Clinical Study

Oncology

Oncology 2016;90:239–247
DOI: 10.1159/000443506

Received: December 14, 2015
Accepted after revision: December 15, 2015
Published online: April 6, 2016

The Proportion of Signet Ring Cell Component in Patients with Localized Gastric Adenocarcinoma Correlates with the Degree of Response to Pre-Operative Chemoradiation

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Key Words
Gastric adenocarcinoma · Histologic grade · Signet ring cells · Predictive factors · Chemoradiation response

Abstract
Background: Patients with localized gastric adenocarcinoma (LGAC), who get pre-operative therapy, have heterogeneous/unpredictable outcomes. Predictive clinical variables/biomarkers are not established. ***Methods:*** We analyzed 107 LGAC patients who had chemoradiation and surgery. LGACs were grouped for (1) presence/absence of signet ring cell histology (SRC) and (2) histologic grade: G2 or G3. %SRC was assessed (0, 1–10, 11–49, and 50–100%) and correlated with pathologic complete response (pathCR) or <pathCR in the resected specimens. ***Results:*** Most patients were men (60%), had stage cIII LGAC (50%), and received chemotherapy before chemoradiation (93%). Most had G3 tumors (78%) and SRC (58%). Presence of SRC was associated with a lower rate of pathCR (11 vs. 36%, $p = 0.004$), and the association remained significant even with a low percentage of SRC (1–10%; $p = 0.014$). The higher the fraction of SRC, the lower was the probability of pathCR ($p = 0.03$). G3 and SRC led to a shorter overall survival (OS) ($p = 0.046$ and $p = 0.038$, respectively). yp stage independently prognosticated OS and recurrence-free survival ($p < 0.001$). ***Conclusion:*** Our novel findings suggest that LGACs with SRC are relatively chemoradiation resistant compared to LGACs without SRC. A higher fraction of SRC is associated with higher resistance. Upon validation/biomarker(s) evaluation, reporting of the fraction of SRC may be warranted.

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0030–2414/16/0905–0239$39.50/0

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Introduction

The incidence of gastric adenocarcinoma (GAC) has been declining steadily, yet it represents the fifth most common malignancy in the world with almost one million new cases estimated globally. It is the third leading cause of cancer-related death in both genders worldwide [1]. In the United States, it is estimated that 26,370 new cases and 10,720 deaths from GAC will occur in 2016 [2]. The high mortality rate reflects the prevalence of advanced disease at presentation [3]. Surgical resection (R0) remains the only curative modality for localized gastric adenocarcinoma (LGAC) [4]. However, survival remains poor (20–50% at 5 years) with surgery alone [5–7], leading to efforts to improve the outcomes for this group of patients with the use of adjunct therapies. Based on randomized phase III trials, perioperative chemotherapy [8] and post-operative chemoradiotherapy [9, 10] are the current standards of care.

Pre-operative chemoradiotherapy is one of the options used that can produce a ~20–30% rate of pathologic complete response (pathCR; no residual tumor cells in the resected surgical specimen) and is associated with prolonged overall survival (OS) [11–15]; however, this strategy is not the standard of care [16] and randomized studies are ongoing.

Patients with LGAC, when treated with pre-operative therapy, have heterogeneous and unpredictable outcomes. There is a need to better select therapies that are effective and avoid ineffective ones. Currently, we lack such tools. Since several studies have shown that the presence of signet ring cells (SRC) is an independent poor prognosticator in GAC as assessed from endoscopic biopsies [17, 18], we chose to examine its role in prediction of response to chemoradiation. The predictive value of SRC has not been reported in LGACs.

Materials and Methods

Patient Selection

We analyzed patients from our prospectively maintained GAC database in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center (MDACC) to find 107 consecutive patients who had histologically confirmed GAC or type 3 proximal GAC [19] and were treated with chemoradiation followed by surgery (trimodality therapy) between 2002 and 2013. All patients had baseline and pre-surgical (post-chemoradiation) staging. The Institutional Review Board of MDACC approved this analysis.

