

# Gastric Linitis Plastica: Clinical Characteristics and Outcomes from the National Cancer Database

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**Abstract.** *Background/Aim:* Gastric linitis plastica (LP) is a rare type of gastric tumor with limited data. We sought to investigate the clinical characteristics, treatment modalities, and outcomes utilizing a national database. *Patients and Methods:* The National Cancer Database (NCDB) was reviewed for LP of the stomach from 2004 to 2017. Kaplan–Meier analysis and Cox proportional hazards model were utilized to evaluate overall survival and predictors of survival. *Results:* Out of 222,488 gastric cancer cases, 896 patients with histologically confirmed primary gastric LP were included. Patients were predominantly white (78.5%), female (51.9%) and presented at advanced stage disease (stage 4=69%). A total of 369 (41.2%) patients underwent surgical resection, 520 (58.0%) received chemotherapy and 158 (17.6%) received radiation therapy. The mean OS (overall survival) of the entire cohort was 16.9 months with 1-year and 5-year OS rates of 33% and 5%, respectively. Mean OS for the patients receiving surgery with chemotherapy and/or radiation, surgery alone, chemotherapy and/or radiotherapy alone, and no treatment was 28.4, 17.1, 12.3, and 8.1 months, respectively ( $p<0.001$ ). On multivariate cox-regression analysis, advanced-stage disease (stage IV) ( $p<0.001$ ), no surgical resection ( $p<0.001$ ), and no receipt of chemotherapy ( $p<0.001$ ) were associated with increased hazards of death. Over time, the proportion of patients receiving surgical resection (30.7% from 48.3%) and radiation therapy decreased (13.8% from 20.6%) and the use of chemotherapy increased (63.9% from 54.8%). *Conclusion:* Gastric LP is

associated with a poor prognosis. Multimodal therapy including surgical resection and systemic therapy in the neoadjuvant setting seems to provide the best long-term outcomes.

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide (1). Linitis plastica (LP) is a rare type of gastric cancer, which is characterized by diffuse tumor infiltration that leads to thickening and stiffness of the gastric wall. There is no standardized definition for gastric LP, hence the exact incidence of these tumors remains unknown. In some regions, the terms “scirrhous adenocarcinoma”, “Borrmann type 4” or “large type 3 gastric cancer” are inconsistently used to describe gastric LP (2-4).

The diagnosis of gastric LP is associated with a poor prognosis. Most of these tumors are diagnosed at an advanced stage with a reported median survival of 5 to 17 months and a 5-year survival rate of around 4% to 29% even after “curative resection” (5-7). These outcomes are thought to be related to its unique biological behavior with a higher risk of perineural invasion, nodal metastasis, peritoneal dissemination, and direct invasion into surrounding tissues (8, 9). Data on outcomes and optimal treatment regimens for gastric LP are limited and constitute mostly single-institution retrospective studies with a small number of patients. This study analyzed the clinical characteristics, outcomes, treatment regimens, and trends for this disease by utilizing a national database.

## Patients and Methods

**Cohort selection.** This retrospective analysis was conducted using the National Cancer Database (NCDB). NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society that represents approximately 70% of all newly diagnosed cancer cases from over 1,500 cancer centers throughout the United States. The NCDB Participant User File corresponding to stomach (2004-2017) was utilized for this study. The ACS and the CoC have not verified and are responsible for neither the analytic or statistical

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**Key Words:** Gastric cancer, linitis plastica, gastrectomy.



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methodology employed, nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from Institutional Review Board evaluation. Patients with gastric LP were identified using the International Classification of Disease for Oncology, third edition (ICD-O-3) histology codes: 8,141 (scirrhous adenocarcinoma) and 8,142 (linitis plastica). The cohort was limited to patients with a diagnosis of gastric LP as the first primary malignancy. Patients with multiple cancers (synchronous) and those with no histological confirmation for diagnosis were excluded.

