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Is Linitis Plastica a Contraindication for Surgical Resection: A Multi-Institution Study of the U.S. Gastric Cancer Collaborative

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Abstract

Background—Current staging and treatment guidelines for gastric adenocarcinoma do not differentiate between linitis plastic (LP) and non-LP cancers. Significant controversy exists regarding the surgical management of LP patients.

Methods—Using the multi-institutional U.S. Gastric Cancer Collaborative database, 869 gastric cancer patients who underwent resection between 2000 and 2012 were identified. Clinicopathologic and outcomes data of 58 LP patients were compared to 811 non-LP patients.

Results—Stage III/IV disease was more common at presentation in LP patients compared with non-LP patients (90 vs. 44 %, $p < 0.01$). Despite the fact that most LP patients underwent total gastrectomy (88 vs. 39 %, $p < 0.01$), final positive margins were more common in LP patients (33 vs. 7 %, $p < 0.01$). The use of frozen section allowed 15 intraoperative positive margins in 38 patients to be converted to negative final margins. Median overall survival (OS) was significantly worse in patients with LP (11.6 vs. 37.8 months, $p < 0.01$). There was no difference in median OS of LP patients based on stage (I/II, 17.3 mo; III, 10.6 mo; IV, 12.0 mo; $p = 0.46$). LP and non-LP

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patients who underwent optimal resection (negative margin and D2/3 lymphadenectomy) had better survival compared with those with nonoptimal resections. The median OS for optimally resected stage III LP (n = 22) and stage III non-LP (n = 185) patients was nearly identical (26.7 vs. 25.3 mo; p = 0.69).

Conclusions—Future staging systems and treatment guidelines should differentiate between LP and non-LP gastric cancers. Long-term survival in select LP patients who undergo optimal resections is comparable to optimally resected non-LP patients.

Linitis plastica (LP) is an uncommon variant of gastric adenocarcinoma found in 7–14 % of cases.[1,2] It represents a diffusely infiltrative and desmoplastic process usually involving the entire stomach giving it a stiffness described as “leather bottle stomach.”[2,3] Also referred to as Borrmann Type IV or scirrhous carcinoma of the stomach, LP portends a poor prognosis compared with other forms of gastric cancer.[4]

The diagnosis of LP carries significant controversy regarding its surgical management. Lymph node involvement is almost always present at the time of diagnosis, and due to its diffuse nature, microscopic disease is often found at the resection margins.[3,5] Peritoneal dissemination is frequently encountered at the time of surgery or as the main site of recurrence.[5–7] As such, curative resection is possible in less than half of patients and early recurrence is common, leading to a dismal median survival, ranging from 6 to 12 months, and 5-year survival between 8 and 13 %.[2,5,6,8–11]

It remains unknown whether its poor prognosis is simply related to its advance stage at presentation or the innate biology of the disease. Furthermore, current treatment guidelines do not differentiate between LP and non-LP cancers, and it is not known if the same staging system should be applied to both subtypes. The number of studies available to assess the clinical outcomes of LP is fairly small and limited mostly to reports from Eastern Asia and Europe.[2,4–6,8,10] The primary purpose of this study was to analyze perioperative and long-term outcomes following the surgical management of LP from a large, multicenter American database and identify potential subgroups of LP patients who derive a survival benefit from surgical resection.

METHODS

Patients were identified from the U.S. Gastric Cancer Collaborative retrospective database who underwent gastric resection for gastric adenocarcinoma between 2000 and 2012 at one of seven major academic centers (Johns Hopkins Hospital, Baltimore, MD; Emory University, Atlanta GA; Stanford University, Palo Alto, CA; Washington University, St. Louis, MO; Wake Forest University, Winston-Salem, NC; University of Wisconsin, Madison, WI; The Ohio State University, Columbus, OH). This study was approved by the Institutional Review Boards of each respective institution. Data regarding patient demographic and clinical characteristics, perioperative variables, tumor pathologic features, and multimodality therapies were retrospectively collected by the individual institutions and combined into a single database for analysis as previously reported.[12,13] Patients with gross peritoneal disease and/or who underwent palliative resection or bypass procedures (n = 77) were excluded. The presence of LP was reported by each individual institution and was

based on clinical assessment (endoscopic or intraoperative) or histologic evaluation. Patients were excluded if the presence or absence of LP was not clearly stated ($n = 19$).

