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ORIGINAL ARTICLE

Prognostic Value of Perineural Invasion in Resected Gastric Cancer Patients According to Lauren Histotype

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Abstract The purpose of this study is to investigate perineural invasion (PNI) as a prognostic factor in gastric cancer patients. 455 patients submitted to extended (D2 or more) lymphadenectomy (median number of 39 retrieved lymph nodes, range: 15–140) between 1995 and 2012 were retrospectively studied. Patients were categorized in two groups according to the PNI status, and PNI positivity was assessed in presence of cancer cells in the perinerium or the neural fascicles using hematoxylin and eosin staining. Median follow-up for surviving patients was 80.3 months. Survival analysis was performed by univariate and multivariate analysis, using a Cox proportional hazards model. 162 patients (33.9%) had positive PNI; this was strongly associated with advanced stages of disease, residual tumor, lymphovascular invasion, Lauren diffuse-mixed histotype and tumor size. Five-year cancer-related survival was 65,7% and 20,6% in PNI negative vs. positive groups, respectively ($p < 0.001$). The prognostic impact of PNI at univariate analysis was particularly evident in patients submitted to R0 surgery, early as well as advanced stage, advanced nodal stage and T status. At multivariate analysis, PNI did not result statistically significant in the overall series, but emerged as an independent prognostic factor in the group of patients with Lauren intestinal histotype ($p = 0.005$, hazard ratio: 1.99, 95% confidence interval 1.24–3.19). PNI is related to advanced stage and poor long-term survival in gastric cancer, and may serve as an adjunctive prognostic factor in the intestinal histotype.

Keywords Gastric cancer · Perineural invasion · Lauren histotype · Extended lymphadenectomy · Prognostic factors

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Introduction

Gastric carcinoma (GC) is one of the leading causes of death for cancer worldwide, and it is the second most common neoplasm of the digestive tract after colo-rectal cancer [1]. Its incidence has been decreasing during the last decades, but long-term survival remains dismal above all in Western Countries, with no significant improvements in recent years [2]. Radical surgery (R0 gastrectomy) is still the mainstay of GC treatment, and D2 lymphadenectomy is nowadays accepted as the standard approach in most treatment guidelines all-over the world [3–5]. However, due to the poor prognosis of advanced forms, neo-adjuvant/adjuvant chemotherapy or chemo-radiotherapy have been proposed, in order to increase the chance of cure [6, 7]. The identification of clinical-pathological prognostic factors is essential, because it can allow a better selection of the patients suitable to tailored treatments. Traditionally, several studies have described histology, lymphovascular infiltration, depth of invasion, nodal status, and tumor site as significant prognostic factors for early and advanced disease [8, 9]. However, for a more accurate definition of prognosis, the finding of new clinical-pathological factors could be of help. Perineural invasion (PNI) is a pathologic parameter strictly related to a poor prognosis in head and neck cancer [10], urinary tract [11] and gastrointestinal neoplasms especially in pancreatic cancer [12]. Although in many reports PNI appears as an independent prognostic factor, its prognostic value in GC is still debated. The aim of this retrospective study is

to evaluate the impact of PNI in the long-term survival of GC patients undergoing extended lymphadenectomy.

Materials & Methods

In this retrospective cohort study, 455 consecutive patients with GC surgically treated in our Unit of General Surgery and Surgical Oncology, University of Siena, Italy, from January 1995 to December 2012 were analyzed. Preoperative staging was assessed by CT-scan, oesophago-gastro-duodenoscopy and, when required, endoscopic ultrasound. The endoscopic biopsies for an appropriate histological evaluation and definition of the neoplasm were always obtained before the surgical procedure. Patients submitted to neo-adjuvant treatments and esophago-gastric junction Siewert type I tumors were excluded. The surgical procedures, total or partial gastrectomy, were performed according to the preoperative staging and tumor location. An extended (D2 or more) lymphadenectomy was performed in all cases, as reported previously [13, 14], and only patients with at least 15 nodes retrieved at pathologic examination were included in the study. Extended surgery, considered as multivisceral resections for locally advanced GC, was also performed when needed (e.g., direct infiltration of spleen, gallbladder, liver, colon, pancreas).

