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Therapeutic strategies and prognostic challenges in linitis plastica

Christodoulidis G *et al.* Linitis plastica and surgery

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Abstract

⁷ Gastric cancer ranks fifth as the most common cancer and third as the leading cause of death worldwide. Risk factors include advancing age, low-fiber diets, high salt intake and *Helicobacter pylori* infection. Diagnosis relies on histological examination following endoscopic biopsy with staging accomplished through various imaging modalities. Early gastric cancer is primarily managed *via* endoscopic resection, while non-early operable cases typically undergo surgery. Advanced cases are addressed through sequential chemotherapy lines, with initial treatment usually comprising a platinum and fluoropyrimidine combination. ⁴ Linitis plastica (LP) presents a rare, aggressive form of gastric cancer characterized by diffuse infiltration in the gastric wall, resulting in poor outcomes even after curative resection. The absence of a standardized definition contributes to uncertainty regarding the precise incidence of these tumors. LP is often diagnosed at advanced stages, with a reported median survival rate of approximately 4%-29%, despite "curative resection". Its distinctive biological behavior includes perineural invasion, nodal metastasis, and peritoneal dissemination. The bleak prognosis for LP patients partly stems from delayed diagnosis and its aggressive biological nature, posing significant challenges for clinical management. Currently, no specialized treatment strategy exists for LP, and clinical approaches typically align with

those used for general gastric cancer treatment. Surgical resection is the primary treatment, but the optimal surgical approach remains contentious. Recent studies have investigated the efficacy of neoadjuvant chemotherapy and radiotherapy in improving survival outcomes for LP patients. However, controversies persist regarding the role of adjuvant chemotherapy and postoperative radiotherapy. LP requires a multidisciplinary approach and personalized treatment strategies tailored to each patient's condition. Further research is needed to elucidate optimal therapeutic interventions and improve outcomes for LP patients.

Key Words: Linitis plastica; Surgery; Chemotherapy; Radiotherapy; Treatment strategies; Gastric cancer

Core Tip: Linitis plastica (LP) gastric cancer poses a significant challenge due to its aggressive nature and poor prognosis. Early detection and personalized treatment strategies are essential for improving outcomes in LP patients. While surgery remains the mainstay of treatment, the role of adjuvant chemotherapy and postoperative radiotherapy is still under debate. Neoadjuvant chemotherapy, particularly with regimens such as docetaxel plus oxaliplatin plus-S-1, shows promise in enhancing survival rates for LP patients. Multidisciplinary collaboration and further research are necessary to optimize therapeutic interventions and improve outcomes in this challenging subset of gastric cancer.

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INTRODUCTION

Gastric cancer is rated in the fifth place as the most common cancer and in the third place as the most frequent cause of death worldwide. Risk factors encompass advancing age, diets low in fibers, high salt intake, and *Helicobacter pylori* infection can lead to this disease. Diagnosis relies on histological examination following endoscopic biopsy, with staging accomplished through computerized tomography, endoscopic ultrasound, PET, and laparoscopy. Also, the disease exhibits significant molecular and phenotypic

diversity. Early gastric cancer is primarily managed *via* endoscopic resection, while non-early operable cases typically undergo surgery. Perioperative or adjuvant chemotherapy enhances survival rates in stage 1B and higher cancers. Advanced cases are addressed through sequential chemotherapy lines, with initial treatment usually comprising a platinum and fluoropyrimidine combination, yielding a median survival of less than a year.