Pathologic classification and TNM staging following surgical resection were defined by AJCC, 7th edition.[14] The extent of lymphadenectomy was recorded based on the Japanese Gastric Cancer Association classification system (D1/D2/D3).[15] Lymph node ratio (LNR) was categorized into four groups (LNR1, ≤1/15; LNR2, 1/15 <LNR ≤3/10; LNR3, 3/10 <LNR ≤7/10; and LNR4, >7/10) as described by Wang et al.[16] Operative complications were classified as minor (grade I/II) and major (grade III/IV) based on the Clavien-Dindo classification system.[17] Optimal resection was defined as patients who underwent D2 or D3 lymphadenectomy and had negative final proximal and distal margins (R0).

Statistical Analysis

Demographic and perioperative characteristics were compared by LP status using ANOVA for continuous variables and Chi squared tests for categorical variables. Overall survival (OS) and recurrence-free survival (RFS) were estimated by using Kaplan–Meier methods. OS was defined as time to death or censorship from date of operation, whereas RFS was defined as time to death, recurrence, or censorship from date of operation. Differences in survival by LP and stage were assessed by using the log-rank test. In patients with LP, univariate and multivariate Cox proportional hazards models were used to quantify the relationships between OS and patient characteristics. The multivariate model was adjusted for age, sex, lymphovascular invasion, total comorbidities, neoadjuvant chemotherapy, adjuvant chemotherapy, adjuvant radiotherapy, type of nodal dissection, complications, and LNR. Hypothesis testing was two-sided and performed at the 0.05 significance level. All analysis was performed in SAS Version 9.4 (Cary, NC).

RESULTS

Of the 869 patients with gastric adenocarcinoma who underwent gastric resection with curative intent, LP was diagnosed in 58 patients (6.7 %). These patients differed from non-LP patients in several ways (Table 1). Most notably, patients with LP were younger (61.1 vs. 65.3 years, $p = 0.017$), had larger tumors (8.9 vs. 4.8 cm, $p < 0.001$), and were more likely to present with advanced-stage disease (stage III/IV; 90 vs. 44 %, $p < 0.001$). Both T-stage and N-stage were proportionally worse in LP patients ($p < 0.001$). As expected, patients with LP were more likely to have poorly differentiated tumors (98 % vs. 57 %, $p < 0.001$). The extent of nodal dissection was similar in both groups (D2/D3; 62 vs. 60 %, $p = 0.756$).

Positive resection margins occurred more often in LP patients (33 vs. 7 %, $p < 0.001$) despite the fact that total gastrectomy was much more commonly performed (88 vs. 39 %, $p < 0.001$). Frozen sections of the proximal or distal margins were performed on 38 LP patients (66 %). Sixteen patients had a positive proximal margin on frozen section. Ten of those patients were converted to a negative final proximal margin by resecting an additional margin. In contrast, of the 20 patients who did not have frozen sections performed on the proximal margin, 9 had a positive final proximal margin. Only 2 of 22 patients with negative proximal margins on frozen section had a positive final proximal margin (91 % NPV; 95 % CI, 71–99 %). Similarly, of 8 patients with a positive distal margin on frozen section, 5

achieved a negative final distal margin by resecting an additional margin. Six of 29 patients without frozen sections performed on the distal margin had positive final distal margins. The NPV for a negative distal margin on frozen section for a negative final distal margin was 100 %.

Perioperative outcomes were no different between LP and non-LP patients. Estimated blood loss (370 vs. 294 mL, $p = 0.067$), the need for perioperative blood transfusion (24 vs. 23 %, $p = 0.873$), and hospital length of stay (11.8 vs. 11.5, $p = 0.815$) were similar in both groups. Likewise, overall morbidity was not statistically different between LP and non-LP patients (48.3 vs 43.2 %, $p = 0.454$) with major complications occurring in 15.5 and 15.1 % of cases, respectively. Operative mortality was higher in the LP group (6.9 vs. 3.1 %), but this was not statistically significant ($p = 0.119$).

Median RFS was 28.4 months in non-LP patients who underwent curative resection compared with only 9.6 months in LP patients ($p < 0.001$). Three- and 5-year RFS was 46 and 37 % for non-LP patients, whereas it was 17 and 9 % in LP patients respectively. Median OS was significantly better in patients with non-LP gastric adenocarcinoma (37.8 vs. 11.6 months, $p < 0.001$). Three- and 5-year OS were 50 and 39 % for patients with non-LP disease compared with 24 and 15 %, respectively, in patients with LP. Kaplan–Meier survival curves are shown in Fig. 1a.

