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Review Article

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Advances in Endoscopic Detection and Therapeutic Strategies for Early Gastric Signet Ring Cell Carcinoma

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Abstract

Signet ring cell carcinoma (SRCC), a highly aggressive adenocarcinoma, characteristically presents with mucin-filled cytoplasm that displaces the nucleus, creating its namesake signet ring appearance. While predominantly found in the stomach, SRCC also affects various organs, manifesting with a unique histopathological profile. Atypical clinical presentations often result in delayed diagnosis, leading to the historically poor prognosis. However, narrow-band imaging (NBI) combined with magnetic endoscopy (ME) and endoscopic ultrasonography (EUS) have revolutionized early detection, leading to a paradigm shift in SRCC management. Narrow-band imaging-magnifying endoscopy (NBI-ME), in particular, has been instrumental in enhancing the visualization of early SRCC, marked by an unclear demarcation line and disrupted microvascular and surface microstructure patterns. Similarly, EUS delineates the invasion depth of SRCC and is instrumental for preoperative staging. However, challenges persist, such as determining precise lesion boundaries and the depth of infiltration—critical factors influencing the decision for endoscopic resection. This article reviews the current knowledge and updates pertaining to the endoscopic diagnosis and treatment of early-stage SRCC. The therapeutic advancements achieved by endoscopic submucosal dissection and endoscopic mucosal resection in the treatment and management of early-stage SRCC were also discussed. Overall, this compendium advocates for continued clinical refinement and research to further enhance early diagnostic precision and expand the therapeutic prospects for SRCC, ultimately improving patient survival and quality of life.

Keywords: Signet ring cell carcinoma (SRCC); Endoscopic imaging techniques; Early detection and diagnosis; Endoscopic Therapy; Endoscopic submucosal dissection (ESD); Prognosis and survival rates.

Introduction

Recognized globally as a unique and highly malignant subtype of adenocarcinoma, signet ring cell carcinoma (SRCC) primarily exhibits its histological presence in the stomach.[1,2] Additionally, this peculiar neoplasm has the potential to originate in other organs, including the colon, rectum, appendix, and breast.[3,4] Research also indicates a higher incidence in younger individuals and a slight male predilection, with SRCC showing more aggressive tendencies than other types of adenocarcinomas.

What sets SRCC apart is its characteristic histopathological appearance resembling signet rings, a result of the mucin-filled cytoplasm sweeping the nucleus to the cell periphery.[4] This standout trait effectively distinguishes it from other adenocarcinomas, highlighting the prominence of unique cellular attributes. SRCC primarily comprises low-adhesion tumor cells, demonstrating properties such as diminished E-cadherin expression, increased invasiveness, and a propensity for distant as well as peritoneal implant metastasis.

Historically, SRCC still poses considerable challenges due to its subtle onset of symptoms, often leading to late-stage diagnosis and frequent metastasis.[5] This late detection has significantly contributed to poor prognosis, with a 5-year survival rate ranging from 9–48%.[6] Recently, however, there have been significant improvements in early diagnosis and treatment techniques for gastric SRCC due to advancements in endoscopic technology.

Epidemiology and clinical symptoms of early gastric SRCC

The incidence of gastric SRCC varies by country. According

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to various studies, the proportion of gastric SRCC among all gastric cancers is 15% in Korea, 10% in Japan, 6–15% in China,[7] and 25–30% in the United States and European countries.[8] Compared to non-SRCC, this disease is more common among females and young patients.[8]

Early gastric SRCC often lacks typical clinical manifestations, with the majority of cases resembling chronic gastritis, such as abdominal pain and distension, leading to potential misdiagnosis as gastritis or peptic ulcers. Poor treatment outcomes following long-term medication or symptoms such as weight loss, ascites, and gastrointestinal bleeding may warrant gastroscopy. By that stage, the disease is often advanced, leading to lower surgical cure rates and poorer prognoses. Reports indicate 43% of early gastric cancers are SRCCs.[9,10] Early gastric SRCC tends to have shallower invasion depths and fewer lymph node transfers. SRCC in its advanced stage is more invasive, with a higher rate of lymph node transfer and a poorer prognosis, with a five-year survival rate of only 31.9%.[9]

