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Gastric Signet Ring Cell Carcinoma: an Overview

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Abstract

Gastric signet ring cell carcinoma (GSRCC) is an important histological type of gastric cancer. Its biological and clinical particularities distinguish it from other gastric cancers in ways that require tailored clinical management and decision-making. This short review provides an overview of what is known about this prevalent clinical entity, highlights recent developments in the research surrounding GSRCC, and covers microbiome, immunology, computational pathology, and clinical research findings.

Keywords: *clinical-updates, gastric cancer, oncology-review, signet-ring-cell, carcinoma*

Review Articles

1. Introduction

The scope of this review is to briefly summarize what is known about the biology and clinical management of gastric signet ring cell carcinoma (GSRCC), as well as to highlight the recent developments and introduce recent reviews that cover several key topics in greater depth. We leveraged modern literature analytics technologies to interactively analyze the citation graph (https://www.researchrabbit.ai/) and identify novel developments in the field of GSRCC.

1.1. Epidemiology

According to GLOBOCAN 2018, stomach cancer is a prevalent cancer with high incidence (>1M new cases in 2018) and was responsible for an estimated 783,000 deaths in 2018 alone (1). Accordingly, gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer death (1). Incidence rates are significantly higher in Eastern Asia in comparison to Northern America and Northern Europe (1).

In high-income countries, the incidence of gastro-esophageal junction cancers has increased (2). Recent studies highlight a decreased incidence rate for the intestinal subtype with non-cardial localization; however, there is increased incidence for both intestinal and Lauren diffuse histological subtypes in gastric cardia and gastro-esophageal junction (GEJ) (2–4).

The incidence of GSRCC has been on the rise, with incidence estimates in the US indicating an increase from 0.3 cases / 100,000 in 1973 to 1.8 cases / 100,000 in 2000 (3). This increase

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happened concurrently with a significant evolution of the histological classification of gastric adenocarcinoma, resulting in the hypothesis that the increase could largely be explained by the increased explicit representation of GSRCC in histological classifications that are widely clinically used. Since 1990, GSRCC has been represented in the WHO classification for gastric cancers as a separate histological type (5).

There are clinical features of GSRCC that are different from those of other gastric adenocarcinomas. For the stomach and GEJ, GSRCC presents at a younger age, at an advanced stage, with lymphatic spread, peritoneal metastasis, rapid progression, and is generally predominant in females (2). There has been much controversy regarding the prognostic value of GSRCC, due to inconsistent results, however, recent research has shown that, for early-stage gastric and GEJ cancer, GSRCC is correlated with better survival in comparison to non-signet cell tumors, whereas the reverse is true for advanced stages (2). For excellent reviews with more coverage of presentation and risk factors, as well as other aspects, see (2,5).

1.2. Classification

It is important to understand where GSRCC resides within the histological classification of gastric adenocarcinomas. Before 1990, GSRCC was not treated as a distinct histological subtype. Instead, it was included within other categories: diffuse by Lauren, infiltrative subtype by Ming, undifferentiated by Nakamura classification, and high grade by The Union International of Cancer Control (UICC) (5). All the enumerated types of tumors are aggressive, suggesting that although GSRCC was not allocated a distinct histological class prior to 1990, it was nevertheless classed within an aggressive family of tumors. Currently, the WHO classification of tumors of the digestive system (6) defines GSRCC as a loosely cohesive adenocarcinoma composed of cancer cells with a mucin-rich cytoplasm and an eccentric, crescent-shaped nucleus. (Fig. 1A).

Molecular classifications for gastric cancers are well-established and include various classifications i.e. intrinsic subtypes, Lei subtypes, The Cancer Genome Atlas (TCGA) subtypes and Asian Cancer Research Group (ACRG) subtypes (7–9).