Pre-Treatment Clinical Staging

Baseline tumor, node and metastasis clinical stage (cTNM) was established using a combination of imaging studies and upper gastroesophageal endoscopy with endoscopic ultrasound. Imaging studies included computed tomography (CT) and/or positron emission tomography (PET) with CT. Peritoneal staging with laparoscopy or laparotomy was performed in all patients. Before proceeding with therapy, each patient was discussed in the multidisciplinary conference where they were formally staged. Clinical staging was based on the American Joint Committee on Cancer (AJCC) Classification, 6th edition [20].

Trimodality Therapy

All patients had chemotherapy with radiotherapy. Prior to chemoradiotherapy, 100 patients (93%) received up to 8 weeks of induction chemotherapy. The total radiation dose delivered was either 45 Gy in 25 fractions or 50.4 Gy in 28 fractions, 5 days per week prescribed to cover 95% of a clinical target volume encompassing the primary tumor and regional lymphatic regions. Approximately 5–7 weeks after the completion of chemoradiotherapy, all patients underwent endoscopic biopsies and an imaging study. All patients then proceeded to surgery. The treating surgeon selected the type of gastrectomy (total, subtotal) or esophagogastrectomy (Ivor-Lewis, transhiatal). Extensive lymph node dissection was carried out.

Pathologic Evaluation

Available routine hematoxylin and eosin slides from patients with endoscopic biopsy prior to treatment (n = 75) were re-reviewed by a gastrointestinal pathologist (J.S.E.) for the degree of differentiation (histologic grade) and the presence/percent of SRC. Histologic grading was determined based on the World Health Organization (WHO) Classification of Tumours of the Digestive System criteria [21]. SRC was defined as tumor cell with 'central optically clear, globoid droplet of cytoplasmic mucin with an eccentrically placed nucleus' as stated in the WHO Classification of Tumours of the Digestive System [21].

Post-therapy surgical resection specimens were routinely processed as described previously [22, 23] and subdivided as complete pathologic response (pathCR) when no residual disease was identified and <pathCR when ≥1% of residual disease was present. The post-therapy pathologic stage was assessed according to AJCC criteria (7th edition) [24].

Follow-Up and Survival

Patients were monitored periodically until 5 years after surgery or until death. Follow-up data were obtained from the MDACC tumor registry and hospital records or the Social Security Database. The estimated median follow-up time was 31 months (range: 6–178 months).

Statistical Analysis

Summary statistics were used to describe the study population. Pearson's χ^2 test (or Fisher's exact test) and the t test (or Wilcoxon's rank sum test) were used to determine differences between groups. OS was calculated as the number of months from start of treatment to death or last follow-up date. Patients who were alive at their last follow-up were censored on that date. The Kaplan-Meier product limit method was used to estimate the median OS for each clinical/demographic factor. Univariate Cox proportional

Table 1. Summary of the baseline patient characteristics

Patients	107
Age at presentation at MDACC, years	
Mean ± SD	59.3±11.4
Median (min.–max.)	60.0 (26–79)
Gender	
Female	43 (40.2)
Male	64 (59.8)
Siewert classification	
Type 3 GEJ	38 (35.5)
Gastric	69 (64.5)
Baseline EUS – T	
T1–T2	10 (9.4)
T3	86 (81.1)
T4	10 (9.4)
Baseline EUS – N	
N0	48 (44.9)
N1 – N2 – NX	59 (55.1)
Baseline clinical stage	
I–II	47 (43.9)
III–IV	60 (56.1)
Presence of SRC	
No	45 (42.1)
Yes	62 (57.9)
Percentage of SRC	
0%	29 (42.6)
1–10%	7 (10.3)
11–49%	8 (11.8)
50–100%	24 (35.3)
Histologic grade	
G2 – moderately differentiated	24 (22.4)
G3 – poorly differentiated	83 (77.6)
Induction chemotherapy	
No	7 (6.5)
Yes	100 (93.5)

Values are shown as n (%), unless otherwise indicated.

hazards regression was used to identify any association with each of the variables and OS. For each factor, medians, hazard ratios, their 95% confidence intervals (CI) and proportional hazards regression p values are presented in tables 1–6. Similar analyses were performed for recurrence-free survival (RFS). Statistical analysis was performed using STATA/SE version 13.1 statistical software (Stata Corp LP, College Station, Tex., USA).