As expected, median OS correlated significantly with stage in patients without LP (Stage I, 103 months; stage II, 49.8 months; Stage III, 19.2 months; stage IV, 8.4 months; $p < 0.001$). However, OS was not significantly difference among LP patients stratified by stage (stage I/II, 17.3 months; stage III, 10.6 months; stage IV, 12.0 months; $p = 0.458$). Survival by stage is summarized in Table 2, and Kaplan–Meier curves are shown in Fig. 1b,c. Only six patients with LP presented with early-stage disease. Median OS (17 months) among these six patients was markedly worse than stage I (103 months, $p = 0.029$) and stage II (49.8 months, $p = 0.291$) non-LP patients, although the comparison is notably underpowered. While median OS was longer among stage III patients without LP (19.2 months) compared with stage III patients with LP (10.6 months), this difference did not reach statistical significance ($p = 0.083$).

Optimal surgical resection (negative margins and D2/D3 lymphadenectomy) was achieved in 466 non-LP patients and 26 LP patients. In comparing optimal resections to nonoptimal resections, there was a significant survival advantage seen in both non-LP ($p = 0.002$) and LP patients ($p = 0.022$) who underwent optimal resection (Fig. 2). After stratifying optimally resected non-LP patients by stage, survival of optimally resected LP patients mirrored stage III non-LP patients. There was no statistical difference in median OS between optimally resected stage III non-LP patients ($n = 185$) and optimally resected stage III LP patients ($n = 22$) as shown in Fig. 3 (25.3 vs. 26.7 months, $p = 0.686$).

Several factors were associated with worse OS in LP patients following curative resection (Table 3), including age [hazard ratio (HR) = 1.22; 95 % CI 1.05, 1.41), number of major comorbidities (HR = 1.65; 95 % CI 1.12, 2.42), postoperative complication (HR = 2.54; 95 % CI 1.33, 4.85), lymphovascular invasion (HR = 2.16; 95 % CI 1.08, 4.31), and LNR4

(HR = 4.38; 95 % CI 1.58, 12.1). Notably, margin status, stage, and the use of perioperative chemotherapy or radiation were not associated with survival. Using Cox regression multivariate analysis, only the number of major comorbidities was predictive of survival (HR = 2.66; 95 % CI 1.34, 5.30).

DISCUSSION

The prognosis for gastric LP is commonly regarded as poor. Symptoms at the time of presentation are nonspecific leading to delayed diagnosis. As such, tumors are large, often transmural, and synchronous lymph node metastasis is almost universal.[2,5] Even in our series of select resectable gastric LP, more than half of the patients had T4 tumors and 83 % had involved perigastric lymph nodes. Furthermore, peritoneal dissemination is common, both at the time of diagnosis and as the main source of recurrent disease.[5,6]

The overall poor prognosis of LP gastric cancer has led some authors to conclude that LP is not a surgical disease, and many oncology providers remain biased against surgical resection for gastric LP.[9,18] Aranha et al. compared 13 unresectable patients with gastric LP with 13 patients with resected gastric LP and noted no difference in OS (6.6 vs. 7.2 months), leading them to conclude that gastrectomy for LP is never curative and may only palliate 20 % of LP patients.[9] It should be noted that more than half of their resected patients had liver, peritoneal, or adjacent organ involvement, and improved survival was reported in resected patients with limited locoregional disease (13.6 months). In another earlier clinical series, Hamy et al. reported a 50 % 1-year survival in 86 patients with LP.[8] However, 5-year survival was 10 %, supporting their conclusion that while overall prognosis is poor, in the absence of alternative effective therapies, surgical resection remains the only means of improved survival or potential cure. Other authors at the time proposed left upper abdominal evisceration for LP (including stomach, spleen, distal pancreas, transverse colon, left adrenal, gallbladder with associated lymphadenectomy) citing significantly improved locoregional recurrence and survival.[19]

Whereas outcomes in these earlier studies were discouraging, more recent focus has identified several prognostic factors that could be used to select patients who benefit from surgical treatment. Complete surgical resection (R0) has consistently been associated with improved survival in LP patients.[2,5,6] Pedrazzani et al. reported a median OS of 16 months in patients who underwent R0 gastrectomy compared with 5.2 months in patients who received an R1 resection (defined as positive margins or positive peritoneal cytology) and 2.8 months in patients deemed unresectable at the time of surgery ($p < 0.001$).[6] Furthermore, several studies have shown no improvement in survival between R1, R2 (palliative), and unresected gastric LP patients, highlighting the importance of complete surgical resection.[2,5,20] Unfortunately, the rate of R0 resection is discouragingly low (30–46 %) among patients taken to the operating room for resection.[2,5,6] Due to the diffuse nature of LP, positive microscopic margins are common (33 % in our series) and peritoneal disease is found at time of resection as often as 44 %.[5] Including patients who underwent palliative gastrectomy ($n = 19$), only 49 % of patients in our series where able to achieve an R0 resection.

