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What reasons lie behind long-term survival differences for gastric cancer within Europe?

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ABSTRACT

Background: Wide geographic variations in survival for gastric cancer in Europe have been reported. The aim of this study was to analyse the effect of stage at diagnosis, treatment and cancer characteristics on long-term survival for gastric cancer in populations covered by cancer registries.

Methods: We analysed survival in 4620 cases of gastric cancer from 17 European population-based cancer registries from 8 countries. Univariate and multivariate regression of relative survival were performed.

Results: Five-year relative survival varied between 10.6% and 24.0%, while 10-year survival ranged from 7.7% to 23.0%. After adjustment for age and sex, the regional excess hazard ratio (EHR) of death was significantly higher in Ragusa, Granada, Yorkshire, Slovakia, Slovenia and Poland than in France, Northern Italy, The Netherlands and the Basque Country.

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After further adjustment for surgical resection versus no resection (a proxy of stage), the EHR of death remained significantly higher only in Granada and Yorkshire than in the reference country (France). After adjustment for stage, the EHR was significantly higher only in Yorkshire (EHR: 1.51; 95% confidence interval (CI): 1.29–1.77). The EHR in this area was limited to the first year following diagnosis.

Conclusion: Differences across Europe in gastric cancer survival depend to a large extent on differences in stage at diagnosis. However they do not explain all variations. Quality of management and treatment can explain some differences.

1. Introduction

Although the incidence of gastric cancer is declining in most Western countries, this cancer remains relatively frequent, accounting for nearly 20% of all digestive tract cancers diagnosed in the European Union.[1] The prognosis remains poor[2] and there has been no major improvement in survival over the past 20 years.[3–5] The EUROCARE II study on cancer survival in Europe showed marked variations in survival from gastric cancer.[6] Few studies have investigated outcome after a longer follow-up. Variations in survival are not easy to interpret. Earlier diagnosis and/or better treatment have often been proposed as an explanation to the observed differences in survival. Variations in gastric cancer survival can also be explained by differences in cancer characteristics, the subsite and histological type, or the sex, age or social class of patients. Population-based studies, using data collected by cancer registries, are needed to understand variations in survival for gastric cancer. Detailed studies at a population level are rare because they require precise data collection which is not widely available in cancer registries. Most available data are provided by specialised centres and as such cannot be used to analyse survival differences because of unavoidable selection bias. The aim of this study was, therefore, to obtain information on gastric cancer characteristics, treatment and stage at diagnosis from a population-based sample of cases of gastric cancer diagnosed in eight European countries and to examine the influence of these factors on long-term survival.

2. Patients and methods

2.1. Population

Seventeen population-based cancer registries participating in the EUROCARE study, from 8 countries (Table 1) adhered to a common protocol to collect data on treatment and stage at diagnosis from the clinical records of individual cases. Cases were recorded between 1986 and 1990 according to the area (Table 1) and were followed for 10 years. At least 200 cases were intended to be contributed by each registry. In most cancer registries, data were collected on all cases recorded over a period of 1–4 years, according to the size of the population. In some large populations (Slovakia, Slovenia), registries provided data from a representative sample of gastric cancers diagnosed over a 1-year period. Detailed clinical information from each case was subsequently abstracted from the clinical notes. Non-epithelial tumours (lymphomas, carcinoïd tumours and sarcomas) were excluded as were cases known to the registries only through death certificates or discovered incidentally at autopsy. A total of 4620 cases were analysed.

Table 1 shows the distribution of cases by sex, age, proportion of cardia cancers, proportion of subsites unknown and percentage of histology verified cases. The proportion of men varied between 53.0% (Genoa, Italy) and 65.4% (Rotterdam, Netherlands) and the proportion of patients over 75 between 29.2% (Slovakia) and 49.0% (Côte-d'Or, France). Age and sex are therefore potential confounding factors in survival comparisons. The proportion of cardia cancers also varied with registry from 6.2% (Varese) to 26.0% (Rotterdam). Site was not taken into account in the analysis because the proportion of missing data was over 20% in six registries. The proportion of known stage at diagnosis varied between 99.2% (Côte-d'Or) and 60.3% (Firenze). The high proportion of cases with unknown stage in some areas was related to the difficulty to find the information in consulted medical files. In the univariate and multivariate survival analysis, we did not include cancer registries with a proportion of unknown stage at diagnosis over 10% (Northern Italy Registry, Ragusa, Polish registries).

