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An aggressive early gastric cancer: Kodama's PenA type

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ABSTRACT

Background: To investigate the role of Kodama PenA subtype in influencing survival in patients with early gastric cancer (EGC).
Methods: All patients surgically treated for EGC at 7 Italian centers (Forlì, Varese, Siena, Verona, Milan, Rome and Perugia) belonging to the Italian Research Group for Gastric Cancer (GIRCG) from January 1982 and December 2009 were included.
Results: PenA patients were 230 (21.5%) while other types were 839 (78.5%). Nodal metastases were more common in PenA (30.7%) than non-PenA (10.4%) EGCs. Among preoperative variables, only age (OR 1.02; 95% CI 1.00–1.03, p = 0.009) and macrotype III (OR 1.95; 95% CI 1.39–2.75, p = 0.0001) were significantly associated with Pen A type. Survival analysis performed on N0 patients demonstrated that only size >2 cm (HR 1.85; 95% CI 1.12–3.05, p = 0.017) and age (HR 1.06; 95% CI 1.03–1.08, p < 0.0001) were independent poor prognostic factor. Among N+ patients age (HR 1.04; 95% CI 1.00–1.07, p = 0.048), number of positive lymph nodes (HR 1.13; 95% CI 1.05–1.20, p = 0.0002) and PenA (HR 4.23; 95% CI 1.70–10.55, p = 0.002) were significantly correlated with poor prognosis at multivariate analysis.
Conclusions: Kodama PenA subtype was the most powerful independent prognostic factor in patients with nodal metastases. Its status should always be investigated in EGCs patients.

Introduction

Early gastric cancer (EGC) is associated with a 5-year survival of more than 90% [1–3]. However, a subgroup of EGC patients shows a significantly worse prognosis. This has been partly explained by the presence of lymph node metastases which has been shown as a powerful factor influencing survival in EGCs [4–6]. Previous GIRCG multicenter analyses on EGC patients confirmed the importance of N status as a prognostic factor and also showed that Kodama's PenA type was an independent predictor of poor prognosis [4,5]. Nevertheless, data about clinico-pathological features of the Kodama's Pen A type are scarce in literature. With this paper we aim to investigate the characteristics of Pen A type, focusing our analysis on its impact on survival.

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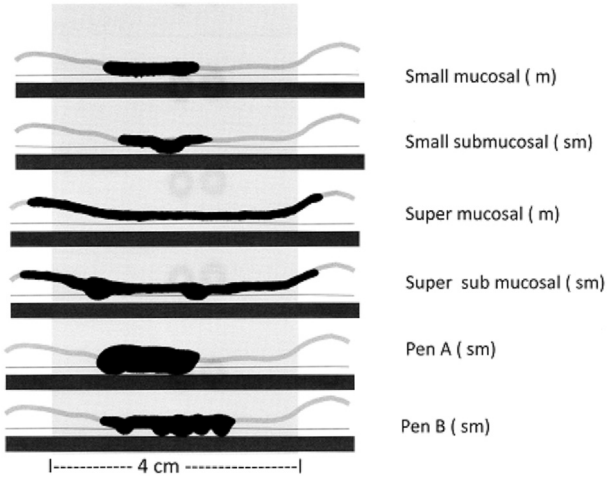

Fig. 1. Scheme representing Kodama's types.

Material and methods

Study populations and definitions

All patients surgically treated for EGC at 7 Italian centers (Forlì, Varese, Siena, Verona, Milan, Rome and Perugia) belonging to the Italian Research Group for Gastric Cancer (GIRCG) from January 1982 and December 2009 were included. Local Ethical Committee approved this study. Informed consent was not required due to the retrospective nature of the study.

As per GIRCG guidelines, the included centers routinely use commonly-defined diagnostic and surgical criteria [7].

All slides were re-revised according to the current guidelines [7] by the dedicated pathologists of each centres.

The EGCs were classified according to macroscopic and microscopic criteria proposed by the Japanese Society of Gastroenterology and Endoscopy (JSGE) and Lauren, respectively [8,9]. ECG was also stratified as per Kodama classification (Fig. 1) [10].

