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PRIMARY GASTRIC SQUAMOUS CELL CARCINOMA: CHALLENGES IN TREATMENT STRATEGY

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ABSTRACT

Background: Primary gastric squamous cell carcinoma (GSCC) is an extremely rare malignancy, accounting for approximately 0.04–0.07% of all gastric malignant tumours. The disease carries a poor prognosis, and there is currently no globally standardised treatment protocol.

Case description: A 59-year-old female patient with no significant medical history presented with prolonged epigastric pain. Gastroscopy revealed a 5 × 7 cm ulcerated mass along the greater curvature of the gastric body; biopsy confirmed squamous cell carcinoma. Computed tomography (CT) demonstrated tumour invasion through the serosa with perigastric fat infiltration and multiple perigastric lymph nodes >1 cm (the largest node in station 10 measuring 5 cm); tumour marker CA72-4 was elevated at 29.3 U/ml. Comprehensive evaluation revealed no primary lesions at other sites, including esophagogastroduodenoscopy, colonoscopy, chest CT and physical examination. Primary squamous cell carcinoma of the gastric body, cT4N2M0. The patient underwent total gastrectomy, distal pancreatectomy, splenectomy and D2+ lymphadenectomy (including stations 12b, 12p, 13). Histopathological examination confirmed poorly differentiated squamous cell carcinoma with serosal invasion, invasion into the greater omentum, lymphovascular invasion (LVI+) and perineural invasion (PNI+), with 7/25 lymph nodes positive for metastasis. Immunohistochemistry showed diffuse positivity for p63, CK5/6 and CK7; p16 was negative. Post-operative staging: pT4bN3aM0, LVI+, PNI+. The patient received adjuvant chemotherapy with eight cycles of the XELOX regimen.

Conclusion: GSCC is a rare disease entity with a poor prognosis. Radical resection combined with adjuvant chemotherapy represents a reasonable approach for resectable disease. Multicentre studies and clinical trials are needed to establish optimal treatment protocols for this rare malignancy.

KEYWORDS

Gastric squamous cell carcinoma (GSCC), rare gastric malignancy, radical surgery, adjuvant chemotherapy

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LEARNING POINTS

- Diagnosis requires systematically excluding other primary squamous cell carcinoma sites (oesophagus, lung, head and neck) before confirming primary gastric squamous cell carcinoma (GSCC).
- Radical resection (R0) combined with aggressive adjuvant chemotherapy is the optimal treatment strategy, offering the best survival chance even in advanced disease (pT4bN3aM0, LVI+/PNI+).
- Treatment must be individualised due to a lack of standardised protocols: for this extremely rare malignancy, the decision between upfront surgery versus neoadjuvant chemotherapy should be based on tumour resect ability, biological characteristics and multidisciplinary tumour board discussion.

INTRODUCTION

Squamous cell carcinoma (SCC) of the gastrointestinal tract commonly occurs in the oesophagus and anal canal. In contrast, primary gastric squamous cell carcinoma (GSCC) is an exceedingly rare entity with only 0.04–0.07% incidence among all gastric malignancies[1]. According to data from the Surveillance, Epidemiology and End Results (SEER) database spanning 1988–2012, GSCC accounted for 0.2% of 66,372 primary gastric cancer cases, with 50% diagnosed at stage IV. Male predominance was noted (72.5%), with a median age at diagnosis exceeding 60 years[2].

The disease is typically diagnosed at advanced stages, characterised by extensive local invasion and early lymph node metastasis, resulting in a poor prognosis. Five-year overall survival (OS) rates range from 17.4 to 51.9%, depending on disease stage and feasibility of radical resection[2,3]. The pathogenesis of GSCC remains incompletely understood, with several hypotheses proposed, including differentiation from pluripotent stem cells, transformation of heterotopic squamous tissue, squamous metaplasia secondary to chronic inflammation, squamous transformation of adenocarcinoma, or association with Epstein-Barr virus (EBV) and human papillomavirus (HPV) infection.

