

# Progress in the Application of Endoscopic Ultrasonography in the Diagnosis of Early Gastrointestinal Cancer

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**How to cite this paper:** Ye, L.S. and Zou, C.X. (2025) Progress in the Application of Endoscopic Ultrasonography in the Diagnosis of Early Gastrointestinal Cancer. *Journal of Biosciences and Medicines*, 13, 1-11.  
<https://doi.org/10.4236/jbm.2025.135001>

**Received:** April 1, 2025

**Accepted:** May 10, 2025

**Published:** May 13, 2025

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## Abstract

The incidence of gastrointestinal tumors is high, the malignancy degree is high, the prognosis is poor, the survival rate is very low, digestive tract early cancer is the depth of infiltration is lower than the submucosa or only in the mucosal layer of digestive tract tumors, including early esophageal cancer, early gastric cancer and early colorectal cancer. Most early cancers of the digestive tract develop from precancerous lesions to early cancers, and then evolve to middle and late stages, so the diagnosis of early cancer of the digestive tract is very important. In recent years, with the continuous development of endoscopic diagnosis and treatment technology, the diagnosis and treatment of early gastrointestinal cancer has made a qualitative leap. Early detection, early diagnosis and treatment and minimally invasive treatment have greatly improved the survival rate and quality of life of patients. Endoscopic ultrasonography (EUS), as an advanced examination method combining endoscopy and ultrasound technology, introduces an ultrasonic probe into the body through an endoscopic tube, and performs real-time ultrasonic scanning of the digestive tract under the direct vision of the endoscope, which can obtain high-resolution images and clearly display the structure of each layer of the digestive tract wall and relevant information about the lesions. EUS plays an important role in the diagnosis of early gastrointestinal cancer (esophageal cancer, gastric cancer and colorectal cancer). The accuracy of EUS in determining the depth of invasion of early esophageal cancer is 85% to 92%, and the survival rate of 5 to 10 years in patients with early gastrointestinal cancer can be increased to 92% through minimally invasive endoscopic treatment (such as ESD and EMR). Based on relevant literatures and guidelines at home and abroad, this paper reviewed the research progress and clinical decision-making value of endoscopic ultrasound in the diagnosis of early gastrointestinal cancer.

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## Keywords

Endoscopic Ultrasonography (EUS), Early Gastrointestinal Cancer, Depth of Invasion, Lymph Node Metastasis, Artificial Intelligence

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## 1. Introduction

Malignant tumor of digestive tract is a very common disease in clinic, with high fatality rate and high recurrence rate. In recent years, the incidence of this type of disease has not only increased year by year but has also gradually shown a trend of younger people. Early digestive tract cancer refers to the early stage of digestive tract cancer. At this time, the lesions of patients have not reached the submucosa and only involve the mucosal layer, so it is also called “intramucosal cancer” in clinical practice. Early diagnosis of early digestive tract cancer is the key [1] to prognosis. A large number of clinical studies have confirmed that the treatment timing of patients with digestive tract cancer directly affects the choice of surgical methods and long-term prognosis. Due to the loss of minimally invasive treatment opportunities, advanced patients need to receive comprehensive treatment such as surgery combined with radiotherapy and chemotherapy, but their 5 - 10 year survival rate is still less than 35% [2], and accompanied by serious complications, significant decline in quality of life and high medical expenditure, which brings a heavy burden to the patient’s family and social medical system. In contrast, early gastrointestinal cancer patients through endoscopic minimally invasive treatment (such as ESD, EMR), the 5 - 10 year survival rate can be increased to 92% [3]. Endoscopic ultrasound (EUS) is an advanced examination method combining endoscopy and ultrasound technology, which is different from traditional endoscopy and other imaging tests, and overcomes the shortcomings of traditional endoscopy and ordinary ultrasound. During operation, EUS can perform real-time ultrasonic scanning of the digestive tract under the direct vision of the endoscope. EUS can perform real-time ultrasonic scanning of the digestive tract under the direct vision of the endoscope, obtain high-resolution images, and then clearly display the relevant information of the digestive tract tube wall and lesions, accurately judge the nature of lesions, and provide a key basis for the early diagnosis, accurate staging and personalized treatment of early gastrointestinal cancer. Different from minimally invasive treatments such as ESD and EMR, EUS is mainly used for disease diagnosis to help doctors accurately judge the condition and then choose the appropriate treatment plan. In this paper, the research progress and clinical decision-making value of endoscopic ultrasonography in the diagnosis of gastrointestinal early cancer and precancerous lesions were reviewed based on relevant literatures and guidelines at home and abroad for clinical reference.

