

Linitis plastica: current prognostic implication of a classic concept

Linitis plástica: implicación pronóstica actual de un concepto clásico

Aingeru Sarriugarte-Lasarte^{1,2,3*}, Eva García-Alberdi⁴, Silvia Pérez-Fernández², Oihane Gutiérrez-Grijalba¹, Patricia Mifsut-Porcel¹, Yanina Kataryniuk-Di Costanzo¹, Patricia Sendino-Cañizares¹ and Iratxe Rodeño-Esteban¹

¹General and Digestive Surgery Department, University Hospital of Cruces; ²Computational Surgery, Biocruces Bizkaia; ³Department of Surgery, University of País Vasco (UPV/EHU); ⁴Anatomical Pathology Department, University Hospital of Cruces. Barakaldo, Vizcaya, Spain

Abstract

Background: Despite having been described for several centuries linitis plastica's (LP) prognostic implication remain unclear. **Objective:** To analyze the impact of LP on the survival of patients undergoing gastrectomy for gastric adenocarcinoma. **Method:** A single-center retrospective study of cases of LP diagnosed and confirmed by pathological anatomy has been carried out in a third-level center for 5 years. **Results:** They were grouped into Linitis Plastica (LP), diffuse non-LP carcinomas (DNLP) and other adenocarcinomas (ADC). 199 gastrectomies performed in the same period of time were included in the comparative analysis. With a median follow-up of 54.5 months (95% CI: 37.0-65.0), the median survival of LP was 14 months (95% CI: 9-27) significantly lower ($p = 0.002$) compared to DNLP 51.5 months (95% CI: 25-70) and the rest of ADC 62 months (95% CI: 43-68). The OS at 1, 3 and 5 years was statistically worse in the LP group (69, 15, 8%) compared to DNLP (82, 54, 44%) and ADC (89, 63, 54%) ($p = 0.073$, $p < 0.001$, $p < 0.001$). In the multivariate analysis, LP was identified as an independent risk factor for OS with an HR of 3.26 ($p = 0.001$). **Conclusions:** LP is an independent prognostic factor associated with higher mortality in gastric cancer.

Keywords: Gastric cancer. Linitis plastica. Prognostic.

Resumen

Antecedentes: A pesar de haber sido descrita hace varios siglos, sigue sin estar clara la implicación pronóstica de la linitis plástica (LP). **Objetivo:** Analizar el impacto de la LP en la supervivencia de los pacientes intervenidos de gastrectomía por adenocarcinoma gástrico. **Método:** E estudio retrospectivo unicéntrico de los casos de LP diagnosticados en nuestro centro durante 5 años. **Resultados:** Se agruparon en LP, carcinomas difusos no LP (DNLP) y resto de adenocarcinomas (ADC). En el análisis comparativo se incluyeron 199 gastrectomías realizadas en el mismo periodo de tiempo. Con una mediana de seguimiento de 54.5 meses (intervalo de confianza del 95% [IC 95%]: 37.0-65.0), la supervivencia mediana de la LP fue de 14 meses (IC 95%: 9-27), significativamente menor ($p = 0.002$) que en los DNLP, que fue de 51.5 meses (IC 95%: 25-70), y que en el resto de los ADC, en los que fue de 62 meses (IC 95%: 43-68). La supervivencia global a 1, 3 y 5 años fue estadísticamente peor en el grupo de LP (69, 15 y 8%) comparado con los grupos de DNLP (82, 54 y 44%) y ADC (89, 63 y 54%) ($p = 0.073$, $p < 0.001$ y $p < 0.001$, respectivamente). En el análisis multivariante se identificó la LP como un factor de riesgo independiente de supervivencia (hazard ratio: 3.26; $p = 0.001$). **Conclusiones:** La LP es un factor pronóstico independiente asociado a mayor mortalidad por cáncer gástrico.

Palabras clave: Cáncer gástrico. Linitis plástica. Pronóstico.

*Correspondence:

Aingeru Sarriugarte-Lasarte

E-mail: aingeru.sarriugartelasarte@osakidetza.eus

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Introduction

Linitis plastica (LP) is the macroscopic appearance of the organs affected by diffuse carcinoma, which is thickened, rigid, and without apparent mucosal ulceration. Known and described for several centuries, it has usually been associated with gastric tumors. However, although exceptionally, it can occur in other locations, such as the colorectal, either as a primary or secondary metastatic tumor¹. It is an uncertain and enigmatic process from the pathological and clinical point of view, but above all, its prognosis and therapeutic approach are not clearly known². In order to assess the prognostic implication of this process in our center, a survival study was carried out with the cases detected.