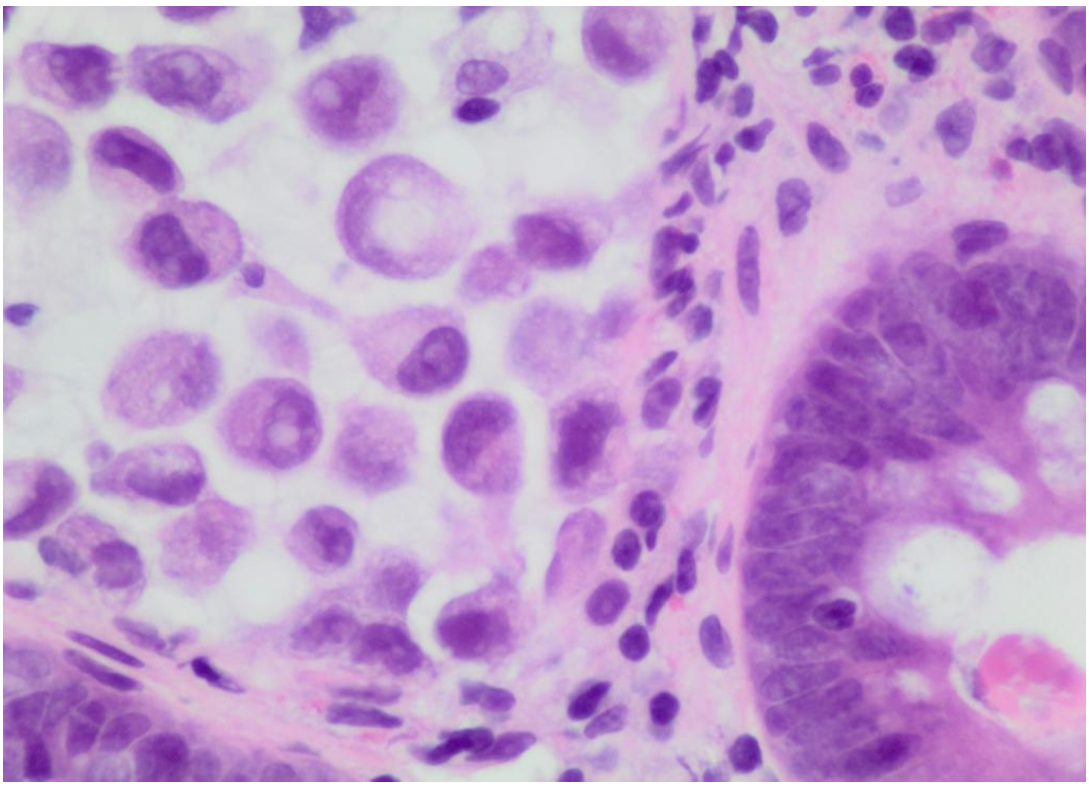

Figure 1A. Gastric signet-cell carcinoma H&E x 40. Image courtesy of Prof. Diana Ionescu - University of British Columbia, Vancouver

The inclusion of GSRCC within a molecular subtype is somewhat inconclusive, possibly due to the fundamental incompatibilities between histological and molecular classifications. Nevertheless, the study that defined the ACRG classification (9), observed that 43.5% of GSRCC belonged to the microsatellite stable/ epithelial-to-mesenchymal transition (MSS/ EMT) molecular subtype, while 8.4% belonged to MSS/TP53$^-$ with other molecular subtypes covering <7%. Although the association was not statistically significant, possibly because of the low sample size for this histological type (37 GSRCC patients). The MSS/EMT subtype by ACRG is closest to the genomically stable subtype of the TCGA classification (10). Including GSRCC in the predominant molecular subtypes of both classifications suggests that it exhibits specific molecular features. Namely, GSRCC bears low mutational load and loss-of-function mutations in cadherin 1 gene (CDH1). The clinical features implied by the molecular classifications are consistent with the observed clinical features of GSRCC, i.e. younger age of presentation, the worst prognosis coinciding with advanced stage GSRCC, and high recurrence rate.