⁴ Linitis plastica (LP) presents a rare form of gastric cancer characterized by diffuse infiltration in the submucosal and mucosal layers, resulting in thickening and rigidity of the gastric wall. Due to the absence of a standardized definition, the precise incidence of these tumors remains uncertain. Variably, terms such as “scirrhous adenocarcinoma,” “Borrmann type 4” or “large (> 8 cm in diameter) type 3 gastric cancer” are inconsistently employed to depict LP. LP is a characteristic finding of scirrhous gastric carcinoma, is identified on barium studies by the stomach’s irregular narrowing and rigidity. As a distinct prognostic factor, SRC may aid in risk satisfaction and optimizing treatment, particularly for patients with locally advanced stages. Often these tumors are identified in advanced stages, with a reported median survival rate of approximately 4%-29%, even following “curative resection”. Such outcomes are attributed to its distinctive biological behavior, including a heightened propensity for perineural invasion, nodal metastasis, peritoneal dissemination, and infiltration into adjacent tissues. Moreover, LP exhibits distinct characteristics, including a younger age at diagnosis, higher prevalence among females, elevated incidence of stages 3 and 4, lymph node invasion, and notably reduced overall survival rates primarily attributed to higher frequency of R1 resection. Metastatic LP can develop through various pathways, including hematogenous spread, lymphatic dissemination, and direct extension. It is clinically indistinguishable from primary scirrhous carcinoma of the stomach

The bleak prognosis for patients with LP partly stems from delayed diagnosis in most cases, compounded by the aggressive and fast-paced growth and invasion of this cancer, posing significant challenges for clinical management. Currently, no specialized treatment strategy exists for GLP, thus clinical approaches typically align with those

used for general gastric cancer treatment. While surgical resection stands as the primary treatment for gastric cancer, the optimal surgical approach remains contentious. Non-curative resection may offer a potential enhancement in the prognosis of individuals afflicted with LP gastric cancer.

SURGERY AND ADVANCING TREATMENT

Given the complexities associated with LP gastric cancer, surgical intervention remains a central component of its management strategy. Surgery has long been a cornerstone in treating gastric cancer. Japanese surgical oncologists initially favored a surgery-first approach due to the effectiveness of D2 Lymph node dissection and the prevalence of surgically treatable cancer cases. A study conducted by Chengcai L. et. al. among patients (36%) that underwent curative resection, patients (40%) that underwent palliative resection and patients (29%) that were judged unresectable, showed that regardless of the tumor stage and grade, overall survival rates at 1, 2 and 5 years were significantly worse in patients who underwent palliative resection but notably better than the patients who were judged unresectable. Another study showed that 88 patients underwent curative surgery, and 80 patients underwent non-curative surgery. The 3-5 year Overall Survival (OS) rate in the curative group was significantly higher than in the non-curative group. In the curative group the most commonly recurrence area was the peritoneum (85.7%) with most recurrences occurring within two years. These findings suggest that the role of surgery is quite limited

Early efforts at combining surgery with postoperative chemotherapy were made, particularly in the Far East where this strategy gained ample evidence for treating Stage II/III gastric cancer. However, a significant drawback emerged as many post-gastrectomy patients struggled with adhering to rigorous combination chemotherapy regimens. The results of the study by Lu et. al. were consistent with the conclusion of a study that was conducted by Aranha et. al. and showed that LP is not surgically curable due to poor post-operative survival. The most researchers argue that the prognosis is notably worse for LP patients who undergo curative resection. Moreover, Lu. et. al.,

⁸ found that the 1-year survival rate in the non-resection group was worse than in the non-curative group.

Despite the central role of surgery in managing LP, there is ongoing debate about the potential benefits of non-curative resection *vs* other treatment modalities. Certain researchers argue that instead of opting for non-curative resection in patients with LP, chemotherapy should be considered as a preferable alternative. ² Adjuvant chemotherapy aims to eliminate micrometastatic tumor cells both before and after curative surgery. Despite numerous Phase III trials investigating the efficacy of postoperative adjuvant chemotherapy, many have failed to show statistical significance or high patient compliance. While treatments like S-1 for 1 year or combination therapy with capecitabine and oxaliplatin for 6 months have proven effective, more intensive chemotherapy is deemed necessary to further enhance survival rates. Neoadjuvant chemotherapy offers advantages such as a high rate of R0 resection, tumor regression, high patient compliance, and the avoidance of unnecessary surgeries.

