Indian Journal of Surgical Oncology (March 2024) 15(1):153–159
https://doi.org/10.1007/s13193-023-01852-3

CASE REPORT

A Rare Case of Primary Gastric Signet Ring Cell Carcinoma: a Review of Guidelines for the Management of Gastric Cancer

Ronald Mauricio Blanco Montecino[1] · Mikhail Sukhorosl[2] · Mayi Ann Francis[3] · Neeraj Kancherla[4] · Ogbonnaya Akuma[5] · Nkiruka Lauretta Nwangene[6] · Shreyas Nandyal[7] · Rohan Raj[8] · Chinaza Mercy Akuma[9] · Tamer Zahdeh[10] · Sharanya Kaushik[11] · Adil M. Khan[12]

Received: 3 August 2023 / Accepted: 18 November 2023 / Published online: 25 November 2023

Abstract

Gastric carcinoma is the fifth most common and the third leading cause of cancer deaths worldwide. The incidence of diffuse-type gastric cancer, of which signet ring cell carcinoma is a subtype, is rising in the world. Due to non-specific gastritis-like symptoms, difficulty in assessing true tumor characteristics owing to its horizontal spread, and non-distinguishable endoscopic appearance from other gastric pathologies, the diagnosis of this subtype is challenging. We present a case of a 67-year-old woman with progressively worsening abdominal pain who came for an endoscopic ultrasound evaluation of an incidentally noted pancreatic cyst on a previous MRI. During endoscopy, a 1-cm gastric ulcer was noted along the lesser curvature of the gastric body. Biopsy confirmed a diagnosis of gastric signet ring cell carcinoma (SRCC) with CDX-2 and keratin positivity. The patient underwent total gastrectomy with Roux-en-Y reconstruction. Gross specimen revealed a diffuse SRCC invading the muscularis propria, along with lymphovascular and perineural invasion. In the context of our case, we discuss the morphological features of SRCC and the effectiveness of treatment options based on existing literature. Early accurate diagnosis and staging play an important role in determining treatment options as well as the clinical course of gastric SRCC.

Keywords Gastric cancer · Gastric signet ring cell carcinoma · Gastric carcinoma

✉ Shreyas Nandyal
shreyasnandyal@gmail.com

1 Universidad de El Salvador, San Salvador, El Salvador

2 S M Kirov Military Medical Academy: Voenno-Medicinskaa Akademia Imeni S M Kirova Ministerstva Oborony Rossijskoj Federacii, Saint Petersburg, Russia

3 Windsor University School of Medicine, Cayon, Saint Kitts and Nevis

4 Andhra Medical College, Visakhapatnam, India

5 Ebonyi State University, Isieke, Nigeria

6 Caribbean Medical University, Curacao Campus, Willemstad, Curaçao

7 Gandhi Medical College, 8-2-601/B/3 G2, Ashoka Silent Valley, Road Number 10, Banjara Hills, Hyderabad, TS 500034, India

8 Nalanda Medical College and Hospital, Patna, India

9 Chamberlain University, Chicago, IL, USA

10 Montefiore, Bronx, NY, USA

11 Bangalore Medical College and Research Institute: Bangalore Medical College, Bengaluru, India

12 University of Illinois Chicago, Chicago, IL, USA

Introduction

Gastric carcinoma was reported to be the fifth most frequent and the third leading cause of cancer deaths in the world in 2020 [1]. Although its incidence is considerably diminished in the USA and Western Europe, gastric cancer (GC) incidence remains high in Eastern Asia and other geographic areas like South and Central America. Historically, gastric cancer has been classified histologically, of which the two most commonly used are the WHO and the Lauren classifications. In this scenario, the incidence of diffuse type cancer, which comprises poorly cohesive cells gastric cancer and includes signet ring cell cancer (SRCC), is steadily rising [2]. Tumor location has been an important component of prognostication and management guidance. Of late, genomic profiling is emerging as a promising tool for developing new therapeutic targets [3].

Gastric cancer management requires a thorough workup and should include an interdisciplinary team [1]. For early gastric cancers, surgical resection is recommended and potentially curative. In cases of very early gastric cancers

that meet specific criteria, an endoscopic approach may be indicated. However, a surgical approach is necessary for tumors not meeting the endoscopic resection criterion. The extent of resection depends on the tumor's location, histological subtype, and TNM category [4]. Recent studies have shown that laparoscopic resection is comparable in oncologic outcomes to open surgery for early gastric cancer. Although selecting a reconstruction procedure affects patients' quality of life following surgery, there is still no consensus on the best reconstruction option [5].