Results

Patient and Tumor Characteristics

The baseline patient characteristics are detailed in table 1. Most of the patients had poorly differentiated (G3; 78%) LGACs with frequent SRCs (58%) in the biopsy specimens.

Table 2. Summary statistics of the relationship between the presence of SRC and the degree of pathologic response

	Presence of SRC		Pearson's χ^2 p value
	no	yes	
Pathologic response*			0.012
P0	15 (35.7)	6 (11.3)	
P1	20 (47.6)	30 (56.6)	
P2	7 (16.7)	17 (32.1)	
Pathologic response			0.004
pathCR	15 (35.7)	6 (11.3)	
<pathCR	27 (64.3)	47 (88.7)	

Values are shown as n (%).

* Pathologic response: complete P0 = no residual tumor cells; major P1 = 1–50% residual tumor cells; minor P2 = >50% residual tumor cells.

Pre-Operative Therapy

Among the 100 patients who received induction chemotherapy, a fluoropyrimidine was used in combination with either a platinum compound (59%), a taxane (5%) or as triplet (36%). With radiation, all 107 patients received a fluoropyrimidine and either a taxane (48%) or a platinum compound (34%) as the second cytotoxic agent during radiation. The radiation dose was 45 Gy in 90 patients or 50.4 Gy in 13 patients.

Post-Therapy Pathologic Stage and Residual Carcinoma

The post-therapy pathologic tumor stage (ypT) was as follows: 21 patients with ypT0 (20%), 11 with ypT1 (10%), 15 with ypT2 (14%), 47 with ypT3 (44%), and 12 with ypT4 (11%). Seventy-one patients had no lymph node metastasis (ypN0, 67%). Post-therapy pathologic stage groupings were: 0 in 21 patients (20%), I in 24 (22%), II in 37 (34%), III in 21 (20%), and IV in 4 patients (4%). Complete surgical resection (R0) was achieved in 94 patients (89%), while a positive margin by microscopic examination (R1) was seen in 12 (11%). PathCR was observed in 21 patients (22%), and 74 patients achieved <pathCR (78%). A degree of pathologic response was not recorded in the post-therapy biopsy reports for the other 12 patients.

Table 2 shows the association between the pathologic response and SRC in pre-treatment endoscopic biopsy. Among the available slides from 75 patients that were re-reviewed, slides from 61 patients were finally evaluated for the degree of pathologic response. Patients with SRC

Table 3. Summary statistics of the relationship between the percentage of SRC and the degree of pathologic response

	Percentage of SRC				Fisher's exact test p value
	0%	1–10%	11–49%	50–100%	
Pathologic response*					0.014
P0	10 (35.7)	2 (28.6)	0 (0.0)	1 (5.0)	
P1	14 (50.0)	1 (14.3)	5 (83.3)	12 (60.0)	
P2	4 (14.3)	4 (57.1)	1 (16.7)	7 (35.0)	
Pathologic response					0.030
pathCR	10 (35.7)	2 (28.6)	0 (0.0)	1 (5.0)	
<pathCR	18 (64.3)	5 (71.4)	6 (100.0)	19 (95.0)	

Values are shown as n (%).
* Pathologic response: complete P0 = no residual tumor cells; major P1 = 1–50% residual tumor cells; minor P2 = >50% residual tumor cells.

