Factors determining microscopic positive resection margins after gastrectomy for gastric adenocarcinoma

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Abstract. Background and Aims: Surgical resection is the only curative treatment for gastric cancer. Resection margins are described as one of the most important factor affecting overall survival. The primary outcome of the study was to identified the factors that are playing significant role in determine microscopic positive resection margins (R1), while the secondary outcomes were the loco-regional recurrence and overall survival. Methods: Study includes 140 patients with gastric adenocarcinoma operated between January 2011 and December 2013 in our Institute. The incidence of R1 margins and its impact on the survival rates were investigated along with factors that determine R1 margins. R1 was defined as a distance of ≤ 1 mm between the tumor and the resection margin. Results: The R1 margins rate was 12.14% (17 cases). Of these, 8 patients (47.05%) had proximal R1 margins, 6 patients (35.29%) circumferential R1 margins and 2 patients (11.76%) had R1 distal margins. One patient (5.88%) had two R1 margins: on proximal and distal. pT3-4 stage (p=0.022), pN2-3 stage (p<0.0001), pL1 stage (p<0.0001) and advance tumour stage (p<0.0001) are factors that play significant roles in appearance of R1 margins. Conclusions: pT3-4 stage, pN2-3 stage, pL1 stage and advance tumour stage are predictive factors for microscopic positive resection margins. Positive resection margin affects overall survival and is a risk factor for local recurrence in gastric adenocarcinoma.

Key Words: positive resection margins; gastric adenocarcinoma; overall survival; local recurrence.

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Introduction

Gastric cancer is the fifth most common type of cancer and the fifth most frequent cause of death in the world (Kamangar et al 2006). The incidence is higher in East Asia, Eastern Europe and South America and men are three times more affected by the disease than women (Karimi et al 2014). More than 90% of gastric cancers are adenocarcinomas.

Surgical resection is the only curative treatment for gastric cancer. The surgery technique is divided into total gastrectomy and subtotal gastrectomy and it is completed with omentectomy and regional lymphadenectomy. The decision of the type of the surgery is based on the location and extension of the tumor (Necula et al 2008, Aurello et al 2014). The specimen will be examined by the anatomopathologist to find the postoperative TNM classification, tumor grade differentiation and staging (Wittekind et al 2009).

It is also important to appreciate the resection margin. According to the UK Royal College of Pathologists guidelines, a R0 resection means a complete macroscopic and microscopic resection of the tumor (Pathologists 2009). The presence of tumor cells ≤ 1 mm from a resection margin is considered a R1 resection.

The incidences of the positive resection margin (R1) after a gastrectomy differs in the literature from 4.5% to 20% and have been associated with advance stage disease (Bickenbach et al 2013, Gall et al 1996, Kim et al 1999, Papachristou and Fortner 1981; Shiu et al 1987, Shiu et al 1989, Wang et al 2009). Aurello et al (2014) made a review and identified a 5.2% of R1 resection. They included 15,008 patients who had a surgery for gastric cancer from 1980 to 2010. A study made by Bickenbach et al (2013) found a rate of 4,5% of R1 resection and they included only patients who had a gastrectomy with curative intent. Woo et al (2014) included in their study only patients with T3-T4 tumors and intentional curative resection and obtained a 2.28% of positive microscopic resection. R1 resections are associated with advanced type of cancer (Cho et al 2007).

R0 resection needs surveillance or chemotherapy if there are positive nodes. Postoperative chemo-radiation is recommended for R1 resections but R2 resection will have a palliative management or chemo-radiation if it wasn't received preoperatively. It is important to know the risk factors of the positive margin, so the surgeon would be more attentive when he treat these patients. Some studies demonstrated that tumor size, the depth invasion of the tumor, positive lymph nodes and intravasation

of the lymph vessels, advanced stages of cancer, histological type are factors that can indicate a high tumor aggressiveness and a risk of a positive resection margin.

The purpose of our study is to determine the main factors that play vital roles in determining microscopic margins positivity in patients with gastric cancer, in particular the surgical technique and the extent of resection, the pathological stage of the tumor (T and N stages) and the tumor location. Secondary we analysed the influence of R1 on loco-regional recurrence and overall survival.