1.3. Molecular alterations

The main pathological hallmarks of GSRCC are cytoplasmic mucin accumulation and decrease in cell-cell adhesion. GSRCC is generally associated with germline mutations in the *CDH1* gene whose product, E-cadherin, is involved in intercellular junctions in epithelia. Radical total gastrectomy with extensive lymphadenectomy is required for patients with *CDH1* mutations (2). Moreover, somatic loss of E-cadherin is characteristic of signet ring cell tumors in multiple organs and has been associated with EMT, a process that is essential to disease progression. E-cadherin loss has been observed to occur early in the progression of GSRCC (2). An interesting question is whether mucin accumulation is a consequence of other oncogenic processes or whether the mucin accumulation itself drives the disease. The latter possibility is supported by strong evidence from mechanistic studies which have identified a positive feedback loop in which mucin 4 activates the ERBB2/ERBB3 complex which, via multiple molecular intermediaries, leads to the loss of junctions and production of mucins (thereby forming the loop), leading to the formation of signet cancer cells (11). Gain-of-function mutations in *RhoA* are specific to the genomically stable molecular subtype of TCGA classification (10), which is the molecular subtype primarily associated with GSRCC. For an excellent recent review that explores in a greater depth molecular alterations, including alterations in other genes, gene fusions, miRNAs, methylation and histone modifications, the reader is referred to (2).

1.4. Clinical management

There are no currently available high-impact and high-confidence recommendations specifically for the clinical management of GSRCC (12). Clinical management is different in early GSRCC and advanced GSRCC or GEJ signet ring cell carcinoma (13), with significant differences in survival: the estimated 5-year overall survival rate in early gastric cancer with signet ring cells is 90.7% and 83.2% in non-signet ring cell carcinoma; for advanced gastric cancer, the estimated survival rate with signet ring cells is 32.1% and 37.9% in non-signet ring cancers. (13). In terms of clinical presentation (13), GSRCC was found to comprise 22.5% of early gastric cancers and, 26.5% of advanced gastric cancers. Note that the presented results originate from the Department of Surgery at Taipei Veterans General Hospital, which could explain the overall higher survival values versus other geographic regions ((The Surveillance Epidemiology, End Results (SEER)) database, an authoritative source of cancer statistics in the US, reports a 27.5% 5-year overall survival rate for GSRCC (Tang et al. 2020)). For recent reviews that detail clinical management, the reader is referred to (2,12,14).

The recommended treatment for early GSRCC is surgery, and endoscopic methods are employed in select cases. This line of treatment differs from that of general early gastric cancers, where endoscopic resection is a recommended option alongside definitive surgery. An important question is whether the

survival rate of early GSRCC is better due to specifics of its tumor biology or other confounding factors. It has been suggested that the better outcomes in early GSRCC with respect to non-signet ring cell gastric cancers could be due to earlier presentation, mucosal restriction of the tumor, and less frequent lymph node invasion (2,5). This suggests that signet ring cell histology is not necessarily an independent predictor for survival. Instead, it appears to be related to survival due to confounding variables such as age of presentation.

Treatment of advanced GSRCC (which is defined by mucosal invasion) is challenging. Although gastrectomy with radical lymph node dissection (D2) is recommended, the role of chemotherapy is not well established (2). In general, perioperative chemotherapy is recommended for advanced gastric cancer (15), but due to the unclear chemosensitivity of GSRCC, it is not clear whether neoadjuvant therapy brings more benefits than the risk of significant disease progression due to the delay of surgery (2). This is supported by studies that have reported no survival benefit from perioperative chemotherapy (16). On the other hand, other studies indicate improved outcomes of neoadjuvant therapy, such as the FLOT4 trial (17), which included a significant proportion of GSRCC cases among all gastric cancer patients, while another study showed improved outcomes in signet ring cell esophagogastric adenocarcinomas (18). Clinical management of advanced GSRCC would greatly benefit from further research into clarifying which treatment algorithms are optimal.