**Variables of interest.** Information on patient demographics (age, sex, race, year of diagnosis, Charlson-Deyo comorbidity score), tumor characteristics (size, stage, location, grade), treatment (including receipt of surgical resection, the extent of resection, lymph node harvest, margins, chemotherapy, and radiation therapy) and outcomes (perioperative mortality, readmission, survival) were retrieved. To evaluate survival outcomes by treatment type, patients were divided into 4 treatment groups: a) no treatment/observation; b) surgery alone; c) surgery with chemotherapy and/or RT and d) chemotherapy and/or RT alone. For comparison of treatment and survival trends over time, the data was split into two equal time periods “2004-2010” and “2011-2017” based on the year of diagnosis. Overall survival (OS) was calculated as the time from surgery to the time of death or last contact.

**Statistical analysis.** Continuous variables were reported as means with standard deviation (SD), and categorical variables were reported as frequencies with percentages. Comparisons between groups were performed using the chi-square test for categorical variables and Student’s *t*-test for continuous variables. A multivariate binary logistic regression model was used to determine characteristics predictive for receipt of surgical resection. Overall survival was compared using Kaplan–Meier analysis and the log-rank test. Cox-regression analysis was used to evaluate predictors of survival. A two-sided *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences Software (SPSS v.23, IBM Corp, Armonk, NY, USA).

## Results

**Demographics and tumor characteristics.** Out of 222,488 gastric cancer cases, 896 patients with histologically confirmed primary gastric LP were included. The mean age at diagnosis was 63.1±14.4 years. Patients were predominantly white (78.5%), female (51.9%), presented at an advanced staged disease (stage IV=59%), and had higher tumor grade on presentation. The mean recorded tumor size was 87.4±55.9 mm, and 63.9% had diffuse involvement of the stomach at diagnosis. Patient characteristics are summarized in Table I.

**Treatment data.** Overall, 369 (41.2%) patients underwent surgical resection, 520 (58.0%) received chemotherapy, and radiation therapy was administered to 158 (17.6%) patients (Table II). In the treatment group, 219 (24.4%) patients

Table I. Baseline patient and tumor characteristics (n=896).

Variable	N (%)
Age at diagnosis, mean (SD)	63.1 (14.4)
Sex	
Female	465 (51.9%)
Male	431 (48.1%)
Race	
White	703 (78.5%)
Black	111 (12.4%)
Others	82 (9.2%)
Charlson-Deyo comorbidity score	
0-1	838 (93.5%)
≥2	58 (6.5%)
Tumor size (mm)	
Mean (SD) (n=176)	87.4 (55.9)
Diffuse/widespread	312 (34.8%)
Unknown/missing	408 (45.5%)
Tumor grade	
I (well differentiated)	8 (0.9%)
II (moderately differentiated)	31 (3.5%)
III (poorly differentiated)	594 (66.3%)
IV (Undifferentiated/anaplastic)	35 (3.9%)
Unknown/missing	228 (25.4%)
Disease stage (AJCC clinical stage)	
I	86 (9.6%)
II	77 (8.6%)
III	72 (8.0%)
IV	333 (37.2%)
Unknown/missing	328 (36.6%)

received no treatment, 115 (12.8%) underwent surgery alone, 238 (26.6%) had surgery with chemotherapy and/or RT and 288 (32.1%) received chemotherapy and/or RT alone.

Among patients who received surgery, total gastrectomy was performed in 189 (51.2%) cases, whereas 139 (37.7%) underwent partial/subtotal gastrectomy. In these surgical patients, R0 resection was achieved in 170 (46.1%) cases and 162 cases (43.9%) had ≥16 lymph nodes examined.

**Survival outcomes and prognostic factors.** The mean overall survival of the entire cohort was 16.9 months with 1-year and 5-year OS rates of 33% and 5%, respectively. Mean OS for the patients receiving surgery with chemotherapy and/or RT, surgery alone, chemotherapy and/or radiotherapy alone, and no treatment was 28.4, 17.1, 12.3, and, 8.1 months, respectively (*p*<0.001) (Figure 1). On multivariate cox-regression analysis, advanced-stage disease (stage IV) (*p*<0.001), no surgical resection (*p*<0.001), and no receipt of chemotherapy (*p*<0.001) were associated with increased hazards of death. Age at diagnosis, comorbidity score, tumor grade, and receipt of radiation therapy did not affect survival in the multivariate model (Table III).