Several studies have shown nodal metastasis to be independently associated with poor survival, whereas extended lymphadenectomy is prognostic in advanced-stage gastric LP.[4,5,10,21] Regional nodal metastasis was present in 83 % of our patients with LP and 43 % had N3 disease (≥7 nodes). The mean number of involved lymph nodes was 8.9 with a LNR of 0.47 among LP patients with nodal metastases. These findings are consistent with other series where nodal disease occurred in 85 to 95 % of patients and N3 was present in at least a third.[2,4] Due to high incidence of nodal involvement, most authors recommend extended lymphadenectomy (D2/3) for patients with gastric LP, although a comparison based on extend of lymphadenectomy has never been done.[10]

With these prognostic factors in mind, we analyzed optimally resected patients (R0 resection with extended lymphadenectomy) and found that optimally resected LP and non-LP patients had improved survival compared with patients with incomplete resection or limited lymphadenectomies. Furthermore, long-term prognosis in optimally resected stage III gastric LP patients was remarkably similar to stage III optimally resected non-LP patients. Five-year survival in these patients is approximately 25 %, suggesting curative resection is possible in some patients, even in the presence of LP. Given these data, if LP patients are deemed to be resectable candidates, aggressive efforts should be made to achieve an R0 resection and at minimum, a D2 lymphadenectomy should be performed. In addition, the predictive value of frozen sections for final margin status was high in our series and a significant number of patients were converted to a negative final proximal/distal margin suggesting that performing frozen sections to assess margin status during surgery for gastric LP is essential.

Given the high incidence of peritoneal disease in gastric LP, cytology of peritoneal washings is another prognostic tool that could help to select patients for resection.[2,20] Kodera et al. found positive cytology in 29 of 70 patients with LP, including 6 patients without macroscopic signs of peritoneal disease.[20] Improved median survival was reported among patients with negative cytology; however, there was no difference in survival among patients with R1 resection ($n = 6$), patients with peritoneal disease ($n = 25$), or patients who did not undergo resection ($n = 11$). No patient with positive cytology survived past 2 years, leading to the conclusion that laparoscopy and peritoneal washings should be performed as part of the staging workup for gastric LP. In our series, only 23 patients underwent staging laparoscopy and only 4 patients had cytology data, because there was no standard approach regarding diagnostic laparoscopy and peritoneal washings among the multiple institutions at the time.

Interestingly, the prognosis for early-stage gastric LP in our series was no better than advanced-stage disease. Stage I/II gastric LP only represented 10 % of our patients, which limits the definitive conclusions that can be made. In contrast, diagnosing gastric cancer in earlier stages is common in Asian countries as a result of generalized screening programs, which do not exist in the United States. Several studies from Asia report higher incidences of early-stage gastric LP and show that pathologic stage is predictive of survival.[4,10,22] A large 10-year review from Samsung Medical Center in Seoul, South Korea found stage I/II disease in 145 of 555 patients (26 %) with Borrmann type IV gastric cancer.[4] When analyzed by stage, Borrmann type IV patients had worse 5-year OS compared with patients

with other types of gastric cancer (stage Ib 61 vs. 89 %, $p < 0.001$; stage II 50 vs. 76 %, $p < 0.001$; stage IIIa 37 vs. 55 %, $p < 0.001$; stage IIIb 15 vs. 39 %, $p = 0.001$; and stage IV 10 vs. 20 %, $p = 0.008$). The fact that even small primary tumors with node-negative disease are biologically aggressive and the prognosis of LP patients is worse stage for stage compared with non-LP patients indicates that staging for LP gastric cancer should not parallel non-LP staging. In another large series from Japan, pathologic T stage and long-term adjuvant S-1 chemotherapy were associated with survival, suggesting that early stage LP disease treated with multimodality therapy may be another subgroup of patients who should be considered for surgical resection.[22] Future treatment guidelines for gastric LP should highlight multimodality therapy and close long-term surveillance similar to advanced gastric cancer.

It is noteworthy that the mortality rate in our series was twice as high in LP patients compared with non-LP patients. LP is almost always treated with total gastrectomy (88 % in our series compared with 39 % of non-LP cases). In addition, LP patients usually present with advance stage and often are treated with neoadjuvant chemotherapy and/or radiation. The combination of advanced disease, prior treatments, and more extensive resection intuitively increases the surgical risk and may explain the higher mortality seen in our patients. While not statistically significant, the higher mortality in LP patients is clinically important and has to be taken into consideration when selecting LP patients for surgery. These operations must go perfectly; otherwise major morbidity will result in delay of further chemotherapy, loss of survival benefit and possibly death.