2. Developments

In the following section, we highlight some of the more recent developments in the research of GSRCC biology and clinical management.

2.1. Microbiome

Recent evidence showing the involvement of microbiota in gastric carcinogenesis (19) is not surprising given that the microbiota is beginning to be considered a metabolically active organ (20). Notably, in a recent study (20), investigations have begun delving into the microbiota differences among subtypes of gastric cancer. The authors separately analyzed formalin-fixed paraffin-embedded (FFPE) samples from GSRCC and adenocarcinoma through 16S rRNA analysis. A major result of the study is that there are significant microbial composition differences among GSRCC and gastric adenocarcinoma, differences which could eventually become microbial biomarkers of disease. The phyla Fusobacteria, Bacteroidetes, Patescibacteria, and BC1 were significantly enriched in GSRCC in comparison to gastric adenocarcinoma (20). The authors note that Fusobacteria and Bacteroidetes, phyla which include anaerobic bacteria, have been observed to be enriched in some cancers, including oral and head cancers (20). Fusobacteria could become an important biomarker for GSRCC. Interestingly, the authors evaluated the differences in active microbial metabolic pathways that are implied by the differences in microbial composition. This led to the observation that the pyrimidine biosynthesis pathway is employed by the microbial community that is specific to GSRCC. Pyrimidine metabolism pathways, which have been associated with progression in lung and breast cancer, could therefore represent specific targets within the microbiota in GSRCC r (20,21). Multiple recent emerging reviews cover the exciting area of cancer-related microbiome research (22–24).

2.2. Immunoregulatory landscape

A recent study measured serum levels of certain immunoregulatory molecules (GITR, OX40L and programmed cell death protein 1 PD-1) and identified a 1.25-fold increase in soluble GITR (sGITR) in GSRCC in comparison to adenocarcinomas, suggesting that this could become a marker for discriminating GSRCC (26). Biologically, GITR is expressed on some regulatory T cells (Tregs) and is a co-stimulatory molecule. Clinical trials have attempted to use GITR agonists to inhibit suppressive Tregs in combination with other compounds used as immunotherapies. More broadly, a recent study that explored predictive factors for response to immunotherapy

(specifically anti-PD-L1 therapy) found that the presence of signet ring cancer cells correlates with non-responder status to PD-L1 targeting: within the GSRCC cases, only 1 responder and 18 non-responders to PD-L1 targeting (27). Nevertheless, the authors highlight that there are only a few reports on the clinical impact of immune checkpoint inhibitor markers on signet ring cells in gastric cancer (27). A 2017 study (28) reports an association between signet ring cancer cells and PD-L1, although the association did not appear to affect prognosis. This foreground the observations of Noh et al, who bring evidence for the high association between non-response status and signet ring cancer cells histology. A likely explanation for the low response rates of immune checkpoint inhibitors in this disease is a low total mutational burden.

2.3. Lymph node metastasis

Early gastric carcinoma (not necessarily GSRCC) is often treated with endoscopic resection, but it is important to perform an evaluation for the requirement of surgery after endoscopic resection. This further requires an assessment of lymph node metastasis likelihood. Conventionally, tumor budding (TB, traditionally defined as isolated single cancer cells or <5 cancer cells in the invasive front (29)) is used for evaluation. Nevertheless, a recent study (29) developed a modified tumor budding (mTB) scoring system as a better independent predictor for lymph node metastasis. mTB is evaluated similarly to TB, the difference being in that mTB excludes signet ring cells from its budding evaluation. The authors argue for excluding signet ring cells on the basis that early stage GSRCC has shown favorable survival (29).