A study conducted by Endo et. al., showed that ¹ the phase III JCOG0501 trial aimed to establish the superiority of neoadjuvant S-1 plus cisplatin followed by D2 gastrectomy over upfront surgery. However, the study revealed ¹ no survival benefit for neoadjuvant S-1 plus cisplatin. Meanwhile, in Korea, the PRODIGY study, a phase III trial investigating neoadjuvant docetaxel plus oxaliplatin plus S-1 for gastric cancer of T2-3N+ or T4Nany, demonstrated a significantly superior progression-free survival (PFS) in the neoadjuvant DOS arm. Consequently, DOS therapy emerges as a promising option for preoperative chemotherapy in cases of LP. In Europe, the standard treatment involves docetaxel, oxaliplatin, fluorouracil, and leucovorin therapy (FLOT), resulting in a 16% observed rate of pathological complete regression. Conversely, in East Asia, DOS is viewed as a promising triple therapy option. Xu et. al. conducted a study to investigate ⁹ the efficacy of neoadjuvant chemotherapy (NAC) using non-S-1 plus cisplatin (non-SP) regimens for LP patients with type 3 gastric cancer and type 4 gastric cancer. The result was unbeneficial for the survival rate of LP patients with type 4 gastric cancer. They showed that the 5-year survival rates for patients with LP with type

3 Gastric Cancer that were treated with NAC and surgery had a 54.5% rate, and the patients with LP who underwent surgery had a 28% rate. The findings demonstrate that NAC can enhance the prognosis of individuals with LP patients with type 3 gastric cancer.

As regards to the strategies, radiotherapy is growing in the area of treatment. Recently, scholars have increasingly emphasized the importance of radiotherapy as a component of comprehensive treatment for LP. Song et. al., demonstrated that surgery and chemoradiotherapy did have a better outcome than surgery and chemotherapy. They indicated that postoperative radiotherapy may offer additional benefits for LP, owing to its extremely aggressive biological nature and potential of metastasis. They conducted a cohort study including 174 patients with non-metastatic GLP and compared the overall survival between the groups that received, surgery alone with a median survival of 8.38 months, surgery with chemotherapy and/or radiotherapy of 13.90 months, chemotherapy and/or radiotherapy of 8.94 months and patients that received no treatment of 2.50 months.

As regards the impact of surgery between the study that was conducted by Chengcai L. et. al. and the study that was conducted by Kim E. Y. et. al. showed that they both focus on the role of surgery in LP . The first study showed a general survival benefit with gastrectomy, whereas the second study provided more granular data, comparing curative and non-curative resections. In this study the curative resection significantly improved three to five years OS but non-curative resections also offered better outcomes than no surgery. However, the study that was conducted by Wasaki Y. introduced the role of neoadjuvant chemotherapy by adding NAC before surgery that further enhances the survival outcomes in comparison to the study conducted by Kim E.Y. Of utmost importance are the results from the study by Kang Y.K. that compared to the results from Wasaki Y. show that NAC followed by surgery is superior to surgery -first plus adjuvant chemotherapy.

The results from these studies suggest that while surgery play a crucial role in managing LP, its efficacy is significantly enhanced when combined with neoadjuvant

chemotherapy. It appears to be the most effective strategy for improving long-term outcomes in these patient groups. Future studies should focus on understanding the molecular and genetic profile of LP focusing on how they can evaluate the treatment approaches. Studies should be focusing on the personalized treatment and taking into account the risk factor that each patient has.

CONCLUSION

In conclusion, LP presents a rare and aggressive form of gastric cancer characterized by diffuse infiltration in the gastric wall, resulting in poor outcomes even after curative resection. Surgery has traditionally been the mainstay of treatment for gastric cancer, with various surgical approaches and adjuvant therapies aimed at improving outcomes. However, controversies persist regarding the optimal surgical strategy and the role of adjuvant chemotherapy.

Overall, the management of LP remains challenging, requiring a multidisciplinary approach and personalized treatment strategies tailored to each patient's unique circumstances. Further research is needed to elucidate the optimal therapeutic interventions and improve outcomes for the patients with LP.

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