Due to its rarity, standardised treatment protocols for GSCC have not been established. Neither the European Society of Medical Oncology nor the National Comprehensive Cancer Network has published specific treatment guidelines for GSCC. Current treatment approaches are primarily based on the feasibility of radical resection and empirical adjuvant chemotherapy. We report a case of GSCC treated at our institution to describe the clinical, paraclinical and histopathological features of the disease, to share our experience with multimodal treatment strategies and to contribute to the medical literature on this rare entity.

CASE DESCRIPTION

A 59-year-old female patient with no significant medical or surgical history, a non-smoker, a non-drinker and no family history of cancer, presented with persistent dull epigastric pain of several days' duration. The pain was rated 2–3/10 on the Visual Analog Scale, without associated nausea, vomiting, dysphagia, heartburn or significant weight loss.

Physical examination on admission revealed Performance Status ECOG 0, good general condition. An abdominal examination revealed a soft abdomen with mild epigastric tenderness, no palpable mass and no hepatosplenomegaly. No peripheral lymphadenopathy or ascites was detected.

Esophagogastroduodenoscopy revealed an ulcerated fungating mass along the greater curvature of the gastric body, measuring >5 cm, located >5 cm from the cardia. The tumour had an irregular, ulcerated surface with easy bleeding on contact. Surrounding mucosa showed congestion. The oesophagus and cardia were normal. Multiple biopsies were obtained from the tumour. The oesophagus, cardia and duodenum showed no lesions other than the described gastric mass *(Fig. 1)*.

Contrast-enhanced CT of chest, abdomen and pelvis revealed the following:

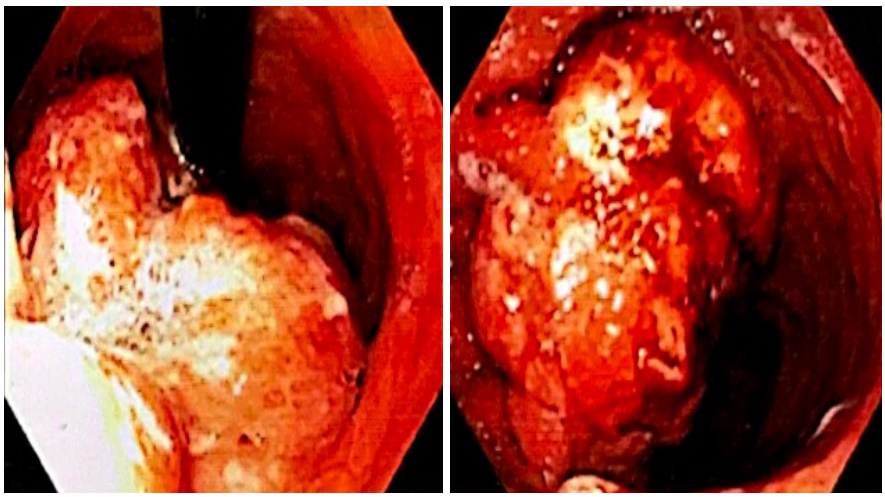


Figure 1. Tumour image on gastroscopy: histopathology (biopsy), squamous cell carcinoma.

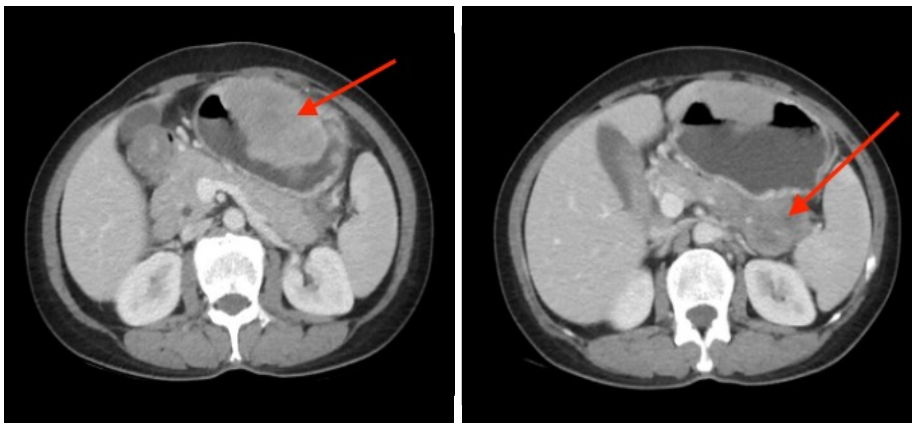


Figure 2. Gastric tumour and station node on computed tomography scan.