Method

Study population

All gastrectomies with curative intent performed during 5 years (2010 to 2014) in a third level hospital were studied. Conversely, cases of LP detected by intraoperative macroscopic assessment and pathologic confirmation of the samples during the same period of time were analyzed. Cases with preoperative suspicion by imaging test not confirmed in vivo were excluded. A descriptive study of LP cases was performed and compared with cases of gastric cancer resected in the same period of time.

Definition

LP is defined as a carcinoma, usually of gastric location, which due to diffuse infiltration of tumor cells produces a circumferential thickening of the gastric wall, which, without necessarily presenting tumor mass, leads to rigidity of the wall.

Clinicopathologic characteristics

A total of 199 cases of gastric cancer were resected with curative intent, of which 63 (32.8%) were of the diffuse type and 13 (6.5%) of them presented LP. In the same period of time, the anatomical pathology service confirmed a total of 25 cases of LP. Nonetheless, tumors resected without curative intent and those of extragastric location were excluded from the comparative analysis: three cases of cancer of colorectal location,

only one of them of primary rectal location and two as distant metastasis of diffuse gastric cancer in the context of the process known as "Blumer's shelf"³; two of primary esophageal location, and another located in the small intestine as metastasis of diffuse gastric cancer.

Type of tumor resection

The main objective of the surgery was to achieve complete removal of the tumor (R0 resection), although in cases of unresectability or peritoneal dissemination no resection was performed or palliative procedures (R2) were carried out to treat tumor-related complications. Cases were staged and lymph node classified according to the American Joint Committee on Cancer (AJCC) pTNM pathologic classification (8th ed.).

Data analysis

Categorical variables are described by frequencies and percentages, and continuous variables by mean and standard deviation, if they follow a normal distribution, or by median and interquartile range otherwise. Comparison between categorical variables was performed with the chi-squared test or Fisher's exact test when the expected frequencies were < 5. For continuous variables, the Student's t-test was used when they followed a normal distribution or the Mann-Whitney U-test otherwise.

Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test, with survival time measured from the date of diagnosis by imaging or biopsy to the date of death or last follow-up. To see which variables influence survival, a univariate Cox regression analysis was performed, and those variables with $p < 0.200$ were included in a multivariate Cox regression analysis. Variables that lost statistical significance ($p > 0.05$) were eliminated until we were left with the model presented in the results section. The results are expressed as hazard ratio (HR) and 95% confidence interval (95% CI).

All analyses were performed with the R statistical program (version 3.6.1) (<https://www.R-project.org/>).

Ethics committee

All patients gave written informed consent for their information to be used for research purposes. Approval

for the conduct of the study was obtained from the hospital ethics committee, and it was performed in accordance with the ethical standards of the Declaration of Helsinki of the World Medical Association.

Results

Resection rate

During the period studied, 19 cases of LP of gastric location were detected, of which 13 (68%) could be resected with curative intent. All the tumors were locally advanced stage T3 or T4 and N+ (stage II/III). The remaining 32% showed M1 distant disease as an intraoperative finding, in the form of peritoneal carcinomatosis, thus complete tumor resection was not performed (R2). Only 61.5% of the resected tumors could be considered R0, since 38.5% showed microscopic involvement of the resection margin (R1).

Cases with palliative resection received palliative chemotherapy and those with R0 resection were treated with chemotherapy and radiotherapy with adjuvant intent.

Of the 199 cases operated with curative intent, 6.5% presented LP. Of the patients with LP, 76.9% were male, with a mean age of 64.8 ($\pm$ 12.2) years. All LP cases were poorly differentiated or undifferentiated. According to Lauren's classification, all LP cases were of diffuse histology, resulting in 15.9% of all diffuse tumors to show LP. According to the World Health Organization (WHO) classification, 38.5% of LP cases had signet-ring cell histology and 61.5% were of poorly cohesive type. Conversely, it is noteworthy that 100% of the LP cases presented T3/T4 transmural gastric involvement, compared to 65% of the rest of the cases, and a very important tumor lymph node burden: N0 7.69% vs. 30.1% and N3 71.6% vs. 23.5%, respectively.

Table 1 presents the main demographic and clinical characteristics of the cohort under study.

Survival analysis

The median survival of patients with LP was 12 months (95% CI: 1-54); 14 months (95% CI: 9-27) in the resected tumor group (16.8 months in the R0) and 3 months in the unresected tumor group. The univariate analysis is reflected in the Kaplan-Meier plots shown in Figure 1 and Table 2. The 1-, 3-, and 5-year survival of LP cases was significantly lower than in

the non-LP diffuse tumor groups and the rest of the adenocarcinomas. The median survival of patients with LP was significantly lower than those with non-LP diffuse gastric carcinoma or all other adenocarcinomas resected in the same time period: 14 months (95% CI: 9-27) vs. 51.5 months (95% CI: 25-70) and 62 months (95% CI: 43-68), respectively. In the multivariate analysis of overall survival, the presence of LP was shown to be an independent risk factor for mortality (HR: 3.26; 95% CI: 1.58-6.72). Other independent factors for overall survival were lymph node infiltration (N) ($p < 0.002$), lymph node dissection with more than 15 nodes ($p < 0.001$), complete tumor resection (R0) ($p < 0.001$), and adjuvant treatment received ($p < 0.013$) (Table 3). In a multivariate analysis performed to exclusively assess the diffuse carcinoma group, LP is also shown to be an independent factor for lower overall survival (HR: 2.97; 95% CI: 1.49-5.94).