Table 4. Summary statistics of the relationship between histologic grade and degree of pathologic response

	Histologic grade		p value
	G2 – moderately differentiated	G3 – poorly differentiated	
Pathologic response*			0.253[a]
P0	8 (33.3)	13 (18.3)	
P1	12 (50.0)	38 (53.5)	
P2	4 (16.7)	20 (28.2)	
Pathologic response			0.125[b]
pathCR	8 (33.3)	13 (18.3)	
<pathCR	16 (66.67)	58 (81.7)	

Values are shown as n (%).
[a] Fisher's exact test. [b] Pearson's $\chi^{2\ test.}$
* Pathologic response: complete P0 = no residual tumor cells; major P1 = 1–50% residual tumor cells; minor P2 = >50% residual tumor cells.

LGACs had a lower rate of pathCR than those without SRC LGACs (11 vs. 36%; p = 0.004). In the sub-analysis (table 3), the percentage of SRC was associated with pathologic response (p = 0.014) and the association remained significant even for a low percentage of SRC (1–10%; p = 0.014). The higher the fraction of SRC, the lower was the pathCR rate (p = 0.03). Table 4 shows that the pathCR rate in patients with G3 LGACs tended to be lower than in those with G2 LGACs in pre-treatment biopsy (18 vs. 33%; p = 0.125).

OS and RFS

The estimated median survival time for all 107 patients was 120 months (95% CI, 84 to not estimable), and the median RFS time was 120 months (95% CI, 66 to not estimable). The estimated OS and RFS rates at 5 years were 70% (95% CI, 57–79 months) and 62% (95% CI, 50–71 months), respectively. As of this writing, 28 patients (26%) have died. An RFS event (recurrence or death) was documented in 38 patients (36%).

Figure 1 shows the Kaplan-Meier OS curves according to the histologic grade (fig. 1a) and the presence of SRC (fig. 1b). OS was better for patients with G2 histology (2 events, median not reached) compared to G3 (26 events, median 120 months), and OS (by Kaplan-Meier) was shorter for patients with G3 tumors with marginal significance (p = 0.046). The median OS duration for patients with SRC histology was 90 months, which was shorter than that observed in patients without SRC (median not reached; p = 0.038).

Table 5 shows the univariate analysis of various clinicopathologic variables and their effects on OS. Factors associated with shorter OS were presence of SRC in the pre-treatment endoscopic biopsy (p = 0.046), achievement of <clinCR (p = 0.042), and advanced post-therapy pathologic stage (III or IV) (p < 0.001). In the multivariate analysis, shown in table 6, post-therapy pathologic stage remained the only significant predictor of decreased OS (p < 0.001; fig. 2).

Factors associated with decreased RFS in the univariate analysis were achievement of <clinCR (p = 0.013), no induction chemotherapy (p = 0.008), and advanced post-

