

# World Journal of *Gastrointestinal Oncology*

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## Esophageal cancer screening, early detection and treatment: Current insights and future directions

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### Abstract

Esophageal cancer ranks among the most prevalent malignant tumors globally, primarily due to its highly aggressive nature and poor survival rates. According to the 2020 global cancer statistics, there were approximately 604000 new cases of esophageal cancer, resulting in 544000 deaths. The 5-year survival rate hovers around a mere 15%-25%. Notably, distinct variations exist in the risk factors associated with the two primary histological types, influencing their worldwide incidence and distribution. Squamous cell carcinoma displays a high incidence in specific regions, such as certain areas in China, where it meets the cost-effectiveness criteria for widespread endoscopy-based early diagnosis within the local population. Conversely, adenocarcinoma (EAC) represents the most common histological subtype of esophageal cancer in Europe and the United States. The role of early diagnosis in cases of EAC originating from Barrett's esophagus (BE) remains a subject of controversy. The effectiveness of early detection for EAC, particularly those arising from BE, continues to be a debated topic. The variations in how early-stage esophageal carcinoma is treated in different regions are largely due to the differing rates of early-stage cancer diagnoses. In areas with higher incidences, such as China and Japan, early diagnosis is more common, which has led to the advancement of endoscopic methods as definitive treatments. These techniques have demonstrated remarkable efficacy with minimal complications while preserving esophageal functionality. Early screening, prompt diagnosis, and timely treatment are key strategies that can significantly lower both the occurrence and death rates associated with esophageal cancer.

**Key Words:** Esophageal cancer; Screening; Early detection; Treatment; Endoscopic mucosal resection; Endoscopic submucosal dissection

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**Core Tip:** Esophageal cancer, characterized by its aggressive nature and low survival rates, is one of the most common malignant tumors globally. Variations in risk factors between the two primary histological types, squamous cell carcinoma (ESCC) and adenocarcinoma (EAC), affect their incidence and distribution worldwide. While ESCC is prevalent in specific areas like China and meets criteria for cost-effective early diagnosis, EAC is predominant in Europe and the United States, with the role of early diagnosis in cases arising from Barrett's esophagus being a subject of controversy. The disparities in early-stage treatment across different regions are due to varying rates of early diagnosis, with countries like China and Japan advancing in endoscopic techniques for treatment. Early screening, diagnosis, and treatment significantly reduce the incidence and mortality of esophageal cancer.

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## INTRODUCTION

Esophageal carcinoma (EC), which ranks as the seventh most common cancer worldwide, was responsible for an estimated 604000 new cases in 2020, placing it in the sixth position in terms of global cancer mortality with approximately 544000 deaths[1]. These data underscore the critical impact of esophageal cancer, as it contributes to a substantial proportion of cancer-related deaths—approximately one in every 18. Notably, this malignancy disproportionately affects nearly 70% of male population. Additionally, there is a marked sex disparity in both the incidence and mortality rates of EC, with 2- to 3-fold greater prevalence and fatality rates observed in males than females[2,3]. EC incidence shows pronounced geographical disparities, with Eastern Asia emerging as the epicenter of the highest incidence for both sexes. This regional specificity is largely attributed to China, which bears a considerable burden of this disease. Remarkably, the incidence of EC in China is exceptionally high. In a global context, new cases and fatalities from China account for a staggering 53.70% and 55.35%, respectively, of the worldwide totals[1,4]. Furthermore, the geographic variability in the incidence of EC is strikingly divergent across its two primary histological subtypes: Squamous cell carcinoma (ESCC) and adenocarcinoma (EAC), each characterized by unique etiological factors. The prevalence of ESCC in specific regions of China is in sharp contrast to the prevalence of EAC predominantly observed in Europe and the United States[1,3]. This divergence greatly informs the development and execution of region-specific screening programs, emphasizing the need for tailored approaches in addressing this malignancy in diverse populations.

The etiology of EC involves a complex interplay of multifaceted factors, encompassing genetic predispositions, lifestyle choices, and environmental exposures. These influences collectively orchestrate alterations across a spectrum of molecular levels, including genomic, transcriptomic, methylation, and epigenomic domains[5]. Despite this knowledge, the exact causative factors for EC have not been fully elucidated. In Western regions, the primary risk factors for ESCC are predominantly associated with the combined effects of excessive alcohol consumption and tobacco smoking[1,6]. In contrast, in lower-income countries, where ESCC accounts for more than 90% of all esophageal cancer cases, the principal risk factors are less clear. However, dietary factors, including nutritional deficiencies and exposure to nitrosamines, have been suggested as potential contributors[7]. Lifestyle factors, encompassing tobacco and alcohol use, coupled with dietary habits, synergize to elevate the risk profile in certain populations[8]. Conversely, EAC accounts for roughly two-thirds of esophageal cancer cases in affluent regions. In these contexts, critical risk factors include excessive body weight, gastroesophageal reflux disease (GERD), and Barrett's esophagus (BE). Additionally, the declining incidence of chronic *Helicobacter pylori* infection, which shows an inverse association with EAC, may also play a contributory role in the disease's epidemiology[9-12].