Data suggests that the addition of peri-operative chemotherapy for patients with resectable stage II and III disease improves 5-year survival, compared to surgery alone [4]. In patients with unresectable or metastatic disease, supportive care and palliative management are an important parts of management. Systemic therapy or chemoradiation may benefit patients with better performance statuses [1].

Case Presentation

A 67-year-old female presented with the chief complaint of progressive abdominal pain over the past few years. The patient reported that she has been having intermittent sharp "pokey" abdominal pain in her epigastrium and left lower quadrant. She also reported that the pain has become more frequent and is associated with intermittent nausea and vomiting. Additionally, she noted that she has felt dizzy and weak over the past two months and has had an increase in her bowel movements from once every day to three-four times every day. She however denied any exacerbating factors or weight loss or any other major symptoms. Physical examination was unremarkable. Her past medical history was significant for osteoporosis, myelodysplasia which was treated with chemotherapy in 2013, and a 2-cm stable pancreatic cyst which was likely side-branch intraductal papillary mucinous neoplasms (IPMN) diagnosed on a surveillance MRI in 2021. Her past surgical history included bilateral cataract surgery, sinus surgery, and open appendectomy as a child. The patient is a former smoker who used to smoke ten cigarettes every day for twenty years, she denied alcohol consumption, and her family history is positive for gastric cancer in both parents.

The patient was initially evaluated by a gastroenterologist and underwent an endoscopic ultrasound (EUS) of her pancreatic cyst. During the procedure, a 1-cm gastric ulcer with an erythematous base and heaped-up edges along the lesser curvature of the proximal body was incidentally found on esophagogastroduodenoscopy (EGD). Biopsies were taken and later showed findings consistent with gastric signet cell ring carcinoma that is positive for keratin and CDX-2. EUS at the time of the procedure showed significant hypoechoic thickening involving the 4th sonographic layer (muscularis propria), indicating a tumor size of at least T2. The patient reported that the ulcer has been noticed on a previous endoscopy procedure in 2021, but biopsies were not taken due to low platelet count, at that time due to risk of bleeding. After confirming the diagnosis with the biopsy, the patient was referred to an oncologist who ordered a diagnostic laparoscopy procedure for gastric cancer staging. Peritoneal washing was negative for malignancy, and fluid analysis was notable for elevated carcinoembryonic antigen (CEA), low clonality in the genes Kirsten rat sarcoma virus (K-RAS), and guanine nucleotide binding protein (GNAS).

Subsequently, the patient was cleared and sent for total gastrectomy with Roux-en-Y esophagojejunostomy. The total gastrectomy specimen measured $23 \times 10 \times 3$ cm, 11 cm along the lesser curvature, and 31 cm along the greater curvature. The wall thickness measured 0.3 cm. The mucosa demonstrated a tan-pink fungating mass along the lesser curvature measuring 2.7×2.0 cm, extending 0.9 cm into the lumen, and 0.5 cm through the gastric wall. The mass was located 2.3 cm from the proximal margin, 2.5 cm from the mesenteric margin, 10.5 cm from the distal margin, and 0.2 cm from the serosal surface. The remaining mucosa was unremarkable with no other masses or polyps. Microscopic examination of the gastric specimen and lymph node revealed a poorly differentiated adenocarcinoma invading the muscularis propria into the perigastric adipose tissue (signet-ring cell type) with lymphovascular and perineural invasion. Metastatic carcinoma was found in seven out of seventeen (7/17) lymph nodes with extranodal extension. All margins were free of tumor. The tumor was found to be mismatch repair protein-proficient and human epidermal growth factor receptor 2 (HER-2) negative by immunohistochemistry. The pathology report confirmed the tumor to be pT3 and pN3a in the pTNM classification.