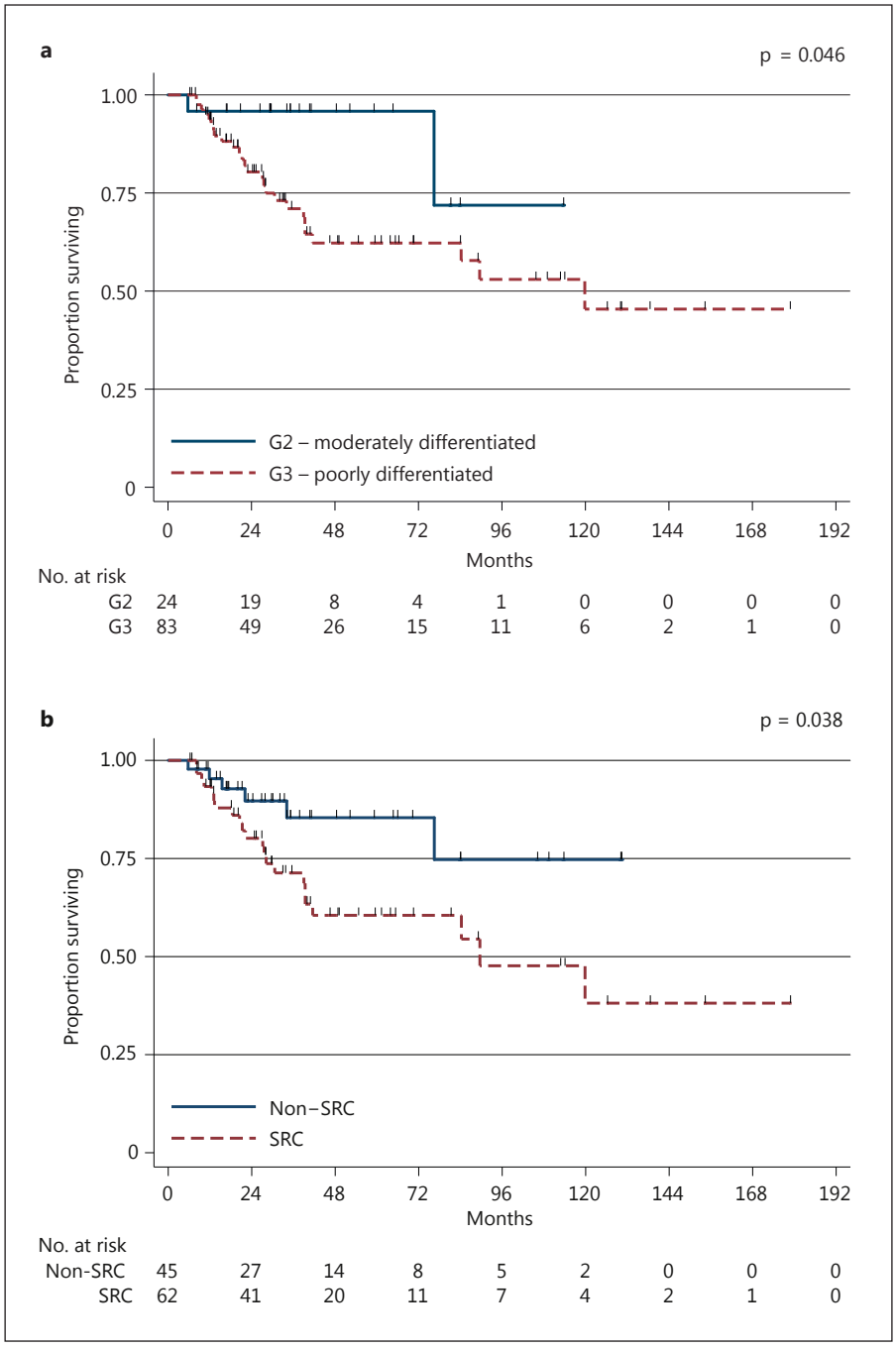

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Fig. 1. Kaplan-Meier OS curves according to histologic grade (**a**) and presence of SRC (**b**).

therapy pathologic stage (III or IV) (p = 0.002). In the multivariate analysis, post-therapy pathologic stage (p = 0.002) and induction chemotherapy (p = 0.022) remained independently associated with RFS.

In this study, the histologic grade and the presence of SRC histology had no impact on OS and RFS in multivariate analysis.

Discussion

LGAC is best managed by combined modality; however, each component of this therapy is associated with considerable morbidity and/or complications. Thus, customization of therapy is desired, but reliable tools are lacking. The value of histologic grade and SRC in predict-