Several limitations of our study are inherent to other multicenter retrospective reviews. The diagnostic criteria of LP were not standardized between institutions; rather LP was assigned based on the clinical and/or histologic assessment by the treating providers. The description of LP is not consistent in the literature and other publications have used either endoscopic or histologic criteria to define LP.[2,4–6] The lack of standardized treatment protocols and the bias that exists among oncology providers concerning gastric LP likely led to the variations in treatment regimens seen in our study. Many of our patients were referred from community medical oncologists and received perioperative systemic treatment outside of our institutions. As such, our data regarding adjuvant chemotherapy are likely underreported. Yet, 76 % of LP patients in our series were in fact treated with perioperative chemotherapy using standard gastric cancer protocols, including combinations of epirubicin, cisplatin, 5-fluorouracil, oxaplatin, carboplatin, paclitaxel, docetaxel, and irinotecan. The most common regimens used in our patients were perioperative epirubicin, cisplatin, fluorouracil (MAGIC regimen), or adjuvant fluorouracil/leucovorin plus radiation (MacDonald regimen).[23,24] Recent phase I/II studies from Japan have shown good response and tolerable toxicity to S-1–based regimens in patients with gastric LP; however, S-1 is not available in the United States.[25–27] Given the high risk of peritoneal and recurrent disease in gastric LP, effective systemic therapy is imperative to improving outcomes, and as such, the role of perioperative chemotherapy requires further investigation.

Our study confirms the poor overall prognosis and advanced stage at presentation of the majority of LP patients. Many LP patients will not benefit from surgery due to peritoneal dissemination or locally advanced disease that precludes complete resection. Our data suggest that LP patients who achieve optimal surgical resection, inclusive of a total

gastrectomy and extensive lymphadenectomy, can expect long-term survival rates similar to stage III non-LP optimally resected patients. Frozen sections have a high negative predictive value in LP cases and provide surgeons the opportunity to salvage incomplete microscopic resections by identifying positive margins intraoperatively. Despite the stigmata and bias against surgical intervention, there are subgroups of LP patient who can achieve acceptable survival, and as such, surgical resection should remain part of the multimodality approach for gastric cancer patients with LP. The challenge is identifying patients with occult peritoneal disease or who will develop early recurrence such that futile resection can be avoided. Based on data from other authors as previously discussed, staging laparoscopy and peritoneal washing cytology may be a vital component of patient selection in LP patients and should be further studied. In the meantime, updated staging systems should differentiate between LP and non-LP gastric cancer, whereas treatment guidelines should consider early stages of LP as advanced stage and treat them accordingly.

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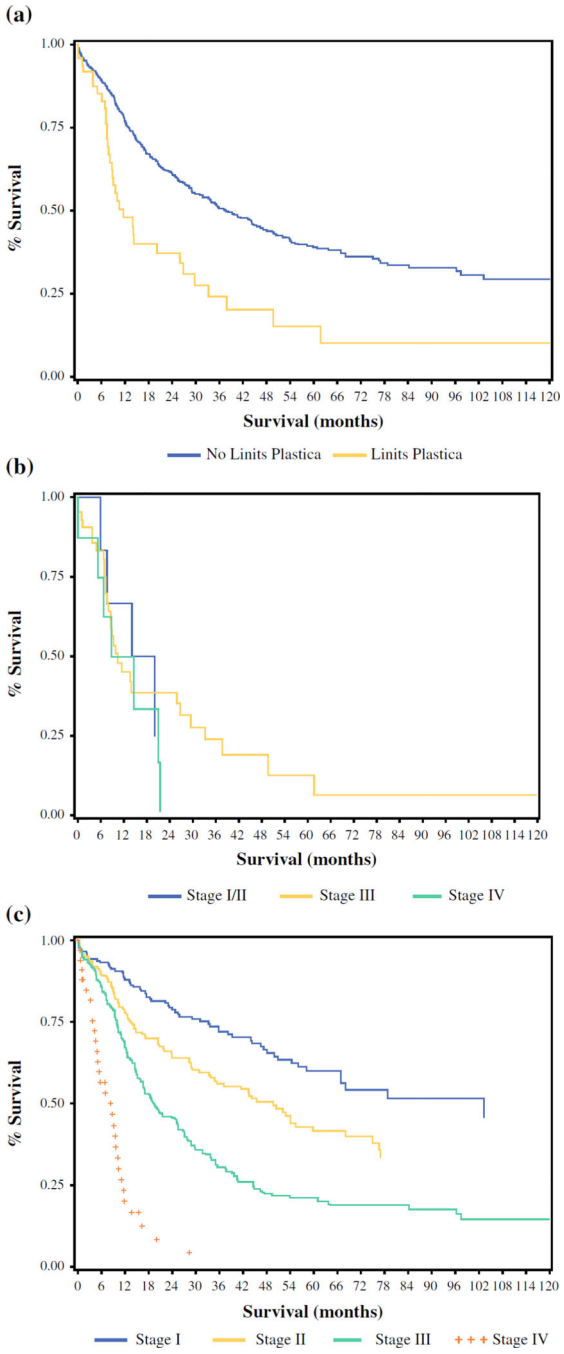

FIG. 1.