2.2. Studied variables

Patients were categorised into three age groups: under 65 years, 65–74 years and 75 years and over. Tumour site was classified according to the International Classification of Diseases for Oncology, ICD-02.[7,8] The ICD-02 classification was also used for the pathological classification. Histological types included adenocarcinoma (8140/8148; 8190; 8210/8211; 8230; 8260/8262; 8310; 8320; 8323; 8510), signet ring cell adenocarcinoma (8142; 8190), mucoïd carcinoma (8480/8483), undifferentiated carcinoma (8020–8021), carcinoma not otherwise stated (8000/8001), epidermoïd carcinoma (8070/8071). In the multivariate analysis, undifferentiated carcinoma ($n = 171$) and the rare epidermoïd carcinoma ($n = 37$), which show the same survival, were grouped together.

Primary treatment was recorded as follows: resected cancer, i.e. surgery to remove the primary gastric tumour whether or not it was judged radical (data were not precise enough in some registries to distinguish resection for cure from palliative resection), and non-resected cancer including surgery that did not aim to remove the primary gastric cancer (bypass, exploratory laparotomy), radiotherapy and/or chemotherapy and best supportive care. Disease stage at diagnosis was defined according to the TNM classification, fourth

Table 1 – Characteristics of patients with gastric cancers by Registry.

	Number of cases	Period of diagnosis	Males (%)	⩾75 years (%)	Cardia (%)	Histologically verified (%)	Known stage at diagnosis
Bas-Rhin	234	1987–1988	56.8	48.3	18.4	98.3	98.7
Calvados	337	1986–1989	64.1	42.1	14.8	97.3	95.3
Côte-d'Or	257	1986–1989	58.0	49.0	17.1	96.5	99.2
Varese	337	1985–1987	62.3	43.6	6.2	87.4	91.7
Firenze	290	1985–1986	64.1	45.5	9.7	74.1	60.3
Genoa	249	1986	53.0	45.8	nc	84.7	69.1
Ragusa	178	1984–1987	64.6	42.1	nc	60.3	77.0
Eindhoven	363	1987	61.7	35.3	17.4	97.5	88.2
Rotterdam	269	1987	65.4	47.2	26.0	97.4	90.4
Yorkshire	276	1987–1988	60.9	42.4	nc	82.3	92.0
Granada	303	1987–1989	61.4	30.0	11.2	91.8	95.4
Slovakia	411	1988	60.1	29.2	11.2	87.3	96.8
Slovenia	465	1988	62.4	32.3	nc	93.9	93.3
Krakow	337	1987–1989	63.8	32.3	nc	62.7	86.0
Warsaw	314	1988	61.5	36.3	nc	75.1	86.9

nc = Not calculated due to proportion of missing data concerning subsite higher than 20%.

revision.[9] Three stages were defined: (1) cancers limited to the gastric wall (T1/3, N0, M0), (2) cancers with locoregional extension (T4, N0, M0), and/or lymph node involvement (all T, N1/2, M0), and (3) cancers with visceral metastasis (M1). Non-resected cases were analysed with metastatic cases and together were called advanced cancers. Patients with resection, whose pathological results were not available, were classified as stage unknown.

3. Statistical analysis

The characteristics of the patients and the distribution of primary treatment and tumour stage at diagnosis were compared between registries with the χ^2 test. Survival was studied for the first 10 years after the date of diagnosis. The proportion of patients lost to follow-up varied between 0% and 2.1% according to the registry. We computed relative survival rates by using the life table and country-specific life tables established for the EUROCARE study.[10,11] Relative survival rates provide an estimate of patients' survival which is corrected for competing causes of death. It is defined as the ratio of the observed survival of gastric cancer patients to the expected survival of cohort matched for age, sex and geographic area. Survival curves were compared using the likelihood ratio test. Within a country, cancer registry data were grouped unless there were significant differences in relative survival curves. Thus for France, cancer registries were grouped together, as was the case for The Netherlands and Poland. In Italy the registries from the North (Firenze, Genoa and Varese) were grouped together, while Ragusa (in the South of Italy) was kept separate. Multivariate analysis was performed using a relative survival model of Esteve et al.[12] using the Maximum Likelihood Estimation method proposed by Dickman et al.[13] This model makes it possible to calculate relative risks, which are adjusted for competing causes of death. The significance of covariates was tested by the likelihood ratio test.