Another study (30) developed a novel preoperative biomarker for predicting lymph node metastasis of GSRCC. The authors show that the derived monocyte to lymphocyte ratio (dMLR = monocyte count / (white blood cell count - neutrophil count)) is an independent predictor of lymph node metastasis and exhibits 60.3% sensitivity and 72.2% specificity, making it a potentially promising biomarker.

2.4. Response to neoadjuvant therapy

A recent study (31) brings further evidence for the association between the presence of signet ring cancer cells and the decreased likelihood of response to standard regimens of neoadjuvant therapy. The authors note that gastric cancer is a heterogeneous disease and that the current approach does not rely on patient selection, but rather on administering broad clinical trial-based regimens to all patients, which is likely leading to many patients not benefiting from neoadjuvant chemotherapy (31). It is therefore suggested that further efforts should be taken to develop methods for effectively predicting response to neoadjuvant therapy.

2.5. Clinicopathological characteristics, prognosis and treatments

An interesting study (25) sheds new light on the impact of GSRCC histology on prognosis, a question which, as previously noted, confused the field due to unsatisfactory and contradictory results. The single-center study investigated the issue by comparing mucinous gastric cancer (a rare histological subtype) and GSRCC, and observed that patients with GSRCC have overall worse survival rates, but that mucinous gastric cancer was predictive of poorer prognosis at an early stage (25), which is consistent with the more general tendency that has been observed when comparing GSRCC to other gastric cancers. The differences were observed when comparing cancer-specific survival (CSS), as opposed to overall survival (OS).

Another recent study reevaluates GSRCC clinicopathological data (32) in order to attempt to clarify some of the more controversial findings, including some of those discussed in this text. The study brings solid evidence to further support that there are distinct features that separate GSRCC from gastric adenocarcinoma. Moreover, independent prognostic factors are inferred: age, T stage, N stage, surgery, tumor size and tumor site (32). Being independent, these factors are effectively employed into the design of a nomogram for predicting overall survival with high accuracy. Nomograms are

commonly used tools in oncology and medicine (33) that allow for rapid and user-friendly computation, e.g. of probabilities and scores. Wei et. al show that GSRCC occurs more frequently in the middle and lower stomach region and that GSRCC is more likely to have bone metastasis (in comparison to other gastric cancers, which tend to have liver and lung metastasis). Importantly, the study found that signet ring cancer cell histology is not independently associated with mortality when disease stage is controlled for, in which case signet ring cell carcinoma is not more aggressive than differentiated cancers (32).

There is a lack of consensus on the optimal non-surgical treatment of GSRCC. This is compounded by the observed lack of chemosensitivity of GSRCC. Therefore, a promising direction is the exploration of targeted therapies for approaching pathways relevant to GSRCC, such as EMT, through chemical inhibitors, monoclonal antibodies or other targeting approaches (12). One active clinical trial has been identified on clinicaltrials.gov (ID NCT03355612) that explores XELOX (oxaliplatin with capecitabine) vs Apatinib with XELOX. Apatinib is a tyrosine kinase inhibitor targeting VEGFR2 that has been previously explored in metastatic gastric adenocarcinoma.

2.6. Classification in whole slide images

Due to cellular morphology and diffuse invasion, GSRCC tends to be more difficult to detect by pathologists (34) (Fig.1B). More precisely, false negatives may occur because of signet ring cancer cells' resemblance to crushed oxyntic glands, crushed mucous neck cells, goblet cells of intestinal metaplasia, and gastric xanthoma (34). In this regard, computational pathology has made progress in developing assistive tools to improve GSRCC detection by pathologists. These efforts have been facilitated by the increasing digitization of Haematoxilin and Eosin slides into whole slide images (WSIs). A recent study (34) successfully developed a deep learning system for signet ring cell carcinoma WSI classification (ROC-AUC = 0.99). The tool has good performance, and can highlight regions with high density of signet ring cancer cells on top of WSI, allowing for interpretation of the tool's output and assisting pathologists by guiding the focus to specific regions that are more likely to harbor signet ring cancer cells.