Despite a noticeable reduction in its incidence in recent years, EC continues to pose a substantial challenge to global health. Paradoxically, even as the incidence of new cases declines, the mortality rate associated with EC remains alarmingly high. This grim reality is highlighted by a 5-year relative survival rate that scarcely reaches 20%, making it the cancer with the second lowest survival rate, exceeded only by pancreatic cancer (10%)[13,14]. A further complicating feature of this situation is the elusive nature of early-stage EC, which often presents without specific clinical symptoms. This absence of distinct indicators results in a distressing scenario in which a substantial number of patients are diagnosed at an advanced stage and miss the window for early detection. Consequently, these individuals face a diminished quality of life and a dire prognosis[15,16]. This pressing situation has led to a surge of research initiatives focused on refining screening methods, enhancing early detection techniques, and improving therapeutic approaches. With this led, both the American and British Societies of Gastroenterology have developed a comprehensive set of

guidelines for the screening and surveillance of BE and EAC[17-22]. Parallel to these efforts, China has also made substantial contributions to global endeavors, issuing a consensus on the screening of early-stage EC and its precancerous lesions[23,24]. In this literature review, we delve deeper into the multifaceted landscape of esophageal cancer, scrutinizing recent breakthroughs and key findings in the domains of screening, early detection, and treatment.

### **Screening approaches for esophageal cancer**

The prevailing uncertainty about the primary etiological factors of EC has left the medical fraternity grappling with a lack of definitive intervention strategies. This ambiguity has resulted in a considerable knowledge gap regarding EC, thus limiting the available options for effective medical intervention. In response to this predicament, secondary prevention has emerged as a crucial strategy. Early diagnosis and prompt treatment are achieved through structured screening processes. This approach has increasingly been recognized as a practical means to diminish the risks associated with advanced stages of EC and to reduce its associated mortality. The customization of screening protocols necessitates a consideration of both genetic and environmental risk factors. A genetic predisposition, when combined with lifestyle elements such as tobacco use and alcohol intake, guides the formulation of specialized screening programs. These programs are designed to cater to the distinct risk profiles prevalent in specific demographic groups[8].

### **Geographical variations in esophageal cancer screening**

The distinct geographic disparities in the incidence of ESCC and EAC necessitate a nuanced understanding of the development of effective screening strategies. Tailoring screening methods to align with the predominant histological subtype in a given region is critical for enhancing cost-effectiveness and early detection efficacy. In areas with a high incidence of ESCC, a cost-effective, endoscopy-based screening might be justified. Such a strategy is aimed at the broader population and focuses on identifying precancerous lesions and early-stage ESCC. In contrast, regions with a higher incidence of EAC require a more targeted approach, focusing on screening high-risk groups such as individuals with GERD or BE. This approach ensures optimal use of resources while increasing the likelihood of detecting early-stage EAC [8,25].

Given the aggressive nature of EC and the commonality of late-stage diagnoses, the implementation of early detection programs is critical, especially in high-incidence areas. Routine screening in these regions can markedly enhance survival rates[8]. For patients with a significant incidence of EAC, vigilant surveillance of BE is vital. Endoscopic screening, particularly for patients with multiple risk factors for BE-related cancer, is recommended. For those with BE but without atypical hyperplasia, endoscopic surveillance every 3 to 5 years is advised, and GERD management aligns with that for patients without BE[4]. Regular endoscopic examinations supplemented by biopsy sampling are need for the early detection of dysplastic changes. The geographical variations in esophageal cancer screening are indicated in [Table 1](#).

### **Strategic implementation of screening programs for esophageal cancer**

Timely medical intervention facilitated by these screening strategies has the potential to halt the progression to invasive carcinoma. While advocating for screening within identified target populations, it is crucial to emphasize that routine endoscopic or non-endoscopic screening methods are not recommended for the general population. It is vital to acknowledge the distinct differences in the high-risk population characteristics for ESCC *vs* EAC. Screening guidelines for EAC specifically focus on particular demographic groups[26]. These groups include males, individuals of Caucasian descent, those with a family history of BE, individuals with a prolonged history of reflux symptoms, and people with additional risk factors such as smoking and obesity. In contrast, the target demographic for ESCC screening is primarily identified by geographical location, focusing on individuals residing in high-risk areas[27,28]. Regarding the recommended age for initiating and ceasing screening, the guidelines for BE and EAC suggest beginning routine screening at 50 years of age for those in high-risk categories. On the other hand, the latest guidelines for ESCC advise starting routine screening at 40 years of age and continuing until 75 years of age, unless the individual's life expectancy is estimated to be under five years[18-20,24]. This approach reflects the need for age-specific screening protocols tailored to the risk profiles of different populations, ensuring efficient and effective detection and management of esophageal cancer.