Discussion

Anatomical pathology

The term "linitis plastica" was coined to describe the thickening of the gastric wall produced by this pathology, referring to the resemblance to linen fibers that the submucosa acquires macroscopically⁴. Over time, it has been used to describe the macroscopic appearance of a diffusely infiltrating carcinoma that affects any hollow organ, retaining its shape, but remaining rigid and contracted, like a leather boot. Microscopically, it is characterized by increased connective tissue in the submucosal layer, with poorly cohesive scanty cellularity, and sometimes in the form of a signet-ring⁵.

Although it usually refers to gastric tumors, sometimes LP can affect other locations of the digestive and urinary tract, presenting as metastasis of gastric or breast tumors⁶. Secondary LP has been described in colorectal location and exceptionally as late metastasis, years after diagnosis, in intestinal location^{7,8}. However, there are also some cases in the literature of primary rectal linitis due to signet-ring cell adenocarcinoma, representing less than 0.1% of colorectal tumors⁹⁻¹³.

It is complex to identify LP within the subtypes of the histopathologic classifications of gastric cancer, but it has almost always been reported as a macroscopic morphology of advanced stages of gastric cancer, without actually being equivalent to any of these.

Table 1. Clinicopathologic characteristics

	All (n = 199)	Non-LP (n = 186)	LP (n = 13)	p
Age, years	68.2 ($\pm$ 11.8)	68.5 ($\pm$ 11.8)	64.8 ($\pm$ 12.2)	0.315
Categorical age				0.249
> 65 years old	123 (61.8%)	117 (62.9%)	6 (46.2%)	
Gender				0.552
Men	134 (67.3%)	124 (66.7%)	10 (76.9%)	
Location				0.021
Upper third	39 (19.6%)	33 (17.7%)	6 (46.2%)	
Body	54 (27.1%)	50 (26.9%)	4 (30.8%)	
Antrum	106 (53.3%)	103 (55.4%)	3 (23.1%)	
Technique				0.001
Total gastrectomy	60 (31.6%)	50 (28.2%)	10 (76.9%)	
Subtotal gastrectomy	130 (68.4%)	127 (71.8%)	3 (23.1%)	
Lauren histological type				< 0.001
Indeterminate or mixed	47 (24.5%)	47 (26.3%)	0 (0.00%)	
Intestinal	82 (42.7%)	82 (45.8%)	0 (0.00%)	
Diffuse	63 (32.8%)	50 (27.9%)	13 (100%)	
WHO histology				< 0.001
Indeterminate or mixed	54 (27.1%)	54 (29.0%)	0 (0.00%)	
Papillary/tubular	73 (36.7%)	73 (39.2%)	0 (0.00%)	
Signet-ring cells	29 (14.6%)	24 (12.9%)	5 (38.5%)	
Mucinous	10 (5.03%)	10 (5.38%)	0 (0.00%)	
Poorly cohesive	33 (16.6%)	25 (13.4%)	8 (61.5%)	
Pathologic T				0.008
T1	25 (12.6%)	25 (13.4%)	0 (0.00%)	
T2	40 (20.1%)	40 (21.5%)	0 (0.00%)	
T3	94 (47.2%)	88 (47.3%)	6 (46.2%)	
T4a/T4b	40 (20.1%)	33 (17.7%)	7 (53.8%)	
Pathologic N				0.011
N0	56 (28.6%)	55 (30.1%)	1 (7.69%)	
N1	37 (18.9%)	37 (20.2%)	0 (0.00%)	
N2	52 (26.5%)	48 (26.2%)	4 (30.8%)	
N3a	38 (19.4%)	32 (17.5%)	6 (46.2%)	
N3b	13 (6.63%)	11 (6.01%)	2 (15.4%)	
Lymph node dissection D				1.000
Palliative (< 15)	11 (5.64%)	11 (6.04%)	0 (0.00%)	
D1	113 (57.9%)	105 (57.7%)	8 (61.5%)	
D2	71 (36.4%)	66 (36.3%)	5 (38.5%)	
Extended resection				0.074
Yes	16 (8.04%)	13 (6.99%)	3 (23.1%)	
Edges at anastomosis				0.008
Negative	175 (88.8%)	167 (90.8%)	8 (61.5%)	
Positive	22 (11.2%)	17 (9.24%)	5 (38.5%)	
G				< 0.001
Well differentiated	47 (25.7%)	47 (27.6%)	0 (0.00%)	
Moderately differentiated	45 (24.6%)	45 (26.5%)	0 (0.00%)	
Poorly differentiated or undifferentiated	91 (49.7%)	78 (45.9%)	13 (100%)	
R				0.005
1 or 2	20 (10.2%)	15 (8.15%)	5 (38.5%)	
Adjuvant				0.447
No	71 (45.2%)	67 (46.5%)	4 (30.8%)	
CT	23 (14.6%)	20 (13.9%)	3 (23.1%)	
CT-RT	63 (40.1%)	57 (39.6%)	6 (46.2%)	

