Journal of Surgical Sciences (2018) Vol. 22 (2) : 125-138

JOURNAL OF SURGICAL SCIENCES

Review Article

Linitis Plastica of The Stomach : A Review

Md. Mizanur Rahman[1]

ABSTRACT

Linitis plastica (LP) is a particular subtype of diffuse gastric cancer and is thought to have a separate entity in respect with its biological behaviour, pathology, presentation and treatment outcome. The poor prognosis of LP gastric cancer is due primarily to its advanced stage at diagnosis. The characteristic histopathological feature of this entity is cellular spread to the submucosa and stroma with minimal mucosal alterations accompanied by an excessive desmoplastic reaction. Despite recent research on alternative therapies, surgical resection appears the only potentially curative approach. Patient selection and multidisciplinary management are paramount when considering surgical resection in patients with gastric LP. The operative approach in patients with LP has historically been questioned because of the poor outcomes. The aim of this review is to highlight different dimension of linitis plastica stomach in respect to its definition, classification, clinico-pathological characters, diagnostic approaches and treatment outcome.

Background

Linitis plastica (LP) of the stomach is a long-known condition, with initial reports oriented from sixteenth and seventeenth century[1]. It was defined as a distinct entity in 1859 by Dr. William Brinton, who described it as a benign disease with peculiar characteristics: the stomach was macroscopically thickened, with inconsistent evidence of mucosal ulceration; pathologically, it showed a prominent submucosal hypertrophy due to an increase in the connective tissue and prominent muscular hypertrophy[2]. Among all morphological subtypes of the gastric cancer it needs special consideration and discussion. Linitis plastica is seen in 3–19% of all gastric adenocarcinomas[3]. It is characterised by a rigidity of a major portion, or all of the stomach, with the absence of a filling defect or extensive ulceration. Gastric carcinoma is notorious for its failure to cause early symptoms so that patients do not present themselves for diagnosis until late in the course of the disease. Because of the rich lymphatic supply, the cancer rapidly disseminates beyond the reach of surgical resection. Consequently, the patients with symptoms generally have far-advanced malignancy[4,5 2].

The term 'linitis plastica' (LP)-Greek for linen cloth or net was introduced by Brinton in 1858 on the basis of macroscopic criteria. Up until 1943 it was unclear whether linitis plastica, also called 'leather bottle stomach', was an inflammatory or a neoplastic disease, when Saphir described the macroscopic morphology, the neoplastic nature, and the progression with metastatic spread of this type of carcinoma[6].

The term "linitis" was due to the presence of irregular bands of filamentous tissue in the hypertrophic submucosa, resembling fibres of linen. Clinically, this disease was unavoidably fatal without treatment. Early reports on the presence of cancerous cells in the setting of LP were notable for the difficulty in identifying malignancy. Malignant cells, when detected, were often

Correspondence to: Prof. Md. Mizanur Rahman, Professor (Retd) of Surgical Oncology, National Institute of Cancer Research and Hospital, Dhaka, Email address: mizannicrh@gmail.com
Received: 29 June 2018 **Accepted:** 30 June 2018

described as few and scattered[2]. As a consequence, for many years, it was controversial if the condition was benign or malignant. Then in 1953 Dr. Arthur Stout clarified the issue, proposing linitis plastica as a specific type of gastric carcinoma characterized by an excessive production of fibrous scar like tissue, with areas in which only scattered cells were present. He expressed doubts about the malignant nature of the cells because of his previous authors' failure to find cancer cells[2]. Like many series of works in Bangladesh, surgeons are sharing this dreadful situation of the patients also. This literature review of linitis plastica will focus on its current concept, highlight the diagnostic challenges, its pathological, clinical, prognostic implications, and the therapeutic options available. Future perspectives for its management are also addressed[6].

Definition

In the intervening years, multiple classifications for gastric carcinoma have been established, reflecting the heterogeneity of this malignancy[7,8]. Each is based on different macroscopic and microscopic aspects of the tumour. LP had been associated with gastric carcinoma (GC), but Stout's classification did not take hold, and LP was never included in any of the other staging systems. In the following years, the definition of LP was separated from the presence of fibrous tissue, becoming more generalized and being increasingly associated with diffuse carcinomas with infiltration of the gastric wall, resulting in the stomach having a stiffened appearance and a partial or complete lack of distensibility[9] ; occasionally, the term has also been extended to include other conditions associated with thickening of the stomach wall without any fibrous component at all (i.e., lymphoma) [10].

Recent reports of LP lack a clear and standardized codification. "Linitis plastica" is used interchangeably with "Bormann type IV carcinoma," "scirrhous carcinoma," "signet-ring cell carcinoma," and "Lauren diffuse carcinoma"[11,12]. However, it is not clear if these terms correctly define this condition, as only some of the tumours in each of these categories have the features of LP.

Due to the lack of agreement on the clinical significance of LP and the difficulty in attributing this condition to the common classification systems, some authors have proposed to abandon this definition[13]. Others, nonetheless, still recognize LP a specific type of gastric cancer with a distinct growth pattern and biological behaviour, and advocate that the identification of such a subset of gastric cancer patients could be useful in risk stratification, in identifying a target for therapeutic management, and in guiding future research[14,15].

Definition: postoperative or preoperative?

LP is, by the original definition, a scirrhous tumour that spreads through the submucosal and muscular layers of the stomach, with thickening of its wall and loss of distensibility. The presence of poorly differentiated, poorly cohesive, or SRCs is often involved.

However, the original definition is based on autopsies and surgical specimens, and it should be noted that it may be difficult to obtain a reliable biopsy documenting both the predominance of the stroma and the cancerous cells in the preoperative setting. Moreover, many of these patients, affected by advanced disease, would not undergo gastrectomy; therefore, analysis on postoperative surgical specimens would not always be possible. In addition, the increasingly common practice of administering preoperative therapy in the form of systemic chemotherapy or radiotherapy may hamper the identification of the typical stromal reaction of LP, as fibrosis is often a consequence of preoperative therapy[16].

Current classifications for gastric carcinoma and their relations to LP

Gastric cancer (GC) has several classifications related to its macroscopic and microscopic aspects. All are commonly used, but none of them has been accepted as the standard system. Hereby the most common ones will be reviewed, addressing their overlap with LP. Bormann classification: first proposed by Bormann in 1926 [2], this classification is most commonly used in Eastern countries[8,12]. It is based on the macroscopic, endoscopical/ endoluminal aspect of the tumour and is most useful as a preoperative assessment tool and a prognostic factor. Bormann type IV tumours are described as diffuse and infiltrative ("tumour without diffuse ulceration or raised margin, the gastric wall is thickened and indurated, and the margin is unclear"[8]. Both Bormann III and Bormann IV tumours show an infiltrative pattern, and even Bormann III tumours may show a consistent desmoplastic reaction. At the same time, not every Bormann IV tumour presents with the typical

demoplastic characteristics of LP [11]. Therefore, LP is often improperly defined as a Bormann IV tumour.

