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Elevated Gastric Juice Carbohydrate Antigen 72.4 (Ca 72.4) Is an Independent Prognostic Factor of Poor Survival for Gastric Cancer Patients

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Abstract. *Background/Aim: As of 2020, carbohydrate antigen 72.4 (Ca 72.4) has been rarely investigated in the gastric juice (GJ) of patients with gastric cancer (GC). Our aim was to analyze the significance and role of this tumor antigen in the GJ of our GC population. Patients and Methods: Between April 2012 and July 2013, 37 patients with operable GC were prospectively investigated to determine the GJ Ca 72.4 levels before surgical manipulation. Results: GJ Ca 72.4 ≥6.49 ng/ml strongly correlated with the traditional categories of aggressive cancer (advanced tumor depth and stage, lymph node invasion and metastatic lymphatic ratio, indication to adjuvant treatment). It also associated with shorter survival (p=0.049) and is, thus, suggested as an independent factor of poor prognosis in GC patients (p=0.047). Conclusion: The GJ Ca 72.4 parameter should be considered an indicator of an aggressive tumor phenotype and should be used in the prognostic assessment of GC patients.*

Despite the fact that its incidence has steadily declined worldwide over the past 50 years, according to GLOBOCAN 2018, data gastric cancer (GC) is still the fifth most frequently diagnosed malignancy (over 1 million new cases yearly) and the third leading cause of cancer-related mortality (783,000 deaths per year) (1, 2). Food preservation and dietary ameliorations as well as eradication of *Helicobacter pylori* infection were precious measures to obtain such a significant decrease in the incidence, but at the same time were not sufficient (3). GC, in fact, is a complex malignancy due to multiple causes and its prognosis is influenced by many factors: hence, providing new diagnostic and prognostic tools, as well as innovative and efficient cures is of utmost importance for present and future patients (4-10). As demonstrated by several studies, the gastric juice (GJ) of GC patients is a potentially optimal source for the investigation of the etiology of this ominous tumor (11-17). As of 2020, the concentration and significance of carbohydrate antigen (Ca 72.4) in the GJ of GC patients has been rarely analyzed (18-22). We think that this type of examination could be of great help to predict more accurately the prognosis of GC patients.

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Key Words: Ca 72.4, gastric cancer, tumor antigen, gastric juice, gastrectomy.

Patients and Methods

We analyzed the clinicopathologic data (including the GJ concentration of Ca 72.4) prospectively collected from 37 surgical patients with GC who were admitted between April 2012 and July 2013 at the Division of General Surgery of St. Andrea Hospital, Faculty of Medicine and Psychology, Sapienza University, Rome, Italy. Our procedure of GJ collection has already been described in former studies: in brief, before surgical manipulation, the GJ was collected under sterile conditions through a naso-gastric tube and immediately transported to laboratory and cytopathology services (23). Ca 72.4 was measured through an electrochemiluminescence sandwich immunoassay method with the Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany). Pathology of surgical specimens was performed following the 7th and 8th edition of AJCC TNM Staging System (24).

Table I. *Clinicopathologic features of the 37 gastric cancer patients and correlation with gastric juice Ca 72.4 values.*

Clinicopathologic feature	Result	Association with GJ Ca 72.4
Gender	M: 22 (59.4%); F: 15 (40.6%)	p=0.462
Age (mean)	64.3 years (range: 39 to 90)	p=0.687
Tumor site	proximal*: 20 (54%)	p=0.712
	distal*: 17 (46%)	
Siewert type	Type 1 and 2: 6 (16.3%)	p=0.09
	Type 3 and non-Siewert cancers: 31 (83.7%)	
Neoadjuvant Th	7 (18.9%)	p=0.515
Adjuvant Th	23 (62%)	**p=0.003**
GL	GL0: 27 (73%); GL1: 10 (27%)	**p=0.012**
T	T category	**p=0.023**
	T1: 5 (13.5%)	**p=0.028**
	T3-T4: 30 (81%)	**p=0.015**
	T4: 19 (51.3%)	**p=0.033**
N	N category	**p=0.023**
	N1-3: 29 (78.3%)	**p=0.034**
N	1: 5; N2: 4; N3: 20	p>0.05
M	M0: 24 (65%); M1: 13 (35%)	p=0.483
Stage	1: 6 (16%)	**p=0.015**
	3-4: 29 cases (78.4%)	**p=0.034**
G	G1: 2; G2: 4; G3: 31	p>0.05
Lauren classification	intestinal: 20 (43%); diffuse: 17 (46%)	p=0.901
WHO type	tubular: 5 (13.5%)	**p=0.027**
Signet ring cells	12 (32%); absence: 25 (67%)	p=0.721
LVI	LVI0: 14 (38%); LVI1: 23 (62%)	p=0.102
PnI	PnI0: 19 (51%); PnI1: 18 (48%)	p=0.260
LNR	LNR2: 6 (16%)	**p=0.047**
	LNR1-3: 29 (78%)	**p=0.034**
No. of lymph nodes	Ca 72.4+: 30; Ca 72.4n: 21	p=0.071
Gastrectomy type	Distal: 15 (53%); Total: 13 (46%)	p=0.709
Operative time (min)	Ca 72.4+: 243; Ca 72.4n: 205	p=0.061
PLS (days)	Ca 72.4+: 10.7; Ca 72.4n: 11.3	p=0.786
Tumor size (mm)	Ca 72.4+: 54; Ca 72.4n: 37.7	**p=0.035**
Preoperative anemia	16 (51%); absence: 15(48%)	**p=0.007**
Postoperative complications	3 (8%)	p=0.477
BMI	Ca 72.4+: 24.9; Ca 72.4n: 22	p=0.536