Material and methods

A retrospective review of patients who underwent curative surgery for gastric cancer between January 2011 and December 2013 at our Institute was performed. Data was collected retrospectively from our Institute's electronic database. From a total of 278 patients with gastric cancer who underwent surgery at our department, we have selected 140 patients with oncological gastric resections in our study. Patients with distant metastasis, those who underwent palliative surgery and patients whose resection status could not be determined were excluded. Pathologic staging of the disease was performed according to the American Joint Committee on Cancer (AJCC) 7xth edition. All patients have signed the informed consent and the study was approved by the ethics committee.

The database included age, gender, surgery type, location, histological tumor type, the number and the site of lymph node involvement, vascular and lymphatic status, stage, tumor grade. The presence of cancer cells at or within 1 mm of the resection margin was considered a positive microscopic margin.

Patient follow-up protocol included every once a year upper endoscopy and computed tomography. Overall survival was defined as the time from the date of surgery to the date of death or the date of the last follow-up of patients who were still alive. We have defined as a loco-regional recurrence any recurrence in the tumor bed, anastomoses, stumps or gastric remnant.

Results were analysed using SPSS 19. The Chi-square test was used for qualitative data, together with the contingency and the uncertainty coefficients. Comparison between the groups was performed and the p was computed in the adjusted form according to Bonferroni. Ordinal variables were evaluated with the help of the Spearman and Kendall coefficients. For quantitative data, comparisons between groups were conducted in two forms –parametric (t Student) or non-parametric tests. In the case of scale variables, the first step of the analysis was to evaluate the normality of the distribution. For normally distributed values, parametric tests can be applied in comparison analyses (the t test). When data is not normally distributed, comparisons are conducted based on non-parametric tests, as the mean value is no longer representative. Kaplan–Meier curves were constructed for the analysis of survival based on microscopic margins status. Three statistic tests were used to assess the validity of the results (Log Rank, Breslow and Tarone-Ware). Multivariate analysis was carried out using the binary logistic regression to assess the factors that influence the appearance of microscopic positive margins. A p value <0.05 were considered statistically significant.

Results

A total of 140 patients, including 85 men (60.71%) and 55 women (39.29%), between 29 and 86 years old, were included in a cohort study. Regarding surgery, 67 patients (47.85%) of them underwent subtotal gastrectomy and the rest 73 patients (52.14%) underwent total gastrectomy (Table I). In all cases at least D1.5 lymphadenectomy was performed. Regarding localization of the tumor, 76 (54.28%) patients had distal tumors and the rest 64 (45.72%) patients had proximal tumors (Table I).

All patients had gastric adenocarcinoma. Twenty-five (17.85%) cases were pT4, 71 (52.14%) cases were pT3, 15 (7.14%) cases were pT2, 26 (18.57%) cases were pT1 and 3 (2.14%) cases were Tis. Staging according to AJCC 7th ed., 2010 is presented in Table I. Forty-six (32.85%) were pN0, 35 (25%) were pN1, 32 (22.85%) were pN2 and 27 (19.28%) were pN3. Eighty-five (60.71%) patients displayed lymphatic and 26 (18.57%) vascular invasion.

Seventeen (12.14%) patients had microscopically positive margins (R1). Of these, 8 patients (47.05%) had proximal R1 margins, 6 patients (35.29%) circumferential R1 margins and 2 patients (11.76%) had R1 distal margins. One patient (5.88%) had two R1 margins: on proximal and distal. Of all factors analysed at the univariate analysis, four proved to be significant for apparition of R1 margins: pT3-4 stage (p=0.041), pN2-3 stage (p<0.0001), pL1 stage (p<0.0001) and advanced tumor stage (p<0.0001). Furthermore, multivariate binary logistic regression was applied to compare the two groups, R0 and R1, and to evaluate the factors that could influence the probability of developing R1 margins. Out of all the aspects considered, pN stage (p=0.015) was found to significantly influence the probability to have R1 margins.