Cancer stromal volume classification: this microscopic classification is part of the Japanese classification[8]. It includes cancers with a medullary type (scanty stroma), a scirrhous type (abundant stroma), and an intermediate type. A similar system is utilized in the World Health Organization (WHO) classification[7], although tumour stroma is less commonly categorized by Western pathologists. In the Eastern setting, this classification is more commonly applied; however, there are few studies focusing on the clinico-pathological aspects of tumours identified by the scirrhous classification system. Scirrhous cancers, in accordance with the original definitions of LP , are strictly related to the LP phenotype, which presents in its classical form only when the submucosa is diffusely fibromatous[2,17].

Lauren classification: this microscopic classification divides gastric tumours into diffuse, intestinal, or mixed and indeterminate types. Diffuse adenocarcinomas are defined by their growth pattern as tumours infiltrating the stroma as discohesive tumour cells arranged singly and in small clusters. The intestinal type is defined by its cytoarchitecture, and characterized by cohesive cells which form gland-like structures. Mixed tumours have both an intestinal and diffuse component, while indeterminate types include most of the undifferentiated tumours[7,18,19].

Diffuse tumours account for 32–49% of GCs. There is a significant correlation between the diffuse histotype, the Bormann III and IV types, and the scirrhous stromal category[20].

WHO classification: The WHO classification is a descriptive system which defines five main types of gastric carcinoma: tubular, papillary, mucinous, poorly cohesive (including signet-ring cell carcinomas and other variants), and mixed adenocarcinomas. Lauren diffuse carcinomas most often have a poorly cohesive histotype. Signet-ring cell (SRC) carcinomas are defined as tumours composed of cells containing intracytoplasmic mucin and eccentrically placed nucleus, in a proportion >50 %. They may form lace-like glands or a microtrabecular pattern in the mucosa, or extend to deeper layers with significant desmoplastic reaction. Irrespective of the category, SRCs may also be present in different tumours, as poorly cohesive variants, mucinous tumours (defined by extracellular mucin >50%), and mixed carcinomas (defined by a clonal mixture of both glandular and poorly cohesive aspects). Hereditary diffuse GC typically presents as a diffuse gastric carcinoma containing SRCs, and often with features of linitis plastica [7,21.]

Histology

The most characteristic feature of LP is the macroscopic thickening of the stomach wall, often diffusely involving the entire stomach, which has been described in detail since its early reports as an impressive increase in the submucosal connective tissue in the form of immature and mature stroma with hypertrophy of the muscle layer and subserosal thickening. These characteristics strictly resemble those of scirrhous carcinoma, which, as mentioned above, is a particular form of GC in which cancer cells trigger a stromal reaction involving mature and immature fibrosis (which are characterized, respectively, by the presence of collagen I and III)[22,23]. The scirrhous reaction is almost always triggered by poorly cohesive neoplastic cells, often with signet-ring morphology. More rarely, cases of schirrous tumours accompanied by moderately differentiated adenocarcinomas have been reported[24,25].

Scirrhous tumours are characterized by a complex interaction between cancer cells and cancer-associated fibroblasts (CAFs), which may represent up to 90% of the tumor and appear to have a primary role in cancer progression. The origin of CAFs is under investigation; these cells seem to be heterogeneous, as they may be local fibroblasts, cells recruited from the bone marrow, or pericytes which undergo endothelial to mesenchymal transition[22,26].

Secondary LP features may be found in other hollow viscus or cystic organs, such as the bowel, bladder, and ovaries[27]. Frequently, SRCs are detected in these types of secondary lesions[28]. At the same time, even secondary LP of the stomach has been described. The most commonly reported cases of secondary LP are those associated with metastatic invasive lobular carcinoma of the breast, which presents with identical radiologic and nearly identical histologic characteristics to primary linitis plastica [29]. Notably, lobular breast carcinoma is also a feature of hereditary diffuse GC[30], and it often contains scattered SRCs[29].

Subtypes:

In regards to the quality of the mucosal involvement, two different subtypes of linitis plastica have been described. In the first type, giant-fold or waffle-like,

the mucosa demonstrates a characteristic morphological change consisting of an enhancement of the design of the folds, which remain flexible but appear prominent and crossing one another. This effect may be due to the relatively normal state of the mucosa in comparison to the involvement and contraction of the submucosal and muscular layers[2, 11]. The pattern of waffle-like LP has been extensively described in several Japanese studies, and in case reports of patients refusing surgery and subsequently being followed for years[11,31]. The first lesion generally originates from the proximal or middle stomach, near the great curve, as a type IIc (flat depressed) early GC.

In the second type, the flat type, submucosal involvement is paralleled by mucosal thickening or atrophy [11]. This type most commonly originates from the antrum, near the lesser curvature, and then extends to involve the antrum circumferentially. Flat type LP development has not been extensively studied. The difference between the characteristic mucosal pattern in waffle-like LP and the mucosal flattening and induration in flat type LP may be due to diffusion of the neoplasm in a more superficial plane (involving the lamina propria, the muscularis propria, or the mucosa itself) in flat type. The tumour is thought to originate near the pylorus, involve the antrum circumferentially, and extend to the entire stomach[5,9]. The flat type is commonly believed to be the most common in Western settings[11]. However, even if the original description by Brinton, most of the LP cases were identified as originating from the distal stomach, with hypertrophic mucosal folds, and a mixture of both subtypes[11]. In 1990, a US study demonstrated that up to 88% patients with scirrhous tumorus present with the radiological features of thickened gastric folds.

Extension and macroscopic features

LP does not always present as complete involvement of the stomach. It may appear in plaques which gives the appearance of a segmental lack of distensibility. Localized and diffuse forms of linitis were found in the early reports of this condition, and subsequently being followed for years[11,31,32].

The first lesion generally originates from the proximal or middle stomach, near the great curve, as a type IIc (flat depressed) early GC. This condition may remain stable for 2–5 years (slow-phase), until the lesion progresses to advanced GC and ulcerates reaching the submucosal layer. At this point, the ulcerative lesion can persist or heal, while the submucosal involvement, once a scirrhous reaction is initiated, enters a fast-phase, involving the entire stomach (LP) in about 1 year[31,32].

Cell lines and their effects

Two new gastric cancer cell lines, designated OCUM-8 and OCUM-11, which developed the characteristic biology of scirrhous gastric carcinoma upon orthotopic implantation in mice. Involvement of lymph nodes and liver metastasis was also found in both orthotopic models. Histologically, these orthotopic models showed proliferation with extensive fibrosis, resembling human scirrhous gastric cancer. Both cell lines were derived from ascites of patients with scirrhous gastric cancer. The growth of OCUM-8 and OCUM-11 cells following the addition of KGF, FGF, and EGF was increased significantly relative to untreated cells.An increase in the number of attached and spreading cells occurred following the addition of TGF-â1 in both cell lines. OCUM-11 cells showed microsatellite instability. Although subcutaneous scirrhous gastric cancer cells show medullary growth, most *in vivo* studies of scirrhous gastric cancer have used xenografted tumours implanted subcutaneously[33].