## 2. Principle and Classification of Endoscopic Ultrasound Imaging

Endoscopic ultrasonography (EUS), as an examination method combin-

ing endoscopic ultrasonography and ultrasound technology, was able to clearly display the structure of each layer of the upper digestive tract wall and the conditions of adjacent tissues and organs outside the wall. The ultrasonic probe was introduced into the body through the endoscopic channel. While the endoscopy visually detected the lesions on the surface of the digestive tract mucosa, real-time ultrasonic observation under the endoscopy was used to clearly display the structure of each layer of the digestive tract wall, surrounding blood vessels and lymph nodes, and the conditions of adjacent tissues and organs, as well as ultrasound images of the depth of the lesions, which could not only dynamically understand the integrity and destructiveness of the digestive tract wall layer. It can also initially determine the size, shape, growth range, level source, depth of invasion, and histological type of the lesions, so as to obtain clear images for the diagnosis of submucosal lesions and deeper lesions. Traditional endoscopy and imaging techniques face a significant bottleneck in the diagnosis of early cancer of digestive tract. Although white light endoscopy can identify superficial mucosal lesions, its accuracy in evaluating the depth of tumor invasion is insufficient [4], with a sensitivity of only 50% - 60%, and it is difficult to detect small infiltration foci in the submucosa, which is likely to lead to treatment decision-making bias [5]. Both CT and MRI are used to evaluate the depth of tumor invasion of esophagus and stomach wall, but these methods cannot determine the mucosal lesions and the depth of invasion. Endoscopic ultrasound can combine the advantages of the two tests to improve the diagnostic efficiency [6] of early gastrointestinal cancer, and the accuracy of judging the depth of early cancer invasion is up to 85% - 92%, which is the most accurate method [7] for local staging of gastrointestinal tumors at present. With the advancement of medical technology, endoscopic ultrasonography equipment has continued to develop, and EUS includes circumferential ultrasonography and longitudinal ultrasonography, L-EUS) and micro probe endoscopic ultrasonography (mini the probe endoscopic ultrasonography, MPS). Annular endoscopic ultrasonography: The ultrasound probe was placed at the head end to obtain a 360° annular image, which can display the wall of the digestive tract and adjacent organs, and has the function of displaying blood vessels. It is used for the diagnosis of lesions in the visual range, but is not suitable for puncture examination and treatment. The early image quality was low, but now, the new product's image clarity and resolution have been greatly improved. Longitudinal sweep type (line formation) endoscopic ultrasound: the ultrasonic probe in the lateral wall of the head, showing fan-shaped image, has the function of blood vessel display, not only can be diagnosed, but also under the guidance of ultrasound puncture and interventional treatment. Early puncture accuracy and operation convenience were insufficient, but now it is equipped with advanced puncture guidance system and operation handle, which is more convenient and safe. Microprobe endoscopic ultrasound: The probe is a thin catheter type, which can explore the digestive tract through the working channel of the endoscope, and is suitable for examining small lesions of the digestive tract submucosa. In the early stage, the frequency is single and imaging is limited. In recent years, multi-frequency microprobes have

come out, such as the multi-frequency high-bandwidth ultrasonic probe developed by the Suzhou Institute of Medical Engineering of the Chinese Academy of Sciences, breaking through the traditional bottleneck and improving the diagnostic accuracy [8]. In addition, endoscopic ultrasound imaging technology continues to innovate, color Doppler, elastic imaging and other technologies to improve the diagnostic capabilities, and narrowband imaging and other technologies are also a trend [9] of integration, these developments make endoscopic ultrasound in the diagnosis of digestive tract early cancer more extensive and accurate, to provide strong support for patients.

