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Research Value Analysis of Ultrasound-Guided Puncture in Precise Sampling for Gastrointestinal Stromal Tumor Biopsy

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Abstract

Gastrointestinal stromal tumor (GIST) is a common tumor originating from the mesenchymal tissue of the gastrointestinal tract. Pathological diagnosis, immunohistochemical detection, and gene mutation analysis before treatment are crucial for formulating treatment plans, and accurate biopsy sampling is the core prerequisite for achieving the above goals. Conventional ultrasound-guided biopsy has limitations such as a low diagnostic accuracy rate and insufficient quality of tissue samples when sampling small lesions and lesions in special anatomical sites because it cannot distinguish between tumor active areas and necrotic/hemorrhagic areas. Contrast-enhanced ultrasound (CEUS) technology can clearly show the tumor microcirculation perfusion status, accurately identify the active areas, and provide accurate targeted guidance for biopsy, which has gradually shown significant advantages. This article reviews the research progress of ultrasound-related technologies such as conventional ultrasound guidance and contrast-enhanced ultrasound guidance in GIST biopsy, systematically analyzes the application value and limitations of various technologies, and briefly describes the application status of other imaging guidance methods. It further explores the problems existing in current research, such as insufficient sample size, lack of unified operating standards, and great influence by operator experience, and looks forward to future development directions such as new ultrasound imaging technologies, artificial intelligence-assisted diagnosis, and "one-stop" diagnosis and treatment models, so as to provide a reference for improving the accuracy of GIST biopsy and optimizing clinical diagnosis and treatment strategies.

Keywords

Gastrointestinal Stromal Tumor, Ultrasound-Guided Puncture, Biopsy, Contrast-Enhanced Ultrasound, Accurate Sampling, Diagnostic Value

1. Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal-derived tumor of the gastrointestinal tract, originating from interstitial cells of Cajal (ICCs) or their homologous stem cells, with different malignant potentials [1]. GIST accounts for about 1% - 3% of gastrointestinal malignant tumors [2], and is more common in the stomach (60% - 65%) and small intestine (20% - 25%), less common in the rectum, colon, and esophagus, and can also be seen outside the gastrointestinal tract (mesentery, omentum, retroperitoneum, about 5% - 7%) [3]. Piotr *et al.* pointed out [4] that the incidence of GIST is about 15/1 million, and the average age of diagnosis is 60 years, which seriously endangers human health. This tumor has an insidious onset and atypical early symptoms [5]. Imaging often shows a solid mass growing into or out of the gastrointestinal wall, which overlaps with the image characteristics of various solid space-occupying lesions in the abdominal cavity, such as gastrointestinal leiomyoma, schwannoma, exophytic colorectal cancer, primary gastrointestinal lymphoma, and gastrointestinal metastases. It is clinically difficult to distinguish only from the morphological characteristics of the sonogram. At the same time, high-quality pathological results obtained by accurate biopsy are the core basis for the implementation of the GIST standard risk stratification system. The 5th edition of the *WHO Classification of Digestive System Tumors* released in 2019 incorporated the modified NIH risk stratification system [6], which refined the risk levels by combining parameters such as tumor size, mitotic count, and primary site, directly determining the accuracy of clinical diagnosis and treatment strategies. Therefore, obtaining accurate pathological diagnosis, immunohistochemical results, and even gene mutation detection before treatment has important clinical significance. It is not only the gold standard for diagnosing GIST, but also allows clinicians to comprehensively evaluate whether to perform surgery or accurately guide the adjustment of drug treatment plans with reference to the results.