Tumor stage was defined according to the 7th pTMN system classification proposed by the International Union Against Cancer [15]. All cases treated before 2010 were revised and restaged according to the last TNM edition, as previously reported [16]. Pathological classification was performed by an experienced pathologist dedicated to

GC diagnosis and staging (C.V.). Clinical and individual characteristics, surgical procedures and histological findings were recorded in a specific database. Patients were submitted to regular outpatient follow-up examinations, according to a standard protocol [9]. All cases were divided in two groups according to the perineural invasion (PNI) status. PNI positivity was assessed by the presence of cancer cells in the perinerium or in the neural fascicles using hematoxylin and eosin staining (Fig. 1). Informed consent for the data management for research studies was obtained for all included patients.

The statistical analysis was performed with the X^2 test or Fisher exact test to compare categorical variables. The Mann–Whitney U test was used to compare continuous variables not normally distributed. Cumulative survival was calculated by the life table method of Kaplan and Meier, and the log-rank test was used to assess significant differences. Multivariate analysis was performed using a Cox proportional hazards model by considering the following risk factors: sex (male vs. female), age (continuous variable), tumor location (upper, middle, others vs. lower), Lauren histotype (diffuse-mixed vs. intestinal) depth of tumor invasion (pT2, pT3 or pT4 vs. pT1), lymph node involvement (pN1, pN2, pN3a or pN3b vs. pN0), M stage (M1 vs. M0), R category (R+ vs. R0), vascular invasion (present vs. absent), lymphatic invasion (present vs. absent), and PNI status (PNI+ vs. PNI-). Significant variables were selected with a forward step procedure. Statistical significance was determined at p value <0.05. The entire statistical analysis was performed with SPSS statistical program (Version 17.0) and reviewed by an expert statistician in gastric cancer surgical research (D.M.).

Fig. 1 Perineural and nerve invasion by a diffuse type of gastric cancer (hematoxylin and eosin staining). A: Immunohistochemistry with CK pool
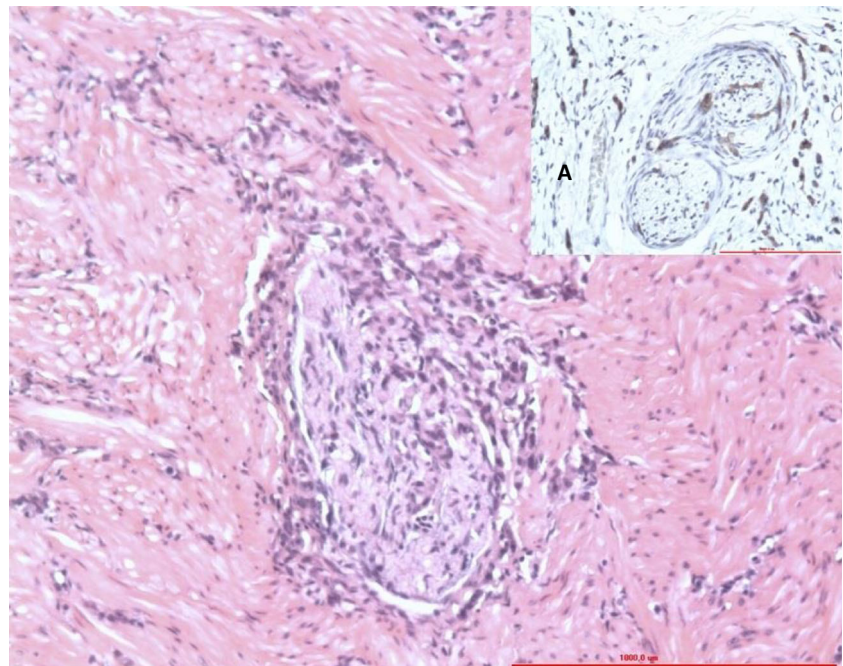
Results