Diagnostic methods for early gastric SRCC

Narrow-band imaging (NBI) combined with magnifying endoscopy (ME)

NBI, an advanced imaging modality, has markedly revolutionized endoscopic diagnosis and treatment.[11] When combined with ME it offers clinicians unprecedented detail, facilitating early detection and stratification of numerous gastrointestinal neoplasms. This innovative fusion of technologies enhances visualization of the microsurface structure and vascular pattern of gastroenterological lesions, providing an inherently non-invasive but highly insightful solution for early cancer detection.[12] By efficiently contrasting mucosal and vascular components, the NBI-ME conjunction enhances the delineation of both benign and malignant lesions, improving the accuracy of histopathological diagnoses. As endoscopic research and practice strides into an era of prevailing technological advancement, the amalgamated NBI-ME system signifies a groundbreaking turn towards exhaustive in vivo diagnostics.[13]

Clinically, various classification systems regarding microvessels and surface microstructures under NBI combined with ME have been identified, with the "VS classification" system being the most common.[13–15] A clear boundary line between normal and abnormal mucosa is a significant marker of suspected carcinogenesis. In a study with 100 early gastric cancer patients, 97% of the lesions had a distinct demarcation line.[14]

Early gastric SRCC has unique characteristics, including an unclear demarcation line; the disappearance of the surface microstructure, or the presence of an irregular surface microstructure represented by an enlarged interpit spacing; and unevenly distributed micro-vessels, which appear twisted, expanded, or even broken without forming a grid, with typical micro-vessel structures being spiral.[16,17] Phalanusitthepha *et al*. discovered that early gastric SRCC has a distinct "stretching sign" under NBI.[16] This sign denotes the dilation and stretching of the irregular microvasculature and stomach glands that are not discernible in non-SRCC patients. Based on these features combined with changes in color fading observed under a conventional white-light endoscope, early gastric SRCC can be diagnosed. In a study of 12 early gastric SRCC lesions, the gastric mucosal surface structure was examined using narrow-band imaging combined with ME and indigo carmine staining.[18] All lesions demonstrated irregular surface microstructures and irregular micro-vessel structures under NBI technology combined with ME. Additionally, there was the manifestation of "expansion sign" i.e., the extension or expansion of the surface microstructure and micro-vessels.[16] An animal experiment study revealed that SRCC originates from the proprium of the gland neck and spreads to the submucosal layer, suggesting that SRCC proliferation in the proprium causes the formation of tumor cell groups, resulting in the "expansion sign" observed during endoscopy. Subsequently, upon histological examination of the resected specimens, infiltration of tumor cells was found in the expanded and edematous mucosal layers. Thus, SRCC can be identified by the expansion or "expansion sign" of the surface microstructure and micro-vessels, allowing for its early diagnosis through NBI combined with ME. A retrospective study of 14 early gastric SRCC cases revealed that NBI all showed a clear, solitary white region. According to the shape of the white area, i.e., the "circle" index, a complete "circle" index was 1, with the index decreasing as the deviation from completeness increased. SRCC showed a higher degree of completeness compared to non-SRCC. The diagnostic value of the "circle" index was then evaluated, with both sensitivity and specificity at 85.7%. Finally, regression analysis revealed the "circle" index to be an essential predictor of SRCC.[19] Case reports of early gastric SRCC demonstrated that irregular gastric pits, intra-mucosal vascular proliferation, and further magnification revealing increased irregularity in the gastric glandular structure, along with microvascular rupture observable under NBI combined with ME.[20]

In summary, studies on the diagnostic value of NBI combined with ME for SRCC have revealed its crucial role in early SRCC diagnosis. It is imperative to master these techniques skillfully in clinical practice to improve the diagnostic accuracy of early gastric SRCC.