4. Results

Table 2 shows 1-, 5- and 10-year relative survival rates by geographic grouping. Overall, they were 37.2%, 17.8% and 15.7%, respectively. There was a more than twofold variation in 5- and 10-year survival rates when comparing the areas with the highest survival and those with the lowest. Ten-year relative survival rates were slightly over 20% in North Italy. They were slightly under 10% in Ragusa, Granada and Poland.

The proportion of patients who underwent surgical resection in each area is shown in Table 3 together with the corre-

Table 2 – One, five and 10-year relative survival rates for gastric cancer patients by geographic area.

	1-year survival		5-year survival		10-year survival	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
France	44.5	40.8–47.9	20.2	17.1–23.5	16.2	13.1–19.6
Northern Italy	40.2	36.8–43.5	22.5	19.4–25.7	21.4	18.2–24.8
Ragusa	35.3	27.7–42.9	14.7	9.0–21.8	9.0	4.4–15.6
Netherlands	40.3	36.3–44.2	20.9	17.3–24.4	18.0	14.1–22.2
Granada	33.9	28.5–39.3	12.6	8.8–17.1	9.6	6.1–14.1
Yorkshire	28.5	23.1–34.1	12.8	8.6–17.5	11.0	7.0–15.9
Slovakia	38.6	33.6–43.5	19.5	15.3–24.0	17.1	12.9–21.8
Slovenia	35.0	30.5–39.5	16.1	12.6–20.0	14.2	10.8–18.1
Poland	27.4	23.9–30.9	10.6	8.2–13.4	7.7	5.4–10.6

Table 3 – Percentage of resected and unresected gastric cancers and the corresponding 5- and 10-year relative survival rates by geographic area.

	Resected							Unresected*				
	Proportion of cases	1-year survival		5-year survival		10-year survival		Proportion of cases	1-year survival		5-year survival	
		%	95% CI	%	95% CI	%	95% CI		%	95% CI	%	95% CI
France	61.4	60.8	55.4–64.4	30.9	26.3–35.5	25.1	20.4–30.1	37.6	17.1	12.9–21.7	1.5	0.6–3.4
Northern Italy	52.5	62.0	57.1–66.4	35.8	30.9–40.8	34.1	28.9–39.3	44.5	9.1	6.4–12.4	0.7	0.2–2.0
Ragusa	29.4	56.4	40.9–69.2	33.2	19.5–47.6	16.5	6.6–30.3	67.8	22.1	14.5–30.7	0.6	0.0–3.9
Netherlands	51.4	63.3	57.5–68.6	34.8	28.9–40.7	29.5	23.1–36.3	47.5	15.1	11.2–19.5	5.6	2.9–9.4
Granada	49.5	53.0	44.6–60.9	23.8	16.7–31.7	18.7	11.9–26.8	47.5	12.8	7.9–18.9	0.1	0.0–1.8
Yorkshire	45.7	55.2	45.6–63.7	27.9	19.3–37.2	23.9	15.3–33.5	54.4	6.3	3.2–11.0	0.2	0.0–2.1
Slovakia	59.4	54.4	47.6–60.8	28.2	22.0–34.7	24.5	18.2–31.3	40.6	15.4	10.3–21.6	5.6	2.6–10.7
Slovenia	44.5	63.0	55.6–69.4	32.8	25.8–39.9	29.0	22.2–36.1	53.6	9.8	6.4–14.0	1.5	0.4–4.1
Poland	29.8	57.3	49.8–64.2	26.1	19.5–33.2	19.3	12.9–26.6	69.4	14.0	10.9–17.4	3.8	2.2–6.1

* The 10-year relative survival was not calculated, being 0% in most areas.

sponding 1-, 5- and 10-year relative survival rates. There was a good correlation between overall survival rates and the proportion of resected cancers ($r = 0.67$, $p = 0.036$). The resection rate was under one-third in Ragusa and in the two Polish registries, which reported the lowest survival rate. There were differences in the 5- and 10-year survival rates of resected cases among geographic groups. The 5-year relative survival rates varied between 23.8% (Granada) and 35.8% (North of Italy) and the 10-year relative survival rates between 16.5% (Ragusa) and 34.1% (North of Italy). For non-resected cases, relative survival rates were poor everywhere, on average 2.7% at 5 years.