After surgery, a feeding J-tube was placed. The patient was also given one unit of packed red blood cells (pRBCs) and one unit of platelets for low Hgb (6.4) and platelets (48 k), respectively. Her pain was controlled with hydromorphone PCA pump, IV Tylenol, and IV Robaxin. Five days after the surgery, an upper gastrointestinal series (UGI) showed narrowing at the esophagojejunostomy with delayed transit of contrast through the anastomosis without evidence of a leak (Fig. 1). Nasogastric tube (NGT) was then removed, and she was started on sips and PO medication. The patient was also started on Octreotide 100 mcg TID due to bilious output drained through the J-tube. CT abdomen and pelvis were obtained for possible duodenal stump leak (Fig. 2). Results showed no discrete fluid collection, contrast extravasation, free fluid, or free air. At the time of discharge, the patient was hemodynamically stable, tolerating fluids, and having bowel function. Her nausea was controlled with Zofran and Phenergan, and her pain was controlled with Tylenol. She and her family had drain teaching and

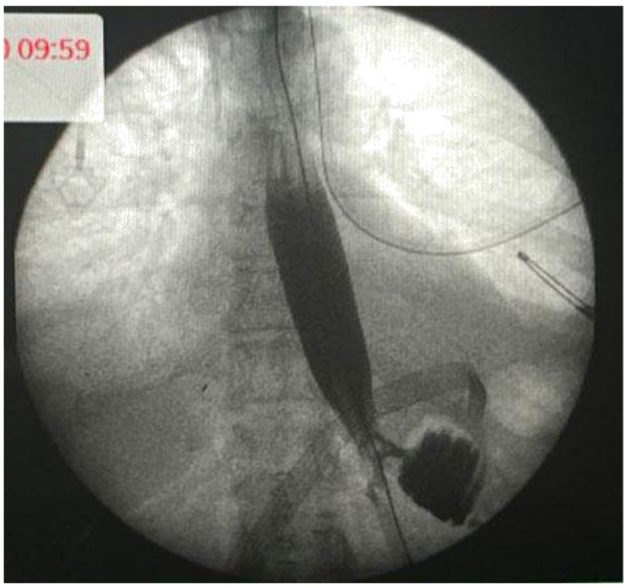

Fig. 1 Upper GI series showing a narrowing at the esophagojejunostomy without evidence of a leak

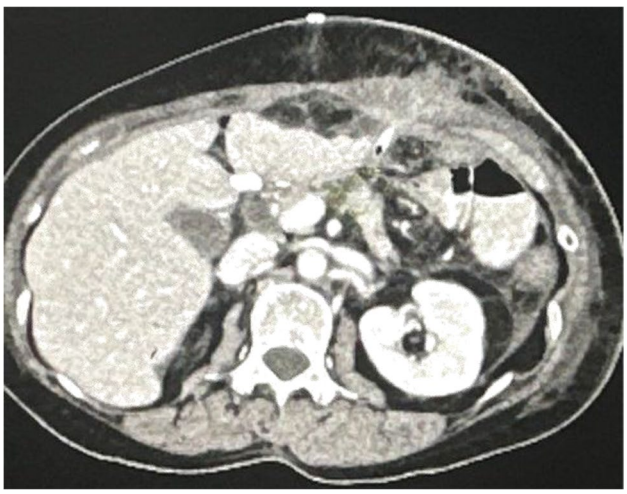

Fig. 2 CT Abdomen after the surgery showing no evidence of a duodenal stump leak

octreotide subcutaneous injection teaching, and the patient was instructed to follow up with her outpatient oncologist.

Discussion

In our case report, we present the case of a 67-year-old female patient who was incidentally found to have a 1-cm ulcer along the lesser curvature on esophagogastroduodenoscopy (EGD). Further investigation revealed that the ulcer was a primary gastric signet ring cell carcinoma (SRCC) invading the muscularis propria into the perigastric adipose tissue and metastasizing to the left gastric lymph nodes (pT3, pN3a, M0). Also, the patient had comorbidities including myelodysplasia and a pancreatic cyst diagnosed with MRI which was suspected to be a side-branch intraductal papillary mucinous neoplasms (IPMN). However, a biopsy of the pancreatic cyst has never been taken.

Gastric cancer (GC) represents a significant health burden, with approximately 1.1 million new cases and 770,000 deaths estimated for 2020 according to the GLOBOCAN database. Incidence rates of GC are higher in males than females, with an average twofold difference (18.3 and 9.6 per 100,000, respectively), although there are variations across countries [6]. Although the overall incidence of gastric cancer has decreased, the incidence of primary gastric cancer is rising worldwide and now comprises about 8–30% of all diagnosed cases of gastric cancer. This increase is attributed to multiple factors, some of which include genetic predisposition (e.g., CDH1 hypermethylation), and lower screening and detection rates in the "low-risk" population in the USA compared to regions such as Japan [7]. SRCC is more commonly observed among young patients compared to non-signet ring cell gastric carcinoma [8–10]. The mean age of presentation is 55–61 years, and it is significantly more common among patients of black, Asian/Pacific Islander, American Indian/Alaska Native, and Hispanic ethnic groups. The incidence among Asian populations is not as high as expected [11]. There are conflicting data regarding the gender distribution of SRCC. Some studies suggest that SRCC is more common in females while others indicate a higher incidence in males [10, 12].