Cancer specific survival, which was the only time-related variable used in the analysis, was defined as the interval from the date of surgery to the date of death caused by gastric cancer.

Statistical analysis

The chi-square test was used to compare categorical data. Continuous data, which were presented as median and interquartile range (IQR) were compared using Mann Whitney *U* test. Sex, age, tumor size (≤2 vs >2), Lauren histotypes and macrotypes according to JSGE (type III vs non type III) were analyzed with logistic regression to assess whether they could predict the diagnosis of PenA. Odds ratio (OR) and 95% confidence interval (95% CI) were calculated when required.

Cox proportional-hazards regression was performed to find those factors influencing cancer-specific survival in the subgroup of N0 and N+ patients. Included variables were Sex (female vs. male), age, tumor size (≤2 vs >2), number of positive lymphnodes, Lauren's histotypes, macrotypes according to JSGE (type III vs non type III), and PenA status (PenA vs non-PenA). Hazard ratios (HR) and 95% confidence interval (95% CI) were calculated when required.

A p value < 0.05 was considered statistically significant. Statistical analysis was performed with MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015).

Results

Data about Kodama subtypes were available for 1069 out of 1074 EGC patients. Six hundred and twenty (58%) were men and 448 (41.9%) women with a median of 67 years of age (range 22–93 years). Kodama PenA were 21.5% (n = 230).

Patients' characteristics grouped according to their PenA status are reported in Table 1.

The median number of lymph nodes harvested was 15 (IQR 10–25) and there was no significant differences between PenA (median 16; IQR 11–26) and non-PenA (median 15; IQR 10–24) (p = 0.366). Multivariate analysis showed that age (OR 1.02; 95% CI 1.00–1.03, p = 0.009) and macrotype (JSGE) III (OR 1.95; 95% CI 1.39–2.75, p = 0.0001) were significantly associated with Pen A type (AUC 0.59; 95% CI 0.56–0.62). Median follow-up was 193 months (range 1–324).

Survival analysis

Multivariate analysis performed on N0 patients (n = 901) demonstrated that only size >2 cm (HR 1.85; 95% CI 1.12–3.05, p = 0.017) and age (HR 1.06; 95% CI 1.03–1.08, p < 0.0001) were significantly correlated with a poor prognosis (Table 2). Ten-year survival was 94.3% for tumors ≤2 cm while it was 89.2% when size was above 2 cm (p = 0.0032) (Fig. 2). Among N positive patients (n = 156) age (HR 1.04; 95% CI 1.00–1.07,p = 0.048), number of positive lymph nodes (HR 1.13; 95% CI 1.05–1.20, p = 0.0002) and PenA (HR 4.23; 95% CI 1.70–10.55, p = 0.002) were the only independent prognostic factors (Table 2). N-positive PenA patients showed a 10-year survival of 63.8% while it was 89.3% for other N positive Kodama types (p = 0.0004) (Fig. 3).

In the whole cohort of 1069 patients PenA had a significantly lower 10-year survival (78.2%) when compared with other submucosal non-PenA (91.5%) and mucosal (94.2%) EGC (p < 0.0001)

Table 1
Patients' and tumor characteristics.

	Kodama		p
	Pen A (n = 230)	Non Pen A (n = 839)	
	No. (%)	No. (%)	
Age n (%) - n = 1046 -			0.01
≤60 years	50 (22)	252 (31.2)	
>60 years	177 (78)	567 (69.2)	
Sex n (%)			0.179
Male	124 (53.9)	496 (59.1)	
Female	106 (46.1)	343 (40.9)	
Lauren's histotype n (%) - n = 1068 -			0.133
Intestinal	173 (75.6)	585 (69.7)	
Diffuse	35 (15.3)	178 (21.2)	
Mixed	21 (9.1)	76 (9.1)	
Size n (%) - n = 1060 -			0.016
≤2 cm	114 (50.2)	495 (59.4)	
>2 cm	113 (49.8)	338 (40.6)	
N stage n (%) - n = 1057 -			<0.001
N0	157 (69.2)	744 (89.6)	
N1	52 (22.9)	63 (7.6)	
N2	17 (7.4)	19 (2.3)	
N3	1 (0.4)	4 (0.5)	
Macrotypes (JSGE) - n = 1051 -			<0.001
I (polypoid)	36 (16.1)	101 (12.2)	
IIa (elevated)	27 (12.0)	88 (10.6)	
IIb (flat)	7 (3.1)	100 (12.1)	
IIc (depressed)	86 (38.4)	390 (47.2)	
III (excavated)	68 (30.4)	148 (17.9)	