The proportion of cases limited to the gastric wall varied between 12.9% and 20.0% according to the geographic area (Table 4). There were large differences in 5- and 10-year survival rates. They varied, respectively, between 45.2% and 66.9% and between 35.4% and 56.1%. They were particularly low in Yorkshire, UK and Slovakia. There were fewer variations in survival rates for gastric cancer with locoregional involvement and their 5-year relative survival rates varied between 15.0% and 22.5%, while 10-year relative survival rate ranged from 11.0% to 19.0%. Advanced stage accounted for 50–60% of all cases and survival rates were low everywhere.

The excess hazard ratio (EHR) of death by geographic area was determined using a multiple regression of relative survival model. The reference category was France, which had the highest number of cases in the study. For the simplest model including only sex, age and geographic groupings the EHR of death was significantly higher in Ragusa, Granada, Yorkshire, Slovakia, Slovenia and Poland than in France, and was no different in Northern Italy and The Netherlands (Table 5). As treatment and stage at diagnosis were closely correlated they were not included together in the multivariate analysis. We thus performed two successive models including treatment (which can be considered as a surrogate of stage) in one and stage at diagnosis in the other. With the model adjusted for resection versus no resection, the range of EHR of death between regions narrowed. They remained significantly higher in Granada and Yorkshire. As mentioned earlier six registries were excluded from the multiple regression analysis including stage. In this model, the EHR of death remained significantly higher in Yorkshire (Table 5).

Table 5 also shows the prognostic role of other studied variables. After adjusting for treatment or stage at diagnosis, age became a borderline significant factor. The EHR of death was lower in women than in men when adjusted for treatment, and was no longer significant when adjusted for stage at diagnosis. Morphology was also an independent prognosis factor. Undifferentiated and epidermoïd carcinomas and signet ring cell adenocarcinomas had a worse prognosis than adenocarcinomas. However, the EHR of death according to geographic area was not influenced by the inclusion or not of morphology in the multivariate analysis (data not shown).

In Table 6, the EHR of death is given separately for the first year following diagnosis and the longer term. After adjustment for age, sex, histological types and resection versus no resection, the higher EHR of death, limited to the first year after diagnosis, was seen in Yorkshire and Slovenia compared to France taken as the reference. No significant differences between the other areas were seen from the second to the fifth year.

5. Discussion

Several methodological issues have to be considered before comparing survival differences between geographic areas because they can affect the comparability of data. Population-based series collected by cancer registries as opposed to hospital-based series have the major advantage of avoiding selection bias. The comparability of data within the EUROCARE study has already been evaluated.[14] The number of patients lost to follow-up was low everywhere. So it can be concluded that incidence and survival differences are real. The aim of this study was to obtain information on gastric cancer characteristics and management in order to examine their influence on survival differences. Some data were nearly complete, in particular those concerning treatment which was used in the analysis as a surrogate of stage. However, the study does have some weaknesses. Information on stage at diagnosis was too often unknown in some Italian and Polish cancer registries, which were thus not included in multivariate analysis. Few registries provided exhaustive information on subsite; as a result, this variable could not be included in the survival analysis. This was a limitation of this study. Data on

Table 4 – Percentage of gastric cancers by stage and the corresponding 5- and 10-year relative survival rate by geographic area.