One important gap in EC screening is the lack of robust evidence to guide optimal surveillance intervals. A landmark endoscopic screening study, involving 33319 volunteers from a region with a high ESCC incidence in China showed notable findings. The cumulative mortality rate in the intervention group was significantly lower than that in the control group. Additionally, the cumulative incidence of ESCC was also significantly lower in the intervention group. These outcomes suggest that endoscopic screening and subsequent interventions can significantly diminish the incidence and mortality of esophageal cancer[29]. Guidelines from esteemed organizations such as the American Gastroenterological Association[17] and the British Society of Gastroenterology[18], recommend a nuanced approach. The authors suggested that patients with BE measuring less than 3 cm or without dysplasia should undergo endoscopic surveillance every 3-5 years. Similarly, the Chinese consensus on ESCC screening presents a tailored perspective. That screening frequency for ESCC should be selectively adjusted, focusing on high-risk populations, with a recommended interval of once every five years. Additionally, in economically challenging regions facing medical resource limitations, extending endoscopic surveillance intervals to as long as a decade is recommended[24,30,31]. This thoughtful approach aims to balance the need for effective screening with practical considerations in regions with limited resources. This finding underscores the importance of customizing screening protocols to align with the specific risk profiles and resource availability of different populations, ensuring that screening efforts are both efficient and sustainable.

### **Challenges and debates in the early detection of esophageal cancer**

The intricate relationship between BE and esophageal EAC highlights the critical importance of vigilant surveillance in

Table 1 Geographical variations in esophageal cancer screening

Country	Governmental/healthcare policies	Definition of high-risk groups	Screening strategies
China	China guideline for the screening, early detection and early treatment of esophageal cancer (2022, Beijing)[26]	(1) Age $\geq 40$ yr from areas with high prevalence of esophageal tumors; (2) Family history of esophageal tumors; and (3) Risk factors for esophageal cancer (smoking, heavy alcohol consumption, squamous carcinoma of the head and neck or respiratory tract, preference for high-temperature and preserved foods, poor oral hygiene, <i>etc</i> )	Endoscopic screening: (1) High-risk groups: endoscopic screening with iodine staining of the esophageal mucosa is recommended (45 yr $\leq$ age $\leq$ 75 yr, every 5 yr); (2) Low-grade intraepithelial neoplasia every 1-3 yr; (3) Low-grade intraepithelial neoplasia combined with endoscopic risk factors or lesions $> 1$ cm in length will undergo endoscopy once a year for 5 yr; (4) Endoscopy is recommended every 3 to 5 yr for patients with Barrett's esophagus without atypical hyperplasia; (5) Endoscopy is recommended every 1 to 3 yr for Barrett's esophagus patients with low-grade intraepithelial neoplasia; (6) A new type of esophageal cell collector is recommended for Barrett esophageal screening; (7) The new esophageal cell collector (Cytosponge) performs cytological examination combined with biomarker detection for effective primary screening of Barrett's esophagus-related dysplasia and early esophageal adenocarcinoma; and (8) Biomarker testing alone not recommended for esophageal cancer screening. Equipment: Lugol color endoscopy or NBI endoscopy is recommended as the first choice for esophageal cancer screening, ordinary white light endoscopy can be chosen for those with insufficient conditions, and magnifying endoscopy can be used in conjunction with NBI endoscopy for those with conditions
American	ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus[21]	(1) Male; (2) More than 5 yr or frequent (at least once per week) symptoms of gastroesophageal reflux disease; and (3) $\geq 2$ risk factors for Barrett's esophagus or esophageal adenocarcinoma, risk factors including age $> 50$ yr, Caucasian ethnicity, centripetal obesity (waist circumference $> 102$ cm or waist-to-hip ratio $> 0.9$ ), history of smoking, and history of first-degree relatives with Barrett's esophagus or esophageal adenocarcinoma	(1) Unsedated transnasal endoscopy can be considered as an alternative to conventional upper endoscopy for Barrett's esophagus screening; (2) For BE patients without dysplasia, endoscopic surveillance should take place at intervals of 3 to 5 yr; and (3) Use of additional biomarkers for risk stratification of patients with Barrett's esophagus is currently not recommended. Equipment: Surveillance should be performed with high-definition/high-resolution white light endoscopy
United Kingdom	British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus[18]	(1) White male; (2) Age $> 50$ yr; (3) Obese; (4) Chronic GERD symptoms for more than 3 yr; and (5) First-degree relative with history of Barrett's esophagus or esophageal adenocarcinoma years	(1) Endoscopic screening can be considered in patients with chronic GERD symptoms and multiple risk factors (at least three of age 50 yr or older, white race, male sex, obesity). However, the threshold of multiple risk factors should be lowered in the presence of family history including at least one first-degree relative with Barrett's or OAC; (2) High-resolution endoscopy should be used in Barrett's oesophagus surveillance; (3) Patients with Barrett's oesophagus shorter than 3 cm, with IM, should receive endoscopic surveillance every 3-5 yr; (4) Patients with segments of 3 cm or longer should receive surveillance every 2-3 yr; and (5) Biomarker panels cannot yet be recommended as routine of screening

NBI: Narrow band imaging; GERD: Gastroesophageal reflux disease; OAC: Oesophageal adenocarcinoma.