Genetic alterations

OCUM-8 cells had Loss of heterogygosity (LOH) at the APC (D5S346) and c-met (D7S501) loci, and a band shift (D3S1611) was found. OCUM-11 cells showed 3 of 11 (27%) microsatellite loci, D2S123, P53-Dinucl, and P53Penta, with a novel band shift, and OCUM-11 cells had LOH at the APC (D5S346) locus. OCUM-11 cells were defined as MSI-positive, but no mutations were found in Fas antigen, BAX, TGFâRII, IGFR II, hMSH3 and hMSH6[33].

Recent studies have revealed that genetic instability is an important predisposition for human multistep carcinogenesis.[34)] MSI was observed in 10 to 20% of gastric carcinoma cases,[)] while the reported prevalence of MSI in human scirrhous gastric carcinoma has varied between studies, ranging from 5% to 75%.[35] Although some colorectal cancer cell lines have MSI status,[36)] few researchers have pursued the establishment of MSI-positive gastric carcinoma cell lines. OCUM-11 cells had MSI status, and therefore might be useful for the study of the characteristic features of MSI in scirrhous gastric carcinoma. no frameshift mutation of the *TGFâ-RII*, *BAX*, or *hMSH3* genes was detected in OCUM-11

cells, whereas *TGF*â-*RII*, *BAX*, and *hMSH3* frameshift mutations have been reported to be frequent in MSI colon cancers.

In conclusion, two new scirrhous gastric cancer cell lines was established, designated OCUM-8 and OCUM-11, which have the characteristic biology of scirrhous gastric carcinoma *in situ*. The two cell lines may be useful for analyzing disease progression and for developing novel therapeutic options[33].

Cell adhesion and CDH1:

It is well settled that diffuse type cancer is composed by non-cohesive cells (with or without signet ring cells).It is now widely accepted that genetic and epigenetic alterations in the host contribute to the development of disease in combination with environmental factors. Diffuse gastric cancer (DGC) has a clear hereditary form and results from E-cadherin deregulation upon genetic or epigenetic alterations[37]. It comes as no surprise that genetic or epigenetic alterations in E-cadherin leads to disturbed epithelial cell-cell adhesion and structure, aberrant stromal interactions, as well as altered cell migration and signalling, with ultimate oncogenic potential[38]. Indeed, functional loss of E-cadherin is a well-established molecular event that occurs during tumour progression, leading to increased invasion of cancer cells to neighbouring tissues and to metastasis[39]. More so, reduced expression of E-cadherin, mostly due to decreased expression at mRNA and protein levels, is regarded as indicative of poor outcome in a variety of malignancies. In fact, only a minor proportion of advanced carcinomas present CDH1 mutations. CDH1 is however regarded as a classical tumour suppressor gene in gastric carcinogenesis, being involved in the initiation and progression of both sporadic and hereditary forms of GC [40]. Of relevance, inherited germline mutations in CDH1 are a causative feature of hereditary diffuse gastric cancer (HDGC), awarding E-cadherin as the culprit for the development of this cancer syndrome[40].E-cadherin has been awarded a key role during the development of cancer, where coordinated cell-cell adhesion is required for proper establishment of the body plan and integrity of tissue differentiation. The recognition of E-cadherin as a key molecule at the intersection of cell-cell adhesion, cell morphology and polarity, and cell life and death, has awarded E-cadherin a leading position in cancer initiation and progression[41].

Clinico-pathological characters

The clinical characteristics of Bormann type IV gastric cancer include a high rate of incidence in young females, delayed diagnosis and detection at an advanced stage, peritoneal dissemination at the first operation, many peritoneal recurrences after a curative resection, low hepatic metastasis and a low curative resection rate[42,43].

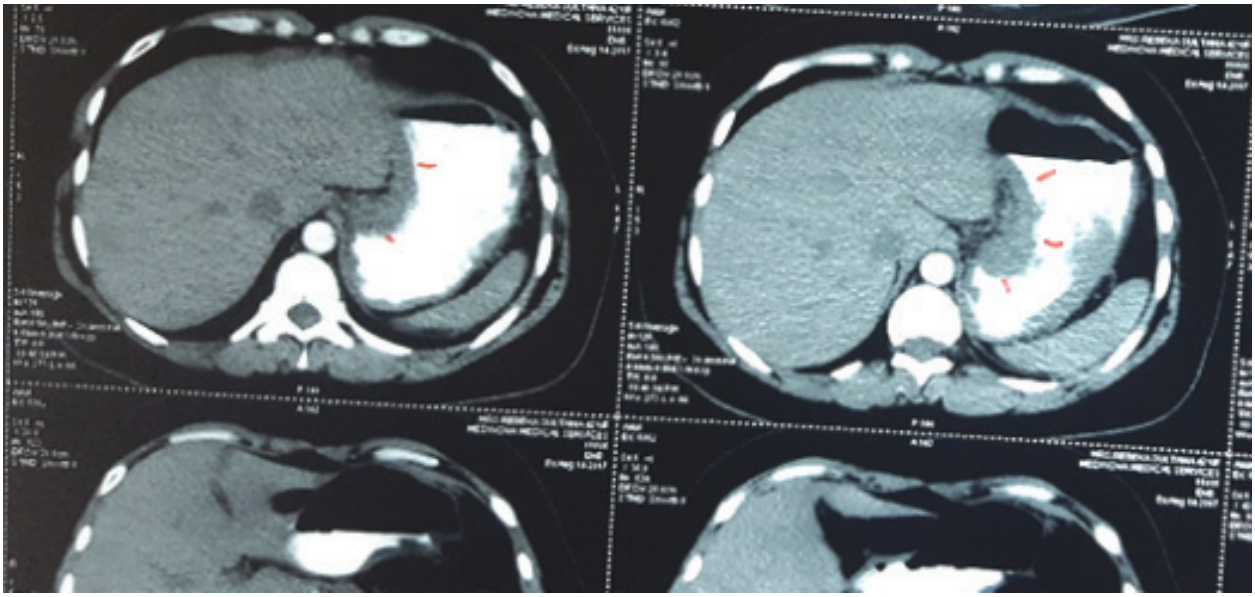

Figure 1. *CT Scan delineating stomach with liniits plastica, stomach wall is thickened throughout the length of lesser and greater curvature.*