Table II. *Treatment data (n=896).*

Variable	N (%)
Surgery performed	
Yes	369 (41.2%)
No	515 (57.5%)
Type of surgical resection (n=369)	
Partial/subtotal gastrectomy	139 (37.7%)
Total gastrectomy	189 (51.2%)
Gastrectomy, NOS	27 (7.3%)
Surgery, NOS	4 (1.1%)
Unknown / missing	10 (2.7%)
Lymph nodes examined (n=369)	
None	21 (5.7%)
<15	179 (48.5%)
≥16	162 (43.9%)
Unknown/missing	7 (1.9%)
Surgical margins (n=369)	
Negative (R0)	170 (46.1%)
Positive (R1/R2)	182 (49.3%)
Unknown/missing	17 (4.6%)
Radiation therapy*	
Yes	158 (17.6%)
No	716 (79.9%)
Chemotherapy*	
Yes	520 (58.0%)
No	374 (41.7%)
Treatment groups*	
None/observation	219 (24.4%)
Surgery alone	115 (12.8%)
Chemo/radiation alone	288 (32.1%)
Surgery + chem/rad	238 (26.6%)

\*Unknown/missing not included, so percentages do not equal to 100%.

**Surgical outcomes.** On multivariate analysis, predictors of receiving surgery were younger age at diagnosis ( $p=0.017$ ), earlier disease stage ( $p<0.001$ ), and non-diffuse involvement of the stomach ( $p<0.001$ ). Patients who underwent surgical resection had higher OS (24.6 vs. 10.9 months,  $p<0.001$ ) compared to patients who did not receive surgery (for the whole cohort and when stratified by stage). In the surgical group, patients who underwent total gastrectomy had a higher readmission rate (10.9% vs. 9.7%), higher 90-day mortality rate (16.7% vs. 13.2%), lower mean OS (20.1 vs. 32.9 months,  $p=0.009$ ) and lower 1-yr OS (47% vs. 52%), compared to patients who received partial/subtotal gastrectomy. Overall, patients who received R0 resection had higher OS compared to R1/R2 resection (35.3 vs. 15.3 months,  $p<0.001$ ).

**Time trends and patterns of treatment.** It was observed that over time, the proportion of patients receiving surgical resection (30.7% from 48.3%) and radiation therapy decreased (13.8% from 20.6%) and the use of chemotherapy increased (63.9% from 54.8%). No statistically significant

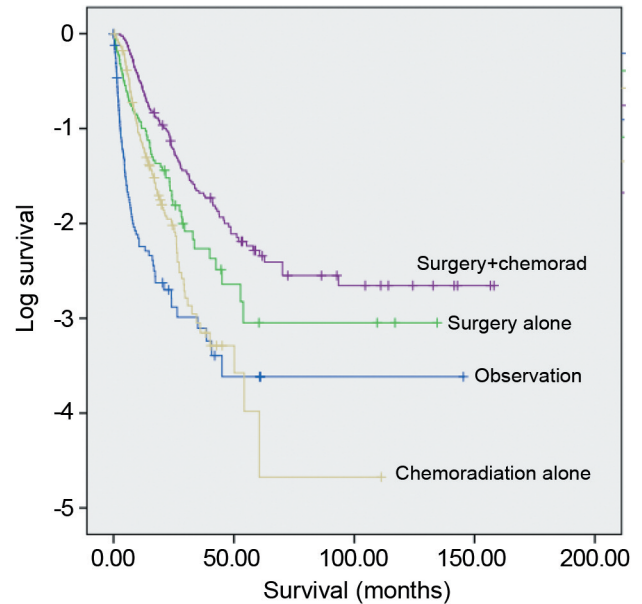


Figure 1. *Kaplan–Meier curves for overall survival stratified by treatment groups.*

difference in overall survival rate was observed in the two time periods (Table IV).