### **3. Application of Endoscopic Ultrasonography in Esophageal Cancer**

As one of the most common malignant tumors of digestive tract after gastric cancer, esophageal cancer seriously threatens people's life and health. Because of its insidious early symptoms, most patients have been diagnosed in the middle and late stage, missing the best treatment opportunity. According to the latest results [10] of the 2020 Global Cancer Statistics report, the annual number of new cases of esophageal cancer is about 604,000, accounting for 3.4% of all cancers, ranking eighth. The annual number of deaths is about 544,000, and the mortality rate is 5.5%, ranking sixth. China is also a country with a high incidence of esophageal cancer, with its incidence and mortality ranking higher than in previous years, ranking fifth and fourth respectively. Therefore, early diagnosis of esophageal cancer is of vital significance for reducing mortality, increasing survival rate and improving prognosis. With the rapid development of endoscopic technology, especially the increasingly mature endoscopic ultrasound (EUS) technology, the detection rate of early esophageal cancer has been significantly improved. Early esophageal cancer means that the cancer tissue is limited to the mucosa and submucosa without lymph node metastasis. EUS can clearly show the five-layer structure of the esophageal wall and judge the depth of tumor invasion. The typical manifestations of early esophageal cancer under EUS are as follows: The mucosal layer of the tube wall is thickened, the layers are disordered and interrupted, the boundaries of each layer disappear, and irregular hypoechoic lesions that are limited to the mucosal layer and do not exceed the submucosal layer appear. The T stages of esophageal cancer in EUS can be summarized as follows: Stage Tx indicates that the primary tumor cannot be evaluated; Stage T0 means no evidence of primary tumor; Tis stage means carcinoma in situ; T1 stage refers to tumor invasion of the mucosal layer or part of the submucosa; T2 stage refers to the invasion of muscoli propria; T3 stage is tumor invasion of the serosal layer, involving the whole layer of esophagus; In the T4 stage, the tumor invaded the whole layer of the esophageal wall and broke through the outer membrane of the esophagus, invading the aorta, and the enlarged lymph nodes could be seen around the wall. According to relevant reports, EUS can judge the depth of invasion of primary esophageal tumors by displaying the hierarchical structure of the esophageal wall, and the accuracy of the T stage of esophageal cancer can reach 74.2% - 87.6%.

However, the accuracy of EUS diagnosis is closely related [11] to the size and specific site of the lesion. Studies at home and abroad have shown that the sensitivity of EUS for N staging ranges from 61.3% to 93.1%, and the specificity ranges from 40.3% to 94.7%. At the same time, EUS is also more sensitive to the diagnosis of lymph node metastasis of esophageal cancer. In order to distinguish the causes of enlarged lymph nodes, endoscopic ultrasound is far from enough. In recent years, EUS-guided fine needle biopsy (EUS-FNA) has gradually developed and become popular, and the tissue biopsy obtained by puncture has further improved the accuracy of N staging of lymph nodes based on pathological diagnosis. Its sensitivity and specificity both increased by more than 95%. In conclusion, the conventional EUS technique is mainly used to determine the depth of tumor invasion. In addition, EUS-FNA can also be used to determine the status of lymph node metastasis, especially for the diagnosis of local metastasis. However, EUS is limited in the diagnosis of distant metastasis (M-stage) due to the influence of ultrasound penetration and lung gas, and its diagnostic reliability is controversial due to various factors. Therefore, EUS is not recommended for TNM stage judgment alone, and should be combined with other techniques for comprehensive diagnosis. Nowadays, EUS is widely used in the diagnosis, staging and selection of surgical modes for early esophageal cancer. Different treatments are selected according to T staging, and N staging is combined with other examinations. When evaluating the diagnostic accuracy of EUS for esophageal cancer in some studies, the sample size was relatively small, which may not fully reflect the diagnostic effect of EUS under different conditions and different populations. In addition, EUS equipment models used in different studies are different, and the experience and technical level of operating doctors are also different, all of which will affect the diagnosis results. Caution should be exercised in interpreting the relevant research results. With the deepening of cognition and technological progress, EUS is expected to help greatly improve the diagnosis and treatment of esophageal cancer.

