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ABOUT COVER

Peer Review of *World Journal of Gastroenterology*, Konosuke Nakaji, FACP, MD, Doctor, Endoscopy Center, Aishinkai Nakae Hospital, Wakayama-shi 640-8461, Japan. parupurikopui@yahoo.co.jp

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EDITORIAL

Advancements in non-invasive diagnosis of gastric cancer

Zhen Wang, Qi Wu

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Abstract

Gastric cancer (GC), a multifaceted and highly aggressive malignancy, represents challenging healthcare burdens globally, with a high incidence and mortality rate. Although endoscopy, combined with histological examination, is the gold standard for GC diagnosis, its high cost, invasiveness, and specialized requirements hinder widespread use for screening. With the emergence of innovative technologies such as advanced imaging, liquid biopsy, and breath tests, the landscape of GC diagnosis is poised for radical transformation, becoming more accessible, less invasive, and more efficient. As the non-invasive diagnostic techniques continue to advance and undergo rigorous clinical validation, they hold the promise of significantly impacting patient outcomes, ultimately leading to better treatment results and improved quality of life for patients with GC.

Key Words: Gastric cancer; Non-invasive; Diagnosis; Imaging; Prognosis

Core Tip: Non-invasive diagnostic methods for gastric cancer (GC) involve various techniques that minimize patient discomfort and potential complications. These approaches aim to detect early signs of the disease or identify individuals at risk for GC.

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INTRODUCTION

Gastric cancer (GC) refers to the uncontrolled growth and proliferation of abnormal cells in the stomach lining, which can eventually invade adjacent tissues and disseminate to distant organs[1,2]. GC poses a significant global health burden, with a high incidence and mortality rate, especially in developing countries. In 2022, China reported approximately 358700 new GC cases, accounting for roughly 30%-40% of the total global incidence[3,4]. The high incidence of GC in China is attributed to multiple factors, such as widespread *Helicobacter pylori* infection, dietary habits, smoking, alcohol consumption, and genetic predisposition. Early diagnosis of GC is crucial for improving patient outcomes and reducing mortality. At an early stage, GC is often curable through surgical resection, with five-year survival rates approaching 90% [5-7]. However, as the disease progresses, survival rates decline dramatically, highlighting the importance of timely intervention. Traditionally, the diagnosis of GC relied heavily on invasive procedures such as endoscopy and biopsy, which are both uncomfortable for patients and carry a risk of complications. Endoscopy allows for direct visualization of the stomach lining and the collection of tissue samples for histological examination, which is considered the gold standard for GC diagnosis[5,8]. However, the high cost, invasiveness, and requirement for specialized equipment and personnel limit the widespread use of endoscopy for GC screening. To overcome these challenges, researchers have focused on developing non-invasive diagnostic techniques that can detect GC at earlier stages, with minimal patient discomfort and risk[9-11]. The following sections discuss the latest advancements in non-invasive GC diagnosis, including advanced imaging, liquid biopsy, and breath tests.

ADVANCED IMAGING

Advanced imaging technologies have made significant strides in the diagnosis of GC, increasing the accuracy and precision of disease detection. These techniques leverage the latest advancements in medical imaging, allowing for earlier identification of cancerous lesions and improved assessment of tumor characteristics.

Computed tomography

With its high spatial resolution and ability to generate detailed cross-sectional images, computed tomography (CT) serves as the preferred imaging method for assessing tumor location, size and depth of invasion in GC patients[12,13]. The advancements in CT technology, including the introduction of multi-detector CT (MDCT) and dual-energy CT (DECT), have further enhanced its diagnostic capabilities[14,15]. MDCT allows for faster scanning speeds and thinner slice thicknesses, resulting in improved image quality and reduced motion artifacts[14,16]. DECT, on the other hand, provides additional information about tissue composition by acquiring images, enabling better distinguishing between normal and pathological tissues[15]. In the diagnosis of GC, CT is routinely used for staging, which is crucial for determining the appropriate treatment plan. CT can accurately depict the thickness of the gastric wall, the presence of ulceration or mass formation, and the extent of tumor invasion into adjacent structures. Furthermore, CT is highly effective in detecting lymph node enlargement, which is an important indicator of nodal metastasis.