- *Chest:* bilateral lungs clear, no mediastinal lymphadenopathy.
- *Abdomen:* gastric body mass along the greater curvature with transmural invasion and peri gastric fat infiltration. Multiple peri gastric lymph nodes >1 cm, with the largest node at station 10 measuring 5 cm. No hepatic lesions; no ascites *(Fig. 2)*.
- *Tumour marker:* CA72-4: 29.3 U/ml (normal <6.9 U/ml)
- *Colonoscopy:* no suspicious lesions identified.
- *Otolaryngologic examination:* no head and neck or nasopharyngeal lesions detected.
- *Laboratory studies:* Complete blood count, liver and renal function tests, and coagulation profile were within normal limits.
- *Preoperative diagnosis:* Primary GSCC, clinical stage cT4N2M0.

A multidisciplinary tumour board consisting of surgeons, medical oncologists, radiologists and pathologists decided on radical resection, given the lack of clear evidence supporting the benefit of neoadjuvant chemotherapy in GSCC and the resettable nature of the tumour.

Surgical intervention was performed on 26 March 2025. A 5 × 7 cm mass was found along the greater curvature of the gastric body with transmural invasion and invasion into the greater omentum. There was no evidence of peritoneal metastasis or ascites. Multiple lymph nodes in stations 7, 8 and 9 measured >1 cm; the station 11p lymph node was >1 cm, firm, invading the splenic vein. The station 10 lymph node measured 4 × 5 cm, invading the pancreatic tail and splenic hilum. The surgical procedure was a total gastrectomy, distal pancreatectomy with splenectomy, D2+ lymphadenectomy (stations 12b, 12p, 13) and reconstruction via Roux-en-Y oesophagojejunostomy.

Post-operative histopathology showed a gastric body mass along the greater curvature, measuring 5 × 5 cm, with an ulcero fungating appearance *(Fig. 3)*.

Microscopy revealed a poorly differentiated SCC with transmural invasion extending into the greater omentum (T4b), with lymphovascular invasion (LVI+) and perineural invasion (PNI+) present; oesophageal and duodenal margins were negative.

Lymph nodes: 7/25 nodes were positive for metastasis (N3a), including the station 10 node showing SCC invading pancreatic and splenic hilar adipose tissue. The splenic parenchyma is free of tumour.

Immunohistochemistry *(Table 1, Fig. 4 and 5)*.

Final post-operative diagnosis: primary GSCC, stage pT4bN3aM0, R0 resection, LVI+, PNI+.

The patient received adjuvant chemotherapy with the XELOX (CAPOX) regimen: oxaliplatin 130 mg/m² IV on day 1, capecitabine (zeloda) 1,000 mg/m² PO twice daily, days 1–14, with the cycle repeated every 21 days. Treatment initiation was May 2025; as of 5 October 2025, the patient had completed seven cycles. At follow-up, an abdominal CT scan after four cycles of chemotherapy showed no evidence of local recurrence or distant metastasis.

DISCUSSION

Gastric adenocarcinoma (GAC) accounts for 95% of gastric cancer cases. GSCC is exceedingly rare with an incidence of only 0.04–0.07% and is typically diagnosed in patients over 60 years of age according to multiple reports. A retrospective analysis from the National Cancer Database (NCDB) of 61,215 gastric cancer cases from 2004–2013 identified GSCC histology in only 1.4% (n=836). The mean age at diagnosis was 65.9 years, with male predominance (72.5%) [2]. SEER data demonstrate that 50% of GSCC patients are diagnosed at stage IV, reflecting the aggressive nature of this disease. No specific epidemiological studies on GSCC exist in Vietnam due to its rarity.

