in 183 patients (33.33%).

Among all patients in the study, 89 underwent neoadjuvant chemotherapy, while the remaining 460 did not receive any neoadjuvant treatment. Out of the 89 patients who underwent preoperative chemotherapy, 11 (12.35%) had positive microscopic margins. In comparison, 62 (13.47%) patients from the group without neoadjuvant treatment had R1 resections.

Seventy-three cases (13.29%) exhibited R1 margins. Among them, proximal R1 margins were noted in 29 patients (39.72%), circumferential positive margins in 49 cases (67.12%), and distal R1 margins in 20 patients (27.39%). Nineteen patients (26.02%) had two R1 margins, while 3 patients had all resection margins microscopically positive (4.10%).

In the univariate analysis, nine factors demonstrated significance for the occurrence of positive margins: tumor dimension ($p = 0.001$), pT stage ($p = 0.001$), invasion in other organs ($p = 0.001$), pN stage ($p = 0.001$), pL1 stage ($p = 0.001$), pV1 stage ($p = 0.001$), pPn stage ($p = 0.001$), Lauren type ($p = 0.01$), and tumor grading ($p = 0.02$).

To identify factors associated with an increased occurrence of R1 margins, multivariate logistic regression was employed. Only the pN stage ($p = 0.015$) significantly influenced the occurrence of R1 margins.

A median survival of 514 days was observed for the R1 group, whereas R0 cases exhibited a median survival of 1864 days (p value < 0.0001). The associated Kaplan-Meier curve is presented in Fig. 1.

Discussion

Some of the factors that play a significant role in the occurrence of R1 following gastrectomy for adenocarcinoma were identified through our study. Significant influences were suggested after univariate analysis for tumor dimension ($p = 0.001$), invasion in other organs ($p = 0.001$), increasing pT stage ($p = 0.001$), increasing pN stage ($p = 0.001$), pL1 stage ($p = 0.001$), pV1 stage ($p = 0.001$), pPn stage ($p = 0.001$), Lauren type ($p = 0.01$), and tumor grading ($p = 0.02$).

Del Rio *et al*. [10] proposed, based on a retrospective study, that tumor size exceeding 2.5 cm and the presence of positive lymph nodes are associated with a poorer prognosis and reduced overall survival in patients who underwent surgery with curative intent for gastric cancer.

In a meta-analysis conducted in 2021 by Jiang *et al*. [11], encompassing 23 retrospective studies and involving 19,992 patients, it was concluded that overall survival was poorer in the R1 group compared to R0 resection after curative intent gastrectomy, as expected. However, in the esophagogastric subgroup, there was no statistically significant difference.

In a 2020 study by Kumazu *et al*. [12], it was demonstrated that risk factors for positive microscopic margins following gastric surgery for oncological purposes included remnant gastric cancer, esophageal invasion, tumors larger than 80 mm, poorly differentiated tumors, pT4 disease, or macroscopic type 4. Additionally, the study showed that the risk of positive margins increases depending on the number of identified risk factors in a single patient.

In a retrospective study conducted in 2017, Rhome *et al*. [13] demonstrated that male gender, Asian race, and year of diagnosis were predictors for R1 margins. Furthermore, a higher T stage, N stage, higher grade (G3) or undifferentiated grade, vascular invasion, lymphatic invasion, the lack of treatment at an academic center, and undergoing robotic intervention (compared to laparoscopic surgery) were associated with an increased risk of R1 margins [13].

Aurello *et al*. [6], in a systematic review from 2014, identified in the literature a range of positive resection margins between 1.8% and 18.2% after gastrectomy for oncological purposes. Our study has further demonstrated a correlation between R1 resection margins and overall survival, thereby identifying it as a predictor for mortality following surgery for gastric cancer.

Different studies have initially demonstrated that in early stages of gastric cancer, R1 resection could serve as a prognostic factor for overall survival. Liang *et al*. [14] in 2015 showed that R1 resection influences prognosis only in TNM stages II, IIIA, and IIIB, while Morgagni *et al*. [15] in 2008, Sun *et al*. [16] in 2009, and Shin *et al*. [17] in 2013 demonstrated increased overall survival and lower morbidity in patients with pT1-2 or pN0-1 status and R0 resection margins.

Conversely, other studies have indicated a benefit for overall survival across all stages of resectable gastric cancer, albeit more pronounced in early stages. Raziee *et al*. [5] conducted a review in 2012 that synthesized results from 22 studies, highlighting the independent influence of tumor dimensions, T stage, N stage, and histology on overall survival. They also concluded that intraoperative frozen section analysis should be employed more frequently during gastrectomy with oncologic intent to prevent positive microscopic margins. Furthermore, they suggested that patients diagnosed at early stages (T1-2 or N0-1) derive the greatest benefit from re-resection in case of positive histological margins [5].