Table 2
Cox regression analyses for N− and N+ EGC patients.

Variables	N−				N+			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95%CI)	P	HR (95% CI)	P	HR (95% CI)	P
Female (yes vs no)	0.77 (0.47–1.28)	0.331			1.17 (0.57–2.39)	0.666		
Age[a]	1.06 (1.03–1.09)	<0.0001[b]	1.06 (1.03–1.08)	<0.0001	1.03 (1.00–1.06)	0.049[b]	1.04 (1.00–1.07)	0.048
Tumor size >2 cm (yes vs no)	2.08 (1.27–3.41)	0.004[b]	1.85 (1.12–3.05)	0.017	0.75 (0.37–1.53)	0.442		
Number of positive lymph nodes[a]					1.1 (1.04–1.17)	0.0005[b]	1.13 (1.05–1.20)	0.0002
Lauren's histotypes								
Diffuse (yes vs no)	0.61 (2.95–1.29)	0.202			0.84 (0.4–1.77)	0.654		
Intestinal (yes vs no)	1.35 (0.75–2.44)	0.314			0.98 (0.48–2.02)	0.966		
Mixed (yes vs no)	1.08 (0.46–2.49)	0.854			1.35 (0.55–3.29)	0.507		
JSGE macrotypes type III (yes vs no)	1.02 (0.55–1.87)	0.954			1.17 (0.53–2.54)	0.696		
Kodama PenA type (yes vs no)	1.87 (1.06–3.28)	0.031[b]			3.9 (1.74–8.73)	0.001[b]	4.23 (1.70–10.55)	0.0004

[a] Analyzed as continuous variable
[b] Included in the multivariate analysis.

(Fig. 4a). Among N positive patients 10-year survival for other submucosal non-PenA and mucosal EGC patients was 84.9 and 96.3%, respectively (Fig. 4b).

Discussion

PenA Kodama type, which represents more than one fifth of all EGCs, is associated with worse prognosis than the other types. This has already been shown by previous studies from our group [4–6]. Differently from these papers, we reported data about a large cohort of 1069 EGC patients, focusing our analysis on the clinico-pathological characteristics of PenA vs other EGC types and on the impact of PenA type in the prognosis of patients according to nodal status. Our analysis confirmed that PenA is a negative prognostic factor especially in patients who are N positive. Among them, non-PenA patients reached a plateaux in terms of survival after 5 years while this is delayed by five more years for PenA patients. This result may suggest that a prolonged follow-up of at least 10 years should be always considered in ECG PenA type patients.

It has already been demonstrated that the submucosal invasion is a negative prognostic factor in EGC [5]. In order to verify whether the pattern of invasion could significantly influence survival among EGCs invading submucosa, we compared PenA with other submucosal types of EGC. This analysis demonstrated that PenA was significantly associated with the worst prognosis among submucosal-invading EGCs, showing that the pattern of invasion was the key factor affecting prognosis.

As it also appeared from our data, PenA displayed a significantly higher incidence of nodal metastases than the other EGCs subtypes [4,5]. PenA was found as a significant risk factor for lymph node spread in a previous analysis on 584 EGC patients by GIRCG [4]. According to these findings PenA patients may benefit from a standard gastrectomy with D2 lymphadenectomy. This would be in contrast with current guidelines, in which a D1+ lymphadenectomy could be considered a radical procedure for EGCs [7,11].