The cellular origin of GSCC remains incompletely understood. Several hypotheses have been proposed:

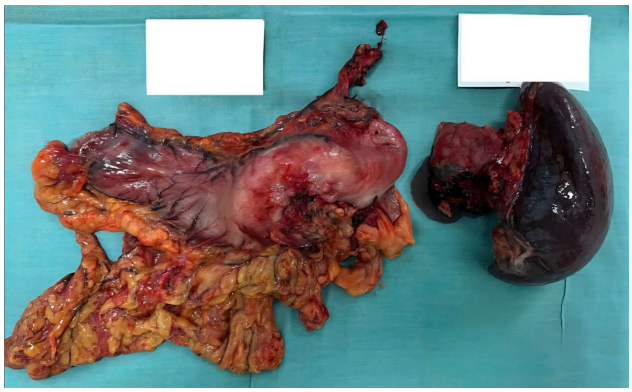


Figure 3. Resected specimen including stomach – pancreatic body-tail – spleen – lymph nodes.

- *Differentiation from pluripotent stem cells:* gastric stem cells may differentiate towards squamous epithelium under pathological conditions.
- *Heterotopia:* abnormal presence of squamous epithelium in the gastric mucosa from embryonic development.
- *Squamous metaplasia:* chronic inflammation, gastric ulceration or chemical injury may induce transformation of glandular to squamous epithelium.
- *Transformation from adenocarcinoma:* some GSCC cases may develop through dedifferentiation and phenotypic transformation.
- *Viral infection:* the role of EBV and HPV remains under investigation, although most GSCC cases are negative for these viruses.

In 1965, Boswell and Helwig described the role of squamous metaplasia in association with gastric ulceration, caustic burns, congenital syphilis and prolonged cyclophosphamide use[4]. However, our patient had none of these apparent risk factors. In 1967, Parks established three criteria for diagnosing GSCC[5]:

1. Carcinoma not located at the cardia;
2. Carcinoma not extending from the oesophageal primary;
3. No evidence of SCC at any other body site.

Our patient fulfilled all three criteria: the tumour was located in the gastric body along the greater curvature, >5 cm from the cardia; esophagoscopy was normal, and other organs (lungs, colorectum, anus, head and neck, skin) showed no SCC lesions.

Boswell and Helwig proposed microscopic criteria requiring at least one of four features[4]:

1. Keratin pearl formation;
2. Mosaic cell arrangement;
3. Distinct intercellular bridges;
4. High sulfhydryl and/or disulfide concentration in tumour tissue.

Immunohistochemistry is crucial in classifying primary tumours in clinical practice. SCC is positive for p40, p63 and CK5/6; negative for CK7, CK20 and CDX2, helping differentiate from adenocarcinoma. P63 and CK5/6 are nuclear and cytoplasmic markers, respectively, characteristic of squamous differentiation. This marker combination strongly suggests SCC. P40 is an antibody targeting ΔNp63, a specific p63 isoform. While CK7 is typically positive in adenocarcinoma, a small percentage of SCC cases may also be positive; therefore, it is not entirely specific for excluding SCC. In recent years, p40 has been considered the gold standard for diagnosing SCC, with sensitivity comparable to but specificity somewhat higher than p63[6]. In our case, P63 (+), CK5/6 (+) and diffuse CK7 positivity confirmed the SCC diagnosis. P16 negative indicated no HPV association.

Due to the rarity of GSCC, no standardised treatment guidelines have been established. Treatment strategies are primarily based on clinical experience and adapted from protocols for advanced gastric adenocarcinoma or oesophageal SCC.

Radical surgical resection is the cornerstone of GSCC treatment when the disease is resettable. Wakabayashi et al. reviewed 56 GSCC cases in Japan, with 94.6% undergoing surgery: 17% achieved R0, 39.6% achieved R1, 43.4% underwent R2 resection and seven cases lacked complete data[7]. This study demonstrated that R0 offers curative potential for localised disease. Akce et al. analysed 836 GSCC cases from the NCDB: only 26% underwent surgery, reflecting the high proportion of patients diagnosed at advanced, inoperable stages[2]. The study showed significantly worse survival in patients who did not undergo surgery.