PNI positivity was detected in 162 out of the 455 GC patients (33.9%). Median age was 69 (inter-quartile range, IQR: 60–75) and 67 (IQR: 60–75) years for PNI- and PNI+ groups, respectively. A total of 271 patients were male: 174 in the group PNI- and 97 in the group PNI+. Subtotal gastrectomy was performed in 292 cases, and total gastrectomy in 163. A median number of 39 lymph nodes (range: 15–140) was retrieved, without statistical difference between the two groups ($p = 0.137$). The correlations between PNI status and clinical-pathological factors are shown in Table 1. PNI positivity was strongly associated with depth of invasion, lymph-node metastasis, tumor grading and stage ($p < 0.001$), and it was also related to lymphovascular invasion, Lauren diffuse-mixed histotype, large tumor size, linitis plastica and upper third location. A large proportion (48.8%) of patients with PNI positivity was submitted to R+ resections. No association between PNI positivity, gender ($p = 0.919$) and age ($p = 0.761$) was found.

Table 1 Perineural invasion according to different clinical-pathological variables in 455 patients under study

	PNI- (%)	PNI+ (%)	p value
Patients (n)	293	162	
Age, y (median; IQR)	69 (60–75)	67 (60–75)	0.761
Sex (male:female)	174:119 (59.4:40.6)	97:65 (59.9:40.1)	0.919
pT			<0.001
1	69 (23.5)	3 (1.9)	
2	61 (20.8)	7 (4.3)	
3	65 (22.2)	26 (16)	
4	98 (33.4)	126 (77.8)	
pN			<0.001
0	139 (47.4)	13 (8)	
1	33 (11.3)	18 (11.1)	
2	41 (14)	24 (14.8)	
3a	48 (16.4)	41 (25.3)	
3b	32 (10.9)	66 (40.7)	
pM			<0.001
M0	257 (87.7)	106 (65.4)	
M1	36 (12.3)	56 (34.6)	
Stage			<0.001
I	96 (32.8)	2 (1.2)	
II	74 (25.3)	23 (14.2)	
III	87 (29.7)	81 (50)	
IV	36 (12.3)	56 (34.6)	
N° of lymphnodes retrieved (median; IQR)	37 (26–50)	38 (30–52)	0.137
N° of metastatic lymphnodes (median; IQR)	1 (0–7)	11 (5–22)	< 0.001
Lauren			< 0.001
Intestinal	197 (67.2)	66 (40.7)	
Diffuse-Mixed	87 (29.7)	92 (56.8)	
NC	9 (3.1)	4 (2.5)	
Lymphatic invasion			< 0.001
No	179 (61.1)	18 (11.1)	
Yes	108 (36.9)	133 (82.1)	
Missing	6 (2)	11 (6.8)	
Vascular invasion			< 0.001
No	220 (75.1)	20 (12.3)	
Yes	69 (23.5)	133 (82.1)	
Missing	4 (1.4)	9 (5.6)	
Grading			< 0.001
G1	29 (9.9)	0	
G2	110 (37.5)	37 (22.8)	
G3-G4	144 (49.1)	121 (74.7)	
NG	10 (3.4)	4 (2.5)	
Primary tumor site			0.009
Linitis plastica	8 (2.7)	14 (8.6)	
Upper third	41 (14)	31 (19.1)	
Middle third	84 (28.7)	44 (27.2)	
Lower third	156 (53.2)	68 (42)	
Gastric stump	4 (1.4)	5 (3.1)	
Radicality (R)			< 0.001
R0	246 (84)	83 (51.2)	
R+	47 (16)	79 (48.8)	
Tumor size (median; IQR)	40 (27–60)	60 (50–80)	< 0.001