Endoscopic ultrasonography (EUS)

Since its inception, EUS has transformed modern gastroenterological diagnostics and therapeutics, leaving an indelible mark in the realm of endoscopy.[21] Distinguished for its unique combination of endoscopy and high-resolution ultrasonography, EUS allows for enhanced visualization and analysis of the gastrointestinal tract and adjacent structures. Additionally, the versatility of EUS extends beyond diagnostics to therapeutic applications, including pseudocyst drainage, targeted tumor ablation, and EUS-guided biliary and pancreatic duct drainage.[22] These innovations have resulted in less invasive alternatives to traditional surgical modalities, reinforcing its prominence in the medical field. Despite the continuous evolution of its techniques, appropriate training and proficiency development remain crucial for fully harnessing the potential of EUS. Among emerging technologies, EUS stands firm in initiating a dynamic shift in gastroenterological diagnostics and treatment, serving as an unparalleled tool that embodies the promising future of endoscopic innovation.[23]

EUS clearly elucidates the depth of tumor infiltration, and intrusions on surrounding tissue and organs, thereby aid-

ing in lymph node staging. EUS has an accuracy rate of 64.8–92% in predicting the depth of tumor infiltration.[24,25] Kuroki *et al* reported that EUS has better sensitivity, specificity,[26] and accuracy in terms of diagnosing infiltration depth for mucosal tumors than conventional endoscopy. A meta-analysis revealed that the overall Sen, Spe, and diagnostic advantage ratio of EUS in diagnosing early gastric cancer (EGC)invasion depth were 0.87 (95% CI: 0.86–0.88), 0.67 (95% CI: 0.65–0.70) and 18.25 (95% CI: 12.61–26.39), respectively. The area under the summary receiver operating characteristic curve was 0.8861, indicating that EUS has a medium value for diagnosing the invasion depth of EGC.[27] Early gastric SRCC tends to spread individually or in small nests, which greatly diminishes the diagnostic accuracy of EUS.[28,29] Nonetheless, EUS can aid in preoperative staging and resectability assessment of early gastric cancer. The absolute indications and expanded indications for endoscopic resection (ER) originate from the Japanese gastric cancer treatment guidelines.[30] The presence of ulcers and indications for ER are two fundamental misdiagnosis risks from EUS, which can guide the understanding of indications for ER in early gastric SRCC. The accuracy rate of EUS in preoperative lymph node staging ranges from 65% to 95%, with a sensitivity and specificity of 71% and 49%, respectively.[31] Pei *et al*. reported that the accuracy,[32] sensitivity, and specificity of preoperative EUS for lymph node staging were approximately 65–95%, 0.82% and 0.68%, respectively. Although EUS is widely used to predict the depth of tumor invasion and lymph node metastasis (LNM) in GC patients, further investigations should be conducted to assess the value of EUS in diagnosing invasion depth and LNM in GSRC patients.

White light endoscopy (WLE)

With the introduction of WLE, traditional endoscopy has made a profound leap.[33] Currently at the forefront of gastroenterology, WLE is a paramount technology that enhances diagnostic precision and therapeutic potential. It achieves comprehensive visualization of the gastrointestinal tract by utilizing a white light spectrum. The striking advantage of WLE lies in its ability to augment mucosal and submucosal details, thereby allowing the detection and characterization of subtle lesions that might evade conventional modalities.[34] Through the integration of high-definition and high-magnification capabilities, WLE provides an unprecedented, articulated view of the gastrointestinal environment. The resulting high-resolution images offer improved detection rates and facilitate effective delineation between benign and malignant pathologies. Additionally, WLE is instrumental in guiding therapeutic interventions.[35] It is important to highlight that the comparative simplicity of WLE coupled with its potential clinical implications underscore its emergent use in gastroenterological practices. Furthermore, the continual advancement in WLE technology promises great potential in expanding its application, thereby enriching the landscape of endoscopic procedures and profoundly influencing patient outcomes.[36]