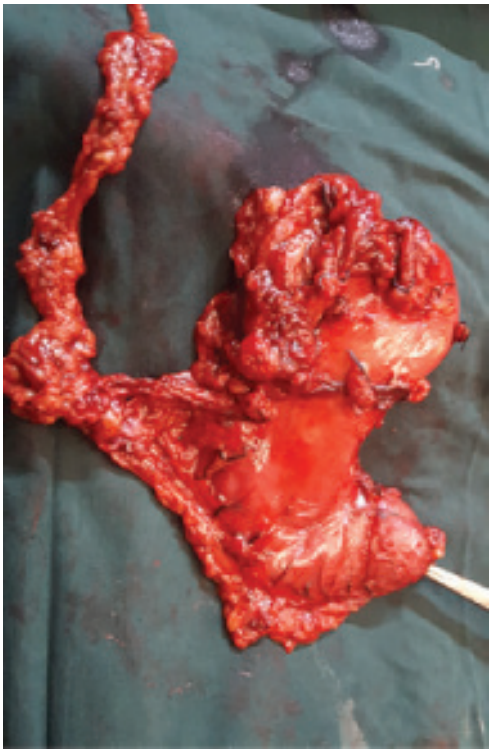

Figure 2. *Total Gastrectomy for linitis plastica stomach*

Epigastric pain combined with progressive dysphagia to both liquids and solids and severe weight loss constitute the most frequent clinical signs. Clinical examination is usually unremarkable and biological markers within normal limits. Rare relative presentations include worsening symptoms of gastric outlet obstruction, haematemesis, gastrointestinal bleeding and perforation. Clinical manifestations of pseudoachalasia secondary to massive invasion of the gastric walls and the cardia are not infrequent [44]. Cases of gastric metastasis simulating LP-type carcinoma from primary rectal lesion present with signs of iron deficiency anemia, recent fecal incontinence, lower colicky abdominal pain and distension, bleeding, diarrhea or complete intestinal obstruction due to gradual narrowing of the bowel lumen. Rectal examination reveals a circumferential, constricting, irregular mass without irritability, but even then, establishing an accurate differential diagnosis is difficult. A case of primary LP involving the entire colon, ileum and appendix has also been described [45].

Gastric LP is often detected at an advanced stage, while metastases to the colon occur via contiguity along mesenteric facial planes. Although a prominent pattern of disease failure is peritoneal carcinomatosis, some patients experience rapid disease progression without signs of intra-peritoneal dissemination. Peritoneal carcinomatosis was the commonest sign of disease progression, while bone metastasis was associated significantly with poor prognosis and lymph node invasion. T4 and N3 histological status proved independent prognostic determinants found in studies. In addition, the increased number of metastatic nodes (>16) was defined as an important risk factor for the development of bone disease in comparison with modest nodal involvement [46].

In LP patients, peritoneal carcinomatosis occurs as a consequence of dissemination of free cancer cells from the primary lesion. Furthermore, cytological examination of peritoneal washing has been proposed to estimate the possibility of intra-peritoneal recurrence in curatively resected cases of LP-type gastric carcinoma. This assessment has recently been added to disease staging and its prognostic value has been confirmed employing immunohistochemistry or reverse transcriptase polymerase chain reaction (RT-PCR). A newly established protocol for rapid, quantitative detection of free cancer cells in peritoneal washings using carcinoembryonic antigen (CEA) mRNA as a neoplastic marker has also been suggested[47,48].

Linitis plastica: diagnostic challenges

Typical symptoms of LP are dyspepsia, nausea, vomiting, and anorexia. Unfortunately, those symptoms are not reliable for establishing a timely diagnosis, as they usually present insidiously, and manifest only in an advanced stage. Available diagnostic instruments for this condition include endoscopy, endoscopic ultrasound (EUS), upper gastrointestinal contrast studies (UGI), computed tomography (CT) and 18-fluorodeoxyglucose (18-FDG) positron emission tomography (PET) scans, and magnetic resonance imaging (MRI).

Endoscopy is considered the gold standard for the diagnosis of GC. However, the peculiar spread pattern of LP tumours involves primarily the submucosa and muscularis propria of the stomach, while mucosal involvement is inconstant and may present as nonspecific gastritis or normal mucosa in up to 30% of cases[11]. The flat type could be confused with atrophic gastritis and suspected by endoscopy sometimes only due to the lack of distension of the

stomach wall. Waffle-like appearance of the mucosa is more characteristic, even if biopsies have the same low diagnostic yield. Due to their poorly cohesive nature, cancer cells are often scattered between the tumour stroma[49] or even absent in some sections [50]. Indeed, studies show high rates of non-diagnostic biopsies (30–36%)[9,51]. Sometimes, the delay in the histologic diagnosis may represent a serious challenge, especially when the clinical and instrumental suspicion of LP is strong, as several different diagnoses are possible in the presence of hypertrophic mucosal folds and/or scarce distensibility of the stomach (gastric lymphoma, Ménétrier disease, granulomatous diseases and metastasis) and not all of them are surgical[19,11]. Gastrectomy is a major procedure with considerable morbidity and mortality, and many clinicians would not perform resection until cancer has been proven by biopsy.

Several endoscopic strategies to better diagnose this disease have been proposed. EUS features include submucosal and muscular thickening, and EUS fine-needle aspiration allows reaching of the submucosal layer[11]. Even with this strategy, however, negative biopsies have been reported[52]. For this reason, EUS is also not considered the gold standard in diagnosis of LP.

Barium studies can be a useful diagnostic instrument, as they could document the thickening of the mucosal folds, and assess in real time the segmental or complete lack of distensibility of the gastric wall. UGI has been progressively discarded as a diagnostic technique for gastric cancer diagnosis and staging; nevertheless, given the low sensibility of conventional endoscopy, it remains of valuable support in evaluating this condition.

CT scan allows for comprehensive staging of the tumour, and could give rise to reasonable suspicion when identifying a stomach with thickened walls, which presents with complete flattening of the mucosal folds or thickened folds even after distension[53]. 18FDG PET, by the contrary, may have scarce diagnostic significance, as poorly differentiated, diffuse, mucinous, and SRC carcinomas have all been reported to be low in 18-FDG uptake [54].

MRI has been recently proposed as an alternative to CT, due to its advantages in characterizing tissue nature and obtaining soft tissue contrast, but the topic is still controversial[55,56].

Suspicion of linitis plastica should prompt consideration for laparoscopy in staging. In consideration of the well-known peritoneal tropism of the disease, a diagnostic laparoscopy with peritoneal washings is a good alternative.

A gold-standard diagnostic instrument for LP has yet to be defined, the development of a diagnostic strategy is difficult. Moreover, macroscopic and microscopic assessments of the stomach are both required to identify the condition. If the suspicion is strong, even in the absence of a positive biopsy, the possible diagnoses should be discussed with the patient, and a diagnostic laparoscopy proposed to avoid deleterious diagnostic delays.

Future diagnostic advancements may be obtained by the use of blood-based biomarkers. In 2000, Ichikawa et al. proposed a high level of trypsinogen as a simple and specific marker to diagnose linitis plastica, but this marker has not been further tested or introduced in clinical practice. “Liquid biopsy” of circulating tumor cells, cDNA, or miRNA may represent a future perspective[57,58] especially as genomic and epigenetic characteristics of GC are better understood. EUS allows the estimation of the invasion depth and extent of lymph node metastasis and aids in determining the TNM staging.[4,5]However, it is difficult to accurately determine the extent of cancer cell infiltration using EUS alone as thickened areas caused by fibrosis may confound the findings[59].