Consequently, it may not be appropriate to attempt either more conservative or endoscopic-assisted minimally invasive approaches in PenA EGCs [12–14].

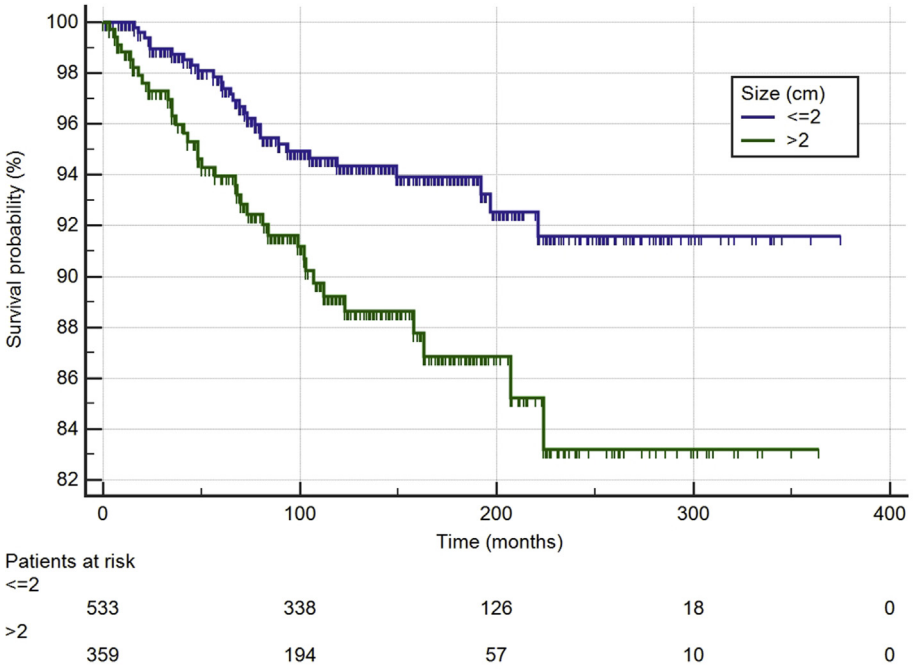

Fig. 2. Kaplan-Meier curves showing survival probability according to tumor size (>2 cm vs. ≤2 cm).

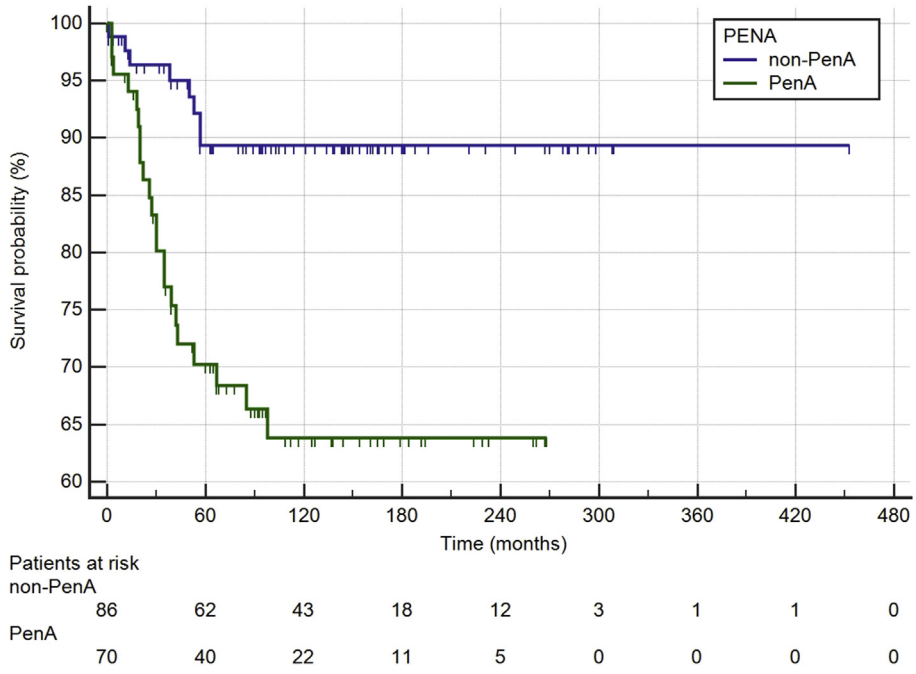

Fig. 3. Kaplan-Meier curves showing survival probability according to Kodama's type (PenA vs other types).