#### **4. Application of Endoscopic Ultrasonography in the Diagnosis of Gastric Cancer**

Among gastrointestinal malignancies, gastric cancer is the second most frequent tumor followed by colon cancer, and it is also the most common tumor in the upper digestive tract. In recent years, the morbidity and mortality in the world are still high, according to the latest global cancer statistics report in 2020, the annual number of new cases is more than 1,00.0 million, the incidence of all cancers is about 5.6%, ranking fifth, the number of deaths is about 769,000, the mortality rate is 7.7%, ranking fourth [10]. The prognosis of gastric cancer is closely related to the stage. The prognosis of advanced gastric cancer is poor, the 5-year survival rate is less than 50%, and the prognosis of early gastric cancer is better, the 5-year survival rate can be higher by 90%. Therefore [12], improving the detection rate of early gastric cancer is the key to improve the survival rate of gastric cancer patients. Early gastric cancer is easy to miss by routine examination because of the limited lesions and not obvious symptoms. Endoscopic ultrasound, with its high-

resolution images, can clearly display the five-layer structure of the gastric wall, accurately determine whether the lesion originated from the mucosal layer, and assess the depth of invasion. Early gastric cancer under endoscopic ultrasound is usually characterized by localized thickening, reduced echo or interruption of the mucosal layer, and relatively clear boundary with surrounding normal tissue. Studies have shown that the diagnostic accuracy of endoscopic ultrasonography for early gastric cancer can reach 80% - 90% [13]. For early gastric cancer, the accurate determination of the depth of invasion is crucial for the selection of treatment. Endoscopic mucosal resection (EMR) is feasible if the cancer is limited to the mucosal layer. If it infiltrates into the submucosa but does not exceed 1/3 of the submucosa, endoscopic submucosal dissection (ESD) can be considered. These minimally invasive endoscopic treatments have less trauma and faster recovery. For advanced gastric cancer, endoscopic ultrasound plays an important role in staging assessment. The staging of gastric cancer is mainly based on the depth of tumor invasion (T), lymph node metastasis (N), and distant metastasis (M). Endoscopic ultrasound can accurately judge the T stage of gastric cancer, and clearly show the levels of tumor invasion of the gastric wall, such as invading into the muscoli propria, the serous layer, or breaking through the serous layer to invade the surrounding tissues and organs. At the same time, endoscopic ultrasound can also probe regional lymph nodes and determine whether metastasis is present or not according to the size, shape, echo and other characteristics of lymph nodes, so as to accurately evaluate the N stage. Although early gastric cancer only emphasizes the depth of tumor invasion, but does not highlight the important feature of lymph node metastasis, studies have shown that lymph node metastasis is closely related to the depth of tumor invasion. Studies have shown that the accuracy rate of endoscopic ultrasound for T stage of gastric cancer can reach [14] 70% - 80%, and the accuracy rate for N stage is 60% - 70%. Accurate staging evaluation is helpful for doctors in making a reasonable treatment plan. For patients with stage T1-T2 and no lymph node metastasis, radical surgical resection can be considered. For patients with stage T3-T4 or with lymph node metastasis, neoadjuvant chemotherapy or radiotherapy may be required before surgery to reduce tumor volume, reduce stage, improve surgical resection rate and patient survival rate. However, in the current studies on endoscopic ultrasonography in the diagnosis of lymph node metastasis in gastric cancer, the criteria for judging lymph node metastasis have not been completely unified, and there are differences in the evaluation indicators used in different studies, which may lead to the limited comparability of study results. In clinical practice, doctors' interpretation of endoscopic ultrasound images may be subjective to some extent, which will also affect the accuracy of diagnosis.