Lesions primarily manifest as a change in color tone, appearing whitened compared to the surrounding normal tissue, often located in the body of the stomach, and frequently present as flat and concave types. Elevated types are sparsely observed, but they can also present as erosions or ulcers. Some patients visit due to Krukenberg tumors in the bilateral ovaries, and the final gastroscopy uncovers gastric SRCC.[8] Therefore, it is mandatory to note the following lesions during endoscopic examination: flat and concave lesions with color tone change; lesions located in the stomach body; and multifocal erosion or ulceration. It is necessary to actively biopsy for the above signs, and a histopathological examination is essential, such as multiple collections and deep collections.[37,38] If required, regular reviews and repeated biopsies are necessary for early diagnosis.

Emerging endoscopic techniques for SRCC

The gold standard in tumor diagnosis is histopathology, necessitating endoscopic biopsy for confirmation. However, biopsies are time-consuming, can result in fibrosis at the biopsy site, and can increase the risk of bleeding, particularly for patients on antithrombotic medications, all of which can interfere with endoscopic therapy.[20] Emerging endoscopic methodologies, such as fluorescence micro-endoscopy, confocal micro-endoscopy, and endocytic cytology, provide real-time in vivo micro-imaging contributing to the feasibility of observing live cells (virtual biopsies) within the body. Gastric early-stage SRCC under fluorescence microendoscopy reveals irregular gastric mucosal structures, large and irregularly shaped dark cells, and atypically thickened cellular borders.[20] After employing a filtering function of the digitizing procedure, there is a visible congregation of mucin-producing cells where nuclei are predominantly peripheral.[20] Confocal microendoscopy can distinguish gastric cancer from normal gastric mucosa by evaluating the mucin phenotype via brush borders and goblet cells.[39] Early gastric SRCC under confocal micro-endoscopy shows the disappearance or disruption of normal glandular structures; reduced, irregularly shaped microvessels; atypical dark cells, and numerous vacuolated cells. Endocytic cytology visualizes the superficial mucosa (to a depth of 50 μm), allowing the examination of signet ring cell components in resected gastric specimens, although corresponding research has been limited.[39]

The efficient application of these diagnostic techniques necessitates a thorough understanding of the histological characteristics of early gastric SRCC. For instance, while gastric SRCC may be more prone to horizontal spreading, various subtypes possibly exist. Further in-depth immunohistochemical studies are required to elucidate the biological behavior of gastric SRCC.

Risk factors for lymph node metastasis

The lymph node metastasis rate for early gastric SRCC ranges between 5.3% and 10.7%.[40,41] Although the overall rate of lymph node metastasis is high, a study by Ha *et al*. revealed that SRCC, which is intramucosal,[42] has a diameter ≤2 cm and lacks vascular invasion, shows no lymph node metastasis. Another study involving 419 cases with early gastric SRCC revealed that when the lesion was intramucosal, had a diameter of <1.5 cm, and lacked vascular invasion, the rate of lymph node metastasis was 0%.[40,43] However, another study reported that SRCC with a diameter of <1 cm, without vascular invasion and confined within the mucosa, does not metastasize to lymph nodes.[44,45] These findings provide robust support for endoscopic treatment of early gastric SRCC.

Independent risk factors for lymph node metastasis in early gastric SRCC include a diameter >2 cm, submucosal invasion and vascular invasion.[44] Undifferentiated and mixed types (mixed components include high, medium, or low differentiated adenocarcinoma) are also risk factors, with mixed-type SRCC exhibiting more aggressive behavior, such as deeper submucosal invasion, greater diameter, and a higher lymph node metastasis rate. The reason for the aggressive nature of mixed-type SRCC is thought to be related to increased expression of proteins such as Ki-67, EMMPRIN, and VEGF in ring cell carcinoma, which promotes cell proliferation, apoptosis, angiogenesis, mucin secretion, and cell adhesion, along with associations with high CpG island methylation.[46] While previous studies did not consider ulceration, in a study by Hirasawa *et al*.,[47] it was found that undifferentiated (low-differentiated and signet-ring cell) early gastric adenocarcinoma satisfying the conditions of a diameter <2 cm, absence of vascular invasion, and no ulceration show no lymph node metastasis, highlighting the importance of ulceration.[48] It is possible that earlier studies on early gastric SRCC included fewer cases, which underscores the need for further investigations with larger sample sizes. The research on the risk factors for lymph node metastasis in early gastric SRCC, but a consensus has yet to be reached, necessitating large prospective cohort studies to confirm the definitive risk factors for lymph node metastasis.

