

# Scirrhou gastric cancer: a critical review

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## Abstract

### Introduction

Scirrhou gastric cancer, diffusely infiltrating carcinoma, or Borrmann type 4, also known as linitis plastica-type carcinoma, is characterised by rapid cancer cell proliferation and infiltration accompanied by extensive stromal fibrosis. Scirrhou gastric cancer cells easily invade and diffusely spread into the gastric wall. The common features of scirrhou gastric cancer include rapidly progressive invasion and a high frequency of metastasis to the peritoneum. Scirrhou gastric cancer accounts for approximately 10% of all gastric cancers and its prognosis is worse than that of other types of gastric cancer due to its aggressive behaviour and the lack of effective therapies. The aim of this critical review is to discuss scirrhou gastric cancer.

### Conclusion

Despite an increase in the understanding of the molecular pathways involved in scirrhou gastric cancer, clinical studies have not identified agents that are effective in the treatment of this disease. The recent understanding of the molecular biology underlying the characteristics of scirrhou gastric cancer might provide a deeper diagnosis and development of treatment strategies for scirrhou gastric cancer.

### Introduction

Gastric cancer (GC) is one of the most lethal human cancers, with approximately 990,000 new cases and 738,000 GC-related deaths reported

worldwide each year<sup>1,2</sup>. Scirrhou GC (SGC) is biologically aggressive, typically infiltrating into the gastric wall and accompanied by peritoneal metastasis<sup>3</sup>. In Japan, approximately 10% of all GCs are of the scirrhou type<sup>1,4</sup>. Although the incidence of GC has been continuously declining, the incidence of SGC has not changed in the past several decades. Majority of the cases of SGC are not detectable at an early stage because tumour cells migrate throughout the submucosa without severely affecting the mucosal lining of the stomach. Despite recent advances in diagnostic techniques and therapies for GC in surgery, chemotherapy and radiotherapy, the prognosis of SGC remains poor. Therefore, new strategies for SGC including prevention, early detection and therapy based on its biological behaviour are necessary to improve the prognosis of SGC patients. In this critical review, we refer to SGC definition, investigate clinicopathological and biological features and discuss current development of diagnostic techniques and therapy based on the findings of clinical and molecular investigations.

### Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

### Definition

SGC is characterised by various macroscopic and microscopic features.

The characteristic macroscopic features of SGC include a grossly thickened and hard wall tumour without marked ulceration or raised margins (Figure 1a and b). This type is categorised as Borrmann's type 4. The common microscopic features of SGC show that undifferentiated cancer cells or signet ring cells proliferate with abundant fibroblasts (Figure 1c). Because most Borrmann's type 4 tumours are of the undifferentiated type, these are often clinically regarded as almost equal to SGC. SGC is also called diffusely infiltrating carcinoma, linitis plastica or leather bottle type. The definitions of these names slightly differ from each other; however, its clinicopathological features are almost the same.

### Clinicopathological features

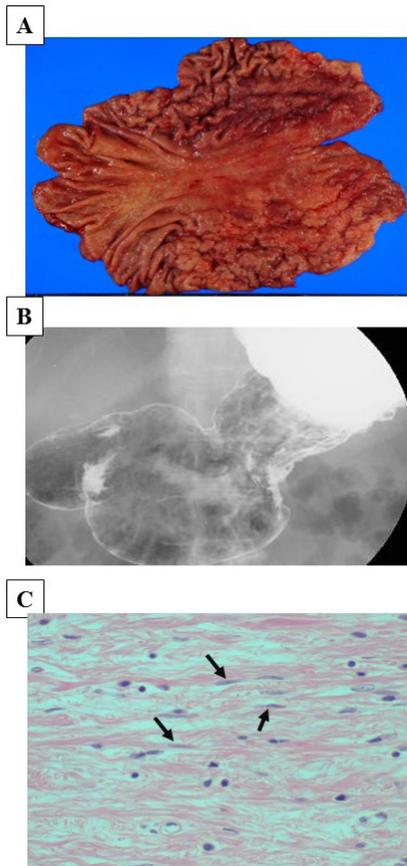
SGC more commonly occurs in younger patients and women<sup>5,6</sup>. Pathological analysis of SGC has shown a high invasion depth, vessel invasion, frequent lymph-node metastases and peritoneal metastasis, resulting in an advanced tumour stage compared with other types of GC<sup>6,7</sup>. The prognosis of SGC is significantly worse than that of other cancers<sup>6</sup>, even at the same stage<sup>8</sup>. The 5-year survival rate of patients with SGC is approximately 10%–20%, whereas for patients with other types of GC, the median survival rate is approximately 60%–70%<sup>1,4</sup>.