Linitis plastica: implications for therapy

As soon as the possibility of a curative treatment for a patient with LP is assessed, other questions arise in regards to the therapeutic management. Though surgery is considered the best option of treatment it is difficult to get a margin free status. For years, ample resection margins (>5 cm) have been advocated to avoid R1 resection in GC patients, and they are considered the current standard for patients with Bormann III and IV tumors, in accordance with the Japanese Guidelines [60]. This topic, however, is extremely controversial. Indeed, a discrete number of studies seem to have disproved the value of wide resection margins, as long as a R0 resection is obtained, while other studies have even been questioning the role of R0 resection in advanced stages. However, studies focusing on diffuse, SRC, and especially on scirrhous tumours are lacking. Thus, caution is needed when performing limited resections in these subgroups. Given its high accuracy[61], a frozen

tissue biopsy should be routinely performed. If a frozen tissue biopsy is not available, a margin of 5 cm currently remains the gold standard. It should also be considered that in scirrhous gastric cancers and LP phenotypes a frozen tissue could be less reliable due to the lack of tumour cellularity.

Recently, much attention has been given to the use of preoperative hyperthermic intraperitoneal chemotherapy (HIPEC) in GC, both for the prevention of peritoneal disease and for its treatment, and a few randomized investigations are ongoing[62]. Given the strong peritoneal tropism of scirrhous and LP tumours, in the near-future, HIPEC could come to the foreground for the routine management of this subgroup of patients.

Neoadjuvant therapy has many theoretical advantages. Among them are the higher rate of treatment compliance in comparison to postoperative therapy, and the possibility of downstaging or downsizing the tumour[63]. As LP tumours often present in an advanced stage, neoadjuvant therapy may be of particular value in improving local control and increasing the rate of potentially curative gastrectomies.

Nevertheless, concerns remain when applying conventional therapeutic agents. The use of radiotherapy as an adjuvant treatment was significantly less effective in diffuse tumours in both the ARTIST trial and the 10-year update of the INT-0116 trial. In vitro testing on the G-DIF gene-expressing subtype demonstrated reduced sensitivity to 5-fluorouracol and oxaliplatin in comparison to cisplatin. In a 2004 survey, the use of cisplatin as intraperitoneal preoperative lavage in patients with CY+ schirrous tumorus gave no survival benefit in comparison to non-operative management. HER-2 activating mutations are rare between the GS, the MSS/EMT, and the mesenchymal metabolic subtypes, so Trastuzumab is rarely an option. Finally, in a retrospective French study, patients with SRC tumours have been reported to show scarce response to standard perioperative chemotherapeutic regimens and poor survival[64], due to possible progression of the disease during neoadjuvant therapy, and a phase III randomized clinical trial is currently ongoing to assess the role of perioperative versus adjuvant chemotherapy in this subset [65].

Currently, targeted therapy is considered only for certain GC subtypes, and almost all the chemotherapeutic regimens are directed solely against the cancerous cells. Scirrhous tumours, though, have several distinct features that may be strictly related to their aggressive biological behaviour. This strategy may represent a real game-change in the context of a multimodal therapeutic management, especially for patients which are non-responders to conventional therapy. In this regard TGF-B and FGF7 receptor inhibitors[66] created interest in association with standard chemotherapy.

Development

The pre-stage of LP type GC

LP type GC was defined by Sugiyama et al.[67] in 1980 as a lesion infiltrating twice as prolifically into the submucosa compared with the mucosa, with no primary localized mass formation. It was later divided into three clinical stages:[11] typical (defined as submucosal infiltration of a tumour occupying more than 1/4 of the total stomach with narrowing of the gastric lumen), latent (defined as tumour invasion of more than 1/4 of the total area without luminal narrowing), and pre-LP (defined as cancer cells invading less than 1/4 of the total area of the submucosal infiltration and as the absence of luminal stenosis)[68].

Retrospective studies of LP type GCs

In 1980, Nakazawa et al[69] identified two distinct courses in the progression of LP type GCs: slow progression (slow phase) and fast progression (fast phase). Takeda et al[70] retrospectively described 16 cases of LP type GCs. According to their results, progression to LP type GC required 21 months if the first lesion was ulcerative. If the presenting lesion was a IIc lesion without ulceration, progression to LP type GC also required a long time. In contrast, if only localized mucosal edema was noted, LP type GC developed in 12 to 21 months. Moreover, if the lesion had giant mucosal folds, it quickly advanced to LP type GC within 10 months.

Ohgushi et al[71] described the progression of seven LP type GCs in a retrospective study. Initially, the primary tumours resembled IIc-like lesions in the fundic gland area or transition zone. After formation of the IIc lesions, the surrounding mucosa became sclerotic, with a flat elevated appearance. Eventually, the lesions became malignant ulcers and gradually invaded the submucosal layer, even if the ulcers were healed.

In 1992, Takizawa[72] surveyed 245 patients with LP type GCs over a 10-year period. The primary lesion occurred in the fundic gland in all patients. Pathologically, most lesions were diagnosed as undifferentiated carcinomas, and lymphatic metastasis was noted in more than 50% of the cases. Observation pared with other types of advance GCs, patients with LP of early gastric cancers (EGCs) with IIc-like lesions revealed type GC were younger at disease onset and more frequently that these lesions progressed to pre-stage LP type GC[73].

Prognosis:

Among the limited studies, according to the findings it was seen that the diffuse type gastric cancer has an extremely bad overall prognosis. The median survival was only 8 months, five year survival 8%. Among the prognostic factors the diagnostic laparoscopy turned out to be a very safe procedure for the diagnosis of the local tumour spread, lymph node status, distant metastases, and the histological proof of peritoneal implants. In 60% of investigated patients peritoneal seeding could only be diagnosed at the time of laparoscopy[74].The tumor marker CA 19-9 (cut-off value of 45u/l), the immunocytochemical detection of FPT has turned out to be an independent additional strong prognostic factor.

Peritoneal carcinomatosis is generally assumed to occur as a result of shedding from tumour cells from the serosal surface of the primary tumour or via the lymphatic drainage system[75]. Lymphoreticular organs, called milkey spots, occur throughout the greater omentum and may represent the barrier to peritoneal seeding. The present data suggest that the release of tumour cells from lymphatic capillaries plays an important role in peritoneal dissemination. A significant survival advantage for patients with linitis plastica can only be achieved after complete resection[76]. Even patients with a multivisceral resection had a significant survival benefit[77].

For potentially resectable LP patients (i.e., stage I-III), 5-year DSS was 0 per cent for no treatment and for radiation therapy alone, 18 per cent for both and surgery and radiation, and 20 per cent for surgery alone($P < 0.001$). LP is a marker of poor survival in patients with GA. However, surgical resection provides the best oncologic outcomes in these patients with a 20 per cent 5-year DSS in patients with loco-regional disease[78].

Role of Surgery:

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[5]. 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[79]. 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[80]. 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[81].

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[82].

It was also seen that 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. So it is speculated that 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[82].