## **5. Application of Endoscopic Ultrasound in the Diagnosis of Colorectal Cancer**

With the continuous changes of human lifestyle and living environment, in recent years, the incidence and fatality rate of colorectal cancer in China have been rising

year by year, and it has developed into a malignant disease that seriously threatens human health. Colorectal high-grade intraepithelial neoplasia (HIGN), as a precancerous lesion of colorectal cancer, has attracted much attention in the medical community. The key difference between HIGN (high-grade intraepithelial neoplasia) and cancer is whether the lesion infiltrates into the submucosa through mucosal myometria. Conventional colonoscopy can only observe the surface of the lesion, and the pathological tissue obtained during colonoscopy biopsy is limited, which makes it impossible to accurately determine the origin, scope, nature, depth of invasion and whether there is macrovascular nourishment of the lesion. Studies have shown [15] that a considerable proportion of patients diagnosed as colorectal high-grade intraepithelial neoplasia by colonoscopy pathology have actually become cancerous. Determining the depth of invasion of the intestinal wall of colorectal cancer is one of the important advantages of endoscopic ultrasound. The colorectal wall is composed of mucosal layer, submucosal layer, muscular layer and serosal layer. Endoscopic ultrasound can clearly display these hierarchical structures, and accurately determine the depth of invasion according to the infiltration of the tumor in each layer, which not only can detect early cancerous changes, but also has great [16] significance for preoperative diagnosis, staging and choice of surgical methods for HIGN patients. Early colorectal cancer is limited to the mucosa and submucosa. Endoscopic ultrasonography shows thickening and echo changes of the mucosa and/or submucosa, and the boundary between the mucosa and surrounding tissue is still clear. With the progression of the tumor, when it invaded the muscular layer, the continuity of the muscular layer was interrupted and the echo was reduced. When the tumor encroaches into the serous layer or the surrounding tissue, it is manifested as the destruction and blurring of the serous layer and the abnormal echo of the surrounding tissue. Relevant foreign studies have shown [17] that the accuracy rate of endoscopic ultrasonography in determining the depth of invasion of colorectal cancer intestinal wall can reach 70% - 90%. Accurate determination of the depth of invasion has important guiding significance for the selection of treatment. Early colorectal cancer can be resected under endoscope, especially for the diagnosis of musculoma propria and serosal carcinoma. Endoscopic ultrasound can also be used to examine the lymph nodes around colorectal cancer to determine whether there is metastasis. By observing the characteristics of the lymph nodes such as size, shape, boundary and internal echo, the nature of the lymph nodes can be preliminarily determined. In general, lymph nodes with a short diameter greater than 5mm, irregular shape, unclear borders, uneven internal echo and low echo are more likely to metastasize. A study of 50 patients with colorectal cancer with endoscopic ultrason [18] ography showed that the accuracy of peripheral lymph node metastasis can reach 70% - 80%, sensitivity is 60% - 70%, and specificity is 80% - 90%. For lymph nodes suspected of metastasis by endoscopic ultrasonography, tissue can also be obtained by fine needle aspiration biopsy for pathological examination to make a definite diagnosis. Knowing the status of lymph node metastasis can help doctors

make treatment plans and evaluate the prognosis of patients. If lymph node metastasis is present, patients may need adjuvant chemotherapy after surgery to reduce the risk of recurrence and improve the survival rate.