Conventional ultrasound examination (US) is an important screening method, with the advantages of convenience, low cost, and speed. In recent years, with the improvement of the resolution and technology of color Doppler ultrasound, abdominal ultrasound examination, especially medium- and high-frequency ultrasound examination, can overcome the interference of intestinal gas, clearly show the stratification of the intestinal wall, and allow for dynamic and repeated observation, becoming one of the important imaging examination methods for the diagnosis of gastrointestinal stromal tumors. The main limitation of traditional ultrasound-guided needle biopsy lies in its reliance on anatomical localization, which fails to accurately distinguish active areas from necrotic/bloody areas within the tumor, leading to suboptimal sampling or the possibility of false-negative results

[7]. Bai [8] also proposed that traditional ultrasound cannot distinguish the necrotic areas in the mass, and it is also difficult to clearly distinguish the adjacent relationship with surrounding large blood vessels, leading to some false-negative results and sampling failures. In clinical practice, there is also the problem that a biopsy cannot obtain enough tumor tissue for molecular biological detection [9], and this problem is particularly prominent in cases of small lesions (<2 cm) and lesions in high-risk anatomical sites (such as the duodenum and gastroesophageal junction). When the lesion is too small, it is more significantly affected by respiratory movement, and a slight deviation may cause the needle to penetrate out of the lesion. At the same time, the amount of tissue obtained is small, and it is easy to be mixed with normal tissue or blood, resulting in an insufficient specimen. Therefore, improving the quality of biopsy is a key problem that needs to be solved urgently in clinical practice.

The 2023 *Guidelines for the Diagnosis and Treatment of Gastrointestinal Stromal Tumors of the Spanish Society of Medical Oncology* (*GEIS*) [10], the *Asian Consensus Guidelines for the Diagnosis and Treatment of Gastrointestinal Stromal Tumors* [11] etc., also emphasize the importance of imaging-guided biopsy in GIST diagnosis and treatment decision-making. At present, CEUS-guided puncture has gradually shown advantages in the biopsy of various lesions. A study involving 820 cases of liver space-occupying lesions confirmed [12] that the diagnostic accuracy rate of the CEUS group was significantly higher than that of the conventional ultrasound group (96.4% vs 92.6%), and there was no significant difference in the complication rate. Studies have shown that contrast-enhanced ultrasound can show the microvascular perfusion of the lesion, identify the necrotic area within the lesion and the non-tumor cell invasion area around the lesion, and guide the biopsy to provide sufficient high-quality tissue samples to meet the needs of immunohistochemical detection and molecular typing, which is crucial for judging the malignant potential of GIST and formulating individualized treatment plans [13]. This article mainly reviews the applications of ultrasound, contrast-enhanced ultrasound, and ultrasound-guided puncture in GIST biopsy, summarizes the relevant research progress, existing shortcomings, and future development directions, and secondarily introduces the applications of other imaging methods in GIST biopsy.

2. Classification and Application of Ultrasound-Related Technologies in GIST Biopsy

2.1. Conventional Ultrasound Guidance

Conventional ultrasound-guided biopsy mainly relies on B-ultrasound to locate the tumor and guide the puncture needle to reach the target area. It is the most basic form of ultrasound-guided biopsy, with a simple operation and wide clinical application [14].

For gastric and rectal GIST, endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) or fine-needle biopsy (FNB) is a commonly used clinical method. Lee *et al.* [15] found that EUS-guided 22G fine-needle aspiration biopsy had a positive diagnosis rate of over 80% for gastric epithelial tumors with a diameter > 2 cm. Na *et al.* [16] compared EUS-guided 19G Trucut biopsy with 22G fine-needle aspiration biopsy, and the results showed that both methods could effectively diagnose gastric epithelial tumors. The tissue acquisition rate of Trucut biopsy was slightly higher, and the diagnostic rate of TCB was 77.8%, higher than the 38.7% of fine-needle aspiration biopsy. TCB accurately diagnosed 90.9% of GISTs and 81.1% of non-GIST SETs, while FNA accurately diagnosed 68.8% of GISTs and 14.3% of non-GIST SETs. At the same time, the size of the lesion also affects the results. Attila [17] and others concluded from their research that for lesions < 20 mm, the diagnostic accuracy rate of EUS-FNA was 50%; for lesions > 20 mm, the diagnostic accuracy rate was 91.6%, proving that a lesion size < 2 cm will significantly reduce the diagnostic rate of EUS-FNA for upper gastrointestinal SELs.

Conventional ultrasound technology has been widely used in the examination of GIST, but conventional ultrasound-guided biopsy has obvious limitations: it cannot show the tumor vascular distribution and active areas, which may lead to the puncture needle entering necrotic tissue, reducing the diagnostic accuracy; for small GISTs with a diameter < 50 mm or tumors with uneven internal echoes, the targeting accuracy of conventional ultrasound is lower [18].