Therapeutic strategy

Although multivariate analysis has shown that curative resection is a significant prognostic factor for the survival of patients with this group of patients like SGC, only about 20% of the patients with SGC benefit from total gastrectomy[83]. Radical operations such as en bloc total gastrectomy, which includes the pancreatic body and tail, spleen, gallbladder, transverse colon and the left adrenal gland, have been previously performed. However, such extensive surgery did not result in a distinct survival benefit. Because the 5-year overall survival rate of patients with SGC at stages II and III after curative surgery remains low; additional effective treatments are necessary to improve patient survival. Although other treatments such as chemotherapy, radiotherapy, hyperthermia, hormonal therapy or immunotherapy have been attempted, their anti-tumour effects have been insufficient in improving the prognosis of patients with LP[84]. Accordingly, novel therapy based on the characteristic biological behaviour is necessary.

Although a targeted therapy for patients with HER2-positive advanced GC have reached satisfactory clinical results, a new targeting therapy for SGC has not been defined. Preclinical studies have demonstrated the efficacy of targeted therapy for advanced GC. Some FGFR2 inhibitors such as tyrosine kinase inhibitor and monoclonal antibodies have decreased the proliferation of SGC cells by inhibiting FGFR2 signalling *in vitro* and *in vivo*. Study proved that combined administration of S1 and FGFR2 inhibitor decreases cell proliferation in SGC more effectively than S1 alone[85,86].

Conclusion:

In conclusion primary LP is to be differentiated from other variety of gastric cancer both in its preoperative and peroperative steps by its schirrous appearance. LP is different by its fatal outcome and biological behaviour. Diagnosis is also very challenging. Sometimes surgeons fail to come to a conclusion by traditional diagnostic tools. Outcome of surgery is still debatable. So decision making for palliative or radical surgery for the best outcome is under the jurisdiction of the surgeon. Though there are options and study on systemic therapy a concrete approval is yet to arrive. The recent accumulation of information provides a deeper understanding of the molecular biology underlying its characteristics which can facilitate the development of treatment strategies.

References:

1. Lyle HH. VIII. Linitis plastica (cirrhosis of stomach): with a report of a case cured by gastro-jejunostomy. Ann Surg. 1911;54:625–68.
2. Annamaria Agnes, Jeannelyn S. Estrella and Brian Badgwell. definition in the era of genomics: linitis plastica. W J Surg oncol 2017;15:123 DOI 10.1186/s 12957-017-1187-3
3. Sasaki T, Koizumi W, Tanabe S, Higuchi K, Nakayama N, Saigenji K. TS-1 as first line therapy for gastric linitis plastica: Historical control study. Anti-Cancer Drugs 2006; 17:581–6.
4. Aranha GV, Georgen R. Gastric linitis plastica is not a surgical disease. Surgery 1989; 106:758–62.
5. Sadaf Jafferbhoy, Hanif Shiwani, Quatullah Rustum. Sultan Qaboos University Med J 2013;13: 451-453
6. M. schauer1, M. Peiper1, J. theisen2, w. Knoefel1. PRognostIc FactoRs In PatIEnts wItH DIFFusE tyPE gastRIc cancER (LInItIsPLastIca) aFtER oPERatIvE tREatMEnt. Eur J Med Res 2011; 16: 29-33
7. Bosman FT, World Health Organization. International Agency for Research on Cancer. WHO classification of tumours of the digestive system. 4th ed. Lyon: International Agency for Research on Cancer; 2010.
8. Association JGC. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011;14:101–12.
9. Levine MS, Kong V, Rubesin SE, Laufer I, Herlinger H. Scirrhous carcinoma of the stomach: radiologic and endoscopic diagnosis. Radiology. 1990;175:151–4.
10. Levine MS, Pantongrag-Brown L, Aguilera NS, Buck JL, Buetow PC. NonHodgkin lymphoma of the stomach: a cause of linitis plastica. Radiology. 1996;201:375–8.
11. Jung K, Park MI, Kim SE, Park SJ. Borrmann type 4 advanced gastric cancer: focus on the

development of scirrhous gastric cancer. Clin Endosc. 2016;49: 336–45.

12. Park MS, Ha HK, Choi BS, Kim KW, Myung SJ, Kim AY, et al. Scirrhous gastric carcinoma: endoscopy versus upper gastrointestinal radiography. Radiology. 2004;231:421–6.
13. Piessen G, Messager M, Leteurtre E, Jean-Pierre T, Mariette C. Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. Ann Surg. 2009; 250:878–87.
14. Pedrazzani C, Marrelli D, Pacelli F, Di Cosmo M, Mura G, Bettarini F, et al. Gastric linitis plastica: which role for surgical resection? Gastric Cancer. 2012; 15:56–60.
15. Blackham AU, Swords DS, Levine EA, Fino NF, Squires MH, Poultsides G, et al. Is linitis plastica a contraindication for surgical resection: a multiinstitution study of the U.S. Gastric Cancer Collaborative. Ann Surg Oncol. 2016;23: 1203–11.
16. Thies S, Langer R. Tumor regression grading of gastrointestinal carcinomas after neoadjuvant treatment. Front Oncol. 2013;3:262.
17. Mastoraki A, Papanikolaou IS, Sakorafas G, Safioleas M. Facing the challenge of managing linitis plastica—review of the literature. Hepatogastroenterology. 2009;56:1773–8.
18. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
19. Palli D, Bianchi S, Cipriani F, Duca P, Amorosi A, Avellini C, et al.Reproducibility of histologic classification of gastric cancer. Br J Cancer. 1991;63:765–8.
20. Chen YC, Fang WL, Wang RF, Liu CA, Yang MH, Lo SS, et al.Clinicopathological variation of Lauren classification in gastric cancer. Pathol Oncol Res. 2016;22:197–202.
21. Wirtzfeld D, Goldberg R, Savarese D. Hereditary diffuse gastric cancer. UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Cited 11-11-14. Available from: URL: http://www.uptodate.com/contents/hereditary-diffuse-gastric-cancer. Accessed 22 June 2018
22. Terai S, Fushida S, Tsukada T, Kinoshita J, Oyama K, Okamoto K, et al. Bone marrow derived "fibrocytes" contribute to tumor proliferation and fibrosis in gastric cancer. Gastric Cancer. 2015;18:306–13.
23. Naito Y, Sakamoto N, Oue N, Yashiro M, Sentani K, Yanagihara K, et al. MicroRNA-143 regulates collagen type III expression in stromal fibroblasts of scirrhous type gastric cancer. Cancer Sci. 2014;105:228–35.
24. Endo K, Sakurai M, Kusumoto E, Uehara H, Yamaguchi S, Tsutsumi N, et al. Biological significance of localized Type IV scirrhous gastric cancer. Oncol Lett. 2012;3:94–9
25. Blackham AU, Swords DS, Levine EA, Fino NF, Squires MH, Poultsides G, et al. Is linitis plastica a contraindication for surgical resection: a multiinstitution study of the U.S. Gastric Cancer Collaborative. Ann Surg Oncol. 2016;23:1203–11.
26. Yashiro M, Hirakawa K. Cancer-stromal interactions in scirrhous gastric carcinoma. Cancer Microenviron. 2010;3:127–35.
27. Burgain C, Germain A, Bastien C, Orry X, Chone L, Claudon M, et al.Computed tomography features of gastrointestinal linitis plastica: spectrum of findings in early and delayed phase imaging. Abdom Radiol (NY). 2016; 41:1370–7.
28. Kanter MA, Isaacson NH, Knoll SM, Nochomovitz LE. The diagnostic challenge of metastatic linitis plastica. Two cases and a consideration of the problem. Am Surg. 1986;52:510–3.
29. Ciulla A, Castronovo G, Tomasello G, Maiorana AM, Russo L, Daniele E, et al. Gastric metastases originating from occult breast lobular carcinoma: diagnostic and therapeutic problems. World J Surg Oncol. 2008;6:78.
30. Itoh H, Nakata H, Nishioka S, Aikawa K, Yokoya Y, Nakayama T, et al. Gastric cancer retrospectively investigated for 9 years and 6 months: a case of linitis plastica. Dig Endosc. 2000;12:191 –5.
31. Oguro Y. Endoscopic diagnosis of scirrhous gastric carcinoma. Gan To Kagaku Ryoho. 1994;21:2384 –91.