individuals at heightened risk. However, the optimal frequency and methods of this surveillance are contentious topics that continue to spark debate within the medical community. Addressing these controversies is pivotal in refining early detection strategies and ensuring effective and timely interventions. The American College of Gastroenterology (ACG) has updated its guidelines for the diagnosis and management of BE. These guidelines now recommend a one-time screening endoscopy for patients with chronic GERD symptoms who also present with three or more additional risk factors. These risk factors include male sex, age older than 50 years, Caucasian ethnicity, tobacco use, obesity, and a family history of BE or EAC in a first-degree relative. Alongside these recommendations, an innovative, non-endoscopic capsule sponge device, which can be swallowed and integrated with a biomarker, has emerged as a promising and more acceptable alternative to traditional endoscopy. This device is particularly suited for screening individuals who exhibit chronic reflux symptoms alongside other risk factors associated with BE[22]. While BE is acknowledged as an important precursor to EAC, with individuals diagnosed with BE facing an increased risk of developing esophageal cancer, the exact role of BE in the early detection of EAC continues to be a topic of intense discussion and research[25]. This ongoing debate underscores the complexity of esophageal cancer screening and the need for continued research to establish the most effective strategies for early detection and prevention.

### Navigating the challenges of surveillance in BE

A primary challenge in managing BE is determining the most appropriate surveillance intervals. The diverse rates at which BE progresses to cancer, coupled with concerns about overdiagnosis, fuel ongoing debates about the frequency of endoscopic surveillance. It is critical to find a balance between the early detection of cancers and the avoidance of unnecessary medical procedures[25]. The ACG guidelines recommend that the frequency of endoscopic surveillance in

patients with BE should be based on the degree of dysplasia observed in previous biopsies[22]. This approach aims to tailor surveillance to the individual patient's risk profile.

Another contentious area is the histological grading of dysplasia within BE tissue. Assessing the risk of progression to EAC based on the severity of dysplasia is complex. The development and utilization of reliable predictive markers are essential for improving risk stratification and guiding early intervention strategies[25]. Recent advancements in imaging technologies are offering new avenues for addressing these challenges. Innovations such as advanced endoscopic techniques and confocal laser endomicroscopy (CLE) provide a more detailed examination of BE. These technologies enhance the ability to accurately stratify risk and detect early changes, potentially transforming the approach to surveillance in BE[32,33]. These developments represent an important step forward in the management of BE, offering the potential for more precise, personalized surveillance strategies that can better identify patients at increased risk of progression to esophageal EAC. As these technologies evolve, the outcomes of patients with BE may substantially improve by the facilitation of earlier and more targeted interventions.

### **The role of advanced imaging technology in the early detection of esophageal cancer**

The evolution of imaging and diagnostic technologies plays a crucial role in enhancing the early detection of esophageal cancer. Innovations in endoscopy and non-invasive imaging modalities are instrumental in identifying precancerous lesions and early-stage tumors, thereby improving patient prognosis. In recent years, remarkable advancements have been made in endoscopic technologies, which markedly aid in the early diagnosis of esophageal cancer. High-definition endoscopy, magnification endoscopy, and virtual chromoendoscopy have substantially improved the visualization of suspicious lesions. These advancements enable clinicians to detect abnormalities at earlier stages, potentially leading to more effective treatments[32]. A notable study highlighting these advancements is a randomized crossover trial that evaluated the effectiveness of high-definition white light endoscopy, following the Seattle protocol, against narrow-band imaging with targeted biopsies for detecting neoplasia. The study involved a cohort of 123 patients with BE. These findings revealed a greater detection rate of dysplasia using narrow-band imaging than using high-definition white light endoscopy (30% *vs* 21%,  $P = 0.01$ )[34]. Significantly, all the detected dysplastic or carcinoma cases displayed distinctive mucosal or vascular irregularities, which were identifiable through narrow-band imaging.

### **CLE**

CLE has become a key tool for real-time, *in vivo* histopathological imaging, providing cellular-level resolution during endoscopy. Moreover, endoscopic ultrasound-fine needle aspiration enhances the ability to distinguish neoplastic changes, aiding in the accurate diagnosis of early-stage esophageal cancer[32]. This technique employs blue laser light following the intravenous administration of fluorescein, enabling high-magnification, real-time imaging and the acquisition of targeted optical biopsies[22]. A systematic review and meta-analysis incorporating seven studies with 473 patients demonstrated a high sensitivity (89%) and specificity (83%) for CLE compared to histopathology[35]. Despite these encouraging results, challenges persist, including the substantial cost, the necessity for intravenous fluorescein, the requisite training for image interpretation, and the prolonged duration of the examination. Moreover, the applicability of these findings to the broader surveillance population remains uncertain, given that most studies were conducted in centers with a high prevalence of dysplasia/neoplasia. While confocal endoscopy shows promise for guiding biopsies and directing therapy, particularly in centers characterized by a high incidence of tumors or dysplasia, its added value compared to high-definition white-light and electron-stained endoscopy remains ambiguous[36].

### **Volumetric laser endomicroscopy**

Volumetric laser endomicroscopy, utilizing optical coherence tomography, captures high-resolution, cross-sectional images of esophageal tissue. It allows for detailed 2-dimensional visualization of the mucosa and submucosa up to a depth of 3 mm[37,38]. This non-invasive imaging modality facilitates the detection of early-stage lesions and helps distinguish between benign and malignant conditions[32]. A study with 29 full scan videos from patients with and without neoplasia demonstrated that experts correctly identified 73% of neoplastic cases and 52% of nondysplastic cases [39].