(Continues)

Table 1. Clinicopathologic features (continued)

	All (n = 199)	Non-LP (n = 186)	LP (n = 13)	p
Recurrence				0.001
Yes	103 (52.8%)	90 (49.5%)	13 (100%)	
TNM stage (8th ed.)				0.055
IA	18 (9.28%)	18 (9.94%)	0 (0.00%)	
IB	23 (11.9%)	23 (12.7%)	0 (0.00%)	
IIA	28 (14.4%)	27 (14.9%)	1 (7.69%)	
IIB	25 (12.9%)	25 (13.8%)	0 (0.00%)	
IIIA	51 (26.3%)	47 (26.0%)	4 (30.8%)	
IIIB	37 (19.1%)	31 (17.1%)	6 (46.2%)	
IIIC	12 (6.19%)	10 (5.52%)	2 (15.4%)	

LP: linitis plastica; WHO: World Health Organization; CT: chemotherapy; RT: radiotherapy.

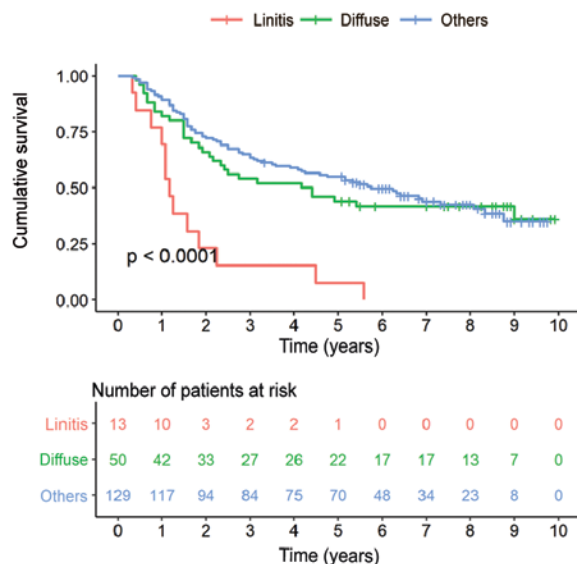


Figure 1. Kaplan-Meier plots of overall survival.

Type IV of Bormann's classification refers to the infiltrative and diffuse type that produces gastric thickening without mucosal involvement and with an uncertain tumor margin^{14,15}. It is microscopically related to the scirrhous carcinoma of the Japanese classification, classified by its abundant stroma formed by collagen I and III, secreted by fibroblasts and myofibroblasts modulated by the few cancer cells, within the process known as desmoplastic reaction¹⁶. In Lauren's classification, the diffuse type carcinoma is the one that presents most LP morphology, and within the WHO classification, it is usually considered among the poorly cohesive tumors, including tumors with signet-ring cells and, in rare occasions, mucinous carcinomas. Apparently, as it occurs in hereditary diffuse gastric cancer linked to the CDH1 gene, dysregulation

Table 2. Overall survival

Overall survival	LP	Diffuse	Non-LP nor diffuse	p
At 1 year	69%	82%	89%	0.073
At 3 years:	15%	54%	63%	< 0.001
At 5 years	8%	44%	54%	< 0.001
Median, months	14 (9-27)	51.5 (25-70)	62 (43-68)	0.002

LP: linitis plastica.

of the intercellular adhesion molecules E-cadherins produces cellular disunion, favoring tumor migration and infiltration. Alternatively, new molecular classifications based on the biological behavior of tumors make it possible to classify the different types of gastric tumors in relation to genomics and epigenetics more specifically, without indeterminate groups, leading to the possible detection of therapeutic targets¹⁷. However, although most cases of LP are possibly included in the genomically stable group, which is closely related to diffuse gastric cancer, none of the classifications make clear reference to LP.