Kaplan–Meier survival curves in gastric cancer patients following surgical resection **a** with or without linitis plastica ($p < 0.001$), **b** with linitis plastica stratified by pathologic stage ($p = 0.458$), and **c** without linitis plastica stratified by pathologic stage ($p < 0.001$)

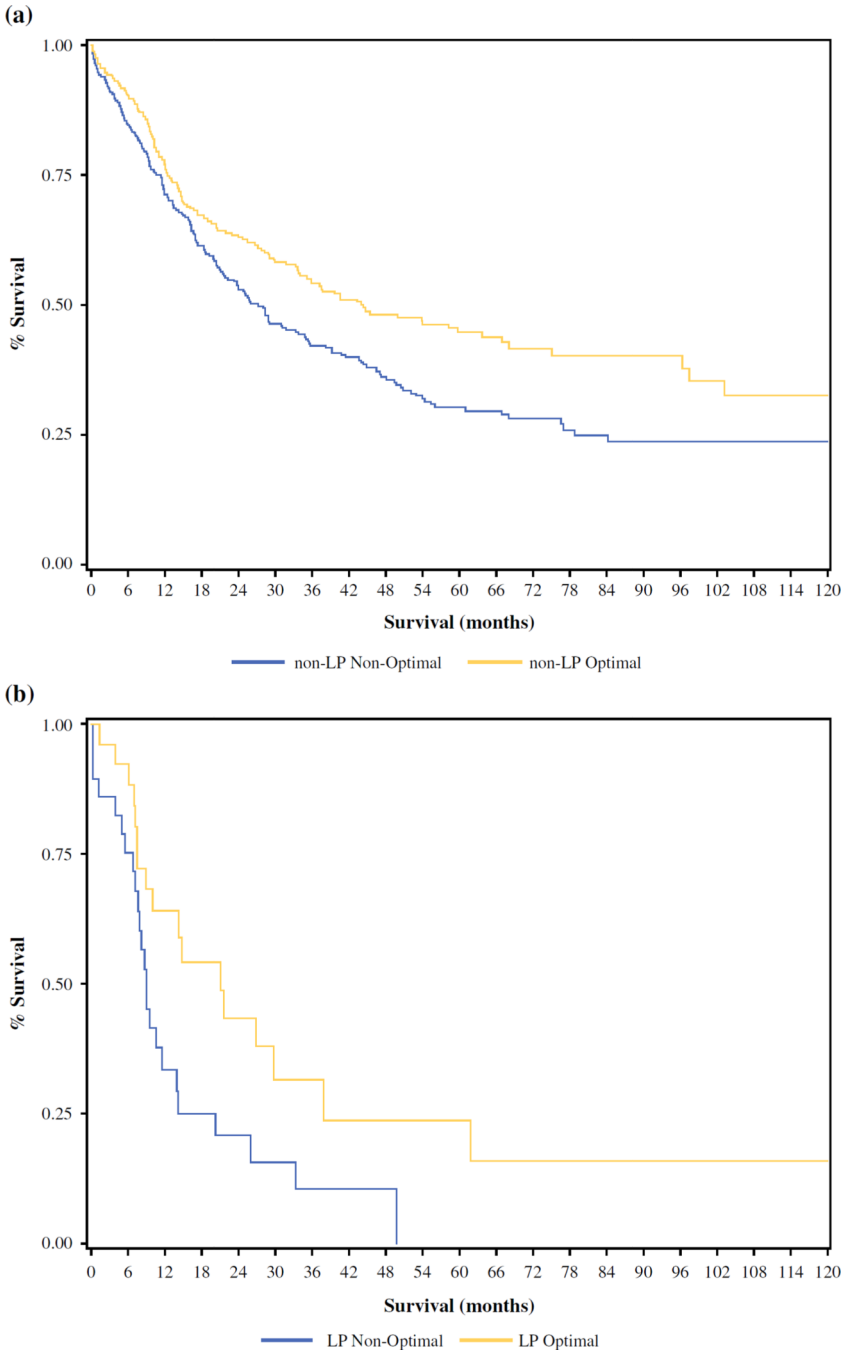

FIG. 2.