### **Artificial intelligence in diagnosis**

The use of artificial intelligence (AI) in image analysis has revolutionized early diagnosis. AI algorithms, trained on vast datasets, can identify subtle abnormalities in endoscopic images and aid in the rapid interpretation of diagnostic information. This approach not only enhances the accuracy of early detection but also addresses challenges related to interobserver variability[32,40]. Machine learning and deep learning (DL) are important parts of AI[41]. A clinical study in the Netherland showed that a DL system could detect tumors in patients with BE more accurately than could endoscopists (sensitivity 90%/specificity 88%) by analyzing 1704 unique high-resolution images of the esophagus from 669 patients[41]. This study demonstrated the high sensitivity and accuracy of deep neural network-based methods for detecting SCC and differentiating from non-cancerous lesions[42]. Additionally, the computer-aided detection algorithm demonstrated enhanced performance compared to that of a group of 53 nonexpert endoscopists. A pilot study examining this system during live endoscopy sessions produced encouraging outcomes[43]. The ongoing development of imaging technologies and AI for esophageal cancer diagnosis holds great promise. Future directions include refining existing techniques, expanding accessibility, and integrating these technologies into routine clinical practice for widespread and effective early detection. These findings underscore the importance of advanced imaging techniques in the early detection of esophageal cancer. Narrow-band imaging, in particular, demonstrates a superior ability to identify subtle changes indicative of dysplasia or early-stage carcinoma. As these technologies continue to evolve and become more widely

adopted in clinical practice, they hold the potential to significantly improve the early detection and management of esophageal cancer, ultimately leading to better patient outcomes.

### **Biomarker integration in screening programs**

Recognizing the limitations of traditional screening methods, the incorporation of biomarkers into screening programs represents a promising avenue for enhancing early detection precision. Biomarkers such as microRNA signatures, circulating tumor DNA (ctDNA), and protein markers hold potential for identifying high-risk individuals and detecting esophageal cancer at its earliest, most treatable stages[44-46]. MicroRNA profiling can reveal specific expression patterns linked to esophageal cancer[45,47]. For example, the level of plasma microRNA-192-5p has been shown to predict the response to chemotherapy and the prognosis in patients with esophageal cancer[48]. ctDNA analysis is a non-invasive method for detecting genetic mutations associated with esophageal cancer, and studies have shown that this method has substantial sensitivity and specificity[49-51]. A quantitative analysis encompassing 15 studies on the application of ctDNA technology, along with 8 studies involving 414 patients, revealed that the overall sensitivity and specificity of ctDNA-based diagnostic methods were 71.0% (ranging from 55.7% to 82.6%) and 98.6% (ranging from 33.9% to 99.9%), respectively, while those of ctDNA-based diagnostic methods were 48.9% (29.4%-68.8%) and 95.5% (90.6%-97.9%), respectively[52]. Certain proteins, epitomized by distinct antigens and enzymes, have emerged as potent indicators in identifying esophageal cancer. Protein marker analysis, often conducted through blood tests, can complement imaging techniques and contribute to a more comprehensive screening approach. Ide *et al*[53] found that angiopoietin-like protein 2 may be a novel biomarker for the diagnosis and prognosis of patients with esophageal cancer[54]. Given the heterogeneity of esophageal cancer, utilizing multimodal biomarker panels can enhance diagnostic accuracy. Integrating different types of biomarkers into a unified screening program allows for a more nuanced assessment, increasing the chances of early cancer detection. Despite these advancements, challenges such as standardization, cost, and validation across diverse populations remain. Ongoing research and collaborative efforts are crucial to refine and integrate these technologies into routine clinical practice, aiming to improve early detection and treatment outcomes for esophageal cancer patients.

### **Therapeutic management disparities in early-stage EC**

The heterogeneities observed in the therapeutic orchestration of incipient EC are intricately linked with the divergences in early diagnostic frequencies discernible across various geographies. This aspect is particularly evident in high-incidence areas such as China and Japan, where advanced early detection capabilities have led to the development of specialized endoscopic techniques for both diagnosis and treatment, [Table 2](#).

### **Region-specific advances**

In locales such as China and Japan, characterized by a heightened prevalence of esophageal cancer, there has been a notable advancement in the infrastructure for early detection[55]. This advancement has translated into distinct treatment approaches tailored to the regional disease profile[56]. The understanding and adoption of these region-specific methodologies can offer insights for improving global treatment outcomes. The disparities in therapeutic management of early-stage EC are intricately linked to regional variations in incidence and the effectiveness of early diagnosis programs. Regions with a higher incidence, such as China and Japan, often exhibit more advanced early detection infrastructures, leading to distinct treatment approaches[57]. Particularly in these high-incidence regions, advanced early diagnosis has elevated the role of specialized endoscopic techniques as a cornerstone in the therapeutic regimen for esophageal cancer [56-58].