In the literature there are few series and cases that define and analyze separately patients with LP among those with gastric cancer treated with curative intent². In addition, there are very different definitions, both preoperative and intraoperative or postoperative, used to define the cases, thus making the groups very diverse. In our study, cases with intraoperative finding of circumferential thickening of the intestinal wall, usually gastric, leading to rigidity, and with subsequent pathological confirmation of diffuse tumor involvement with desmoplastic reaction without the

Table 3. Univariate and multivariate analysis of the overall survival

	Univariate analysis			Multivariate analysis		
	HR	(95% CI)	p	HR	(95% CI)	p
Age, years	1.02	(1.00-1.03)	0.028	1	(0.98-1.03)	0.7
Sex, female	0.93	(0.63-1.35)	0.689	1.33	(0.85-2.09)	0.213
LP AP, yes	4.11	(2.28-7.39)	< 0.001	3.26	(1.58-6.72)	0.001
Location (ref. cardia)			0.106			
Body	0.59	(0.35-1.00)	0.049			
Antrum	0.67	(0.43-1.05)	0.080			
Grade of differentiation (ref. 1)			0.001			
2	1.86	(1.02-3.38)	0.041			
3-4	2.56	(1.52-4.32)	< 0.001			
Pathologic T_rec1 (ref. T1)			< 0.001			
2	1.48	(0.60-3.64)	0.389			
3	3.74	(1.71-8.17)	0.001			
4	7.93	(3.49-18.0)	< 0.001			
Pathologic N rec (ref. N0)			< 0.001			
Pathologic N: N1	1.56	(0.82-2.96)	0.173			
Pathologic N: N2	3.28	(1.92-5.60)	< 0.001	3.44	(1.57-7.54)	0.002
Pathologic N: N3	5.13	(2.07-12.7)	< 0.001	4.33	(2.01-9.33)	< 0.001
Lymph node dissection D: D1	0.29	(0.15-0.56)	< 0.001	0.15	(0.07-0.33)	< 0.001
Lymph node dissection D: D2	0.28	(0.14-0.56)	< 0.001	0.14	(0.06-0.31)	< 0.001
R (ref. R0)			< 0.001			
1 or 2	3.01	(1.84-4.91)	< 0.001	3.62	(1.92-6.81)	< 0.001
Adjuvant (ref. No)			0.003			
CT	0.76	(0.44-1.31)	0.318	0.43	(0.22-0.84)	0.013
CT-RT	0.49	(0.32-0.74)	0.001	0.31	(0.18-0.54)	< 0.001

AP: anatomical pathology; HR: hazard ratio; 95% CI: 95% confidence interval; LP: linitis plastica; CT: chemotherapy; RT: radiotherapy.

necessary presence of mucosal tumor mass were classified as LP (Fig. 2).

As discussed in our study, the literature also shows that, mostly, LP affects somewhat younger men than those with gastric cancer in general. LP presents silently, without producing symptomatology until advanced stages, in which the decrease in gastric distensibility can produce nausea and vomiting, making early diagnosis complex. Endoscopy and biopsy are the reference method in the diagnosis of gastric cancer¹⁸. Nevertheless, in cases of LP, the cells can spread through the submucosa to rapidly develop into a transmural tumor, preserving an intact mucosa in up to 30% of cases¹⁹. On occasions when ulceration is not seen in the mucosa, the mucosa may appear as a flat surface with an atrophic appearance or as thickened folds caused by submucosal contraction. Therefore, LP can affect only a part of the stomach, producing a reduced distensibility of that segment,

and progressively extend to the entire stomach²⁰. Although the literature shows that it can be diagnosed from early stages (T1-2), most cases are diagnosed in advanced stages of local infiltration (T3-4 > 70%). In our study, presentation as a transmural tumor from diagnosis accounted for 100% of cases, which is probably related to the definition that served as inclusion criteria.

Conversely, the low cellularity of the tumor compared to the abundant stroma can lead to a significant number of negative biopsies (30-36%), thus a high degree of clinical suspicion is required to perform random or echoendoscopy-guided biopsies that, although with possible false negatives, will lead to diagnosis²¹. *In vivo* optical biopsy by confocal microscopy is under development and could be useful for early diagnosis of LP²².

If the presence of LP is suspected prior to surgery, either by identification on imaging tests (barium

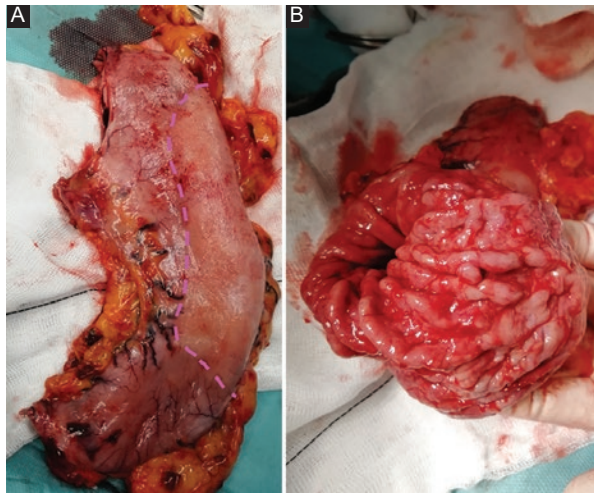


Figure 2. A: surgical specimen in which the gastric mural thickening produced by the linitis plastica can be appreciated. B: surgical specimen showing normal mucosa.