32. Satoru Takemura, Masakazu Yashiro,[1] Takeshi Sunami, Masashige Tendo and Kosei Hirakawa.Novel models for human scirrhous gastric carcinoma in vivo.Cancer sci 2004;95:893-900.

33. Semba S, Yokozaki H, Yamamoto S, Yasui W, Tahara E. Microsatellite instability in precancerous lesions and adenocarcinomas of the stomach. Cancer 1996; 77: 1620–7.

34. Buonsanti G, Calistri D, Padovan L, Luinetti O, Fiocca R, Solcia E, Ranzani GN. Microsatellite instability in intestinal- and diffuse-type gastric carcinoma. J Pathol 1997; 182: 167–73

35. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Meltzer SJ, Rodriguez-Bigas MA, Fodde R, Ranzani GN et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 1998; 58: 5248–57.

36. Paredes, J., Figueiredo, J., Albergaria, A., Oliveira, P., Carvalho, J., Ribeiro, A.S., Caldeira, J., Costa, A.M., Simoes-Correia, J., Oliveira, M.J., et al. Epithelial E- and P-cadherins: Role and clinical significance in cancer. Biochim. Biophys. Acta 2012; 297–311 :1826 , http://dx.doi.org/10.1016/j.bbcan.2012.05.002.

37. Berx, G. and van Roy, F. Involvement of members of the cadherin superfamily in cancer. Cold Spring Harb. Perspect Biol.2009; 1, a003129, http://dx.doi.org/10.1101 /cshperspect.a003129.

38. De Wever, O., Derycke, L., Hendrix, A., De Meerleer, G., Godeau, F., Depypere, H. and Bracke, M. Soluble cadherins as cancer biomarkers. Clin. Exp. Metastasis 2007;24, 685–697, http://dx.doi.org/10.1007/ s10585-007-9104-8.

39. Guilford, P., Humar, B. and Blair, V. (2010) Hereditary diffuse gastric cancer: translation of CDH1 germline mutations into clinical practice. Gastric Cancer 13, 1–10, http://dx.doi.org/10.1007/s10120-009-0531-x.

40. Patrícia Carneiro [a], Maria Sofia Fernandes [a], Joana Figueiredo [a,b], Joana Caldeira [a,c], Joana Carvalho [a,b], Hugo Pinheiro [a], Marina Leite [a], Soraia Melo [a], Patrícia Oliveira et al. E-cadherin dysfunction in gastric cancer - Cellular consequences, clinical applications and open questions. FEBS Letters 586 (2012) 2981–2989

41. Berrada S, Alami A, Diouri M, Finech B, Kadiri B: [Linitis plastica of the digestive tract. A case with involvement of the stomach and rectum]. Ann Gastroenterol Hepatol (Paris) 1996; 32:120-122

42. Yamashita K, Sakuramoto S, Katada N, Futawatari N, Moriya H Hirai K, Kikuchi S, Watanabe M: Diffuse type advanced gastric cancer showing dismal prognosis is characterized by deeper invasion and emerging peritoneal cancer cell: the latest comparative study to intestinal advanced gastric cancer. Hepatogastroenterology 2009; 56:276-281.

43. Negreanu L, Assor P, Bumsel F, Metman EH: An Endoscopic View in Gastric Linitis. A Case Report. J Gastrointestin Liver Dis 2007; 16:321-323.

44. Park JY, Han DS, Lee HL, Kim JB, Sohn JH, Choi HS, Nam YS, Park YW, Hahm JS: A case of linitis plastica involving the entire colon, ileum, and appendix. Korean J Gastroenterol 2003; 42:237-241.

45. Kodera Y, Ito S, Mochizuki Y, Yamamura Y, Misawa K, Ohashi N, Nakayama G, Koike M, Fujiwara M, Nakao A: The number of metastatic lymph nodes is a significant risk factor for bone metastasis and poor outcome after surgery for linitis plastica-type gastric carcinoma. World J Surg 2008; 32:2015-2020.

46. Kodera Y[1], Nakanishi H, Ito S, Mochizuki Y, Yamamura Y, Fujiwara M, Hibi K, Ito K, Akiyama S, Tatematsu M, Nakao A. Detection of disseminated cancer cells in linitis plastica-type gastric carcinoma. Jpn J Clin Oncol. 2004 Sep;34(9):525-31.

47. Aikaterini Mastoraki, Ioannis S. Papanikolaou, George Sakorafas, Michael Safioleas. Facing the challenge of managing linitis plastica – Review of the literature.Hepatogastroenterology 2009;93:1-6.

48. Kanter MA, Isaacson NH, Knoll SM, Nochomovitz LE. The diagnostic challenge of metastatic linitis plastica. Two cases and a consideration of the problem. Am Surg. 1986;52:510–3.

49. Raskin MM. Some specific radiological findings and consideration of linitis plastica of the gastrointestinal tract. CRC Crit Rev Clin Radiol Nucl Med. 1976;8:87–106.

50. Shabot JM, Roark GD, Brannan M, Patterson M. Endoscopic prognosis in gastric cancer. J Clin Gastroenterol. 1983;5:25–8.

51. Chiyo T, Kobara H, Mori H, Katsuki N, Haba R, Masaki T. Submucosal endoscopic sampling for indefinite gastric linitis plastica infiltrating into the submucosal layer. J Gastrointestin Liver Dis. 2015;24:375–8.

52. Chen CY, Jaw TS, Wu DC, Kuo YT, Lee CH, Huang WT, et al. MDCT of giant gastric folds: differential diagnosis. AJR Am J Roentgenol. 2010;195:1124–30.

53. Song W, Chen CY, Xu JB, Ye JN, Wang L, Chen CQ, et al. Pathological diagnosis is maybe non-essential for special gastric cancer: case reports and review. World J Gastroenterol. 2013;19:3904–10.