The median overall survival time of the R1 group was 740 days, and that of the R0 group was 1534 days. There were significant differences between the R1 and R0 groups on OS rate, p-value<0.0001. Figure 1 shows the Kaplan-Meier for OS function for the two groups of patients. Overall, 10 (7.14%) patients developed loco-regional recurrences during a median follow-up period of 1614 days, 6 of them belonged to the R0 group, while the other 4 to the R1 type. Loco-regional recurrence rates in patients with R1 margins were 23.52%, significantly higher (p=0.011) than in those with R0 margins (4.87%).

Discussions

Our study identified the factors that are playing significant role in positivity the microscopic margins following gastric adenocarcinoma surgery. Univariate analysis denoted that pT3-4 stage (p=0.041), pN2-3 stage (p < 0.0001), pL1 stage (p < 0.0001) and advanced tumour stage (p < 0.0001) are independent factors for predicting microscopic margins positivity.

Kim et al (1999) demonstrated that a positive resection margin was associated with advanced type of cancer and it depended on T and N stage. R1 resection was more frequent for diffuse adenocarcinomas (Lauren classification). There was not a difference between proximal or distal lesions but whole stomach cancers were associated much frequent with a positive resection. These findings are confirmed by the Morgagni's results. Authors also compared the complication observed on patients with positive and negative margins and hadn't found a significantly

Table 1. Patients and tumor characteristics

| Variable	R0	R1	p
Age	64.89 ± 10.46	59.82 ± 10.62	0.06
	67 (57-72)	60 (49.5-69)	
Tumor size	4.83 ± 2.39	6.41 ± 4.33	0.085
	4 (3-6)	5 (4-7)	
Gender			374
Male	73 (85.9%)	12 (14.1%)	
Female	50 (90.9%)	5 (9.1%)	
Surgery			0.269
Subtotal gastrectomy	61 (91%)	6 (9%)	
Total Gastrectomy	62 (84.9%)	11 (15.1%)	
Localization			0.247
Proximal	54 (84.4%)	10 (15.6%)	
Distal	69 (90.8%)	7 (9.2%)	
T stage			0.041
1	24 (92.3%)	2 (7.7%)	
2	15 (100%)	0 (0%)	
3	62 (87.3%)	9 (12.7%)	
4	19 (76%)	6 (24%)	
N stage			<0.0001
0	45 (97.8%)	1 (2.2%)	
1	34 (97.1%)	1 (2.9%)	
2	26 (81.3%)	6 (18.8%)	
3	18 (66.7%)	9 (33.3%)	
L stage			<0.0001
0	54 (98.2%)	1 (1.8%)	
1	69 (81.2%)	16 (18.8%)	
V stage			0.054
0	104 (91.2%)	10 (8.8%)	
1	19 (73.1%)	7 (26.9%)	
G			0.305
0	3 (100%)	0 (0%)	
1	24 (88.9%)	3 (11.1%)	
2	34 (91.9%)	3 (8.1%)	
3	62 (84.9%)	11 (15.1%)	
Tumor stage			<0.0001
0	3(100%)	0	
IA	19(95%)	1(5%)	
IB	12(100%)	0	
IIA	21(95.45%)	1(4.54%)	
IIB	18(100%)	0	
IIC	2(100%)	0	
IIIA	19(86.36%)	3(13.63%)	
IIIB	22(68.75%)	10(31.25%)	
IIIC	6(75%)	2(25%)	
Urgency			0.403
No	104 (86.7%)	16 (13.3%)	
Hemorage	12 (100%)	0 (0%)	
Stenosis	7 (87.5%)	1 (12.5%)	
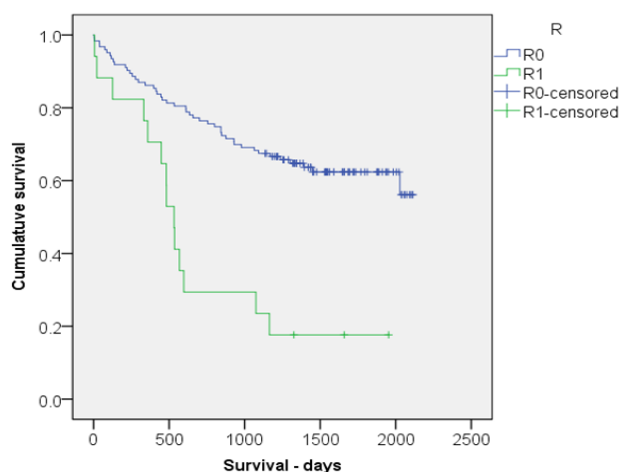
Figure 1. Kaplan-Meier plot illustrating overall survival by resection margins after gastric cancer surgery