Kaplan–Meier survival curves in gastric cancer patients who underwent optimal surgical resection (negative margins, R0, and a D2/3 lymphadenectomy) compared with those who did not receive optimal resection in patients **a** without linitis plastica ($p = 0.002$) and those **b** with linitis plastica ($p = 0.022$)

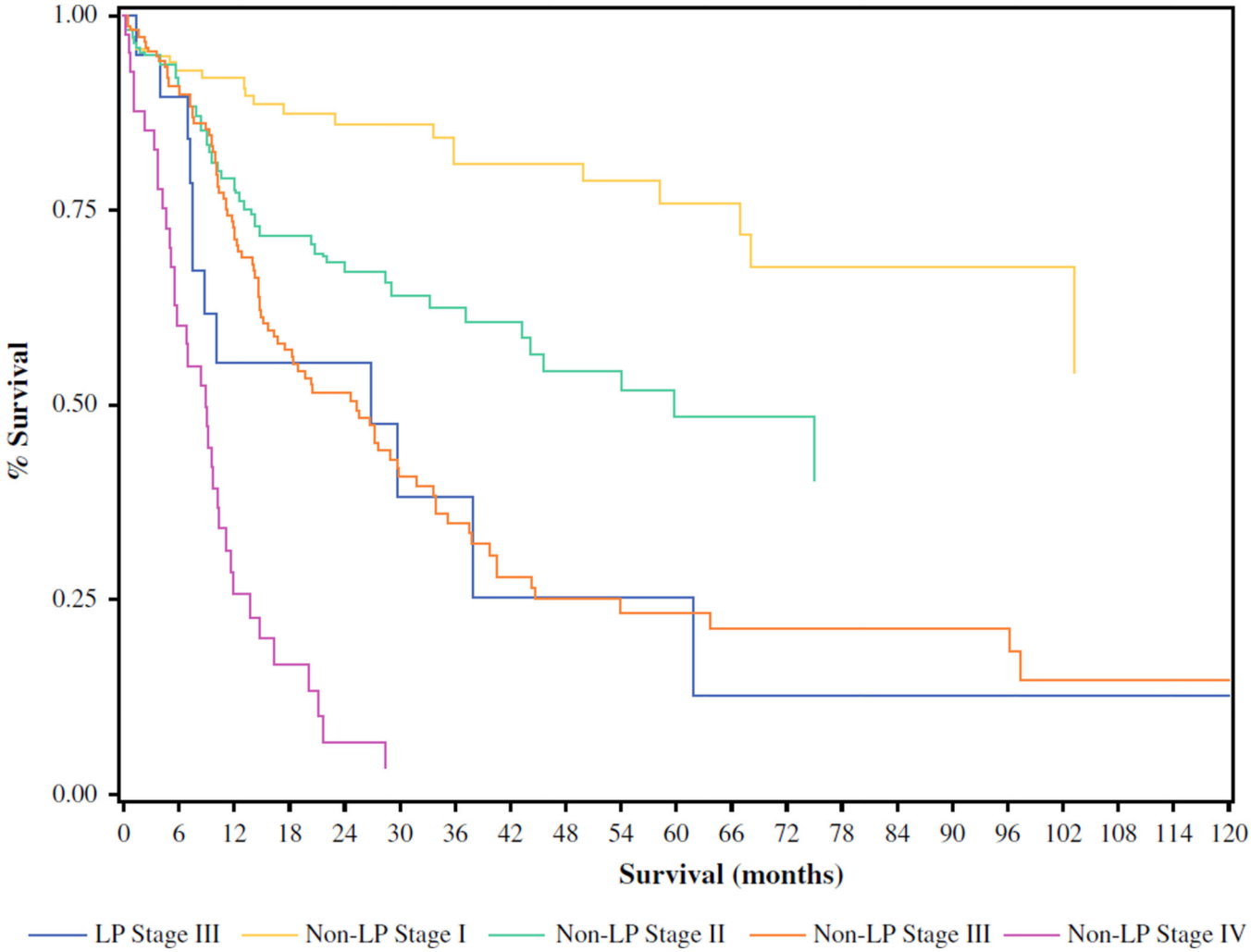

FIG. 3.

Kaplan–Meier survival curves in gastric cancer patients following optimal surgical resection (negative margins, R0, and a D2/3 lymphadenectomy) stratified by the presence of linitis plastica (LP) and stage

TABLE 1

Comparison of demographic and perioperative data among gastric cancer patients with or without linitis plastica who underwent curative gastric resection