Complete follow-up data were available for 392 patients (median follow-up for surviving patients: 80.3 months, IQR: 38–122). The 5-year cancer-related survival (CRS) was 65.7% in PNI-negative patients vs. 20.6% in PNI-positive group ($p < 0.001$) (Fig. 2). The potential impact of PNI status on long-term survival was evaluated stratifying our series according to different pathological factors (Table 2). This analysis revealed that PNI status was strongly associated with worse prognosis in patients with different tumor locations, histotype, surgical radicality and in advanced as well as early stages of diseases (Fig. 3). However, the highest prognostic effect was identified in distal tumors, more advanced nodal status, M0 cases, and patients submitted to R0 resection. When analyzing CRS according to Lauren hystotype, both intestinal and diffuse PNI-positive patients had worse prognosis compared to negative cases (Fig. 4). Multivariate analysis identified pN status ($p < 0.001$), pT status ($p < 0.001$), radicality ($p < 0.001$), age ($p = 0.010$), sex ($p = 0.010$), and vascular invasion ($p = 0.013$) as independent prognostic factors, whereas PNI status was not confirmed as a significant factor (Table 3). However, when PNI status was evaluated in patients with different Lauren hystotypes, it was identified as an independent prognostic factor in the intestinal type subgroup ($p = 0.005$, HR 1.99, 95% C.I. 1.24–3.19), whereas it did not results as statistically significant in the diffuse-mixed cases ($p = 0.273$).

Discussion

PNI is defined as the presence of cancer cells along the sides of nerves and/or inside the epineurial, perineurial and endoneurial spaces of the neuronal sheath [17].
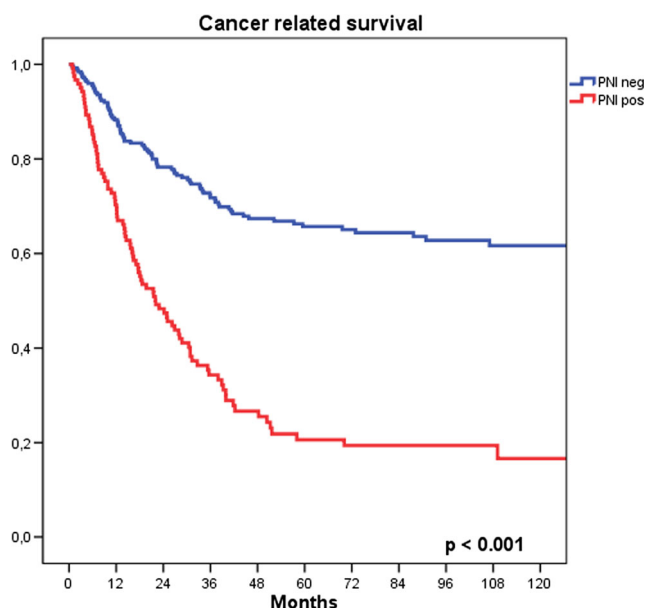

Fig. 2 Cancer-related survival (Kaplan-Meir method) according to PNI status

This feature, investigated by several authors, is a marker of poor outcome and it has been associated with worse survival in many malignancies, like pancreatic, colorectal, prostate head and neck cancers [18]. Fouquet et al. [19] analyzed the impact of PNI on early tumor recurrence in patient submitted to pancreaticoduodenectomy for adenocarcinoma of the head of the pancreas, showing PNI as the most important factor associated to 1-year recurrence and poor disease-free and overall survival. Moreover, in prostate cancer, PNI positivity is associated with higher mortality rates, increased risk of recurrence and positive surgical margins [20–22].

In GC, PNI was investigated in some studies, but its role as an independent prognostic factor remains still debated.

In the present analysis, conducted in a consecutive series of patients submitted to extended lymphadenectomy, with a high number of median removed lymph nodes, PNI positivity was found in 33.9% of the patients. These results are in line with the published literature: in a recent meta-analysis, the median percentage of PNI positivity is 40.9% (range 6.8%–75.6%) [18].

As described in other papers [23, 24], there is a strong association between PNI and stage of GC. PNI positivity notably increases with depth of invasion and number of metastatic lymphnodes; it was observed in 3/72 (4.2%) of T1 vs. 126/224 (56.3%) of T4 tumors, as reported by others [23, 24]. Regarding the N status, PNI positivity was detected only in the 8.6% of N0 patients vs. 57.2% of N3 patients. Bilici et al. [25] observed PNI positivity in 41 out of 45 (91.1%) pN3 patients. Despite we did not found any difference between two groups in the number of harvested lymph nodes, the median number of metastatic lymph nodes in PNI+ group is notably higher than PNI-negative group (11 vs. 1; $p < 0.001$), which confirms the very high propensity of PNI-positive cases to lymph nodal spread. According to our data, PNI was also linked to lymphovascular invasion, and similar results are reported in different papers [26, 27]. This behavior could be linked to the infiltration of the vasa nervorum and the lymphatic network around the nerves [26].