According to the classic Lauren classification, gastric SRCC is classified as gastric diffuse adenocarcinoma, and according to the World Health Organization (WHO) classification, it is considered to be a poorly cohesive gastric carcinoma [13, 14]. In this case report and literature review, we used the definition of SRCC as a type of cancer characterized by the presence of a substantial amount of mucins within the cytoplasm of over 50% of tumor cells [15]. This mucin accumulation occupies a significant portion of the cellular space, resulting in a displacement of the nuclei to the periphery. This distinct morphological feature gives the cancer cells their characteristic appearance. However, a group of experts from the European Chapter of the International Gastric Cancer Association (IGCA) argues that reclassification is needed to standardize SRCC, suggesting that SRCC should specifically refer to cases in which more than 90% of tumor cells exhibit signet ring cell morphology [16].

The meta-analysis by Zhao has identified several risk factors associated with lymph node metastasis (LNM) in early signet ring cell carcinoma, including female gender, submucosal invasion, lymphovascular invasion, and tumor size larger than 20 mm [17]. Patients with early gastric SRCC often present with chronic gastritis-like symptoms, such as

abdominal pain and distension, which can be misdiagnosed as gastritis or peptic ulcer [10]. Gastric SRCC typically spreads horizontally in the lamina propria without invading the gastric epithelium, making it difficult to accurately assess the size and margins of the tumor using endoscopy. However, later in its course, it is characterized by aggressive invasion and abdominal implantation metastasis due to the down-regulation of E-cadherin [10].

Early-stage SRCC has better survival outcomes than other histological types, with the prognosis for patients with advanced disease being worse [15, 18, 19]. The meta-analysis by Zhang showed that early-stage SRCC and non-signet ring cell adenocarcinoma have comparable survival outcomes, but prognosis of late-stage SRCC was worse [8]. This data underscores the importance of diagnosing SRCC at early stages. However, due to the specific clinical characteristics mentioned above, early diagnosis remains a challenge. Modern technological advancements in endoscopy, such as narrow-band imaging, magnifying endoscopy and endoscopic ultrasonography, have significantly improved the accuracy and sensitivity of diagnosis for patients with early-stage SRCC [10]. SRCC tumors when viewed under ME-NBI (magnified endoscopy with narrow band imaging) have either an irregular microvascular pattern or an irregular microsurface with a demarcation line [20]. Early GSRC has a specific "stretching sign" under NBI [21].

Establishing guidelines for the nonsurgical treatment of GC is challenging due to the existence of various options that are adopted differently across continents. Apart from curative surgical resections, other treatment modalities include perioperative chemotherapy, adjuvant chemotherapy, or adjuvant chemoradiotherapy [22]. Kang et al., demonstrated that SRCC is not more aggressive than differentiated cancer and may be considered for endoscopic treatment [23]. Lee et al. found that patients with early gastric cancer with signet cell-type histology can be best treated by gastrectomy with lymph node dissection [24]. Bozzeti et al., in their cohort study of 618 patients, noted that both gastrectomy and subtotal gastrectomy offered similar survival probability; however, they suggest that subtotal gastrectomy might be a better option, due to improved nutritional status and quality of life. [25]. Endoscopic submucosal dissection (ESD) has emerged as a standard treatment option for early gastric SRCC, showing comparable results to surgery when the criteria for ESD selection and evaluation are met [12]. The criteria for endoscopic resection is according to the Japan Gastric Cancer Association guidelines. Endoscopic mucosal resections can be offered for well or moderately differentiated tumors, tumors of size less than 2 cm, tumors limited to the mucosa, and non-ulcerated tumors. For patients with incomplete resection or positive lateral margins, repeat endoscopic resection can be considered. Endoscopic submucosal dissection (ESD) can be offered for well differentiated and ulcerated tumors with size less than 3 cm and limited to the mucosa and for undifferentiated and non-ulcerated tumors with size less than 2 cm and limited to the mucosa. However, studies have found that early SRCC patients who undergo ESD have an unfavorable complete resection (CR) rate. Kim et al. reported a CR rate of 70.7% for SRCC patients, and Bang et al. detected a CR rate of only 36.4% for patients after ESD [26, 27]. Accurate evaluation of tumor size, determination of the resection margin, four-quadrant biopsies, and ESD must be performed if all the biopsies are negative for tumor involvement [10].