	Linitis plastica (%)	Non-Linitis plastica (%)	*p* value
Total patients (n = 869)	58	811	
Age (yr)	61 ± 13	65 ± 12	0.017
Gender			
Male	27 (47)	470 (58)	0.090
Female	31 (53)	341 (42)	
Race			
White	41 (72)	512 (64)	0.381
Black	10 (17)	133 (16)	
Asian	2 (4)	94 (12)	
Latino	2 (4)	32 (4)	
Other/unknown	2 (4)	35 (4)	
Body mass index	24.7 ± 5.6	26.0 ± 5.8	0.137
Number of major comorbidities *	0.7 ± 0.9	1.1 ± 1.1	0.023
Current or past smoker			
Yes	16 (29)	319 (41)	0.067
No	40 (71)	459 (59)	
Neoadjuvant chemotherapy			
No	41 (71)	653 (81)	0.068
Yes	17 (29)	157 (19)	
Neoadjuvant radiation			
No	46 (96)	637 (96)	0.848
Yes	2 (4)	24 (4)	
Adjuvant chemotherapy			
No	18 (33)	361 (48)	0.040
Yes	36 (67)	395 (52)	
Adjuvant radiation			
No	31 (60)	492 (66)	0.332
Yes	21 (40)	251 (34)	
Type of resection			
Wedge resection	0 (0)	8 (1)	<0.001
Distal gastrectomy	0 (0)	144 (18)	
Subtotal gastrectomy	7 (12)	339 (42)	
Total gastrectomy	51 (88)	317 (39)	
Type of nodal dissection			
D0/D1	22 (38)	324 (40)	0.756
D2/D3	36 (62)	486 (60)	
Tumor size (cm)	8.9 ± 6.1	4.8 ± 3.3	<0.001

	Linitis plastica (%)	Non-Linitis plastica (%)	*p* value
Tumor stage			
T0	0 (0)	9 (1)	$p < 0.001$
T1	1 (2)	194 (24)	
T2	1 (2)	114 (14)	
T3	25 (43)	253 (32)	
T4	31 (53)	232 (29)	
Nodal stage			
N0	9 (15)	322 (40)	$p = 0.002$
N1	8 (14)	154 (19)	
N2	16 (28)	139 (17)	
N3	25 (43)	193 (24)	
Lymph node ratio	0.41 ± 0.3	0.23 ± 0.3	<0.001
Histologic grade			
Well	0 (0)	59 (8)	<0.001
Moderate	1 (2)	278 (35)	
Poor	55 (98)	450 (57)	
Lymphovascular invasion			
No	24 (50)	393 (54)	0.558
Yes	24 (50)	330 (46)	
Margin status			
Negative	39 (67)	749 (93)	<0.001
Positive	19 (33)	58 (7)	

*Includes hypertension, pulmonary disease, diabetes, cardiac disease and peripheral vascular disease

TABLE 2

Overall survival (OS) by stage in gastric cancer patients following surgical resection with or without linitis plastica

	Stage I/II		Stage III	Stage IV
Linitis plastica (n=)	6		44	8
3-year survival (SE)	24 % (20 %)		24 % (8 %)	0 %
5-year survival (SE)	25 % (20 %)		13 % (7 %)	0 %
Median OS (mo) *	17.3		10.6	12.0
	Stage I	Stage II	Stage III	Stage IV
Non-linitis plastica (n=)	237	207	320	34
3-year survival (SE)	72 % (4 %)	56 % (4 %)	30 % (3 %)	4 % (4 %)
5-year survival (SE)	60 % (4 %)	42 % (5 %)	21 % (3 %)	4 % (4 %)
Median OS (mo) **	103	49.8	19.2	8.4

SE standard error

* $p = 0.458$;

** $p < 0.001$

TABLE 3

Univariate analysis of clinical and perioperative variable for survival in patients with LP

	Hazard ratio (95 % CI)	***p* value**
Age (5-yr intervals)	1.22 (1.05, 1.41)	0.008
Gender (male reference)		
Female	1.05 (0.56, 1.95)	0.886
Number of comorbidities	1.65 (1.12, 2.42)	0.012
Use of neoadjuvant chemotherapy	1.67 (0.65, 2.88)	0.410
Use of adjuvant chemotherapy	0.53 (0.26, 1.05)	0.069
Use of adjuvant radiation	0.68 (0.36, 1.32)	0.260
Type of nodal dissection (D0/1 reference)		
D2/3	0.624 (0.34, 1.16)	0.137
Lymph node ratio (LNR1 reference)		
LNR2	1.04 (0.39, 2.72)	0.945
LNR3	0.70 (0.27, 1.81)	0.455
LNR4	4.38 (1.58, 12.1)	0.005
Postoperative complications	2.54 (1.33, 4.85)	0.005
Lymphovascular invasion	2.16 (1.08, 4.31)	0.029
Negative resection margin(s)	0.85 (0.45, 1.61)	0.612
Stage (stage I/II reference)		
Stage III	0.77(0.27, 2.25)	0.636
Stage IV	1.22 (0.36, 4.19)	0.751