Table 5. Univariate analysis for OS

	Patients	Events	Median	log-rank	HR (95% CI)	p value
Siewert classification						
Type 3 GEJ	38	8	119.82	0.278		
Gastric	69	20	NR		1.57 (0.69–3.57)	0.282
Baseline EUS – T						
T1–T2	10	1	NR	0.118		
T3	86	25	119.82		5.10 (0.68–37.95)	0.112
T4	10	1	NR		1.68 (0.10–26.96)	0.716
Baseline EUS – N						
N0	48	11	119.82	0.413		
N1 – N2 – NX	59	17	NR		1.37 (0.64–2.93)	0.415
Baseline clinical stage						
I–II	47	11	119.82	0.257		
III–IV	60	17	NR		1.55 (0.72–3.32)	0.261
Presence of SRC						
No	45	6	NR	0.038		
Yes	62	22	89.59		2.51 (1.02–6.21)	0.046
Percentage of SRC						
0%	29	4	NR	0.528		
1–10%	7	2	NR		2.39 (0.43–13.12)	0.317
11–49%	8	3	NR		2.24 (0.50–10.12)	0.293
50–100%	24	8	89.59		2.28 (0.69–7.58)	0.179
Histologic grade						
G2 – moderately differentiated	24	2	NR	0.046		
G3 – poorly differentiated	83	26	119.82		3.90 (0.92–16.54)	0.064
Chemotherapy						
No	7	3	34.07	0.074		
Yes	100	25	NR		0.34 (0.10–1.17)	0.088
clinCR						
No	70	22	89.59	0.035		
Yes	37	6	NR		0.39 (0.16–0.97)	0.042
Path T						
pT0	21	4	119.82	0.004		
pT1–pT2	26	2	NR		0.47 (0.09–2.58)	0.386
pT3–pT4	59	22	41.53		2.95 (1.01–8.63)	0.048
Path N						
pN0	71	14	119.82	0.004		
pN1 – pN2 – pN3	35	14	41.53		2.86 (1.36–6.04)	0.006
Path M						
pM0	103	26	119.82	<0.001		
pM1	4	2	13.31		13.71 (2.78–67.67)	0.001
Post-therapy pathologic stage						
0	21	4	119.82	<0.001		
I	24	2	NR		0.50 (0.09–2.73)	0.422
II	37	9	NR		1.57 (0.48–5.12)	0.457
III	21	11	22.08		6.81 (2.13–21.81)	0.001
IV	4	2	13.31		29.35 (4.53–190.17)	<0.001

Table 5 (continued)

	Patients	Events	Median	log-rank	HR (95% CI)	p value
Pathologic response						
path CR	21	4	119.82	0.152		
<path CR	74	20	89.59		2.18 (0.73–6.53)	0.162
R margin						
Negative	94	24	NR	0.110		
Positive	12	4	39.36		2.36 (0.80–6.97)	0.121
Lymphovascular invasion						
No	44	7	NR	0.077		
Yes	34	11	NR		2.30 (0.89–5.95)	0.086

GEJ = Gastroesophageal junction; NR = not reached; clinCR = clinical complete response.

Table 6. Multivariate analysis for OS

	Full model		Reduced model[a]	
	HR (95% CI)	p value	HR (95% CI)	p value
Presence of SRC				
No – SRC				
Yes – SRC	1.41 (0.48–4.18)	0.532		
Histologic grade				
G2 – moderately differentiated				
G3 – poorly differentiated	1.65 (0.30–9.04)	0.562		
clinCR				
No				
Yes	1.63 (0.28–9.58)	0.590		
Post-therapy pathologic stage				
0				
I	0.55 (0.08–3.66)	0.537	0.50 (0.09–2.73)	0.422
II	2.06 (0.27–15.44)	0.483	1.57 (0.48–5.12)	0.457
III	8.17 (0.93–71.67)	0.058	6.81 (2.13–21.81)	0.001
IV	32.73 (2.28–469.05)	0.010	29.35 (4.53–190.16)	<0.001

[a] The model uses stepwise backward elimination methods with $p < 0.15$ as significance level for removal from the model.

ing response is not reported in the literature. Piessen et al. [17] showed that SRC histology is an independent prognostic factor of poor prognosis in GAC. In a more recent study, they showed that SRC assessment by endoscopy is reliable [18]. Similarly, we believe that determination of the presence and percentage of SRC would be a more objective marker compared to classifying tumors based on the Lauren classification (diffuse vs. intestinal), which is susceptible to significant subjectivity.