Taxane therapy may be effective in the treatment of gastric SRCC. However, the chemosensitivity of SRCC compared to non-SRCC is still unclear and controversial since there are no specific studies in this regard. Perioperative chemotherapy did not show significant benefits in terms of R0 resection rate or survival in a retrospective study of resected SRCC cases [28]. A study by Heger et al. noted that the response to neoadjuvant chemotherapy is rare in gastric SRCC, and, however, it is associated with a better outcome [29]. Rougier et al. demonstrated that fluorouracil in combination with cisplatinum is the most effective way in terms of tumor response in AGC with metastasis. Recent data indicate that SRCC and diffuse gastric cancer are more sensitive to mitomycin C, doxorubicin, and docetaxel than intestinal-type gastric cancer, while they show limited sensitivity to fluorouracil and cisplatin [12]. Kim et al. also indicated the potential benefit of taxane-based chemotherapy in their study [30]. Recent data also indicates that while taxane-based therapy may be more effective in SRCC, studies show benefits in mixed SRCC but conflicting results in pure SRCC according to Chen et al. [31]. However, while chemotherapy significantly impairs the quality of life, results are not always satisfactory. Cunningham et al. found no significant difference between survival and tumor location and time duration of treatment among patients who underwent surgery [32]. Lu et al. in a cohort study of 2,199 patients found that first-line chemotherapy was not associated with better survival [33]. Similar conclusions were found by Lemoine et al. [34]. According to one study, the most effective treatment with an acceptable toxicity profile is a combination of docetaxel, leucovorin/oxaliplatin, and fluorouracil, which may allow surgical resection in initially unresectable patients [35, 36].

The current National Comprehensive Cancer Network (NCCN) guidelines do not individualize management based on histology. Surgical resection is recommended for localized clinical stage I GC, specifically for T1a or T1b tumors. Surgical resection alone offers equivalent survival outcomes to multimodality therapy for patients with concordant pathologic stage I disease. Adjuvant therapy represents a favorable salvage strategy for patients who have been upgraded to stage II or III for definitive pathology [37]. In our case, total gastrectomy was performed, although there is data that total

gastrectomy does not increase overall survival compared to subtotal gastrectomy [38, 39].

Regarding molecular and genetic considerations, one of the most common mutations involved in sporadic SRCC pathogenesis is CDH1 gene mutation [40]. CDH1 gene encodes E-cadherin, although E-cadherin or cytokeratin subtyping do not aid in the identification of signet ring cells [16]. In our patient, CDX-2 staining was performed which turned out to be positive. Although CDX-2-positivity is associated with increased tumor size and higher TNM stage, gastric cancer is more likely to be resectable, and patients with CDX-2 positive gastric carcinomas have better survival rates [41, 42]. This seeming contradiction is probably explained by the early diagnosis of tumors with large size. Although a subset of gastric cancers have HER2 amplification (our patient's tumor was HER-2 negative), HER-2 is not a reliable prognostic factor, and additionally monoclonal antibodies to HER2 have shown limited success in treating gastric cancer, unlike the significant response seen in HER2 positive breast cancer [7, 43]. Our patient was found to have a low probability of microsatellite instability-high (MSI-H). There is data that gastric cancers with MSI-H are characterized by older age at diagnosis, distal tumor location, and increased tumor size [44].

Early diagnosis of signet ring cell carcinoma (SRCC) is of paramount importance in managing the clinical course of the disease. Although many contradictions exist, most studies have reported a worse prognosis for signet cell carcinoma compared to other subtypes [45–49]. As with other subtypes of gastric adenocarcinoma, lymph node metastasis and curative resection are significant factors that affect survival rate [46]. In our case, the patient presented with a previously noted gastric ulcer, but it was not biopsied due to decreased platelet levels as a consequence of myelodysplasia at the time of diagnosis. Consequently, the patient was diagnosed at an advanced stage of the disease and underwent surgical treatment with total gastrectomy. It is worth noting that the gastric SRCC observed in our patient could have potentially originated from the pancreatic cyst, which exhibited features consistent with a side-branch intraductal papillary mucinous neoplasm (IPMN) based on its MRI appearance, as reported by Sakai in a separate case report [50]. However, definitive confirmation of this relationship could not be established.