In our series PNI positivity was more often found in the upper third lesions. This finding could be justified by the anatomic features of the stomach. In the upper third of the stomach there are relatively large autonomic nerves with larger perineural space, so the tumor cells could easily spread through the gap between the nerves and tissue [26]. Linitis plastica is a very aggressive disease, with a propensity to the massive infiltration of the gastric wall, and the higher frequency of PNI fit well with the behavior of this particular form of GC.

We found statistically significant correlation between PNI positivity and diffuse-mixed Lauren histotype, as also reported by Zhou et al. [28]. These results are not confirmed by other authors [25, 27].

In our cohort, we observed a notable difference in terms of long-term survival between PNI+ and PNI- patients

Table 2 Cancer-related survival according to PNI status, stratified for different pathological variables

	PNI -		PNI +		
	N° patients	5- yr. Survival	N° patients	5- yr. Survival	p value
Tumor site					
Linitis plastica	8	33.3	10	0	0.243
Upper third	37	47.2	26	15.7	0.017
Middle third	75	69.5	37	25.3	< 0.001
Lower third	138	69.3	55	24.1	< 0.001
Gastric stump	3	N.A.	3	N.A.	N.A.
Lauren					
Intestinal	179	67.6	54	23.8	< 0.001
Diffuse-mixed	74	64.3	75	17.5	< 0.001
pT					
T1	57	100	3	N.A.	N.A.
T2	54	75.9	6	30	0.028
T3	58	75.4	21	44.1	0.024
T4	92	34.2	101	14	0.011
pN					
N0	124	89.2	12	70.1	0.166
N1	27	84.1	12	60	0.05
N2	36	36.6	22	25.5	0.647
N3a	44	43.5	30	15.8	0.097
N3b	30	23.8	55	5	0.014
M					
M0	226	69.2	89	24.5	< 0.001
M1	35	44.3	42	14.2	0.028
Stage					
I-II	148	87.9	20	65.9	0.039
III-IV	113	36.1	111	13.2	0.001
Radicality					
R0	216	73.7	68	32.6	< 0.001
R+	45	23.3	63	6.2	0.026

N.A. not calculated

($p < 0.001$). Even when stratifying according to UICC stages, we identified a strong correlation between PNI positivity and a poor survival, in advanced (III-IV) as well as early stages (I-II). Even if the present retrospective study is not able to identify potential impact of adjuvant therapies in early stages of GC, cases with PNI positivity could benefit from adjuvant treatments, which should be confirmed in specifically designed prospective studies.
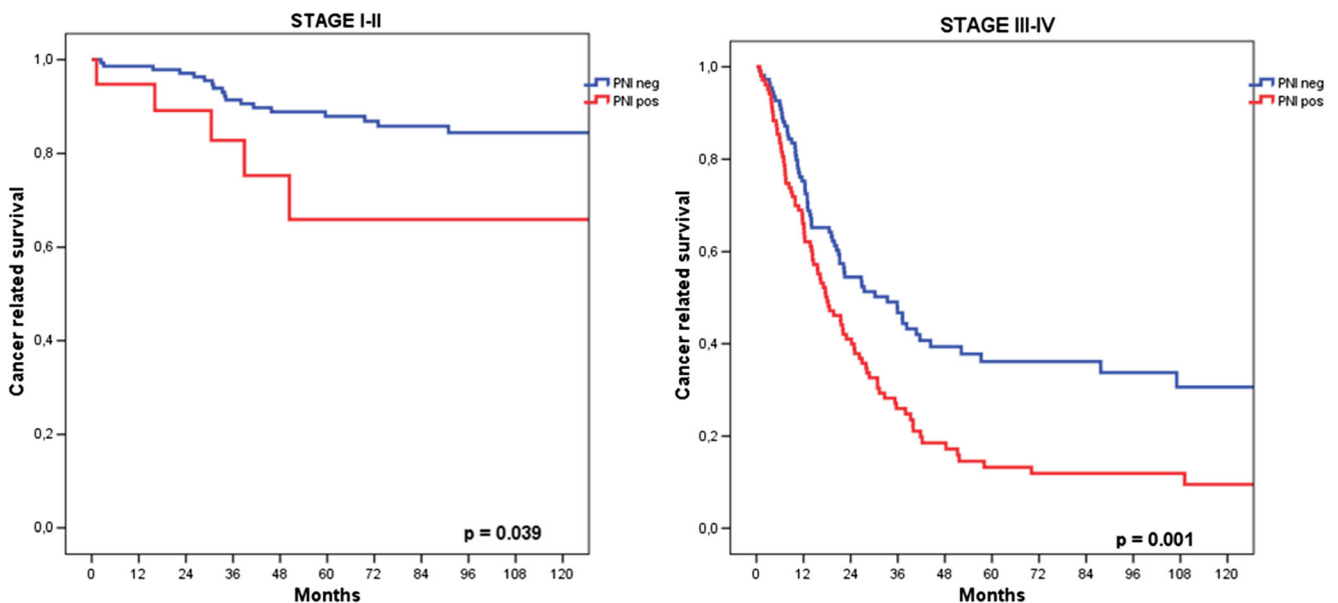