54. Choi JI, Joo I, Lee JM. State-of-the-art preoperative staging of gastric cancer by MDCT and magnetic resonance imaging. World J Gastroenterol. 2014;20: 4546–57.

55. Kwee RM, Kwee TC. Imaging in local staging of gastric cancer: a systematic review. J Clin Oncol. 2007;25:2107–16

56. Tsujiura M, Ichikawa D, Konishi H, Komatsu S, Shiozaki A, Otsuji E. Liquid biopsy of gastric cancer patients: circulating tumor cells and cell-free nucleic acids. World J Gastroenterol. 2014;20:3265–86.

57. Ueda T, Volinia S, Okumura H, Shimizu M, Taccioli C, Rossi S, et al. Relation between microRNA expression and progression and prognosis of gastric cancer: a microRNA expression analysis. Lancet Oncol. 2010;11:136–46.

58. Shinji Muraoka, MD, Kouhei Tsuchida, MD, PhD , Mari Iwasaki, MD, Naoya Izawa, MD, Hidehito Jinnai et al. Medicine ;2017: 96:50

59. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011;14:113-23.

60. Shin D, Park SS. Clinical importance and surgical decision-making regarding proximal resection margin for gastric cancer. World J Gastrointest Oncol. 2013;5:4–11.

61. Yonemura Y, Canbay E, Li Y, Coccolini 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.

62. Biondi A, Lirosi MC, D'Ugo D, Fico V, Ricci R, Santullo F, et al. Neo-adjuvant chemo (radio)therapy in gastric cancer: current status and future perspectives. World J Gastrointest Oncol. 2015;7:389–400.

63. Messager M, Lefevre JH, Pichot-Delahaye V, Souadka A, Piessen G, Mariette C, et al. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. Ann Surg. 2011;254:684–93.

64. 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 - ADCI002. BMC Cancer. 2013;13:281.

65. Shinto O, Yashiro M, Kawajiri H, Shimizu K, Shimizu T, Miwa A, et al. Inhibitory effect of a TGFbeta receptor type-I inhibitor, Ki26894, on invasiveness of scirrhous gastric cancer cells. Br J Cancer. 2010;102:844–51. 91.

66. Yashiro M, Shinto O, Nakamura K, Tendo M, Matsuoka T, Matsuzaki T, et al. Synergistic antitumor effects of FGFR2 inhibitor with 5-fluorouracil on scirrhous gastric carcinoma. Int J Cancer. 2010;126:1004–16.

67. Sugiyama N, Baba Y, Takagi K, Nakamura K. A study of the clinical course of linitis plastica type cancer of the stomach: comparison between the clinical course and the development curve of gastric cancer. Stomach Intest 1980;15:1153-1163.

68. Nakamura K, Kato Y, Misono T, et al. Growing process to carcinoma of linitis plastica type of the stomach from cancer-development. Stomach Intest 1980;15:225-234.

69. Nakazawa S, Kawaguchi S, Yoshino J, et al. Linitis plastica retrospective study for early detection. Stomach Intest 1980;15:1145-1151.

70. Takeda S, Suto Y, Kohli Y, et al. Initial findings and developments of linitis plastica type of gastric cancer. Stomach Intest 1980;15:1137-1144.

71. Ohgushi H, Yao T, Iwashita A. The primary foci of linitis plastics type of gastric cancer and their chronological changes. Stomach Intest 1980;15:1129-1136.

72. Takizawa T. Distinctive features of linitis plastica type gastric carcinoma with reference to lymphangiosis carcinomatosa. Stomach Intest;1992; 27:591-598.

73. Kyoungwon Jung, Moo In Park, Sung Eun Kim and Seun Ja Park. Borrmann Type 4 Advanced Gastric Cancer: Focus on the Development of Scirrhous Gastric Cancer. Clin Endosc 2016;49:336-345 . http://dx.doi.org/10.5946/ce

74. Sotiropoulos gc, Kaiser gM, Lang H, treckmann J, Brokalaki EI, Pottgen c, gerken g, Paul a, Broelsch cE. staging laparoscopy in gastric cancer. Eur J Med Res. 2005 Feb 28;10(2):88-91.

75. Maehara y, Hasuda s, Koga t, tokunaga E, Kakeji y, sugimachi K. Postoperative outcome and sites of recurrence in patients foliowing curative resection of gastric cancer. BrJ surg 2000; 87: 353—357.

76. Mastoraki a, Papanikolaou Is, sakorafas g, safioleas M. Facing the challenge of managing linitis plastica—review of the literature. Hepatogastroenterology. 2009 novDec;56(96):1773-8.

77. M. schauer1, M. Peiper1, J. theisen2, w. Knoefel.. PRognostIc FactoRs In PatIEnts wItH DIFFusE tyPE gastRIc cancER (LInItIs PLastIca) aFtER oPERatIvE tREatMEnt. Eur J Med Res 2011; 16: 29-33

78. Chang JM, Lara KA, Gray RJ, Pockaj BA, Wasif N. Clinical Outcomes after Surgery for Linitis Plastica of the Stomach: Analysis of a Population Cancer Registry. Am Surg. 2017 Jan 1;83(1):23-29.

79. Aranha GV, Georgen R. Gastric linitis plastica is not a surgical disease. Surgery. 1989; 106(4):758–762.

80. Hamy A, Letessier E, Bizouarn P, et al. Study of survival and prognostic factors in patients undergoing resection for gastric linitis plastica: a review of 86 cases. Int Surg. 1999; 84(4):337–343.

81. Furukawa H, Hiratsuka M, Iwanaga T. A rational technique for surgical operation on Borrmann type 4 gastric-carcinoma—left upper abdominal evisceration plus Applebys method. Br J Surg. 1988; 75(2):116–119.

82. Aaron U. Blackham, MD[1], Doug S. Swords, MD[1], Edward A. Levine, MD[1], Nora F. Fino, MS[2], Malcolm H. Squires, MD[3], George Poultsides, MD[4], Ryan C. Fields, MD[5], Mark Bloomston,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(4): 1203–1211. doi:10.1245/s10434-015-4947-8.

83. Kunisaki C, Shimada H, Nomura M, Matsuda G, Otsuka Y, Ono H, Akiyama H. Therapeutic strategy for scirrhous type gastric cancer. Hepato gastroenterology. 2005 ;52(61):314– 8

84. Kinoshita T, Sasako M, Sano T, Katai H, Furukawa H, Tsuburaya A, et al. Phase II trial of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer (JCOG 0002). Gastric Cancer:;2009 ;12(1):37–42.

85. Yashiro M, Shinto O, Nakamura K, Tendo M, Matsuoka T, Matsuzaki T, et al. Synergistic antitumor effects of FGFR2 inhibitor with 5-fluorouracil on scirrhous gastric carcinoma. Int J Cancer. 2010 ;126(4):1004–16.

86. M Yashiro, T Matsuoka. Scirrhous gastric cancer: a critical review. OA Cancer 2014 25;2(1):4.