Conclusion

This study presents the case of a 67-year-old female with progressive abdominal pain, ultimately diagnosed with primary gastric signet ring cell carcinoma (SRCC). A 1-cm gastric ulcer was incidentally found during an endoscopic ultrasound, leading to the SRCC diagnosis. The tumor had invaded the muscularis propria and metastasized to the left gastric lymph nodes. Gastric SRCC, with rising incidence rates, represents a significant health burden globally. Clinical characteristics of SRCC, its subtle endoscopic appearance and horizontal spread in the lamina propria, pose challenges in diagnosing and staging the tumor. Treatment options include resection, perioperative chemotherapy, and adjuvant therapy. Endoscopic submucosal dissection has emerged as a viable treatment option for early-stage SRCC, offering comparable results to surgery, when specific criteria are met. However, the complete resection rate with ESD remains lower for SRCC than for other histological types.

Chemotherapy, particularly taxane-based regimes, may be promising in treating SRCC. However, the chemosensitivity of SRCC compared to non-SRCC remains controversial, and further studies are needed to better understand effective chemotherapy for this subtype.

Mutations in the CDH1 gene, which encodes E-cadherin, are commonly involved in SRCC pathogenesis. Additionally, CDX -2 positivity has been associated with increased tumor size and higher TNM stage, although it may indicate a better prognosis and higher likelihood of resectability. Early diagnosis and appropriate management of gastric SRCC are crucial for improving patient outcomes. Advancements in endoscopic imaging and genetic testing may aid in early detection. Further research is necessary to better understand the molecular and genetic characteristics of SRCC and develop effective, targeted therapies for this aggressive form of gastric cancer.

Declarations

Conflict of Interest The authors declare no competing interests.

References

1. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Cooke D, Corvera C et al (2022) Gastric cancer, Version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 20(2):167–92
2. Drubay V, Nuytens F, Renaud F, Adenis A, Eveno C, Piessen G (2022) Poorly cohesive cells gastric carcinoma including signet-ring cell cancer: Updated review of definition, classification and therapeutic management. World J Gastrointest Oncol 14(8):1406–1428
3. Johnston FM, Beckman M (2019) Updates on management of gastric cancer. Curr Oncol Rep 21(8):67
4. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G et al (2022) Gastric cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 33(10):1005–1020
5. Shen J, Ma X, Yang J, Zhang JP (2019) Digestive tract reconstruction options after laparoscopic gastrectomy for gastric cancer. World J Gastrointest Oncol 12(1):21–36
6. Morgan E, Arnold M, Camargo MC, Gini A, Kunzmann AT, Matsuda T et al (2022) The current and future incidence and mortality