To the best of our knowledge, our study is the first to demonstrate that the presence of SRC and its proportion in the pre-treatment endoscopic biopsy correlate with chemoradiation response. Our data are also consistent with similar data in esophageal cancer where SRC correlated with response [25]. However, we have taken one additional step of sub-classifying tumors by the percentage of SRC. By doing so, we found that tumors with a higher percentage of SRC were more likely to exhibit

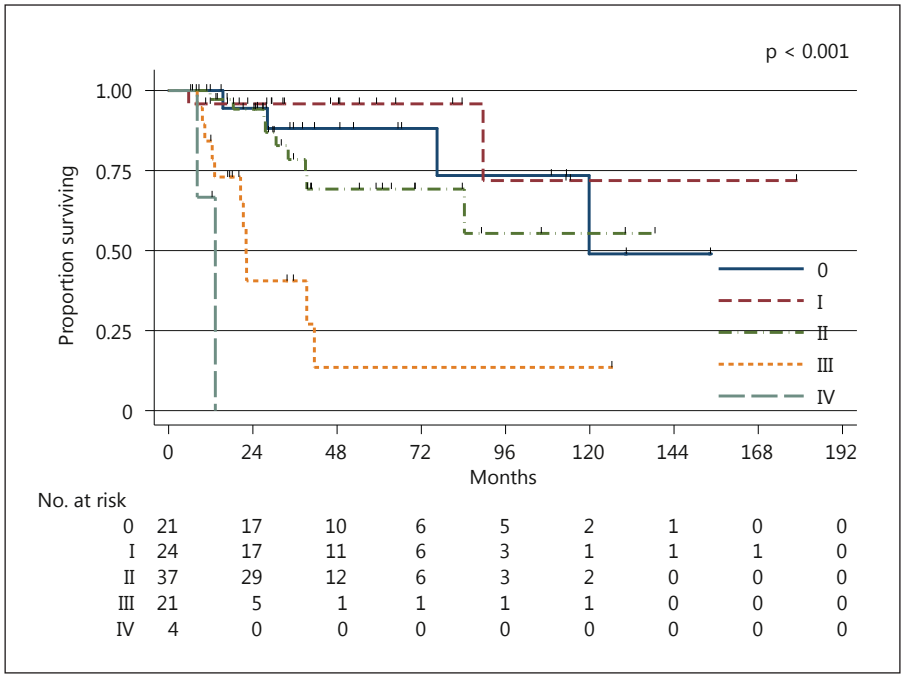

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Fig. 2. Kaplan-Meier OS curves according to the post-therapy pathologic stage.

<pathCR and significantly associate with treatment resistance (p = 0.03).

Our study, being retrospective, has some shortcomings. It is a single high-volume center experience and the total denominator is relatively small. However, our data have strengths that can contribute to the management of patients with LGAC: (1) these were all uniformly treated patients with thoroughly staged disease (that included baseline CT or PET/CT, baseline endoscopic ultrasound, laparoscopy, post-chemoradiation CT or PET/CT and post-chemoradiation endoscopic biopsies, etc.), (2) association of SRC with response is a novel finding, and finally (3) fraction of SRC is highly associated with response as well. Our data, however, are clearly insufficient to change current practice and need further refinement/validation and maybe addition of biomarkers.

In conclusion, our study describes the importance of the presence and percentage of SRC in pre-treatment endoscopic biopsy as predictors of response to chemoradiation. Further refinement/validation of these findings is needed.

Acknowledgements

This study was supported by generous grants from the Caporella, Dallas, Sultan, Park, Smith, Frazier, Oaks, Vanstekelenberg, McNeill, Planjery, and Cantu families as well as by the Schecter Private Foundation, Rivercreek Foundation, Kevin Fund, Myer Fund, Dio Fund, Milrod Fund, and multidisciplinary grants from the University of Texas MD Anderson Cancer Center, Houston, Tex., USA. It was supported in part by the National Cancer Institute awards CA138671, CA172741, and CA129926 (JAA). Nikolaos Charalampakis was awarded a scholarship from the Hellenic Society of Medical Oncology.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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