difference (Morgagni et al 2008). Sun et al (2009) identified that tumor size, infiltrative macroscopic appearance (Bormann type 4), invasion of lymphatic or blood vessels are also a predictor for a positive resection margin.

A systematic review published in 2014 mentioned rates of R1 margins between 1.8 % and 18.2 % after cancer gastric surgery (Aurello et al 2014). In what concerns the influence of R1 margin on the overall survival, our study showed that R1 margin is an independent prognostic factor for overall survival. Other studies demonstrated that the resection margin is an important prognostic factor only in incipient stages of cancer. The authors found out that patients with a negative resection and adenocarcinoma stage IIIc have a similar survival to patients with a positive resection margin in early stages. They concluded that R1 resection could be a predictive factor only for tumors with TNM stages II, IIIa, IIIb (Liang et al 2015).

The stage I-II neoplasm, with pT1-2 or pN0-1 and a negative resection margin is correlated with a lower morbidity and mortality than positive resections. But there was not a statistic significant difference of survival in advanced stages III-IV (Morgagni et al 2008, Shin and Park 2013, Sun et al 2009). One of the studies found a 100% 5-years survival rate for T1 tumors and a R1 resection. The authors recommend a reintervention for T2 tumors because they found an important survival difference: 8% for R1 resection and 64% for R0 resections (Morgagni et al 2008). The results were the same for our study, the 2 patients with R1 margins and T1 had 100% 5-years survival rate (no signs of local recurrence at the upper digestive endoscopy performed periodically).

The Bickenbach study (2013) also demonstrated that positive margin is an independent predictor of survival only for T1-T2 tumors with less than 3 positive nodes. R1 resection has a worse prognostic for more advanced cancers too but it is not an independent predictor anymore.

Another study demonstrated that the median 5-year survival time was worse for positive resection (34 months) than for patients with negative resection margins (68 months). But the difference was obtained only for node-negative tumor. Patience with node-positive disease had a lower survival rate regardless of the resection margin (Cho et al 2007).

It is well know that the resection margin is an independent risk factor of the cancer recurrence. We also demonstrated the role of

R1 margins in local recurrences. The Bickenbach's study (2013) had a 76% of recurrence after 18 months for patients with R1 resection. The rate of recurrence wasn't lower for patients who had received a local treatment, such as reintervention, radiotherapy or chemoradiotherapy. Another study demonstrated that recurrence after a positive resection margin is higher especially for advanced tumor (T3-T4). Woo mentioned a 63,6% recurrence rate after R1 resection which was higher than for negative resection margin tumors (39,7%) (Woo et al 2014).

But not all the patients with a positive resection margin will develop a recurrence. It can be explained by the postoperative chimioradiation or patients' immune system that will destroy the restant tumor cells. The cancer recurrence after a R1 resection can be loco-regional or distant. Some studies showed that the positive resection margin is associated more frequent with distant recurrence but also a gastrectomy with negative margin can lead to a locoregional recurrence. The aggressiveness of the cancer affects the resection margin, so a gastric cancer with a R1 resection is much more aggressive (Shin and Park 2013).

Conclusions

pT3-4 stage, pN2-3 stage, pL1 stage and advance tumour stage are predictive factors for microscopic positive margins at univariate analysis. 3-years survival rate for gastric cancer is influenced by the resection margins status (R1/R0). Microscopic positive resection margin is a risk factor for loco-regional recurrence in gastric adenocarcinoma.

Acknowledgement

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