Spectral CT (sCT), owing to its material decomposition ability, can quantify the iodine concentration within tumor tissue, which is a key aspect for evaluating tumor invasiveness, invasion depth, angiogenesis, and systemic treatment responsiveness[17,18]. A recent breakthrough in this field is the application of sCT-iodine mapping (IM) analysis for detecting human epidermal growth factor receptor 2 (HER2) expression, which is a crucial biomarker affecting treatment strategies and prognostic evaluation[19]. Zhang *et al*[19] conducted a comprehensive evaluation of 19 histogram-derived parameters from 101 GC patients who underwent preoperative sCT. Notably, the analysis revealed that HER2-positive tumors exhibited notably lower values for maximum, mean, standard deviation, variance, entropy, and percentile parameters compared to HER2-negative counterparts, reinforcing the potential of sCT-IM histogram analysis as a predictive tool. Moreover, the study underscores the clinical relevance of the Lauren classification and GC differentiation to HER2 status, highlighting the intricate interplay between histopathological features and tumor biology. Notably, the 99th percentile parameter emerged as the most discriminative and demonstrated the highest diagnostic performance (area under receiver-operating characteristic is 0.740), accompanied by a sensitivity of 76.2% and specificity of 65.0%. This finding highlights the significance of sCT-IM histogram analysis in non-invasively predicting HER2 status in GC. This study contributes to advancing the research frontier of CT technology in GC diagnosis, fostering personalized treatment approaches and improved clinical outcomes.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has emerged as an important tool in the field of GC diagnosis, offering unique advantages in assessing tumor characteristics, and guiding treatment strategies[20]. Owing to its multi-parametric, multi-sequence, and multi-directional imaging capabilities, MRI provides exceptional soft tissue resolution, enabling the clear visualization of gastric wall layers, tumor extent, and adjacent organ. In the diagnosis of GC, MRI has been shown to accurately depict tumor size, invasion depth, and lymph node involvement, thereby facilitating precise TNM staging[20]. Studies have reported the high specificity and sensitivity of MRI in detecting both early and advanced stages of GC, with notable abilities to differentiate between benign and malignant ulcers on the basis of their morphological and signal characteristics[21]. Diffusion weighted imaging and dynamic enhanced (DCE)-MRI have further enhanced the diagnostic ability of this modality by providing functional information about tumor aggressiveness, perfusion, and microvascularity [22,23]. These advanced sequences have been instrumental in assessing treatment response and monitoring tumor recurrence. Moreover, the non-invasive and non-radiative features of MRI makes it an attractive option for repeated

assessments, particularly in young patients and those requiring serial follow up. In terms of GC management, MRI plays a pivotal role in preoperative planning, enabling surgeons to evaluate tumor resectability, determine the extent of lymph node dissection, and assess the feasibility of minimally invasive surgical approaches. During surgery, MRI-compatible navigation systems can be integrated to provide real-time intraoperative guidance, raising the precision and safety of the procedure. Postoperatively, MRI has emerged as a valuable tool for evaluating surgical outcomes, detecting residual disease, and monitoring for disease recurrence[24]. As such, MRI holds great promise in advancing the early detection, accurate staging, and personalized treatment of GC, ultimately contributing to improved patient outcomes.

LIQUID BIOPSY

Liquid biopsy refers to the analysis of biological fluids, primarily blood, for the presence of tumor-derived biomarkers, including circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and exosomes[10,25]. These biomarkers can provide insights into tumor biology, monitor disease progression, and guide personalized therapy. The key advancements in liquid biopsy for GC diagnosis can be summarized as follows.

CTCs

CTCs originate from primary and metastatic cancerous lesions and play a pivotal role in disease progression by contributing to the formation of new distant metastases[26,27]. The commonly definition of CTCs is cells with a round or oval morphology, featuring a round or oval nucleus within the cytoplasm[28,29]. Morphologically, CTCs are classified into two categories: (1) Single CTCs; and (2) Clustered CTCs. Cancer metastasis typically occurs *via* clustered CTCs, prompting the use of clinical biomarkers such as tumor markers and radiological diagnostic features as surrogate markers for the detection of clustered CTCs[30]. Given that CTCs are typically present at less than one unit per milliliter of peripheral blood, detecting them requires methods with high sensitivity, specificity, and reproducibility. Techniques such as immunocytochemistry, RT-PCR, flow cytometry, and the semi-automated immunomagnetic separation system (CellSearch®) have been employed for CTCs detection. Notably, CellSearch® is the only CTCs isolation device currently approved by the United States Food and Drug Administration. Several studies have reported the clinical significance of CTCs in GC. For example, high levels of CTCs have been associated with poor treatment response, shorter overall survival, and increased disease aggressiveness[28,31]. However, the low abundance of CTCs in peripheral blood and the technical challenges associated with their isolation and characterization limit their widespread clinical application[25,28].

ctDNA

The ctDNA is fragmented DNA released from apoptotic or necrotic tumor cells into the bloodstream. The ctDNA exists in plasma or serum, exhibits multiple tumor-related molecular features, including single-nucleotide mutations, methylation changes, and tumor specific sequences[32]. Recent studies have demonstrated that integrating ctDNA with protein biomarkers can effectively screen for multiple cancer types, including GC, hepatocellular carcinoma and breast cancer[33-35]. At present, ctDNA offers a cost-effective and highly sensitive tool with potential clinical applications in the diagnosis of GC patients. First, it enables early cancer screening by detecting tumor-specific genetic alterations in blood samples, thereby facilitating early intervention and improving patient outcomes. Second, ctDNA analysis allows monitoring of treatment response, enabling physicians to adjust therapeutic strategies promptly in the event of treatment failure or drug resistance. Additionally, ctDNA can serve as a valuable marker for identifying therapeutic targets, guiding precision medicine methods tailored to individual patient tumor characteristics. Furthermore, ctDNA assessment has shown promise in evaluating patient prognosis and predicting tumor recurrence, providing valuable insights into disease progression and recurrence risk. Finally, ctDNA analysis can be used to monitor drug resistance, promoting the timely implementation of alternative treatment plans to combat resistance mechanisms. Overall, the clinical application of ctDNA in the diagnosis of GC patients is rapidly developing, and ongoing research aims to improve detection methods, validate biomarkers, and establish standardized protocols. Therefore, ctDNA represents a promising minimally invasive approach that has the potential to fundamentally change the management of GC patients.