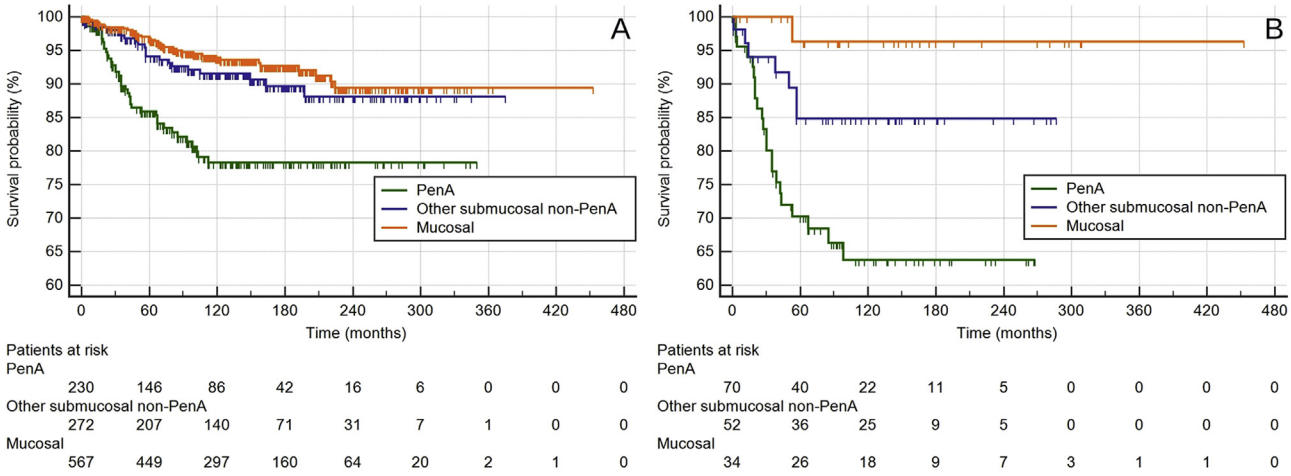

Fig. 4. Kaplan-Meier showing survival probability of PenA vs Other submucosal vs Mucosal types in the whole cohort **(A)** and in N+ patients **(B)**.

To date, it seems not possible to identify PenA subtypes preoperatively and, therefore, to offer EGC patients the most adequate treatment. Our analysis found age and JSGE macrotype III as the only predictor variables positively associated with PenA type. Unfortunately, these two variables are too uncertain and their predictor model showed a very low accuracy with an AUC of 0.59 (95% CI 0.56–0.62).

Currently, the research institute of one of the GIRCG centres (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST)) has been investigating potential biochemical and molecular markers which may help in identifying PenA at an early stage of the diagnostic process. This study has some limitations mainly due to the retrospective nature of the analysis. First, the study interval is very wide and it may have included different modalities of care for the patients. Second, we could not provide information about patients who underwent adjuvant chemotherapy and, thus, we could not verify whether, among N positive patients, there would have been differences between the two groups in terms of adjuvant treatments. Third, pathological factors, like lymphovascular invasion, which might have had an impact on survival, could not be retrieved and were not included in the analysis.

In conclusion, we showed that, in patients with nodal metastases, Kodama PenA subtype was the most powerful independent prognostic factor. Its status should always be investigated in EGCs patients, who should benefit from a D2 lymphadenectomy and a 10-years long follow up.

Further studies are needed with the aim of identifying PenA preoperatively in order to address patients to the most appropriate treatment option.

Conflict of Interest

The authors declare that they have no conflict of interest.

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