The role of neoadjuvant chemotherapy in GSCC remains unclear. Schizas et al. reported that 50% of patients had pT4 disease, 47% had nodal metastasis and only 2.6% received neoadjuvant treatment[3]. The lack of strong evidence for the benefit of neoadjuvant chemotherapy necessitates individualised treatment decisions.

Post-operative adjuvant chemotherapy tends to improve prognosis, particularly for disease beyond T1. Wakabayashi et al. reported that 35.7% of patients received adjuvant chemotherapy with various regimens: mitomycin, 5-FU, cisplatin, docetaxel, epirubicin/adriamycin[7]. Combined surgery and chemotherapy appeared superior to surgery alone.

Marker	Result	Notes
P63	Positive	Diffuse
CK5/6	Positive	Diffuse
CK7	Positive	Diffuse
P16	Negative	Not suggestive of HPV infection
Conclusion: Immunohistochemical findings are consistent with poorly differentiated SCC and are not HPV-related.		

Table 1. Immunohistochemistry results.

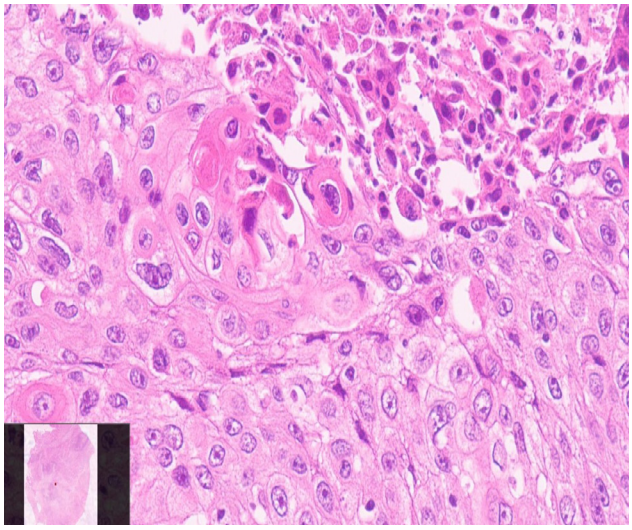


Figure 4. Histopathological image with haematoxylin-eosin staining.

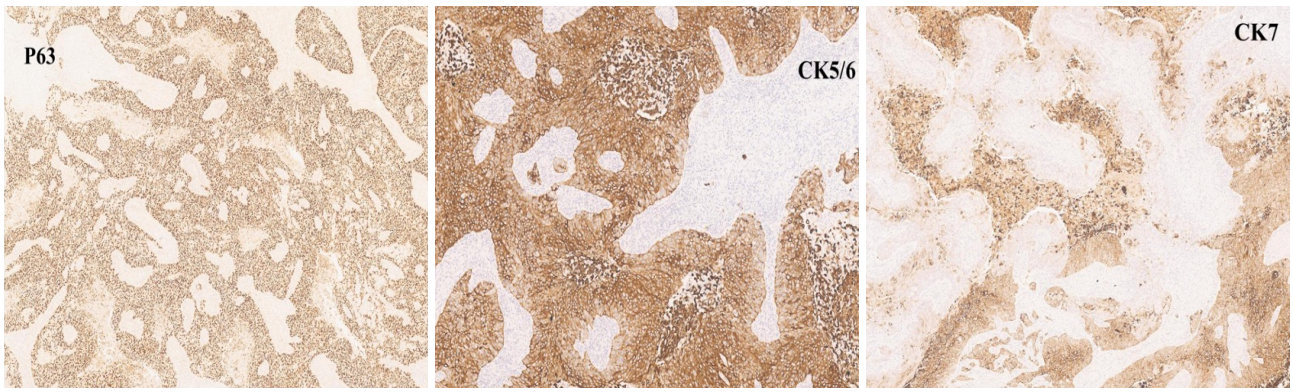


Figure 5. Immunohistochemistry staining images: P63 – CK5/6 – CK7.