### **Endoscopic resection methods**

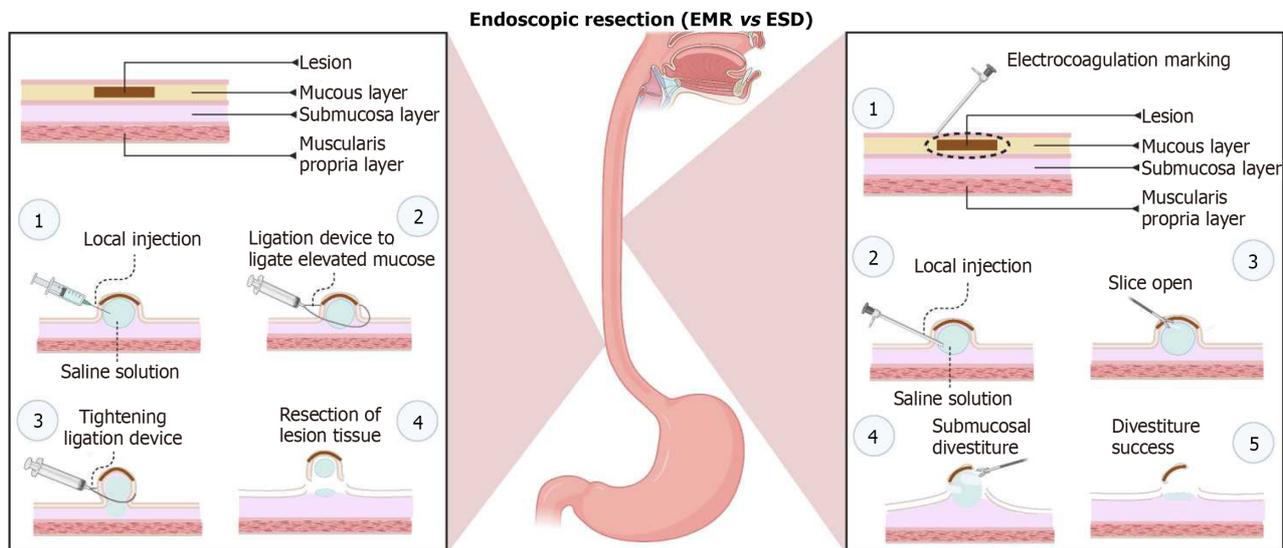
Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have demonstrated remarkable efficacy in treating early-stage esophageal cancer while preserving esophageal functionality[59]. EMR[60,61] and ESD[62] are increasingly recognized for their minimally invasive nature and potential in providing effective treatment with reduced morbidity compared to traditional surgical approaches ([Figure 1](#)).

**EMR:** EMR stands as a pivotal technique in the treatment of early-stage esophageal cancer. This minimally invasive approach involves the removal of cancerous or precancerous tissue from the mucosal layer while preserving the underlying structures and esophageal function. European guidelines recommend EMR for lesions under 10 mm, highlighting the importance of en bloc resection to improve disease-free survival due to the risk of lymph node metastasis in ESCC[63]. The judicious selection of candidates for EMR is critical to avoid poor prognosis. In Japan, EMR has been meticulously guided by the Japanese Society for Gastrointestinal Endoscopy's guidelines, addressing various clinical questions from preoperative diagnosis to postoperative surveillance[58]. Derived from a comprehensive review of scientific literature, this guideline offers insights on 18 clinical queries encompassing aspects such as preoperative diagnosis, indications for surgery, resection techniques, evaluating the potential for cure, and monitoring patients who have undergone endoscopic esophagectomy for esophageal cancer. Empirical evidence from a retrospective study, which scrutinized 44 patients with clinical stage I (T1a-MM, T1bcN0M0, in Japan) esophageal cancer using EMR demonstrated that EMR provides both disease control and adequate treatment of the lesion[64]. In addition, EMR is an effective treatment for superficial esophageal cancer. However, a study of 30 cT<sub>2</sub>N<sub>0</sub>M<sub>0</sub> patients treated with EMR showed that EMR successfully cleared all known disease in 17/30 patients. In the 17 patients where EMR successfully eradicated all detectable disease, there were neither recurrences nor cancer-related fatalities. This outcome indicates that EMR is a safe diagnostic approach for cT<sub>2</sub>N<sub>0</sub>M<sub>0</sub> esophageal cancer. Additionally, EMR tends to be favored for older patients presenting with smaller tumors and lower SUV<sub>max</sub> values[65].