transit, CT or MRI) or by direct visualization by endoscopy or echoendoscopy, with or without pathological confirmation in biopsies, exploratory laparoscopy with intraoperative lavage and macro-biopsy should be considered, since, as in our study (32%), several series have shown the coexistence of peritoneal carcinomatosis in up to 64% of cases²³. However, on many occasions the first suspicion of LP is intraoperative, due to the observation in the surgical act of a gastric area with a suspicious appearance, without a previous pathological diagnosis of undifferentiated tumor, which makes it difficult to make decisions regarding treatment. Alternatively, distant metastases with the same diffuse infiltration profile have been described, sometimes of gastric signet-ring cell or breast neoplasms in the colon, rectum or small intestine, even years after the diagnosis of the disease⁹.

Various studies have searched for biomarkers in peripheral blood, as well as circulating cells, cDNA or miRNA, but possibly the low cellularity of these tumors has not allowed a standardized diagnostic method to be found^{24,25}. Future proteomic analyses on biopsy tissue or blood samples could lead to an earlier and more accurate preoperative diagnosis, in order to personalize treatment and improve prognosis.

In our series, a significant number of LP cases were located in the upper third (46.2%) of the stomach, and in order to achieve wide resection margins, total gastrectomy was the most commonly used technique (76.9%), as reported in the literature (62.5-88%). Although some authors doubt the possibility of offering curative surgical treatment in cases of LP, wide safety

margins (5-8 cm) have been classically proposed with the aim of achieving an R0 resection in diffusely infiltrating tumors²⁶. Nevertheless, some studies have attempted to prove that such wide margins are not necessary for the resection of this type of tumors²⁷. In the specific absence of studies analyzing the value of safety margins in case of LP, it is recommended to resect a sufficiently wide safety margin that avoids R1 resection, evaluating it by means of frozen intraoperative sections, without the need to perform a total gastrectomy upfront in all patients with LP, in order to avoid the morbidity and mortality that this entails. Moreover, systematic total gastrectomy does not guarantee R0 removal of the tumor in the surgical specimen, since the limits of infiltration are macroscopically imprecise and can microscopically go beyond the esophagogastric junction into the esophagus. In our case, 38.5% presented positive margins (R1), a figure in accordance with the literature, which reports high rates of insufficient resection (31-69%). Therefore, one must be cautious with limited resections, as false negatives of freezing resection margins caused by low cellularity of scirrhous tumors with desmoplastic reaction have sometimes been described. Possibly, near-total or 95% gastrectomy, with intraoperative biopsy of the surgical margins, could meet the resection conditions in some cases, combining the advantages of wide safety margins and low postoperative morbidity and mortality rates of subtotal gastrectomy²⁸. Such resection, together with a complete D2 lymph node dissection, could be the standard of care for gastric cancer with resectable LP.

In view of the greater number of cases of microscopic peritoneal implants, techniques such as complete omentectomy and bursectomy take on greater importance in the case of LP, and may be recommended in T3/T4 tumors²⁹. Alternatively, in recent years intraoperative chemotherapy (HIPEC, hyperthermic intraperitoneal chemotherapy) has begun to be developed in gastric cancer³⁰. Although for the moment no study has specifically described its usefulness in LP, this technique is encouraging due to the importance of the peritoneal dissemination of these tumors, thus new studies are being carried out³¹.

Similarly, when LP occurs in a location other than the gastric one, en bloc tumor resection with wide margins and extensive lymph node dissection is recommended in the case of primary lesions. However, most of the time these are secondary metastatic lesions of a primary gastric or breast tumor, so treatment will be palliative⁶⁻¹³.

Neoadjuvant treatment of gastric cancer has several theoretical advantages, such as better local control and a lower rate of R1 resections, and since these are generally locally advanced tumors at the time of diagnosis, it could be considered in many cases of LP. However, the results of different chemotherapeutic schemes, from MAGIC to the current FLOT, seem to show a lower response in diffuse infiltrating tumors^{32,33}. Therefore, although some studies propose upfront radical surgery based on the possible futility of these treatments and the progression of the disease during their application, they probably present a different chemosensitivity profile, so new studies are being conducted to determine the usefulness of adjuvant treatments in this type of tumors³⁴. In our series, the most commonly used treatment in patients with LP was postoperative chemotherapy and radiotherapy according to the Mc Donald scheme (46.2%), which is the most commonly used treatment in locally advanced tumors prior to the use of the currently most widely accepted neoadjuvant therapies.