of gastric cancer in 185 countries, 2020–40: a population-based modelling study. EClinicalMedicine 47:101404
7. Sexton RE, Hallak MN Al, Uddin MdH, Diab M, Azmi AS (2020) Gastric cancer heterogeneity and clinical outcomes. Technol Cancer Res Treat. 19:153303382093547
8. Zhang C, Liu R, Zhang WH, Chen XZ, Liu K, Yang K et al (2021) Difference between signet ring cell gastric cancers and non-signet ring cell gastric cancers: a systematic review and meta-analysis. Front Oncol 11
9. Zaafouri H, Jouini R, Khedhiri N, Khanchel F, Cherif M, Mesbahi M et al (2022) Comparison between signet-ring cell carcinoma and non-signet-ring cell carcinoma of the stomach: clinicopathological parameters, epidemiological data, outcome, and prognosis—a cohort study of 123 patients from a non-endemic country. World J Surg Oncol 20(1):238
10. Tang YH, Ren LL, Mao T (2023) Update on diagnosis and treatment of early signet-ring cell gastric carcinoma: a literature review. World J Gastrointest Endosc 15(4):240–247
11. Pernot S (2015) Signet-ring cell carcinoma of the stomach: impact on prognosis and specific therapeutic challenge. World J Gastroenterol 21(40):11428
12. Xu Z, Jin Y, Fang X (2018) Advances in the research of gastric signet ring cell carcinoma. Zhonghua Wei Chang Wai Ke Za Zhi 21(10):1196–1200
13. Laurén P (1965) The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. Acta Pathol Microbiol Scand 64(1):31–49
14. Berlth F, Bollschweiler E, Drebber U, Hoelscher AH, Moenig S (2014) Pathohistological classification systems in gastric cancer: diagnostic relevance and prognostic value. World J Gastroenterol 20(19):5679–5684
15. Zhao B, Lv W, Zhang J, Zhang J, Huang B, Lin J (2020) Different prognostic significance of signet ring cell histology for early and advanced gastric cancer patients: a systematic review and meta-analysis. Expert Rev Gastroenterol Hepatol 14(6):499–509
16. Mariette C, Carneiro F, Grabsch HI, van der Post RS, Allum W, de Manzoni G (2019) Consensus on the pathological definition and classification of poorly cohesive gastric carcinoma. Gastric Cancer 22(1):1–9
17. Zhao X, Cai A, Xi H, Song Y, Wang Y, Li H et al (2017) Predictive factors for lymph node metastasis in early gastric cancer with signet ring cell histology: a meta-analysis. ANZ J Surg 87(12):981–986
18. Kao YC, Fang WL, Wang RF, Li AFY, Yang MH, Wu CW et al (2019) Clinicopathological differences in signet ring cell adenocarcinoma between early and advanced gastric cancer. Gastric Cancer 22(2):255–263
19. Wang Z, Zhang X, Hu J, Zeng W, Zhou Z (2015) Clinicopathological features and outcomes in patients undergoing radical resection for early gastric cancer with signet ring cell histology. J Visc Surg 152(6):357–361
20. Yao K, Anagnostopoulos G, Ragunath K (2009) Magnifying endoscopy for diagnosing and delineating early gastric cancer. Endoscopy 41(05):462–467
21. Phalanusitthepha C, Grimes KL, Ikeda H, Sato H, Sato C, Hokierti C et al (2015) Endoscopic features of early-stage signet-ring-cell carcinoma of the stomach. World J Gastrointest Endosc 7(7):741
22. Machlowska J, Pucułek M, Sitarz M, Terlecki P, Maciejewski R, Sitarz R (2019) State of the art for gastric signet ring cell carcinoma: from classification, prognosis, and genomic characteristics to specified treatments. Cancer Manag Res 11:2151–2161
23. Kang SH, Kim JS, Moon HS, Lee ES, Kim SH, Sung JK et al (2017) Signet ring cell carcinoma of early gastric cancer, is endoscopic treatment really risky? Medicine 96(33):e7532
24. Lee JH, Choi IJ, Kook MC, Nam BH, Kim YW, Ryu KW (2010) Risk factors for lymph node metastasis in patients with early gastric cancer and signet ring cell histology. Br J Surg 97(5):732–736
25. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L (1999) Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian gastrointestinal tumor study group. Ann Surg 230(2):170–8
26. Kim JH, Lee YC, Kim H, Song KH, Lee SK, Cheon JH et al (2009) Endoscopic resection for undifferentiated early gastric cancer. Gastrointest Endosc 69(4):e1-9
27. Bang CS, Park JM, Baik GH, Park JJ, Joo MK, Jang JY et al (2017) Therapeutic outcomes of endoscopic resection of early gastric cancer with undifferentiated-type histology: a Korean ESD Registry Database Analysis. Clin Endosc 50(6):569–577
28. Robb WB, Messager M, Gronnier C, Tessier W, Hec F, Piessen G et al (2015) High-grade toxicity to neoadjuvant treatment for upper gastrointestinal carcinomas: what is the impact on perioperative and oncologic outcomes? Ann Surg Oncol 22(11):3632–3639
29. Heger U, Blank S, Wiecha C, Langer R, Weichert W, Lordick F et al (2014) Is preoperative chemotherapy followed by surgery the appropriate treatment for signet ring cell containing adenocarcinomas of the esophagogastric junction and stomach? Ann Surg Oncol 21(5):1739–1748
30. Kim S, Fiteni F, Paget-Bailly S, Ghiringhelli F, Lakkis Z, Jary M et al (2015) The impact of taxane-based preoperative chemotherapy in gastroesophageal signet ring cell adenocarcinomas. J Hematol Oncol 8(1):52
31. Chen L, Shi Y, Yuan J, Wu Q, Han Y, Qin R et al (2014) Evaluation of docetaxel- and oxaliplatin-based adjuvant chemotherapy in postgastrectomy gastric cancer patients reveals obvious survival benefits in docetaxel-treated mixed signet ring cell carcinoma patients. Med Oncol 31(9):159
32. Cunningham S, Kamangar F, Kim M, Hammoud S, Haque R, Maitra A et al (2005) Survival after gastric adenocarcinoma resection: eighteen-year experience at a single institution. J Gastrointest Surg 9(5):718–725
33. Lu M, Yang Z, Feng Q, Yu M, Zhang Y, Mao C et al (2016) The characteristics and prognostic value of signet ring cell histology in gastric cancer. Medicine 95(27):e4052
34. Lemoine N, Adenis A, Bouche O, Duhamel A, Heurgue A, Leteurtre E et al (2016) Signet ring cells and efficacy of first-line chemotherapy in advanced gastric or oesogastric junction adenocarcinoma. Anticancer Res 36(10):5543–5550
35. Pernot S, Mitry E, Samalin E, Dahan L, Dalban C, Ychou M et al (2014) Biweekly docetaxel, fluorouracil, leucovorin, oxaliplatin (TEF) as first-line treatment for advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: safety and efficacy in a multicenter cohort. Gastric Cancer 17(2):341–347
36. Pernot S, Dubreuil O, Tougeron D, Soudan D, Bachet JB, Lepère C et al (2015) Docetaxel, 5FU, oxaliplatin (TEFOX) in 1st line treatment of signet ring cell and/or poorly differentiated gastric adenocarcinoma: a retrospective study of AGEO. J Clin Oncol 33(15_suppl):e15048
37. Turgeon MK, Gamboa AC, Rupji M, Lee RM, Switchenko JM, El-Rayes BF et al (2021) Should signet ring cell histology alter the treatment approach for clinical stage I gastric cancer? Ann Surg Oncol 28(1):97–105
38. Arer IM, Yabanoglu H, Akdur A, Akkapulu N, Kus M (2017) Total versus subtotal gastrectomy for signet ring cell carcinoma of the stomach. J Coll Physicians Surg Pak 27(10):616–620
39. Moslim MA, Handorf E, Reddy SS, Greco SH, Farma JM (2021) Partial gastrectomy is associated with improved overall survival in signet-ring cell gastric cancer. J Surg Res 266:27–34
40. Pernot S, Voron T, Perkins G, Lagorce-Pages C, Berger A, Taieb J (2015) Signet-ring cell carcinoma of the stomach: impact on prognosis and specific therapeutic challenge. World J Gastroenterol 21(40):11428–11438