**Table 2** The pros and cons of diagnostic and therapeutic protocols in esophageal carcinoma

Diagnostic and therapeutic protocols	Indications	Pros	Cons
<p>(1) For patients with early-stage EC who meet the absolute and relative indications for endoscopic resection, ESD being the first choice; (2) When the long diameter of the lesion is ≤ 10 mm, if the whole piece can be guaranteed resection, EMR treatment can also be considered; (3) For patients with early-stage EAC after EMR resection, ablation treatment is recommended; (4) Endoscopic radiofrequency ablation (RFA) can be used to treat ESCC limited to the lamina propria of the mucosa; and (5) For patients with lesions infiltrating to a depth of submucosal (&gt; 200 μm) T1b stage EC patients with lymph node or vascular invasion and tumor low differentiation (≥ G3), esophagectomy should be performed. Those who refuse surgery or are intolerant to surgery should be treated with concurrent radiotherapy and chemotherapy [26]</p>	<p>(1) The absolute indication of endoscopic resection of EC is that the lesion is limited to the epithelial layer and lamina propria of T1a esophageal cancer, and the risk of lymph node metastasis is low; (2) The relative indications of endoscopic resection: the lesion extends to the muscularis mucosa or slightly infiltrates the submucosa (the depth of submucosal infiltration is less than 200 μm), the range is ≥ 3/4 of esophageal circumference, and the risk of stenosis after resection is high. However, patients should be fully informed of postoperative stenosis and other risks; (3) Lesions with infiltration depths (&gt; 200 μm) up to the submucosal layer (T1b) are associated with metastasis, in which case they should be treated in the same way as advanced cancers, even if they are classified as superficial [26,55]</p>	<p>(1) EMR: Easy to operate and less invasive. Short operation time, low risk and quick recovery; (2) ESD: Larger tumors, especially those larger than 2 cm in diameter, can be completely removed at once, reducing the likelihood of recurrence; (3) RFA has a relatively short recovery time and demonstrates a low recurrence rate; (4) Surgery: Completely remove the tumor, thereby reducing the risk of recurrence, and providing exact pathological staging information, which helps to assess the progression of the cancer and plan subsequent treatment; and (5) CRT: Providing good local lesion control and helping to reduce tumor size, which may make surgery easier or, in some cases, avoid it; being effective in reducing the rate of tumor recurrence for some patients; and making CRT an effective treatment option for patients who can't afford to have surgery due to health issues</p>	<p>(1) EMR: Difficulty in removing large or poorly defined tumors at one time, which may require multiple treatments and a relatively high rate of recurrence; (2) Technically demanding, the procedure takes longer and may increase the risk of complications, such as bleeding or perforation; (3) RFA: Narrow range of indications; may increase risks and complications, include pain, bleeding, esophageal stricture or perforation, requiring specialized equipment and trained physicians; (4) Surgery: There are risks associated with the surgery itself (<i>e.g.</i>, infection, bleeding, anesthesia complications, <i>etc.</i>), possible postoperative complications (<i>e.g.</i>, esophageal stricture, dysphagia, malnutrition, <i>etc.</i>), and negative impact on the patient's quality of life, especially in terms of digestive function and eating habits. In addition, the long postoperative recovery time may require additional nutritional support and rehabilitation; and (5) CRT: Include a wide range of possible side effects from chemotherapy and radiation (<i>e.g.</i>, nausea, vomiting, hair loss, fatigue, loss of appetite, <i>etc.</i>); the potential for a long-term decline in quality of life, such as digestive problems and difficulty swallowing; and the potential for a wide-ranging impact on a patient's overall health status, especially for patients who are older or who have other health problems</p>

EC: Esophageal carcinoma; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; CRT: Concurrent radiotherapy; RFA: Radiofrequency ablation.



**Figure 1** Endoscopic resection methods (endoscopic mucosal resection vs endoscopic submucosal dissection). EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection. Created with BioRender.com.

**ESD:** ESD, a technique originating and perfected in Japan, has primarily been applied in the management of superficial ESCC. As an advanced endoscopic method, ESD facilitates the en-bloc resection of larger lesions, epitomizing precision and meticulousness. This precise and meticulous procedure is particularly effective in treating early-stage EC, providing a greater chance of complete tumor removal with minimal impact on surrounding tissues. Over the preceding decade, an escalating scholarly interest in esophageal ESD has manifested in Western medical circles. Notably, the Western landscape is characterized by the prevalence of EAC, overshadowing ESCC, which has exhibited a discernible decline

over recent decades. The utility of ER in BE has garnered substantiated recognition as a pivotal modality, affording comprehensive insights into staging, prognosis, and the extirpation of neoplastic manifestations associated with BE. This approach uniformly receives commendation across authoritative societal guidelines, especially in the context of managing high-grade dysplasia (HGD) and tumors confined to the muscularis mucosa (T1a)[19,66,67].

ESD has been widely used to treat superficial esophageal cancer, advantages of ESD include high rates of whole-mount resection and accurate pathologic diagnosis. Even in cases with clinical T<sub>1b-SM</sub> cancer, subsequent treatments can potentially lead to a radical cure, depending on the risk of metastasis. The role of ESD in the treatment of esophageal cancer will become increasingly important[68]. A study involving 66 patients with pathologic staging of T<sub>1b</sub> from 7 United State centers showed that 54 patients underwent preoperative staging, 27 patients (50%) were T<sub>1s</sub>/T<sub>1a</sub> and 27 patients (50%) were T<sub>1b</sub>. The rate of complete resection was 92.4% (61/66) and the rate of R0 resection was 54.5% (36/66). 10 patients who underwent ESD resection within the criteria for cure had no recurrence after 13 months of follow-up. Ten patients who underwent ESD resection had no recurrence after 13 months of follow-up. Ten of the 39 patients (25.6%) who underwent noncurative resection had residual/recurrent disease[69]. Consequently, these findings from this study should alleviate persistent worries about prolonged procedure durations and increased rates of adverse events associated with ESD in the esophagus. Ongoing improvements in ESD techniques, exemplified by innovations such as counter-traction, hold promise for achieving even more profound dissection planes and favorable outcomes, though further investigation is warranted in this regard. Prospective studies are imperative to explore the potential efficacy of adjuvant chemotherapy and radiation post-ESD, particularly for patients ineligible for surgical options, are imperative. Furthermore, the evolving landscape anticipates a pivotal role for advanced imaging and AI. Their application is envisaged to discern Tis/HGD/T1a from T1b disease, particularly given the current dearth of precise staging methods preceding the ER of early esophageal cancer[70]. Global standardization of treatment protocols, informed by successes in high-incidence areas, is crucial. Sharing best practices, lessons learned, and technological advancements can contribute to the development of universally effective therapeutic strategies for early-stage EC.