## **6. Application of Advanced EUS Technology and Artificial Intelligence**

### **6.1. Confocal Laser Microendoscope**

Confocal laser microendoscopy achieves high resolution imaging at the cellular level and microscopic observation of digestive tract tissues in the living state, which can more accurately identify the small lesions of early gastrointestinal cancer and provide more powerful support for the early diagnosis of the disease. Relevant studies have shown that in the diagnosis of early gastric cancer, it can clearly display the morphology, structure and microvascular changes of gastric mucosa cells, and help to find small cancer foci [19] that are difficult to detect by conventional endoscopy. However, at present, the equipment cost of this technology is high, the operation is relatively complicated, and there are some limitations in the wide clinical application.

### **6.2. AI-Assisted Diagnosis**

The application of artificial intelligence in endoscopic ultrasound diagnosis provides a new idea and method for image analysis and auxiliary diagnosis. By learning a large number of endoscopic ultrasound images, artificial intelligence algorithm can quickly and accurately identify the characteristics of lesions, assist doctors in diagnosis, and improve the efficiency and accuracy [20] of diagnosis. Some studies have used deep learning algorithm to analyze endoscopic ultrasound images, and achieved good results in judging the depth of invasion and lymph node metastasis of early gastrointestinal cancer. However, AI-assisted diagnosis still faces some challenges, such as the accuracy and stability of the algorithm need to be further improved, the universality of the model trained by different data sets is poor, and the data privacy and security issues.

## **7. Cost-Effectiveness and Clinical Guidelines of EUS**

### **7.1. Cost-Benefit Analysis**

Although EUS may be relatively expensive compared to other diagnostic protocols (such as CT and MRI), it can more accurately determine the lesions in the diagnosis of early gastrointestinal cancer and avoid unnecessary surgery and treatment, which has certain advantages in terms of overall medical costs. For example, for patients with early esophageal cancer, EUS can accurately determine the depth of invasion and select the appropriate endoscopic minimally invasive treatment, which can avoid the high cost of open surgery and the cost of postoperative complications. At present, studies on the cost-effectiveness of EUS are not comprehensive enough, and the cost varies greatly among different regions and medical institutions, so more studies are needed for comprehensive evaluation.

## 7.2. Clinical Guidelines

Current clinical guidelines provide some guidance [21] on the use of EUS in the diagnosis of early gastrointestinal cancer. For example, in the diagnosis of early esophageal cancer, the guidelines recommend EUS as an important test to assess the depth of tumor invasion and lymph node metastasis. However, there are some differences in the timing, operation and diagnostic criteria of EUS among different guidelines. In practical application, clinicians need to reasonably select EUS examination according to the specific conditions of patients and refer to different guidelines, so as to improve the diagnostic accuracy and treatment effect of early gastrointestinal cancer.

In conclusion, endoscopic ultrasonography, with its unique working principle and technical advantages, has high application value in the diagnosis and treatment of early gastrointestinal cancer, and greatly improves the diagnosis rate of early gastrointestinal cancer. It can clearly display the structure of each layer of the digestive tract wall, and accurately judge the depth of invasion and lymph node metastasis of the lesions, which provides an important basis for clinicians to choose a reasonable treatment plan. Compared with traditional endoscopy and other imaging examinations, endoscopic ultrasound has significant advantages in the early detection of small lesions and the determination of lesion nature. When combined with them, it can draw on each other's strengths and further improve the diagnostic accuracy of early gastrointestinal cancer. The emergence [22] of new endoscopic ultrasound techniques, such as confocal laser microendoscopy, has achieved high resolution imaging at the cellular level, bringing new breakthroughs in the diagnosis of early gastrointestinal cancer. The application of artificial intelligence in endoscopic ultrasound diagnosis also provides new ideas and methods for image analysis and auxiliary diagnosis, which is expected to improve the efficiency and accuracy of diagnosis. It is believed that in the future, more and better new technologies in the field of EUS will be applied and popularized.

## Conflicts of Interest

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

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