2.2. Contrast-Enhanced Ultrasound Guidance

Contrast-enhanced ultrasound-guided biopsy uses contrast agents to enhance the visualization of the tumor microcirculation, accurately identify the tumor's active areas with rich blood supply, avoid necrotic or fibrotic tissue, and significantly improve the accuracy of biopsy sampling [19].

Wu *et al.* [18] confirmed that contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) can effectively distinguish the malignant risk of small GISTs (<50 mm) by showing their enhancement patterns, and that guiding biopsy based on this can further improve the diagnostic accuracy. Stock [20] and others also reported that contrast-enhanced ultrasound can visualize the central necrotic area of the lesion and confirmed that the imaging measurement values are highly consistent with the postoperative pathological size, indicating that CEUS can also accurately measure the diameter. Zhang *et al.* [21] reported a case of rectal epithelial lesions. Before endoscopic ultrasound-guided transperineal core needle biopsy, the blood supply of the tumor was evaluated by contrast-enhanced ultrasound, and pathological tissue was successfully obtained and diagnosed as GIST.

Contrast-enhanced ultrasound also helps to distinguish GIST from other morphologically similar epithelial tumors. Gastric schwannoma often shows a similar appearance to GIST in conventional ultrasound, but contrast-enhanced ultrasound can show the differences in their enhancement patterns, assist in preoperative differential diagnosis, and guide targeted biopsy [22], which is consistent with the "rapid washout of schwannoma" and "sustained high perfusion of GIST" found by Stock [20] and others, and can be used as a new indicator for differential diagnosis by contrast-enhanced ultrasound.

3. Applications of Other Technologies in GIST Biopsy

In addition to ultrasound-related guidance technologies, other imaging guidance technologies such as computed tomography (CT) guidance, magnetic resonance imaging (MRI) guidance, and positron emission tomography-computed tomography (PET-CT) assisted positioning are also involved in GIST biopsy.

CT-guided biopsy has certain application value in GIST lesions that are difficult to be visualized by ultrasound, such as those in the retroperitoneum and the deep part of the small intestine, by virtue of the advantages of high spatial resolution and wide anatomical coverage. It is especially suitable for larger or deeply located tumors and can reduce the risk of puncture-related complications through accurate positioning. However, this technology has limitations such as radiation exposure and the inability to provide real-time dynamic guidance [23].

MRI-guided biopsy is characterized by no radiation and high soft tissue resolution, which can clearly show the anatomical relationship between the tumor and surrounding blood vessels and nerves, and has the potential to evaluate the internal structure and active areas of the tumor. Gupta [24] and others affirmed the application value of MRI in GIST with central nervous system metastases. However, it takes a long time to examine, has high equipment costs, and is significantly affected by respiratory movement.

Currently, its application in GIST biopsy is relatively limited. Although PET is not the preferred method for directly guiding biopsy, it can assist in identifying the hypermetabolic areas of GIST by detecting the metabolic activity of tumor cells, providing a reference for the selection of biopsy targets, especially in scenarios such as differentiating tumor active foci from necrotic foci and judging recurrent and metastatic foci. The preoperative imaging examination of GIST cannot accurately diagnose its degree of malignancy. The research results of Narushima [25] and others pointed out that FDG-PET is a very useful imaging marker for diagnosing malignant GIST (such as high-risk groups and poor-prognosis groups), and believed that tumor size, mitotic count, and Ki-67 index were significantly positively correlated with the maximum standardized uptake value of GIST.

In addition, endoscopic techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [26] can achieve "diagnosis and treatment integration" in the biopsy and treatment of some superficial or small-volume GIST, but their applicability to deeply invasive or larger tumors is low. These technologies have their own advantages and disadvantages. In clinical practice, it is necessary to reasonably combine them with ultrasound guidance technologies according to the location, size, anatomical characteristics of GIST lesions, and the individual conditions of patients to further improve the accuracy and safety of biopsy.