Alternatively, most tumors that can produce LP are HER-2 negative, thus targeted therapy with trastuzumab is not indicated. Future proteomics trials should be directed at detecting potential therapeutic targets, not only cellular, but also in the abundant stroma that LP tumors present, so that personalized therapies can be applied.

Prognosis

Several studies have tried to establish the prognosis of tumors that can produce LP, but the different definitions of LP make the results heterogeneous. Median survival is 8 to 13.8 months, reaching 16.7 months in patients with resected tumors². As observed in our series, LP appears to have different prognostic characteristics from non-LP cases: more advanced stages at diagnosis; greater lymphatic infiltration with high lymph node burden and peritoneal dissemination, but with a lower rate of liver metastases; higher rate of R1 resections (31-69%) with positive surgical margins despite a higher rate of total gastrectomy (62.5-100%); and higher perioperative morbidity and mortality. However, although some groups report that LP does not differ in terms of prognosis from other gastric cancers if adjusted by stage^{35,36}, in our study it has been shown to be an independent risk factor for overall cancer mortality (HR: 3.26; 95% CI: 1.58-6.72). Even when performing a multivariate analysis taking into account only diffuse tumors, LP is shown to be an independent poor prognostic factor (HR: 2.97; 95% CI: 1.49-5.94).

Conclusions

LP is an old concept that has reached the present day in different histopathological classifications without there really being a clear definition of it. It is a macroscopic condition, in which a rigid organ with thickened walls is seen, with microscopic expression, caused by tumors with low cellularity with little cohesion between them and abundant intercellular stroma that presents a diffuse infiltration of the affected tissues. Although it most often affects the stomach primarily, it can appear throughout the digestive tract and has been described in colorectal and intestinal locations, either as the origin of the disease or as metastases of poorly cohesive carcinomas from other locations.

It is an uncertain process both therapeutically and prognostically. In this study, LP has been shown to be an independent factor related to cancer mortality. Therefore, a high degree of clinical suspicion is necessary to enable an early diagnosis of this insidious pathology, allowing treatment with curative intent. In this sense, surgery should continue to be proposed as part of a potentially curative multidisciplinary treatment of gastric cancer producing LP. However, more diagnostic tools, such as biological markers, are needed to allow individualized therapeutic decisions and modification of surgical strategies, as well as to detect therapeutic targets within the context of personalized medicine.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and with the World Medical Association and the Declaration of Helsinki.

Data confidentiality. The authors declare that they have followed the protocols of their work center regarding the publication of patient data.

Right to privacy and informed consent. The authors have received an informed consent from the patients and/or subjects referred to in this article. This document is in possession of the corresponding author.