Fig. 3 Cancer-related survival (Kaplan-Meir method) according to PNI status, stratified for tumor stage

Several studies have evaluated the prognostic value of PNI in GC. Bilici et al. in a cohort of 238 patients submitted to curative surgery, identified PNI as an independent prognostic factor at multivariate analysis [25]. Similar results are reported by several Authors [24, 29]. Scartozzi et al. [30] evaluated 734 gastric cancer patients surgically treated with curative intent. Cohort was divided in two groups according to the presence or absence of lymphovascular invasion (LV) and PNI status, and LV/PNI positivity was strongly related to poor survival at multivariate analysis.

One of the largest studies (7757 patients enrolled) was performed by Kim et al. [31]. The prognostic value of PNI at univariate analysis was statistically significant; however, multivariate analysis for the evaluation of independent factors affecting both overall and disease-free survival was not performed. These authors also focused on the evaluation of risk factors of recurrence demonstrating that PNI presence is related to higher risk of GC recurrence.

On the other hand, in other papers PNI positivity did not result as an independent prognostic factor [23, 28]. The results of our study are in line with the papers above mentioned. We observed that PNI-positive tumors had a poor survival compared to PNI-negative tumors, but at multivariate analysis PNI was not an independent prognostic factor, not providing any additional information to the other prognostic parameters already known. This may be due to the very high correlation between PNI status and advanced stages, which limited its prognostic value when controlling for stronger prognostic variables, above all in well-staged tumors with a high number of removed and analyzed lymphnodes.

In a further analysis of our series, we stratified the prognostic value of PNI according to Lauren histotype, and PNI positivity emerged as independent prognostic factor in the intestinal subgroup of patients. This is a new finding in literature, and could require more potential explanations. Several studies reported different impact of conventional or biological prognostic factors in different Lauren histotypes [32, 33]. Besides histomorphometrical characteristics, the intestinal and the diffuse histotypes show evident differences in epidemiological, clinical and molecular features [34]. The intestinal type is more common in males and older patients, whereas the diffuse type usually affects younger patients with a lower male-female ratio. A characteristic of the diffuse type is also the greater biological aggressiveness, in particular the higher propensity to peritoneal dissemination and lymph nodal spread. Differences in clinical and molecular characteristics may be also at the basis of the variability in the prognostic weight of pathological factors as PNI status.

The correlation between Lauren histotype and the prognostic value of PNI could justify the different results in current literature. Indeed, when analyzing different series, we noted that PNI status emerged as a strong prognostic factor in series with a higher percentage of intestinal histotypes [25, 27].