In geographical areas marked by elevated incidences of EC, such as China and Japan, endoscopic techniques have become integral components of the therapeutic landscape. Their success is underscored by the ability to treat a substantial number of cases at an early stage, contributing to improved overall survival rates. The efficacy of endoscopic techniques lies not only in their ability to effectively remove early-stage tumors but also in their potential to minimize complications. By avoiding the need for major surgery, patients undergoing EMR or ESD experience shorter recovery times and reduced postoperative morbidity. A crucial advantage of endoscopic techniques is the preservation of esophageal functionality. Unlike more invasive surgical procedures, EMR and ESD are designed to remove cancerous tissue while maintaining the structural integrity and function of the esophagus.

### **Challenges in esophageal cancer screening and future perspectives**

Implementing population-wide screening programs for EC is fraught with challenges, including resource constraints and the need for well-established infrastructure. Overcoming these challenges requires a multidisciplinary approach involving healthcare policymakers, clinicians, and researchers to design effective and sustainable screening initiatives.

**Resource constraints:** Population-based screening programs are hindered by financial, infrastructural, and human resource limitations. Addressing these constraints is critical to enable widespread and equitable access to screening services.

**Infrastructure development:** The establishment and maintenance of infrastructure for screening are complex tasks, especially in resource-limited settings. This involves setting up facilities, training healthcare professionals, and ensuring the availability of diagnostic tools.

**Education and awareness:** Public awareness about esophageal cancer, its risk factors, and the significance of early detection is often lacking. Educational campaigns are crucial to enhance understanding and participation in screening programs.

**Overcoming cultural and social barriers:** Cultural beliefs and social norms can impede participation in screening initiatives. It's important to design culturally sensitive programs and engage communities to overcome these barriers.

**Ensuring equity and accessibility:** Ensuring equitable access to screening, particularly for underserved populations, is essential. This requires targeted efforts to reach rural areas and marginalized groups.

**Monitoring and evaluation:** Effective monitoring and evaluation mechanisms are essential for assessing the impact of screening programs, identifying areas for improvement, and optimizing resource allocation.

## **CONCLUSION**

Addressing the global burden of esophageal cancer requires an understanding of regional variances in incidence, risk factors, and histological types. The development of tailored screening strategies, resolving debates in early detection, and adopting advanced treatment methods are key to enhancing patient outcomes. Future efforts should focus on: Global collaboration: Sharing best practices, research findings, and technological advancements on an international scale is vital for progress in prevention, early detection, and treatment of esophageal cancer. Technological innovation: Continued

investment in innovative diagnostic and treatment technologies, including advanced endoscopic techniques, AI-driven diagnostic tools, and novel biomarkers, will play a significant role in advancing esophageal cancer care. Holistic approach: Combining medical advancements with public health initiatives, including lifestyle modification campaigns and risk factor management, is necessary for a comprehensive approach to esophageal cancer prevention and treatment. Personalized medicine: Emphasizing personalized screening and treatment strategies based on individual risk profiles and genetic predispositions will enhance the effectiveness of interventions. Research and development: Ongoing research into the etiology, pathogenesis, and optimal management of esophageal cancer is crucial to uncover new insights and improve clinical practices.

In summary, a multifaceted and collaborative approach, integrating medical advances with public health strategies, is essential for effectively tackling the complexities of esophageal cancer globally.

## FOOTNOTES

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**Author contributions:** Miao YD conceptualization, writing-review and editing, funding acquisition, and project administration; Zhang F conceptualization, writing-review and editing, supervision; Qu HT performed literature retrieval, writing-original draft; Li Q performed literature retrieval, writing-original draft; Hao L and Ni YJ performed Literature retrieval and data analysis; Luan WY, Yang Z, Chen XD, and Zhang TT software and prepared Figures; Qu HT and Li Q contributed equally to this work. Miao YD and Zhang F were designated as co-corresponding authors. Zhang F was responsible for the formulation or evolution of overarching research goals and aims, specifically critical review, commentary, or revision-including pre-or postpublication stages, management and coordination responsibility for the research activity planning and execution, acquisition of the financial support for the project leading to this publication, while Miao YD was responsible for review and editing the draft, oversight, and leadership responsibility for the research activity planning and execution, including mentorship external to the core team. This designation reflects their equal contributions and shared responsibility in overseeing the project and correspondence related to this research. All authors approved the final manuscript.

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