	T1/T3 N0 M0				T4 N0 M0/all N + M0				Advanced stages*		
	Proportion of cases	1-year survival %	5-year survival %	10-year survival %	Proportion of cases	1-year survival %	5-year survival %	10-year survival %	Proportion of cases	1-year survival %	5-year survival %
France	19.6	90.6 (83.6–94.7)	66.9 (56.7–75.3)	53.8 (42.4–63.9)	31.0	49.4 (42.9–55.5)	15.0 (11.5–21.0)	11.0 (6.8–16.4)	46.9	18.5 (14.6–22.8)	2.2 (0.9–4.5)
Netherlands	17.3	86.6 (77.5–92.2)	62.7 (50.4–72.8)	54.8 (39.9–67.4)	20.1	58.9 (49.4–62.3)	22.6 (15.1–31.1)	14.4 (7.8–22.9)	52.4	16.6 (12.7–20.9)	6 (3.5–9.6)
Granada	12.9	85.0 (66.8–93.7)	52.3 (32.6–68.7)	41.4 (21.3–60.6)	21.5	53.6 (40.5–65.1)	17.3 (8.6–28.8)	10.8 (4.3–20.6)	61.1	16.8 (11.7–22.5)	1.6 (0.3–5.0)
Yorkshire	14.9	80.6 (61.8–90.8)	46.6 (27.3–63.8)	35.4 (17.5–53.9)	19.9	43.9 (30.1–56.7)	15.2 (6.6–27.1)	11.5 (4.3–22.7)	57.3	6.7 (3.5–11.3)	0.2 (0.0–2.1)
Slovakia	20.0	78.4 (66.9–86.4)	45.2 (32.3–57.2)	37.3 (24.3–50.3)	25.8	51.8 (41.4–61.2)	21.8 (13.5–30.8)	19 (10.7–29.0)	51.1	14.8 (10.2–20.2)	6.2 (3.2–10.4)
Slovenia	13.8	82.4 (68.9–90.4)	59.4 (44.1–71.8)	56.1 (40.7–69.0)	20.2	58.8 (47.7–68.3)	22.5 (12.9–30.8)	16.1 (8.9–25.2)	59.4	12.5 (8.9–16.9)	1.7 (0.1–2.9)

*M+ and unresected cases; 95% CI in parentheses.

morphology were complete and consistent with other population-based studies.[15–17] Signet ring cell adenocarcinoma, undifferentiated carcinomas and the rare epidermoïd carcinomas had the worst prognosis. Though morphology was an independent prognostic factor, it did not explain survival differences between registries. Patients with no information on morphology had a significantly greater risk of death, independently of stage at diagnosis. There were considerable differences among geographic areas in the proportion of cases without microscopic verification. As approximately only half patients overall were operated on, endoscopy was the principal way of obtaining a histological diagnosis. The proportion of microscopically verified cases is a good indication of the use of gastroscopy in each country involved, and indirectly of the quality of the health care system. It was particularly low in Ragusa and in Poland. The proportion of patients aged 75 and over was generally lower in East European countries. It can be explained by both a lower life expectancy and under-registration. Failure to diagnose and thus to register incident cases among the elderly might induce an overestimation of survival and make unadjusted reported survival differences even more variable.

Surgical resection is currently the only treatment that can lead to cure. The proportion of patients who received surgical resection correlated positively with 5-year relative survival. However, among resected and non-resected cases or among individual stage categories, there were also some survival differences. Differences in the distribution of stage at diagnosis among resected cases can play a role, but they are unlikely to explain all the reported differences. Heterogeneity of surgical practices is also likely to explain some of the variations. Surgical treatment represents a proxy for stage thus making it possible to distinguish between advanced cancers (M+ or non-resectable) and non-advanced cancers. Adjusting for cancer resection versus no resection, explained the differences in the HER of death in Ragusa, Slovenia, Slovakia and Poland compared to the reference geographic area. However, the EHR of death remained significantly higher in Yorkshire. It was smaller but remained significant in Granada.

The almost complete disappearance of survival differences in the multivariate relative survival model that adjusted for stage (except in Yorkshire) identifies stage as a major factor influencing geographical differences in survival. The classification used in this study was consistent with TNM staging. It took into account both clinical extension and the pathological extension in the resected specimen. However, the quality of routine pathology examination may vary between laboratories. It depends in particular on the thoroughness of the examination and the completeness of lymph node resection. The most recent edition of the TNM classification states that at least 15 lymph nodes must be examined in order to form an accurate evaluation of the node status.[9] A population-based study strongly suggests that staging is reliable if at least 10 nodes are examined.[18] The wider variation in survival for cancers limited to the gastric wall can be partly explained by differences in determining lymph node involvement leading to extensive cancers being misclassified as local or to unrecognised more advanced disease. Unfortunately data were not accurate enough to investigate this hypothesis.