Probably the presence of PNI in GC could be considered as the clinical-pathological phenotypic expression of distinct molecular features. Cristescu et al. [35] identified four GC molecular subtypes linked to different patterns of genomic alterations: microsatellite stable epithelial-to-mesenchymal transition (MSS/EMT), microsatellite instability (MSI), microsatellite stability with intact TP53 activity (MSS/TP53+) and microsatellite

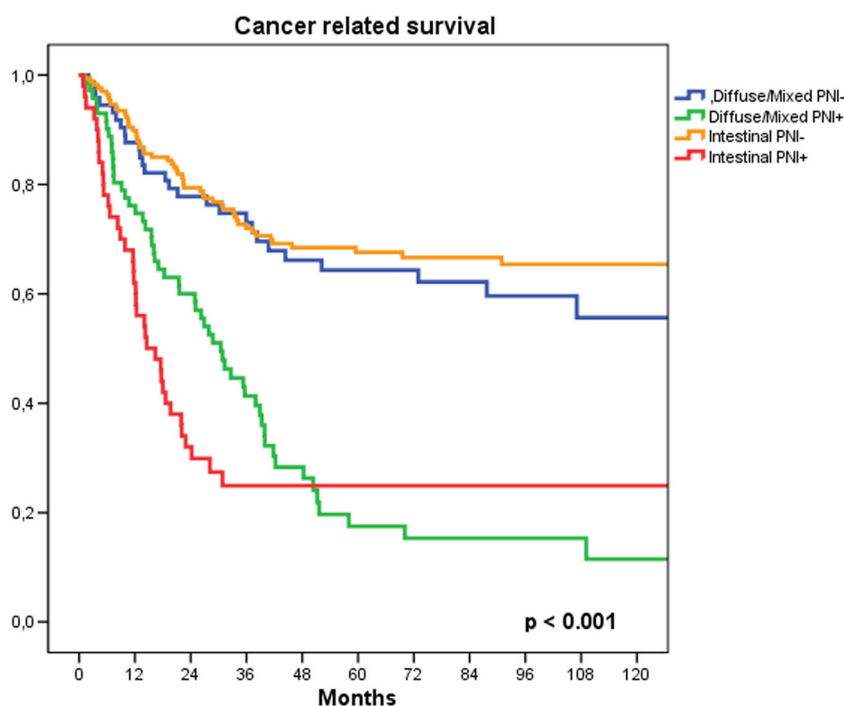**Fig. 4** Cancer-related survival (Kaplan-Meir method) according to PNI status and Lauren histotype

Table 3 Significant prognostic factors for cancer-related survival at multivariate analysis

Factor	HR	95% C.I.	p value
Sex			0.01
Male	1.53	1.11–2.10	
Female	1		
Age	1.02	1–1.03	0.010
UICC-R			< 0.001
R0	1		
R+	1.98	1.4–2.8	
V.I.			0.013
Negative	1		
Positive	1.6	1.1–2.33	
T status			<0.001
T1	1		
T2	4.2	0.94–19.5	
T3	5.55	1.27–24.29	
T4	11.14	2.57–48.18	
N status			<0.001
N0	1		
N1	0.9	0.38–2.15	
N2	3.15	1.71–5.82	
N3a	2.97	1.6–5.48	
N3b	4.46	2.36–8.43	

HR hazard ratio, *V.I.* vascular invasion

stability with TP53 functional loss (MSS/TP53-). These molecular subtypes are related not only to specific genomic features but also to clinical characteristics, recurrence pattern and prognosis. They observed that tumors in MSS/EMT subtype are generally diffuse histotype, diagnosed at advanced stage and with the worst prognosis. Interesting, PNI positivity is significantly associated with MSS/EMT subtype. PNI in GC deserves further investigations in the future regarding the molecular characteristics and potential indications to targeted therapies.

Conclusion

The analysis of a large series of GC patients treated by extended lymphadenectomy confirmed the strong association between PNI status and more advanced stage, which involved a poor prognosis of PNI-positive group. Survival multivariate analysis in different subgroups identified PNI status as an independent prognostic factor in the intestinal type group, but not in the diffuse-mixed histotypes. This new finding may shed more light on the real clinical value of PNI status in GC patients.

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