4. Risks of GIST Biopsy

As an invasive procedure, the core risks of biopsy include bleeding, perforation, infection, and tumor seeding along the needle tract. Bleeding is the most common and main complication of GIST biopsy, and the incidence rate varies depending on the puncture method. Mucosa-incision-assisted biopsy (MIAB), as one of the biopsy methods for upper gastrointestinal submucosal tumors, has a clinically significant bleeding incidence rate of about 5.03%, mainly related to damage to blood vessels on the tumor surface or rupture of the digestive tract mucosa. Most cases can be controlled by endoscopic hemostasis, and there are no reports of fatal bleeding [27]. Yamashita *et al.* retrospectively analyzed the MIAB procedures of 48 gastric GIST patients. The results showed that the puncture sampling success rate was 96%, and only 1 case had postoperative bleeding (incidence rate of 2%), and there were no cases of recurrence or metastasis, further confirming the safety of MIAB in gastric GIST puncture [28]. The bleeding risk of CT-guided percutaneous biopsy is relatively low, mainly manifested as a small amount of bleeding along the needle tract, which can usually be stopped by local compression and can be naturally absorbed within 1 week.

Perforation is a rare but serious complication, mostly related to the tumor being located in the weak part of the gastrointestinal wall or improper control of the puncture depth. Once it occurs, emergency surgical repair is required. The overall risk of infection is extremely low, mostly related to non-standard aseptic operation or low immunity of patients, manifested as local inflammation or digestive tract infection, which can be cured by the use of prophylactic antibiotics or postoperative anti-infection treatment. Yeh's research pointed out that the infection incidence rate of various puncture methods did not exceed 1% [29].

The risk of tumor seeding in GIST biopsy has long been a concern, but clinical studies have confirmed that its incidence rate is extremely low and controllable. Modern puncture techniques isolate tumors from normal tissues using catheter needles and optimize puncture paths to avoid blood vessels and lymphatic vessels, which can significantly reduce the shedding and implantation of tumor cells. Moreover, the fibrin formed locally after puncture can further lower the possibility of metastasis. A study on 393 high-risk GIST patients [29] showed that there was no significant difference in recurrence-free survival (RFS) and overall survival (OS) between those who underwent preoperative percutaneous biopsy and those who did not. Even in patients with large tumors with a diameter ≥ 10 cm, the risk of recurrence did not increase after puncture, confirming that adjuvant targeted therapy can further offset the potential seeding risk.

The risks of GIST biopsy are generally controllable, and its safety has been confirmed by many studies and guidelines. Ultrasound-guided percutaneous biopsy in GIST patients with failed gastroscopy sampling only showed mild pain as an adverse event, and there was no report of serious complications, with a diagnostic success rate of 100%. There was no significant difference in the complication rate between EUS-FNA/FNB and electronic gastroscopy combined with endoscopic ultrasound examination (39.5% vs 31.6%), and most of these were mild and controllable local reactions [30].

5. Conclusions

Ultrasound-guided biopsy techniques have significant advantages in GIST diagnosis: conventional ultrasound provides real-time positioning for biopsy, laying the foundation for minimally invasive sampling; contrast-enhanced ultrasound further improves the accuracy of biopsy by showing the tumor microcirculation and obtaining active tissue samples [12]. Clinical studies have confirmed that contrast-enhanced ultrasound-guided biopsy can significantly improve the positive diagnosis rate of GIST. For example, the retrospective study of Lai *et al.* [22] showed that contrast-enhanced ultrasound-guided fine-needle biopsy was superior to traditional fine-needle biopsy in the diagnosis of epithelial lesions, with a higher positive diagnosis rate. For GIST that requires gene detection such as c-KIT and PDGFRA, contrast-enhanced ultrasound-guided biopsy can obtain sufficient high-quality tissue, providing reliable support for targeted therapy [31]. At the same time, ultrasound-guided biopsy has high safety. Compared with other imaging guidance methods, it has a lower risk of complications such as bleeding and perforation and can be repeated if necessary, which is particularly important for patients who need to evaluate the treatment response [32].