## Discussion

In this study, we reviewed a national database to evaluate the characteristics and outcomes of patients with gastric LP. Our results validate the findings of previous studies that these tumors are associated with a poor prognosis. In our analysis, we observed that surgical resection with systemic therapy (chemotherapy and/or radiation therapy) is associated with higher overall survival. We also observed that in a select group of patients, subtotal gastrectomy may be performed with acceptable perioperative mortality and good long-term outcomes, compared to a total gastrectomy.

Gastric LP is a rare gastric tumor with limited data, hence the optimum treatment strategy for this disease is not established yet. Historically, it was believed that these tumors represent a non-surgical entity as most patients present at an advanced stage disease with diffuse involvement of the stomach, nodal metastasis, peritoneal dissemination, and/or direct invasion into surrounding tissues (8, 10). In addition, the disease was associated with a high non-curative resection rate as well as high rates of locoregional and peritoneal recurrence following resection (11, 12). Therefore, it was proposed that patients with gastric LP should not be considered for surgery. However, on the contrary, few studies reported significant survival benefit of surgical resection in carefully selected patients.

Table III. Multivariate Cox-regression for overall survival.

Variable	Odds ratio	95%CI for OR		p-Value
		Lower	Upper	
Age at diagnosis	1.008	1.000	1.017	0.057
Charlson-Deyo score				
1-2 (ref)				
≥2	0.986	0.624	1.560	0.953
AJCC stage				0.001
Stage I (ref)				
Stage II	1.190	0.808	1.750	0.378
Stage III	1.341	0.885	2.030	0.166
Stage IV	1.851	1.321	2.593	0.000
Tumor grade				0.416
Grade I (ref)				
Grade II	1.567	0.574	4.277	0.381
Grade III	1.624	0.665	3.966	0.287
Grade IV	1.143	0.412	3.169	0.797
Surgery performed (vs. no surgery)	0.499	0.386	0.646	0.000
Radiation therapy (vs. no radiation therapy)	1.230	0.914	1.655	0.171
Chemotherapy (vs. no chemotherapy)	0.380	0.297	0.484	0.000

Yoshikawa *et al.* performed a retrospective analysis of 233 patients with primary scirrhous gastric carcinoma out of which 182 (78.1%) underwent surgical resection. They observed a median survival of 380 days (12.5 months) in the resection group compared to 88 days (2.8 months) in the non-surgical group. They also reported that the median survival of patients whose tumors were curatively resected was 727.0±116.3 days, significantly longer than 272±34.9 days for those in whom resection ended non-curatively (13). Similarly, Schauer *et al.* reported their experience with 120 gastric LP patients who underwent total gastrectomy, out of which R0 resection was achieved in 37 (30.8%) patients. The overall median survival in their cohort was 8 months, whereas those who achieved R0 resection reached a median survival of up to 17 months (14). Pedrazzani *et al.* reviewed 102 patients with gastric LP out of which 92 underwent surgical exploration, with resection performed in 60 cases. Only 27.5% of patients in their study received R0 resection. The overall median survival was 5.7 months, and the median overall survival for patients receiving R0 resection was 15.8 months (15). Our review of NCDB validates the findings of these studies that surgical resection is associated with higher survival rates compared to non-surgical groups (OS, 24.6 vs. 10.9 months,  $p<0.001$ ) and an R0 resection is associated with better outcomes (OS, 35.3 vs. 15.3 months,  $p<0.001$ ).

In our results, we also noted a higher overall survival in patients receiving systemic therapy along with surgical resection. These findings are consistent with data reported previously demonstrating the best oncological outcomes associated with a multimodal strategy including both surgery

Table IV. Time trends and patterns of treatment.