References

- Brinton W. The diseases of the stomach, with an introduction on its anatomy and physiology; being lectures delivered at St. Thomas's hospital. London: J. Churchill; 1859.
- Agnes A, Estrella JS, Badgwell B. The significance of a nineteenth century definition in the era of genomics: linitis plastica. *World J Surg Oncol*. 2017;15:123.
- Haubrich, WS. Blumer of Blumer's shelf. *Gastroenterology*. 2000;118:30.
- IARC Publications. Digestive System Tumours. World Health Organization. 5th ed. Volume 1. Chapter 3. Tumours of the stomach. Lyon, France. 2019.
- Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76(2):182-188. doi:10.1111/his.13975
- Dixon CF. Carcinoma of linitis plastica type involving intestine. *Ann Surg*. 1936;103:263-72.
- Katsinelos P, Papaziogas B, Chatzimavroudis G, Katsinelos T, Dimou E, Atmatzidis S, et al. Secondary rectal linitis plastica as first manifestation of urinary bladder carcinoma. *Ann Gastroenterol*. 2012;25:173-5.
- Fahl JC, Dockerty MB, Judd ES. Scirrhus carcinoma of the colon and rectum. *Surg Gynecol Obstet*. 1960;111:759-66.
- Rodríguez Ortega M, Carabias Hernández A, Rodríguez Barbero JM, Montano Navarro E, Limones Esteban M. Linitis plástica intestinal, metástasis tardía de adenocarcinoma gástrico en anillo de sello. *Rev Esp Enferm Dig*. 2006;98:391-2.
- Laufman H, Saphir O. Primary linitis plastica type carcinoma the colon. *Arch Surg*. 1951;62:79-91.
- Murayama H, Miura K, Sakamoto J. Primary linitis plastica of the rectum: report of four cases and review of the literature. *Surg Today*. 1996;26: 875-81.
- Nadel L, Mori K, Shinya H. Primary linitis plastica of the colon and rectum. *Dis Colon Rectum*. 183;26:738-42.
- Dominguez-Adame E. Linitis plástica primaria rectal: presentación de un caso clínico con abordaje quirúrgico laparoscópico. *Cirugía. Casos Clínicos*. 2008;3:2-7.
- Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer*. 2021;24(1):1-21.
- Hu B, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A. Gastric cancer: classification, histology and application of molecular pathology. *J Gastrointest Oncol*. 2012;3:251-61.
- Minamoto T, Ooi A, Okada Y, Mai M, Nagai Y, Nakanishi I. Desmoplastic reaction of gastric carcinoma: a light- and electron-microscopic immunohistochemical analysis using collagen type-specific antibodies. *Hum Pathol*. 1988;19:815-21.
- Bass AJ, Thorsson V, Shmulevich I, Reynolds SM, Miller M, Bernard B, et al.; Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513: 202-9.
- Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27:v38-v49.
- Jung K, Park MI, Kim SE, Park SJ. Borrmann type 4 advanced gastric cancer: focus on the development of scirrhus gastric cancer. *Clin Endosc*. 2016;49:336-45.
- Endo K, Sakurai M, Kusumoto E, Uehara H, Yamaguchi S, Tsutsumi N, et al. Biological significance of localized type IV scirrhus gastric cancer. *Oncol Lett*. 2012;3:94-9.
- Park MS, Ha HK, Choi BS, Kim KW, Myung SJ, Kim AY, et al. Scirrhus gastric carcinoma: endoscopy versus upper gastrointestinal radiography. *Radiology*. 2004;231:421-6.
- Goetz M, Watson A, Kiesslich R. Confocal laser endomicroscopy in gastrointestinal diseases. *J Biophotonics*. 2011;4:498-508.
- Kodera Y, Nakanishi H, Ito S, Mochizuki Y, Yamamura Y, Fujiwara M, et al. Detection of disseminated cancer cells in linitis plastica-type gastric carcinoma. *Jpn J Clin Oncol*. 2004;34:525-31.
- Ichikawa Y, Koshikawa N, Hasegawa S, Ishikawa T, Momiyama N, Kunizaki C, et al. Marked increase of trypsin(ogen) in serum of linitis plastica (gastric cancer, borrmann 4) patients. *Clin Cancer Res*. 2000;6:1385-8.
- Dakubo GD. Cancer biomarkers in body fluids. Switzerland: Springer; 2017. 509 p.
- Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer*. 2017;20:1-19.
- Squires 3rd MH, Kooby DA, Poultides GA, Pawlik TM, Weber SM, Schmidt CR, et al. Is it time to abandon the 5-cm margin rule during resection of distal gastric adenocarcinoma? A multi-institution study of the U.S. Gastric Cancer Collaborative. *Ann Surg Oncol*. 2015;22: 1243-51.
- Azagra JS, Sarriugarte A, Ibáñez FJ. Estado actual de la gastrectomía por cáncer. «Less is often more». *Cir Esp*. 2018;96:603-5.
- Marano L, Polom K, Bartoli A, Spaziani A, De Luca R, Lorenzon L, et al. Oncologic effectiveness and safety of bursectomy in patients with advanced gastric cancer: a systematic review and updated meta-analysis. *J Invest Surg*. 2018;31:529-38.
- Yonemura Y, Canbay E, Li Y, Cocolini F, Glehen O, Sugarbaker PH, et al. A comprehensive treatment for peritoneal metastases from gastric cancer with curative intent. *Eur J Surg Oncol*. 2016;42:1123-31.
- Brown ZJ, Hernandez JM, Ripley, RT, Davis JL. Heated intraperitoneal chemotherapy and gastrectomy for gastric cancer in the U.S.: the time is now. *J Gastrointest Oncol*. 2017;8:1109-13.
- Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11-20.
- Al-Batran SE, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol*. 2016;17:1697-708.
- Piessen G, Messager M, Le Malicot K, Robb WB, Di Fiore F, Guilbert M, et al. Phase II/III multicentre randomised controlled trial evaluating a strategy of primary surgery and adjuvant chemotherapy versus peri-operative chemotherapy for resectable gastric signet ring cell adenocarcinomas - PRODIGE 19 - FFCD1103 - ADIC002. *BMC Cancer*. 2013;13:281.
- Blackham AU, Swords DS, Levine EA, Fino NF, Squires MH, Poultides G, et al. Is linitis plastica a contraindication for surgical resection: a multi-institution study of the U.S. Gastric Cancer Collaborative. *Ann Surg Oncol*. 2016;23:1203-11.
- Thompson RJ, Ranaghan L, Kennedy R, Clements W, Carey PD, Kennedy JA. Survival following operative management of gastric linitis plastica compared with non-operative management. *Ann R Coll Surg Engl*. 2017;99:228-32.