### Diagnostic approaches for SGC

SGC cells are predominantly located in the submucosa, and the overlying mucosa appears normal, which makes it difficult to detect cancer using upper gastrointestinal (UGI) series or endoscopy. The sensitivity of endoscopy has been reported to be low in SGC compared with other types of gastric tumours<sup>9</sup>. Negative

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**Figure 1:** Scirrhus gastric cancer: (a) Macroscopic findings indicate that scirrhus gastric carcinoma diffusely infiltrates a broad region of the stomach without a prominent ulceration and elevation. (b) Radiographic findings show loss of distensibility with effacement of folds and narrowing of stomach. (c) Microscopical views of scirrhus gastric carcinoma have the appearance of abundant fibrosis (arrows) with the occasional presence of poorly differentiated cancer cells.

findings at endoscopic biopsy often cause a delay in the treatment of SGC. Because the predominant proliferation of SGC cells at the submucosal layers is one of the reasons that a negative diagnosis is obtained by endoscopic biopsy, a careful repetitive biopsy targeting a small ulcer of a  $I_{IIc}$  lesion on the mucosa, which

represents an initial locus of SGC, might be useful in the detection of cancer cells in biopsy specimens. Fold thickening and rigidity or narrowing of the gastric wall are important features in the UGI series of SGC, whereas the detection of SGC at an early stage using a UGI series is considerably difficult<sup>9</sup>. No specific biomarker for SGC has been reported, although some useful markers for GC have been proposed<sup>10</sup>. Although some studies have shown that the UGI series was superior to endoscopy in determining the correct tumour localisation and diagnosis of SGC<sup>9,11</sup>, both endoscopy and UGI series might be useful in the diagnosis of SGC.

SGC shows a high frequency of metastasis to the peritoneum<sup>6,12</sup>. In SGC, palliative gastrectomy did not show any surgical advantage, unlike other macroscopic types of GC with peritoneal metastasis<sup>13</sup>. Real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis of the carcinoembryonic antigen (CEA) and/or CK20 transcripts in the peritoneal lavage fluid is useful in predicting peritoneal recurrence in patients who undergo curative resection for GC<sup>14</sup>. Therefore, diagnostic laparoscopy with identification of cancer cells in the peritoneal cavity by cytology and RT-PCR could provide valuable information on the tumour stage and can prevent invalid surgery in patients with SGC<sup>5</sup>.

### Biological features

Tumour progression has recently been recognised as the product of a cross talk between the cancer cells and its surrounding tissue or tumour stroma<sup>3</sup>. SGC cells proliferate with fibrosis when the cancer cells invade the submucosa, which contains abundant stromal cells. These typical histological findings of rapid growth with fibrosis suggest that its development may be controlled by intercellular interactions between the SGC cells and the stromal fibroblasts. The proliferative and infiltrative ability of SGC

cells is closely correlated with growth factors that are produced by organ-specific fibroblasts<sup>3</sup>. Conditioned medium from gastric fibroblasts also stimulates the proliferation and invasion of SGC cells, suggesting that the progression of SGC cells is affected by orthotopic fibroblasts. Fibroblast growth factor-7 (FGF-7) has been identified as one of growth-stimulating factors from gastric fibroblasts that affect SGC cells<sup>15</sup>. Fibroblast growth factor receptor (FGFR)2IIIb, which is identical to the amplified *K-sam-II* gene in the SGC cell line, KATO-III, is a specific receptor of FGF-7 and is frequently expressed in SGC. FGF-7, which is secreted by fibroblasts, is important in the proliferation of SGC, with *K-sam-II* amplification occurring in a paracrine manner. In addition, transforming growth factor- $\beta$  (TGF $\beta$ ) has been reported as one of the invasion-stimulating factors from gastric fibroblasts in SGC<sup>3</sup> that commonly shows transforming growth factor- $\beta$  receptor (TGF $\beta$ R) and Smad2 overexpression<sup>13</sup>. Tumour-stroma interactions might therefore be an attractive target for cancer therapy in SGC.