41. Xiong ZF, Shi J, Fu ZH, Wan HP, Tu LX (2017) Phenotypic classification of gastric signet ring cell carcinoma and its relationship with K-ras mutation. Genet Mol Res 16(2)
42. Masood MA, Loya A, Yusuf MA (2016) CDX2 as a prognostic marker in gastric cancer. Acta Gastroenterol Belg 79(2):197–200
43. Fisher SB, Fisher KE, Squires MH, Patel SH, Kooby DA, El-Rayes BF et al (2014) HER2 in resected gastric cancer: is there prognostic value? J Surg Oncol 109(2):61–66
44. Seo HM, Chang YS, Joo SH, Kim YW, Park YK, Hong SW et al (2009) Clinicopathologic characteristics and outcomes of gastric cancers with the MSI-H phenotype. J Surg Oncol 99(3):143–147
45. Hu B, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A (2012) Gastric cancer: classification, histology and application of molecular pathology. J Gastrointest Oncol 3(3):251–261
46. Zhang M, Zhu G, Zhang H, Gao H, Xue Y (2010) Clinicopathologic features of gastric carcinoma with signet ring cell histology. J Gastrointest Surg 14(4):601–606
47. Kim JP, Kim SC, Yang HK (1994) Prognostic significance of signet ring cell carcinoma of the stomach. Surg Oncol 3(4):221–227
48. Ribeiro MM, Sarmento JA, Simões MAS, Bastos J (1981) Prognostic significance of Lauren and Ming classifications and other pathologic parameters in gastric carcinoma. Cancer 47(4):780–784
49. Hass HG, Smith U, Jäger C, Schäffer M, Wellhäußer U, Hehr T et al (2011) Signet ring cell carcinoma of the stomach is significantly associated with poor prognosis and diffuse gastric cancer (Lauren's): single-center experience of 160 cases. Onkologie 34(12):682–6
50. Sakai T, Koshita S, Ito K, Kanno Y, Ogawa T, Kusunose H et al (2018) Signet-ring Cell Carcinoma derived from a main duct-type intraductal papillary mucinous neoplasm of the pancreas: a case report with long-term follow-up. Intern Med 57(8):1093–1099