	2004-2010	2011-2017	p-Value
Age at diagnosis (years)	62.6	64	0.144
Stage III/IV at diagnosis	74.9%	67.2%	0.113
Radiation therapy	20.6%	13.8%	0.011
Chemotherapy	54.8%	63.9%	0.008
Surgery performed	48.3%	30.7%	0.001
Overall survival (months)	16.9	14.5	0.712

and systemic therapy (chemotherapy and/or radiation). Thompson *et al.* in their review of 54 patients with gastric LP reported that a combination of surgery and chemotherapy resulted in a higher median survival (24.8 months) than surgery alone (9.9 months) (16). Another study by Chang *et al.* who reviewed the Surveillance, Epidemiology, and End Results (SEER) database, observed higher survival rates in patients who underwent surgical resection and/or radiation therapy compared with no surgery or no radiation (5). Unfortunately, the SEER database lacks information on the use of chemotherapy therefore, we utilized the NCDB which provides chemotherapy data in addition to surgery and radiotherapy. We observed a mean survival up to 28 months in patients receiving surgery + systemic therapy, compared to surgery alone (17 months) or systemic therapy alone (12 months). However, even in NCDB, important information on whether the systemic therapy was administered as a neoadjuvant, or adjuvant modality was lacking for most of the patients included in this cohort.



A review of previous literature also revealed limited data on neoadjuvant and adjuvant strategies in patients with gastric LP. Recently, Ikoma *et al.* in their institutional review of 150 patients with gastric LP observed that upfront systemic therapy, followed by gastrectomy provides the best long-term outcomes (6). The authors also proposed that preoperative chemotherapy could be a reliable strategy for testing the tumor's biologic behavior and proposed the selective use of gastrectomy in patients who do not experience progression during preoperative systemic therapy. In addition, they proposed that preoperative systemic therapy may also shrink the tumor which can potentially help in achieving RO resection, which is an independent prognostic factor for better survival in gastric cancer. However, in contrast, JCOG0501, a randomized phase III trial, consisting of 316 patients (158 in the neoadjuvant arm and 158 in non-neoadjuvant arm) failed to demonstrate a survival benefit of neoadjuvant therapy in patients with Borrmann type 4 or large ( $\geq 8$  cm) type 3 gastric cancer (17).

This study has limitations which include its retrospective nature and the inherent issues of using a national registry, therefore, all observations and outcomes should be interpreted with caution. These limitations include lack of data on tumor size, extent, anatomical location (central *vs.* peripheral, proximal *vs.* distal), extent of lymphadenectomy (D1 *vs.* D2), and neoadjuvant *vs.* adjuvant setting of systemic therapy. In addition, patient selection for any treatment modality is unknown and it is possible that patients who received these treatments had better functional status and favorable surgical or anatomical factors or maybe better responders to any neoadjuvant therapy than patients who did not receive either or any treatment. Finally, and perhaps, most importantly, a significant limitation is how LP was defined in the database. Heterogeneity in the definition amongst different regions and lack of consensus on the diagnostic criteria for gastric LP is a limitation acknowledged by previous studies as well. Although, to date, there is still lack of consensus on the diagnostic criteria and definition of gastric LP, Ikoma *et al.* recently proposed a diagnostic criterion that may help standardize the terminology and diagnosis (6). In their study, gastric LP was defined as thickening of the gastric wall, with a lack of distensibility and stiffening that involved more than 1/3 of the gastric surface of at least some part circumferentially. They recommended that these features must have been confirmed using at least two of three staging methods (endoscopic, radiological, and laparoscopic).

## Conclusion

In conclusion, this study represents the largest series of patients with gastric LP and provides valuable data on characteristics, treatment, and outcomes. Based on the current analysis and evidence reviewed from the literature, these

patients seem to survive longer if they receive neoadjuvant systemic therapy and surgical resection. Total gastrectomy seems to be associated with higher perioperative morbidity and mortality and in select group of patients, subtotal/partial gastrectomy has acceptable outcomes. The findings from this study reiterate the importance of multidisciplinary decision making for this disease to determine an optimal treatment strategy including the type and setting of systemic therapy (chemo *vs.* rad, neoadjuvant *vs.* adjuvant) and selection of patients who would benefit from surgery.

## Conflicts of Interest

All Authors disclose no financial or personal relationships or conflicts of interests related to this study.

## Authors' Contributions

AA and BN were involved in data collection, analysis, and manuscript writing. AP, VK and DT were involved in study design and critical review.

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