In recent years, several studies have identified specific genes that are highly associated with SGC. It has been reported that hereditary diffuse GC is caused by a germ line mutation in the *E-cadherin* gene, which is located on chromosome 16q22<sup>16</sup>. Loss of *E-cadherin* and p53 resulted in the development of SGC in mice<sup>17</sup>. Genetic or epigenetic alterations in the *E-cadherin* gene appear to be important carcinogenic events in the pathogenesis of SGC. Reduced miR-200 may have participated in the development of SGC by reducing *E-cadherin* expression. Loss of desmoglein-2, overexpression of ephrin-B1 and phosphorylated mammalian target of rapamycin (mTOR) and c-MET amplification are common features of diffuse-type GC.

### Therapeutic strategy for SGC

Although multivariate analysis has shown that curative resection is a

significant prognostic factor for the survival of patients with SGC<sup>7</sup>, only about 20% of the patients with SGC benefit from total gastrectomy<sup>5</sup>. Radical operations such as en bloc total gastrectomy, which includes the pancreatic body and tail, spleen, gall-bladder, transverse colon and the left adrenal gland, have been previously performed<sup>18</sup>. 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<sup>19</sup>; 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 SGC<sup>5,20</sup>. Accordingly, novel therapy based on the characteristic biological behaviour in SGC is necessary.

Although a targeted therapy for patients with HER2-positive advanced GC have reached satisfactory clinical results<sup>21</sup>, a new targeting therapy for SGC has not been defined. Pre-clinical studies have demonstrated the efficacy of targeted therapy for advanced GC<sup>22</sup>. 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*<sup>23-25</sup>. The combined administration of S1 and FGFR2 inhibitor decreases cell proliferation in SGC more effectively than S1 alone<sup>26</sup>. FGFR2 phosphorylation inhibitors appear to be therapeutically promising agents in SGC with FGFR2 amplification. A phase II clinical trial of dovitinib monotherapy is currently in progress for metastatic or unresectable GC that harbours FGFR2 amplifications after the failure of first- or second-line chemotherapies (NCT01719549).

TGF $\beta$  is secreted by a range of tumour cells and mediates the

interaction of SGC cells with stromal fibroblasts. TGF $\beta$ R phosphorylation inhibitors, A-77 and Ki26894, significantly decrease the invasion ability of SGCs<sup>27,28</sup>. It has been previously suggested that TGF $\beta$ R phosphorylation inhibitors reduce the invasiveness of cancer cells by suppressing the intercellular interactions between the SGC and surrounding fibroblasts. TGF $\beta$  probably functions as a tumour suppressor before the initiation of cancer and during the early stages of carcinogenesis. In contrast, during the advanced stages of cancer, TGF $\beta$  signalling promotes cancer progression and metastasis. Multiple phase II studies are currently in progress involving patients with advanced pancreatic cancer, recurrent glioma and hepatocellular carcinoma<sup>29</sup>. Additional studies on the clinical effect of TGF $\beta$ R inhibitors on the progression of gastric carcinoma at both the early and advanced stages are warranted. Moreover, c-Met and mTOR appear to be promising targets in SGC.

### Conclusion

SGC remains to be a fatal disease with extensive progression and aggressive metastasis. A novel target therapy based on the biological behaviour of SGC is imperative. The recent accumulation of information provides a deeper understanding of the molecular biology underlying the characteristics of SGC, which can facilitate in the establishment of a foundation for the diagnosis and development of treatment strategies for SGC.

### Abbreviations list

FGF-7, fibroblast growth factor-7; FGFR2, fibroblast growth factor receptor 2; GC, gastric cancer; RT-PCR, reverse transcription-polymerase chain reaction; SGC, scirrhous gastric cancer; TGF $\beta$ , transforming growth factor- $\beta$ ; TGF $\beta$ R, transforming growth factor- $\beta$  receptor; UGI, upper gastrointestinal.

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