Endoscopic therapy

The current endoscopic treatments for early gastric cancer primarily include endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR).[49] Patients meeting absolute indications can undergo EMR, and those fulfilling expanded indications may undergo ESD. These procedures can reduce the need for surgical treatment and better maintain normal digestive tract function.[50]

Based on the above studies on the lymph node metastasis rate of early gastric SRCC, early gastric SRCC is appropriate for endoscopic surgery when the indications include being intramucosal, having a diameter ≤2 cm, and lacking vascular invasion.[51] In a study of early gastric SRCC patients (79.4%, 77/97) undergoing ESD therapy, the en bloc resection rate was 99.0% (96/97), the R0 resection rate was 90.7% (88/97), and the curative resection (CR) rate was 63.9% (62/97). In terms of complications, the delayed bleeding rate was 4.1% (4/97), the intraoperative perforation rate was 3.1% (3/97), and the delayed perforation rate was 1.0% (1/97). No intraoperative bleeding occurred, and the 5-year cumulative incidence of metachronous gastric cancer in patients with CR was 11.4%.[52] Another Korean study reported an en bloc resection rate of 93.3% (83/89) after ESD for early gastric SRCC, a complete resection rate of 83.1% (74/89), and a CR rate of 37.1% (33/89), with a delayed bleeding rate of 1.1% (1/89) and a perforation rate of 2.2% (2/89).[53] Thus, although CR rates are lower with ESD for SRCC than with differentiated gastric cancer, preoperative evaluation and careful postoperative follow-up are necessary, paying attention to the development of metachronous cancer.[54]

Studies have also shown that early SRCC patients undergoing ESD have an unfavorable CR rate. For example, Kim *et al*. reported a CR rate of 70.7% for SRC patients,[55] while Bang *et al*. detected a CR rate of only 36.4% for patients who achieved CR after ESD.[53] For CR, the following considerations are crucial preoperatively. First, the tumor size must be determined. Tumors with a diameter ≥2 cm at endoscopic biopsy are easily underestimated. Early gastric SRCC presents as an irregular surface microstructure and a spiral or destructive interrupted microvessel pattern under NBI combined with ME, aiding in the determination of lesion size. Therefore, endoscopists should be aware that the actual diameter of early gastric SRCC is larger than the typical area observed, and thorough evaluation is required to determine the size of the lesion. Second, the determination of tumor boundaries is critical. Due to the different growth patterns of early gastric SRCC from other tumors, it tends to spread laterally beneath the epithelium, especially in areas of surrounding mucosa showing atrophy or intestinal metaplasia. Third, judgment of tumor infiltration depth is crucial. The accuracy of NBI combined with ME to predict infiltration depth is 78.9%.[49,56] Although the accuracy is not high, combining endoscopic ultrasonography and NBI aids in the prediction of tumor depth. Furthermore, discerning ulcers during the early stages of the disease can be challenging under endoscopy. Moreover, only with ESD can an entire piece be accurately assessed based on postoperative pathological findings. Addressing these issues can improve the cure rate of early gastric SRCC endoscopic therapy, necessitating more clinical research on precisely evaluating early gastric SRCC endoscopic resectability.