Exosomes

Exosomes are nanoscale vesicles with a lipid bilayer structure and have become promising diagnostic biomarkers in GC [36]. These vesicles with diameters between 30 nanometers and 150 nanometers are actively secreted by various cancer cells and contain a range of bioactive molecules such as proteins, lipids, DNA, miRNAs, and circRNAs[36,37]. These molecular cargoes facilitate intercellular communication and regulate diverse biological processes, making exosomes ideal candidates for non-invasive diagnostic tools. Recent studies reveled the crucial role of exosomes in the progression, metastasis, and drug resistance of GC. For example, tumor-associated neutrophils accelerated GC metastasis by promoting the secretion of exosomes miR-4745-5p/3911[38]. Moreover, exosome circATP8A1 expression was increased in the GC tissues and circATP8A1 promoted GC proliferation, invasion and metastasis by inducing M2 polarization[39]. In summary, exosomes and their molecular cargoes, particularly miRNAs and circRNAs, represent an abundant source of diagnostic information for GC. They can reflect disease status, progression, and response to treatment, making them promising candidates for non-invasive diagnostic tools. Ongoing research is expected to further reveal the complexity of exosome communication in GC and contribute to the development of more effective diagnostic strategies.

EXHALED BREATH TEST

Breath tests has become a promising non-invasive diagnostic tool for the early detection of GC, offering significant advantages over traditional invasive methods. Recent research has shown remarkable progress in identifying GC-related biomarkers *via* exhaled breath analysis[40,41]. A study published in *JAMA Oncology* highlighted the potential of a novel exhaled breath test to detect subtle changes in volatile organic compounds (VOCs)[40]. This study developed a diagnostic model based on five VOCs, achieving an overall sensitivity of 80%, and specificity of 81%. The scientific rationale behind these breath tests lies in the unique VOCs profiles produced by cancerous cells during metabolism, which are subsequently exhaled. VOCs such as ethanol, 2-butanone, decanal and hexanoic acid have been identified as potential biomarkers for GC. Researchers can analyze these compounds in exhaled breath to detect early signs of GC before symptoms become apparent *via* high-sensitivity mass spectrometry and nanoarrays. The attraction of breath tests lies in their non-invasive nature, ease of use, rapid results and low cost. These tests can potentially be administered in primary care settings, enabling large-scale screening of populations and timely referrals for further diagnostic procedures like endoscopy. While the current studies demonstrate promising results, further research is needed to validate the diagnostic accuracy of breath tests in early-stage GC and to identify potential confounding factors that may affect test outcomes.

LIMITATION

Despite its potential, the clinical implementation of non-invasive diagnostic tools is not without challenges and limitations. For starters, the need for further validation in large-scale studies remains a critical hurdle. While preliminary results may be encouraging, the robustness and reliability of these methods must be rigorously tested across diverse patient populations and geographic regions to ensure their widespread applicability. Moreover, the standardization of protocols is another significant barrier. Variations in technique, sample collection, and analysis can introduce inconsistencies in test results, making it difficult to compare data across studies and clinics. Developing universally accepted standards and protocols for these non-invasive tests is essential for ensuring accuracy and reproducibility. Furthermore, the accuracy and sensitivity of these non-invasive diagnostic tools are still in the process of being refined and optimized. While they offer significant advantages, they may not yet be capable of detecting all cases of GC, particularly in its earliest stages. This limitation necessitates ongoing research to explore new biomarkers and technologies that can further enhance the diagnostic capabilities of these tools.

CONCLUSION

The advancement of non-invasive diagnostic techniques for GC is an important step in combating this deadly disease. Advanced imaging, liquid biopsy, and breath testing provide promising alternatives to traditional invasive methods, with the potential to improve early detection rates and provide information for personalized treatment strategies. With the continuous development and clinical validation of these technologies, we can expect to see significant improvements in patient prognosis, including earlier GC detection, more personalized treatment strategies, and better quality of life. Thus, further research should focus on improving and optimizing these non-invasive diagnostic tools, and exploring new biomarkers and technologies to further enhance their accuracy and sensitivity. Collaboration between researchers, clinical doctors, and industry partners is crucial to driving progress in this field and ultimately bringing the benefits of non-invasive GC diagnosis to patients worldwide.

FOOTNOTES

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