*Proximal site: Cardio-fundic and gastric body carcinomas; distal site: antro-pyloric cancers; Th: therapy; GL: gastric lavage with (GL1) or without (GL0) cancer cells; LVI: lymphovascular invasion; PnI: peri-neural invasion; LNR: metastatic lymph node ratio; PLS: postoperative length of stay; BMI: body mass index; Ca 72.4+: group with elevated levels of gastric juice Ca 72.4; Ca 72.4n: group with normal gastric juice Ca 72.4. p-values written in bold are statistically significant (<0.05).

Statistics. Statistical analysis was performed using MedCalc Statistical Software version 19.1.3 (MedCalc Software bv, Ostend, Belgium). The optimal cut-off value of Ca 72.4 in the GJ was measured by analyzing the Receiver Operating Characteristic (ROC) curve associated with the area under the curve (AUC). Categorical, ordinal and continuous variables were compared using the Chi-square, Kruskal–Wallis and Student's t-test, respectively. Overall survival (OS) was evaluated as previously described (25). Survival curves were evaluated and compared with the Kaplan–Meier method and the log-rank test, respectively. Univariate and multivariate analysis were performed (through one-way or two-way ANOVA test, multiple linear regression and Cox proportional hazards model) to assess significant association and independency among prognostic factors. p-Values <0.05 were considered statistically significant.

Results

The main clinicopathologic features of the examined population as well as the associations with the GJ Ca 72.4 parameter are listed in Table I. Mean GJ Ca 72.4 value was 53.3 ng/ml. Differently from other GJ tumor markers (such as CEA, CA 19.9 and CA 50), GJ Ca 72.4 was the only antigen to attain a statistical significance not only in ROC analysis (sensitivity and specificity of 100% with a cut-off value >6.49 ng/ml, p<0.001, Figure 1), but also in the association with the presence of GJ malignant cells (p=0.012). In particular, at a median follow-up of 79.3 months (range=62-88 months), all the 8 GC patients who were alive had GJ levels <6.49 ng/ml whereas 18 (62%)

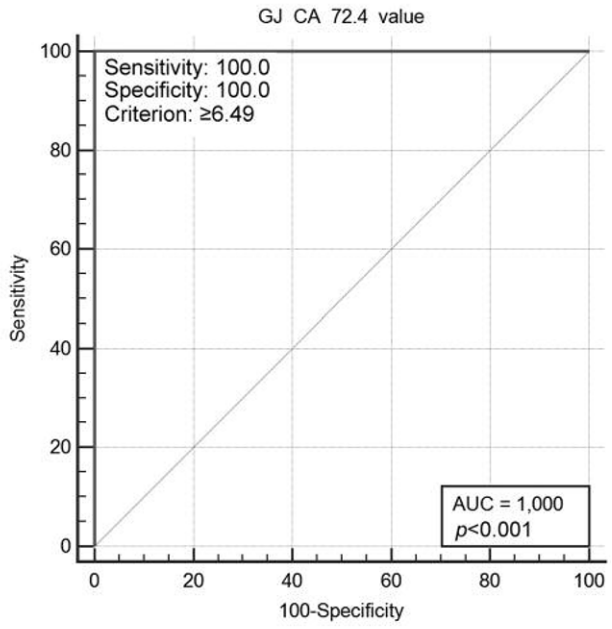

Figure 1. *The receiver operating characteristic (ROC) curve associated with the area under the curve (AUC) demonstrated that, as for Ca 72.4, a gastric juice level of 6.49 ng/ml was the cut-off criterion to get maximal sensitivity and specificity with statistical significance.*

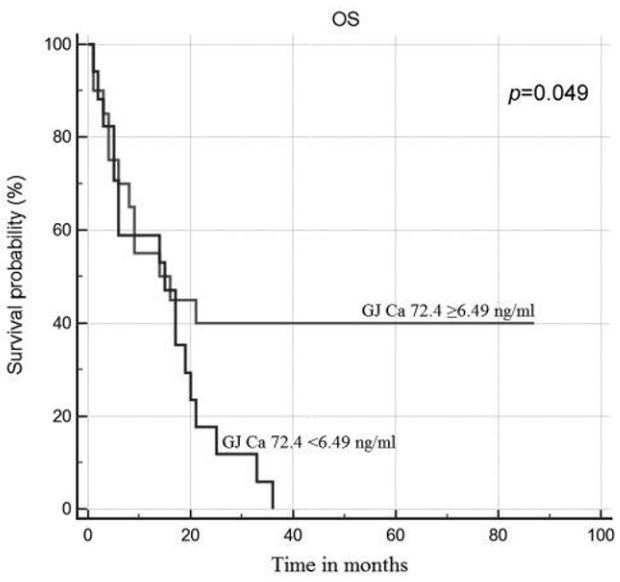

Figure 2. *Differences in overall survival (OS) between groups with higher and lower levels of gastric juice Ca 72.4 levels.*