Following Morgagni *et al*. [15] in 2008, the 5-year survival rate after an R1 resection in T1 stage was reported as 100%. Similar findings were observed in our study, where only one T1 case with an R1 resection margin survived after 5 years [15].

In a retrospective study conducted in 2023 by Hirata *et al*. [18], it was concluded that the 5-year survival rate for patients who underwent curative surgery with contemporary neoadjuvant treatment was 6% in cases of R0 resection compared to 60% for those with microscopic positive margins (R1).

The prognosis of gastric cancer has significantly improved over the past decade with modern protocols of oncological treatment.

Numerous chemotherapy trials have demonstrated the benefit of neoadjuvant treatment in enhancing overall survival in resectable gastric adenocarcinoma. For instance, the MAGIC trial focusing on resectable gastroesophageal adenocarcinoma revealed a 5-year survival rate of 36% for the group that received ECF (epirubicin, cisplatin, and fluorouracil) neoadjuvant chemotherapy followed by gastrec-

tomy, compared to a 23% survival rate for patients treated with surgery alone. Presently, the standard protocol is based on the FLOT4-AIO trial, which demonstrated the superiority of fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) over ECF or ECX (where X refers to capecitabine), presenting a 45% versus 36% survival rate at 5 years [19,20].

A study conducted by Del Rio *et al*. [21] in 2013 demonstrated the benefits of neoadjuvant chemotherapy in gastric cancer, including downstaging and achieving R0 resection margins.

Furthermore, various studies are investigating the role of HER2-targeted agents and VEGF inhibition in the preoperative setting of resectable gastric adenocarcinoma. The randomized phase II PETRARCA trial showed an improved pathologic complete response (pCR) rate (35% vs. 12%), while higher nodal negativity rates (68% vs. 39%) were achieved by adding trastuzumab and pertuzumab to the preoperative FLOT protocol in resectable gastroesophageal adenocarcinoma HER2-positive cases [22].

Adjuvant chemotherapy was initially shown to improve survival, as evidenced by the CLASSIC trial, which reported a three-year disease-free survival of 74% versus 59% in the capecitabine and oxaliplatin chemotherapy group compared to surgery alone [23].

Additionally, Garofalo A *et al*. [24] demonstrated in a 2020 study involving 356 patients that total or subtotal gastrectomy with curative intent, along with D2 lymphadenectomy and adjuvant chemotherapy, had a significant impact on overall survival.

The National Comprehensive Cancer Network (NCCN) guidelines reserve adjuvant chemoradiation for patients after R1 or R2 resection or for patients with non-optimal D2 lymphadenectomy with pT3-T4 or pN+ stage [25].

Neoadjuvant chemoradiation is not as well established, being categorized as a 2B recommendation [25] in the NCCN guidelines.

Furthermore, our study did not demonstrate an improvement in R0 resection and overall survival in the group that underwent neoadjuvant chemotherapy compared to the group that underwent surgery alone. It is important to note that patients received neoadjuvant treatment according to the guidelines available at the time of the study.

Conclusions

Tumor dimension, invasion in other organs, pT stage, pN stage, pL1 stage, pV1 stage, pPn stage, Lauren type, and tumoral grading have been identified as factors that increase the probability of R1 resection in gastric adenocarcinoma. Moreover, the presence of R1 margins can significantly influence overall survival.

Availability of Data and Materials

The datasets used or analysed during the current study are available from the corresponding authors on reasonable request.

Author Contributions

Conceptualization, EM, FG, NAH, ICP, AP, FZ, CI, and CP; Data acquiration, SM, IR, VIN, and DV; Formal analysis, LF, DV, VIN, and SM; Funding acquisition, EM, CP, NAH and FG; Investigation, LF, IR DV, AP, VIN, and SM; Methodology, EM, NAH, FG, FZ, CI, ICP and LF; Project administration, EM, NAH, FG, FZ, CP and AP; Resources, EM, CP, AP, FG, FZ, IR and LF; Software, DV, VIN, and SM; Supervision, NAH, ICP, CI and FG; Validation, NAH, FG, IR, AP, EM and LF; Writing—original draft, LF, IR, SM, VIN and DV; Writing—review and editing, ICP, NAH, FG, EM, AP, CP, FZ and CI. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All patients included in the study provided informed consent. The study was conducted in accordance with the Declaration of Helsinki, and approved by the ”Iuliu Hațieganu” University of Medicine and Pharmacy Ethics Committee (number 384/10.11.2014).

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Conflict of Interest

The authors declare no conflict of interest.

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