The requirement for additional surgery after ESD and follow-up work is also critical. For patients with non-CR, we strongly recommend additional surgery due to the high rate of lymph node metastasis and recurrence. The choice of surgical method is dependent on the decisions made by the surgeon. Procedures such as laparoscopic radical gastrectomy are feasible, with a prognosis similar to that of open gastrectomy, minimal surgical complications, less intraoperative blood loss, shorter hospital stays, and lower recurrence rates. For patients with CR, close follow-up is needed. Regular gastric endoscopy biopsy and chest and abdominal CT scans can determine whether there is recurrence or metastasis, and if recurrence occurs, additional surgery or ESD is necessary.

Prognosis of SRCC

The prognosis of early-stage SRCC of the stomach remains controversial, but most studies indicate a favorable outcome.[57] In a study involving ESD treatment for early gastric SRCC (79.4%, 77/97), with a median follow-up time of 36 months, the 5-year mortality rate for CR was 7.0%, the five-year mortality rate for non-CR plus additional surgery was 6.7%, whereas non-CR without supplementary surgery had a 5-year mortality rate of 17.5%.[52,58] When comparing long-term results of early gastric SRCC patients undergoing ESD and surgical treatment, of the 111 ESD patients, 73 had SRCC, while out of the 382 patients undergoing surgery, 253 had SRCC. Although the disease-free survival rate was lower in the ESD group than in the surgery group (93.1 months vs 117.8 months, $p < 0.001$), the overall survival rate was not significantly different (99.8 months vs 114.5 months, $p = 0.286$), with a 5-year survival rate of 96.6%.[32] The long-term prognosis of ESD is comparable to that of surgery, supporting the application of ESD treatment for early gastric SRCC

patients.[59] The 5-year survival rate of early gastric SRCC is 99.7%, whereas those of differentiated and undifferentiated adenocarcinoma are 99.1% and 97.2%, respectively.[42] There is no clear evidence that it is worse than other histological types (highly differentiated adenocarcinoma or poorly differentiated adenocarcinoma).

A meta-analysis indicates that SRCC is a better prognostic factor for early gastric cancer (HR = 0.57, p = 0.002), considering characteristics such as a higher percentage of depressed lesions (OR = 2.11, p = 0.022), more instances confined to the mucosa (OR = 1.68, p = 0.001), a lower lymph node metastasis rate (OR = 0.68, p = 0.054), and a high concentration of mucin-filled cytoplasm and eccentric nuclei in depressed lesions, enabling earlier detection during endoscopic examination and biopsy pathology.[60] Furthermore, this difference might also be related to the younger age group of patients with early gastric SRCC.

Conclusions

In summary, early gastric SRCC exhibits distinctive biological behavior with a favorable prognosis. White light endoscopy and NBI combined with ME provide relatively typical manifestations, while endoscopic ultrasonography plays a vital role in determining tumor infiltration depth and regional lymph node metastasis. Lesions qualifying for expanded indications of early gastric SRCC can be treated through endoscopic resection. Postoperative pathological evaluations are essential for establishing a rational follow-up plan. The ongoing studies on the clinical pathology features resulting from its biological behavior aims to improve early detection rates of SRCC through endoscopy and offer more patients the opportunity for early minimally invasive treatment, thereby increasing five-year survival rates and quality of life. Currently, the clinical exploration of methods for diagnosing and treating early gastric SRCC still has a long way to go and requires more clinical data accumulation.

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Conflict of interest

The authors have no conflicts of interest related to this publication to declare.

Author contributions

Conceptualization: FY, CM; data curation: JX, FY, MC; formal analysis: JX, SW; methodology: LR, ZT, TM; investigation: MC, CM; visualization: JX, XL; project administration: ZT, TM; funding acquisition: TM; validation: MC, SW, XL; supervision: LR, CM, XL, ZT; writing-original draft: JX, FY; writing review & editing: FY, LR, TM. All authors revised the manuscript critically and approved the version to be published.

Abbreviations

SRCC, signet ring cell carcinoma; NBI, narrow-band imaging; ME, magnifying endoscopy; EUS, endoscopic ultrasonography; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; WLE, white light endoscopy.

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