Table II. *Multivariate analysis of prognostic factors for overall survival*

Independent variables	b	SE	t	*p*-Value	$r_{partial}$	$r_{semipartial}$
GJ Ca 72.4	–0.1703	0.08213	–2.073	**0.0475**	–0.3648	0.1732
EGC	9.4739E-016	0.2292	4.134E-15	1.0000	7.8124E-016	3.4538E-016
T3-T4	–1.1199	0.2840	–3.943	**0.0005**	0.5975	0.3295
N	–0.8808	0.05861	–1.503	0.1441	–0.2732	0.1256
N 1-3	0.4360	0.2120	2.057	**0.0492**	0.3622	0.1718
Stage 3-4	0.1411	0.1923	0.734	0.4692	0.1374	0.06131
Adjuvant therapy	0.1344	0.1154	1.165	0.2538	0.2151	0.09735
LNR	–0.07231	0.05989	–1.207	0.2374	–0.2224	0.1009
Overall model fit: ***p*<0.0001**						

b: The regression coefficient beta; SE: standard error; t: time; $r_{partial}$ and $r_{semipartial}$: partial and semipartial correlation coefficients. LNR: metastatic lymph node ratio; variables and *p*-values written in bold are statistically significant (<0.05).

of the 29 GC patients who had died had values ≥6.49 ng/ml. The Kaplan–Meier model showed that patients with GJ Ca 72.4 levels greater than 6.49 ng/ml had shorter OS compared to subjects with inferior values (14.4 *vs*. 39.6 months, respectively, p=0.049, Figure 2). At univariate analysis, the aforementioned GJ Ca 72.4 criterion was a significant prognostic factor for OS (p=0.002). Furthermore, multivariate analysis demonstrated the GJ Ca 72.4 cut-off value to be an independent prognostic factor of OS (p=0.047 at multiple linear regression with an overall model fit of p<0.001, Table II).

Discussion

As of 2020, differently from the serum concentration, the Ca 72.4 levels in the GJ of GC patients have rarely been investigated (18-22, 26-32). In keeping with former studies, our research has also provided interesting results. First of all, similarly to previous demonstrations, the association between serum and GJ levels of this tumor antigen was not statistically significant (p=0.973) (22). This is probably due to the fact that GJ Ca 72.4 is directly released by the tumor in the stomach

content whereas the serum component is in part eliminated by the liver (19). Secondly, high intragastric levels of this antigen correlate well with traditional clinicopathologic features of aggressive cancers, such as lymphatic invasion (19), advanced depth of invasion (T3-T4, p=0.015) and staging (stage 3-4, p=0.034), larger tumor size (p=0.035), greater number of metastasized lymph nodes (p=0.047), the need of receiving adjuvant therapy (p=0.003) and the concomitant intraluminal presence of malignant cells (p=0.012) (Table I). Thirdly, we focused on the prognostic role of GJ Ca 72.4 for GC patients. Huang and colleagues had already demonstrated that the difference in GJ Ca 72.4 levels between pre- and post-gastrectomy could indicate a bad prognosis ($p\leq$0.005), serving as a sensitive indicator of pathologically undetected metastasis or remnant tumor cells (16). In line with them, our study also pointed out that GC patients with GJ Ca 72.4 levels ≥6.49 ng/ml have shorter survival compared to subjects with inferior values (14.4 *vs*. 39.6 months, respectively, p=0.049, Figure 2). Furthermore, at the multivariate analysis of our case series, GJ Ca 72.4 for the first time resulted to be an independent prognostic factor of poor OS (p=0.047 with an overall model fit of p<0.001, Table II).

Conclusion

GJ Ca 72.4 could be recognized as an indicator of an aggressive tumor phenotype and can be employed as a useful prognostic biomarker for GC patients. We think that the scarce application of this testing is not justified and encourage gastrointestinal oncologists and surgeons to introduce this biomarker in future routine practice.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

All the Authors agreed with the content of the article. Dr. Virgilio conceived of the presented research. Dr. Proietti, Dr. D'Urso and Dr. Cardelli performed the laboratory measurements of GJ CA 72.4. Dr. Giarnieri, Prof. Giovagnoli, Mrs. Montagnini and Mrs. Villani performed the cytopathologic examinations of GJ. Dr. Virgilio wrote the manuscript and performed the statistical analyses. Dr. Balducci and Dr. Cavallini supervised the entire project.

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