Ultrasound plays a key role in the whole process of GIST diagnosis and treatment: preoperative contrast-enhanced ultrasound-guided biopsy can clarify the diagnosis of GIST, evaluate the malignant potential, and guide the selection of treatment strategies [10]; for advanced GIST, contrast-enhanced ultrasound-guided biopsy can obtain tissue samples for molecular detection, helping to formulate targeted treatment plans such as imatinib [13]. For recurrent or metastatic GIST, contrast-enhanced ultrasound can detect small lesions and guide biopsy to confirm recurrence, providing a basis for adjusting treatment plans [10]. Andresciani *et al.* [33] reported that contrast-enhanced ultrasound can clearly show the imaging characteristics of presacral recurrent GIST, assisting in accurate biopsy and diagnosis.

6. Research Limitations

Despite the significant advantages of ultrasound-guided biopsy techniques, certain technical shortcomings persist: For GISTs located in the deep small intestine or retroperitoneum, the imaging quality of conventional ultrasound and contrast-enhanced ultrasound (CEUS) may be compromised by intestinal gas or anatomical location, leading to targeting difficulties [33]. Additionally, the procedure is highly operator-dependent—professional training is required for interpreting enhancement patterns and selecting biopsy sites, resulting in potential variations in diagnostic accuracy across different medical institutions.

Most current studies on CEUS-guided GIST biopsy are retrospective or small-sample case reports, lacking large-scale, multi-center randomized controlled trials. This limitation hinders the further validation of the technology's clinical value [19].

Furthermore, there is no unified standard for the selection of contrast agents and biopsy needles in guided biopsy. Differences in contrast agent types and puncture needle specifications across studies make horizontal comparisons of results challenging [16].

Even with CEUS guidance, the tissue acquisition rate may remain low for tiny GISTs (diameter < 1 cm) or tumors with extensive necrosis [14]. In addition, some GISTs share similar imaging features with other mesenchymal tumors (e.g., leiomyomas, schwannomas), making definitive differentiation difficult through biopsy alone and necessitating a combination of multiple examination methods [22].

7. New Perspectives and Future Directions

The emergence of novel ultrasound imaging technologies has opened new avenues for GIST biopsy. Yamashita *et al.* [34] developed an endoscopic ultrasound imaging technique that visualizes microcirculation without contrast agents, simplifying the guided biopsy workflow and reducing examination costs. High-frame-rate CEUS can more accurately depict dynamic changes in tumor blood flow, aiding in identifying the optimal biopsy time window and further improving sampling precision. The application of three-dimensional (3D) CEUS enables comprehensive visualization of tumor spatial structure and blood supply distribution, facilitating the planning of biopsy paths [22].

Future research should focus on optimizing CEUS-guided biopsy strategies: For instance, large-sample studies are needed to determine the optimal puncture needle type and number of punctures for GISTs of varying sizes and locations. Additionally, integrating rapid on-site evaluation (ROSE) into endoscopic ultrasound (EUS)-guided biopsy can promptly confirm whether the obtained tissue meets diagnostic requirements, reducing the rate of repeated punctures.

The integration of artificial intelligence (AI) with ultrasound imaging is expected to become a new research hotspot. AI can automatically analyze CEUS images—for example, Bai *et al.* [35] used deep learning models to classify different types of solid renal parenchymal tumors based on CEUS images. AI can also identify tumor active regions and optimize biopsy paths: Brooks *et al.* [36] systematically reviewed AI applications in CEUS of liver tumors, including "automatic active region segmentation + puncture path simulation". These technical modules can be extended to GIST biopsy: AI locks onto the core active areas of tumors by recognizing contrast agent enhancement patterns and automatically optimizes puncture angle and depth based on anatomical structures, reducing reliance on operator experience and improving the standardization of biopsies.

With the continuous advancement of ultrasound technology, CEUS-guided biopsy may be applied to more special types of GISTs, such as extra-gastrointestinal stromal tumors (EGISTs) located in the peritoneum or retroperitoneum, and multiple GISTs complicated by other diseases. Furthermore, combining CEUS-guided biopsy with minimally invasive treatment technologies (e.g., radiofrequency ablation) can achieve "one-stop" diagnosis and treatment for small-volume GISTs, improving treatment efficiency and patient prognosis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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