Table 5 – Gastric cancer excess hazard ratio (EHR) of death in selected European populations as determined by multivariate regression models.

	EHR	95% CI	EHR	95% CI	EHR	95% CI
France	1		1		1	
Northern Italy	1.03	0.92–1.15	1.06	0.94–1.18	–	–
Ragusa	1.22*	1.01–1.48	0.81*	0.67–0.99	–	–
Netherlands	1.10	0.97–1.24	0.97	0.86–1.10	0.98	0.86–1.12
Granada	1.43**	1.24–1.66	1.24*	1.07–1.44	1.08	0.93–1.25
Yorkshire	1.43**	1.22–1.66	1.35**	1.15–1.58	1.51**	1.29–1.77
Slovakia	1.24*	1.08–1.42	1.06	0.92–1.22	1.01	0.87–1.16
Slovenia	1.19*	1.05–1.36	1.03	0.90–1.18	1.04	0.91–1.20
Poland	1.73**	1.54–1.94	0.98	0.86–1.11	–	–
Males	1		1		1	
Females	0.87**	0.81–0.93	0.88**	0.82–0.94	0.97	0.88–1.06
<65 years	1		1		1	
65–74 years	1.28**	1.17–1.39	1.13*	1.04–1.23	1.17*	1.05–1.30
⩾75 years	1.59**	1.47–1.73	1.06	0.98–1.16	1.07	0.96–1.20
Surgical resection		1				
No resection		3.87**	3.58–4.19			
Adenocarcinomas/NOS[a]	1		1			
Epidermoïd/undifferentiated	1.59**	1.34–1.87	1.93**	1.53–2.44		
Signet ring cells		1.14*	1.01–1.29	1.14	1.00–1.31	
Mucoïd carcinomas		1.13	1.00–1.27	1.04	0.88–1.22	
No histology			1.22**	1.10–1.36	1.31*	1.11–1.54
T1/T2 N0 M0				1		
T4 N0 M0/all TN + M0				2.62**	2.23–3.08	
Advanced stages[b]				7.46**	6.39–8.70	

* $p < 0.05$.

** $p < 0.001$.

[a] NOS = not otherwise specified.

[b] M+ and non-resected cases likelihood ratio test.

Table 6 – Excess hazard ratio (EHR) of death within five years of diagnosis with 95% confidence interval (CI) among patients diagnosed with a gastric cancer.

	First year		Second to fifth years	
	EHR	95% CI	EHR	95% CI
France	1		1	
Northern Italy	1.08	0.94–1.23	0.98	0.77–1.26
Ragusa	0.76*	0.61–0.96	1.04	0.67–1.62
Netherlands	0.97	0.84–1.12	0.85	0.66–1.11
Granada	1.21*	1.01–1.44	1.22	0.89–1.68
Yorkshire	1.52**	1.28–1.81	1.23	0.85–1.78
Slovakia	1.09	0.92–1.28	0.93	0.69–1.26
Slovenia	1.19*	1.02–1.39	0.93	0.68–1.26
Poland	0.99	0.85–1.14	1.00	0.74–1.36

Adjusted for age, sex, morphology and surgical resection.

* p-Value for trend <0.05.

** p-Value for trend <0.001.

Our results confirm the existence of survival differences among European countries for gastric cancer while clarifying their possible origins. They are mainly due to the stage at diagnosis, evaluated on either the resected cancer rate or the TNM classification. After adjusting for resection versus no resection or stage at diagnosis, survival differences between studied geographic areas diminished considerably suggesting that these factors were the main reason for the lower survival reported in some geographic areas compared to others. These results suggest that improvements in the diagnosis and treatment facilities are needed in the areas with the lowest survival. Significant differences, however, persisted with Yorkshire. They were limited to the first year following diagnosis. Delay in diagnosis, under-treatment, accessibility to specialised facilities, co-morbidities are possible explanations for the early excess mortality (not explained by age and stage

differences) in this time period. The inability to adjust fully for the subsite location of the tumour (due to a high proportion of missing data) may also account for residual differences, Cardia cancers may be more common in the Yorkshire population and are associated with a worse prognosis (Verdecchia reference).

Conflict of interest statement

None declared.

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