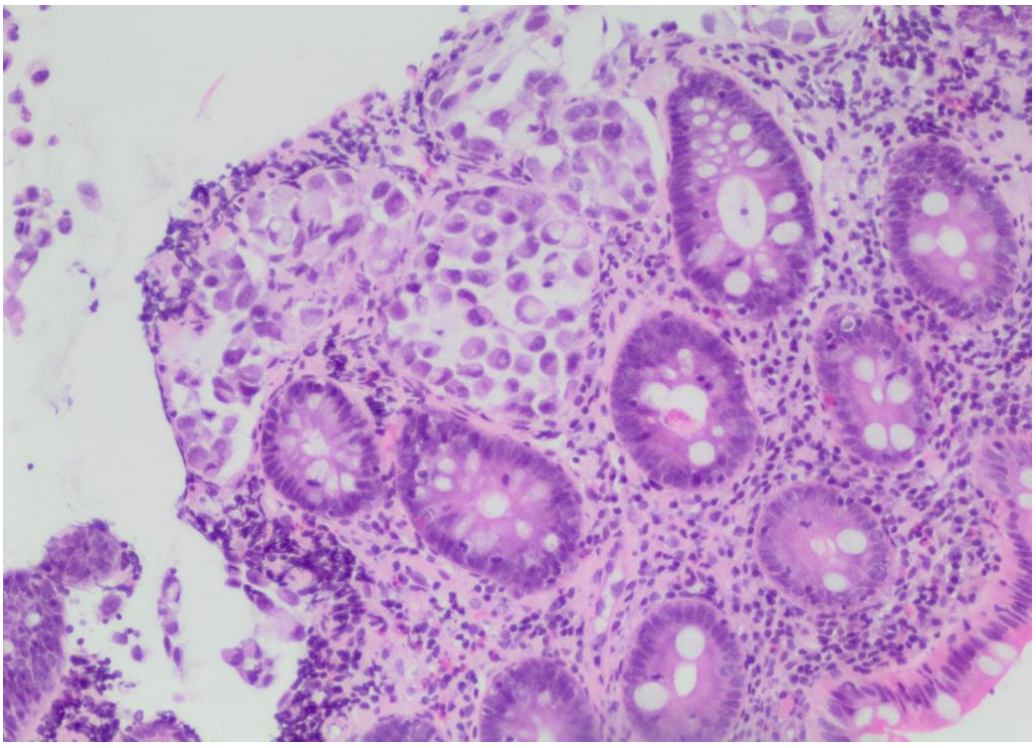

Figure 1B. Gastric signet-cell carcinoma H&E x 10. Image courtesy of Prof. Diana Ionescu - University of British Columbia, Vancouver

3. Conclusion

Research into gastric signet ring cell carcinoma is on the rise, with 135 research papers published in 2021 alone, as identified using PubMed. Comprising an estimated 16.9% of all gastric cancers (35), it remains a prevalent clinical entity that distinguishes itself from other gastric cancers and identifies a population of high unmet medical need and thus requires further results for guiding optimal.

Abbreviations:
ACRG - Asian Cancer Research Group
CSS - cancer-specific survival
dMLR - derived monocyte count to lymphocite ratio
EMT - epithelial-mesenchymal transition
FFPE - formalin-fixed, paraffin-embedded
GEJ - gastroesophageal junction
GSRCC - gastric signet ring cell carcinoma
MSS - microsatellite-stable
OS - overall survival
ROC-AUC - area under the curve for receiver operating characteristic curve
PD-1 - programmed cell death protein 1
SEER - surveillance, epidemiology, end results
TCGA - The Cancer Genome Atlas
TNM - Tumor, nodes, metastasis classification of malignant tumors
Tregs - regulatory T cells
UICC - The Union International of Cancer Control
U.S.- United States
VEGFR - vascular endothelial growth factor receptor
WSI - whole slide images

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