Schizas et al. reported that 60% of patients received adjuvant chemotherapy[3]. For tumours >T1, most patients appeared to benefit from post-operative adjuvant chemotherapy despite the lack of strong evidence from randomised controlled trials. De Lange et al. supported this approach while proposing perioperative chemotherapy with the FLOT regimen (5-FU, leucovorin, oxaliplatin, docetaxel) combined with surgical resection and D2 lymphadenectomy[8]. However, this recommendation was primarily based on guidelines for gastric adenocarcinoma.

In our patient, with preoperative staging of cT4N2M0, the standard approach for adenocarcinoma would include neoadjuvant chemotherapy, surgical resection then adjuvant chemotherapy. However, we decided to proceed with surgery first due to lack of evidence for neoadjuvant chemotherapy efficacy in GSCC, the radical resettable ability of the tumour and the risk of disease progression during chemotherapy, given the aggressive invasive characteristics of GSCC. The patient underwent total gastrectomy, distal pancreatectomy, splenectomy and extended D2+ lymphadenectomy (including stations 12b, 12p, 13). While guidelines exist for gastric adenocarcinoma[9], specific recommendations for lymphadenectomy extent in GSCC are lacking; however, given the rarity of this disease, poor prognosis, aggressive invasion and advanced stage, we performed an extended lymphadenectomy to maximise oncological clearance.

The post-operative stage of pT4bN3aM0 with LVI+ and PNI+ represents adverse prognostic factors. We selected the XELOX regimen (capecitabine + oxaliplatin) because it is a standard regimen for adjuvant treatment of advanced gastric cancer, there is better tolerance compared to FLOT and it is appropriate for patients' post-major surgery.

There is a strong evidence base in gastric adenocarcinoma. The CLASSIC trial demonstrated that XELOX improved disease-free survival and survival in stage II–III gastric cancer following D2 resection[10].

Akce et al. reported that 48.1% of GSCC patients received radiation therapy, primarily for locally advanced disease or palliation[2]. The role of adjuvant radiotherapy in GSCC remains undefined. For our patient, following R0 resection with planned complete adjuvant chemotherapy, we did not recommend adjuvant radiotherapy.

GSCC has a worse prognosis compared to gastric adenocarcinoma at the same stage. Akce et al.'s analysis of 836 GSCC cases showed one-year (OS) 43.7%, five-year OS 17.4%. Compared to GAC at the same stage: one-year OS 52.4%, five-year OS 21.6%. For stage I disease, the median OS for GSCC was 16.1 months versus 32.2 months for GAC[2]. Schizas reported better outcomes in patients undergoing radical resection: three-year OS 62.2%, five-year OS 51.9% and disease-free survival of 38% in radically resected patients[3]. Differences in prognosis between studies may be explained by varying rates of radical resection, disease stage at diagnosis, rates of adjuvant treatment and tumour biological characteristics.

Poor prognostic factors include advanced T stage (T3–T4), extensive nodal metastasis (N2–N3), lymphovascular invasion (LVI+), perineural invasion (PNI+), inability to achieve radical resection and late-stage presentation.

For our patient, despite multiple adverse prognostic factors (pT4b, N3a, LVI+, PNI+), achieving R0 resection and aggressive adjuvant treatment may improve prognosis. However, long-term follow-up is required to assess treatment outcomes fully.

This case has some limitations: GSCC is exceedingly rare, making large-scale randomised controlled trials impractical. Treatment protocols are primarily adapted from advanced gastric adenocarcinoma or oesophageal SCC. No studies on the molecular and genetic characteristics of GSCC have been conducted in Vietnam.

CONCLUSION

GSCC is an extremely rare malignancy, accounting for <0.1% of gastric malignant tumours, with a worse prognosis than gastric adenocarcinoma at the same stage. The disease is typically diagnosed at advanced stages due to non-specific clinical symptoms. Currently, no specific or standardised treatment protocol exists for this entity. Studies uniformly support radical resection when feasible and adjuvant chemotherapy; however, additional evidence and clinical trials are needed to clarify the role of various treatment modalities.

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